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

Norditropin SimpleXx
(somatropin)

DK/W/0013/pdWS/002

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 SimpleXx
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-I (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 10 mg/1,5 ml

I. EXECUTIVE SUMMARY

No SmPC and PL changes are proposed.

II. RECOMMENDATION

No further action required.

III. INTRODUCTION

On 4 June 2015, the MAH submitted a completed paediatric study for Norditropin SimpleXx, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

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 SimpleXx and that there is no consequential regulatory action.

IV. SCIENTIFIC DISCUSSION

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

Norditropin® is the registered trademark for Novo Nordisk's recombinant hGH product somatropin. Norditropin® SimpleXx® is the cartridge with liquid hGH to be used in a durable pen. In this trial Norditropin® SimpleXx® was used as a comparator.

The primary action of somatropin is the stimulation of linear growth in children. Norditropin® SimpleXx® has proven to be a safe and efficacious treatment in both children with Growth Hormone Deficiency and Adult GHD patients and is approved worldwide for these and related indications.

Children and adults with GHD currently require many years or lifelong treatment and persistence with a daily subcutaneous (s.c.) injection regimen. Studies investigating compliance have shown that approximately 25% of children on hGH treatment miss more than 2 injections per week. GH and therapeutic proteins in general have a short in vivo half-life, which necessitates their administration by continuous infusion or frequent injections. Consequently, there could be a rationale for developing a formulation of rhGH with a prolonged half-life.

NNC0195-0092 is a long-acting hGH derivative intended for once-weekly treatment of GHD in children and adults (AGHD). A once-weekly hGH addresses an important convenience aspect by reducing the number of required injections (from 365 to 52 per year). NNC0195-0092 is expected to have at least the same efficacy and safety profile as daily administered hGH.

NNC0195-0092 is in early development, and trial NN8640-4042 was performed in a limited number of patients to compare pharmacology and safety of NNC0195-0092 with children treated with the well established Norditropin SimpleXx. Due to small sample size no evaluation of efficacy was possible.

IV.2 Clinical aspects

1. Introduction

The MAH submitted a final report for:

A randomised, open-labelled, active-controlled, multinational, dose-escalation trial investigating safety, tolerability, pharmacokinetics and pharmacodynamics of a single-dose of long-acting growth hormone (NNC0195-0092) compared to daily dosing of Norditropin® SimpleXx® in children with growth hormone deficiency.
Trial ID: NN8640-4042

2. Clinical study(ies)

- **Description**

- **Methods**

Objective(s)

Primary objective

- To evaluate safety and tolerability of a single s.c. dose of NNC0195-0092 compared to daily dosing of Norditropin® SimpleXx® for 7 days in children with GHD.

Secondary objectives

- To evaluate PK and PD of a single s.c. dose of NNC0195-0092 in children with GHD.
- To evaluate local tolerability (i.e., injection site reactions) of a single s.c. dose of NNC0195-0092 compared to daily dosing of Norditropin® SimpleXx® for 7 days in children with GHD.

Study design
The trial was conducted at 14 sites in 8 countries. All 14 sites screened and randomised/assigned patients to treatment. There were no trial sites that only screened children. There were no active trial sites that were closed prematurely. The purpose of this trial was to investigate safety, tolerability, PK and PD of single s.c. dosing of NNC0195-0092 in children with GHD. The primary therapeutic indication considered for the NNC0195-0092 compound is GHD in children.

Study population /Sample size
The trial was a randomised, open labelled, active controlled, multinational, dose-escalation trial investigating safety, tolerability, PK and PD of a single s.c. dose of NNC0195-0092 compared to daily dosing of Norditropin® SimpleXx® in children with GHD.
Four (4) cohorts with 8 children with GHD in each cohort were investigated (n=32). Within each cohort, the children were randomised to receive either a single s.c. dose of NNC0195-0092 (0.02, 0.04, 0.08 or 0.16 mg/kg, n=6) or a once-daily dose of Norditropin® SimpleXx® for 7 days (0.03 mg/kg; n=2). The trial population was pre-pubertal children with GHD (boys: 6−13 years; girls: 6−12 years).

Table 10–1 Subject disposition by treatment

	Norditropin	NNC0195-0092	Total
Screened Subjects, N *			34
Randomised subjects, N (%)	8 (100.0)	24 (100.0)	32 (100.0)
Exposed subjects, N (%)	8 (100.0)	24 (100.0)	32 (100.0)
Completed subjects, N (%)	8 (100.0)	24 (100.0)	32 (100.0)
Withdrawn subjects, N (%)	0 (0.0)	0 (0.0)	0 (0.0)

* Re-screened subjects are counted only once

Inclusion criteria

For an eligible patient, all inclusion criteria must be answered "yes".

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial.
2. Confirmed diagnosis of GHD as defined by two different GH stimulation tests, peak GH level ≤ 7.0 ng/mL. For children with three or more pituitary hormone deficiencies only one GH stimulation test will be needed. If in accordance with country specific practice GHD can be defined by only one GH stimulation test, peak GH level ≤ 7.0 ng/mL.
3. Pre-pubertal children at the time of signing informed consent.
a. Boys: Tanner stage 1 and age ≥ 6 years and < 13 years.
b. Girls: Tanner stage 1 and age ≥ 6 years and < 12 years.
4. Body weight ≥ 16.0 kg and ≤ 50.0 kg.
5. Stable hGH replacement treatment ≥ 3 months.
6. Children previously treated for intracranial tumours can be included if negative signs of intracranial tumour or tumour growth have been confirmed by computer tomography (CT) or magnetic resonance imaging (MRI) scan within 12 months prior to randomisation.

Exclusion criteria

For an eligible patient, all exclusion criteria must be answered "no".

1. Known or suspected hypersensitivity to trial products or related products.
2. Previous participation in this trial. Participation is defined as randomised.
3. Receipt of any investigational medicinal product (IMP) within 3 months before randomisation.
4. History or presence of malignancy.
5. Overt diabetes mellitus (fasting blood glucose ≥ 7.0 mmol/l (126 mg/dl)).
6. History of hypoglycaemic episode(s) after cessation of hGH treatment.
7. Known chromosomal abnormalities and medical “syndromes” (Turner syndrome, Noonan syndrome or absence of GH receptors).
8. Congenital abnormalities (causing skeletal abnormalities), Russell-Silver Syndrome, skeletal dysplasias.
9. Poorly controlled or uncontrolled pituitary insufficiencies of other axes (e.g., thyroid stimulating hormone, adrenocorticotropic hormone/cortisol, vasopressin deficiency), defined as: Stable replacement therapy for less than 3 months for other hormonal deficiencies prior to enrolment.
10. Major medical conditions and/or presence of contraindication to hGH treatment.
11. Any disorder which, in the opinion of the investigator, might jeopardise patient’s safety or compliance with the protocol.
12. Any clinically significant abnormal haematology or biochemistry screening tests, as judged by the investigator.

13. Active hepatitis B, measured by surface antigen B (HBsAg) and/or active hepatitis C, measured by positive hepatitis C virus antibody test.
14. Clinically significant abnormal ECG at screening, as evaluated by investigator.
15. Surgery or trauma with significant blood loss within the last 3 months prior to randomisation.
16. Mental incapacity of the child, parents/legal guardian or language barriers which preclude adequate understanding or cooperation, who are unwilling to participate in the trial or who in the opinion of their general practitioner or the investigator should not participate in the trial.
17. The patient and/or the parent/legal guardian are likely to be noncompliant in respect to trial conduct, as judged by the investigator.

Treatments
A single dose of NNC0195-0092 was compared to a once-daily dose of Norditropin® SimpleXx® for 7 days (1 week). Four (4) dose levels of NNC0195-0092 (0.02, 0.04, 0.08 or 0.16 mg/kg) were investigated. The Norditropin® SimpleXx® dose was 0.03 mg/kg.
The Norditropin® SimpleXx® once-daily dose of 0.03 mg/kg was selected since this dose is within the recommended dose range for hGH treatment of children with GHD.

Outcomes/endpoints
No efficacy end-points are applied to this study. Analysis is limited to safety evaluation after short-term (1 week) treatment.

Statistical Methods
No statistical analysis is applied to the limited safety data set in 8 patients.

- **Results**

Recruitment/ Number analysed
Eight children with GHD were randomised to Norditropin SimpleXx.

Baseline data
The mean age ranged from 7.8−9.0 years across dose groups (min: 6.0 years; max: 11.0 years). The mean weight ranged from 23.1−27.8 kg across dose groups (min: 17.0 kg; max: 41.2 kg). In the NNC0195-0092 0.02 mg/kg dose group, the mean weight seemed to be lower than in the other dose groups. The mean BMI ranged from 15.6−17.4 kg/m2 (min: 12.6 kg/m2; max: 22.1 kg/m2), though BMI may not be applicable in children. The mean height was similar across the dose groups.

Physical examinations were normal for all children, except for one. No clinically relevant differences were observed in physical examination between groups. Abnormal, clinically significant findings were reported in 1 subject at baseline (NNC0195-0092 0.04 mg/kg: bilateral convergent strabismic amblyopia and wide-based gait).

Efficacy results
Efficacy end-points were not part of the objectives of the trial.

Safety results
A total of 19 AEs were reported in 11 (46%) children with GHD following NNC0195-0092 single dose exposure and 2 AEs were reported in 1 child (13%) following once-daily Norditropin® SimpleXx® treatment. All AEs were of mild severity. All AE except one were reported as unlikely related to trial products. Mild haematuria (NNC0195-0092 0.02 mg/kg) was reported as possibly trial product related. The AEs reported in at least 2 subjects were nasopharyngitis, headache and vomiting. All subjects recovered from the AEs.

There were no serious AEs reported. There were no AEs leading to withdrawal.

Table 12–3 Frequent AEs (≥5%) by SOC and preferred term – safety analysis set

	0.03 mg/kg Norditropin N % E	0.02 mg/kg NNC0195-0092 N % E	0.04 mg/kg NNC0195-0092 N % E	0.08 mg/kg NNC0195-0092 N % E	0.16 mg/kg NNC0195-0092 N % E	Total NNC0195-0092 N % E
Subjects exposed	8	6	6	6	6	24
All AEs	1 13% 2	2 33% 3	4 67% 9	2 33% 3	3 50% 4	11 46% 19
MedDRA SOC/PT						
Infections/infestations						
Nasopharyngitis	0	1 17% 1	1 17% 1	0	0	2 8% 2
Nervous system dis						
Headache	0	0	0	1 17% 1	1 17% 1	2 8% 2
Gastrointestinal dis						
Vomiting	1 13% 1	0	1 17% 1	0	1 17% 1	2 8% 2
Nausea	1 13% 1	0	0	0	0	0

N: number of subjects having the event, or an event in the given SOC at least once.
E: number of AEs reported. %: percentage of exposed subjects having the event.
SOC: system organ class; PT: preferred term; dis: disorders

Biochemical measurements during one week of therapy were unremarkable with no adverse reactions observed.

Anti-hGH antibodies

Assessment of antibodies against hGH in serum from children randomised to Norditropin® SimpleXx® treatment was performed by Novo Nordisk A/S using a validated antibody binding assay. The assay was a bridging ELISA developed by Novo Nordisk A/S to specifically determine antibody levels against hGH. Since no antibodies were detected, neutralising effect was not investigated.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

In this small study with a very limited number of patients treated with Norditropin SimpleXx (n=8) for only 1 week the safety was unremarkable and no new signals of interest were observed. The results of the study do not change the benefit/risk ratio of the product, which has been widely used in many years to children with GHD.
The results for the experimental drug NNC0195-0092 are not part of the assessment.

- **Recommendation**

No further action required.