

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

**Norditropin SimpleXx, Norditropin NordiLet,
Norditropin NordiFlex, Norditropin FlexPro
Somatropin**

DK/W/013/pdWS/001

Marketing Authorisation Holder: Novo Nordisk

| | |
|---|-----------------|
| Rapporteur: | Denmark |
| Finalisation procedure (day 90): | 13 January 2011 |
| Date of finalisation of PAR | 2 March 2011 |

ADMINISTRATIVE INFORMATION

| | |
|--|--|
| Invented name of the medicinal product: | Norditropin SimpleXx Norditropin NordiLet Norditropin NordiFlex Norditropin FlexPro |
| INN (or common name) of the active substance(s): | Somatropin |
| MAH: | Novo Nordisk |
| Currently approved Indication(s) | Growth hormone deficiency in children; Turner Syndrome; Chronic renal insufficiency in children; growth disturbance in small children born small for gestational age; growth hormone deficiency in adults. Outside EU: Noonan syndrome; skeletal dysplasia |
| Pharmaco-therapeutic group (ATC Code): | H01AC01 |
| Pharmaceutical form(s) and strength(s): | Solution for injection 5 mg/1,5 ml (3,3 mg/ml), 10 mg/1,5 ml (6,7 mg/ml) og 15 mg/1,5 ml (10 mg/ml) |

I. EXECUTIVE SUMMARY

No SmPC and PL changes are proposed.

II. RECOMMENDATION¹

No further action required.

III. INTRODUCTION

On 22 September 2010, 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.

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

Norditropin is approved for the paediatric indication “small for gestational age”. Since the marketing of Norditropin a clinical trial in this indication has been completed in Japan. The MAH submits the report from the trial.

GHLiquid-1516 was a 104-week, multi-centre, randomised, double-blind, parallel-group, no treatment controlled (open-label) trial investigating the efficacy and safety of two doses of Norditropin in subjects with short stature born SGA. The trial consisted of a Visit 1 (screening) to assess subjects’ eligibility and 104-week (0.033 mg/kg/day group and 0.067 mg/kg/day group) or 52-week (No treatment group) treatment period. The efficacy and safety of GHLiquid-1516 was in agreement with previous documentation for rhGH products, and the results have been assessed previously. The present dossier contains data from the extension trial GHLiquid-1517.

GHLiquid-1517 was conducted in subjects in 44 sites in Japan who had completed GHLiquid-1516 and given informed consent for participating in this trial. The treatment period of this trial was originally planned to be 208 weeks and 156 weeks for the subjects allocated to the No treatment group and active treatment groups in GHLiquid-1516, respectively. As a result of GHLiquid-1516, the doses of 0.033 and 0.067 mg/kg/day were both efficacious for treatment of children with short stature born SGA, and the height gain was greater with 0.067 mg/kg/day.

The trial was planned in accordance with the Declaration of Helsinki¹, the Ministry of Health and Welfare (MHW) Ordinance on GCP (MHW Ordinance No. 28; 27 March 1997) and the applicable relevant regulations.

¹ The recommendation from section V can be copied in this section

Primary Objective:

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

Secondary Objective(s):**After 260 weeks of treatment or 208 weeks of treatment**

1) To investigate the long-term safety profile of 0.033 mg/kg/day and 0.067 mg/kg/day as assessed by AEs, clinical laboratory tests, oral glucose tolerance test (OGTT), glycosylated haemoglobin A_{1c} (HbA_{1c}) and bone age.

2) To investigate the growth promoting effect of 0.033 mg/kg/day and 0.067 mg/kg/day as assessed by height velocity SDS for CA.

3) To compare the relationship between BA and height increase of 0.033 mg/kg/day and 0.067 mg/kg/day as assessed by delta height SDS for BA.

4) To compare the relationships between concentrations of IGF-I and IGFBP-3 and growth promoting effect of 0.033 mg/kg/day and 0.067 mg/kg/day.

5) To compare the score obtained from questionnaire survey between 0.033 mg/kg/day and 0.067 mg/kg/day.

Treatment period was as follows:

1) At least 156 weeks for subjects in the 0.033 mg/Norditropin group and 0.067 mg/Norditropin group (not including treatment period in GHLiquid-1516)

2) At least 208 weeks for subjects in the 0.033 mg/No treatment group and 0.067 mg/No treatment

Group

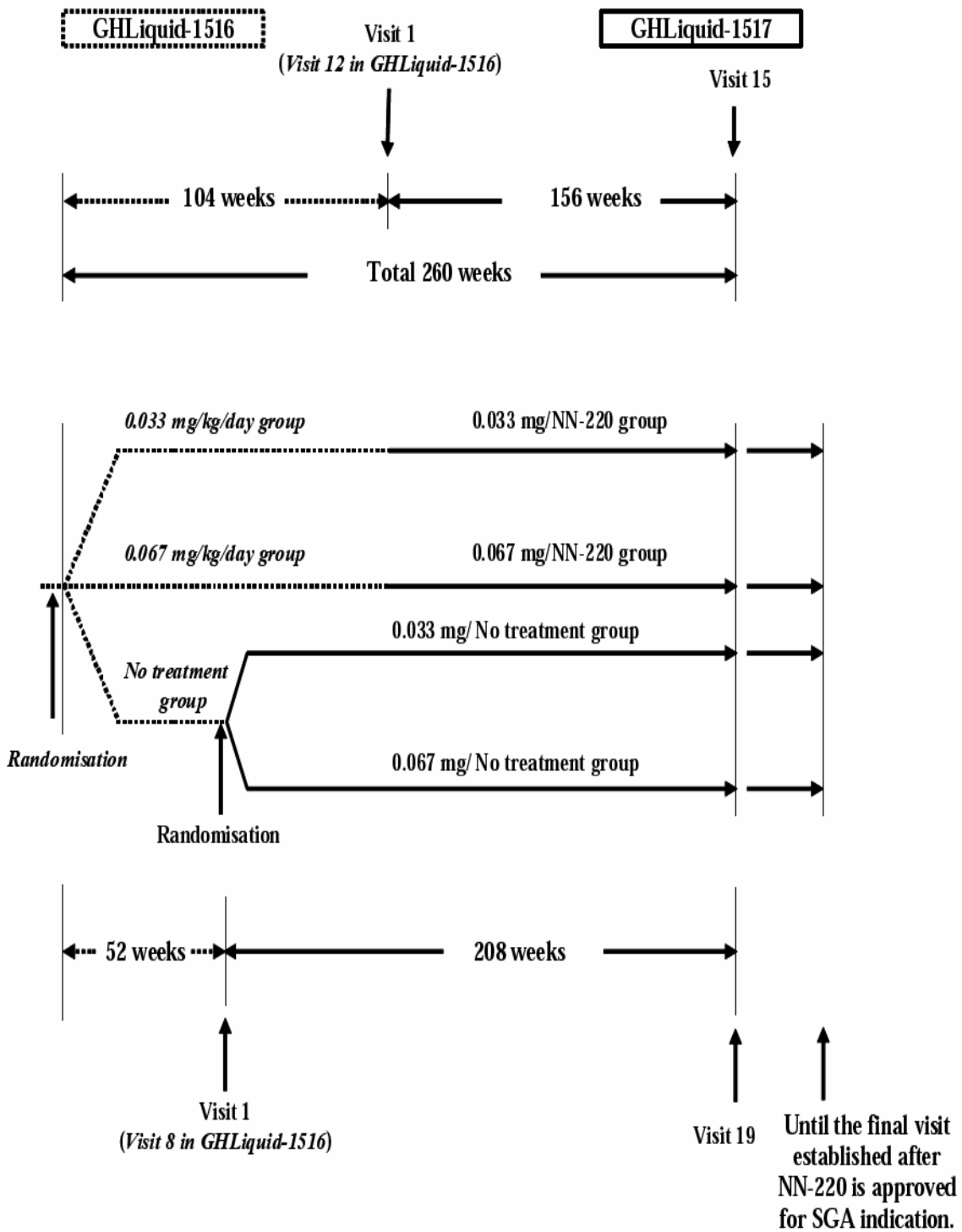
This trial had four parallel treatment arms:

1+ 2) 0.033 mg/Norditropin group and 0.067 mg/Norditropin group

The subjects were treated with the same dose as that in GHLiquid-1516, and therefore they were not randomised in this trial.

3 + 4) 0.033 mg/No treatment group and 0.067 mg/No treatment group

The subjects were randomised to one of two groups (0.033 mg/No treatment group and 0.067 mg/No treatment group) in this trial. The subjects in the 0.033 mg/No treatment group were treated with 0.033 mg/kg/day of Norditropin. The subjects in the 0.067 mg/No treatment group were treated with 0.067 mg/kg/day of Norditropin.



The trial products were 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.

Table 10-1 Subject Disposition

| | 0.033 mg / NN-220 | 0.067 mg / NN-220 | 0.033 mg / No treatment | 0.067 mg / No treatment | Total |
|---|----------------------|----------------------|----------------------------|----------------------------|-------|
| Screened in GHLiquid-1516 | | | | | 109 |
| Screening failures in GHLiquid-1516 | | | | | 11 |
| Randomised in GHLiquid-1516 | 39 | 38 | 21 *4 | | 98 |
| Not exposed | 1 | 0 | 0 *4 | | |
| Exposed*1 | 38 (100.0) | 38 (100.0) | 21 (100.0) *4 | | |
| Withdrawals in GHLiquid-1516 after receiving trial product | 2 (5.3) | 2 (5.3) | 1 (4.8) *4 | | |
| Adverse event | 1 (2.6) | 0 (0.0) | 0 (0.0) *4 | | |
| Non-compliance with protocol | 0 (0.0) | 0 (0.0) | 1 (4.8) *4 | | |
| Ineffective therapy | 0 (0.0) | 0 (0.0) | 0 (0.0) *4 | | |
| Other | 1 (2.6) | 2 (5.3) | 0 (0.0) *4 | | |
| Completed GHLiquid-1516 | 36 (94.7) | 36 (94.7) | 20 (95.2) *4 | | |
| Did not participate in GHLiquid-1517*2 | 3 (7.9) | 3 (7.9) | 0 (0.0) *4 | | |
| Participate in GHLiquid-1517 | 33 (86.8) | 33 (86.8) | 20 (95.2) *4 | | |
| Randomised in GHLiquid-1517 | | | 10 | 10 | |
| Not exposed | | | 0 | 0 | |
| Exposed*3 | | | 10 (100.0) | 10 (100.0) | |
| Withdrawals in GHLiquid-1517 after receiving trial product | 10 (26.3) | 6 (15.8) | 3 (30.0) | 5 (50.0) | |
| Adverse event | 1 (2.6) | 0 (0.0) | 1 (10.0) | 0 (0.0) | |
| Non-compliance with protocol | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (10.0) | |
| Ineffective therapy | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| Other | 9 (23.7) | 6 (15.8) | 2 (20.0) | 4 (40.0) | |
| Completed GHLiquid-1517 | 23 (60.5) | 27 (71.1) | 7 (70.0) | 5 (50.0) | |
| Safety Analysis Set | 31 (81.6) | 34 (89.5) | 7 (70.0) | 8 (80.0) | |
| Full Analysis Set (FAS) | 31 (81.6) | 34 (89.5) | 7 (70.0) | 8 (80.0) | |
| Endpoint Analysis Set | 28 (73.7) | 29 (76.3) | 7 (70.0) | 8 (80.0) | |
| Completer's Set | 23 (60.5) | 27 (71.1) | 6 (60.0) | 6 (60.0) | |
| Per Protocol Set (PPS) | 22 (57.9) | 26 (68.4) | 6 (60.0) | 6 (60.0) | |

(): percent

*1: The denominator for percent is the number of exposed subjects in GHLiquid-1516 for 0.033 mg/NN-220 and 0.067 mg/NN-220. For no treatment group, the number of subjects obtaining any available data after 0 week in GHLiquid-1516 is used as denominator for percentage during GHLiquid-1516.

*2: Regarded as a withdrawal in 0.033 mg/NN-220 and 0.067 mg/NN-220.

*3: The denominator for percent is the number of exposed subjects in GHLiquid-1517 for 0.033 mg/No treatment and 0.067 mg/No treatment.

*4: Out of analysis period, i.e. data in no treatment period is not used in statistical analysis.

Endpoint Analysis Set: subjects who participated in GHLiquid-1517 trial in FAS.

Note: Main analyses for change from baseline on Height SDS for chronological age, IGF-I, IGFBP-3 and Questionnaire survey were performed on Endpoint Analysis Set.

Cross-reference: [EOT Table 14.2.1.1](#)

A total of 92 subjects completed GHLiquid-1516. Of these subjects, all in the Norditropin treatment group of GHLiquid-1516, 6 subjects did not participate in GHLiquid-1517. Consequently, a total of 86 subjects were enrolled in GHLiquid-1517. The subjects in the “No treatment group” of GHLiquid-1516 (20 subjects) were randomised to one of two groups (0.033 mg/No treatment group: 10 subjects, 0.067 mg/No treatment group: 10 subjects). The subjects in the Norditropin treatment groups of GHLiquid-1516 have continued with the same treatment in this trial.

A total of 24 subjects (10 subjects in the 0.033 mg/Norditropin group, 6 subjects in the 0.067 mg/Norditropin group and 3 subjects in the 0.033 mg/No treatment and 5 subjects in the 0.067 mg/No treatment groups) were withdrawn after the start of treatment in GHLiquid-1517. The most common reason for withdrawal was “Other reason” and main comment in “Other reason” was withdrew consent by subject. A total of 2 subjects were withdrawn due to AEs (“IgA nephropathy” in the 0.033 mg/Norditropin group, “hyperinsulinaemia” in the 0.033 mg/No treatment group).

Primary Endpoint

Change in Height SDS for CA after 260 weeks of treatment

After 260 weeks (5 years) of treatment, the mean height SDS for CA improved from – 3.00 to – 1.78 in the 0.033 mg/Norditropin group and from – 2.83 to – 0.82 in the 0.067 mg/Norditropin group. The change in height SDS from baseline to 260 weeks (LOCF) was 1.21 (0.11) and 2.03 (0.11) in the 0.033 mg/Norditropin and 0.067 mg/Norditropin groups, respectively, expressed as least squares mean (LSMean) standard error (SE). A significantly greater increase in height SDS was observed for 0.067 mg/Norditropin group compared to the 0.033 mg/Norditropin group ($p < 0.0001$), with an estimated mean difference (95% CI) of 0.82 (0.51, 1.13).

Table 11-6 Analysis of Change in Height SDS for CA at 260 weeks for EAS (0.033mg/NN-220 and 0.067mg/NN-220 groups)

| Basic statistics | | 0.033 mg / NN-220 | 0.067 mg / NN-220 |
|--|--|----------------------|----------------------|
| Number of Subjects | | 28 | 29 |
| Baseline | | | |
| N | | 28 | 29 |
| Mean (SD) | | -2.9988 (0.6336) | -2.8304 (0.6244) |
| Median | | -2.8775 | -2.7800 |
| Min ; Max | | -4.814 ; -2.045 | -4.833 ; -1.872 |
| 260 weeks (LOCF) | | | |
| N | | 28 | 29 |
| Mean (SD) | | -1.7755 (0.7775) | -0.8191 (0.7446) |
| Median | | -1.7605 | -0.8510 |
| Min ; Max | | -4.424 ; -0.367 | -2.900 ; 0.418 |
| Change from baseline to 260 weeks (LOCF) | | | |
| N | | 28 | 29 |
| Mean (SD) | | 1.2233 (0.5183) | 2.0113 (0.6432) |
| Median | | 1.2900 | 1.9620 |
| Min ; Max | | 0.390 ; 2.756 | 0.009 ; 3.528 |

Analysed subjects: who have both baseline and 260 weeks (LOCF)

Note: Endpoint Analysis Set: Subjects who participated in GHLiquid-1517 trial in FAS

| Item | Factor | NDF | DDF | F-value | P-value | LSMeans (SE) # | Point estimate and 95% C.I. # (0.067mg - 0.033mg) |
|-------------------|--------|-----|--------|-----------|---------|-------------------|---|
| Height SDS for CA | | | | | | | |
| Treatment group | 1 | 53 | 27.942 | <0.0001** | | 0.033 mg / NN-220 | |
| Baseline | 1 | 53 | 2.583 | 0.1140 | | : 1.2066(0.1102) | 0.8208(0.5093,1.1322) |
| Age | 1 | 53 | 0.267 | 0.6074 | | 0.067 mg / NN-220 | |
| | | | | | | : 2.0274(0.1083) | |

+:p<0.10, *:p<0.05, **:p<0.01

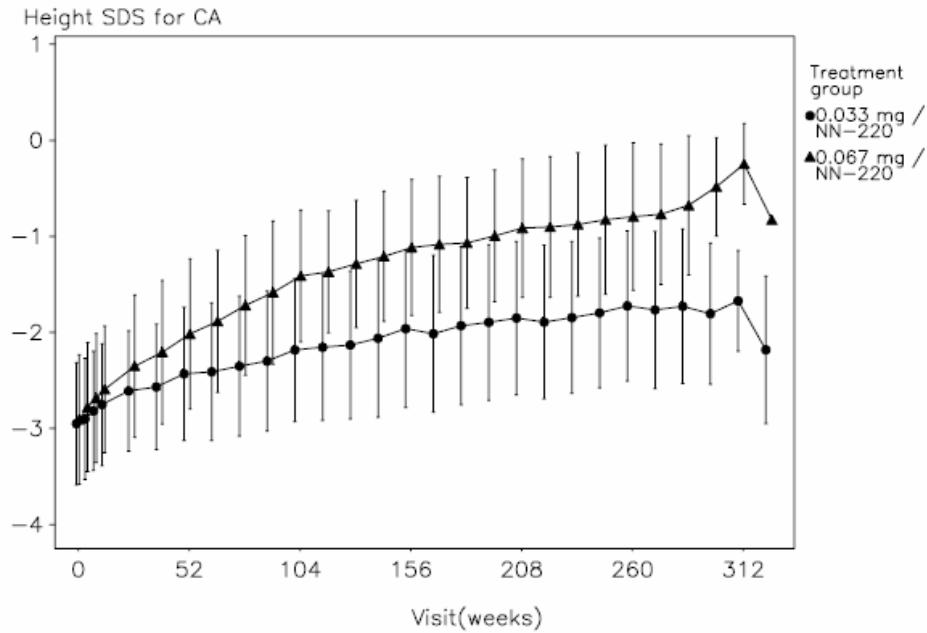
The statistics are calculated under the ANOVA model with treatment group as a fixed effect and baseline and age as covariates.

Analysed subjects : who have both baseline and 260 weeks (LOCF)

Note: Endpoint Analysis Set: Subjects who participated in GHLiquid-1517 trial in FAS

Cross-reference: [EOT Table 14.2.4.1](#) and [14.2.4.2](#)

Figure 14.2.4.15 Height SDS for chronological age in 0.033mg/NN-220 and 0.067mg/NN-220: Mean \pm SD



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Cross-reference: [EOT Figure 14.2.4.15](#)

Figure 11-1 Plot of Height SDS for CA (mean \pm SD) (0.033mg/NN-220 and 0.067mg/NN-220 groups)

For patients randomised to Norditropin treatment following “No treatment” in GHLiquid-1516 the sample size is very limited, but a marked growth improvement was observed in agreement with experience rhGH in SGA children.

Table 11-7 Analysis of Change in Height SDS for CA at 208 weeks for EAS (0.033mg/No treatment and 0.067mg/No treatment groups)

| Basic statistics | | 0.033 mg / No treatment | 0.067 mg / No treatment |
|--|--|----------------------------|----------------------------|
| Number of Subjects | | 7 | 8 |
| Baseline | | | |
| N | | 7 | 8 |
| Mean (SD) | | -2.9603 (0.6689) | -2.7481 (0.3524) |
| Median | | -3.1520 | -2.8055 |
| Min ; Max | | -3.938 ; -2.000 | -3.341 ; -2.130 |
| 208 weeks (LOCF) | | | |
| N | | 7 | 8 |
| Mean (SD) | | -1.9486 (0.8187) | -0.7560 (0.7544) |
| Median | | -2.0340 | -0.8850 |
| Min ; Max | | -3.169 ; -0.568 | -2.000 ; 0.652 |
| Change from baseline to 208 weeks (LOCF) | | | |
| N | | 7 | 8 |
| Mean (SD) | | 1.0117 (0.4678) | 1.9921 (0.6670) |
| Median | | 0.7710 | 1.8560 |
| Min ; Max | | 0.427 ; 1.778 | 0.811 ; 2.782 |

Analysed subjects : who have both baseline and 208 weeks (LOCF)
 Note: Endpoint Analysis Set: Subjects who participated in GHLiquid-1517 trial in FAS

| Item | Factor | NDF | DDF | F-value | P-value | LSMeans (SE) # | Point estimate and 95% C.I. # (0.067mg - 0.033mg) |
|-------------------|--------|-----|-------|---------|---------|------------------|---|
| Height SDS for CA | | | | | | | |
| Treatment group | 1 | 11 | 5.277 | 0.0422* | | 0.033 mg / NT | |
| Baseline | 1 | 11 | 0.277 | 0.6091 | | : 1.0997(0.2453) | 0.8154(0.0341,1.5966) |
| Age | 1 | 11 | 1.140 | 0.3086 | | 0.067 mg / NT | |
| | | | | | | : 1.9151(0.2275) | |

+ :p<0.10, * :p<0.05, ** :p<0.01

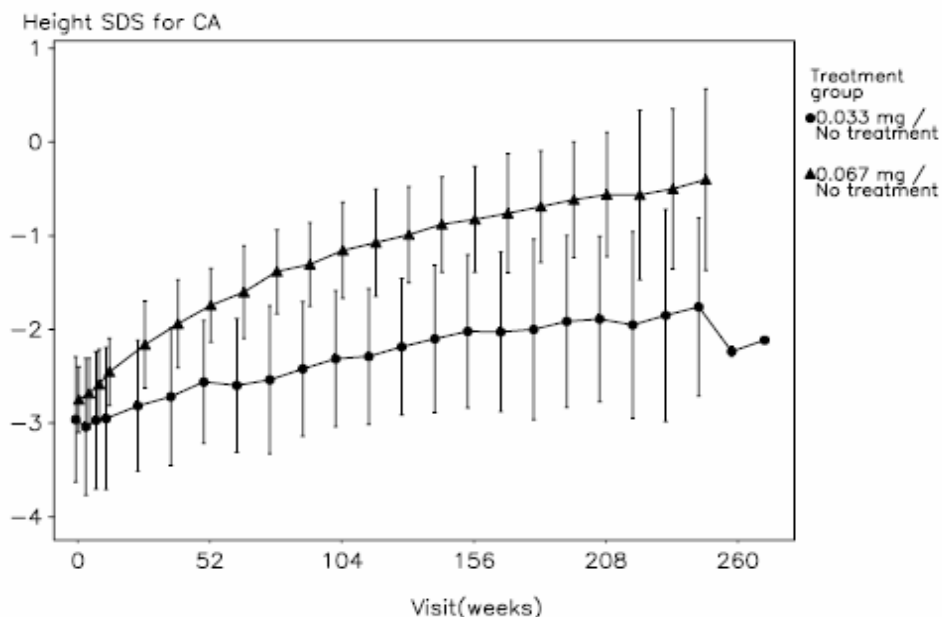
The statistics are calculated under the ANOVA model with treatment group as a fixed effect and baseline and age as covariates.

Analysed subjects : who have both baseline and 208 weeks (LOCF)

Note: Endpoint Analysis Set: Subjects who participated in GHLiquid-1517 trial in FAS
 "NT" in the group names means "No treatment"

Cross-reference: [EOT Table 14.2.4.7](#) and [14.2.4.8](#)

Figure 14.2.4.16 Height SDS for chronological age in 0.033mg/No treatment and 0.067mg/No treatment: Mean±SD



/SGA/GHLiquid-1517/freeze_30Apr2010
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Cross-reference: [EOT Figure 14.2.4.16](#)

Figure 11-2 Plot of Height SDS for CA (mean ± SD) (0.033mg/ No treatment and 0.067mg/ No treatment groups)

Assessor's comments: The efficacy results of the prolonged treatment of patients in GHLiquid-1517 confirm previous reports with various rhGH products in the indication SGA. For patients randomized to Norditropin following a period of no treatment in the prior GHLiquid-1516 study a clear growth improvement was observed. However, the sample size for this group (n=20) was limited. The efficacy results of GHLiquid-1517 do not alter the earlier assessments of Norditropin for the indication SGA.

Safety

A total of 80 subjects were included in the safety analysis set.
There were no deaths during the treatment period.

Table 12-1 Frequency Distribution of Duration of Exposure to Trial Product

| Item | Category | 0.033 mg / NN-220 | 0.067 mg / NN-220 | 0.033 mg / No treatment | 0.067 mg / No treatment |
|---|--------------|----------------------|----------------------|----------------------------|----------------------------|
| Number of Subjects | | 31 | 34 | 7 | 8 |
| Duration of exposure to trial product (weeks) | 0 <= < 26 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | 26 <= < 52 | 2 (6.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | 52 <= < 78 | 0 (0.0) | 1 (2.9) | 1 (14.3) | 1 (12.5) |
| | 78 <= < 104 | 1 (3.2) | 2 (5.9) | 0 (0.0) | 0 (0.0) |
| | 104 <= < 130 | 1 (3.2) | 2 (5.9) | 0 (0.0) | 0 (0.0) |
| | 130 <= < 156 | 2 (6.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | 156 <= < 182 | 0 (0.0) | 1 (2.9) | 0 (0.0) | 0 (0.0) |
| | 182 <= < 208 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (12.5) |
| | 208 <= < 234 | 0 (0.0) | 1 (2.9) | 2 (28.6) | 2 (25.0) |
| | 234 <= < 260 | 2 (6.5) | 0 (0.0) | 2 (28.6) | 3 (37.5) |
| | 260 <= < 286 | 3 (9.7) | 4 (11.8) | 2 (28.6) | 1 (12.5) |
| | 286 <= < 312 | 16 (51.6) | 16 (47.1) | 0 (0.0) | 0 (0.0) |
| | 312 <= | 4 (12.9) | 7 (20.6) | 0 (0.0) | 0 (0.0) |

() :percent

Cross-reference: [EOT Table 14.2.2.1](#)

A total of 57 serious adverse events (SAEs) were reported during trial. In the 0.033 mg/Norditropin and 0.067 mg/Norditropin groups, 22 and 8 SAEs were reported during GHLiquid-1516 (Week 0-104) and 10 and 12 SAEs were reported during GHLiquid-1517 (after Week 104), respectively. There were no apparent differences in the proportion of subjects experiencing SAEs between the 0.033 mg/Norditropin and 0.067 mg/Norditropin groups and between the 0.033 mg/No treatment and 0.067 mg/No treatment groups. A total of 4 SAEs (joint dislocation, IgA nephropathy, tonsillar hypertrophy, and adenoidal hypertrophy) were assessed as possibly related to the trial product by the investigator.

Table 12-2 Overview of Adverse Events

| | 0.033 mg/NN-220 | 0.067 mg/NN-220 | 0.033 mg/ No treatment | 0.067 mg/ No treatment |
|--------------------------------|-----------------|-----------------|---------------------------|---------------------------|
| Safety Analysis set | 31 | 34 | 7 | 8 |
| Mean treatment period (weeks) | 257 | 264 | 218 | 209 |
| | N(%)E | N(%)E | N(%)E | N(%)E |
| AEs | 31(100.0) 741 | 34(100.0) 1039 | 7(100.0) 123 | 8(100.0) 220 |
| AEs possibly/probably related | 9(29.0) 12 | 16(47.1) 33 | 1(14.3) 1 | 3(37.5) 7 |
| SAEs | 12(38.7) 32 | 11(32.4) 20 | 1(14.3) 1 | 2(25.0) 4 |
| SAEs possibly/probably related | 2(6.5) 2 | 0(0.0) 0 | 0(0.0) 0 | 1(12.5) 2 |
| Mild | 31(100.0) 700 | 34(100.0) 998 | 7(100.0) 121 | 8(100.0) 216 |
| Moderate | 16(51.6) 38 | 13(38.2) 36 | 2(28.6) 2 | 1(12.5) 1 |
| Severe | 2(6.5) 3 | 4(11.8) 5 | 0(0.0) 0 | 1(12.5) 3 |

N=Number of Subjects with event, %=Proportion of exposed subjects having the event, E=Number of adverse events

More SAEs were reported in the 0.033 mg/Norditropin group than in the 0.067 mg/Norditropin group (32 events versus 20 events) during the trial, but the number of SAEs reported after 104 weeks was comparable between groups (10 events versus 12 events). Moreover, there was no increase in the number of SAEs after 104 weeks, compared to before 104 weeks.

There were 3 withdrawals due to AEs:

During GHLiquid-1516 trial, subject 3305 (male, 6 years) in the 0.033 mg/Norditropin group withdrew after 33.9 weeks of exposure due to dermatitis atopic. The event was mild in severity and assessed to be unlikely related to the trial product. The trial product was discontinued permanently according to the subject's wishes.

After the initiation of this trial, subject 0701 (female, 7 years) in the 0.033 mg/No treatment group was withdrawn after 212.4 weeks of exposure due to hyperinsulinaemia. The event was mild in severity and assessed to be possibly related to the trial product. The outcome was remitted. The trial product was discontinued permanently by the investigator.

After the initiation of this trial, subject 3901 (male, 4 years) in the 0.033 mg/Norditropin group was withdrawn after 151.0 weeks of exposure due to IgA nephropathy. The event was an SAE, moderate in severity and assessed to be possibly related to the trial product. The trial product was discontinued permanently by the investigator.

Clinical Laboratory Evaluation

No significant difference for change in AUC_{glucose} was observed between the 0.033 mg/Norditropin and 0.067 mg/Norditropin groups. When compared to the baseline, a slight but significant increase in AUC_{glucose} was observed at 260 weeks for the 0.067 mg/Norditropin group.

Table 12-12 Analysis of AUCs of Blood Glucose and Insulin in OGTT at 260 weeks (0.033mg/NN-220 group and 0.067mg/NN-220 groups)

| Item | Basic statistics | 0.033mg / NN220 | 0.067mg / NN220 |
|---|------------------|------------------------|---------------------|
| AUC of Blood glucose (hour*mg/dL) | | | |
| Number of subjects | | 31 | 34 |
| Baseline | | | |
| N | | 29 | 34 |
| Geometric mean | | 227.10 | 238.31 |
| Median | | 227.80 | 236.15 |
| Min ; Max | | 174.8 ; 290.5 | 170.5 ; 366.5 |
| (95% C.I. for Geometric mean) | | 218.30, 236.25 | 226.02, 251.27 |
| 260 weeks (LOCF) | | | |
| N | | 29 | 34 |
| Geometric mean | | 234.46 | 254.97 |
| Median | | 241.50 | 256.40 |
| Min ; Max | | 184.0 ; 311.0 | 188.0 ; 357.8 |
| (95% C.I. for Geometric mean) | | 223.65, 245.80 | 243.16, 267.36 |
| Ratio | | | |
| N | | 29 | 34 |
| Geometric mean | | 1.032 | 1.070 |
| Median | | 1.040 | 1.080 |
| Min ; Max | | 0.83 ; 1.37 | 0.73 ; 2.03 |
| (95% C.I. for Geometric mean) | | 0.984, 1.083 | 1.000, 1.145 |
| Point estimate and 95% C.I. (0.067mg / 0.033mg) | | 1.036(0.953, 1.127) | |
| AUC of insulin (hour*mcU/mL) | | | |
| Number of subjects | | 31 | 34 |
| Baseline | | | |
| N | | 6 | 2 |
| Geometric mean | | 28.993 | 33.201 |
| Median | | 31.215 | 51.765 |
| Min ; Max | | 10.90 ; 66.48 | 12.05 ; 91.48 |
| (95% C.I. for Geometric mean) | | 15.419, 54.517 | 0.000, 13002925.662 |
| 260 weeks (LOCF) | | | |
| N | | 6 | 2 |
| Geometric mean | | 67.933 | 79.005 |
| Median | | 59.155 | 86.350 |
| Min ; Max | | 25.85 ; 180.98 | 51.50 ; 121.20 |
| (95% C.I. for Geometric mean) | | 33.332, 138.452 | 0.344, 18158.242 |
| Ratio | | | |
| N | | 6 | 2 |
| Geometric mean | | 2.3431 | 2.3796 |
| Median | | 2.5001 | 2.3796 |
| Min ; Max | | 0.750 ; 5.700 | 1.325 ; 4.274 |
| (95% C.I. for Geometric mean) | | 1.1661, 4.7079 | 0.0014, 4054.7486 |
| Point estimate and 95% C.I. (0.067mg / 0.033mg) | | 1.0156(0.2534, 4.0696) | |

Analysed subjects: who have both baseline and 260 weeks (LOCF).

Note: In the analysis it is assumed that log-transformed ratio has normal distribution.

Cross-reference: [EOT Table 14.3.5.1.3](#)

After 260 weeks of treatment, slight but significant increases from baseline in HbA_{1c} were observed for both the 0.033 mg/Norditropin and 0.067 mg/Norditropin groups, with a mean (95% CI) of 0.18 (0.09, 0.26)% and 0.32 (0.26, 0.38)%, respectively. A significant difference between two groups was observed, with an estimated difference (95% CI) of 0.14 (0.04, 0.24)%.

Table 12-15 Analysis of HbA_{1c} (%) at 260 weeks (0.033mg/NN-220 and 0.067mg/NN-220 groups)

| Item | Basic statistics | 0.033mg / NN220 | 0.067mg / NN220 |
|---|------------------|-----------------|-----------------|
| HbA_{1c} (%) | | | |
| Number of subjects | | 31 | 34 |
| Baseline | | | |
| N | | 30 | 34 |
| Mean (SD) | | 4.76 (0.29) | 4.66 (0.19) |
| Median | | 4.85 | 4.70 |
| Min ; Max | | 4.1 ; 5.3 | 4.4 ; 5.2 |
| (95% C.I. for mean) | | 4.66, 4.87 | 4.59, 4.72 |
| 260 weeks (LOCF) | | | |
| N | | 30 | 34 |
| Mean (SD) | | 4.94 (0.19) | 4.98 (0.21) |
| Median | | 4.90 | 5.00 |
| Min ; Max | | 4.5 ; 5.2 | 4.5 ; 5.5 |
| (95% C.I. for mean) | | 4.87, 5.01 | 4.91, 5.05 |
| Difference | | | |
| N | | 30 | 34 |
| Mean (SD) | | 0.18 (0.23) | 0.32 (0.18) |
| Median | | 0.20 | 0.30 |
| Min ; Max | | -0.4 ; 0.7 | 0.0 ; 0.7 |
| (95% C.I. for mean) | | 0.09, 0.26 | 0.26, 0.38 |
| Point estimate and 95% C.I. (0.067mg - 0.033mg) | | | |
| 0.14(0.04, 0.24) | | | |

Analysed subjects: who have both baseline and 260 weeks (LOCF).

Cross-reference: [EOT Table 14.3.5.2.2](#)

After 260 weeks of treatment, the mean total cholesterol and LDL-cholesterol decreased from 181.4 mg/dL to 167.6 mg/dL and from 104.7 mg/dL to 89.3 mg/dL, respectively, in the 0.067 mg/Norditropin group, whereas those in the 0.033 mg/Norditropin group were almost unchanged. The changes of total cholesterol and LDL-cholesterol were significantly different between the two dose groups, with the estimated difference (0.067 mg/Norditropin – 0.033 mg/Norditropin) of – 15.1 (95% CI: – 28.2, – 2.1) mg/dL, – 11.0 (– 21.3, – 0.6) mg/dL, respectively.

The mean HDL-cholesterol increased from 56.9 mg/dL to 62.5 mg/dL at 260 weeks in the 0.033 mg/Norditropin group whereas that in the 0.067 mg/Norditropin group was almost unchanged. The changes of HDL-cholesterol were significantly different between the two dose groups, with the estimated difference (0.067 mg/Norditropin – 0.033 mg/Norditropin) of – 5.7 (95% CI: – 11.2, – 0.2) mg/dL.

These changes were, however, small and can be considered not clinically relevant.

In the 0.033 mg/No treatment and 0.067 mg/No treatment groups as well, no significant changes in lipids were observed during 208 weeks of treatment.

During the treatment period, anti-hGH antibodies were detected in a total of 14 subjects (4, 9 and 1 subjects in the 0.033 mg/Norditropin group, 0.067 mg/Norditropin group and 0.033 mg/No treatment group, respectively). Of these, 2 were reported as AEs with probable relation in the 0.067 mg/Norditropin group in 2 subjects (subject 2001 at 26 weeks and subject 5301 at 39 weeks).

The first positive result was obtained at 26 weeks for the 0.067 mg/Norditropin group, at 52 weeks for the 0.033 mg/Norditropin group and at 39 weeks for the 0.033 mg/No treatment group. The highest levels of anti-hGH antibody were observed at 169 weeks and 234 weeks for subject 2201 in the 0.033 mg/Norditropin group, where 16 times dilution of the blood sample was

required to obtain negative result. Improvement in height SDS over time for these 14 subjects did not seem to be influenced by the formation of anti-hGH antibody.

Assessor's comments:

No overall safety concerns were observed based on the AEs reported. During the treatment period, all exposed subjects (100%) experienced at least 1 AE. The majority of AEs were mild to moderate in severity. The most common AEs were related to infection and infestation. The number of AEs was higher in the high dose groups compared to the low dose groups. Most common AEs with possible/probable relation were pain in extremity and arthralgia. A total of 57 SAEs were reported during the treatment period. A total of 4 SAEs (joint dislocation, IgA nephropathy, tonsillar hypertrophy and adenoidal hypertrophy) were assessed as possibly related to the trial product by the investigator.

After 260 or 208 weeks, profiles of blood glucose in OGTT remained almost unchanged from the baseline. No subjects were categorised as diabetic type during the treatment period. After 260 weeks of treatment, slight but significant increases from baseline in HbA_{1c} were observed in both the 0.033 mg and 0.067 mg groups, with an estimated mean (95% CI) of 0.18 (0.09, 0.26)% and 0.32 (0.26, 0.38)%, respectively. A significant difference between two groups was observed, with an estimated mean difference (95% CI) of 0.14 (0.04, 0.24)%. HbA_{1c} appeared to increase slightly during the initial 2 years and then remained at the same level until 260 weeks. No subject had an HbA_{1c} above the reference range (4.3–5.8%) during the treatment period.

After 260 weeks of treatment, a significant difference in the change of laboratory parameters between the two dose groups was observed for total cholesterol, LDL-cholesterol and HDL-cholesterol. These changes were, however, small and considered not clinically relevant. No clinically relevant changes were observed for other clinical laboratory parameters. During the treatment period, anti-hGH antibodies were detected in 14 subjects without apparent impact on efficacy.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

➤ Overall conclusion

Results from the extension trial GHLiquid-1517 in children with SGA document efficacy and safety in agreement with previous experience from other trials with this indication. The observed adverse events are well described in the approved SmPC, and well known to paediatricians. Based on the submitted data the benefit/risk assessment remains unchanged for Norditropin for the indication SGA and no amendment to the SmPC is required.

➤ Recommendation

No further action required