CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-148

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-148/N-000

Generic name, dose and formulation:	Somatropin (rDNA origin) 5 mg, 10 mg or 15 mg cartridges for subcutaneous injection
Trade name:	Norditropin® SimpleXx™
Sponsor:	Novo Nordisk Pharmaceuticals Inc.
Type of submission:	Original NDA, Category 3S
Date of submission:	06/30/1999, 09/29/1999, 02/25/2000, 03/08/2000, 03/16/2000
Reviewer:	Monique Wakelkamp-Barnes, M.D., Ph.D.

I SYNOPSIS

Norditropin® (somatropin, synthetic human growth hormone, Novo Nordisk) is currently approved and marketed as a lyophilized drug product in 4 and 8 mg vials for long-term treatment of children who have growth failure due to inadequate secretion of endogenous growth hormone.

The NDA 21-148/N-000 for Norditropin® SimpleXx™ was submitted on 06/30/1999 by Novo Nordisk Pharmaceuticals Inc. (100 Overlook Center, Princeton NJ 08540-7810), as a new dosage form for subcutaneous injection. Norditropin® SimpleXx™ (somatropin, rDNA origin, 5 mg, 10 mg or 15 mg cartridges) is a pre-mixed liquid formulation for use with the NordiPen™ injection pen. The currently available Norditropin® is a powder that requires reconstitution with 1.5% benzyl alcohol prior to administration. According to the sponsor, Norditropin® SimpleXx™ has been developed with the aim to ease the injection process for patients and to improve patient compliance.

The Human Pharmacokinetics and Bioavailability section of the NDA contained an *in vivo* bioequivalence study (GHPHKIN/BDP/14/UK) which compared each of the new liquid formulations with the 8 mg approved formulation and with each other. The study had a randomized, single-blind, four-period cross-over design and included 24 healthy subjects. The $AUC_{(0\text{-}24h)}$ and C_{max} values for human growth hormone were evaluated after single-dose s.c. administration of 5 mg of each of the liquid Norditropin formulations 5 mg, 10 mg or 15 mg and of the lyophilized Norditropin® 8 mg formulation. It was found that Norditropin® SimpleXx™ is bioequivalent to Norditropin®.

Reviewer comment
The original NDA submission did not contain sufficient information about certain aspects of the growth hormone assay methodology. On 03/01/2000 and 03/09/2000, the sponsor was requested to submit additional information with regard to the inter- and intra-assay accuracy of the quality controls during the pre-study assay validation, as well as during the assay of the actual samples

from the bioequivalence study. This information was submitted 03/16/2000 and showed that the accuracy of the assay method was satisfactory.

II RECOMMENDATION

The Human Pharmacokinetics and Bioavailability section of NDA 21-148 is acceptable to support the BA and BE regulation covered by 21 CFR part 320. Labeling comments outlined in the labeling section of the review should be conveyed to the sponsor as appropriate. <page 12>*

Reviewer Date

151

Monique Wakelkamp-Barnes, M.D., Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

Clinical Pharmacology and Biopharmaceutics briefing held on 03/20/2000
Attendees: Hunt, Ahn, Shore, Malozowski.

Final version signed by Hae-Young Ahn, Ph.D., Team leader 151

cc NDA 21-148/N-000:

	Division File
HFD-870:	Shiew-Mei Huang
	Monique Wakelkamp-Barnes
HFD-510:	Hae-Young Ahn
	Robert Shore
	Saul Malozowski
	Robert Perlstein
	Chrystal King

CDR

III BACKGROUND

Q.	***What is somatropin? What is Norditropin?***

Somatropin is synthetic human growth hormone (hGH, somatotropin) for the treatment of growth hormone deficiency or insufficiency. Somatropin is a 191 amino-acid polypeptide with an amino-acid sequence and 2 internal disulphide bridges identical to that of the major (molecular weight 22,000) component of human pituitary growth hormone. The drug is produced by means of recombinant DNA technology using a [redacted]

The currently available Norditropin formulation is a powder, which requires reconstitution prior to (subcutaneous) administration. The drug is administered using a regular syringe and needle. Two different formulations are available. The formulation currently approved in the U.S. contains a [redacted] buffer and the one available outside the U.S. contains a [redacted] buffer. The currently approved U.S. formulation (in 2 dosages, abbreviated below as Nor 4 mg or Nor 8 mg) is used for the indication of long-term treatment of children who have growth failure due to inadequate secretion of endogenous growth hormone. The new formulation proposed is Norditropin SimpleXx, a pre-mixed liquid formulation for use with the NordiPen injection pen. According to the sponsor, the new formulation may ease the injection process and improve patient compliance.

Current dosing recommendations for treatment with somatropin vary with different products and indications, but typically range from 0.16 mg/kg to 0.30 mg/kg per week for pediatric patients with growth hormone deficiency. The recommended dosing for Norditropin SimpleXx is [redacted] 6-7 times a week. Outside the U.S., dosing recommendations are sometimes given in mg per body surface area (BSA).

IV FORMULATION

Q.	***What differences in composition are there between the liquid formulation and the lyophilized (powder) formulation?***
Q.	***Are there any differences between the formulation used for study GHPHKIN/14/UK and the to-be-marketed formulation?***

The differences in composition between the new proposed liquid formulations and the approved lyophilized formulations are displayed in Tables 1 and 2. The active ingredient is unchanged, but some of the excipients are different, with histidine serving as a [redacted] poloxamer 188 as a [redacted] phenol as a [redacted] mannitol as a [redacted] and water as a [redacted].

According to the sponsor, the size of the [redacted] batches used for study GHPHKIN/14/UK was at least [redacted] of the production scale batch size. The liquid Norditropin formulations used in this study were identical to the to-be-marketed formulations. The production site was also identical.

Norditropin SimpleXx			
Component	**5 mg Cartridge**	**10 mg Cartridge**	**15 mg Cartridge**
Somatropin	5 mg	10 mg	15 mg
Histidine	1 mg	1 mg	1.7 mg
Poloxamer 188	4.5 mg	4.5 mg	4.5 mg
Phenol	4.5 mg	4.5 mg	4.5 mg
Mannitol	60 mg	60 mg	58 mg
HCl/NaOH	q.s.	q.s.	q.s.
Water for Injection	ad 1.5 mL	ad 1.5 mL	ad 1.5 mL

Table 1. Composition of the liquid somatropin formulation Norditropin SimpleXx.

Norditropin Component	
(4 mg (approximately 12 IU) Vial)*	
Somatropin	4 mg
Disodium Phosphate Dihydrate ($Na_2HPO_4,2H_2O$)	1.3 mg
Sodium Dihydrogen Phosphate Dihydrate ($NaH_2PO_4,2H_2O$)	1.1 mg
Mannitol	44 mg
(8 mg (approximately 24 IU) Vial)*	
Somatropin	8 mg
Glycine	8.8 mg
Disodium Phosphate Dihydrate ($Na_2HPO_4,2H_2O$)	1.3 mg
Sodium Dihydrogen Phosphate Dihydrate ($NaH_2PO_4,2H_2O$)	1.1 mg
Mannitol	44 mg

* each 4 or 8 mg package also contains a vial of diluent [redacted] of water with 1.5% benzyl alcohol)

Table 2. Composition of the lyophilized somatropin formulation Norditropin.

V ASSAY METHODOLOGY AND VALIDATION

Q.	***What are the assay methods for the determination of human growth hormone concentrations? How sensitive and specific are the assays?***

Human growth hormone levels in serum samples were determined by using a [redacted] available assay kit [redacted]

The assay method is based on a [redacted]

The lower limit of quantitation (LOQ) as used by the sponsor was [redacted]

Reviewer comment:
On 03/01/2000, the sponsor was asked to submit additional information with regard to whether the (published) method had been modified by the sponsor, possible cross-reactivity of the method with somatropin degradation products and to clarify and provide with additional inter- and intra-assay accuracy and precision data. The sponsor's reply on 03/08/2000 indicated that the assay method had not been modified and that it was assumed not to distinguish between somatropin and somatropin degradation products. During a pre-study assay validation, mean intra-assay precision at [redacted] was found to be [redacted] respectively. Mean inter-assay precision was [redacted], respectively. On 03/09/2000, the sponsor was requested to submit additional information with regard to the inter- and intra-assay accuracy of the quality controls during the pre-study assay validation, as well as accuracy and precision during the assay of the actual samples from the bioequivalence study. On 03/16/2000, this information was submitted. During the pre-study assay validation, (mean) intra-assay accuracy was found to range from [redacted] at [redacted] from [redacted] at [redacted] and from [redacted] at [redacted]. Inter-assay accuracy at [redacted] and [redacted] was found to be [redacted], respectively. Accuracy and precision data from the assay runs of the actual study samples were submitted as well, and found to be satisfactory. In summary, the combined submissions indicated the assay methodology and assay data to be adequate.

VI CLINICAL PHARMACOLOGY

Q.	***Is there bioequivalence between the liquid Norditropin formulation and the lyophilized formulation?***

Yes.
The bioequivalence between the new liquid Norditropin formulations and the reference product Norditropin 8 mg, containing ——— , buffer (Nor 8 mg) was investigated in a randomized, single-blind, four-period cross-over study. In the same study, the bioequivalence between the three different strengths of the liquid formulation (5, 10 and 15 mg per 1.5 ml) was assessed as well. The study included 24 healthy subjects, age 19-50 years. Twenty-three subjects could be evaluated for safety, 21 for efficacy. Nineteen of 23 evaluable subjects were male.

Each of the four hGH products were given to each subject once, according to a randomized procedure. The washout period between the 4 study days was 7-14 days. On each study day, in order to inhibit the release of endogenous growth hormone, the subjects received a continuous i.v. infusion of somatostatin (120 mg/h, = 40 ml/h) for 24 h. At 2 h after the start of the somatostatin infusion, subjects received a single dose of 5 mg hGH of one of the four products, administered subcutaneously in the anterolateral thigh. Blood samples were taken 120, 20 and 10 min before hGH injection and up to 24 hours after the injection.

The two one-sided hypotheses at the 5% level were tested for $AUC_{(0-24\ h)}$ and C_{max} by constructing 90% confidence intervals for the ratios 5 mg/Nor 8 mg, 10 mg/Nor 8 mg and 15 mg/Nor 8 mg. Confidence intervals were constructed for 15 mg/10 mg, 15 mg/5 mg and 10 mg/5 mg ratios as well. The two endpoints $AUC_{(0-24h)}$ and C_{max} were evaluated as non-standardized, standardized by actual dose/body weight and standardized by actual dose/BSA. The endpoint T_{max} was analysed non-parametrically using the Wilcoxon signed rank test on the paired differences. For C_{max}, results were analyzed with and without exclusion of data from subject 62, liquid Norditropin 15 mg. In this case, the hGH concentration profile was unusually high compared to all the other subjects and treatments. No evident reason could be found for this observation.

The analysis results for the non-standardized variables $AUC_{(0-24\ h)}$ and C_{max} are shown below in Tables 3 through 6. The findings indicate that the Norditropin SimpleXx formulation is bioequivalent to the Norditropin formulation. All analyses for $AUC_{(0-24\ h)}$ and C_{max}, including non-standardized results and standardized results for actual dose/body weight and actual dose/BSA are shown in Attachment 1.

Reviewer comment:
When all C_{max} data for calculation of 90% confidence intervals for C_{max} were included, the 5mg/Nor 8 mg ratio still passed the lower interval limit for bioequivalence for unstandardized C_{max}, but not for C_{max} standardized by actual dose/body weight and actual dose/BSA. However, unstandardized C_{max} values are more relevant than standardized C_{max} values. In any case, the sponsor's approach to exclude subject 62, liquid Norditropin 15 mg, seems appropriate and the conclusion of bioequivalence between the two formulations justified (see Attachment 1).

$AUC_{(0\text{-}24h)}$ (ng/ml x h).	5 mg	10 mg	15 mg	Nor 8 mg
n	20	21	21	20
Missing	1	0	1	0
Geometric mean	395.60	418.78	422.76	432.52
CV	20.45	14.27	18.44	20.25
Minimum	255.3	315.4	250.4	236.8
Maximum	516.6	529.8	543.8	565.7

Table 3. Summary data of non-standardized endpoint $AUC_{(0\text{-}24h)}$ (ng/ml x h).

$AUC_{(0\text{-}24h)}$ Comparison	n	Estimated mean ratio	Lower 90% CI	Upper 90% CI
5mg/Nor 8 mg	20	0.914	0.870	0.961
10 mg/Nor 8 mg	20	0.976	0.928	1.025
15 mg/Nor 8 mg	20	0.984	0.936	1.034
15 mg/10 mg	21	1.009	0.961	1.059
15 mg/5 mg	20	1.076	1.024	1.131
10 mg/5 mg	20	1.067	1.015	1.121

Table 4. Analysis results of non-standardized endpoint $AUC_{(0\text{-}24h)}$ (ng/ml x h).

C_{max} (ng/ml)	5 mg	10 mg	15 mg	Nor 8 mg
n	20	21	20	20
Missing	1	0	1	0
Geometric mean	38.77	41.86	40.15	43.08
CV	29.84	22.28	30.47	23.31
Minimum				
Maximum				

Table 5. Summary data of non-standardized endpoint C_{max} (ng/ml). Data from subject 62, liquid Norditropin 15 mg excluded.

C_{max} Comparison	n	Estimated mean ratio	Lower 90% CI	Upper 90% CI
5mg/Nor 8 mg	20	0.905	0.823	0.984
10 mg/Nor 8 mg	20	0.990	0.907	1.083
15 mg/Nor 8 mg	20	1.000	0.864	1.034
15 mg/10 mg	21	1.010	0.873	1.041
15 mg/5 mg	20	1.105	0.960	1.149
10 mg/5 mg	20	1.094	1.008	1.205

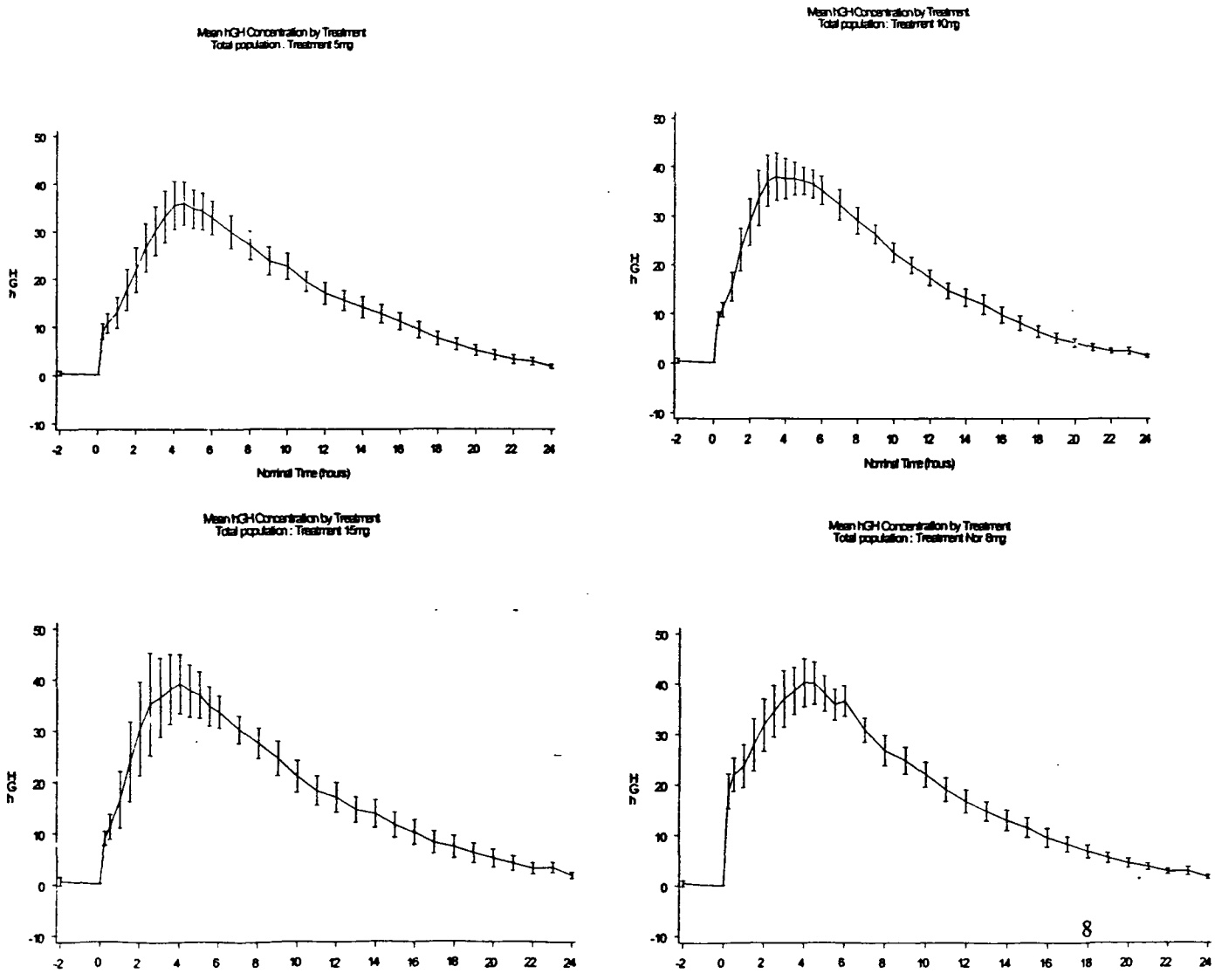
Table 6. Analysis results of non-standardized endpoint C_{max} (ng/ml). Data from subject 62, liquid Norditropin 15 mg excluded.

Q.	***Since the study involved healthy subjects, is it likely that endogenous growth hormone levels could have significantly influenced the study results?***

No.

Endogenous growth hormone secretion is of a strongly pulsatile and variable nature. Published data indicate that endogenous growth hormone levels, as measured in normal children, range from about 1 to 8.7 ng/ml during the night and 0.6 to 3.9 ng/ml during the day, using an assay with a detection limit of 0.5 ng/ml. Although it cannot be excluded that even higher levels may be reached, it seems likely that the hGH concentration profiles obtained during the study were due to the administered somatropin. Also, it was attempted to suppress endogenous hGH levels by means of a continuous infusion of somatostatin. If a study group with administration of somatostatin only (without Norditropin) had been included into the design of this study, this would have better allowed for assessment of the efficacy of the somatostatin infusion. However, hGH levels from –2 to 0 hours were lower than 0.15 ng/ml before Norditropin dosing for all subjects (Figure 1).

Figure 1. Mean ± SEM hGH concentrations before and after subcuteanous administration of a single dose of 5 mg hGH given as liquid Norditropin formulation 5, 10 and 15 mg and as lyophilized formulation Nor 8 mg. The subjects received a continuous i.v. infusion of somatostatin (120 mg/h) for 24 h.



8 pages redacted from this section of the approval package consisted of draft labeling

Table C1
Summary of Primary Endpoints

Efficacy Population

	AUC(0-24h) (ng/ml x h)			
	5mg	10mg	15mg	Nor 8mg
n	20	21	21	20
missing	1	0	1	0
geometric mean	395.60	418.78	422.76	432.52
CV	20.45	14.27	18.44	20.25
minimum	255.3	315.4	250.4	236.8
maximum	516.6	529.8	543.8	565.7

Table D1
Analysis Results of Primary Endpoint AUC(0-24), (ng/ml x h)

Efficacy Population

	n	Estimated mean ratio	Lower 90% C.I.	Upper 90% C.I.
Type				
5mg/Nor 8mg	20	0.914	0.870	0.961
10mg/Nor 8mg	20	0.976	0.928	1.025
15mg/Nor 8mg	20	0.984	0.936	1.034
15mg/10mg	21	1.009	0.961	1.059
15mg/5mg	20	1.076	1.024	1.131
10mg/5mg	20	1.067	1.015	1.121

Table C1
Summary of Primary Endpoints
Standardised by dose/weight
Efficacy Population

	AUC(0-24h) (ng/ml x h)/(mg/kg)			
	5mg	10mg	15mg	Nor 8mg
n	20	21	21	20
missing	1	0	1	0
geometric mean	5849.10	6361.38	6579.93	6462.32
CV	17.25	12.00	13.23	13.74
minimum	4104.2	4948.6	4956.6	4523.6
maximum	7337.3	7625.9	8059.3	8461.2

Table D1
Analysis Results of Primary Endpoint AUC(0-24), (ng/ml x h)/(mg/kg)
Standardised by dose/weight
Efficacy Population

	n	Estimated mean ratio	Lower 90% C.I.	Upper 90% C.I.
Type				
5mg/Nor 8mg	20	0.905	0.857	0.956
10mg/Nor 8mg	20	0.996	0.943	1.052
15mg/Nor 8mg	20	1.030	0.975	1.088
15mg/10mg	21	1.034	0.980	1.091
15mg/5mg	20	1.138	1.077	1.202
10mg/5mg	20	1.101	1.042	1.163

Table C1
Summary of Primary Endpoints
Standardised by dose/body surface area
Efficacy Population

	AUC(0-24h) (ng/ml x h)/(mg/m²)			
	5mg	10mg	15mg	Nor 8mg
n	20	21	21	20
missing	1	0	1	0
geometric mean	149.47	163.15	168.17	164.76
CV	18.48	11.65	14.09	16.00
minimum	102.6	132.0	114.8	105.4
maximum	198.8	197.0	210.1	222.5

Table D1
Analysis Results of Primary Endpoint AUC(0-24), (ng/ml x h)/(mg/m²)
Standardised by dose/body surface area
Efficacy Population

	n	Estimated mean ratio	Lower 90% C.I.	Upper 90% C.I.
Type				
5mg/Nor 8mg	20	0.907	0.859	0.958
10mg/Nor 8mg	20	0.999	0.947	1.055
15mg/Nor 8mg	20	1.029	0.975	1.086
15mg/10mg	21	1.030	0.977	1.086
15mg/5mg	20	1.135	1.075	1.198
10mg/5mg	20	1.101	1.043	1.163

Table C3.2
Summary of Secondary Endpoints, Cmax*

Efficacy Population

	Cmax (ng/ml)			
	5mg	10mg	15mg	Nor 8mg
n	20	21	20	20
missing	1	0	1	0
geometric mean	38.77	41.86	40.15	43.08
SD	11.57	9.65	12.21	9.40
CV	29.84	22.28	30.47	23.31
minimum				
maximum				

Table D2.2
Analysis of Secondary Endpoints, Cmax (ng/ml)*

Efficacy Population

	Estimate	P-value	df	Lower 90% C.I.	Upper 90% C.I.
Type					
5mg/Nor 8mg	0.900	0.052	54	0.823	0.984
10mg/Nor 8mg	0.992	0.873	54	0.907	1.083
15mg/Nor 8mg	0.945	0.298	54	0.864	1.034
15mg/10mg	0.953	0.367	54	0.873	1.041
15mg/5mg	1.050	0.365	54	0.960	1.149
10mg/5mg	1.102	0.074	54	1.008	1.205

*Excludes subject 62, Liquid Norditropin 15mg

Table C3.2
Summary of Secondary Endpoints, Cmax*
Standardised by dose/weight
Efficacy Population

	Cmax (ng/ml)/(mg/kg)			
	5mg	10mg	15mg	Nor 8mg
n	20	21	20	20
missing	1	0	1	0
geometric mean	573.20	635.86	626.34	643.69
SD	145.45	117.44	172.94	123.96
CV	25.60	18.29	26.94	18.47
minimum				
maximum				

Table D2.2
Analysis of Secondary Endpoints, Cmax (ng/ml)/(mg/kg)*
Standardised by dose/weight
Efficacy Population

	Estimate	P-value	df	Lower 90% C.I.	Upper 90% C.I.
Type					
5mg/Nor 8mg	0.891	0.046	54	0.810	0.979
10mg/Nor 8mg	1.013	0.826	54	0.921	1.113
15mg/Nor 8mg	0.991	0.876	54	0.901	1.091
15mg/10mg	0.979	0.704	54	0.891	1.075
15mg/5mg	1.113	0.068	54	1.011	1.225
10mg/5mg	1.137	0.028	54	1.034	1.250

*Excludes subject 62, Liquid Norditropin 15mg

Table C3.2
Summary of Secondary Endpoints, Cmax*
Standardised by dose/body surface area
Efficacy Population

	Cmax (ng/ml)/(mg/m^2)			
	5mg	10mg	15mg	Nor 8mg
n	20	21	20	20
missing	1	0	1	0
geometric mean	14.65	16.31	16.01	16.41
SD	4.12	3.50	4.99	3.34
CV	27.76	20.55	29.87	20.36
minimum				
maximum				

Table D2.2
Analysis of Secondary Endpoints, Cmax (ng/ml)/(mg/m^2)*
Standardised by dose/body surface area
Efficacy Population

	Estimate	P-value	df	Lower 90% C.I.	Upper 90% C.I.
Type					
5mg/Nor 8mg	0.893	0.050	54	0.812	0.981
10mg/Nor 8mg	1.016	0.785	54	0.924	1.116
15mg/Nor 8mg	0.991	0.869	54	0.901	1.090
15mg/10mg	0.976	0.659	54	0.888	1.071
15mg/5mg	1.110	0.074	54	1.009	1.221
10mg/5mg	1.137	0.026	54	1.035	1.250

*Excludes subject 62, Liquid Norditropin 15mg

Table C3.1
Summary of Secondary Endpoints, Cmax

Efficacy Population

	Cmax (ng/ml)			
	5mg	10mg	15mg	Nor 8mg
n	20	21	21	20
missing	1	0	1	0
geometric mean	38.77	41.86	42.36	43.08
SD	11.57	9.65	21.45	9.40
CV	29.84	22.28	39.44	23.31
minimum				
maximum				

Table D2.1
Analysis of Secondary Endpoints, Cmax (ng/ml)

Efficacy Population

	Estimate	P-value	df	Lower 90% C.I.	Upper 90% C.I.
Type					
5mg/Nor 8mg	0.905	0.149	55	0.807	1.014
10mg/Nor 8mg	0.990	0.885	55	0.884	1.109
15mg/Nor 8mg	1.000	0.997	55	0.893	1.120
15mg/10mg	1.010	0.879	55	0.904	1.129
15mg/5mg	1.105	0.147	55	0.986	1.238
10mg/5mg	1.094	0.192	55	0.976	1.226

(all data included)

Table C3.1
Summary of Secondary Endpoints, Cmax
Standardised by dose/weight
Efficacy Population

	Cmax (ng/ml)/(mg/kg)			
	5mg	10mg	15mg	Nor 8mg
n	20	21	21	20
missing	1	0	1	0
geometric mean	573.20	635.86	659.34	643.69
SD	145.45	117.44	310.31	123.96
CV	25.60	18.29	36.01	18.47
minimum				
maximum				

Table D2.1
Analysis of Secondary Endpoints, Cmax (ng/ml)/(mg/kg)
Standardised by dose/weight
Efficacy Population

	Estimate	P-value	df	Lower 90% C.I.	Upper 90% C.I.
Type					
5mg/Nor 8mg	0.896	0.122	55	0.797	1.007
10mg/Nor 8mg	1.011	0.874	55	0.900	1.136
15mg/Nor 8mg	1.047	0.511	55	0.932	1.176
15mg/10mg	1.036	0.610	55	0.924	1.161
15mg/5mg	1.169	0.030	55	1.040	1.314
10mg/5mg	1.129	0.089	55	1.004	1.269

(all data included)

Table C3.1
Summary of Secondary Endpoints, Cmax
Standardised by dose/body surface area
Efficacy Population

	Cmax (ng/ml)/(mg/m^2)			
	5mg	10mg	15mg	Nor 8mg
n	20	21	21	20
missing	1	0	1	0
geometric mean	14.65	16.31	16.85	16.41
SD	4.12	3.50	8.19	3.34
CV	27.76	20.55	38.18	20.36
minimum				
maximum				

Table D2.1
Analysis of Secondary Endpoints, Cmax (ng/ml)/(mg/m^2)
Standardised by dose/body surface area
Efficacy Population

	Estimate	P-value	df	Lower 90% C.I.	Upper 90% C.I.
Type					
5mg/Nor 8mg	0.898	0.129	55	0.799	1.009
10mg/Nor 8mg	1.014	0.840	55	0.903	1.139
15mg/Nor 8mg	1.047	0.514	55	0.932	1.175
15mg/10mg	1.032	0.645	55	0.921	1.156
15mg/5mg	1.166	0.032	55	1.037	1.309
10mg/5mg	1.129	0.087	55	1.005	1.269

(all data included)

Table C4
Summary of Secondary Endpoints, Tmax

Efficacy Population

	Tmax (h)			
	5mg	10mg	15mg	Nor 8mg
n	20	21	21	20
missing	1	0	1	0
median	4.51	4.50	4.00	4.24
SD	1.08	1.24	2.43	0.84
minimum	2.5	2.0	2.0	3.0
maximum	7.0	7.0	14.0	6.0

Table D3
Analysis of Secondary Endpoints, Tmax (h)

Efficacy Population

	n	Estimate	P-value	Lower 90% C.I.	Upper 90% C.I.
Type					
5mg-Nor 8mg	20	0.500	0.041	0.000	1.000
10mg-Nor 8mg	20	0.000	0.898	-0.500	0.492
15mg-Nor 8mg	20	-0.121	1.000	-0.750	0.517
15mg-10mg	21	0.000	0.964	-0.750	0.500
15mg-5mg	20	-0.513	0.135	-1.258	0.242
10mg-5mg	20	-0.492	0.173	-1.067	0.250

King

Filing Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Clinical Pharmacology and Biopharmaceutics

Date: 05-AUG-99
From: Robert M. Shore, Pharm.D.
Through: Hae-Young Ahn, Ph.D., Team Leader
To: Crystal King, CSO
Re: Norditropin® Simplexx™ (somatropin)
NDA 21-148 / N-000 submitted 30-JUN-99
Novo Nordisk Pharmaceuticals, Inc.

LST
LST

SYNOPSIS:

Norditropin is currently approved and marketed as lyophilized drug product in 4 and 8 mg vials for long-term treatment of children who have growth failure due to inadequate secretion of endogenous growth hormone. The sponsor is proposing to introduce Norditropin Simplexx which is a pre-mixed liquid formulation for use with the NordiPen injection pen. Norditropin Simplexx would be available in 5, 10, and 15 mg cartridges. This submission includes one primary *in vivo* bioequivalence study (GHPHKIN/BPD/14/UK) which compares each of the new liquid formulations with the 8 mg approved formulation. This study used 20 somatostatin-suppressed healthy subjects in a single-dose (5mg SC), 4-period, cross-over design.

There are also supportive study summaries submitted: GHPHKIN/BPD/13/UK which compares a non-US approved lyophilized formulation with each of the new liquid formulations (the US approved formulation contains a —— buffer while the non-US formulation contains a —— buffer); and GHPHKIN/J/3/J which is a pharmacokinetic study in 14 healthy Japanese subjects. Full reports are not provided for these two studies and therefore they cannot be reviewed.

Other studies submitted in the NDA include GHLIQUID/BPD/1/D-DK-NL which investigated acceptability/pain perception/safety in children, and GHD/J/3/J and GHD/J/4/J which were efficacy/safety studies conducted in Japan.

The sponsor has submitted volumes 1.1 and 1.18-1.22 to the human pharmacokinetics and bioavailability section.

Validation data for the —— assay are provided for the primary bioequivalence study (GHPHKIN/BPD/14/UK) only (Vol. 1.19, p. 5).

RECOMMENDATIONS:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-2) has evaluated NDA 21-148/N-000 dated 30-JUN-99 for filing. Based on this review, DPE-2 has determined that the application is fileable. Comments should be forwarded to the sponsor as

appropriate.

COMMENTS:

1. The sponsor should submit labeling on disk (preferably in Word format) which clearly distinguishes portions of approved product labeling from portions which are proposed for Norditropin Simplexx (e.g., different colored text or underlining/strikeouts).

2. How does the lot/batch size and production site/method of Norditropin Simplexx used in study GHPHKIN/BPD/14/UK compare with the proposed commercial lot/batch size and production method/site.

CC: NDA 21-148/N-000 (orig., 1 copy), HFD-510(Malozowski, Perlstein, King, Berlin, Steigerwalt), HFD-870(Ahn, ChenME), CDR (Barbara Murphy)