



**HAL**  
open science

# Multiple doses of pegylated long-acting growth hormone is well tolerated in healthy male volunteers and possesses a potential once-weekly treatment profile

Michael Højby Rasmussen, Lene Jensen, Thomas William Anderson, Thomas Klitgaard, Jesper Madsen

## ► To cite this version:

Michael Højby Rasmussen, Lene Jensen, Thomas William Anderson, Thomas Klitgaard, Jesper Madsen. Multiple doses of pegylated long-acting growth hormone is well tolerated in healthy male volunteers and possesses a potential once-weekly treatment profile. *Clinical Endocrinology*, 2010, 73 (6), pp.769. 10.1111/j.1365-2265.2010.03863.x . hal-00593444

**HAL Id: hal-00593444**

**<https://hal.science/hal-00593444v1>**

Submitted on 16 May 2011

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



**Multiple doses of pegylated long-acting growth hormone is well tolerated in healthy male volunteers and possesses a potential once-weekly treatment profile**

Journal:	<i>Clinical Endocrinology</i>
Manuscript ID:	CEN-2010-000377.R1
Manuscript Type/Office:	1 Original Article - UK/Europe
Date Submitted by the Author:	22-Jul-2010
Complete List of Authors:	Rasmussen, Michael; Novo Nordisk, Global Development Jensen, Lene; Novo Nordisk, Global Development Anderson, Thomas; Novo Nordisk, Preclinical Development Klitgaard, Thomas; Novo Nordisk, Global Development Madsen, Jesper; Novo Nordisk, Global Development
Key Words:	Growth hormone < Hormones/related: < Pituitary, Growth disorders < Conditions: < Paediatric endocrinology, Hypopituitarism < Conditions: < Pituitary

1  
2  
3  
4  
5  
6  
7  
8  
9

## Multiple doses of pegylated long-acting growth hormone is well tolerated in healthy male volunteers and possesses a potential once-weekly treatment profile

10 Michael Højby Rasmussen<sup>1</sup>, Lene Jensen<sup>1</sup>, Thomas William Anderson<sup>2</sup>, Thomas Klitgaard<sup>1</sup> and  
11  
12 Jesper Madsen<sup>1</sup>  
13  
14  
15

16  
17 <sup>1</sup> Global Development, Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd, Denmark  
18

19 <sup>2</sup> Preclinical Development, Novo Nordisk Park, DK-2760 Maaloev, G8.2.24, Denmark  
20  
21  
22

23 Correspondence should be addressed to:

24 Michael Højby Rasmussen, MD. PhD, MSc

25 Medical & Science, Global Development, Novo Nordisk A/S, Krogshøjvej 55, DK-2880

26  
27  
28  
29 Bagsværd, Denmark

30  
31  
32 Tel: +45 30791619

33  
34  
35 Email: mhr@novonordisk.com

36  
37  
38  
39 Clinical trial registration number: NCT00722540

40  
41  
42  
43 Short title: Tolerability, PK and IGF-I response of a long-acting GH

44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65  
66  
67  
68  
69  
70  
71  
72  
73  
74  
75  
76  
77  
78  
79  
80  
81  
82  
83  
84  
85  
86  
87  
88  
89  
90  
91  
92  
93  
94  
95  
96  
97  
98  
99  
100  
101  
102  
103  
104  
105  
106  
107  
108  
109  
110  
111  
112  
113  
114  
115  
116  
117  
118  
119  
120  
121  
122  
123  
124  
125  
126  
127  
128  
129  
130  
131  
132  
133  
134  
135  
136  
137  
138  
139  
140  
141  
142  
143  
144  
145  
146  
147  
148  
149  
150  
151  
152  
153  
154  
155  
156  
157  
158  
159  
160  
161  
162  
163  
164  
165  
166  
167  
168  
169  
170  
171  
172  
173  
174  
175  
176  
177  
178  
179  
180  
181  
182  
183  
184  
185  
186  
187  
188  
189  
190  
191  
192  
193  
194  
195  
196  
197  
198  
199  
200  
201  
202  
203  
204  
205  
206  
207  
208  
209  
210  
211  
212  
213  
214  
215  
216  
217  
218  
219  
220  
221  
222  
223  
224  
225  
226  
227  
228  
229  
230  
231  
232  
233  
234  
235  
236  
237  
238  
239  
240  
241  
242  
243  
244  
245  
246  
247  
248  
249  
250  
251  
252  
253  
254  
255  
256  
257  
258  
259  
260  
261  
262  
263  
264  
265  
266  
267  
268  
269  
270  
271  
272  
273  
274  
275  
276  
277  
278  
279  
280  
281  
282  
283  
284  
285  
286  
287  
288  
289  
290  
291  
292  
293  
294  
295  
296  
297  
298  
299  
300  
301  
302  
303  
304  
305  
306  
307  
308  
309  
310  
311  
312  
313  
314  
315  
316  
317  
318  
319  
320  
321  
322  
323  
324  
325  
326  
327  
328  
329  
330  
331  
332  
333  
334  
335  
336  
337  
338  
339  
340  
341  
342  
343  
344  
345  
346  
347  
348  
349  
350  
351  
352  
353  
354  
355  
356  
357  
358  
359  
360  
361  
362  
363  
364  
365  
366  
367  
368  
369  
370  
371  
372  
373  
374  
375  
376  
377  
378  
379  
380  
381  
382  
383  
384  
385  
386  
387  
388  
389  
390  
391  
392  
393  
394  
395  
396  
397  
398  
399  
400  
401  
402  
403  
404  
405  
406  
407  
408  
409  
410  
411  
412  
413  
414  
415  
416  
417  
418  
419  
420  
421  
422  
423  
424  
425  
426  
427  
428  
429  
430  
431  
432  
433  
434  
435  
436  
437  
438  
439  
440  
441  
442  
443  
444  
445  
446  
447  
448  
449  
450  
451  
452  
453  
454  
455  
456  
457  
458  
459  
460  
461  
462  
463  
464  
465  
466  
467  
468  
469  
470  
471  
472  
473  
474  
475  
476  
477  
478  
479  
480  
481  
482  
483  
484  
485  
486  
487  
488  
489  
490  
491  
492  
493  
494  
495  
496  
497  
498  
499  
500  
501  
502  
503  
504  
505  
506  
507  
508  
509  
510  
511  
512  
513  
514  
515  
516  
517  
518  
519  
520  
521  
522  
523  
524  
525  
526  
527  
528  
529  
530  
531  
532  
533  
534  
535  
536  
537  
538  
539  
540  
541  
542  
543  
544  
545  
546  
547  
548  
549  
550  
551  
552  
553  
554  
555  
556  
557  
558  
559  
560  
561  
562  
563  
564  
565  
566  
567  
568  
569  
570  
571  
572  
573  
574  
575  
576  
577  
578  
579  
580  
581  
582  
583  
584  
585  
586  
587  
588  
589  
590  
591  
592  
593  
594  
595  
596  
597  
598  
599  
600  
601  
602  
603  
604  
605  
606  
607  
608  
609  
610  
611  
612  
613  
614  
615  
616  
617  
618  
619  
620  
621  
622  
623  
624  
625  
626  
627  
628  
629  
630  
631  
632  
633  
634  
635  
636  
637  
638  
639  
640  
641  
642  
643  
644  
645  
646  
647  
648  
649  
650  
651  
652  
653  
654  
655  
656  
657  
658  
659  
660  
661  
662  
663  
664  
665  
666  
667  
668  
669  
670  
671  
672  
673  
674  
675  
676  
677  
678  
679  
680  
681  
682  
683  
684  
685  
686  
687  
688  
689  
690  
691  
692  
693  
694  
695  
696  
697  
698  
699  
700  
701  
702  
703  
704  
705  
706  
707  
708  
709  
710  
711  
712  
713  
714  
715  
716  
717  
718  
719  
720  
721  
722  
723  
724  
725  
726  
727  
728  
729  
730  
731  
732  
733  
734  
735  
736  
737  
738  
739  
740  
741  
742  
743  
744  
745  
746  
747  
748  
749  
750  
751  
752  
753  
754  
755  
756  
757  
758  
759  
760  
761  
762  
763  
764  
765  
766  
767  
768  
769  
770  
771  
772  
773  
774  
775  
776  
777  
778  
779  
780  
781  
782  
783  
784  
785  
786  
787  
788  
789  
790  
791  
792  
793  
794  
795  
796  
797  
798  
799  
800  
801  
802  
803  
804  
805  
806  
807  
808  
809  
810  
811  
812  
813  
814  
815  
816  
817  
818  
819  
820  
821  
822  
823  
824  
825  
826  
827  
828  
829  
830  
831  
832  
833  
834  
835  
836  
837  
838  
839  
840  
841  
842  
843  
844  
845  
846  
847  
848  
849  
850  
851  
852  
853  
854  
855  
856  
857  
858  
859  
860  
861  
862  
863  
864  
865  
866  
867  
868  
869  
870  
871  
872  
873  
874  
875  
876  
877  
878  
879  
880  
881  
882  
883  
884  
885  
886  
887  
888  
889  
890  
891  
892  
893  
894  
895  
896  
897  
898  
899  
900  
901  
902  
903  
904  
905  
906  
907  
908  
909  
910  
911  
912  
913  
914  
915  
916  
917  
918  
919  
920  
921  
922  
923  
924  
925  
926  
927  
928  
929  
930  
931  
932  
933  
934  
935  
936  
937  
938  
939  
940  
941  
942  
943  
944  
945  
946  
947  
948  
949  
950  
951  
952  
953  
954  
955  
956  
957  
958  
959  
960  
961  
962  
963  
964  
965  
966  
967  
968  
969  
970  
971  
972  
973  
974  
975  
976  
977  
978  
979  
980  
981  
982  
983  
984  
985  
986  
987  
988  
989  
990  
991  
992  
993  
994  
995  
996  
997  
998  
999  
1000

Keywords: Growth hormone, IGF-I, IGFBP-3

Abstract word count: 240 words

Text word count: 3674 words.

## Summary

*Objective:* Recombinant human growth hormone (rhGH) replacement therapy in children and adults currently requires daily subcutaneous injections for several years or lifelong. The current study examined safety, tolerability, pharmacokinetic and pharmacodynamic response parameters after single and multiple doses of a long-acting rhGH preparation (NNC126-0083).

*Design:* Randomized, double-blind, placebo-controlled, multiple-dose, dose-escalating (0.02, 0.04, 0.08 and 0.16 mg protein/kg), sequential dose group trial.

*Subjects:* Forty adult Japanese healthy males (age 20–45 years; BMI: 18.0–27.0 kg/m<sup>2</sup>). Five groups ( $n = 8$ ) were randomized to receive multiple doses of NNC126-0083 ( $n = 6$ ) or placebo ( $n = 2$ ).

*Methods:* Primary outcome was safety and tolerability of multiple doses of NNC126-0083 compared with placebo. Blood samples for assessment of pharmacokinetics and pharmacodynamics response (IGF-I and IGFBP-3) were taken after multiple ascending doses.

*Results:* NNC126-0083 was well tolerated and not associated with any local injection-site reactions or lipoatrophy. Following administration, NNC126-0083 levels increased rapidly and remained elevated for several days, returning to baseline before each weekly injection. Steady-state pharmacokinetics was achieved after the third dosing. A more than dose-proportional exposure was observed at the highest NNC126-0083 dose (0.16 mg protein/kg). A strong dose-dependent pharmacodynamic response in circulating concentrations of both IGF-I and IGFBP-3 compared with placebo ( $p < 0.0001$ ) were observed during administration of all doses.

1  
2  
3 *Conclusions:* Multiple administration of NNC126-0083 in healthy male volunteers indicates that  
4  
5 NNC126-0083 has the potential for an efficacious, well-tolerated, once-weekly rhGH compound  
6  
7  
8 in the treatment of GH deficiency.  
9

## 10 11 **Introduction**

12  
13 Recombinant human GH (rhGH) is the standard treatment for severe growth retardation resulting  
14  
15 from GH deficiency or insufficiency in children, and other conditions such as Turner's  
16  
17 syndrome, small for gestational age, and Noonan syndrome, and the efficacy of GH replacement  
18  
19 in GH-deficient adults is now well established (1–3). Therapy with GH may therefore be  
20  
21 necessary throughout life. Currently, treatment guidelines recommend that GH is administered as  
22  
23 daily subcutaneous (s.c.) injections (2, 3) which may be both inconvenient and distressing for  
24  
25 patients leading to poor concordance with GH therapy (4–7). Daily injections effectively  
26  
27 increase height in children (8) and improve body composition and other abnormalities resulting  
28  
29 from the adult GHD syndrome (9, 10). Despite the fact that once-daily injections are generally  
30  
31 used, accumulated data in humans suggest that intermittent administration or continuous infusion  
32  
33 is just as efficacious (11, 12). Development of longer-acting GH preparations would not only  
34  
35 allow less frequent injections but would also likely improve compliance by reducing the  
36  
37 inconvenience of daily injections as well as reducing the impact of needle phobia. In one study,  
38  
39 50% of pediatric patients failed to comply with all aspects of a GH treatment regimen (4) and in  
40  
41 other studies 23–25% missed more than 2 injections per week (5, 6). Furthermore, it has been  
42  
43 recently reported that children as well as adolescents and adults receiving GH treatment had a  
44  
45 low compliance after 2 years of treatment and that difficulties with injections plays a significant  
46  
47 role (7). Several approaches have been taken to develop long-acting forms of GH, including a  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 microionized, zinc-stabilized GH encapsulated in microspheres, crystalline GH and pegylated  
4  
5 GH (13–18).  
6  
7

8  
9 NNC126-0083 is a pegylated long-acting hGH molecule in which a 43kDa polyethylene  
10  
11 glycol (PEG) residue is attached at glutamine 141 of the hGH molecule. Pegylation prolongs the  
12  
13 *in vivo* mean residence time by increasing the absorption time and slowing the elimination phase.  
14  
15

16  
17 This study was carried out to examine the pharmacokinetics (PK), pharmacodynamics (PD),  
18  
19 safety and local tolerability of NNC126-0083 given once weekly for 3 weeks, in healthy adult  
20  
21 Japanese subjects.  
22  
23

## 24 25 **Subjects and methods**

### 26 27 ***Subjects***

28  
29 In order to obtain sufficient data to evaluate the results based on descriptive statistics, 40 subjects  
30  
31 were randomized into active treatment or placebo in each of five dose cohorts. Sample size for  
32  
33 this study was not based on formal statistical methods but was considered a reasonable size to  
34  
35 address the study objectives. Groups of six active and two placebo treatments are commonly  
36  
37 used to evaluate a new chemical entity in human subjects.  
38  
39

40  
41 The study population was to include healthy, male, Japanese volunteers who fulfilled the  
42  
43 following criteria: age 20–45 years; body mass index (BMI), 18.0–27.0 kg/m<sup>2</sup>; body weight, 50–  
44  
45 100 kg, with Japanese passport and Japanese-born parents. Subjects were to be in good physical  
46  
47 health and to have no medical history of malignant disease, diabetes, cardiovascular disease or  
48  
49 other condition likely to interfere with the conduct of the study. On dosing day, subjects were  
50  
51 excluded if they had participated in strenuous exercise, had consumed alcohol in the previous 24  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 hours or were not fasted from midnight prior to dosing. Written informed consent was obtained  
4  
5  
6 from each subject prior to study inclusion.  
7

8 The study was conducted in accordance with the guidelines of the Helsinki Declaration  
9  
10 on human experimentation. All subjects were admitted to the metabolic ward (Profil, Germany).  
11  
12 Protocol approval was obtained from Independent Ethics Committee (Ärzttekammer Nordrhein)  
13  
14 and from the Competent Authority (Budesinstitut für Arzneimittel und Medizinprodukte  
15  
16 (BfArM)).  
17  
18  
19

### 20 21 **Study design**

22 Subjects were randomized to active treatment or placebo at one of four sequential dose levels  
23  
24 (0.02, 0.04, 0.08 or 0.16 mg protein/kg) with two cohorts being allocated to the 0.08 mg  
25  
26 protein/kg dose level. After each dose level, an evaluation of safety and PK were performed  
27  
28 before new subjects were entered into the next higher dose level. An additional cohort was added  
29  
30 at the 0.08 mg protein level to verify the exposure data. Doses were administered once weekly  
31  
32 during a three-week period. All test doses were administered as s.c. injections into a lifted  
33  
34 skinfold.  
35  
36  
37

38  
39 Subjects were randomized to the lowest available patient number from the randomization  
40  
41 list generated by the sponsor. Treatment was double-blinded with regard to NNC126-0083  
42  
43 versus placebo. For each patient number, a sealed code was kept at the trial site, at the sponsor's  
44  
45 local office, at the sponsor's international product safety office, and by the unblinded person at  
46  
47 the clinical unit in the event that the treatment allocation was required.  
48  
49  
50

51 The study consisted of a screening visit, a three-week treatment period, and an end-of-  
52  
53 study follow-up visit. Subjects received weekly injections of either NNC126-0083 or placebo on  
54  
55 Day 1, Day 8 and Day 15. After the first and third dosing, subjects remained in-house for 80  
56  
57

1  
2  
3 hours for post-dose study assessments (vital signs, ECG and blood sampling for PK and PD  
4 assessments) and were then discharged. Subjects returned to the clinic each morning for vital  
5 signs, ECG, and blood samples for PK and PD and safety assessments. Following the second  
6 dosing, subjects were allowed to leave the clinic and returned for assessments the day before the  
7 third dosing. A follow-up visit was performed (Days 35–42) for final clinical evaluation.  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Subjects fasted after midnight before each dosing and prior to study assessments in the morning.

### ***NNC126-0083 dosage form***

The active trial drug, NNC126-0083, was delivered as a lyophilized powder in vials. Placebo was also supplied as a lyophilized powder, comparable to the NNC126-0083 drug product except for the active ingredient. Each vial was reconstituted in 1.3 ml of sterile water providing 20 mg/ml of NNC126-0083 after reconstitution, corresponding to 6.8 mg/ml protein. Individual doses were prepared according to dose level and the subject's bodyweight.

### ***Safety measures***

At the screening visit, all subjects had the following tests: vital signs, haematology, biochemistry and urinalysis, 12-lead ECG, fasting plasma glucose and fasting insulin. The 12-lead ECG, haematology, biochemistry and urinalysis were repeated prior to dosing and on Days 2, 3, 4, 5, 16, 17, 18, 19, 22, 25 and at the follow-up visit (the ECG was not performed on Days 5, 19 or 22). Antibodies to NNC126-003 were assessed prior to dosing on Day 1, 8 and 15 and on Day 22 and at the follow-up visit by a bridging enzyme-linked immunosorbent assay (ELISA) test to specifically determine antibody levels against NNC126-0083. Samples for fasting insulin and plasma glucose were taken daily at all clinic visits.



### ***Local tolerability***

Local tolerability assessment done by investigator at each timepoint included scoring of pain/tenderness, itching, rash, redness, induration and skin dimpling on a scale indicated by the patient of 0 (none) to 3 (severe). Redness, induration and dimpling were measured in mm at the affected site.

### ***Pharmacokinetic and pharmacodynamic sample collection***

Plasma samples for NNC126-0083 (PK analyses) were taken before dosing and for 7 and 10 days post-first and -third dose, respectively, at 15 minutes then 1, 2, 4, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 54, 60, 66, 72, 80, 96, 120, 144, 168, 192, 216 and 240 hours post-dose as applicable. Serum samples for insulin-like growth factor I (IGF-I), IGF binding protein 3 (IGFBP-3) and growth hormone binding protein (GHBP) (PD analyses) were taken every 12–24 hours. Serum from blood samples (PK: 3 ml; PD: 4 ml) taken at each timepoint was stored frozen for analysis.

### ***Analytical methodology***

NNC126-0083 was measured using an NNC126-0083-specific sandwich ELISA using a specific anti-NNC126-0083 capture antibody, a biotinylated anti-human hGH antibody as the detection antibody, a streptavidin-horseradish peroxidase conjugate as the enzyme label, and tetramethylbenzidine/H<sub>2</sub>O<sub>2</sub> as the enzyme substrates.

Analyses of serum levels of IGF-I, IGFBP-3 and GHBP were performed by Laboratorium für Klinische Forschung GmbH (LKF), Germany by means of commercially available validated chemiluminescence immunoassays (CLIA) (IGF-I and IGFBP-3) performed on a Siemens Immulite 2000 analyser or ELISA (GHBP) performed manually. Reference ranges for IGF-I were age-related and within the range 101–358 µg/l. No difference was ascribed to the

1  
2  
3 normal range between males and females. The interassay coefficient of variation (CV) for IGF-I  
4 was 8%. For IGFBP-3, reference ranges were age-related and within the range 3.3–6.6 µg/ml.  
5  
6 Interassay CV for IGFBP-3 was 7%.  
7  
8

9  
10 Blood samples for measurement of antibodies against NNC126-0083 and against hGH  
11 were collected: prior to dosing with NNC126-0083, 10 days after dosing with NNC126-0083 and  
12 at the follow-up visit 28–40 days after last dosing with NNC126-0083. Determination of  
13 antibodies towards NNC126-0083 in serum was performed by screening samples with a bridging  
14 ELISA developed by Novo Nordisk A/S that detects antibodies that bind to NNC126-0083.  
15  
16 Antibody specificity to either NNC126-0083 or hGH was analysed by a competitive inhibition  
17 test in which samples, which were positive in the screening assay, were analysed with and  
18 without pre-incubation with either NNC126-0083 or hGH. Antibody responses were furthermore  
19 characterised for *in vitro* neutralising effect using a BAF-3 cell-based proliferation assay. The  
20 BAF-3 cells were stably transfected with hGHR, resulting in dependence on either  
21 NNC126-0083 or hGH for growth and survival. The cell line shows a dose-related stimulation of  
22 proliferation by adding increasing concentrations of hGH or hGH analogues. An antibody  
23 response would be characterised as *in vitro* neutralising if it inhibits cell proliferation. The  
24 analysis was carried out at Novo Nordisk A/S (Maaloev, Denmark).  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43

#### 44 **Pharmacokinetic analyses**

45 Plasma NNC126-003 PK parameters were computed by standard non-compartmental methods of  
46 analysis. The following PK parameters were determined after the first and third dosing:  
47  
48 maximum plasma concentration of NNC126-003 ( $C_{\max}$ ), time of  $C_{\max}$  ( $t_{\max}$ ) and AUC from 0–  
49 168 hours after dosing ( $AUC_{0-168h}$ ). AUC from time of dosing to infinity ( $AUC_{0-\infty}$ ) was  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 determined after the first dose. Dose proportionality of  $AUC_{0-\infty}$ ,  $AUC_{0-168h}$  after third dosing and  
4  
5  $C_{max}$  after first and third dosing, respectively, were evaluated.  
6  
7  
8  
9

### 10 11 ***Pharmacodynamic analyses***

12 PD parameters were derived from serum profiles of IGF-I and IGFBP-3 after the first and third  
13  
14 dosing and included  $AUC_{0-168h}$  and  $C_{max}$ .  
15  
16  
17

### 18 19 ***Statistical methods***

20 Safety, PK and PD analyses included all enrolled subjects who had received trial drug. Dose  
21  
22 proportionality was investigated by estimating the slope in the linear regression model of log  
23  
24 ( $AUC$  or  $C_{max}$ ) versus log (dose) (dose in mg protein/kg). Estimated slopes were described with  
25  
26 95% confidence intervals (CI). A slope of 1 indicated dose-proportional PK. The accumulation  
27  
28 ratio between  $AUC_{0-168h}$  after third dosing and  $AUC_{0-168h}$  after first dosing was used to evaluate  
29  
30 the extent of accumulation of NNC126-0083 following the third dose by using an ANOVA  
31  
32 model with the log-transformed ratio as the dependent variable and dose as a factor. The mean  
33  
34 ratio was estimated overall and for each dose and 95% CIs were calculated. Steady-state  
35  
36 investigations of IGF-I and IGFBP-3 were done by visual inspection of the mean  
37  
38 concentration–time profiles. All PD endpoints were analysed using an ANOVA model with dose  
39  
40 level as factor and the pre-dose value corresponding to first dosing as covariate. Mean ratios  
41  
42 between the doses of NNC126-0083 and placebo were estimated and 95% CIs were calculated.  
43  
44  
45  
46  
47  
48

49 A significance level of 5% was used with no adjustment for multiple testing. The  
50  
51 analyses of PD endpoints included all placebo subjects who were pooled assuming no cohort  
52  
53 effect. All safety endpoints were analysed using descriptive statistics.  
54  
55  
56  
57  
58  
59  
60

## Results

### *Subjects*

A total of 40 subjects (30 on NNC126-0083 and 10 on placebo) were enrolled and completed the study. The demographic characteristics of these subjects are summarized in Table 1. All subjects were adult Japanese males. Ages ranged from 23–44 years (mean 30.1 years). Mean BMI was 21.6 kg/m<sup>2</sup> (range 18.5 to 26.3 kg/m<sup>2</sup>). Dose cohorts were comparable in terms of demographic characteristics.

### *Pharmacokinetic profile of NNC126-0083*

Plasma NNC126-0083 concentrations after administration (mean concentration–time profiles) are shown in Figure 1 by dose. After administration of NNC126-0083, serum levels showed an extended peak at 12–30 hours after the dose. A diurnal variation in NNC126-0083 levels was observed.

Summary statistics for PK parameters are listed in Table 2. Following a single injection of NNC126-0083, mean  $t_{\max}$  ranged from 12.6 to 24.6 hours and mean  $t_{1/2}$  ranged from 30 to 48 hours. Following three once-weekly injections of NNC126-0083, mean  $t_{\max}$  ranged from 16.1 to 26.2 hours and mean  $t_{1/2}$  ranged from 37.5 to 64.5 hours (Table 2). A statistically significant deviation from dose-proportionality was observed in AUC<sub>0–168h</sub> (3rd dose) (estimated slope of the regression line 1.44 [95% CI: 1.07; 1.82],  $p = 0.0231$ ). The deviation appeared to be inferior at doses up to 0.04 mg protein/kg whereas at the highest dose (0.16 mg protein/kg) more than dose-proportional exposure was observed. In the higher-dose groups, some of the concentration–time profiles were non-linear in appearance, consistent with this finding (data not shown).

Systemic exposure to NNC126-0083 increased with increasing dose except after third dose

1  
2  
3 where dosing at 0.04 mg protein/kg resulted in similar or slightly higher mean values compared  
4  
5 with 0.08 mg protein/kg.  
6  
7

8 PK steady state appeared to have been reached after the third dose. The estimated rate of  
9  
10 accumulation, calculated from  $AUC_{0-168h} (3rd\ dose) / AUC_{0-168h} (3rd\ dose)$ , for all doses (pooled) was  
11  
12 1.05 (95% CI: 0.89; 1.24), showing that no or insignificant accumulation was observed.  
13  
14

### 15 16 ***Pharmacodynamic parameters***

17 Median (range) serum IGF-I concentration at baseline (pre-first dose) was 178.0 (83.0–302.0)  
18  
19 ng/ml. Mean serum IGF-I levels are illustrated in Figure 2. A clear dose-dependent increase in  
20  
21 IGF-I levels was observed at all GH doses tested (Fig. 2).  
22  
23

24  
25 Summary statistics for PD parameters are listed in Table 3. During the first dosing, the  
26  
27 estimated mean IGF-I  $C_{max}$  increased by up to 3.22 (95% CI: 2.68; 3.85) times compared with  
28  
29 placebo. Mean  $AUC_{0-168h}$  increased by up to 2.89 (95% CI: 2.47; 3.38) times versus placebo.  
30  
31 Following the third dosing, increases in mean IGF-I  $C_{max}$  and mean  $AUC_{0-168h}$  were up to 3.39  
32  
33 (95% CI: 2.86; 4.01) and 3.37 (95% CI: 2.84; 4.00) times, respectively, compared with placebo.  
34  
35 All increases were statistically significant compared with placebo ( $p < 0.0001$ ). Steady-state  
36  
37 IGF-I was achieved following the second dosing (Fig. 2). The PD profile of IGFBP-3 (Fig. 3)  
38  
39 was largely consistent with the PD profile of IGF-I. A dose-dependent increase in IGFBP-3  
40  
41 levels was observed. In the 0.02 mg protein/kg group, peak levels were recorded at more than  
42  
43 504 hours after first dosing. The two subjects receiving placebo in this cohort also showed a  
44  
45 similar peak, suggesting that the effect is likely not to be directly related to NNC126-0083. A  
46  
47 dose-dependent increase in mean IGF-I/IGFBP-3 molar ratio was observed (Fig. 4).  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## **Safety**

Twelve subjects reported 14 adverse events during the trial. One patient on placebo had a fracture of the humerus that was reported as a serious adverse event; all other events were of mild severity. The most frequent adverse events were nasopharyngitis (one event on placebo and two in subjects on NNC126-0083), headache (two events in subjects on placebo and one event in a subject on NNC126-0083) and increased blood creatinine phosphokinase (two events in subjects on placebo and one event in a subject on NNC126-0083). The investigator assessed relationship to study medication as possible for three events (two events of headache (one in each of the 0.04 mg protein/kg and placebo groups) and one event of fever in a subject in the 0.04 mg protein/kg group)) during NNC126-0083 administration.

Fasting serum glucose during NNC126-0083 administration was moderately increased within normal range during the first and third dosing for the two highest doses administered. No clinically relevant abnormal laboratory parameters were observed. No samples were positive for NNC126-0083 antibodies. There were no signs of injection-site reactions or lipoatrophy in any subject during the trial and no pain/tenderness or itching were reported.

## **Discussion**

The GH products currently marketed in the EU and US are all short-acting (i.e. the treatment regimen follows daily injections).

Although GH treatment has proved both efficacious and safe, one major drawback of the treatment has been the need for daily s.c. injections, which represents a burden for the children and their parents, resulting in very low compliance in some cases (4). In recent studies approximately 25% missed three injections or more per month using needle and syringe administration and 13% missed over half of the prescribed dose (5, 6); and it has been reported

1  
2  
3 that children as well as adolescents and adults receiving GH treatment had a low compliance  
4 after 2 years of treatment and that difficulties with injections plays a significant role (7).  
5  
6

7  
8 Development of liquid GH and convenient pen devices has simplified the administration process.  
9

10 However, these advancements still necessitate GH injections every day. Thus, a medical need  
11 exists for a treatment with less frequency of injections when administering GH.  
12  
13  
14

15  
16 The long-acting preparation of GH (NNC126-0083) reported in the present study was  
17 well tolerated when given as three once-weekly doses to healthy adult Japanese males. No  
18 injection-site reactions or other local tolerability adverse events such as pain and tenderness were  
19 observed. In contrast, a very recent publication reported 13 cases of injection-site lipoatrophy  
20 following administration of a once-weekly pegylated GH formulation, PHA-794428, in GH-  
21 deficient adults (19). In that report most cases were observed after repeated injections at the same  
22 site, but three cases occurred following the first injection (19). These reactions appeared to be  
23 independent of PEG-dose or of IGF-I levels. In another study, Nutropin Depot, an rhGH  
24 encapsulated in microspheres of biocompatible, biodegradable poly(lactide coglycolide)  
25 copolymer, was associated with injection-site reactions in nearly all patients and lipoatrophy was  
26 observed following 11% of injections (13). In the current study the long acting GH preparation  
27 was administered according to an injection rotation plan and no signs of lipoatrophy were  
28 observed. Thus, rotation of injection site seems to be crucial as most cases of lipoatrophy has  
29 been reported to occur after repeated GH injections at the same site (19). Another observation is  
30 that injection site pain was the most frequently reported treatment-related adverse event reported  
31 after administration of the PHA-794428 pegylated GH-formulation (19), whereas injection site  
32 pain was not observed in the current study. Thus, we can speculate that the difference observed  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 in local tolerability may also be related to difference between the GH-formulations (e.g.  
4  
5 excipients in the formulation).  
6  
7

8  
9 The PK profile demonstrated that NNC126-0083 resulted in a sustained increase in serum  
10 levels of NNC126-0083 over several days from this pegylated formulation. Conjugation with  
11 PEG is a widely used approach for improving the stability of peptide and protein drugs (20, 21)  
12 and a number of pegylated products are approved for clinical use. The main PK outcomes of  
13 pegylation include changes in tissue distribution, absorption and elimination pathways of the  
14 parent drug, and it is especially useful in prolonging the exposure and duration of action of short-  
15 half-life proteins subject to renal clearance or enzymatic hydrolysis (22).  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25

26 Serum NNC126-0083 concentration after s.c. injection increased rapidly and increased  
27 levels were observed for several days but returned towards baseline values before each weekly  
28 injection, indicating that there was no accumulation. The mean time (geometric mean) to  
29 maximum serum concentration of NNC126-0083 ranged from 12.6 to 26.2 hours with no  
30 apparent dependency on dose level or dosing occasion, approximately four to five times longer  
31 than that reported after a single s.c. injection of rhGH. Steady-state PK appeared to have been  
32 achieved following the third dosing and no accumulation was observed. Both NNC126-0083  
33  $C_{\max}$  and AUC were approximately proportional to the dose of NNC126-0083 administered at  
34 doses up to, and including, 0.08 mg protein/kg. A deviation from dose-proportionality, as shown  
35 in an earlier study (23) was, however, noted at the highest dose (0.16 mg protein/kg) tested,  
36 where more than dose-proportional exposure was observed. The non-linear shapes of some of the  
37 concentration–time profiles in the higher-dose groups support this finding.  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



1  
2  
3 Similar to in a previous trial (23), a diurnal variation in NNC126-0083 was observed in  
4 the present study. This may be attributed to diurnal variation in lymphatic drainage in the  
5 subcutaneous tissue (24), although this needs to be further explored.  
6  
7  
8  
9

10  
11 Reducing the frequency of injections for patients on lifelong therapy is suggested to  
12 positively affect treatment compliance. In adult patients with GH-deficiency, thrice-weekly  
13 injections were shown to elicit stable, normal IGF-I concentrations (25). Other sustained-release  
14 preparations for use with GH have been described. A depot formulation, in which microionized  
15 particles of zinc-stabilized GH were embedded in biocompatible, biodegradable microspheres  
16 designed for once-monthly injection, was shown to be associated with sustained GH  
17 concentrations for up to 10–15 days; however, more than 50% of GH was released during the  
18 initial two days following injection (14, 15, 26). A pegylated formulation, PHA-794428,  
19 synthesized by addition of a branched 40kD PEG to the GH molecule at the N terminus, has also  
20 recently been developed. Comparison of the PK of this molecule (dose range 10–500 µg/kg) with  
21 somatropin (3.6 mg) demonstrated that the pegylated formulation had a 10–20-fold increase in  
22 AUC and a similar increase in half-life in comparison with somatropin (at equivalent s.c. doses)  
23 (27).  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42

43 Statistically significant dose dependent increases in serum concentrations of both IGF-I  
44 and IGFBP-3 when compared to placebo were observed during administration of NNC126-0083.  
45 Peak IGF-I levels were generally achieved between 2.5 and 3.5 days after NNC126-0083  
46 administration, and then returned towards baseline values. Similar to IGF-I, levels of IGFBP-3  
47 increased in a dose-dependent manner following injection of NNC126-0083.  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 The safety results indicate that NNC126-0083 is safe and well tolerated. The adverse  
4 events profile was not different from that reported with daily GH injections. No consistent  
5 changes were reported in laboratory evaluations or vital signs that were considered to be  
6 drug-related. At the two highest dosing levels, fasting plasma glucose and insulin levels were  
7 moderately increased during the first and third dosing with NNC126-0083.  
8  
9

10  
11  
12  
13  
14  
15  
16 In conclusion, multiple doses of NNC126-0083, a long-acting GH preparation, were  
17 associated with effective pharmacokinetics and pharmacodynamics in healthy Japanese adult  
18 males. A significant dose-dependent IGF-I response was induced with elevated IGF-I levels at all  
19 doses of NNC126-0083. Importantly, NNC126-0083 was not associated with any clinically  
20 relevant adverse effects, and no injection-site reactions or antibodies were observed. Clinical  
21 trials need to determine whether long-term administration with NNC126-0083 is efficacious and  
22 safe in GHD adults and children. Results from the present study indicate that NNC126-0083 has  
23 the potential for an efficacious, well-tolerated, once-weekly compound in the treatment of GHD  
24 in adults and children.  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37

### 38 **Conflicts of interest**

39 All the authors are employees and shareholders of Novo Nordisk A/S.  
40  
41  
42

### 43 **Acknowledgements**

44 The trial was financially supported by Novo Nordisk A/S. The authors wish to thank Anna  
45 Laurén, Cell and Antibody Analysis, Novo Nordisk A/S for antibody analyses and for scientific  
46 advice in the interpretation of results and Anne-Mette Paarup, who provided medical writing  
47 services on behalf of Novo Nordisk A/S.  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## References

1. Richmond, E.J. & Rogol, A.D. (2008) Growth hormone deficiency in children. *Pituitary*, **11**, 115–120.
2. Molitch M.E., Clemmons D.R., Malozowski S., *et al.* Merriam GR, Shalet SM, Vance ML, Stephens PA. Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society Clinical Practice Guideline (2006). *Journal of Clinical Endocrinology & Metabolism*, **91** 1621-1634.
3. Ho, K.K. (2007) GH Deficiency Consensus Workshop Participants. Consensus guidelines for the diagnosis and treatment of adults with GH deficiency II: a statement of the GH Research Society in association with the European Society for Pediatric Endocrinology, Lawson Wilkins Society, European Society of Endocrinology, Japan Endocrine Society, and Endocrine Society of Australia. *European Journal of Endocrinology*, **157**, 695–700.
4. Smith, S.L., Hindmarsh, P.C. & Brook, C.G.D. (1993) Compliance with growth hormone treatment - are they getting it? *Archive of Disease in Childhood*, **68**, 91–93.
5. Desrosiers, P., O'Brien, F. & Bletchen, S. (2005) Patient outcomes in the GH-Monitor: the effect of delivery device on compliance and growth. *Pediatric Endocrinology Reviews*, **2(Suppl. 3)**, 327–331.

- 1  
2  
3  
4  
5  
6 6. Kapoor, R.R., Burke, S.A., Sparrow, S.E. *et al.* (2008) Monitoring of concordance in growth  
7  
8 hormone therapy. *Achieves of Disease in childhood*, **93**, 147-148.  
9  
10  
11  
12 7. Rosenfeld, R.G. & Bakker, B. (2008) Compliance and persistence in paediatric and adult  
13  
14 patients receiving growth hormone therapy. *Endocrine Practice*, **14**, 143–154.  
15  
16  
17  
18  
19 8. Ranke, M.B., Lindberg, A., Albertsson-Wikland, K. *et al.* (2005) Increased response, but  
20  
21 lower responsiveness, to growth hormone (GH) in very young children (aged 0-3 years) with  
22  
23 idiopathic GH Deficiency: analysis of data from KIGS. *Journal of Clinical Endocrinology and*  
24  
25 *Metabolism*, **90**, 1966–1971.  
26  
27  
28  
29  
30  
31 9. Attanasio, A.F., Howell, S., Bates, P.C. *et al.* (2002) Confirmation of severe GH deficiency  
32  
33 after final height in patients diagnosed as GH deficient during childhood. *Clinical*  
34  
35 *Endocrinology*, **56**, 503–507.  
36  
37  
38  
39  
40  
41 10. Gibney, J., Wallace, J.D., Spinks, T. *et al.* (1999) The effects of 10 years of recombinant  
42  
43 human growth hormone (GH) in adult GH-deficient patients. *Journal of Clinical Endocrinology*  
44  
45 *and Metabolism* 1999 **84** 2596–2602.  
46  
47  
48  
49  
50  
51 11. Giavoli, C., Cappiello, V., Porretti, S. *et al.* (2003) Growth hormone therapy in GH-deficient  
52  
53 adults: continuous vs alternate-days treatment. *Hormone and Metabolic Research*, **35**, 557–561.  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 12. Laursen, T., Gravholt, C.H., Heickendorff, L. *et al.* (2001) Long-term effects of continuous  
4 subcutaneous infusion versus daily subcutaneous injections of growth hormone (GH) on the  
5 insulin-like growth factor system, insulin sensitivity, body composition, and bone and lipoprotein  
6 metabolism in GH-deficient adults. *Journal of Clinical Endocrinology and Metabolism*, **86**,  
7  
8 1222–1228.  
9

10  
11  
12  
13  
14  
15  
16  
17 13. Reiter, E.O., Attie, K.M., Moshang, T. Jr, *et al.* (2001) Genentech, Inc.-Alkermes, Inc.  
18 Collaborative Study Group. A multicenter study of the efficacy and safety of sustained release  
19 GH in the treatment of naive pediatric patients with GH deficiency. *Journal of Clinical*  
20 *Endocrinology and Metabolism*, **86**, 4700–4706.  
21  
22  
23  
24  
25  
26  
27  
28

29 14. Cook, D.M., Biller, B.M., Vance, M.L. *et al.* (2002) The pharmacokinetic and  
30 pharmacodynamic characteristics of a long-acting growth hormone (GH) preparation  
31 (nutropin depot) in GH-deficient adults. *Journal of Clinical Endocrinology and Metabolism*, **87**,  
32 4508–4514.  
33  
34  
35  
36  
37  
38  
39  
40

41 15. Hoffman, A.R., Biller, B.M., Cook, D. *et al.* (2005) Genentech Adult Growth Hormone  
42 Deficiency Study Group. Efficacy of a long-acting growth hormone (GH) preparation in patients  
43 with adult GH deficiency. *Journal of Clinical Endocrinology and Metabolism*, **90**, 6431–6440.  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60
16. Bidlingmaier, M., Kim, J., Savoy, C. *et al.* (2006) Comparative pharmacokinetics and pharmacodynamics of a new sustained-release growth hormone (GH), LB03002, versus daily GH in adults with GH deficiency. *Journal of Clinical Endocrinology and Metabolism*, **91**, 2926–2930.
17. Harris, P.E., Didier, E., Kantaridis, C. *et al.* (2006) First in human study of pegylated recombinant growth hormone. *Hormone Research*, **65(Suppl. 4)**, 30.
18. Abs, R., Didier, E., Boonen, A. *et al.* (2006) The pharmacokinetics, pharmacodynamics and safety of pegylated recombinant human growth hormone after single subcutaneous injections in adult male patients with growth hormone deficiency. *Hormone Research*, **65(Suppl. 4)**, 148.
19. Touraine, P., D'Souza, G.A., Kourides, I. *et al.* (2009) GH Lipoatrophy Study Group. Lipoatrophy in GH deficient patients treated with a long-acting pegylated GH. *European Journal of Endocrinology*, **161**, 533–540.
20. Veronese, F.M., Mammucari, C., Schiavon, F. *et al.* (2001) Pegylated enzyme entrapped in poly(vinyl alcohol) hydrogel for biocatalytic application. *Farmaco*, **56**, 541–547. PubMed PMID: 11601638.
21. Harris, J.M., Martin, N.E. & Modi, M. (2001) Pegylation: a novel process for modifying pharmacokinetics. *Clinical Pharmacokinetics*, **40**, 539–551.

- 1  
2  
3 22. Hamidi, M., Azadi, A. & Rafiei, P. (2006) Pharmacokinetic consequences of pegylation.  
4  
5 *Drug Delivery*, **13**, 399–409.  
6  
7  
8  
9  
10 23. Rasmussen, M.H., Bysted, B., Anderson, T.W. *et al.* (2010) Pegylated long-acting human  
11 growth hormone is well-tolerated in healthy subjects and possesses a potential once-weekly  
12 pharmacokinetic and pharmacodynamic treatment profile. *Journal of Clinical Endocrinology and*  
13 *Metabolism*, doi:10.1210/jc.2009-2813.  
14  
15  
16  
17  
18  
19  
20  
21  
22 24. Porter, J.H., Edwards, G.A. & Charman, S.A. (2001) Lymphatic transport of proteins after  
23 s.c. injection: implications of animal model selection *Advanced Drug Delivery Reviews*,  
24  
25 **50(Issues 1–2)**, 157–171.  
26  
27  
28  
29  
30  
31  
32 25. Amato, G., Mazziotti, G., Di Somma, C. *et al.* (2000) Recombinant growth hormone (GH)  
33 therapy in GH-deficient adults: a long-term controlled study on daily versus thrice weekly  
34 injections. *Journal of Clinical Endocrinology and Metabolism*, **85**, 3720–3725.  
35  
36  
37  
38  
39  
40  
41 26. Kemp, S.F., Fielder, P.J., Attie, K.M. *et al.* (2004) Pharmacokinetic and pharmacodynamic  
42 characteristics of a long-acting growth hormone (GH) preparation (nutropin depot) in GH-  
43 deficient children. *Journal of Clinical Endocrinology and Metabolism*, **89**, 3234–3240.  
44  
45  
46  
47  
48  
49  
50 27. Webster, R., Xie, R., Didier, E. *et al.* (2008) PEGylation of somatropin (recombinant human  
51 growth hormone): impact on its clearance in humans. *Xenobiotica*, **38**, 1340–1351.  
52  
53  
54  
55  
56  
57  
58  
59  
60

## TABLES

**Table 1** Demographic and Other Baseline Characteristics of Subjects Included in the Pharmacokinetic/Pharmacodynamic and Safety Analyses by Dose Cohort

Dose (mg protein/kg)	Number of subjects	Age (years)	Height (cm)	BMI (kg/m <sup>2</sup> )	Waist circumference (cm)
Placebo	10	28.0 (2.6)	173.1 (6.4)	22.7 (2.6)	80.1 (6.8)
0.02	6	29.5 (2.6)	173.3 (4.8)	21.5 (2.8)	79.8 (6.4)
0.04	6	32.7 (6.7)	171.8 (6.0)	20.3 (0.9)	74.8 (4.0)
0.08	12	29.8 (3.2)	170.9 (4.1)	21.5 (2.3)	76.5 (7.1)
0.16	6	32.5 (6.5)	174.5 (6.2)	21.3 (1.3)	77.2 (4.2)

Data are presented as mean (SD).



**Table 2** Summary of Pharmacokinetic Parameters Following the First and Third Weekly Dose of NNC126-0083 to Healthy Japanese Subjects

Dose (mg protein/kg)	AUC <sub>0-168h</sub> (h*ng protein/mL)	C <sub>max</sub> (ng protein/mL)	t <sub>max</sub> (h)	t <sub>1/2</sub> (h)
<b>First dosing</b>				
0.02	367 (177)	9.8 (5.8)	12.6 (8.2)	31.0 (13.3)
0.04	1033 (966)	20.0 (29.0)	18.2 (11.4)	48.2 (18.1)
0.08	1573 (742)	29.6 (20.8)	19.4 (16.0)	34.1 (15.4)
0.16	6230 (6524)	114.1 (94.0)	24.6 (12.8)	30.1 (9.7)
<b>Third dosing</b>				
0.02	280 (131)	8.1 (4.6)	16.1 (9.7)	64.5 (22.4)
0.04	1433 (596)	31.9 (14.8)	24.4 (11.2)	53.2 (21.4)
0.08	1414 (924)	28.2 (26.2)	26.2 (16.3)	54.0 (12.8)
0.16	9193 (13382)	179.4 (151.6)	25.8 (11.9)	37.5 (20.2)

Data are presented as geometric mean (SD)

**Table 3 Summary of Pharmacodynamic Parameters for Serum IGF-I Following the First and Third Weekly Dose of NNC126-0083 to Healthy Japanese Subjects**

<b>Dose (mg protein/kg)</b>	<b>AUC<sub>0-168h</sub>/168h (ng/mL)</b>	<b>C<sub>max</sub> (ng/mL)</b>
<b>First dosing</b>		
placebo	191.4 (61.2)	221.2 (67.2)
0.02	262.4 (59.5)	313.7 (65.3)
0.04	253.9 (40.5)	313.3 (36.9)
0.08	371.4 (86.1)	474.1 (106.8)
0.16	579.0 (119.4)	749.3 (172.3)
<b>Third dosing</b>		
placebo	185.5 (49.4)	217.0 (52.4)
0.02	263.1 (66.0)	318.5 (70.4)
0.04	321.9 (57.9)	396.5 (52.6)
0.08	410.8 (85.1)	494.7 (102.3)
0.16	618.2 (85.5)	733.2 (120.9)

Data are presented as geometric mean (SD)

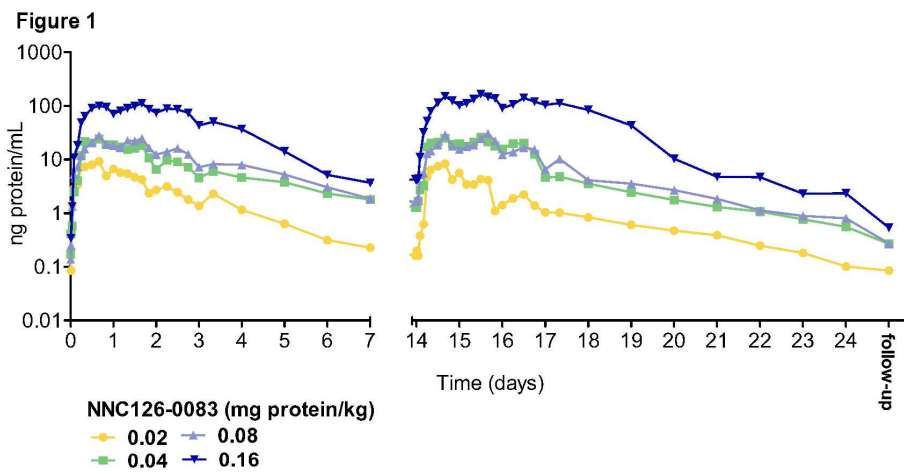
**FIGURE LEGENDS**

**Figure 1** Mean Plasma NNC126-0083 Concentrations (ng protein/mL) vs. Time Profiles Following the First and Third Weekly Dose to Healthy Male Japanese Subjects

**Figure 2** Mean IGF-I Concentration (ng/mL) vs. Time Profiles Following the First and Third Weekly Dose of NNC126-0083 to Healthy Male Japanese Subjects

**Figure 3** Mean IGFBP-3 Concentration (ng/mL) vs. Time Profiles Following the First and Third Weekly Dose of NNC126-0083 to Healthy Male Japanese Subjects

**Figure 4** Mean IGF-I/IGFBP-3 Molar Ratio vs. Time Following the First and Third Weekly Dose of NNC126-0083 to Healthy Male Japanese Subjects

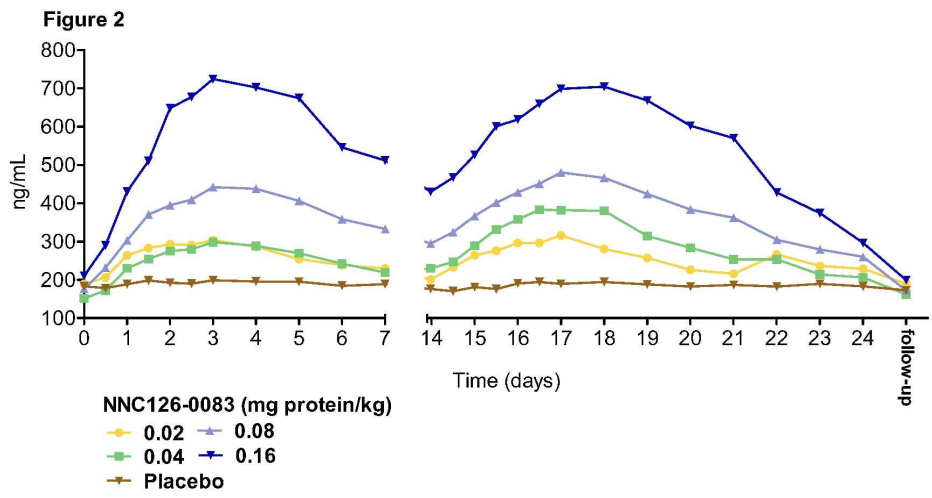


236x116mm (600 x 600 DPI)

Peer Review

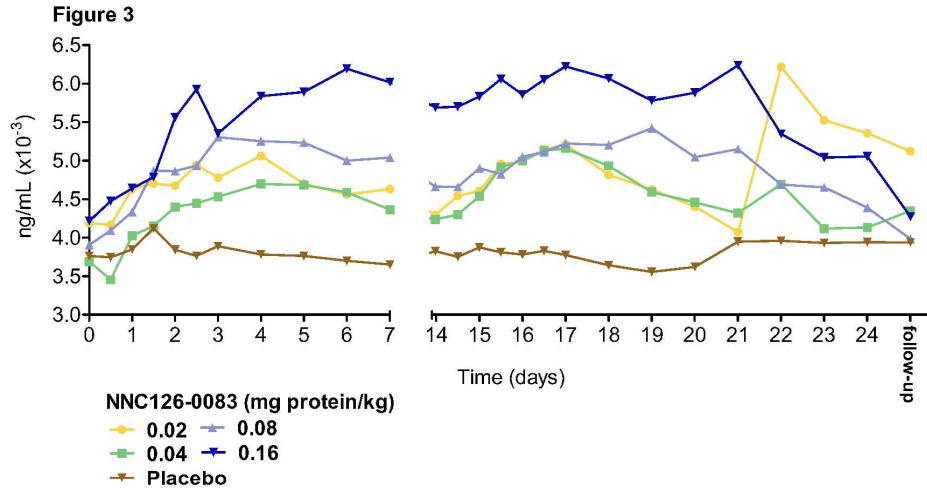
1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



235x121mm (600 x 600 DPI)

Peer Review

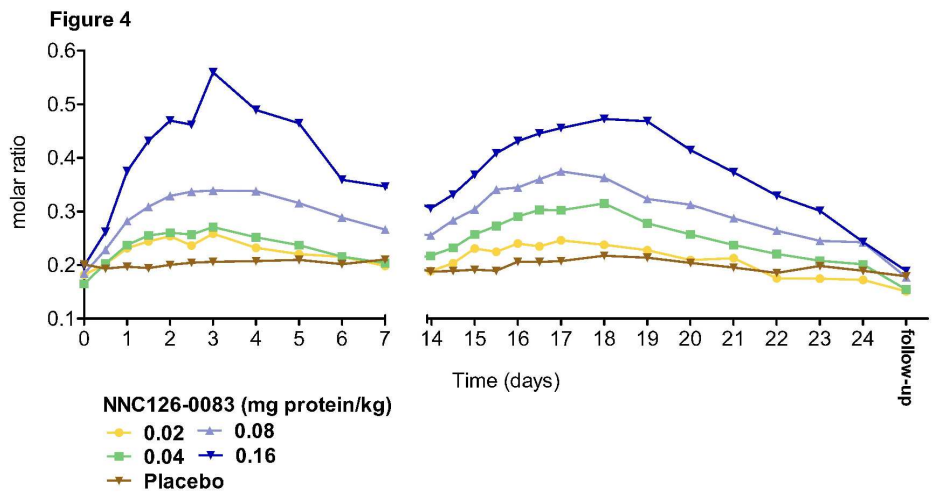


236x121mm (600 x 600 DPI)

Peer Review

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



235x121mm (600 x 600 DPI)

Peer Review