

# Inhibition of Dipeptidyl Peptidase IV Improves Metabolic Control Over a 4-Week Study Period in Type 2 Diabetes

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**OBJECTIVE** — Glucagon-like peptide-1 (GLP-1) has been proposed as a new treatment modality for type 2 diabetes. To circumvent the drawback of the short half-life of GLP-1, inhibitors of the GLP-1–degrading enzyme dipeptidyl peptidase IV (DPP IV) have been examined. Such inhibitors improve glucose tolerance in insulin-resistant rats and mice. In this study, we examined the 4-week effect of 1-[[2-[(5-cyanopyridin-2-yl)amino]ethyl]amino]acetyl]-2-cyano-(S)-pyrrolidine (NVP DPP728), a selective, orally active inhibitor of DPP IV, in subjects with diet-controlled type 2 diabetes in a placebo-controlled double-blind multicenter study.

**RESEARCH DESIGN AND METHODS** — A total of 93 patients (61 men and 32 women), aged  $64 \pm 9$  years (means  $\pm$  SD) and with BMI  $27.3 \pm 2.7$  kg/m<sup>2</sup>, entered the study. Fasting blood glucose was  $8.5 \pm 1.5$  mmol/l, and HbA<sub>1c</sub> was  $7.4 \pm 0.7\%$ . Before and after treatment with NVP DPP728 at 100 mg  $\times$  3 ( $n = 31$ ) or 150 mg  $\times$  5 ( $n = 32$ ) or placebo ( $n = 30$ ), subjects underwent a 24-h study with standardized meals (total 2,000 kcal).

**RESULTS** — Compared with placebo, NVP DPP728 at 100 mg t.i.d. reduced fasting glucose by 1.0 mmol/l (mean), prandial glucose excursions by 1.2 mmol/l, and mean 24-h glucose levels by 1.0 mmol/l (all  $P < 0.001$ ). Similar reductions were seen in the 150-mg b.i.d. treatment group. Mean 24-h insulin was reduced by 26 pmol/l in both groups ( $P = 0.017$  and  $P = 0.023$ ). Although not an efficacy parameter foreseen in the study protocol, HbA<sub>1c</sub> was reduced to  $6.9 \pm 0.7\%$  in the combined active treatment groups ( $P < 0.001$ ). Laboratory safety and tolerability was good in all groups.

**CONCLUSIONS** — We conclude that inhibition of DPP IV is a feasible approach to the treatment of type 2 diabetes in the early stage of the disease.

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**Abbreviations:** DPP IV, dipeptidyl peptidase IV; FPG, fasting plasma glucose; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide-1; NVP DPP728, 1-[[2-[(5-cyanopyridin-2-yl)amino]ethyl]amino]acetyl]-2-cyano-(S)-pyrrolidine.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

The gut hormones glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) are both incretin hormones that are released postprandially and markedly augment glucose-stimulated insulin secretion through sensitizing the  $\beta$ -cell action of glucose (1–3). GLP-1 also exhibits other effects of importance for glucose homeostasis, viz., inhibiting glucagon secretion, delaying gastric emptying, and stimulating insulin biosynthesis (2,3). These effects, along with a potential increase in peripheral insulin action (4), will together be antidiabetic. GLP-1 has also been shown to reduce postprandial and fasting glycemia in subjects with type 1 and type 2 diabetes (3,4–9) and may, therefore, be a potentially useful new therapeutic agent in the treatment of diabetes. However, GLP-1 is rapidly degraded in plasma by the enzyme dipeptidyl peptidase IV (DPP IV), resulting in the short circulating half-life of intact GLP-1 being  $<1$  min (3,10,11). Therefore, GLP-1 is unattractive as chronic therapy because multiple daily injections are required to maintain glycemic control.

The short half-life of GLP-1 has prompted development of alternate strategies to harness the potent antidiabetic activity of GLP-1. One approach is to inhibit DPP IV activity, thereby prolonging the circulating half-life of endogenous GLP-1 (11). DPP IV (or CD26) is an enzyme that is found throughout the body in both plasma and the endothelial lining of several organs, such as the kidney, liver, and intestine (12). It cleaves a number of biologically active peptides, including GLP-1, which is degraded from the active form of GLP-1, i.e., GLP-1<sub>7–36</sub>amide, yielding GLP-1<sub>9–36</sub>amide (10,13,14). DPP IV also degrades GIP through a similar mechanism, removing the two first NH<sub>2</sub>-terminal amino acids (12,13); therefore, inhibiting this enzyme will prolong the circulating half-life of the two most important incretins. Interestingly, the degradation product of GLP-1, GLP-1<sub>9–36</sub>amide, has been shown to exhibit GLP-1 receptor antagonistic properties

(11,14), suggesting that DPP IV inhibition increases the level of an antagonist, GLP-1<sub>9-36</sub>amide. The potential of using this approach in the treatment of diabetes is illustrated in studies showing that DPP IV-deficient mice (15) and rats (16) exhibit increased insulin secretion and glucose tolerance. Animal studies have confirmed the potential of this strategy because inhibition of DPP IV with valine pyrrolidide potentiates the insulinotropic action of GLP-1 in pigs (17). Furthermore, in diabetic animal models, improved glucose tolerance and insulin response to oral glucose have been demonstrated by several different DPP IV inhibitors (18–20). However, no studies have so far been reported on the potential use of this principle in the treatment of type 2 diabetes in humans.

In this study, we examined the anti-diabetic effect of daily administration of 1-[[[2-[(5-cyanopyridin-2-yl)amino]ethyl]amino]acetyl]-2-cyano-(S)-pyrrolidine (NVP DPP728) for 4 weeks in drug-naive subjects with type 2 diabetes previously treated with a diet and exercise regimen only. As previously reported in detail (21), NVP DPP728 is an orally active and highly selective DPP IV inhibitor containing a 2-cyanopyrrolidide moiety that is responsible for a slow-binding mechanism characterized by high potency, competitive behavior, and rapid reversibility inhibiting both human and rodent DPP IV activity. The compound has been shown to reduce DPP IV activity in plasma and to improve glucose tolerance in diabetic Zucker rats (19). Based on pharmacokinetic and pharmacodynamic data in healthy subjects, a total daily dose of 300 mg was selected for NVP DPP728, and our study compared the therapeutic usefulness of this dose administered twice daily or three times per day with placebo.

## RESEARCH DESIGN AND METHODS

### Study design

The study was a randomized, double-blind, placebo-controlled, multicenter study comprising a 4-week run-in period followed by a 4-week study period in which patients were randomized to receive blinded treatment with either placebo or NVP DPP728 100 mg t.i.d. or 150 mg b.i.d.. Five centers in Sweden participated (the University Hospitals in Lund, Malmö, Göteborg, and Umeå and the Karolinska Hospital in Stockholm). The

study was approved by the Ethics Committee at these institutions and by the Swedish Medical Products Agency (Uppsala, Sweden). Written informed consent was obtained from each participant. Patients attended at weeks -4, -2, 0, 2, and 4, at which time fasting blood samples were collected and details of adverse events were obtained. At weeks -4, 0, and 4, a clinical examination was also performed. At weeks 0 and 4, the subjects underwent a 24-h study with standardized meals and frequent sampling for glucose and insulin levels. During these days, patients received a standard meal schedule comprising a total of 2,000 kcal, consisting of 55% carbohydrate, 25% fat, and 20% protein (23% consumed at breakfast, 36% consumed at lunch, 36% consumed at dinner, and 5% consumed at snack time). Breakfast consisted of 450 kcal with 50% as carbohydrate, 23% as fat, and 27% as protein. After the 24-h study period at week 0, patients were randomly assigned to placebo, NVP DPP728 100 mg t.i.d., or NVP DPP728 150 mg b.i.d.. Participants were provided with glucometers and instructed to monitor their blood glucose levels if they experienced symptoms of hypoglycemia. NVP DPP728 was administered as either 100- or 150-mg tablets or identical placebo tablets. Tablets were taken 10 min before breakfast and dinner in the twice-daily arm and 10 min before breakfast, lunch, and dinner in the three-times-daily arm. In each arm, a 2:1 randomization was used to achieve an overall equal number of patients on each active treatment regimen and on placebo.

### Subjects

Patients eligible for the study were men or women aged >30 years with a history of type 2 diabetes diagnosed at least 12 weeks before entry into the study. Women were required to be nonfertile or using a medically approved method of birth control. Patients were excluded from randomization if they had mean fasting blood glucose concentration <7.2 or >10.0 mmol/l, mean HbA<sub>1c</sub> level <6.3% or >10.0% (reference value <5.3%), or BMI <20 or >32 kg/m<sup>2</sup>. Also excluded were patients with evidence of diabetic end-organ disease (renal, cardiac, neurological, retinal), other clinically relevant conditions (for example, previous gastric surgery), clinically significant laboratory abnormalities, or any conditions that

might alter drug absorption or metabolism or gastric emptying.

### Analyses

Glucose was measured by the glucose oxidase method (Boehringer Mannheim, Mannheim, Germany), insulin levels were measured by radioimmunoassay (Pharmacia, Uppsala, Sweden), HbA<sub>1c</sub> levels were determined by ion-exchange high-performance liquid chromatography, and triglycerides and cholesterol were measured with an enzymatic method (Johnson & Johnson, Rochester, NY).

### Safety and tolerability

Safety parameters included physical examination, vital signs, electrocardiographic evaluations, laboratory evaluations (hematology, chemistry, and urinalysis), adverse events, and self-monitoring of blood glucose levels for suspected hypoglycemia. Symptomatic suspected hypoglycemic episodes were recorded even if not confirmed by a low blood glucose level. Asymptomatic low blood glucose levels (<2.8 mmol/l) obtained on fingerstick were also recorded.

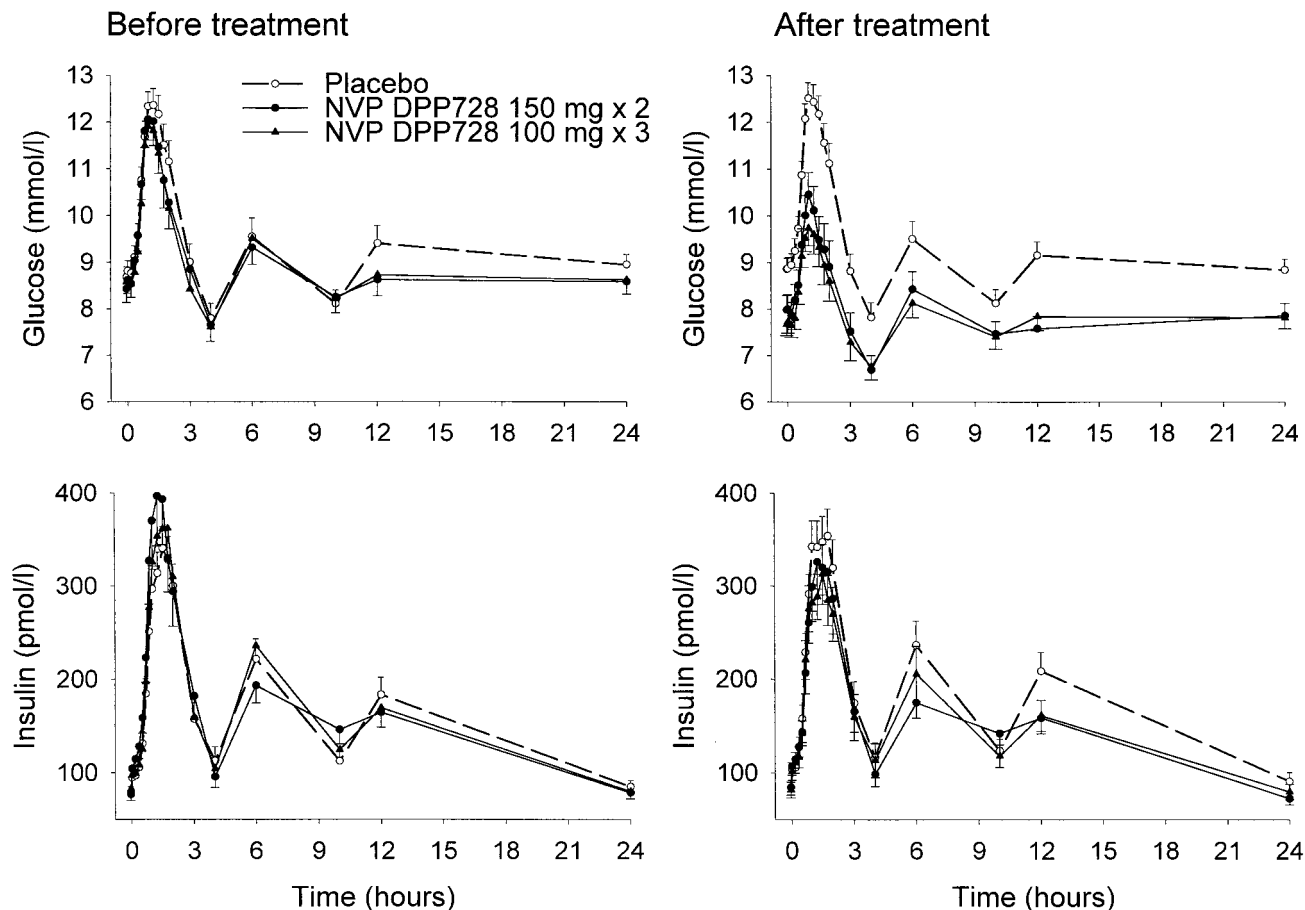
### Statistics

The primary efficacy parameter was the change in mean 24-h glucose, calculated as the area under the 24-h glucose curve divided by 24 compared with placebo. Secondary parameters included mean 24-h insulin, fasting plasma glucose (FPG) and the prandial glucose excursion (defined as the difference between the maximum glucose value observed in the 4-h postbreakfast period minus the mean of the prebreakfast measurements). All values were expressed as means ± SEM unless otherwise stated. Statistical comparisons were made between each of the treatment groups and the placebo group for the primary and the secondary efficacy parameters by analysis of variance. Although not included in the study protocol as an efficacy parameter because of the short treatment duration, the change in HbA<sub>1c</sub> between baseline and study end was also evaluated.

## RESULTS

### Patients

Of the screened 141 Caucasian patients, 93 (61 men) were eligible for the study. Median or mean values for age (median 64; mean ± SD 64 ± 9; range 35–80



**Figure 1**—24-h Glucose and insulin levels before and after 4 weeks of treatment with placebo ( $n = 32$ ) or NVP DPP728 at 100 mg t.i.d. ( $n = 30$ ) or 150 mg b.i.d. ( $n = 30$ ) in subjects with type 2 diabetes (means  $\pm$  SEM).

years), duration of diabetes ( $3.6; 4.6 \pm 5.6$ ;  $0.2$ – $27$  years), BMI ( $27.2; 27.0 \pm 2.9$ ;  $21.3$ – $31.9$  kg/m<sup>2</sup>), HbA<sub>1c</sub> ( $7.2; 7.4 \pm 0.7$ ;  $6.3$ – $9.9\%$ ), FPG ( $8.1; 8.6 \pm 1.5$ ;  $7.2$ – $10.1$  mmol/l), or fasting insulin ( $80; 79 \pm 6$ ;  $36$ – $101$  pmol/l) did not differ significantly between the three study groups.

#### 24-h Glucose and insulin levels

The 24-h plasma glucose and insulin levels before and after 4 weeks' treatment in the three study groups are shown in Fig. 1. After treatment, both groups receiving NVP DPP728 displayed a significantly reduced mean 24-h glucose compared with those receiving placebo. The reduction in the 24-h mean glucose (difference from placebo) was  $-1.0$  mmol/l (95% CI  $-1.4$  to  $-0.7$  mmol/l;  $P < 0.001$ ) in the patients who had received 100 mg t.i.d. and  $-1.0$  mmol/l ( $-1.4$  to  $-0.6$  mmol/l;  $P < 0.001$ ) in those who had received 150 mg b.i.d.. Also, mean 24-h insulin levels were significantly reduced in both active treatment groups. In the patients receiving

100 mg t.i.d., the reduction compared with the placebo group was  $-26$  pmol/l ( $-46$  to  $-5$  pmol/l;  $P = 0.017$ ); in those receiving 150 mg b.i.d., the reduction was  $-26$  pmol/l ( $-47$  to  $-4$  pmol/l;  $P = 0.023$ ).

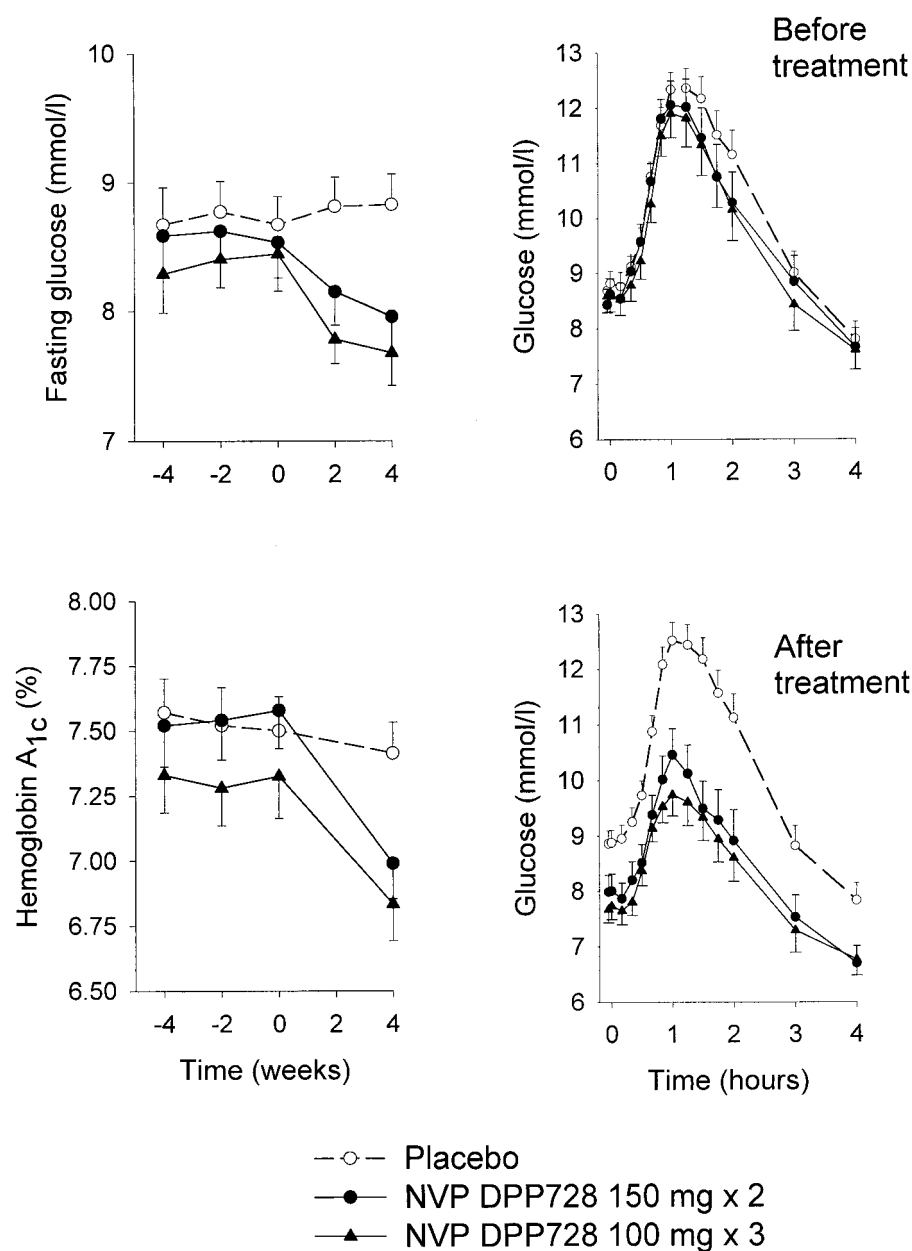
#### FPG and prandial glucose and insulin levels

FPG was significantly reduced over the 4-week period in both active treatment groups; the reduction (difference from placebo) was  $-1.0$  mmol/l in the 100 mg t.i.d. group (95% CI  $-1.4$  to  $-0.6$  mmol/l;  $P < 0.001$ ) and  $-0.7$  mmol/l in the 150 mg b.i.d. group ( $-1.2$  to  $-0.3$  mmol/l;  $P < 0.001$ ) (Table 1 and Fig. 2). There was also a significant difference between the groups in the number of patients achieving an FPG  $< 7$  mmol/l after treatment. Therefore, 35% of the subjects in the group treated with 100 mg t.i.d. and 37% in the group treated with 150 mg b.i.d. achieved an FPG  $< 7$  mmol/l after active treatment, versus only 3% in the

placebo group. Also, the prandial glucose excursion was reduced by NVP DPP728, the difference from placebo being  $-1.2$  mmol/l in the 100 mg t.i.d. group ( $-1.7$  to  $-0.7$  mmol/l;  $P < 0.001$ ) and  $-1.3$  mmol/l in the 150 mg b.i.d. group ( $-1.8$  to  $-0.7$  mmol/l;  $P < 0.001$ ) (Fig. 2). In contrast, fasting and postprandial insulin levels were not significantly altered (Table 1, Fig. 1). However, peak postprandial insulin divided by peak postprandial glucose (i.e., insulin-to-glucose excursion ratio) increased in the 150 mg b.i.d. group versus the placebo group ( $P = 0.038$ ) (Table 1).

#### HbA<sub>1c</sub>

Although it was not one of the efficacy parameters defined in the study protocol, because of the short treatment period, HbA<sub>1c</sub> was also reduced compared with placebo in both active treatment groups; the change from baseline (mean  $\pm$  SD) in the treatment groups was  $-0.1 \pm 0.3\%$  with placebo,  $-0.5 \pm 0.4\%$  with 100 mg



**Figure 2**—Fasting blood glucose and HbA<sub>1c</sub> values during the 4-week run-in period and after 4 weeks' treatment (left) and the 4-h glycemic response to breakfast ingestion before and after the 4-week treatment period with placebo (n = 32) or NVP DPP728 at 100 mg t.i.d. (n = 30) or 150 mg b.i.d. (n = 30) in subjects with type 2 diabetes (means ± SEM).

t.i.d., and  $-0.5 \pm 0.3\%$  with 150 mg b.i.d. (Fig. 2). The difference from placebo (Student's *t* test) was significant ( $P < 0.001$ ) for both active treatments. Because this analysis was not preplanned, these *P* values should, however, be regarded as descriptive.

**Lipids**

Except for a small but still significant reduction compared with placebo in total

cholesterol in the two active treatment groups and a similar reduction in VLDL cholesterol and triglycerides in the 100 mg t.i.d. treatment group, lipid levels did not change during the treatment period (Table 1).

**Safety and tolerability**

Body weight was not altered during the study period (Table 1). Treatment was well tolerated. The adverse events in the

active treatment groups are shown in Table 2. Four patients taking NVP DPP728 and one patient in the placebo group reported symptoms that could have indicated hypoglycemia, but only one of the patients given NVP DPP728 had a blood glucose level  $<3.3$  mmol/l. Of patients taking NVP DPP728, four experienced symptoms of nasopharyngitis and five experienced pruritus. These symptoms were short-lived and transient, despite continuation of therapy. Finally, one patient in the NVP DPP728 b.i.d. treatment group developed a transient nephrotic syndrome during the first week of active treatment. This patient, however, already had albuminuria during the run-in period. Treatment was discontinued in this patient.

**CONCLUSIONS**— This study provides the first evidence that pharmacological DPP IV inhibition is feasible for the treatment of type 2 diabetes in humans. The patients studied all had mild type 2 diabetes (HbA<sub>1c</sub> 7.4%) during treatment with diet and exercise only. HbA<sub>1c</sub> or FPG did not change during the 4-week run-in period or during the 4-week treatment in the placebo group, confirming that the diabetes in the patients studied was stable. Therefore, the marked improvement in glycemic control, as determined by the 24-h glucose profile, the fasting glucose levels, and the 4-h prandial glucose excursion during the 4-week treatment with NVP DPP728, is a clear effect of the treatment. We also found that there was no difference between a three-times-daily treatment schedule versus a twice-daily treatment schedule with NVP DPP728, indicating that either dosing regimen could probably be used with equal efficacy. Despite the short duration of the study period (4 weeks), a reduction in HbA<sub>1c</sub> levels by 0.6% was observed after treatment with NVP DPP728. Combined, these results encourage further development of DPP IV inhibition in the treatment of type 2 diabetes.

This study was not designed to establish the mechanisms underlying the beneficial effects of NVP DPP728 on the glycemic control in humans, which therefore remains to be established. Nevertheless, an increased insulin response to glucose might contribute, because the prandial insulin levels were not significantly altered in combination with re-



**Table 1—Effect of 4-week treatment with placebo or NVP DPP728 at 100 mg t.i.d. or 150 mg b.i.d. in subjects with type 2 diabetes on body weight, fasting and prandial glucose, and insulin and lipid levels**

		Placebo (n = 32)	NVP DPP728	
			100 mg t.i.d. (n = 30)	150 mg b.i.d. (n = 30)
Body weight (kg)	Baseline	82.6 ± 2.4	79.9 ± 2.0	77.9 ± 2.0
	Change	−0.2 ± 0.3	0.1 ± 0.3	−0.1 ± 0.3
24-h plasma glucose (mmol/l)	Baseline	9.2 ± 0.3	8.9 ± 0.3	8.8 ± 0.3
	Change	−0.1 ± 0.1	−1.1 ± 0.1*	−1.0 ± 0.1*
24-h plasma insulin (pmol/l)	Baseline	157 ± 12	157 ± 13	153 ± 15
	Change	16 ± 8	−9 ± 8†	−9 ± 8†
FPG (mmol/l)	Baseline	8.7 ± 0.2	8.5 ± 0.3	8.5 ± 0.3
	Change	0.1 ± 0.2	−0.9 ± 0.2*	−0.6 ± 0.2‡
Glucose excursion§ (mmol/l)	Baseline	4.1 ± 0.3	3.9 ± 0.2	4.1 ± 0.3
	Change	−0.1 ± 0.2	−1.2 ± 0.2*	−1.3 ± 0.2*
Prandial glucose   (mmol/l per h)	Baseline	6.0 ± 0.8	4.8 ± 0.7	5.5 ± 0.7
	Change	−0.0 ± 0.6	−2.8 ± 0.6*	−3.0 ± 0.6*
Fasting insulin (pmol/l)	Baseline	79 ± 6	81 ± 8	78 ± 7
	Change	4 ± 5	−1 ± 5	5 ± 0
Insulin-to-glucose excursion rate¶ (pmol/mmol)	Baseline	12.6 ± 0.9	16.2 ± 1.7	15.9 ± 2.8
	Change	1.7 ± 0.8	3.6 ± 2.0	7.4 ± 2.1†
Total cholesterol (mmol/l)	Baseline	5.8 ± 1.0	5.7 ± 0.8	5.5 ± 0.9
	Change	0.1 ± 0.1	−0.2 ± 0.17†	−0.2 ± 0.1†
HDL cholesterol (mmol/l)	Baseline	1.3 ± 0.5	1.3 ± 0.3	1.3 ± 0.3
	Change	0.01 ± 0.03	0.03 ± 0.03	0.02 ± 0.03
LDL cholesterol (mmol/l)	Baseline	3.7 ± 0.9	3.6 ± 0.8	3.5 ± 0.8
	Change	0.02 ± 0.09	−0.17 ± 0.08	−0.18 ± 0.09
VLDL cholesterol (mmol/l)	Baseline	0.35 ± 0.15	0.32 ± 0.16	0.32 ± 0.14
	Change	0.03 ± 0.02	−0.02 ± 0.02†	−0.01 ± 0.02
Triglycerides (mmol/l)	Baseline	1.7 ± 0.7	1.7 ± 1.1	1.6 ± 0.7
	Change	0.14 ± 0.09	−0.14 ± 0.09†	−0.09 ± 0.09

Data are means ± SEM. \* $P < 0.001$ ; † $P < 0.05$  versus placebo; ‡ $P < 0.05$ ; §glucose excursion = difference between maximum glucose in the 4-h postbreakfast period minus mean of prebreakfast glucose; ||prandial glucose = area under the 4-h plasma glucose curve after breakfast; ¶peak  $\Delta$  postprandial insulin divided by peak  $\Delta$  postprandial glucose after breakfast.

duced prandial glucose excursion after 4 weeks of treatment, which was also illustrated by the increased insulin-to-glucose excursion ratio by NVP DPP728 versus placebo. This could be exerted by GIP and GLP-1, which increase the  $\beta$ -cell sensitivity to glucose, because inhibition of DPP IV results in increased levels of these incretins (11). Other mechanisms, however, may also be contributing, because GLP-1 has been shown to delay gastric emptying and inhibit glucagon secretion (2–4), both of which would reduce plasma glucose levels. In addition, the significant reduction in fasting glucose suggests that mechanisms beyond the prandial period may also be playing a role, but further studies will be needed to define the exact mechanism or mechanisms by which NVP DPP728 and similar drugs achieve their clinical effects.

The dyslipidemia associated with type 2 diabetes has been shown to be im-

proved in conjunction with improved diabetic condition after treatment with GLP-1 (22). We found, however, only minimal changes in the lipid profile after the 4-week treatment with NVP DPP728. Further studies will be needed to elucidate the possible long-term effect of DPP-IV inhibition on lipid levels in type 2 diabetic patients.

Overall, NVP DPP728 was well tolerated in the patients. Four patients receiving active treatment exhibited symptoms suggestive of hypoglycemia, but these were generally not associated with low blood glucose values and therefore cannot be classified as true hypoglycemia. Hypoglycemia was confirmed by a blood glucose value  $< 3.3$  mmol/l in only one subject. This patient, however, had reported heavy use of alcohol the evening before the event, and a causal relation to NVP DPP728 is therefore doubtful. However, the occurrence of hypoglycemia af-

ter treatment with DPP IV inhibitors should be monitored carefully in future studies in view of a previous report that hypoglycemia can occur after administration of GLP-1 to fasted individuals (23), even though it is likely to be very rare due to the glucose dependency of the action of GLP-1 (1). A more important safety concern is that DPP IV inhibition will slow or completely prevent the degradation of  $> 20$  other bioactive peptides in addition to GLP-1 and GIP, of which insulin-like growth factor-1, neuropeptide Y, GLP-2, and substance P may be of interest for the treatment of type 2 diabetes (12). The occurrence of pruritus in five patients treated with NVP DPP728 might be explained by increased levels of other biologically active peptides apart from GLP-1 and GIP, such as substance P, which has been suggested to be associated with pruritus (24). However, in all of these five cases, the pruritus, localized mainly to

Table 2—Adverse events recorded during the 4-week treatment period with NVP DPP728 at 100 mg t.i.d. or 150 mg b.i.d. or with placebo in subjects with type 2 diabetes

	NVP DPP728			Placebo (N = 32)
	100 mg t.i.d. (n = 30)	150 mg b.i.d. (n = 31)	Total active (n = 61)	
Pruritus	2	3	5	0
Diarrhea	3	1	4	1
Nasopharyngitis	1	3	4	0
Hypoglycemia	1	3	4	1
Dizziness	0	4	4	2
Headache	0	3	3	1
Vertigo	2	0	2	0
Nausea	1	1	2	0
Depression	1	1	2	0
Urinary frequency	1	1	2	1
Night sweats	1	1	2	0
Constipation	1	0	1	0
Hiatal hernia	0	1	1	0
Weakness	0	1	1	0
Stye	1	0	1	0
Decreased appetite	0	1	1	1
Myalgia	1	0	1	0
Hypertonia	0	1	1	0
Paresthesia	0	1	1	0
Nephrotic syndrome	0	1	1	0
Hoarseness	0	1	1	0
Allergic rhinitis	1	0	1	0
Increased sweating	0	1	1	0
Tremor	0	1	1	0

Data are n. All events recorded in the active treatment groups are shown. Eight further adverse events occurring only in the placebo arm have been omitted.

the palms, was transient and disappeared within 48 h; treatment was not discontinued in any of these patients. To what extent peptides other than GLP-1 and GIP contribute to the improved metabolic control or side effects during treatment with NVP DPP728 remains to be established.

The present study in human subjects with type 2 diabetes shows that DPP IV inhibition as monotherapy is feasible as a treatment for type 2 diabetes in patients at a relatively early stage in the disease. Because the study had a duration of only 4 weeks, further long-term studies will be needed to examine the long-term effects of DPP IV inhibition as well as to fully understand the mechanism of the effects and to define the use of this approach in patients with more advanced diabetes and in combination with other antidiabetic drugs.

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