# Treatment With the Human Once-Weekly Glucagon-Like Peptide-1 Analog Taspoglutide in Combination With Metformin Improves Glycemic Control and Lowers Body Weight in Patients With Type 2 Diabetes Inadequately Controlled With Metformin Alone

## A double-blind placebo-controlled study

MICHAEL A. NAUCK, MD[1]
ROBERT E. RATNER, MD[2]
CHRISTOPH KAPITZA, MD[3]
RACHELE BERRIA, MD[4]
MARK BOLDRIN[4]
RAFFAELLA BALENA, MD, PHD[5]

**OBJECTIVE** — To evaluate the efficacy and safety of taspoglutide (R1583/BIM51077), a human once-weekly glucagon-like peptide-1 analog, in patients with type 2 diabetes inadequately controlled with metformin.

**RESEARCH DESIGN AND METHODS** — Type 2 diabetic ($n$ = 306) patients who failed to obtain glycemic control (A1C 7–9.5%) despite 1,500 mg metformin daily were randomly assigned to 8 weeks of double-blind subcutaneous treatment with placebo or taspoglutide, either 5, 10, or 20 mg once weekly or 10 or 20 mg once every 2 weeks, and followed for 4 additional weeks. All patients received their previously established dose of metformin throughout the study. Glycemic control was assessed by change in A1C (percent) from baseline.

**RESULTS** — Significantly greater ($P < 0.0001$) reductions in A1C from a mean ± SD baseline of 7.9 ± 0.7% were observed in all taspoglutide groups compared with placebo after 8 weeks of treatment: –1.0 ± 0.1% (5 mg once weekly), –1.2 ± 0.1% (10 mg once weekly), –1.2 ± 0.1% (20 mg once weekly), –0.9 ± 0.1% (10 mg Q2W), and –1.0 ± 0.1% (20 mg Q2W) vs. –0.2 ± 0.1% with placebo. After 8 weeks, body weight loss was significantly greater in the 10 mg (–2.1 ± 0.3 kg, $P = 0.0035$ vs. placebo) and 20 mg (–2.8 ± 0.3 kg, $P < 0.0001$) once-weekly groups and the 20 mg once every 2 weeks (–1.9 ± 0.3 kg, $P = 0.0083$) group than with placebo (–0.8 ± 0.3 kg). The most common adverse event was dose-dependent, transient, mild-to-moderate nausea; the incidence of hypoglycemia was very low.

**CONCLUSIONS** — Taspoglutide used in combination with metformin significantly improves fasting and postprandial glucose control and induces weight loss, with a favorable tolerability profile.

*Diabetes Care* **32:1237–1243, 2009**

From the [1]Diabeteszentrum, Bad Lauterberg im Harz, Germany; the [2]Medstar Research Institute, Hyattsville, Maryland; the [3]Profil Institute, Neuss, Germany; the [4]Roche Laboratories, Nutley, New Jersey; and [5]Hoffmann-La Roche, Basel, Switzerland.
Corresponding author: Raffaella Balena, raffaella.balena@roche.com.
Received 30 October 2008 and accepted 23 March 2009.
Published ahead of print at http://care.diabetesjournals.org on 14 April 2009. DOI: 10.2337/dc08-1961. Clinical trial reg. no. NCT00423501, clinicaltrials.gov.


Approximately 50% of patients with type 2 diabetes fail to achieve the American Diabetes Association–recommended target A1C level of 7% (1), indicating the need for additional treatment options. A new class of antidiabetic agents is the glucagon-like peptide-1 (GLP-1) receptor agonists, which act through multiple mechanisms (2), similar to the incretin hormone GLP-1 (3–6). Taspoglutide (R1583/BIM51077) is a human GLP-1 analog with a pharmacokinetic profile suitable for weekly subcutaneous administration, through two amino acid substitutions in positions 8 and 35 with aminoisobutyric acid and a sustained release formulation. Taspoglutide has 93% homology with endogenous GLP-1 and comparable in vitro potency. Taspoglutide is resistant to degradation by dipeptidyl peptidase-4 and other proteases, resulting in a 12-fold increase in stability over the native GLP-1 when incubated in rat serum (7). Taspoglutide has been shown to enhance the rate of glucose-induced insulin secretion from isolated, cultured rat islets and the perfused ZDF rat pancreas (7,8). Furthermore, in vivo studies with taspoglutide in Sprague-Dawley rats and diabetic *db/db* mice have shown a dose-related enhancement of glucose-dependent insulin release, which lowered blood glucose in the *db/db* mouse model of type 2 diabetes (9). Thus, the biological activity of taspoglutide is similar to that of native GLP-1, with the added benefit of a prolonged action profile.

The sustained release formulation of taspoglutide showed a release profile up to 26 days in dogs, making it an attractive candidate for human investigation (10). Of note, in patients with type 2 diabetes

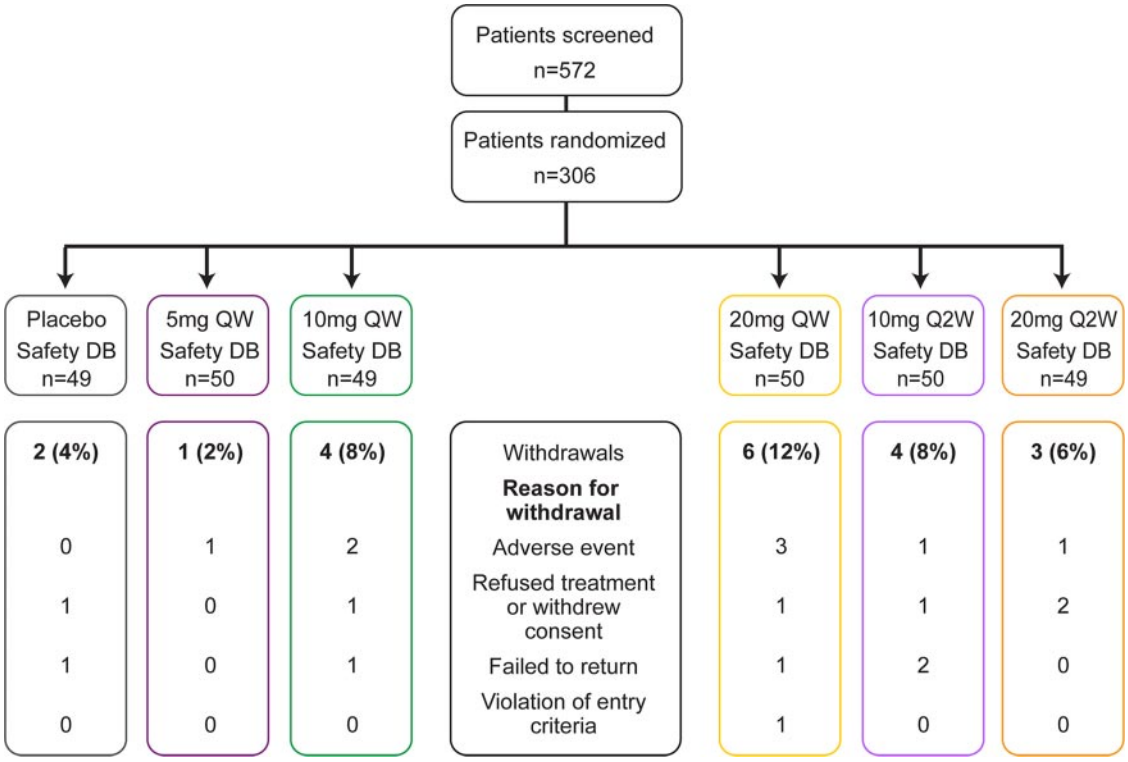


**Figure 1—***Patient flow diagram. DB, database; QW, once weekly; Q2W, once every 2 weeks.*

not well controlled with metformin, a single 30-mg dose of the same 10% formulation of taspoglutide improved fasting and postprandial glucose for up to 14 days in nearly all subjects treated (11). The aim of the current study was to evaluate the efficacy, safety, and tolerability of a range of doses of taspoglutide, given either once weekly or once every 2 weeks, in patients with type 2 diabetes inadequately controlled with metformin alone.

## RESEARCH DESIGN AND METHODS

— This was a randomized, double-blind, parallel group, placebo-controlled, multicenter, phase 2b clinical study, consisting of a screening (up to 3 weeks), a treatment (8 weeks), and a follow-up period (4 weeks). The study was conducted in accordance with guidelines of all the institutional review boards, with the principles of the Declaration of Helsinki, and with the laws and regulations of the countries where the research was conducted.

The primary objectives of this study were to determine the efficacy, safety, and tolerability of multiple doses and regimens of taspoglutide, when added to metformin therapy. Secondary objectives were to compare the effects of taspoglutide versus placebo on body weight and additional parameters of glycemic and lipid control.

The study population comprised men and postmenopausal or surgically sterilized women with type 2 diabetes, treated with a daily dose of metformin (≥1,500 mg/day) monotherapy for at least 3 months before screening. Key inclusion criteria at screening were age 18–75 years, A1C between 7.0 and 9.5% (inclusive), fasting plasma glucose (FPG) >126 mg/dl (7.0 mmol/l) and ≤240 mg/dl (13.3 mmol/l), BMI >25 and ≤45 kg/m$^2$, and stable weight (±10%) for at least 3 months before screening.

Key exclusion criteria were history of type 1 diabetes; treatment with any antihyperglycemic medication other than metformin during the prior 3 months (except insulin use in acute situations or during surgery for up to 7 days); previous exposure to GLP-1, GLP-1 analogs, or exenatide; weight-lowering medications in the prior 3 months; impaired liver or kidney function, clinically significant gastrointestinal disease, or uncontrolled hypertension at screening; or a stroke or myocardial infarction within 6 months before screening.

Patients were randomly assigned by a central randomization system (interactive voice response system) to either placebo once weekly or one of the following doses and regimens of taspoglutide: 5 mg once weekly; 10 mg once weekly; 20 mg once weekly; 10 mg once every 2 weeks; or 20 mg once every 2 weeks. Patients were asked to follow their prestudy diet and exercise plan and metformin regimen throughout the study. Patients reported to the study site for weekly visits. At each visit the lyophilized peptide was reconstituted at the study site with the diluent (zinc chloride solution). Patients in the placebo group received 0.9% NaCl. Study medication was administered by personnel not involved with the preparation of study drug to maintain the blinding and injected subcutaneously in the abdomen in a different site each time, according to a given scheme.

Patients measured their fasting blood glucose levels using a glucometer (ACCU-CHEK) while at home in the morning at least once weekly or more frequently if they felt unwell or had any symptoms of hypo- or hyperglycemia or if requested by local guidelines. A subset of patients ($n$ = 118, ~20 per group) consumed a mixed-meal test with Ensure (350 kcal; 50 g carbohydrate, 13 g protein, and 11 g fat) at baseline and after 8 weeks of treatment. Central laboratories (Covance, Geneva, Switzerland; Harrogate, U.K.; Indianapolis, IN) were

**Table 1—*Baseline demographics, disease characteristics, and changes after the 8-week treatment***

| | Once weekly | | | | Once every 2 weeks | |
|---|---|---|---|---|---|---|
| | Placebo | 5 mg | 10 mg | 20 mg | 10 mg | 20 mg |
| *n* | 49* | 50* | 49* | 50* | 50* | 49* |
| Sex (female/male) | 57/43 | 48/52 | 39/61 | 64/36 | 48/52 | 55/45 |
| Age (years) | 56 ± 6 | 57 ± 7 | 56 ± 8 | 56 ± 8 | 53 ± 11 | 56 ± 7 |
| BMI (kg/m$^2$) | 31.8 ± 4.9 | 33.2 ± 5.3 | 32.6 ± 4.7 | 32.4 ± 5.2 | 33.1 ± 5.1 | 33.2 ± 5.1 |
| Duration of diabetes (years) | 5 ± 4 | 6 ± 6 | 5 ± 5 | 5 ± 4 | 5 ± 4 | 6 ± 5 |
| Metformin dose (mg/day) | 2,019 ± 63 | 1,897 ± 51 | 1,888 ± 53 | 1,998 ± 57 | 2,011 ± 68 | 1,934 ± 56 |
| Systolic blood pressure (mmHg) | 129 ± 13 | 127 ± 13 | 128 ± 14 | 131 ± 14 | 132 ± 13 | 132 ± 13 |
| Diastolic blood pressure (mmHg) | 77 ± 9 | 78 ± 8 | 78 ± 8 | 80 ± 9 | 81 ± 8 | 81 ± 7 |
| A1C (%) | 8.0 ± 0.1 | 7.9 ± 0.1 | 7.9 ± 0.1 | 7.8 ± 0.1 | 8.0 ± 0.1 | 7.9 ± 0.1 |
| Δ | −0.2 | −1.0 | −1.2 | −1.2 | −0.9 | −1.0 |
| *P* | | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| Fructosamine (μmol/l) | 310 ± 6 | 310 ± 6 | 300 ± 6 | 292 ± 6 | 309 ± 6− | 290 ± 6 |
| Δ | −5 ± 4 | −44 ± 4 | −51 ± 4 | −48 ± 4 | −35 ± 4 | −40 ± 4 |
| *P* | | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| Fasting glucose (mg/dl) | 173 ± 5 | 187 ± 5 | 175 ± 5 | 164 ± 5 | 175 ± 5 | 171 ± 5 |
| Δ | −14 | −33 | −45 | −45 | −22 | −26 |
| *P* | | 0.0002 | <0.0001 | <0.0001 | 0.13 | 0.02 |
| Proinsulin-to-insulin ratio | 0.590 ± 0.032 | 0.579 ± 0.032 | 0.594 ± 0.032 | 0.550 ± 0.032 | 0.606 ± 0.031 | 0.613 ± 0.032 |
| Δ | 0.002 | −0.079 | −0.120 | −0.166 | −0.091 | −0.055 |
| *P* | | 0.0738 | 0.0076 | 0.0003 | 0.0372 | 0.2054 |
| Lipid parameters | | | | | | |
| Total cholesterol (mg/dl) | 211 ± 6 | 201 ± 6 | 195 ± 6 | 194 ± 6 | 196 ± 6 | 200 ± 6 |
| Δ | +7 | −8 | −12 | −9 | −7 | −12 |
| LDL cholesterol (mg/dl) | 127 ± 5 | 117 ± 5 | 116 ± 5 | 113 ± 5 | 114 ± 5 | 114 ± 5 |
| Δ | +5 | −3 | −8 | +1 | −0 | −6 |
| HDL cholesterol (mg/dl) | 47 ± 2 | 45 ± 2 | 45 ± 2 | 45 ± 2 | 44 ± 2 | 43 ± 2 |
| Δ | +0 | −1 | −2 | −1 | −1 | 0 |
| Triglycerides (mg/dl) | 224 ± 27 | 220 ± 27 | 188 ± 28 | 199 ± 27 | 220 ± 27 | 256 ± 27 |
| Δ | +9 | −22 | −26 | −48 | −28 | −27 |

Data are means ± SD for baseline characteristics and mean ± SEM for disease characteristics.

used to measure all laboratory parameters including drug concentrations of taspoglutide.

### Study end points

The primary efficacy end point was the change from baseline in A1C (percent), assessed 1 week after 8 consecutive weeks of treatment. Secondary end points included the percentage of patients achieving the treatment goals of A1C <7% and <6.5% and the absolute changes from baseline in FPG, body weight, fructosamine, C-peptide, fasting insulin, proinsulin, proinsulin-to-insulin molar ratio, fasting glucagon, and lipid parameters. Safety assessments included vital signs, physical examination, clinical laboratory tests, electrocardiogram, local tolerance at the injection site, anti-taspoglutide antibodies, and adverse event reporting.

### Statistical methods

Randomization was stratified based on severity of disease (A1C <8% and ≥8%) and participation in the meal test. The sample size of 264 patients (44 patients per group) was calculated to provide 90% power to detect a 1% difference in the change of A1C from baseline in the individual comparison of all five active dose groups versus placebo, assuming a common SD of 1.2%, two-sided $\alpha = 0.05$, and 20% dropout rate. ANCOVA with fixed-effect terms for region, treatment, and baseline A1C as covariates was used to assess possible differences in the changes in A1C among the treatment groups.

The intent-to-treat population consisted of all patients who were randomly assigned, received at least one dose of study medication, and had a baseline and at least one postbaseline A1C assessment. Missing data were handled using the last observation carried forward method. The safety population consisted of all patients who received at least one dose of study medication.

## RESULTS

### Baseline demographics and clinical characteristics

Of 572 patients screened, 306 of them were randomly assigned into six treatment arms. Of the 306 randomly assigned patients, 297 received at least one dose of study medication and were included in the safety database (Fig. 1). There were no clinically meaningful differences in baseline demographic, anthropometric, or disease characteristics among treatment groups (Table 1). Patients were treated with common medications for a diabetic population including ACE inhibitors, thiazide diuretics, angiotensin receptor blockers, statins, and β-blockers (data not shown).

### Pharmacokinetics

The taspoglutide mean plasma concentrations, based on the trough levels between weeks 3 and 8, were 41.2, 77.5, and 96.6 pmol/l for the 5, 10, and 20 mg once-weekly groups and 29.7 and 51.8 pmol/l in

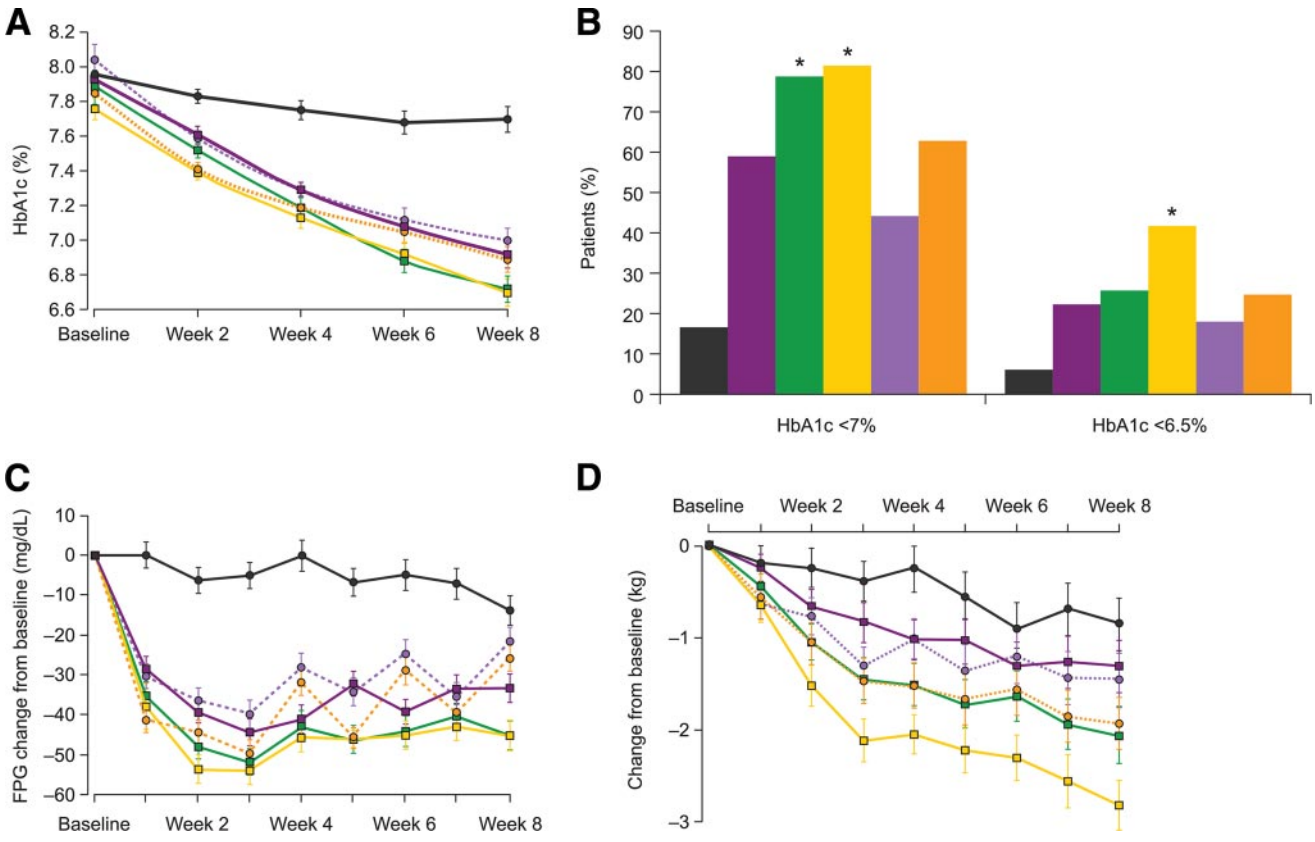


**Figure 2—***Effects of taspoglutide and placebo on A1C. All taspoglutide doses were statistically significant* (P < *0.0001)* (A). *Percentage of patients achieving target A1C,* *P < *0.0001 vs. placebo* (B); *fasting plasma glucose* (C); *and body weight* (D). *Black, placebo; magenta, 5 mg once weekly; green, 10 mg once weekly; yellow, 20 mg once weekly; purple, 10 mg once every 2 weeks; orange, 20 mg once every 2 weeks.*

the 10 and 20 mg once every 2 weeks group.

## Glycemic control

After 8 weeks of treatment, the reductions in A1C from baseline were statistically significant compared with placebo in all groups that received taspoglutide ($P < 0.0001$) (Fig. 2*A*, Table 1). Reductions in A1C were apparent after 1 week of treatment with taspoglutide, with the greatest reductions observed in the 10 and 20 mg once weekly dose groups at the end of treatment. As expected, patients with higher baseline A1C values (≥8.0%) showed greater reductions in all treatment groups, including placebo; the change from baseline was –1.3%, –1.5%, and –1.4% in the 5, 10, and 20 mg once-weekly groups and –1.2% and –1.3% in the 10 and 20 mg once every 2 weeks group vs. –0.3% in the placebo group.

More than 44% reached a target A1C <7% in all active doses and regimens, with 79 and 81% achieving this goal with 10 and 20 mg taspoglutide once weekly, respectively, versus 17% with placebo (Fig. 2*B*). Serum fructosamine significantly ($P < 0.0001$) decreased in all treatment groups, consistent with the A1C data (Table 1).

Reductions in FPG were apparent within 1 week after initiation of treatment. At the end of the treatment period, weekly administration of taspoglutide resulted in a statistically significant decrease of FPG by 33 mg/dl ($P = 0.0002$) with 5 mg and 45 mg/dl ($P < 0.0001$) with both 10 and 20 mg doses versus a decrease of 14 mg/dl in the placebo group (Fig. 2*C*; Table 1). When only four doses of taspoglutide were administered every 2 weeks (i.e., 10 and 20 mg taspoglutide once every 2 weeks), FPG rebounded during the second week after drug administration, as shown in Fig. 2*C*. Nevertheless, the decrease in FPG (–26 mg/dl) in the 20 mg once every 2 weeks group was statistically significant (Table 1).

## β-Cell function and glucagon

Mean fasting C-peptide concentrations ranged from 0.8 to 1.0 nmol/l at baseline and increased in all treatment arms after 8 weeks of treatment. All treatment arms showed an increase from baseline, with the 20 mg once weekly group showing a trend ($P = 0.069$) and the 10 mg once every 2 weeks group achieving statistical significance ($P = 0.009$) after 8 weeks of treatment.

The fasting proinsulin-to-insulin molar ratio ranged between 0.5 and 0.6 at baseline and decreased in all treatment arms (Table 1). A placebo-corrected, statistically significant decline from baseline could be shown for the 10 mg ($P = 0.008$) and 20 mg ($P = 0.0003$) once-weekly groups as well as for the 10 mg once every 2 weeks ($P = 0.037$) group. The mean fasting glucagon concentration ranged between 6.9 and 7.8 pg/ml at baseline and showed a decrease in all treatment groups without reaching statistical significance (data not shown).

## Lipid profile

Baseline levels of fasting lipid parameters and changes after 8 weeks are shown in Table 1. All active treatment groups showed a decline in triglycerides after the treatment, compared with a slight increase in the placebo control group. Placebo-corrected changes ranged from –32

**Table 2—*Most frequently reported adverse events***

| | Once weekly | | | | Once every 2 weeks | |
|---|---|---|---|---|---|---|
| | Placebo | 5 mg | 10 mg | 20 mg | 10 mg | 20 mg |
| *n* | 49* | 50* | 49* | 50* | 50* | 49* |
| Nausea | 3 (6) | 11 (22) | 12 (24) | 26 (52) | 16 (32) | 20 (10) |
| Diarrhea | 4 (8) | 4 (8) | 5 (10) | 5 (10) | 8 (16) | 9 (18) |
| Vomiting | 2 (4) | 2 (4) | 2 (4) | 11 (22) | 6 (12) | 12 (24) |
| Headache | 3 (6) | 1 (2) | 3 (6) | 6 (12) | 7 (14) | 6 (12) |
| Decreased appetite | — | — | 5 (10) | 3 (6) | 4 (8) | 3 (6) |
| Dyspepsia | — | — | 4 (8) | 6 (12) | 3 (6) | 2 (4) |
| Abdominal distension | — | — | 2 (4) | 2 (4) | 3 (6) | 6 (12) |

Data are *n* (%). *All patients who received at least one dose of study drug treatment ($n = 297$) were included in the safety database.

mg/dl in the 5 mg once weekly group to a maximum decrease of –58 mg/dl in the 20 mg once weekly group.

Placebo-corrected changes in total cholesterol levels varied from –15 to –20 mg/dl. Placebo-corrected changes in LDL cholesterol levels ranged from –4 to –13 mg/dl, with no clear dose response. There was a trend for a minimal decrease of HDL cholesterol levels during this treatment period.

### Body weight

Body weight decreased progressively and dose dependently throughout the 8-week treatment period, with clinically meaningful and statistically significant reductions in the 10 mg once weekly (–2.1 ± 0.3 kg, $P = 0.0035$), 20 mg once weekly (–2.8 ± 0.3 kg, $P < 0.0001$), and 20 mg once every 2 weeks (–1.9 ± 0.3 kg, $P = 0.0083$) groups compared with the placebo group (–0.8 ± 0.3 kg) (Fig. 2*D*).

### Postprandial glucose and insulin

After treatment with taspoglutide, the median percent decrease from baseline in plasma glucose 120 min after a mixed meal was 21.6, 22.0, and 18% in the 5, 10, and 20 mg once-weekly groups and 12.0 and 5.5% in the 10 and 20 mg once every 2 weeks groups vs. 10.5% in the placebo group (complete postprandial glucose data are shown in supplementary Table 1, available in an online appendix at http://care.diabetesjournals.org/cgi/content/full/dc08-1961/DC1). Furthermore, the median percent change in plasma insulin levels at 120 min was +22.2, +28.5, and +44.9% in the 5, 10, and 20 mg once-weekly groups and –0.6 and –13% in the 10 and 20 mg once every 2 weeks group vs. –15.3% in the placebo group.

### Safety and tolerability

Table 2 summarizes the most frequent adverse events. Nausea and vomiting tended to occur during the first day after study drug administration, was associated with peak plasma drug concentration, and resolved within 1 day. Subsequent administrations of taspoglutide were less likely to induce nausea. The highest dose of taspoglutide (20 mg once weekly) was associated with nausea and vomiting in 52 and 22% of patients, respectively.

Hypoglycemia occurred infrequently (only seven events in six patients, two of which were asymptomatic). No cases of severe hypoglycemia occurred in the taspoglutide-treated patients. No cases of pancreatitis were identified.

Six patients experienced serious adverse events, including two in the placebo group, all considered by the investigators to be unrelated to the study drug. These were perineal fibroma and otitis media in the placebo group and colonic polyp, wrist fracture, coronary artery occlusion, and unstable angina in the treated groups. The last two led to withdrawal from the study. Eight patients discontinued prematurely because of adverse events. These were nausea ($n = 3$, one patient in the 10 mg once weekly and two in the 20 mg once weekly groups), vomiting ($n = 1$), hyperglycemia ($n = 1$), hepatic cirrhosis ($n = 1$), unstable angina ($n = 1$), and coronary artery occlusion ($n = 1$). Hepatic cirrhosis, unstable angina, and coronary artery occlusion were all deemed by the investigators to be unrelated to treatment. Mild and moderate injection site reactions were observed, which did not result in treatment discontinuation. There were no clinically relevant abnormalities in scheduled electrocardiograms, vital signs (including heart rate), or any laboratory parameters after treatment with taspoglutide.

**CONCLUSIONS** — This study demonstrates that taspoglutide in patients with type 2 diabetes inadequately controlled with metformin produced statistically significant and clinically meaningful improvements in glycemic control in all treatment groups, compared with placebo. This magnitude of improvement in glycemic control observed with taspoglutide after 8 weeks (–1.1% decrease in A1C from a baseline of 7.9 ± 0.7%) compares favorably with that seen with other GLP-1 receptor agonists, such as exenatide (12–14) and liraglutide (15). Both fasting and postprandial glucose levels were reduced by taspoglutide. Improvement in glucose control during postprandial as well as fasting periods is important for reaching goal A1C (16). Our data indicate that four of five patients treated with 10 and 20 mg taspoglutide once weekly achieved the treatment target A1C <7% recommended by the American Diabetes Association (17).

In addition, in type 2 diabetic patients in whom metformin monotherapy had failed, taspoglutide treatment produced progressive, dose-dependent weight loss with no evidence of a plateau after four or eight injections at 8 weeks. The weight loss is consistent with published clinical trial data with other GLP-1 receptor agonists (12–15). It is notable that the observed weight loss occurred without any specific diet or weight management regimen.

The beneficial effects of taspoglutide on glycemic control and body weight loss were accompanied by a meaningful improvement of the proinsulin-to-insulin molar ratio. An elevation of this ratio is predictive of subsequent development of type 2 diabetes (18), and its decrease is considered a sign of improved β-cell function (19). In addition, the observed increase in postprandial insulin coupled with reduced postprandial glucose after taspoglutide treatment is suggestive of enhanced glucose-dependent insulin secretion. These results are consistent with the mechanism of action of the class of incretin-based treatments (6,12,20).

Type 2 diabetes is typically accompanied by cardiovascular and metabolic disorders, including hypertension, dyslipidemia, and obesity (21). Despite recent advances in therapy, diabetes is still associated with excess cardiovascular morbidity and mortality (21,22), medi-

ated in part by exacerbation of risk factors, including obesity. The salutary effects of 8 weeks of taspoglutide treatment on glycemic control, body weight, and lipid profile may improve the overall metabolic and cardiovascular risk profile of type 2 diabetic patients. However, further studies of longer duration, involving a large number of patients, will be required to fully assess long-term cardiometabolic effects of taspoglutide.

Consistent with the available data on other GLP-1 receptor agonists, the most frequent adverse event seen with taspoglutide treatment was dose-dependent, transient, mild-to-moderate nausea (12). However, the majority of gastrointestinal events were transient and resolved spontaneously without sequelae. Moreover, it should be noted that the present study was performed with fixed doses. There is evidence with both exenatide (23) and liraglutide (15) that gradual and progressive dose escalation can reduce the incidence of nausea (these adverse events). To reduce the incidence of gastrointestinal events, an uptitration scheme has been included in the ongoing phase 3 program.

In summary, taspoglutide, given weekly or every 2 weeks in combination with metformin, resulted in significant improvements in glycemic control and weight loss after four to eight injections and was well tolerated in the vast majority of patients. Thus, taspoglutide (10 and 20 mg weekly) appears to offer the benefits of a weekly GLP-1 analog: potent glycemic control, weight loss, and a low risk of hypoglycemia.

**Acknowledgments**— This trial was supported by F. Hoffmann-La Roche, Basel, Switzerland. M.A.N. and R.E.R. have received consulting and advisory board honoraria from Roche as well as from other pharmaceutical companies developing incretin-based antidiabetic medications whose products may be perceived as being competitive to taspoglutide. No other potential conflicts of interest relevant to this article were reported.

Parts of this study were presented in abstract form at the 68th Scientific Sessions of the American Diabetes Association, San Francisco, California, 6–10 June 2008 (Abstract 108-OR) and at the 44th Annual Meeting of the European Association for Study of Diabetes, Rome, Italy, 8–11 September 2008 (Diabetologia 51 [Suppl. 1]: Abstract 871).

We thank the Taspoglutide BC20688 Clinical Study Group (a complete list of the members can be found in an online appendix, available at http://care.diabetesjournals.org/cgi/content/full/dc08-1961/DC1) for their assistance in the conduct, reporting, and quality control of the study, as well as the patients who volunteered to participate in the study. We also thank F. Leigh from Cheshire, U.K., for her assistance in the editing and formatting of this manuscript.

**References**

1. Resnick HE, Foster GL, Bardsley J, Ratner RE. Achievement of American Diabetes Association clinical practice recommendations among U.S. adults with diabetes, 1999–2002: the National Health and Nutrition Examination Survey. Diabetes Care 2006;29:531–537
2. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet 2006; 368:1696–1705
3. Nauck MA, Bartels E, Orskov C, Ebert R, Creutzfeldt W. Additive insulinotropic effects of exogenous synthetic human gastric inhibitory polypeptide and glucagon-like peptide-1-(7-36) amide infused at near-physiological insulinotropic hormone and glucose concentrations. J Clin Endocrinol Metab 1993;76:912–917
4. Näslund E, Bogefors J, Skogar S, Grybäck P, Jacobsson H, Holst JJ, Hellström PM. GLP-1 slows solid gastric emptying and inhibits insulin, glucagon, and PYY release in humans. Am J Physiol 1999;277: R910–R906
5. Gutzwiller JP, Drewe J, Göke B, Schmidt H, Rohrer B, Lareida J, Beglinger C. Glucagon-like peptide-1 promotes satiety and reduces food intake in patients with diabetes mellitus type 2. Am J Physiol 1999;276:R1541–R1544
6. Holst JJ, Deacon CF, Vilsbøll T, Krarup T, Madsbad S. Glucagon-like peptide-1, glucose homeostasis and diabetes. Trends Mol Med 2008;14:161–168
7. Woon CW, Taylor JE, Dong JZ, Shen Y, Skinner S, Carlile L, Sullivan T, Nolan AL, Morgan BA, Cawthorne MA, Culler M. BIM 51077, a stable glucagon-like peptide-1 (GLP-1) analogue with preserved gluco-incretin property in vitro (Abstract P1-359). In *Proceedings of the Endocrine Society Meeting, Denver, CO, 2001*. Chevy Chase, MD, The Endocrine Society
8. Wargent E, Nolan AL, Shen Y, Dong J, Taylor JE, Culler M, Morgan B, Woon CW, Cawthorne MA. Insulin secretagogue activity in vitro and in perfused pancreas of dipeptidase IV resistant GLP-1 analogs (Abstract). Diabetologia 2000;44 (Suppl. 1):A532
9. Culler MD, Carlile L, Sullivan T, Taylor JA, Sennitt M, Nolan A, Stocker C, Cawthorne MA, Dong J, Shen Y, Jackson S, Woon C. BIM-51077, a novel glucagon-like peptide-1 (GLP-1) analog with enhanced in vivo efficacy (Abstract P1-360). *Proceedings of the Endocrine Society Meeting, Denver, CO, 2001*. Chevy Chase, MD, The Endocrine Society
10. Ramis J, Menargues A, Allue JA, Peraire C, Cordero JA, Cherif-Cheikh R. Pharmacokinetic profile of a SRF formulation of BIM51077, a novel GLP-1 analog, in the beagle dog (Abstract). Diabetes 2006;55 (Suppl. 1):AP-547
11. Kapitza C, Klein O, Obach R, Birman P, Jallet K, Balena R. Long acting human GLP-1 analogue R1583: safety, pharmacokinetic and pharmacodynamic properties after a single administration in subjects with type 2 diabetes (Abstract). Diabetes 2008;57 (Suppl. 1):506-P
12. DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. Diabetes Care 2005;28:1092–1100
13. Buse JB, Henry RR, Han J, Kim DD, Fineman MS, Baron AD, Exenatide-113 Clinical Study Group. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. Diabetes Care 2004; 11:2628–2635
14. Kendall DM, Riddle MC, Rosenstock J, Zhuang D, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. Diabetes Care 28:1083–1091, 2005
15. Nauck M, Frid A, Hermansen K, Shah NS, Tankova T, Mitha IH, Zdravkovic M, Düring M, Matthews DR, LEAD-2 Study Group. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (Liraglutide Effect and Action in Diabetes)-2 study. Diabetes Care 2009;32:84–90
16. Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of A1C. Diabetes Care 2003;26:881–885
17. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, Zinman B. Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: update regarding thiazolidinediones: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2008;51:173–175
18. Nijpels G, Popp-Snijders C, Kostense PJ, Bouter LM, Heine RJ. Fasting proinsulin and 2-h post-load glucose levels predict the conversion to NIDDM in subjects with impaired glucose tolerance: the Hoorn Study. Diabetologia 1996;39:113–118

19. Tura A, Pacini G, Kautzky-Willer A, Ludvik B, Prager R, Thomaseth K. Basal and dynamic proinsulin-insulin relationship to assess β-cell function during OGTT in metabolic disorders. Am J Physiol Endocrinol Metab 2003;285:E155–E162
20. Charbonnel B, Karasik A, Liu J, Wu M, Meininger G, Sitagliptin Study 020 Group: Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone. Diabetes Care 2006;29:2638–2643
21. Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH Jr, Probstfield JL, Simons-Morton DG, Friedewald WT, Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008; 358:2545–2559
22. Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998;339: 229–234
23. Fineman MS, Shen LZ, Taylor K, Kim DD, Baron AD. Effectiveness of progressive dose-escalation of exenatide (exendin-4) in reducing dose-limiting side effects in patients with type 2 diabetes. Diabetes Metab Res Rev 2004;20:411–417