

# Safety and Efficacy of Repaglinide in Type 2 Diabetic Patients With and Without Impaired Renal Function

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**OBJECTIVE** — To evaluate the influence of renal impairment on the safety and efficacy of repaglinide in type 2 diabetic patients.

**RESEARCH DESIGN AND METHODS** — This multinational, open-label study comprised a 6-week run-in period, continuing prestudy antidiabetic medication, followed by a titration period (1–4 weeks) and a 3-month maintenance period. Patients with normal renal function ( $n = 151$ ) and various degrees of renal impairment ( $n = 130$ ) were treated with repaglinide (maximal dose of 4 mg, three times daily). Safety and efficacy assessments were performed at baseline (end of run-in) and at the end of study treatment.

**RESULTS** — The type and severity of adverse events during repaglinide treatment were similar to the run-in period. The number of patients with adverse events was not significantly related to renal function during run-in or repaglinide treatment. Percentage of patients with hypoglycemic episodes increased significantly ( $P = 0.007$ ) with increasing severity of renal impairment during run-in but not during repaglinide treatment ( $P = 0.074$ ). Metabolic control ( $HbA_{1c}$  and fasting blood glucose) with repaglinide was unchanged from that on previous antidiabetic medication. Final repaglinide dose tended to be lower for patients with severe and extreme renal impairment than for patients with less severe renal impairment or normal renal function ( $P = 0.032$ ).

**CONCLUSIONS** — Repaglinide has a good safety and efficacy profile in type 2 diabetic patients complicated by renal impairment and is an appropriate treatment choice, even for individuals with more severe degrees of renal impairment.

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Repaglinide, a nonsulfonylurea insulin secretagogue, is a prandial glucose regulator used for the treatment of type 2 diabetes (1). Like the sulfonylureas, repaglinide produces a hypoglycemic effect by stimulating insulin secretion from the pancreatic  $\beta$ -cells, but in contrast to the sulfonylureas, its action is at least in part glucose mediated (2) and is effected via a different high-affinity binding site on the  $\beta$ -cell (3,4).

Repaglinide is rapidly absorbed following oral administration, reaching peak concentrations 30–60 min postdosing. The drug has a fast onset and a relatively short duration of action. Thus, it can be taken just before main meals, enhancing the prandial insulin response and reducing postprandial glucose excursions, thereby improving overall glycemic control. Repaglinide has a very fast elimination (plasma half-life [ $t_{1/2}$ ]) of  $\sim 1$  h (5,6). In

patients with normal kidney function, the drug is almost completely (98%) metabolized in the liver and is excreted primarily through the bile. Only a very small fraction ( $<8\%$ ) of the administered dose is excreted through the urine (6–8). None of the major metabolites contribute to the glucose-lowering effect of repaglinide and the drug does not appear to accumulate with repeated dosing (9).

Since repaglinide has a short duration of action and is excreted independently of renal function, it may be suitable for use in patients with type 2 diabetes with renal impairment. However, two previous short-term clinical studies on the pharmacokinetics of repaglinide in subjects with renal impairment showed some slight differences compared with patients with normal renal function (10,11). One study showed that the area under the curve (AUC) and maximum serum concentration ( $C_{max}$ ) for repaglinide were significantly higher in subjects with renal impairment than in healthy subjects, but were independent of the degree of renal impairment (10). A second study showed that the elimination of repaglinide was slower in patients with severe renal impairment (creatinine clearance [ $CL_{CR}$ ] of 39–20 ml/min) than in those with normal or mild/moderately impaired renal function (11). In both studies, repaglinide was well tolerated by subjects with impaired renal function. The present study was designed to investigate the long-term safety and efficacy of repaglinide in type 2 diabetic patients with mild to severe renal impairment.

## RESEARCH DESIGN AND METHODS

### Study participants.

A total of 281 patients, aged  $\geq 35$  years, entered the study. Subjects were required to have type 2 diabetes treated with an oral hypoglycemic agent and/or insulin for at least 1 year and a BMI of 21–37  $kg/m^2$ . Individuals with  $HbA_{1c} > 12.0\%$ ,

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**Abbreviations:** ALT, alanine aminotransferase; AUC, area under the curve;  $CL_{CR}$ , creatinine clearance;  $C_{max}$ , maximum serum concentration; FBG, fasting blood glucose;  $\gamma$ GT,  $\gamma$  glutamyl transpeptidase; ITT, intention-to-treat; LKF, Laboratorium für Klinische Forschung.

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

a history of unstable proliferative retinopathy, evidence of liver disease,  $CL_{CR} < 20$  ml/min, severe cardiac problems, uncontrolled hypertension, or glucagon-stimulated C-peptide  $< 0.6$  nmol/l were excluded. Patients were stratified into five renal function groups based on a single  $CL_{CR}$  at screening: normal function ( $CL_{CR} > 80$  ml  $\cdot$  min $^{-1}$   $\cdot$  1.73 m $^{-2}$ ), mild ( $60 \leq CL_{CR} \leq 80$  ml  $\cdot$  min $^{-1}$   $\cdot$  1.73 m $^{-2}$ ), moderate ( $40 \leq CL_{CR} < 60$  ml  $\cdot$  min $^{-1}$   $\cdot$  1.73 m $^{-2}$ ), severe ( $30 \leq CL_{CR} < 40$  ml  $\cdot$  min $^{-1}$   $\cdot$  1.73 m $^{-2}$ ), and extreme renal impairment ( $20 \leq CL_{CR} < 30$  ml  $\cdot$  min $^{-1}$   $\cdot$  1.73 m $^{-2}$ ), irrespective of the underlying renal disease.

All individuals provided written informed consent to participate, and the study protocol received approval by relevant local ethics committees and/or health authorities. The study was performed in accordance with the Declaration of Helsinki (12).

### Study design

This open-label study, performed in 32 centers in three countries, consisted of a 6-week run-in period designed to assess the safety profile at baseline, during which patients continued their prestudy antidiabetic medication. After this run-in period patients were switched to repaglinide treatment, including a 4-week (maximum) repaglinide titration period, and a 3-month maintenance period. Subjects started on 0.5 mg repaglinide at each main meal (i.e., three times daily), which was titrated to a maximum dose of 4 mg three times daily in order to achieve optimal glycemic control: a fasting blood glucose (FBG) level of 4.4–6.1 mmol/l in the absence of adverse effects, including hypoglycemic episodes. Patients not reaching target in the titration period could enter the maintenance period if FBG was  $\leq 10$  mmol/l. Further dose adjustment was permitted during the maintenance period to achieve or maintain optimal glycemic control.

### Study evaluations

**Safety assessments.** During screening, at the first titration visit, and at the end of the study evaluations, subjects received a complete physical examination, routine laboratory tests, vital signs measurements, and an electrocardiogram. Adverse events were monitored throughout the study. Symptoms of hypoglycemia (e.g., sweating, dizziness, tremor) and/or

a blood glucose  $\leq 2.5$  mmol/l (45 mg/dl) were recorded throughout the study and were defined as either minor (hypoglycemic symptoms that could be treated/corrected by the patient without assistance of other persons) or major (the patient required third-party help). Patients were asked to have their blood glucose measured if possible at the time of the symptoms and to document the value in their diary.  $CL_{CR}$  was measured at screening (for stratification of renal impairment) and at the end of the study (to determine changes in creatinine clearance from baseline during repaglinide treatment). Fasting serum levels of repaglinide were measured at the beginning of the maintenance period and at the end of the study. Treatment compliance during the study was assessed by drug accountability.

**Efficacy assessments.** The efficacy evaluation was based primarily on HbA $_{1c}$  and secondarily on FBG, lipid profiles, and dose level of repaglinide at the end of the study. HbA $_{1c}$  and lipids were measured at screening, first titration visit, and end of study.

### Sample analysis

HbA $_{1c}$ , hematology, and biochemistry and lipid (triglycerides, total cholesterol, and HDL cholesterol) values were determined using standard laboratory tests at a central laboratory (Laboratorium für Klinische Forschung [LKF]). Urine analysis was performed using test strips provided by LKF. Repaglinide serum levels were determined using liquid chromatography and mass spectrometry after solid-phase extraction (13). The quantification range of the assay was 0.2–250 ng/ml. FBG was measured using a standard blood glucose meter (One Touch Basic; LifeScan).

### Statistical analysis

All analyses were based on the intention-to-treat (ITT) population, which consisted of all patients exposed to at least one dose of repaglinide. For the continuous variables—HbA $_{1c}$ , FBG, triglycerides, total and HDL cholesterol, hematology and biochemistry—three hypotheses were tested: 1) all (five) renal function groups are equal; 2) the (four) renal impairment subgroups are equal; and 3) the pooled group, consisting of the (four) renal impairment subgroups, is equal to the normal renal function group, with respect to the mean baseline value and the mean change from baseline to end of treatment,

respectively. The following model was applied for the continuous variables (both for the baseline values and for the changes from baseline at the end of the treatment period): the response depends on a (fixed) renal status effect and a random error term. The random error was assumed to follow a Gaussian distribution with mean zero. ANOVA tables were presented for the chosen model. In addition to these analyses, number of patients with adverse events, number of patients with hypoglycemic episodes, and number of patients with fasting serum repaglinide above the detection limit were tested for a potential relationship to the degree of renal impairment using trend tests. A Cochran-Armitage test was used for a binomial response and a Jonckheere-Terpstra test for an ordered response. Adverse events were coded using the preferred term in accordance with the World Health Organization Adverse Reaction Dictionary.

## RESULTS

### Demographics

Demographic characteristics of the 281 patients who entered the repaglinide maintenance period are summarized in Table 1. Most, 84% of the patients (235 of 281), completed the study. Half of the withdrawals occurred during the titration period. The percentage of patients completing was lowest in the moderate renal impairment group (34 of 44; 77%) and highest in the extreme renal impairment group (10 of 10; 100%). Ineffective therapy was the most common reason for withdrawal (27 of 46). Of these 27 patients, 12 had been on oral hypoglycemic agent combination therapy or insulin at baseline. Seven patients were withdrawn during the run-in period after an increase in HbA $_{1c} > 1\%$  point (withdrawal criteria). Treatment compliance was high; 97% of patients received  $> 75\%$  of the required trial medication.

### Safety assessment

The baseline adverse event profile was similar between groups. The overall adverse event profile during repaglinide treatment was similar to that of the 6-week run-in period (Fig. 1). The most frequently reported adverse events were upper respiratory tract infections (normal 7.9%, impaired 6.9%) and headaches (normal 7.9%, impaired 2.3%). Renal status did not influence the incidence of ad-

Table 1—Baseline characteristics of the study population at screening

	Degree of renal impairment (creatinine clearance, ml · min <sup>-1</sup> · 1.73 m <sup>-2</sup> )				
	Normal renal function	Mild (≥60 and ≤80)	Moderate (≥40 and <60)	Severe (≥30 and <40)	Extreme (≥20 and <30)
Demographics					
Number of patients	151	64	44	12	10
Age (years)	60.4 (9.2)	65.8 (7.6)	69.8 (8.2)	67.3 (8.3)	67.3 (9.2)
Sex (%)					
Male	101 (66.9)	28 (43.8)	18 (40.9)	8 (66.7)	7 (70.0)
Female	50 (33.1)	36 (56.3)	26 (59.1)	4 (33.3)	3 (30.0)
BMI (kg/m <sup>2</sup> )	29.6 (3.7)	28.5 (4.0)	28.4 (3.7)	30.5 (4.0)	28.6 (4.3)
Albumin/creatinine ratio (μg/mg creatinine)*	13.6 (7.6:62.7)	18.0 (8.6:36.5)	75.2 (20.1:523)	1028 (80.4:2,285)	624 (57.8:2,755)
Creatinine (mg/dl) (mean [SD])	0.8 (0.2)	0.9 (0.3)	1.2 (0.5)	1.9 (0.6)	2.6 (1.3)
Diabetic history					
Known duration of diabetes (years)	8.4 (6.3)	10.0 (7.0)	9.9 (6.9)	12.8 (6.4)	10.9 (6.9)
HbA <sub>1c</sub> (%)	7.8 (1.3)	7.9 (1.5)	7.9 (1.3)	7.1 (1.1)	8.0 (1.1)
Stimulated C-peptide (nmol/l)	1.8 (0.7)	1.7 (0.8)	2.0 (0.9)	1.9 (1.1)	2.7 (0.9)
Antidiabetic medication, n (%)					
Sulphonylurea (SU)	66 (43.7)	33 (51.6)	23 (52.3)	6 (50.0)	8 (80.0)
Metformin	20 (13.2)	6 (9.4)	3 (6.8)	1 (8.3)	—
Acarbose/miglitol	4 (2.6)	3 (4.7)	2 (4.5)	—	—
Insulin	4 (2.6)	1 (1.6)	—	2 (16.7)	1 (10.0)
SU + metformin	35 (23.2)	11 (17.5)	9 (20.5)	1 (8.3)	—
Insulin + OHA	5 (3.3)	2 (3.1)	—	—	—
SU + acarbose	7 (4.6)	6 (9.4)	6 (13.6)	2 (16.7)	1 (10.0)
Metformin + acarbose	2 (1.3)	2 (1.3)	—	—	—
Other combinations	7 (4.6)	—	—	—	—
Concomitant medication, n (%)					
Hypertension	94 (62.3)	41 (64.1)	37 (84.1)	12 (100)	7 (70)
Heart disease	40 (26.5)	19 (29.7)	11 (25.0)	5 (41.7)	4 (40)
Hyperlipidemia	22 (14.6)	12 (18.8)	8 (18.2)	1 (8.3)	1 (10.0)

Data for demographics and diabetic history are means (SD); data for medication and albuminuria n (%) \*Expressed as median (lower quartile, upper quartile).

verse events, either during the run-in period ( $P = 0.41$  for trend) or during the repaglinide treatment period ( $P = 0.46$  for trend).

Three deaths occurred during the repaglinide treatment period (due to bronchial carcinoma and cardiac failure, respectively, in two patients in the normal renal group and due to sudden death in one patient in the renal impairment group). None of the deaths were assessed as related to repaglinide treatment.

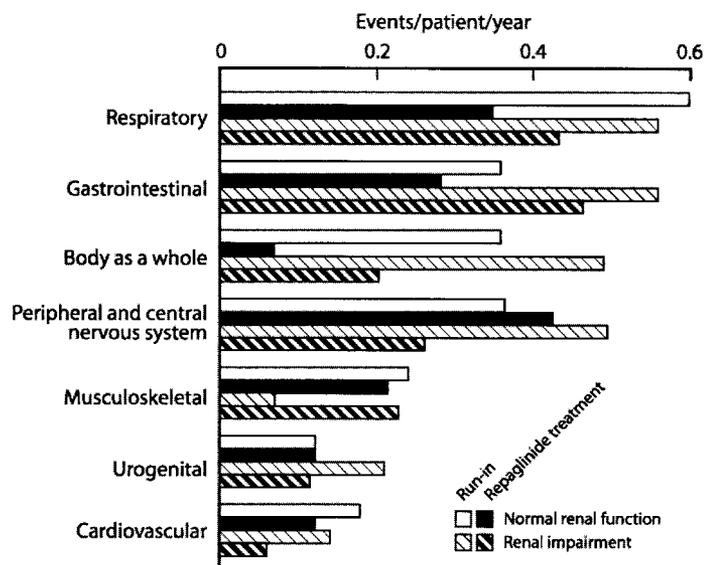
Serious adverse events were reported by four (2.6%) of the patients in the normal renal function group and eight (6.1%) in the renally impaired groups. In addition to the three serious adverse events, which led to death, the serious adverse events included two other cases of cardiac failure and one event of hypoglycemia in the renally impaired group. Only the episode of hypoglycemia was evaluated as possibly related to study treat-

ment. This was the only major hypoglycemic episode reported. Overall, few ( $n = 16$ ) adverse events were considered possibly or probably related to the study medication; most common among these were gastrointestinal events (four events: gastritis, diarrhea, flatulence, and abdominal pain) and four events involving transient increases in liver enzymes (increased levels of  $\gamma$  glutamyl transpeptidase [ $\gamma$ GT  $\times 2$ ] and alanine aminotransferase [ALT  $\times 2$ ]). No adverse events related to the study medication were reported for patients with severe or extreme renal impairment.

Symptoms of hypoglycemia were reported in 10% (15 of 151) of patients with normal renal function and in 15% (20 of 130) of those with renal impairment. The incidence rate was slightly higher during repaglinide therapy (1.0 episodes  $\cdot$  patient<sup>-1</sup>  $\cdot$  year<sup>-1</sup>) than in the run-in phase (0.6 episodes  $\cdot$  patient<sup>-1</sup>  $\cdot$  year<sup>-1</sup>) but was

only significantly associated with the degree of renal impairment during run-in ( $P = 0.007$ ; Fig. 2).

Significant differences were observed between patients with normal renal function and those with impaired renal function in baseline levels of hemoglobin (14.7 vs. 13.8 g/dl,  $P = 0.0001$ ) and leukocyte-count (6.6 vs. 6.9 nl<sup>-1</sup>,  $P = 0.0006$ ). With the exception of a small decrease in leukocyte-counts in patients with extreme renal impairment, no clinically relevant changes in these variables occurred during treatment in either group. Mean values of ALT and AST were within reference ranges at baseline (0–22 and 0–18 units/l, respectively), and no clinically relevant changes were reported during the study. A significant difference in mean (SD) ALT between the normal (14.3 [7.1]) and impaired (10.3 [4.2]) renal function groups was evident at baseline ( $P = 0.0023$ ).



**Figure 1**—Adverse events occurring in the run-in and repaglinide treatment period by system/organ classes.

No significant changes in serum creatinine, creatinine clearance, body weight, or blood pressure occurred during treatment in any group. Mildly abnormal electrocardiogram findings, reported at baseline in 22 patients, were unchanged during treatment.

### Glycemic control

Glycemic control on repaglinide at the end of the treatment period was generally similar to that at baseline. No significant differences were observed between the different renal function groups with regard to the effect of repaglinide on HbA<sub>1c</sub> and FBG. A small decrease from baseline in mean (SD) HbA<sub>1c</sub> (7.7% [0.9] to 7.1% [0.5]) occurred in the extreme renal im-

pairment group, while a small increase (7.3% [0.9] to 7.6% [1.0]) occurred in the severe renal impairment group. These changes were mirrored by small changes in mean (SD) FBG of 7.9 mmol/l (3.1) to 6.7 mmol/l (2.7) in the extreme renal impairment group and 7.7 mmol/l (2.0) to 9.0 mmol/l (3.1) in the severe renal impairment group. No change in glycemic control occurred in the remaining groups.

### Lipids

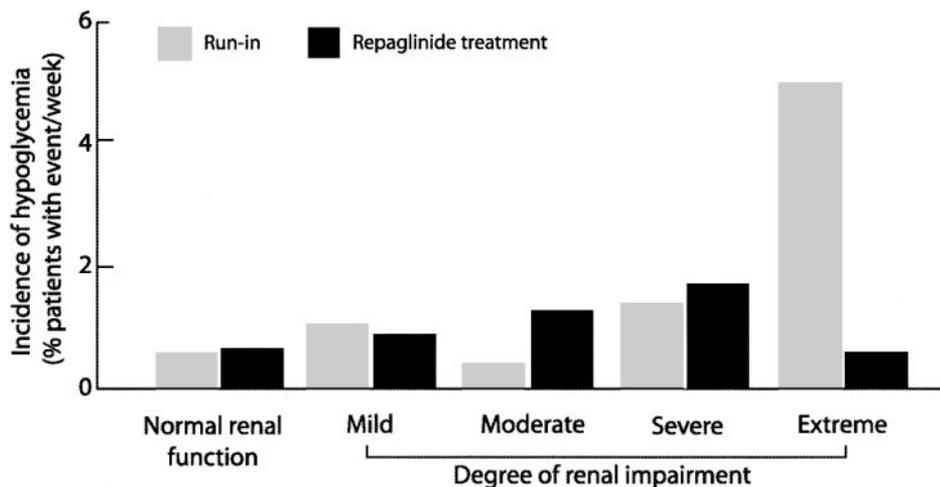
Renal impairment groups differed significantly at baseline in total cholesterol levels. The mean (SD) ranged from 5.63 mmol/l (1.03) in the normal renal function group to 6.35 mmol/l (0.78) in the severe renal impairment group ( $P =$

0.0225). However, changes during treatment were small and showed no association with degree of renal impairment. No differences between groups or changes with treatment were recorded for HDL cholesterol or triglyceride.

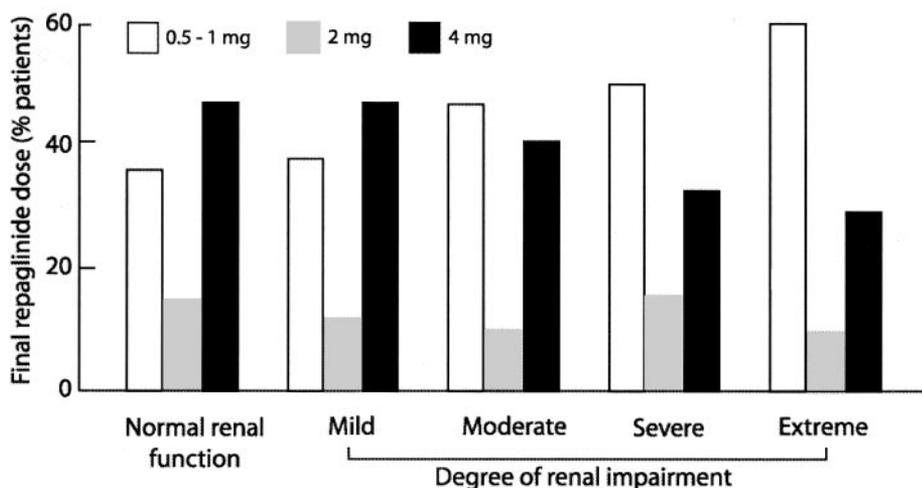
### Repaglinide dose

In patients with normal renal function, 48% had been titrated to the highest allowed repaglinide dose (4 mg with meals) by the end of the study. Similar proportions of the mild and moderate renal impairment groups also reached this dose (48 and 41%, respectively), whereas in the severe and extreme renal impairment groups only 33 and 30% of patients, respectively, reached the highest dose level. Overall, there was a significant trend toward a lower final dose level with increasing degree of renal impairment ( $P = 0.032$  for trend; Fig. 3).

A number of patients in all groups, including those with normal renal function, retained detectable fasting (or nadir) levels of serum repaglinide at the end of the titration (115 patients) and maintenance (120 patients) periods. The percentage of patients with repaglinide levels above the detection limit at the end of these periods increased significantly ( $P = 0.002$  for trend) with increasing severity of renal impairment (normal, 54.0%; mild 56.7%; moderate, 79.5%; severe, 72.7%; extreme, 80.0%). However, with few exceptions, elevated levels of repaglinide were within the range 0.200–0.700 ng/ml and were considered too low to be biologically active.



**Figure 2**—Incidence of hypoglycemia in relation to the degree of renal impairment during repaglinide treatment. Significant association between the incidence of hypoglycemia and degree of renal impairment was seen only during the run-in period ( $P = 0.007$ ).



**Figure 3**— Final repaglinide dose received in relation to the degree of renal impairment. As the degree of renal impairment increased, there was a significant trend toward a lower final dose level ( $P = 0.032$  for trend).

**CONCLUSIONS**— No relationship was found between the degree of renal impairment and the risk of hypoglycemia in patients treated with repaglinide, including those with severe or even extreme degrees of renal impairment. No adverse changes in laboratory variables or increases in overall adverse events occurred during treatment. Furthermore, the incidence of adverse events in renally impaired patients who received repaglinide was comparable to that in patients with normal renal function. These are important endorsements of the safety of this agent in a group of patients who are often in need of enhanced metabolic control but who are also often at risk for hypoglycemia due to (often unknown) renal impairment on the other side (14).

Although patients were receiving varied antidiabetic therapy at baseline, including combinations of oral hypoglycemic agents or insulin, switching to repaglinide monotherapy was not associated with deterioration in glycemic control in any group during the treatment period.

While the relatively small numbers of patients in our severe and extreme renal impairment groups illustrate the difficulties in conducting studies in such patients, stratification of patients using a single 24-h measurement of  $CL_{CR}$  can result in some patients being incorrectly grouped due to unpredictable variations in  $CL_{CR}$ . Mean serum creatinine levels increased with increasing severity of renal impairment, confirming that the majority of patients were allocated to the correct renal function group. The present data are consistent with those from a previous

short-term study showing that hypoglycemic risk and the adverse event profile are independent of renal function status during treatment with repaglinide (11). The higher number of females than males observed in the severe and extreme renal impairment groups (Table 1) is in contrast to what is usually seen among Caucasian individuals with type 2 diabetes (15,16). This discrepancy is most likely due to the difficulties observed in recruiting such patients for the present study.

The incidence of patients with symptoms of hypoglycemia in the present study was slightly higher during repaglinide treatment than during the run-in; this may be the result of switching therapies, especially since a number of patients at baseline were on metformin or acarbose monotherapy or metformin/acarbose combination therapy—therapies that have a very low risk of hypoglycemia under normal circumstances.

A number of patients in all groups had detectable fasting levels of serum repaglinide in the morning, before dosing, and at the beginning and end of the maintenance period. While the percentage of patients with detectable fasting repaglinide levels increased significantly ( $P = 0.002$  for trend) with increasing severity of renal impairment, there was no increase in frequency of hypoglycemic or other adverse reactions, and the measured levels of repaglinide were not generally considered to be biologically active. In a previous study, evidence of a slower elimination of repaglinide in individuals with severe renal impairment was shown, with higher AUC and  $t_{1/2}$  values after multiple dosing (11), and it is known that

renal impairment can affect hepatic, as well as renal, drug metabolism to some extent (17–19); recent animal studies have confirmed that downregulation of CYP 450 activity, the hepatic enzyme primarily responsible for repaglinide metabolism, is correlated to degree of renal function, although the mechanism underlying this effect remains unclear (20). In the present study, these relations are mirrored by the somewhat more cautious titration of repaglinide in patients with severe and extreme renal impairment, with fewer patients reaching maximal repaglinide doses. It should, however, be noted that the dosing and titration schedule for repaglinide was the same as that recommended in everyday practice. Thus, provided titration is performed according to these recommendations, these data do not indicate that severely renally impaired patients require different dosing practice to those with normal renal function. The duration of the maintenance period of 3 months may be too short to draw in-depth conclusions of the present study. However, five studies of 12 months' duration including >1,200 type 2 diabetic patients with serum creatinine levels <140  $\mu\text{mol/l}$  (1.6 mg/dl) have not raised any safety concerns (21,22).

In conclusion, repaglinide may be used in type 2 diabetic patients with any degree of impaired renal function, in the same manner recommended for patients with normal renal function, without compromising safety or loss of efficacy.

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## APPENDIX

### The Multinational Repaglinide Renal Study Group

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