Glimepiride Versus Metformin as Monotherapy in Pediatric Patients With Type 2 Diabetes

A randomized, single-blind comparative study

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OBJECTIVE — To compare the efficacy and safety of glimepiride versus metformin in pediatric subjects with type 2 diabetes inadequately controlled with diet and exercise alone or oral monotherapy.

RESEARCH DESIGN AND METHODS — This 26-week, single-blind, active-controlled, multinational study randomized 285 subjects to receive glimepiride (1–8 mg once daily) or metformin (500–1000 mg twice daily) for 24 weeks. The primary end point was mean change in A1C from baseline to week 24. Safety was assessed by incidence of hypoglycemia and other adverse events.

RESULTS — Significant reductions from baseline A1C were seen in both the glimepiride (−0.54%, $P = 0.001$) and metformin (−0.71%, $P = 0.0002$) groups. A total of 42.4% (56 of 132) and 48.1% (63 of 131) of subjects in the glimepiride and metformin groups, respectively, in the intent-to-treat population achieved A1C <7.0% at week 24. No significant differences were observed between groups in reductions in A1C and self-monitored blood glucose levels, changes in serum lipid concentrations, or hypoglycemia incidence. Significant differences were observed in mean changes from baseline in BMI between groups (0.26 kg/m^2 for glimepiride and −0.33 kg/m^2 for metformin; $P = 0.003$). The adjusted mean body weight increase was 1.97 kg for glimepiride and 0.55 kg for metformin ($P = 0.005$). A hypoglycemic episode with blood glucose <50 mg/dl (<2.8 mmol/l) was experienced by 4.9 and 4.2% of glimepiride- and metformin-treated subjects, respectively. A single severe hypoglycemic event occurred in each group.

CONCLUSIONS — Glimepiride reduced A1C similarly to metformin with greater weight gain, and there was comparable safety over 24 weeks in the treatment of pediatric subjects with type 2 diabetes.

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The incidence of type 2 diabetes has been rapidly increasing in the pediatric population (1). Type 2 diabetes rarely was seen in pediatric subjects before the 1990s, but by 1999 estimates of new-onset type 2 diabetic cases in this population ranged from 8 to 45%, depending on ethnicity and geographic location (1). This increase may, in part, be attributed to the dramatic rise in childhood obesity (now estimated at 15–20% of the pediatric population). Further, increased intake of calories and dietary fats combined with inadequate physical activity may be contributing to the development of childhood obesity and type 2 diabetes (1,2).

As in adults, type 2 diabetes in children and adolescents results from both insulin resistance and relative pancreatic β-cell secretory failure, with most subjects presenting with symptomatic hyperglycemia (2). This similarity, combined with the documented efficacy of oral antidiabetic therapy in adults, suggests that oral agents will be equally effective in children and adolescents (2). Type 2 diabetes may have an earlier and more aggressive course in pediatric patients (3,4); therefore, they are likely to be at a higher risk for developing complications and need the best possible glycemic control in the early stage of their disease. Although use of oral antidiabetic agents in adults with type 2 diabetes is well established, much less is known about use in pediatric patients. Thus, efficacy and safety data in the pediatric population are urgently needed to meet the goals of improved glycemic control and long-term outcomes in type 2 diabetes.

Metformin is a biguanide that suppresses basal hepatic glucose uptake and increases insulin-mediated glucose uptake in peripheral muscle. Because metformin does not stimulate insulin secretion, hypoglycemia is uncommon with monotherapy (5), making it an attractive agent for use in children and adolescents. Currently, metformin is the only oral antihyperglycemic agent specifically approved for pediatric use by the Food and Drug Administration (6).

Glimepiride (Amaryl; Aventis Pharmaceuticals, Bridgewater, NJ) is a potent sulfonylurea and is associated with a low rate of hypoglycemia (0.9–1.7%) in adults (7,8). In addition to effects on pancreatic β-cell function, glimepiride also

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Abbreviations: SMBG, self-monitored blood glucose.

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

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may enhance tissue sensitivity to insulin and has a favorable safety and efficacy profile with once-daily dosing of 1–8 mg/day (7). Although the safety and efficacy of glimepiride are well documented in adults, studies in the pediatric population are lacking. Thus, the current study was conducted to evaluate the safety and efficacy of glimepiride and metformin in pediatric subjects with type 2 diabetes.

RESEARCH DESIGN AND METHODS

— This was a 26-week, randomized, single-blind, active-comparator, parallel-group, multinational study of the safety and efficacy of glimepiride and metformin in pediatric subjects with type 2 diabetes with inadequate control despite treatment with either diet and exercise alone or diet and exercise combined with oral monotherapy. After a 2-week stabilization period, subjects were stratified by age (≤12 or >12 years) and randomly assigned in a one-for-one ratio to receive glimepiride or metformin for 24 weeks (a 12-week titration period and a 12-week maintenance period).

Pediatric subjects with type 2 diabetes and A1C >7.1 and <12.0% and aged 8–17 years at the time of randomization were eligible (the first subject was enrolled on 11 October 2002; the last subject completed the study on 15 November 2004). All subjects failed to respond to treatment with diet and exercise alone for at least 2 weeks before randomization or failed to respond to 3 months of ongoing or previous oral antihyperglycemic therapy combined with diet and exercise. All subjects were negative for islet cell antigen autoantibodies and/or glutamic acid decarboxylase autoantibodies and had serum C-peptide levels ≥1.5 ng/ml (at 90 min following a Boost challenge). In accordance with the Declaration of Helsinki, all subjects and their parent or legal guardian gave written informed consent before participation.

Exclusion criteria included history of acute metabolic decompensation, such as diabetic ketoacidosis within 3 months before screening, current insulin therapy, or having received insulin for >6 weeks within the 3 months before randomization. Also excluded were subjects who were receiving weight reduction medications; who had known hypersensitivity to biguanides, sulfonamides, or insulin; or who were on chronic medications known to affect glucose metabolism (i.e., systemic or inhaled corticosteroids), as well as those with clinically significant renal or hepatic disease and those with gastrointestinal disorders that might interfere with study drug absorption. In addition, subjects who were pregnant or lactating, who had a history of drug or alcohol use, who were noncompliant with follow-up medical care, or who had any disease or clinically significant abnormality/clinical condition that could affect study outcome were excluded. Sexually active female subjects were required to use adequate birth control throughout the study.

Treatment

Subjects randomly were assigned to receive either glimepiride or metformin. Glimepiride was initiated at a dose of 1 mg orally once daily and titrated by doubling the dose at weeks 4, 8, and 12 to a maximum dose of 8 mg once daily in the morning. The target self-monitored blood glucose (SMBG) level was <140 mg/dl (<7.8 mmol/l). A protocol amendment toward the end of the study lowered this target to <126 mg/dl (<7.0 mmol/l); four patients followed the amended target. Metformin was initiated at a dose of 500 mg twice daily and titrated once at week 12 to 1,000 mg twice daily if the SMBG level was >140 mg/dl (>7.8 mmol/l) or >126 mg/dl (>7.0 mmol/l) later in the study. To maintain blinding, subjects on glimepiride took a placebo pill in the evening.

Efficacy and safety measures

The primary efficacy outcome measure was the mean change in A1C from baseline to week 24. Secondary efficacy outcome measures included the mean change in A1C from baseline to week 12, the proportion of subjects achieving an A1C <7.0% at week 24, and the mean change in fasting SMBG from baseline to weeks 4, 8, 12, 18, and 24. Mean changes in serum lipid concentrations (i.e., total, LDL, and HDL cholesterol and triglycerides) were assessed at weeks 0 and 24 (or study discontinuation). Changes in BMI and body weight also were assessed. Safety outcome measures included recording the occurrence of adverse events and hypoglycemic episodes as well as the results of standard laboratory parameters and vital signs. Clinically relevant hypoglycemia was defined as serum glucose of <70 mg/dl (3.9 mmol/l). Severe hypoglycemia was defined as episodes requiring assistance and either a blood glucose ≤36 mg/dl (≤2.0 mmol/l) or the use of countermeasures (oral carbohydrates, intravenous glucose, or subcutaneous glucagon).

Statistical methods

All statistical tests were two sided and performed at a significance level of $\alpha = 0.05$. Change in A1C from baseline to weeks 12 and 24 was analyzed using an ANCOVA, with the baseline value as the covariate and treatment, Tanner stage, and pooled countries as the fixed effects. Changes in secondary outcome measures for changes from baseline through week 24 also were done using ANCOVA. Categorical variables were analyzed using the Cochran-Mantel-Haenszel test, controlling for pooled countries, and by logistic regression, controlling for pooled countries and Tanner stage. The number and frequencies of subjects with treatment-emergent adverse events were included for each treatment group by body systems.

RESULTS

Baseline demographic and clinical characteristics

A total of 536 subjects were screened for enrollment in the study (Fig. 1). Of these, 285 subjects were randomized to glimepiride or metformin therapy, 284 subjects (142 glimepiride and 142 metformin) were evaluable for safety, 263 subjects (132 glimepiride and 131 metformin) were evaluable for efficacy (i.e., the intent-to-treat population), and 210 subjects (103 glimepiride and 107 metformin) completed the study. Reasons for not completing the study included adverse events, patient choice, protocol violations, lack of follow-up, treatment failure, and no A1C measurement. The intent-to-treat population included patients who received at least one dose of study medication and had at least one A1C measurement beyond randomization. Overall, 98% (257 of 263) of the intent-to-treat population had at least 75% adherence (based on pill counting) with their study medications. The mean age was 13.8 years in both groups, and approximately two-thirds of the subjects in each group were female. The treatment groups generally were well matched with respect to the remaining baseline characteristics (Table 1). Prior metformin use was noted in 13.4 and 14.1% of glimepiride and metformin patients, respectively. Prior insulin use was reported in 7.0 and 7.7% of patients in the glimepiride and metformin groups, respectively, whereas prior use of other agents (glyburide, acar-

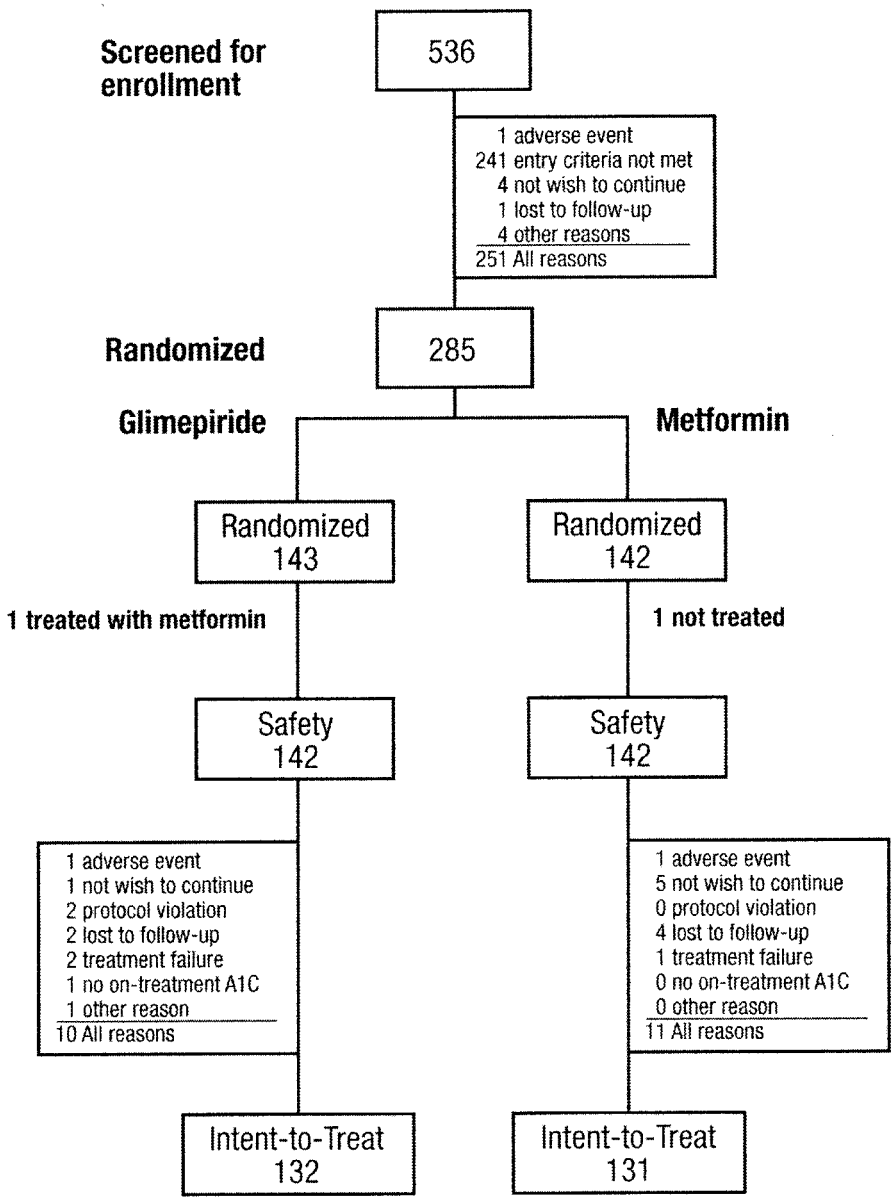

Figure 1—*Disposition of subjects.*

bose, glipizide, or rosiglitazone) was <5% in both groups.

Study dose

The mean final dose for glimepiride was 3.8 mg/day (range 1–8) and for metformin 1,408 mg/day (500–2,000).

Efficacy

Changes in A1C. To evaluate the efficacy of glimepiride and metformin therapy in children and adolescents with type 2 diabetes, we evaluated the mean change in A1C from baseline to weeks 12 and 24 of treatment. Significant reductions from baseline A1C were seen in both treatment groups at weeks 12 and 24 (Fig. 2). Results of the ANCOVA showed no significant difference between the two groups at week 12 (adjusted mean change from baseline A1C: −0.69% with glimepiride vs. −0.76% with metformin, $P = 0.749$) or at week 24 (adjusted mean change from baseline A1C: −0.70% with glimepiride vs. −0.85% with metformin, $P = 0.542$).

Proportion achieving A1C <7.0%. Efficacy was further assessed by determining the proportion of subjects who achieved an A1C <7.0% at week 24 of the study. The proportion of subjects was similar for both groups: 42.4% of glimepiride-treated subjects compared with 48.1% of metformin-treated subjects ($P = 0.347$). No significant differences were seen when the results were stratified by Tanner stage at baseline.

Changes in fasting SMBG and fasting plasma glucose. The mean changes in fasting SMBG levels between baseline and weeks 4, 8, 12, 18, and 24 were evaluated in each study group. Significant differences were observed in the metformin group between baseline and weeks 18 and 24 (Fig. 3) but not in the glimepiride group. However, no significant differences were observed between the two study groups during the course of the study. No significant changes were observed in fasting plasma glucose between baseline and any visit day for either treatment group or between groups.

Changes in lipid profile and BMI. There were no significant differences in the mean change from baseline in any of the serum lipid concentrations between the glimepiride and metformin groups, respectively, including total (4.7 vs. −0.3 mg/dl), LDL (2.3 vs. −1.7 mg/dl), and HDL (2.3 vs. 2.4 mg/dl) cholesterol or triglycerides (3.3 vs. −0.1 mg/dl). When the adjusted mean changes from baseline BMI were compared between groups, significant differences were seen at week 12 (0.55 vs. 0.07 kg/m^2 for glimepiride and metformin, respectively; $P < 0.001$) and at week 24 (0.26 and −0.33 kg/m^2, respectively; $P = 0.003$).

Safety

The incidence of adverse events and episodes of hypoglycemia were evaluated in 284 subjects (142 glimepiride and 142 metformin) who were randomized and received at least one dose of study medication. Overall, the proportion of subjects experiencing one or more adverse events was comparable between the glimepiride (59.2%) and metformin (57.7%) groups. Adverse events considered possibly related to treatment were seen in 11 glimepiride-treated subjects (7.7%) and 19 metformin-treated subjects (13.4%). The most common adverse events (occurring in >1% of subjects) observed in the glimepiride and metformin groups, respectively, were hyperglycemia (2.8 vs. 0.7%), upper abdominal pain (1.4 vs. 0.7%), abdominal pain (1.4 vs. 1.4%), diarrhea (0.7 vs. 4.2%), nausea (0.7 vs. 2.8%), and headache (0 vs. 2.1%).

No deaths occurred during the study. Two subjects had serious adverse events considered possibly related to treatment: one subject in the glimepiride group had hyperglycemia, diabetic ketoacidosis, and

Table 1—*Baseline demographic and clinical characteristics

Characteristics	Glimepiride	Metformin
n	132	131
Mean age (years)	13.8 ± 2.3	13.8 ± 2.3
<12 years of age	23 (17.4)	21 (16)
≥12 years of age	109 (82.6)	110 (84.0)
Sex		
Male	44 (33.3)	44 (33.6)
Female	88 (66.7)	87 (66.4)
Race		
White	17 (12.9)	21 (16.0)
African American/black	30 (22.8)	28 (21.4)
Asian/Pacific Islander	23 (17.4)	19 (14.5)
Hispanic	52 (39.4)	52 (39.7)
Other	10 (7.6)	11 (8.4)
Body weight (kg)	82.60 ± 25.60	83.83 ± 27.47
BMI (kg/m^2)	31.57 ± 8.48	31.60 ± 8.17
Duration of diet/exercise (months) (median)	7	4
A1C (%)	8.52 ± 1.58	8.54 ± 1.57
Fasting plasma glucose (mg/dl)	174.4 ± 66.7	172.0 ± 70.7
SMBG (mg/dl)	173.3 ± 60.8	167.4 ± 67.4
Tanner stage		
1	7 (5.3)	11 (8.5)
2	9 (6.9)	11 (8.5)
3	24 (18.3)	21 (16.3)
4	42 (32.1)	34 (26.4)
5	49 (37.4)	52 (40.3)
Completed the study out of intent-to-treat population (%)	103 (78.0)	107 (81.7)
Mean final dose (mg) (range)	3.8 (1–8)	1,408 (500–2,000)

Data are means ± SD or *n* (%), unless otherwise indicated. *Intent-to-treat population.

increased serum osmolarity, and one subject in the metformin group had a nonhypoglycemic convulsion. The incidence of clinically relevant hypoglycemia was similar for both groups: 10.6% with glimepiride vs. 8.5% with metformin ($P = 0.554$). The proportion of subjects with SMBG <50 mg/dl (2.8 mmol/l) also was similar: 4.9% (7 of 142) for glimepiride and 4.2% (6 of 142) for metformin. A single episode of severe hypoglycemia was reported in each group.

No clinically significant differences were observed in vital signs and laboratory parameters throughout the study from baseline to end point within each group or between treatment groups. Subjects grew a mean of 1 cm in height in both groups during the study, and a significant weight increase of 1.3 kg was seen in the glimepiride-treated subjects ($P < 0.001$) at week 24. No significant weight change was seen in metformin-treated subjects. The adjusted mean increase in body weight from baseline to week 24 was 1.97 kg in the glimepiride group and 0.55 kg in the metformin group ($P = 0.005$).

CONCLUSIONS — Currently, an estimated 25–45% of children and adolescents with newly diagnosed diabetes have type 2 diabetes. The increasing prevalence of obesity is a principal factor behind the rise of type 2 diabetes in pediatric patients (25–35% of children and adolescents are above the 80th percentile in weight, and 10–15% are above the 95th percentile in weight for chronological age). Other risk factors include ethnicity, family history, and female sex.

Despite the rising incidence of type 2 diabetes in pediatric patients, treatment options remain limited. Diet and exercise therapy sometimes is effective but for a short time and in a small number of individuals. Currently, metformin is the only oral agent specifically approved for the treatment of type 2 diabetes in pediatric

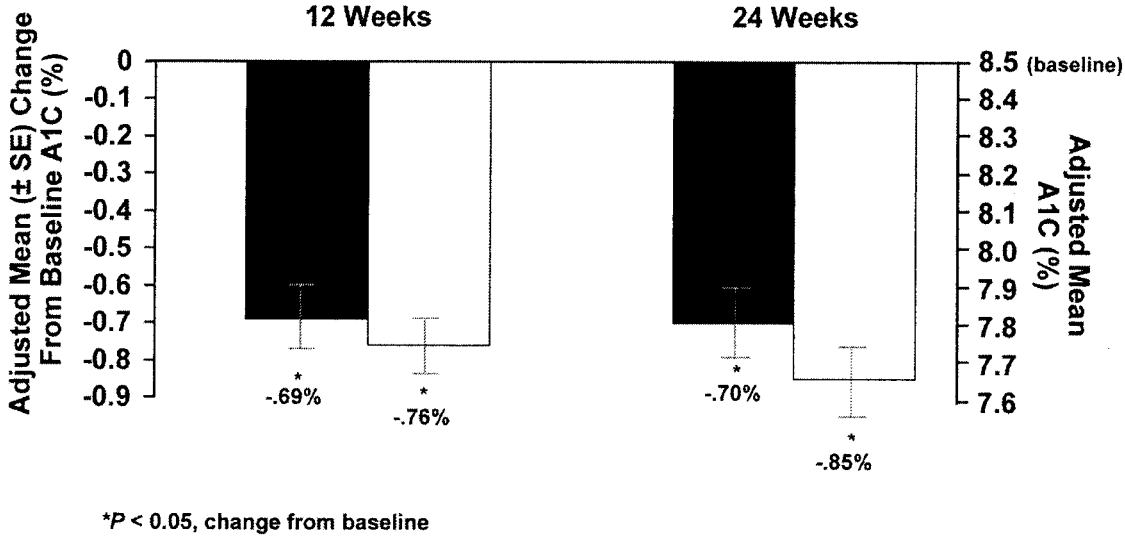

**Figure 2—*Adjusted mean change from baseline A1C in pediatric subjects with type 2 diabetes receiving either glimepiride* (n = *132) or metformin* (n = *131). ■, glimepiride; □, metformin.*

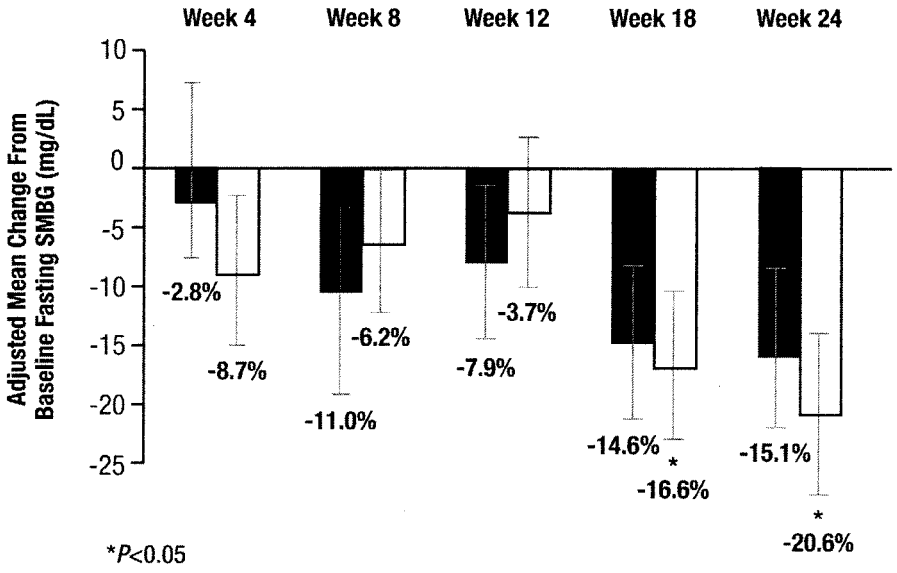

Figure 3—*Adjusted mean change from baseline in fasting SMBG in pediatric subjects with type 2 diabetes treated with glimepiride* (n = *132) or metformin* (n = *131).* ■*, glimepiride;* □*, metformin.*

subjects. Additional treatment options for children are urgently needed.

This study demonstrates that over 24 weeks, glimepiride is safe and effective for the treatment of type 2 diabetes in children and adolescents and reduced A1C levels to a similar degree as metformin. The incidence of hypoglycemia was similar for both groups, and no significant differences were found between treatments in the mean change in serum lipid concentrations; however, the small sample size reduced the power to detect differences between secondary end points. It also should be noted that the mean end-of-study glimepiride dose was relatively low (3.8 mg/day), no significant changes from baseline were seen in fasting plasma glucose, and the mean SMBG values were lower at weeks 18 and 24 for the metformin group compared with the glimepiride group, indicating that the investigators may have been conservative with glimepiride dose titration. A double-blind design using a double-dummy technique would have reduced this possibility. In studies in adults, glimepiride generally was associated with a lower risk of hypoglycemia and less weight gain than other sulfonylureas (9–11). The low rate of hypoglycemia in this pediatric study is consistent with these findings. Weight gain is a known side effect of sulfonylurea treatment. Therefore, it was not surprising to observe weight gain in the glimepiride group rather than weight loss as seen with metformin.

In conclusion, the results of this study indicate that glimepiride is safe and effective for use in the pediatric population over 24 weeks and provide a needed addition to what is known about the use of antihyperglycemic agents in this population. Longer-term studies that include additional assessments, such as testing of β-cell function, are needed to better establish the safety and efficacy profile in pediatric patients. As has been observed in adults, individually tailored therapeutic regimens are likely to be necessary to reach adequate glycemic control and prolong the period to late complications in pediatric patients with type 2 diabetes. Further studies are warranted to determine the optimal combination of diet, exercise, and oral antihyperglycemic therapy to improve short- and long-term outcomes in pediatric subjects with type 2 diabetes.

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