

# Efficacy of Benfluorex in Combination With Sulfonylurea in Type 2 Diabetic Patients

An 18-week, randomized, double-blind study

PHILIPPE MOULIN, MD, PHD<sup>1</sup>  
MARIE ANDRE, MD<sup>2</sup>  
HASAN ALAWI, MD<sup>3</sup>  
LELITA C. DOS SANTOS, MD<sup>4</sup>  
ABDUL K. KHALID, MD<sup>5</sup>

DRAGOMIR KOEV, MD<sup>6</sup>  
RAY MOORE, MRCP<sup>7</sup>  
VIOREL SERBAN, MD<sup>8</sup>  
BRIGITTE PICANDET, MD<sup>2</sup>  
MARIE FRANCILLARD, MD, PHD<sup>2</sup>

**OBJECTIVE** — The aim of this study was to demonstrate the superiority of benfluorex over placebo as an add-on therapy in type 2 diabetic patients in whom diabetes is insufficiently controlled by sulfonylurea monotherapy and who have a limitation for the use of metformin.

**RESEARCH DESIGN AND METHODS** — Type 2 diabetic patients with HbA<sub>1c</sub> (A1C) (7–10%) who were receiving the maximum tolerated sulfonylurea dose and had a contraindication to or poor tolerance of metformin were randomly assigned (double blind) to receive benfluorex 450 mg/day (*n* = 165) or placebo (*n* = 160) for 18 weeks. The main efficacy criterion was A1C, analyzed as the change from baseline to the end of treatment using ANCOVA with baseline and country as covariates. Secondary criteria were fasting plasma glucose (FPG), insulin resistance, and plasma lipid level.

**RESULTS** — Both groups were similar at baseline in the intention-to-treat population. A1C significantly decreased with benfluorex from  $8.34 \pm 0.83$  to  $7.52 \pm 1.04\%$  ( $P < 0.001$ ) and tended to increase with placebo from  $8.33 \pm 0.87$  to  $8.52 \pm 1.36\%$  (NS), resulting in a mean adjusted difference between groups of  $-1.01\%$  (95% CI  $-1.26$  to  $-0.76$ ;  $P < 0.001$ ). The target A1C ( $\leq 7\%$ ) was achieved in 34% of patients receiving benfluorex versus 12% of patients receiving placebo. Significant between-group differences in favor of benfluorex were observed for mean FPG ( $-1.65$  mmol/l) ( $P < 0.001$ ) and for homeostasis model assessment of insulin resistance. Overall tolerance was similar in both groups. Serious adverse events were more frequent in the benfluorex group, without evidence of causality relationship.

**CONCLUSIONS** — Benfluorex as an add-on therapy was superior to placebo in lowering A1C with a between-group difference of 1% in type 2 diabetic patients whose disease was insufficiently controlled with sulfonylurea alone and in whom metformin was contraindicated or not tolerated.

*Diabetes Care* 29:515–520, 2006

The incidence and progression of microvascular complications in type 2 diabetes are strongly associated with the degree of hyperglycemia. Following the results of the U.K. Prospective Diabetic

Study (UKPDS) in 1998, recommended target values for HbA<sub>1c</sub> (A1C) in type 2 diabetes were reduced from 7 to 6.5% or even lower (1,2). To achieve such goals, early initiation of combined ther-

From the <sup>1</sup>Endocrinology Department, Cardiovascular Hospital, University Claude Bernard, Lyon, France; the <sup>2</sup>Institut de Recherches Internationales Servier, Courbevoie, France; <sup>3</sup>Schwerpunkt Diabetologie Klinik, Saarlouis, Germany; the <sup>4</sup>University Hospital of Coimbra, Coimbra, Portugal; the <sup>5</sup>Universiti Kebangsaan, Kuala Lumpur, Malaysia; the <sup>6</sup>University of Sofia, Sofia, Bulgaria; the <sup>7</sup>Umhlanga Hospital, Durban, South Africa; and the <sup>8</sup>Spitalul Judetean, Timisoara, Romania.

Address correspondence and reprint requests to Prof. P. Moulin, Service d'Endocrinologie—Unite 11, Hôpital Cardio-Vasculaire Louis Pradel, 28 avenue Doyen Lepine, 69677 Bron Cedex, France. E-mail: philippe.moulin@chu-lyon.fr.

Received for publication 2 August 2005 and accepted in revised form 20 November 2005.

**Abbreviations:** FPG, fasting plasma glucose; FSI, fasting serum insulin; HOMA-IR, homeostasis model assessment of insulin resistance; ITT, intention to treat; NCEP, National Cholesterol Education Program; UKPDS, U.K. Prospective Diabetes Study.

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

© 2006 by the American Diabetes Association.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

apy is being recognized as desirable in type 2 diabetes. According to the pathophysiological mechanism of the disease, the combination of an insulin secretagogue with an insulin sensitizer is the most common drug treatment proposed for type 2 diabetic patients, in addition to diet, lifestyle counseling, and exercise. Insulin sensitizers are not a homogenous drug class. For many years, metformin was the only drug of this type on the market; now thiazolidinediones are an alternative. Both metformin and thiazolidinediones have limitations on their use: gastrointestinal intolerance is common with metformin, and although serious complications such as lactic acidosis are very infrequent, caution should be exercised in patients with cardiovascular, pulmonary, or renal insufficiency, which may be associated with hypoxia or drug accumulation (3). In prescribing thiazolidinediones, caution is required in patients with fluid retention, mildly elevated liver enzyme levels, or underlying cardiac insufficiency. Thus, alternative drugs can be useful in patients with intolerance of or contraindications to metformin and/or thiazolidinediones. Benfluorex (2-[[[(1R)-1-methyl-2-[3-(trifluoromethyl)phenyl]ethyl]-amino]ethyl benzoate hydrochloride) is a compound with both lipid-lowering and antihyperglycemic actions. Benfluorex is almost completely absorbed after oral administration. It is fully metabolized by a circulating esterase and mainly eliminated in urine. It was initially developed in patients with metabolic syndrome, mainly for European market. In further preclinical and clinical studies, benfluorex has been shown to improve insulin sensitivity, decrease hepatic glucose production, and improve aerobic glucose utilization in skeletal muscle (4–7). Benfluorex decreases gluconeogenesis by affecting the expression of genes encoding enzymes involved in both glucose and fatty acid metabolism. The mechanisms of these metabolic actions in liver and muscle differ from those of metformin: in particular, benfluorex decreases gluconeogenesis by inhibition of  $\beta$ -oxidation (4). These findings prompted the development of the product in overt type 2 diabetes. A small-scale exploratory

trial demonstrated that in overweight diabetic patients whose diabetes was poorly controlled by a sulfonylurea as monotherapy, the combination with benfluorex over 3 months led to a significant improvement in blood glucose control (8). A recent large-scale, 6-month trial in diet-failed type 2 diabetic patients demonstrated the efficacy of benfluorex versus placebo in monotherapy, with a significant 0.86% reduction in A1C and a good safety profile (9). The most common side effects are gastrointestinal disorders, asthenia, somnolence, dizziness, and headache. These data, together with the assumption of a potential benefit of benfluorex in combination with a sulfonylurea, led to the design of the present study to confirm the antidiabetic properties of benfluorex and to demonstrate its superiority over a placebo as add-on therapy in type 2 diabetic patients whose diabetes is insufficiently controlled with sulfonylurea monotherapy. In Europe the first-line therapy for this group of patients involves the combination of a sulfonylurea and metformin; patients who could not be given this combination due to a contraindication or intolerance to metformin were selected for this first pivotal trial.

## RESEARCH DESIGN AND METHODS

— Eligibility criteria were type 2 diabetes with age  $\geq 18$  years, BMI of 25–40 kg/m<sup>2</sup>, and A1C of 7–10% (inclusive) despite monotherapy with a sulfonylurea at the maximum tolerated dose for at least 4 months. All patients had to have either a history of gastrointestinal intolerance to metformin or a contraindication to its use, such as renal impairment or any cardiac or respiratory condition with a potential for tissue hypoxia (3). Exclusion criteria were severe renal impairment, an alanine aminotransferase or aspartate aminotransferase plasma level three times above the upper limit of normal, active proliferative retinopathy, uncontrolled high blood pressure ( $\geq 180/100$  mmHg), or any disorder that could interfere with the study conduct or end point evaluation. Patients were withdrawn for lack of efficacy, which was defined as two fasting plasma glucose (FPG) measurements  $\geq 15$  mmol/l, after at least 1 month of study treatment.

A randomized, placebo-controlled, double-blind, parallel-group study, with an 18-week comparative treatment period, was conducted in 63 centers in seven countries. After a 2- to 4-week run-in period, patients were centrally randomly assigned to receive tablets contain-

ing either placebo or 150 mg benfluorex (Les Laboratoires Servier Industrie, Gidy, France), the dose being gradually increased over the first 3 weeks from one tablet per day to the recommended dose of one tablet three times daily. The dose of sulfonylurea was to be maintained throughout the study, except in patients with severe or repeated hypoglycemia. Subjects were asked to maintain their usual diet and physical activity. The primary efficacy end point was A1C. The secondary end points were FPG, fasting serum insulin (FSI), and lipid profile, each assessed at inclusion and at weeks 4, 10, and 18, and insulin resistance index evaluated at baseline and week 18. An interactive voice response system was used for centralized randomization, stratified by baseline A1C ( $\leq 8$  or  $>8\%$ ) and geographic area. The protocol was approved by each institution's ethics committee. The trial was conducted in accordance with the ethical principles stated in the Declaration of Helsinki 1964, as revised in Edinburgh, U.K., in October 2000. All subjects provided written informed consent.

## Assessments

A1C, FPG, FSI, and standard biochemical, hematological, and lipid parameters were assessed centrally (MDS Pharma Services, Hamburg, Germany). Creatinine clearance was calculated according to the Cockcroft formula (10). A1C was assayed using an National Glycohemoglobin Standardized Program–certified high-performance liquid chromatography method (BioRad Variant I). FPG was assessed by a hexokinase method; all glucose and lipid assays were performed on a Hitachi 747 instrument (Boehringer Mannheim, Mannheim, Germany). FSI was measured by a specific radioimmunoassay; the insulin resistance index (homeostasis model assessment of insulin resistance [HOMA-IR]) was calculated using the classic homeostasis assessment model (11). Safety was assessed by adverse event spontaneous reporting, physical examination, recording of vital signs, laboratory tests, and 12-lead electrocardiogram at baseline and at week 18. Hypoglycemic events were recorded from the patient diary and were based on suggestive clinical symptoms only.

## Statistical analysis

Sample size was estimated based on a 0.6% between-group difference in A1C and an assay standard deviation of 1.5%,

using a two-sided Student's *t* test for independent samples with 90% power, a type 1 error of 5%, and a 10% drop-out rate. The intention-to-treat (ITT) population was defined as all randomly assigned patients exposed to the study drug with a baseline value and at least one A1C value during treatment. Per-protocol patients were defined as patients who completed the study without a deviation affecting the A1C evaluation. For efficacy analyses, the difference between benfluorex and placebo treatment was studied as the change from baseline to last value with treatment using ANCOVA with baseline and geographic area as covariates. The within-group evolution between baseline and the last value during treatment was studied in each treatment group using a two-sided paired Student's *t* test. Nonparametric approaches were performed for triglyceridemia and HOMA-IR analyses. Three subgroups were predefined according to regulatory requirements (12): A1C at inclusion  $>8\%$ , age at selection  $>65$  years, and creatinine clearance  $\leq 80$  ml/min. Safety analyses were performed on all patients exposed to at least one dose of study treatment. Final values for withdrawn patients corresponded to the last values during treatment. All statistical analyses were performed using SAS software (version 8.2; SAS, Cary, NC).

## RESULTS

### Demographic and baseline characteristics

A total of 325 patients were included: 165 were randomly assigned to benfluorex and 160 to placebo. There were 317 patients (97%) in the ITT population. Thirty withdrawals (9.2%) occurred, 21 for patients receiving benfluorex and 9 for patients receiving the placebo; 18 patients withdrew because of adverse events (12 receiving add-on benfluorex and 6 receiving the placebo), 2 patients withdrew because of lack of efficacy (1 in each group), and 10 patients withdrew for nonmedical reasons. There were 265 patients (81%) in the per-protocol population. The ITT and per-protocol populations were similar at inclusion. Baseline characteristics were broadly similar in the two groups (Table 1). Overall, 73% of patients had a metabolic syndrome [modified National Cholesterol Education Program (NCEP) Adult Treatment Panel III definition (13)] and 57% of patients had previous gastrointestinal intolerance to metformin. Concomitant treatment was being taken by

Table 1—Baseline characteristics in the randomized population

	Benfluorex	Placebo
n	165	160
Age (years)	62.9 ± 10.8	64.8 ± 10.3
Sex (men/women)	86/79	68/92
Diabetes duration (years)	6.8 ± 5.8	7.5 ± 6.1
BMI (kg/m <sup>2</sup> )	29.5 ± 3.7	29.3 ± 3.7
Presence of metabolic syndrome (%)	72.1	73.1
Hypertension (%)	68.5	70.6
Sitting systolic blood pressure (mmHg)	139.2 ± 13.3	138.7 ± 14.0
Sitting diastolic blood pressure (mmHg)	80.9 ± 7.3	80.0 ± 7.2
Diabetes complications		
Coronary heart disease (%)	35.2	37.5
Nephropathy (%)	12.1	11.9
Neuropathy (%)	14.5	15.0
Ophthalmologic (%)	10.9	12.5
A1C (%)	8.32 ± 0.83	8.32 ± 0.87
FPG (mmol/l)	9.87 ± 2.54	9.67 ± 2.39
HOMA-IR (index)*	6.62 ± 7.99	6.35 ± 7.95
Creatinine clearance (ml/min)	93.2 ± 33.5	86.0 ± 28.6
Creatinine clearance ≤80 ml/min (%)	60.6	50.0
Total cholesterol (mmol/l)	5.54 ± 1.04	5.49 ± 1.13
LDL cholesterol (mmol/l)	3.57 ± 0.80	3.55 ± 0.89
HDL cholesterol (mmol/l)	1.27 ± 0.31	1.28 ± 0.28
Triglycerides (mmol/l)	2.35 ± 2.01	2.16 ± 1.33

Data are means ± SD unless otherwise indicated. \*HOMA-IR was calculated for the ITT population.

280 patients (86%), mainly ACE inhibitors and antihypertensive drugs. Lipid-lowering agents were being taken by 70 patients (22%), 54 of whom were receiving statins. Less than 5% of patients had their sulfonylurea dose modified. The subgroup of patients with A1C >8% (94 patients receiving add-on benfluorex and 91 receiving placebo), of age >65 years (72 patients receiving benfluorex and 84 on placebo), and of creatinine clearance ≤80 ml/min (65 patients receiving benfluorex and 80 receiving placebo) accounted for 57, 48, and 45%, respectively, of the included patients.

### Efficacy

In the add-on benfluorex group, glycemic control was markedly improved by week 4 and continued to improve throughout the study (Fig. 1A). After 18 weeks, A1C decreased in the ITT population by  $-0.82\%$  ( $P < 0.001$ ) (Table 2). With add-on placebo, there was a trend toward an increase in A1C from weeks 4 to 18 (NS), resulting in a between-group difference of  $-1.01\%$  ( $P < 0.001$ ). A decrease in A1C of  $\geq 1\%$  was seen in 42.9% of patients receiving add-on benfluorex versus 14.7% receiving placebo ( $P < 0.001$ ). A decrease in A1C of  $\geq 0.5\%$  was seen in 69.6% of patients receiving benfluorex

versus 27.5% receiving placebo ( $P < 0.001$ ). Target values of  $\leq 7\%$  were achieved by 34.2% of patients receiving benfluorex versus 11.5% of patients receiving placebo ( $P < 0.001$ ), whereas 18.5% of patients achieved an objective of  $\leq 6.5\%$  with benfluorex versus 4.5% with placebo ( $P < 0.001$ ). In patients with baseline A1C in the range of 7 to 8%, a target value of  $\leq 7\%$  was achieved by 47.1% of patients in the benfluorex group versus 14.9% in the placebo group ( $P < 0.001$ ). Similar results were observed in the per-protocol population, with a  $-1.08\%$  difference of A1C between the benfluorex and placebo groups. FPG consistently decreased with benfluorex, with a between-group difference after 18 weeks of  $-1.65$  mmol/l ( $P < 0.001$ ) (Table 2 and Fig. 1B). Similar changes over time in A1C and FPG were seen in the subgroups according to A1C >8%, age >65 years, and impairment of renal function. A slight decrease in weight was observed in both groups, with a nonclinically relevant difference between benfluorex and placebo:  $-1.3$  kg with benfluorex versus  $-0.7$  kg with placebo ( $P < 0.01$ ). The superiority of benfluorex

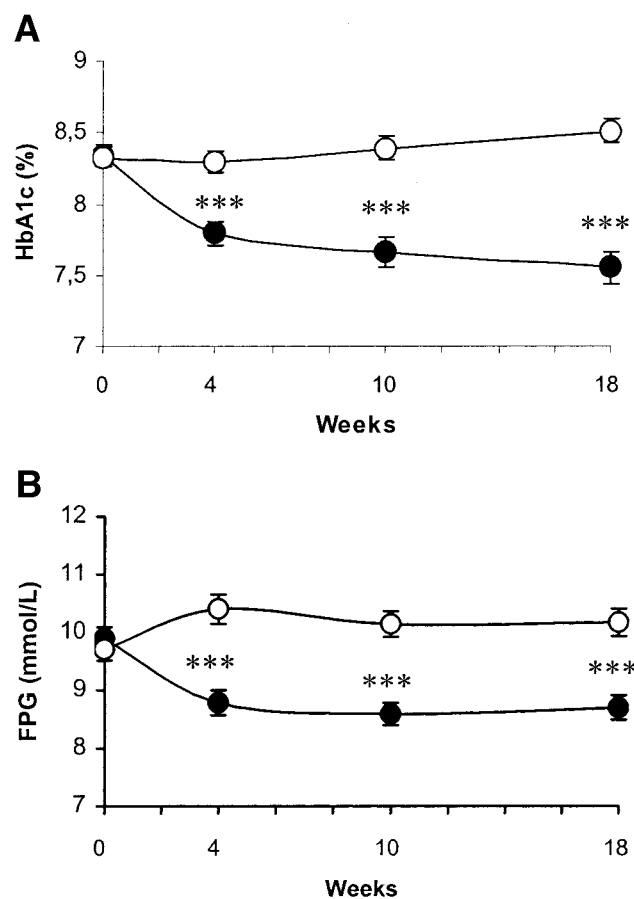


Figure 1—Changes in A1C (A) and FPG (B) over time in the ITT population. Data are means ± SEM. \*\*\* $P < 0.001$  with between-group test. ●, benfluorex group; ○, placebo group.

over placebo with respect to A1C was independent of the decrease in body weight: the estimated between-group difference in A1C from the covariance analysis performed with adjustment for weight evolution was  $-0.96\%$  ( $P < 0.001$ ).

Insulin resistance as assessed by HOMA-IR decreased over the study by 20% (from  $6.62 \pm 7.99$  at baseline to  $4.87 \pm 3.67$ ) with benfluorex and by 5% (from  $6.35 \pm 7.95$  to  $5.93 \pm 5.35$ ) with placebo, with a statistically significant between-group difference ( $P < 0.01$ ) (Table 2). In terms of the lipid profile (Table 2), with benfluorex, LDL cholesterol decreased by 6% and triglycerides by 7%. More than one-third (35.5%) of the patients treated with benfluorex had a favorable evolution of their LDL cholesterol: from  $\geq 130$  mg/dl at baseline to below this level at the end of the study [cutoff point as used in the NCEP recommendations (14)] compared with 14.3% of patients receiving a placebo. At the end of the study, 34.5% of patients receiving benfluorex had plasma triglycerides  $< 2.2$  mmol/l (baseline  $\geq 2.2$  mmol/l) versus 24.1% of patients receiving placebo. The changes from baseline in the benfluorex group were  $-0.27 \pm 0.73$  mmol/l for calculated LDL cholesterol and  $-0.05 \pm 2.08$  mmol/l for triglycerides (median  $-0.12$  mmol/l), with a significant between-group difference in favor of benfluorex ( $P < 0.001$  for LDL cholesterol and  $P = 0.027$  for triglycerides). No change in HDL cholesterol was observed.

### Safety and tolerability

A similar proportion of patients in each group (53.0% receiving benfluorex and 51.3% receiving a placebo) reported at least one adverse event. Gastrointestinal disorders were the most common adverse events, occurring in 15.1% of patients in the benfluorex group and 10.0% of patients in the placebo group, and mostly involved diarrhea (6.0% of patients receiving benfluorex vs. 1.9% receiving placebo). Two patients treated with benfluorex were withdrawn because of diarrhea (1.2%). In patients with known previous intestinal intolerance to metformin, the incidence of gastrointestinal disorders was the same with benfluorex and placebo (15.2 vs. 15.3%, respectively).

Hypoglycemic symptoms were more frequently reported with sulfonylurea and benfluorex (24 episodes in 14 patients) than with sulfonylurea and placebo (13 episodes in 6 patients). No

episode required external assistance or hospitalization. Headache was reported by 2.4% of patients receiving benfluorex and by 2.5% receiving placebo. Other adverse events were reported in fewer than 2% of patients. Very few adverse events were considered related to the study drug (6.6% of patients receiving benfluorex vs. 1.3% receiving placebo, mostly diarrhea or abdominal pain). Serious adverse events (fatal and nonfatal) occurred in 11 patients. Two fatal events were reported in the benfluorex group, without any obvious causal relationship: one patient committed suicide (4 weeks after a ischemic cerebrovascular attack) and the other died as a result of cerebrovascular hemorrhage. One patient in the placebo group had two independent serious nonfatal adverse events (unstable angina and hyperglycemia). Nine patients in the benfluorex group had 10 serious nonfatal adverse events: diabetic neuropathy, pyelonephritis and ovarian cyst, nephrolithiasis, cerebrovascular accident, lumbar radiculopathy, biliary neoplasm, cardiac failure after inappropriate termination of diuretic therapy, pleural metastasis, and abdominal pain. Of these, the last three led to patient withdrawal. Only for abdominal pain was there thought to be a causal relationship; the others reasons were considered to be related to each patient's medical history or concomitant pathologic conditions. There were no significant changes in the electrocardiogram or biological safety chemical parameters, including liver enzyme levels. Mean sitting diastolic and systolic blood pressures were similar in the benfluorex group and the placebo group, with no clinically relevant changes at the end of the study.

**CONCLUSIONS**— This is the first large-scale study of the efficacy and safety of benfluorex as add-on therapy in type 2 diabetic patients whose diabetes was suboptimally controlled with sulfonylureas at their maximum tolerated dose. The design versus placebo, the good compliance with the protocol procedure and with treatment (drop-out rate  $< 10\%$  with no patients lost to follow-up), and the consistency of results across the analyses make the analysis of the results reliable. Moreover, the patient population was representative of patients with type 2 diabetes in terms of disease duration (mean  $\pm$  SD  $7.1 \pm 6.0$  years), BMI (mean  $29$  kg/m<sup>2</sup>), presence of metabolic syndrome (in 73% of patients), and the presence of diabetic cardiovascular complications and hyperten-

sion. They had inadequate glycemic control, with a mean A1C of 8.32%.

This study demonstrates that the agent studied, benfluorex, as add-on therapy behaved throughout the trial as an active glucose-lowering drug that significantly and markedly improved glycemic control. After 18 weeks, the mean A1C was significantly reduced by  $-0.82 \pm 1.04\%$  in the benfluorex group with a between-group difference of  $-1.01\%$ . This reduction in A1C was seen in each subgroup, especially in patients with a baseline A1C  $> 8\%$ , with a between-group difference of  $-1.10\%$ . More than 40% of the patients receiving benfluorex (vs. 15% receiving placebo) had an A1C decrease  $\geq 1\%$ , and a significantly larger number of patients than in the placebo group achieved a target A1C  $\leq 7\%$  or even a target of  $\leq 6.5\%$ . This amplitude of A1C decrease has been demonstrated to be of significant clinical benefit. In the UKPDS 35, a 1% reduction in A1C corresponded to a 37% reduction in risk of microvascular complications and a 21% reduction in the risk of death related to diabetes (15). Although the majority of patients did not have any major plasma lipid abnormalities at baseline, some mild improvements were observed, particularly for LDL cholesterol. An interesting finding is the concomitant improvement in other metabolic parameters, especially the insulin resistance index and plasma triglycerides, which have been shown to be independent risk factors for coronary heart disease in the type 2 diabetic patient population, whereas no deleterious effect was observed on weight and blood pressure (12). Finally, the reduction in A1C with benfluorex in this study is consistent with the findings of previous studies: means  $\pm$  SEM  $-0.86 \pm 0.17\%$  ( $P < 0.001$ ) after 29 weeks of monotherapy in 294 patients whose diabetes was inadequately controlled by diet alone (9) and, in a less powered study (68 patients),  $-0.66\%$  after 12 weeks of combined treatment with sulfonylurea and benfluorex (8). The magnitude of the effect of benfluorex on blood glucose control is comparable with those observed with other recently registered drugs. Thus, trials using rosiglitazone in combination with a sulfonylurea showed between-group differences versus placebo of  $-1.0$  and  $-0.9\%$  for A1C (16,17).

As expected, episodes suggestive of hypoglycemia were more frequent with benfluorex than with placebo, although overall there were not many of these hy-

poglycemic events as a consequence of the sulfonylurea treatment and of the improvement in glycemic control demonstrated in the benfluorex group. The downward shift in glucose levels over 18 weeks combined with the known improvement in insulin sensitivity may explain the small increase in the rate of hypoglycemia. Previous studies have shown that benfluorex does not have any effect on insulin secretion by itself.

This trial was specifically carried out in patients for whom metformin use was inappropriate due to known intolerance or a contraindication. According to this patient selection strategy, it was easy to establish that there is obviously no overlap between poor gastrointestinal tolerance to metformin and gastrointestinal side effects (mainly diarrhea) related to benfluorex; the proportion of patients who did not tolerate metformin before the trial and who developed such a side effect was 15% with both benfluorex and placebo treatment. Moreover, in the whole study population, gastrointestinal effects remained moderate, resulting in eight patients withdrawing (five in the benfluorex group and three in the placebo group). Overall tolerance was similar in both groups. Serious adverse events were more frequent in the benfluorex group but without evidence of any causality relationship. No concern was raised in previous studies with 5,093 patients taking benfluorex from 2 weeks to 3 years.

This trial confirms the efficacy of benfluorex in achieving targets for glycemic control and suggests the possibility of using benfluorex as a first-line insulin sensitizer, particularly for an unmet medical need when metformin is not tolerated or contraindicated. To properly confirm and evaluate the clinical relevance of this new authentic antidiabetic agent, it will be of interest to perform additional trials to assess by direct comparison the efficacy and safety profile of benfluorex versus other recent insulin sensitizers such as the thiazolidinediones in type 2 diabetic patients.

**Acknowledgments**— This trial was sponsored by Institut de Recherches International Servier, Courbevoie, France, and supervised by the authors, who were national coordinators.

Parts of this work were presented as an oral presentation at the 41st annual meeting of the European Association for the Study of Diabetes (EASD), Athens, Greece, September 2005.

**Table 2—Changes in glycemic and lipid parameters in the ITT population**

	Benfluorex			Placebo			Between-group difference	P value
	n	Baseline	Final	n	Baseline	Final		
A1C overall (%)	161	8.34 ± 0.83	7.52 ± 1.04	156	8.33 ± 0.87	8.52 ± 1.36	0.19 (0.11)	<0.001
A1C >8% (%)	93	8.93 ± 0.53	7.78 ± 1.11	89	8.96 ± 0.56	8.90 ± 1.39	-0.06 (0.15)	<0.001
Age >65 years (%)	70	8.28 ± 0.80	7.42 ± 0.89	82	8.31 ± 0.87	8.28 ± 1.24	-0.03 (0.13)	<0.001
Creatinine clearance ≤80 ml/min (%)	62	8.17 ± 0.76	7.38 ± 0.97	78	8.32 ± 0.87	8.59 ± 1.34	0.27 (0.15)	<0.001
FPG (mmol/l)	159	9.89 ± 2.57	8.67 ± 2.46	156	9.71 ± 2.39	10.22 ± 2.88	0.51 (0.23)	<0.001
HOMA-IR (index)	157	6.62 ± 7.99	4.87 ± 3.67	150	6.35 ± 7.95	5.93 ± 5.35	-0.42 (0.65)	<0.01
LDL (mmol/l)	149	3.60 ± 0.80	3.33 ± 0.72	152	3.52 ± 0.89	3.56 ± 0.92	0.04 (0.05)	<0.001
HDL cholesterol (mmol/l)	151	1.25 ± 0.28	1.23 ± 0.30	152	1.28 ± 0.28	1.25 ± 0.31	-0.03 (0.02)	NS
Triglycerides (mmol/l)	151	2.26 ± 1.62	2.21 ± 2.18	152	2.11 ± 1.32	2.13 ± 1.18	0.05*	<0.05

Data are estimates of the change for end minus baseline for the within-group analysis and estimates of the difference for benfluorex minus placebo of adjusted group means and are expressed as means ± SD for baseline. \*Nonparametric test.

References

1. European Diabetes Policy Group 1999: A desktop guide to type 2 diabetes mellitus. *Diabet Med* 16:716–730, 1999
2. American Diabetes Association: Standards of medical care in diabetes. *Diabetes Care* (Suppl. 1)28:S4–S36, 2005
3. Howlett HC, Bailey CJ: A risk-benefit assessment of metformin in type 2 diabetes mellitus. *Drug Saf* 20:489–503, 1999
4. Kohl C, Ravel D, Girard J, Pegorier JP: Effects of benfluorex on fatty acid and glucose metabolism in isolated rat hepatocytes: from metabolic fluxes to gene expression. *Diabetes* 51:2363–2368, 2002
5. Bianchi R, Bongers V, Bravenboer B, Erkelens DW: Effects of benfluorex on insulin resistance and lipid metabolism in obese type II diabetic patients. *Diabetes Care* 16:557–559, 1993
6. De Feo P, Lavielle R, De Gregoris P, Bolli GB: Anti-hyperglycaemic mechanisms of benfluorex in type II diabetes mellitus. *Diabetes Metab Rev* 9 (Suppl. 1):35S–41S, 1993
7. Riccio A, Vigili de Kreutzenberg S, Dorella M, Da Tos V, De Biasi L, Marescotti MC, Tiengo A, Del Prato S: Mechanism(s) of the blood glucose lowering action of benfluorex. *Diabetes Metab Rev* 9 (Suppl. 1): 19S–27S, 1993
8. Stucci N, De Gregoris P, Lavielle R, Tomasi F: Therapeutic benefit of benfluorex in type II diabetic patients treated with sulfonylureas. *J Diabetes Complications* 10: 267–273, 1996
9. Del Prato S, Erkelens DW, Leutenegger M: Six-month efficacy of benfluorex vs. placebo or metformin in diet-failed type 2 diabetic patients. *Acta Diabetol* 44:20–27, 2003
10. Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron* 16:31–41, 1976
11. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28:412–419, 1985
12. The European Agency for the Evaluation of Medicinal Products: *Evaluation of Medicines for Human Use*. London, May 2002 (CPMP/EWP/1080/00)
13. NCEP Adult Treatment Panel III: Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 285:2486–2497, 2001
14. Grundy SM, Cleeman JI, Merz NB, Brewer B Jr, Clark LT, Hunninghake DB, Pasternak RC, Smith SC Jr, Stone NJ, for the Coordinating Committee of the National Cholesterol Education Program: Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 110:227–239, 2004
15. U.K. Prospective Diabetes Study Group: Association of glycaemia with macrovascular and microvascular complications of type II diabetes: prospective observational study (UKPDS 35). *BMJ* 321:405–412, 2000
16. *Rosiglitazone Prescribing Information 2004*. GlaxoSmithKline Clinical Trial Register—Clinical Trial Information for Study 49653/015
17. *Rosiglitazone prescribing information 2004*. GlaxoSmithKline Clinical Trial Register—Clinical Trial Information for Study 49653/096