XENical in the Prevention of Diabetes in Obese Subjects (XENDOS) Study

A randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients

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OBJECTIVE — It is well established that the risk of developing type 2 diabetes is closely linked to the presence and duration of overweight and obesity. A reduction in the incidence of type 2 diabetes with lifestyle changes has previously been demonstrated. We hypothesized that adding a weight-reducing agent to lifestyle changes may lead to an even greater decrease in body weight, and thus the incidence of type 2 diabetes, in obese patients.

RESEARCH DESIGN AND METHODS — In a 4-year, double-blind, prospective study, we randomized 3,305 patients to lifestyle changes plus either orlistat 120 mg or placebo, three times daily. Participants had a BMI ≥30 kg/m^2 and normal (79%) or impaired (21%) glucose tolerance (IGT). Primary endpoints were time to onset of type 2 diabetes and change in body weight. Analyses were by intention to treat.

RESULTS — Of orlistat-treated patients, 52% completed treatment compared with 34% of placebo recipients ($P < 0.0001$). After 4 years' treatment, the cumulative incidence of diabetes was 9.0% with placebo and 6.2% with orlistat, corresponding to a risk reduction of 37.3% ($P = 0.0032$). Exploratory analyses indicated that the preventive effect was explained by the difference in subjects with IGT. Mean weight loss after 4 years was significantly greater with orlistat (5.8 vs. 3.0 kg with placebo; $P < 0.001$) and similar between orlistat recipients with impaired (5.7 kg) or normal glucose tolerance (NGT) (5.8 kg) at baseline. A second analysis in which the baseline weights of subjects who dropped out of the study was carried forward also demonstrated greater weight loss in the orlistat group (3.6 vs. 1.4 kg; $P < 0.001$).

CONCLUSIONS — Compared with lifestyle changes alone, orlistat plus lifestyle changes resulted in a greater reduction in the incidence of type 2 diabetes over 4 years and produced greater weight loss in a clinically representative obese population. Difference in diabetes incidence was detectable only in the IGT subgroup; weight loss was similar in subjects with IGT and or NGT.

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Obesity is a serious health concern affecting >300 million people worldwide, representing a 50% increase in only 7 years (1). A number of studies (2–4) show that the risk of developing type 2 diabetes is closely linked to the presence and duration of overweight and obesity. Indeed, ~90% of individuals with type 2 diabetes are either overweight or obese (5). The World Health Organization has estimated that the number of adults with diabetes will more than double from an estimated 143 million in 1997 to 300 million by 2025 (5).

The Swedish Obese Subjects (SOS) study has demonstrated that large weight losses in obese patients are associated with an 80% reduction in the 8-year incidence of diabetes (6). The Finnish Diabetes Prevention Study (DPS) and the Diabetes Prevention Program (DPP) have also demonstrated that modest weight loss achieved by lifestyle changes (diet and exercise) can significantly reduce the risk of developing type 2 diabetes in obese patients with impaired glucose tolerance (IGT) (7,8). A retrospective analysis of obese patients with IGT receiving orlistat treatment has shown that this weight loss agent may also be effective in reducing the progression to type 2 diabetes (9).

The prospective XENDOS (XENical in the prevention of Diabetes in Obese Subjects) study was primarily conducted to determine the long-term effect of orlistat, a gastrointestinal lipase inhibitor, in combination with lifestyle changes in reducing progression to type 2 diabetes and body weight over 4 years in obese, nondiabetic patients who had either normal glucose tolerance (NGT) or IGT. Secondary aims were to determine the effect of orlistat treatment on weight-related metabolic abnormalities associated with increased risk for cardiovascular disease and the safety and tolerability of orlistat over 4 years.

RESEARCH DESIGN AND METHODS

— XENDOS was a 4-year, double-blind, randomized, placebo-controlled prospective study carried out at 22 Swedish medical centers between 1997 and 2002. Details of the study design and the system for centralized patient recruitment and scheduling of patients and staff at the centers have been described previously (10). The study proto-

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Abbreviations: BLCF, baseline observation carried forward; DPP, Diabetes Prevention Program; DPS, Diabetes Prevention Study; IGT, impaired glucose tolerance; ITT, intention to treat; LOCF, last observation carried forward; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; XENDOS, XENical in the prevention of Diabetes in Obese Subjects.

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

col was approved by all relevant ethics review committees in Sweden and was conducted in accordance with the Declaration of Helsinki. All study subjects gave written informed consent.

Participants

Eligible patients were 30–60 years of age, with a BMI ≥30 kg/m^2. Patients were required to have nondiabetic glucose tolerance as assessed by a 75-g oral glucose tolerance test (OGTT) performed at baseline using venous whole blood and the 1994 World Health Organization criteria (2-h whole blood glucose <10.0 mmol/l and fasting whole blood glucose <6.7 mmol/l) (11). Patients with IGT were also eligible for inclusion, and the criteria for IGT were fasting whole blood glucose <6.7 mmol/l and 2-h whole blood glucose 6.7–10.0 mmol/l (11). (These criteria for IGT correspond to fasting venous plasma glucose <7.8 mmol/l and 2-h plasma glucose 7.8–11.1 mmol/l [11].)

Exclusion criteria included diabetes and ongoing and active cardiovascular and gastrointestinal disease and are described in detail elsewhere (10).

After screening, eligible patients were randomized according to sex and OGTT results to receive either placebo or orlistat in a one-to-one ratio, using a centralized randomization procedure and schedule. Blinding was ensured by use of matching placebo and orlistat capsules. The investigators received sealed envelopes for each patient that contained the identity of the study medication.

Treatment regimen

During the entire study period, all patients were prescribed a reduced-calorie diet (~800 kcal/day deficit) containing 30% of calories from fat and not more than 300 mg of cholesterol per day. The prescribed energy intake was readjusted every 6 months to account for any weight lost during the preceding months. Participants received dietary counseling every 2 weeks for the first 6 months and monthly thereafter. Patients were also encouraged to walk at least 1 extra kilometer a day in addition to their usual physical activity. All patients kept physical activity diaries.

Patients were randomized to orlistat 120 mg or placebo t.i.d. with breakfast, lunch, and dinner. Compliance was determined by counting the number of capsules returned by the patients at clinic visits and comparing the estimated percentage used against that dispensed.

Assessments

A 75-g OGTT was performed at baseline and then at every 6 months. Diagnosis of type 2 diabetes was based on a single 2-h whole blood glucose measure ≥10 mmol/l. After the first 6 months of the study, by a protocol amendment, patients with a diabetic OGTT underwent a repeat OGTT within 4 weeks. A repeat positive test was based on a 2-h whole blood glucose ≥10 mmol/l, a whole blood fasting glucose ≥6.7 mmol/l, or two consecutive fasting whole blood glucose measurements ≥6.7 mmol/l. Patients diagnosed with type 2 diabetes remained in the study and had fasting whole blood glucose levels measured at 6-month intervals.

Body weight was recorded at every study visit (every 3 months). Waist circumference was assessed at baseline, months 3 and 6, and every 6 months thereafter. Waist circumference was measured halfway between the lower rib margin and the iliac crest in the recumbent position after a normal expiration.

Standard clinical laboratory parameters, as well as plasma levels of the fat-soluble vitamins (vitamin A [retinol], 1,25-hydroxyvitamin D, 25-hydroxyvitamin D, vitamin E [α-tocopherol], and vitamin K_1), were assessed every 6 months. Fasting blood samples were obtained before taking study medication and were analyzed by a central laboratory (Nova Medical Medi-Lab, Copenhagen, Denmark). Energy intake was estimated with a validated self-administered food questionnaire (12).

Outcome measures

The primary outcome measures were time to onset of type 2 diabetes and change in body weight after 4 years' treatment. Exploratory subgroup analyses of these variables were also conducted for patients with IGT or NGT at baseline.

Secondary efficacy variables included change from baseline in anthropometric measurements, metabolic profile, and (in baseline NGT subjects) time to onset of IGT.

Statistical analysis

Based on a literature survey and previous experience, the hazard ratio for the onset of type 2 diabetes was assumed to be two-to-one for placebo-to-orlistat. Therefore, a two-sided log-rank test would require a minimum of ~95 primary cases of type 2 diabetes in both study groups combined to have 90% power of detecting a significant outcome at $\alpha = 0.05$. With this event-based design, 3,305 patients were randomized and followed until sufficient events occurred. As a consequence of the design, study power would be unaffected by dropout rate.

The intent-to-treat (ITT) population, used for the primary end point of time to onset of type 2 diabetes, consisted of all randomized patients who received at least one dose of study drug and had at least one follow-up efficacy assessment. Based on the ITT population, cumulative incidence rates of type 2 diabetes were calculated using a Kaplan-Meier estimate-of-survival function with partitions at 6-month intervals (the interval at which OGTTs were conducted). Because OGTT measurements were taken less frequently than body weight measurements (the first OGTT after randomization was taken at week 24), fewer patients were included in the ITT analyses of diabetes than of weight loss. The safety population consisted of all patients who received at least one dose of orlistat with a safety follow-up.

Statistical significance of differences between treatment groups for the primary end point of time to onset of diabetes were determined by the log-rank test (SAS PROC LIFETEST; SAS/STAT version 8). If significant, hazard ratios were determined as an estimate of relative risk of developing diabetes. The hazard ratio was derived using SAS PROC PHREG (Proportional Hazards Regression Methods; SAS/STAT version 8) with stratification factors of baseline glucose tolerance (IGT or NGT) and sex. To determine the effect of age and BMI on the relative risk of developing type 2 diabetes, age and BMI subgroups were categorized at baseline as above or below the median.

Quantitative changes in primary and secondary efficacy parameters were analyzed at yearly time points using an ANCOVA model. This included change from baseline as the response variable and center, treatment, and center-by-treatment interaction as the independent variables. Baseline values were used as covariates. For lipid parameters, the response variable was percentage change. We also analyzed body weight changes categorically. Descriptive statistics for all secondary parameters involving changes over time used observed data. Descriptive statistics

Table 1—*Demographic and clinical characteristics of the study participants at baseline ITT population*

	Placebo + lifestyle	Orlistat + lifestyle
n	1,637	1,640
Sex (*n* [%])		
Female	905 (55.3)	905 (55.2)
Male	732 (44.7)	735 (44.8)
Age (years)	43.7 ± 8.0	43.0 ± 8.0
Weight (kg)	110.6 ± 16.5	110.4 ± 16.3
BMI (kg/m^2)	37.4 ± 4.5	37.3 ± 4.2
Waist circumference (cm)	115.4 ± 10.4	115.0 ± 10.4
IGT patients (*n* [%])	344 (21)	350 (21.3)
Whole blood glucose		
Fasting (mmol/l)	4.6 ± 0.6	4.6 ± 0.6
2 h (mmol/l)	5.5 ± 1.6	5.5 ± 1.6
AUC (mmol · min^{-1} · l^{-1})	799 ± 179	804 ± 175
Serum insulin		
Fasting (pmol/l)	83.6 ± 47.2	86.1 ± 50.1
2 h (pmol/l)	344.9 ± 298.5	370.9 ± 336.7
AUC (nmol · min^{-1} · l^{-1})	47.7 ± 28.4	49.7 ± 31.3
Diastolic BP (mmHg)	82.3 ± 10.0	82.0 ± 10.0
Systolic BP (mmHg)	130.4 ± 15.4	130.8 ± 15.8
Total cholesterol (mmol/l)	5.8 ± 1.0	5.8 ± 1.0
LDL cholesterol (mmol/l)	3.8 ± 0.9	3.7 ± 0.9
HDL cholesterol (mmol/l)	1.2 ± 0.3	1.2 ± 0.3
LDL-to-HDL ratio	3.3 ± 1.0	3.2 ± 1.1
Triglycerides (mmol/l)	1.9 ± 1.2	1.9 ± 1.0
Fibrinogen (μmol/l)	11.7 ± 2.0	11.7 ± 2.2
Plasminogen activator inhibitor-1 (U/ml)	22.9 ± 10.0	23.1 ± 10.0
Energy intake (kcal/day)	2,927 ± 1,148	2,909 ± 1,030

Data are means ± SD, unless otherwise noted. AUC, area under the curve, BP, blood pressure.

for change in body weight and categorical body weight changes used last observation carried forward (LOCF) data unless otherwise noted. Observed, LOCF, and baseline observation carried forward (BLCF) (13) methods were used for hypothesis testing of quantitative parameters.

RESULTS — From August to December 1997, 3,305 study participants were randomized to treatment with orlistat plus lifestyle changes (n = 1,650) or placebo plus lifestyle changes (n = 1,655), of which 3,304 were treated. The last 4-year examination was completed in February 2002. The ITT population comprised 1,640 (orlistat group) and 1,637 (placebo group) patients. The baseline demographic and clinical characteristics of the two treatment groups were similar (Table 1). The safety population comprised 1,649 and 1,655 patients, respectively. A greater number of orlistat-treated patients completed treatment compared with placebo-treated patients (850 of 1,650 [52%] vs. 564 of 1,655 [34%]; $P <$ 0.0001). For both the orlistat and placebo groups, the most common causes of premature discontinuation were refusal of treatment (14 and 20%, respectively) and insufficient therapeutic response (8 and 19%, respectively).

Baseline data were compared between completers and noncompleters. There was no substantial difference at baseline in age, weight, BMI, or the male-to-female ratio between completers and noncompleters in either treatment group (data not shown).

Adherence

For the ITT population, the actual calorie deficit over the 4 study years was similar to the prescribed 800 kcal/day deficit: −673 ± 825 kcal/day in orlistat-treated patients and −744 ± 935 kcal/day in placebo-treated patients. Orlistat- and placebo-treated patients walked similar additional distances over the 4 years (mean ± SD: an extra 9.5 ± 6.6 and 9.9 ± 8.3 km/week, respectively).

Average compliance with study drug administration from first dose until treatment termination was 93.3% for orlistat patients and 92.8% for placebo patients. This difference was not statistically significant.

Primary efficacy parameters

Incidence of type 2 diabetes. During 4 years of treatment, orlistat plus lifestyle changes significantly decreased the progression to type 2 diabetes compared with placebo plus lifestyle changes (log-rank P = 0.0032). Cumulative incidence rates after 4 years were 6.2 vs. 9.0% (Fig. 1).

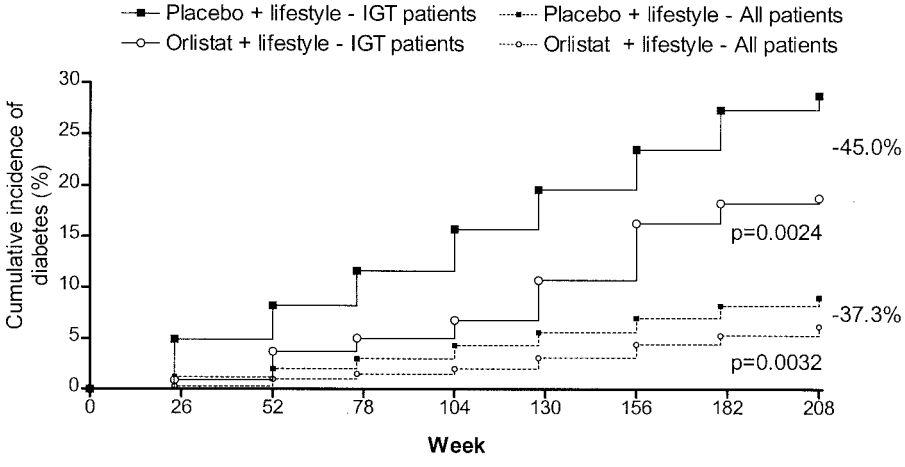

Figure 1—*Cumulative incidence of diabetes by study group in all obese patients (IGT or NGT at baseline) and only in obese patients with IGT at baseline. The decrease in the risk of developing diabetes with orlistat plus lifestyle compared with placebo plus lifestyle is indicated. P values shown are for the log-rank test.*

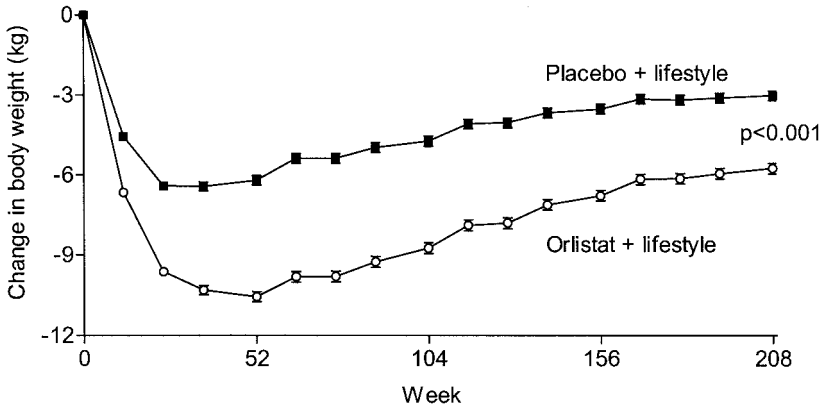

Figure 2—*Weight loss (means ± SEM) during 4 years of treatment with orlistat plus lifestyle changes or placebo plus lifestyle changes in obese patients (LOCF data).*

The hazard ratio (0.627 [95% CI 0.455–0.863]) corresponds to a 37.3% decrease in the risk of developing diabetes with orlistat compared with placebo.

Weight change. Mean weight loss was significantly greater with orlistat than placebo at 1 year (10.6 vs. 6.2 kg; $P < 0.001$) and remained significantly greater at the end of the 4-year study (5.8 vs. 3.0 kg; $P < 0.001$) (Fig. 2). The least-square mean difference between orlistat and placebo groups after 4 years of treatment was −2.7 kg ($P < 0.001$) by LOCF analysis. A second analysis in which the baseline weights of subjects who dropped out of the study was carried forward (i.e., assuming these subjects lost no weight) also demonstrated greater weight loss in the orlistat group (3.6 vs. 1.4 kg; $P < 0.001$). For those patients who completed 4 years of treatment (52% of the orlistat patients and 34% of the placebo patients initially randomized), weight loss was significantly greater with orlistat than placebo at year 1 (11.4 vs. 7.5 kg; $P < 0.001$) and year 4 (6.9 vs. 4.1 kg; $P < 0.001$).

Significantly more orlistat patients (72.8%) than placebo patients (45.1%) achieved weight loss ≥5% after 1 year of treatment ($P < 0.001$). A similar significant difference was apparent for patients achieving a weight loss ≥10% (41.0% with orlistat vs. 20.8% with placebo; $P < 0.001$). For those patients who completed 4 full years of treatment, 52.8 and 37.3%, respectively, lost ≥5% of baseline body weight ($P < 0.001$) and 26.2 and 15.6%, respectively, lost ≥10% of baseline body weight ($P < 0.001$).

Exploratory analyses. The cumulative incidence of type 2 diabetes diagnosed on the basis of a repeat positive test was significantly lower with orlistat plus lifestyle treatment (log-rank $P = 0.028$). The cumulative incidence rate of type 2 diabetes after 4 years was 2.9% with orlistat versus 4.2% for placebo, corresponding to a 41% risk reduction (hazard ratio 0.593).

In patients with IGT at baseline, orlistat plus lifestyle changes significantly decreased the progression to type 2 diabetes when diagnosed on the basis of a single test (log-rank $P = 0.0024$). Cumulative incidence rates after 4 years were 18.8 vs. 28.8% (Fig. 1), corresponding to a 45% risk reduction (hazard ratio 0.551). In addition, orlistat plus lifestyle changes significantly decreased the progression to type 2 diabetes when diagnosed by repeat positive testing in this subgroup with IGT (log-rank $P = 0.0171$). Cumulative incidence rates after 4 years were 8.3% with orlistat versus 14.2% with placebo, corresponding to a 52% risk reduction (hazard ratio 0.482).

In patients with NGT at baseline, the progression rate to type 2 diabetes with placebo was very low (2.7% over 4 years) and insufficient to detect a statistically significant difference compared with orlistat (2.6% over 4 years).

Independent of orlistat or placebo treatment, the relative risk of developing type 2 diabetes was greater in patients with IGT than in those with NGT, in men than in women, in older than in younger individuals, and in individuals with a higher BMI (Table 2). Weight loss was significantly greater with orlistat than placebo in both patients with IGT at baseline (5.7 kg with orlistat vs. 3.0 kg with placebo; $P < 0.01$) and patients with NGT (5.8 vs. 3.0 kg, respectively; $P < 0.001$).

Secondary efficacy parameters

Treatment with orlistat plus lifestyle changes resulted in early and significant improvements in cardiovascular risk factors that were sustained throughout the study, including blood pressure, waist circumference, and lipids (Table 3). Total and LDL cholesterol and the LDL-to-HDL cholesterol ratio decreased significantly more with orlistat than placebo, at both 1 and 4 years. Consistent with this, HDL cholesterol increased less with orlistat.

There was no difference in the progression rate from NGT to IGT over 4 years between orlistat- and placebo-treated individuals (27.6 vs. 30.5%, $P = 0.1521$).

Safety

Orlistat was well tolerated during the study. The overall incidence of adverse events was similar in the two treatment groups, with the exception of a higher incidence of gastrointestinal events. Most gastrointestinal events were mild to moderate in intensity and occurred during the early phase of treatment. During the first year of treatment, the proportion of patients experiencing at least one gastrointestinal event with orlistat or placebo was 91 vs. 65%, respectively. This compares with 36 vs. 23% for orlistat or placebo, respectively, during the 4th year.

Over the 4-year period, a similar pro-

Table 2—*The effect of baseline strata on the relative risk of developing type 2 diabetes over 4 years in patients, irrespective of treatment*

Variable	Hazard ratio	95% CI	*P*
Treatment group: orlistat versus placebo	0.63	(0.46–0.87)	0.0052
Glucose tolerance: impaired versus normal	10.60	(7.30–15.40)	<0.0001
Sex: male versus female	1.41	(1.02–1.96)	0.0390
Age (years): >44* vs. ≤44	1.44	(1.02–2.04)	0.0383
BMI (kg/m^2): ≥37 vs. <37*	1.36	(0.97–1.91)	0.0726

*Median.

Table 3—*Mean change from baseline of cardiovascular risk factors at years 1 and 4 in all patients (observed data)*

	Year 1			Year 4		
	Placebo + lifestyle	Orlistat + lifestyle	*P* between treatments*	Placebo + lifestyle	Orlistat + lifestyle	*P* between treatments*
n	1,295	1,487		567	851	
Diastolic BP (mmHg)	−2.6	−3.6	<0.01	−1.9	−2.6	<0.01
Systolic BP (mmHg)	−5.2	−7.3	<0.01	−3.4	−4.9	<0.01
Total cholesterol (%)	−1.3	−8.8	<0.01	−2.3	−7.9	<0.01
LDL cholesterol (%)	−1.6	−11.4	<0.01	−5.1	−12.8	<0.01
HDL cholesterol (%)	8.5	3.4	<0.01	9.1	6.5	<0.01†
LDL-to-HDL ratio	−0.3	−0.5	<0.01	−0.4	−0.6	<0.01
Triglycerides (%)	−6.3	−6.2	<0.05‡	2.9	2.4	NS
Waist circumference (cm)	−7.0	−9.6	<0.01	−4.4	−6.4	<0.01
Venous whole blood glucose (mmol/l)						
Fasting	0.2	0.1	<0.01§	0.2	0.1	<0.01‖
2 h	−0.4	−0.6	<0.01	−0.2	−0.4	<0.01¶
AUC (mmol · min^{-1} · l^{-1})#	−27	−51	<0.01	3	−14	<0.01
Serum insulin (pmol/l)						
Fasting	−17.0	−26.5	<0.01	−20.6	−32.0	<0.01
2 h	−107.5	−157.4	<0.01	−76.7	−115.4	<0.01¶
AUC (nmol · min^{-1} · l^{-1})#	−11.0	−14.6	<0.01	−8.4	−10.9	<0.01
Fibrinogen (μmol/l)	0.1	0.2	NS	−0.5	−0.4	<0.05‖
Plasminogen activator inhibitor-1 (U/ml)	−3.0	−7.1	<0.01	0.1	−3.0	<0.01

**P* values apply to analyses by LOCF ITT, BLCF ITT, and observed data, except where indicated; †LOCF and BLCF = NS; ‡LOCF and observed = NS; §BLCF $P < 0.05$; ‖BLCF = NS; ¶observed = NS; #calculated by trapezoid rule, including all areas above the line $y = 0$, from measurements immediately before and 30, 60, 90, and 120 min after dose. AUC, area under the curve; BP, blood pressure.

portion of placebo-treated patients had at least one serious adverse event as compared with orlistat-treated patients (13 vs. 15%). Similar proportions of serious gastrointestinal events occurred in the placebo ($n = 32$; 2%) and orlistat ($n = 32$; 2%) groups. No deaths were attributed to study medication. Overall, 4% of placebo patients and 8% of orlistat patients withdrew from the study because of adverse events or laboratory abnormalities; the difference was primarily due to gastrointestinal events.

There were statistically significant decreases in the orlistat group compared with the placebo group after 4 years of treatment for all assessed fat-soluble vitamins (vitamin A −0.22 vs. −0.19 μmol/l, $P < 0.05$; 25-hydroxyvitamin D −17.2 vs. −13.0 nmol/ml, $P < 0.001$; vitamin E −2.8 vs. 0.4 μmol/l, $P < 0.001$; and vitamin K_1 −0.08 vs. 0.07 μg/l, $P < 0.001$), with the exception of 1,25-hydroxyvitamin D (−15.8 vs. −14.0 pmol/ml). However, the mean level of each assessed vitamin remained well within its reference range at all times during the 4-year study for both the orlistat and placebo groups. Decreases were seen early and then were maintained over the treatment period. In patients with normal baseline vitamin levels, the proportions with two subsequent, consecutive abnormally low values was similar in the orlistat and placebo groups for vitamin A (5.5 vs. 4.4%, respectively) and notably different only for vitamin E (3.2 vs. 0.5%, respectively). Proportions for all other vitamin levels were <1% and similar between treatment groups.

CONCLUSIONS — XENDOS was a 4-year, prospective, randomized, double-blind, placebo-controlled study conducted in a representative cohort of obese patients with NGT or IGT. The study demonstrated that orlistat plus lifestyle changes significantly reduced the incidence of type 2 diabetes over 4 years and improved weight loss when compared with placebo plus lifestyle changes. The overall effect of orlistat in preventing diabetes in our study population was primarily due to the beneficial effect in IGT patients. Because the cumulative incidence of diabetes in patients with baseline NGT was low, no between-treatment difference was discernable in this subgroup. Furthermore, cardiovascular risk factors were improved with orlistat treatment, with sustained and significantly better improvements than with placebo for most measures. The XENDOS study has also demonstrated the long-term safety of orlistat. The adverse events profile for orlistat in this 4-year study was consistent with that observed in previous 2-year studies (14–16).

The XENDOS study represents a further step forward in the evolution of diabetes preventive studies. In contrast to other prevention studies, both groups in XENDOS were prescribed intensive lifestyle changes in addition to receiving either a placebo or an active treatment, in this case the weight-reducing agent orlistat. Early studies that were not fully controlled indicated that lifestyle change might reduce the incidence of diabetes in obese individuals with IGT (17,18). The beneficial effects of intensive lifestyle changes (compared with standard care) in preventing diabetes in individuals with IGT were later demonstrated in the DPS (7) and DPP (8). In parallel, the DPP (8), the Study to Prevent (STOP)-NIDDM (19), and the Troglitazone in the Prevention of Diabetes (TRIPOD) (20) trials demonstrated that antidiabetic drugs were similarly more effective than stan-

dard care alone. However, in the study with an intensive lifestyle group (8), drug treatment was less effective. In the current study, the placebo group was treated with lifestyle changes and lost a meaningful amount of weight over the 4 years; adding orlistat to lifestyle changes produced more weight loss and led to a significantly lower risk of developing type 2 diabetes.

Our results indicated that patients treated with placebo plus lifestyle changes achieved a weight loss of 3.0 kg over 4 years, which is comparable with that in the intensive lifestyle intervention arms of the DPS (3.5 kg) (7) and DPP (3.5 kg) (8). The addition of orlistat to lifestyle changes resulted in a significantly greater weight loss, which was similar among patients with IGT and patients with NGT at baseline. Therefore, XENDOS has demonstrated for the first time that a weight loss agent in combination with lifestyle changes over 4 years is of greater benefit than lifestyle changes alone for producing long-term weight loss and improvements in cardiovascular risk factors. The difference in weight loss between orlistat- and placebo-treated patients was similar whether assessed by LOCF or BLCF analysis.

The cumulative incidence of repeat positive diabetes in the XENDOS placebo plus lifestyle group for our baseline IGT subjects (14.2%) was of a similar magnitude to that of the intensive intervention groups in the comparable DPS and DPP studies (11–14.4%) (7,8). The addition of orlistat to lifestyle changes in XENDOS reduced the incidence of type 2 diabetes in subjects with IGT by 52% when compared with the placebo and lifestyle group. Although comparisons between studies should be done with caution, the risk reduction for orlistat plus lifestyle changes compared with standard care may be substantial.

In the IGT population, using the cumulative incidence rates provided, our results suggest that treating 10 patients with orlistat plus lifestyle (rather than lifestyle alone) for 4 years would prevent the development of one case of diabetes.

It should be noted that our study was powered to detect differences in progression to type 2 diabetes in the overall cohort, which was a clinically representative population of obese subjects having either NGT or IGT. Because of the high proportion of emergent cases in subjects with IGT at baseline, significant exploratory results were obtained from this subgroup. However, the study was not powered to detect treatment differences in the subgroup with NGT at baseline, for which the progression rate to type 2 diabetes turned out to be very low.

One consideration in long-term weight loss studies is the proportion of patients who discontinue prematurely. In our study, retention rates of 52% with orlistat and 34% with placebo after 4 years were not unexpected in view of previous obesity studies with up to 2 years' duration (14,15,21,22). Overall, there were fewer withdrawals with orlistat, possibly due to the greater weight loss in this group. Withdrawals due to insufficient response were more than twice as frequent in the placebo group compared with that of the orlistat group. Because of the event-based study design, the discontinuation rate did not affect the power of the study.

One limitation of XENDOS was that repeat testing of patients with a positive OGTT result was not instituted until the majority of patients had completed the 6-month examination. Therefore some repeat positive tests were not captured. However, 87% of all cases of type 2 diabetes were diagnosed after the 6-month time point, at which the second OGTT was introduced. Analyses using only those patients with data available from a repeat positive test show similar results compared with the results from only one positive test.

In summary, the addition of orlistat to lifestyle changes significantly reduces the incidence of type 2 diabetes in obese subjects. With our study design, reduction was only apparent in the IGT subgroup. Adding orlistat also significantly increases weight loss in obese patients with either IGT or NGT and improves other cardiovascular risk factors. Orlistat treatment is safe and well tolerated over 4 years of treatment.

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