

Year Two

Weight Loss (Completers)

For Year-2, three groups are discussed. The groups are defined by treatment during Year 1/Year 2: orlistat 120mg/120mg vs orlistat 120mg/60mg and orlistat 120mg/placebo. Subjects in the orlistat 120mg/120mg group regained significantly less weight than subjects in the 120mg/placebo group (3.0 vs 5.5 kg, respectively, $p=0.002$). Weight regained during Year 2 in the 120mg/placebo and 120mg/60mg groups was similar.

Secondary Efficacy Parameters

The levels of total and LDL-C and Apo B increased during Year 2 in all groups. The increases were significantly lower in both orlistat groups compared to the placebo group with the exception of Apo B levels which was significantly different only for the 120mg/120mg vs 120mg/placebo groups. The increase in levels of HDL-C was significantly greater in the placebo group compared to the two orlistat groups. Mean levels of blood pressure also increased in all three groups during Year 2; the increase in systolic blood pressure in the 120mg/120mg group was significantly less compared to the 120mg/placebo group. The levels of fasting glucose increased in all groups, but the increase was significantly lower in both orlistat groups compared to the placebo group. Interestingly, despite weight gain from the end of Year 1 to the end of Year 2 in all groups the levels of fasting insulin decreased by 1.2 and 11.7 pmol/L in the 60mg and 120mg groups, respectively, and increased in the placebo group by 2.4 pmol/L. The difference between the 120mg/120mg and the 120mg/placebo groups was statistically significant ($p=0.02$). The values for the AUCs for glucose and insulin increased in the three groups during Year 2, but the increase in the glucose AUC was significantly lower in the 120mg/60mg group compared to the 120mg/placebo group.

Two-Year Data

This section entails review of two two groups (Year 1/Year 2): orlistat 120mg/120mg and placebo/placebo.

Weight loss (Completers)

Analysis of the Means

The mean change in body weight from baseline to Week 104 for the placebo group was -1.2 kg and -3.8 kg in the 120mg group ($p=0.07$).

Categorical Analysis

After two years of treatment 43% of the orlistat subjects and 30% of the placebo patients lost at least 5% of baseline body weight ($p=0.08$), and 25% of the active-treatment subjects and 14% of placebo subjects lost at least 10% of baseline body weight ($p=0.07$).

Secondary Efficacy Parameters

Following 104 weeks of treatment, the levels of total cholesterol increased by 6.4% in the placebo group and decreased by 0.4% in the 120mg group ($p=0.001$). Similarly, the levels of LDL-C increased 4.8% in the placebo group and decreased by 2.7% in the 120mg group ($p=0.006$), and levels of Apo B increased by 74 mg/L in the placebo group and by 7.2 mg/L in the 120mg group ($p=0.007$). Levels of blood pressure did not change appreciably during the two-year study in either group. Fasting glucose levels increased by 0.27 mmol/L in the placebo group and decreased by 0.07 mmol/L in the orlistat group ($p=0.02$). Similarly, fasting insulin increased by 17.1 pmol/L in the placebo group and decreased by 21.8 pmol/L in the orlistat group ($p<0.001$). And finally, the levels of glucose and insulin AUCs increased in the placebo group while they decreased in the orlistat group; the differences between groups were statistically significant.

SAFETY DATA

8.5.7 Deaths

Two patients died of car accidents during the study, one during the placebo lead-in phase and the other on Day 637. The second patient received placebo throughout the study.

Symptom-Related Adverse Events

By far, complaints related to the GI system were the most commonly reported by orlistat patients (81%) and placebo patients (66%). Symptoms reported with a markedly increased frequency by orlistat vs placebo patients included oily spotting, flatus with discharge, fecal urgency, oily evacuation, and fatty/oily stool. The majority of the complaints were coded as mild to moderate, with the exception of fecal urgency in which a sizable portion of orlistat patients were coded as severe. In general, it appeared that the incidence of GI adverse events was lower during the second year of the study.

Plasma Fat-Soluble Vitamin Levels

Following one year of treatment the mean levels of vitamin D and β -carotene decreased by a statistically significant extent in the orlistat compared to the placebo group; although the mean values remained within the "normal" range. There were 39 patients in the 120mg group and 12 patients in the placebo group that required vitamin or β -carotene supplementation during two years of study. Of note, 13 of 21 patients supplemented for low levels of vitamin D had a low level at the last visit.

Ultrasounds of the Gallbladder and Kidney

Following two years of treatment the incidence of new gallstones was 3.2% in the placebo group and 6.0% in the orlistat group. While this is a doubling of the incidence rate, the relatively small numbers of patients make it difficult to draw meaningful conclusions. There was no evidence that treatment with orlistat increased the risk for kidney stones in this study. As stated previously, pooling of the data (ISS) will likely shed more light on the issue of orlistat's potential to increase gallstone or kidney stone formation.

MEDICAL OFFICER'S CONCLUSIONS

Patients who completed one year of treatment with 120 mg tid of orlistat lost statistically significantly

more weight than patients who received placebo; however, the difference between the two groups in the change in mean percent weight loss was only 3%. Despite a reduction in mean body weight, the placebo group had increases from baseline to Week 52 in the levels of total cholesterol, LDL-C, and Apo B, whereas the orlistat group had reductions from baseline in these parameters. As one would expect, the reduction in dietary fat induced by orlistat resulted in a smaller increase in the levels of HDL-C when compared to placebo. Although there were no statistically significant differences between the two groups in the levels of fasting glucose and insulin following one year of treatment, the AUCs for glucose and insulin during an OGTT were significantly reduced in comparison to the placebo responses.

The continued use of orlistat during the second year of the study resulted in less regained weight when compared to subjects who received placebo during this time. Subjects who were switched from 120mg of orlistat during Year 1 to 60mg during Year 2 regained an amount of weight similar to the placebo group.

The subjects who received orlistat 120mg tid for two years lost an average of 3.8 kg compared to a mean reduction in weight of 1.2 kg in the subjects that received placebo for two years ($p=0.07$). There were improvements in the levels of total and LDL cholesterol in the orlistat-treated subjects compared to the placebo-treated subjects; however, the differences between the groups were of marginal clinical significance.

The adverse event profiles for the orlistat groups were similar to those reported in previous studies, as were the changes in the levels of fat-soluble vitamins and β -carotene.

STUDY NM14302

BEST POSSIBLE

OBJECTIVES

8.6.1 The primary objective of this study was to determine the efficacy of the maintenance of lost weight and prevention of weight regain of orlistat (30mg, 60mg, 120mg) or placebo in combination with appropriate dietary and behavioral counseling when given tid with meals for 12 months after a six-month program of diet-induced weight loss.

PROTOCOL DESIGN

8.6.2 This was a 18-month, multi-center (17), randomized, double-blind, placebo-controlled study of 1313 patients. During the first six-months of the study all patients were prescribed a hypocaloric diet with behavior modification and diet counseling. Afterwards, patients were randomized to one of four treatment arms: (1) placebo, (2) 30mg orlistat tid, (3) 60mg orlistat tid or, (4) 120mg orlistat tid. Patients had to have lost at least 8% of their baseline weight during the first six months of the study and have normal levels of vitamins A, D, and E, and β -carotene to be eligible for the following 12-month treatment period. In addition, patients were randomized into two weight loss strata: $\leq 10\%$ of initial body weight lost or $>10\%$ of initial body weight lost.

During the first six months of the study subjects were instructed to consume a diet that consisted of 30% fat, 50% carbohydrate, and 20% protein. Further, the diet was designed to cause a 1000 kcal/day deficit. The minimum allowable prescribed calorie level was 1000 kcals/day. At Day 1 of randomization the diet was altered to facilitate body weight maintenance and help prevent weight regain. Subjects kept 3-day

food diaries during the six-month weight loss phase and during the 12-month double-blind period. Throughout the study patients were encouraged to attend behavior-modification sessions and to engage in regular aerobic exercise (walking 20-30 minutes, five times per week). At the start of the study patients received vitamin supplementation with once-daily Centrum tablet (5000 I.U. vitamin A, 30 I.U. vitamin E, 400 I.U. vitamin D, and 25 mcg vitamin K). The protocol specified that the investigators provide supplementation with breakfast.

STUDY POPULATION

8.6.3 Eligible patients included men and women aged 18 years and older with a BMI between 28 and 38 kg/m². The major exclusion criteria included:

- Hx or presence of significant cardiac, renal, hepatic, GI, or endocrine disorders
- MI, CABG, or PTCA within six months prior to screening
- SBP \geq 165 mmHg or DBP \geq 105 mmHg on two consecutive visits
- Episode of nephrolithiasis within one year of screening
- Active GI disease
- History of pancreatitis
- Drug-treated diabetes
- Abnormal laboratory tests

Patients were excluded if they were taking or had taken within four weeks of screening the following medications:

- appetite suppressants
- fish oil supplements
- retinoids
- anticoagulants
- digoxin, anti-arrhythmics
- lipid-soluble vitamin supplements
- oral hypoglycemics
- insulin
- tricyclic antidepressants
- resins for lowering lipids
- nicotine replacement

ENDPOINTS

8.6.4 Body weight was measured at frequent intervals and the average of two measurements was recorded in the CRF. Other efficacy parameters included the waist to hip ratio, serum lipids, fasting insulin and glucose, and blood pressure (considered efficacy and safety).

In addition to the standard hematology and chemistry parameters, the levels of plasma retinol, vitamin D, alpha-tocopherol, beta-carotene, TSH, and prothrombin time were measured. Hemeoccult, chest x-ray, ECG, and gallbladder ultrasounds were also performed.

STATISTICAL CONSIDERATIONS

8.6.5 The primary hypothesis — the expected mean percent regain of lost weight is the same among patients in all four treatment groups after 52 weeks of double-blind treatment — was tested using an ANCOVA model including center, stratum, center-by-stratum, treatment, center-by-treatment, and stratum-by-treatment as covariates. In addition a Student-Newman-Keuls Multiple Range test was used to illustrate the dose-response relationship. For the secondary efficacy parameters, an ANCOVA model was used to evaluate the change from the start to the end of the double-blind treatment. The model included terms for center, treatment, center-by-treatment interaction, and the value for the parameter measured just before the start of the double-blind period as a covariate.

RESULTS

POPULATIONS ENROLLED/ANALYZED

8.6.6 Patient Disposition

A total of 1313 patients were enrolled into the study. During the six-month diet-induced weight loss phase 584 patients withdrew, 35% because of failure to lose 8% of initial body weight. Therefore, at the start of the double-blind phase 188 patients were randomized to placebo; 187 to 30mg of orlistat; 173 to 60mg; and 181 to 120mg. Seventy-three percent, 75%, 77%, and 70% of the subjects in the placebo, 30mg, 60mg, and 120mg groups, respectively, completed the 12-month double-blind phase.

Baseline Demographics

Aside from a lower percentage of Caucasians in the 120mg group (86%) compared to 88-90% in the other groups ($p=0.04$), the groups were well matched for baseline demographics. Over 80% of the subjects were female, the mean age was 46 years, and the mean BMI was 29 kg/m².

Baseline Risk Factors

The groups were well matched for baseline risk factors (see table below). Approximately 10-12% of the subjects were hypertensive at baseline, only 7-10% were taking medication to lower their blood pressure, none of the subjects had NIDDM, and 2-3% were taking lipid lowering medication at baseline.

BASELINE RISK FACTORS (means)

	Orlistat 120mg	Orlistat 60mg	Orlistat 30mg	Placebo	P value
SBP (mmHg)	116	116	115	115	0.9
DBP (mmHg)	75	76	75	75	0.8
TC (mmol/L)	5.13	5.14	5.15	5.10	0.9
LDL (mmol/L)	3.19	3.23	3.24	3.14	0.7
HDL (mmol/L)	1.30	1.28	1.29	1.33	0.6
TG (mmol/L)	1.44	1.38	1.32	1.32	0.4

EFFICACY ENDPOINT OUTCOMES

Weight Loss (Completers)

Analysis of the Means

The mean percent reduction in body weight during the six-month diet lead-in phase was approximately 11% for the four groups. The mean percent regain of body weight lost during the six-month lead-in phase was 54% for the placebo group, 50% for the 30mg group, 49% for the 60mg group, and 31% for the 120mg group ($p=0.004$, placebo vs 120mg, other comparisons not significant).

Secondary Efficacy Parameters

The only statistically significant change in lipid parameters noted during the 52-week double-blind phase was an increase from baseline in the levels of triglycerides in the 30mg and 60mg groups compared to placebo. All groups had small increases (1.6 to 4.0 mmHg) from baseline in systolic and diastolic blood pressure, and the differences among the groups were not significant. The levels of fasting glucose increased slightly in all groups, but the increase was significantly less in the subjects receiving 60mg and 120mg doses of orlistat when compared to placebo. Fasting insulin levels also increased in all the groups, with the increase in the 60mg group being significantly greater than the increase in the placebo group.

SAFETY DATA

8.6.7 Deaths

One patient died in a car accident; this event occurred during the six-month diet lead-in phase

Symptom-Related Adverse Events

GI-related adverse events were the most commonly reported complaints in the placebo and orlistat groups. In general, the incidence of adverse events coded to the GI system increased with higher doses of orlistat. The events reported more frequently by the orlistat-treated patients compared to the placebo-treated subjects were similar to those reported in the previous trials. Very few of these events were recorded as severe. Five placebo patients and 61 orlistat patients withdrew from the study because of an adverse event. Forty-three of the 61 orlistat-treated patients withdrew because of a GI-related adverse event compared to one placebo patient.

Plasma Levels of Fat-Soluble Vitamins

All patients received one Centrum multivitamin per day starting at the beginning of the six-month diet lead-in phase. At the completion of the 52-week double-blind period, the mean levels of vitamins D, E, and β -carotene were significantly reduced compared to the average levels in the placebo group. Thirty-four orlistat patients required an additional vitamin supplement during the study compared to only seven placebo patients. Very few of these patients had a low vitamin or β -carotene level at the last visit.

Ultrasounds of the Gallbladder

There was no evidence of an increased incidence of gallstone formation in the subjects that received orlistat. Renal ultrasounds were not done in this study.

MEDICAL OFFICER'S CONCLUSIONS

Following six-months of caloric restriction and weight loss, the use of orlistat 120mg tid for 52 weeks was associated with significantly less regained weight when compared to placebo (31% vs 54%, respectively). In addition, the 120mg dose was more effective at preventing weight regain than the 60mg and 30mg doses.

Of interest, all subjects received a multivitamin supplement during this study, and yet, plasma levels of vitamins D, E, and β -carotene still fell. In addition, thirty-four orlistat patients required an additional supplement compared with only seven placebo patients. In the absence of a group of drug-treated patients that received a placebo instead of a multivitamin, it is difficult to draw valid conclusions about the efficacy of universal vitamin supplementation. Nevertheless, the results of this study suggest that providing the vitamin supplement with breakfast, and thus with orlistat, is an inappropriate dosing scheme. Above all else, additional study of a practical and efficacious method to stabilize fat-soluble vitamin and β -carotene levels during long-term treatment with orlistat appears justified.

STUDY NM14336

OBJECTIVE

8.7.1 The primary objective of this study was to compare the long-term weight loss effect of orlistat 120mg tid to placebo in obese patients with NIDDM maintained on a sulfonylurea.

PROTOCOL DESIGN

8.7.2 This was a 57-week, multi-center, randomized, double-blind, placebo-controlled study of 391 patients. There was a five-week, single-blind lead-in placebo phase followed by a 52-week, double-blind treatment period. Following the five-week period patients were randomized to one of four groups as follows:

- (1) weight loss \leq 2.0 kg, fasting glucose 100 - 160 mg/dl
- (2) weight loss \leq 2.0 kg, glucose 161 - 220 mg/dl
- (3) weight loss $>$ 2.0 kg, glucose 100 - 160 mg/dl
- (4) weight loss $>$ 2.0 kg, glucose 161 - 220 mg/dl

Patients were maintained on a diet consisting of 30% fat, 50% carbohydrate, and 20% protein. The diet was designed to cause a 500 kcal/day deficit. At the end of 29 weeks the diets were adjusted to reduce the total caloric intake by 300 kcal/day. Patients maintained food intake records throughout the study and met with dietitians to discuss their food choices. Subjects were also encouraged to attend behavioral modification classes at four time points during the first six months of the double-blind phase.

STUDY POPULATION

8.7.3 Eligible patients included men and women aged 18 years and older with a BMI between 28 and 40

kg/m². Patients had to have been treated with any sulfonylurea for at least six months and currently clinically stable on a second generation sulfonylurea: glyburide or glipizide. The HbA1c level must have been between 6.5 and 10%. The major exclusion criteria included:

- insulin-treated diabetes
- NIDDM controlled with diet alone
- proliferative retinopathy
- serum creatinine \geq 2.0 mg/dL
- 24-hour urine protein \geq 500 mg
- significant peripheral vascular disease
- significant peripheral/autonomic neuropathy
- Hx or presence of significant cardiac, renal, hepatic, GI, or endocrine disorders
- MI, CABG, or PTCA within six months prior to screening
- SBP \geq 165 mmHg or DBP \geq 105 mmHg on two consecutive visits
- Episode of nephrolithiasis within one year of screening
- Active GI disease
- History of pancreatitis
- Drug-treated diabetes
- Abnormal laboratory tests

Patients were excluded if they were taking or had taken within four weeks of screening the following medications:

- appetite suppressants
- fish oil supplements
- retinoids
- anticoagulants
- digoxin, anti-arrhythmics
- lipid-soluble vitamin supplements
- oral hypoglycemics
- insulin
- tricyclic antidepressants
- nicotine replacement

ENDPOINTS

8.7.4 Body weight was measured at frequent intervals and the average of two measurements was recorded in the CRF. Other efficacy parameters included the change in dosage of oral hypoglycemic medication, HbA1c, waist to hip ratio, serum lipids, fasting insulin and glucose, and blood pressure (considered efficacy and safety). The dose of the hypoglycemic agent was decreased one step when a patient met one of the following criteria:

- two episodes of symptomatic hypoglycemia confirmed on home glucose monitoring
- fasting glucose was \leq 65 mg/dl at any one visit
- fasting glucose was 66-90 mg/dl on two consecutive visits

In addition, a patient was discontinued from the study if the dose of oral hypoglycemic medication reached a lower limit of 2.5 mg/day for glipizide, 1.25 mg/day for glyburide or 1.5 mg/day for glynase.

The dose of medication was increased one step when the patient's fasting glucose was 220 mg/dl on two consecutive visits. Patients were discontinued from the study if the dose of oral agent reached 40 mg/day for glipizide, 20 mg/day for glyburide, or 12 mg/dl for glynase.

In addition to the standard hematology and chemistry parameters, the levels of plasma retinol, vitamin D, alpha-tocopherol, beta-carotene, TSH, and prothrombin time were measured. Hemeocult, chest x-ray, ECG, and gallbladder ultrasounds were also performed.

STATISTICAL CONSIDERATIONS

8.7.5 The null hypothesis for the primary efficacy parameter, weight loss, was the expected mean weight loss was the same for placebo and orlistat-treated patients after 52 weeks of double-blind treatment. This was tested by an ANOVA model with center, stratum, center-by-stratum, treatment, center-by-treatment, and stratum-by-treatment as independent variables. The secondary efficacy variables were tested in a similar fashion with the appropriate baseline value included as a covariate. To examine the changes in dosage of medications a categorical analysis was performed with the following categories: medication discontinued, reduced, not changed, increased, and patient dropped out due to abnormal fasting blood sugar. The baseline dose was a covariate in the model.

RESULTS

POPULATIONS ENROLLED/ANALYZED

8.7.6 Patient Disposition

A total of 391 patients were enrolled into the study. Sixty-nine subjects withdrew during the lead-in phase. Thus, 159 patients were randomized to placebo and 163 to orlistat. Eighty-five percent of the orlistat-treated subjects completed the study and 72% of the placebo subjects completed one year of treatment. Twelve orlistat subjects and 23 placebo subjects withdrew because of an adverse event.

Baseline Demographics

There were slightly more females in the orlistat group (51%) compared to the placebo group (47%) ($p=ns$). The other baseline demographic characteristics were similar for the two groups. The mean age was 55 years (range 27-76 yrs), most of the subjects were Caucasian (88%), and the mean BMI was 33.5 kg/m².

Baseline Medications

Ninety-eight percent of the placebo subjects and 99% of the orlistat subjects were on an oral hypoglycemic agent at baseline. Approximately 18.5% of the subjects in each group were taking a calcium channel blocker at baseline and 18% of the subjects were on an ACE-inhibitor at the start of the study.

Baseline Risk Factors

The baseline systolic blood pressure was statistically significantly higher in the orlistat group compared to the placebo group (130 vs 125 mmHg; $p=0.004$). The other risk factors were well matched (see table below).

BASELINE RISK FACTORS (means)			
	Orlistat	Placebo	P value
SBP (mmHg)	130	125	0.004
DBP (mmHg)	79	79	0.9
TC (mmol/L)	4.99	5.01	0.8
LDL (mmol/L)	3.10	3.17	0.4
HDL (mmol/l)	1.03	1.03	0.4
TG (mmol/L)	2.11	2.02	0.4

A similar percentage of patients in each group (43%) were hypertensive at baseline, and a similar percentage of these patients (40%) were taking antihypertensive medication at baseline. There was no significant difference between the two groups in the percentage of patients taking lipid lowering medication at baseline (9 vs 14%, 120mg vs placebo, $p=0.1$).

The following table illustrates that the two groups were well matched for measures of glycemic control at baseline.

BASELINE MEASURES OF GLYCEMIC CONTROL (means)			
	Orlistat	Placebo	P value
Dose of Oral Hypoglycemic Agent†	47%	48%	0.7
HbA1C (%)	7.5	7.5	0.9
Fasting Glucose (mmol/L)	7.9	7.9	0.7
Fasting Insulin (pmol/L)	145	150	0.7

† Based on the % of maximum allowable dose.

EFFICACY ENDPOINT OUTCOMES

Weight Loss (Completers)

Analysis of the Means

During the five-week lead-in phase both groups lost an average of 2 kg (2%). Following 12 months of treatment, the orlistat group had a mean reduction in baseline body weight of 3.8 kg and the placebo group had a reduction of 1.8 kg ($p=0.003$). The reduction in mean percent body weight from baseline was 4.2% vs 2.1% in the orlistat and placebo groups, respectively.

Categorical Analysis

Compared to placebo, twice as many orlistat subjects lost at least 5% of initial body weight (34% vs 16%, $p=0.001$). Very few patients reached the 10% weight loss level: 10% of orlistat subjects and 5% of placebo subjects ($p=0.09$).

Secondary Efficacy Parameters

Hypoglycemic Medication

For the intent-to-treat population there was a significant difference in the reduction in the mean standardized dose of oral hypoglycemic agent between the two groups (-23% vs -9%; orlistat vs placebo, respectively, $p=0.002$). For the completers, the mean change from baseline in the standardized dose of hypoglycemic medication was -10 mg for the orlistat group and -4 mg in the placebo group ($p=0.06$). In the categorical analysis, the only difference between the groups was in the percentage of patients who dropped out of the study because of abnormal blood glucose levels (9% vs 3%, placebo vs orlistat).

Fasting Glucose and Insulin

Of the patients that completed the study, the mean levels of fasting glucose increased to a lesser degree in the orlistat group compared to the placebo group [0.05 (0.9 mg/dl) vs 0.50 mmol/L (9.0 mg/dl), orlistat vs placebo, respectively, $p=0.03$]. The mean levels of fasting insulin decreased in both groups by completion of the study. The reduction was 20.5 pmol/L in the orlistat group compared to 17 pmol/L in the placebo group ($p=0.7$).

HbA1c

In the completers dataset, the mean HbA1c levels decreased 0.15% in the orlistat group and increased 0.19% in the placebo group ($p=0.02$).

Lipoprotein Lipids

As shown in the table below, there were relative improvements in the levels of total and LDL cholesterol and triglycerides in the orlistat group compared to the placebo group.

PARAMETER	ORLISTAT	PLACEBO	P VALUE
TC	-0.3%	9%	<0.001
LDL-C	-3.0%	10%	<0.001
TG	5%	16%	0.04

Blood Pressure

The levels of blood pressure changed very little by the completion of the study and the differences between the groups were not clinically or statistically significant.

Pharmacodynamics: Fecal Fat Content

The mean level of fecal fat increased by 25 grams/24hrs in the orlistat group and by 0.70 grams/24hrs in the placebo group.

SAFETY DATA

8.7.7 Deaths

No deaths occurred during or within four weeks of completion of the study.

Symptom-Related Adverse Events

As observed in the studies of obese non-diabetic patients, adverse events related to the GI system were reported by more orlistat-treated patients (79%) compared to placebo-treated subjects (59%). The most commonly reported GI adverse event in the orlistat group was flatus with discharge (40%). Other common complaints (reported by > 15% of patients) in the active-treatment group were oily spotting, fecal urgency, flatulence, abdominal pain, and liquid stools. Most of the adverse events were coded as mild to moderate. Seven orlistat and two placebo subjects withdrew from the study because of a GI-related adverse event

Plasma Fat-Soluble Vitamins

The level of β -carotene decreased by 0.12 $\mu\text{mol/L}$ in the orlistat group and by 0.03 $\mu\text{mol/L}$ in the placebo group ($p < 0.001$). The changes in the mean levels of vitamins A, D, and vitamin E/total cholesterol did not differ significantly between the groups. Of note, the percentage of subjects with at least two consecutive low vitamin D levels was 22% in the orlistat group and 9% in the placebo group ($p = 0.002$) and for β -carotene the percentages were 12% and 1% of the orlistat and placebo subjects, respectively ($p = 0.0002$). Forty-four patients in the orlistat group required vitamin supplementation compared with only 12 placebo patients. All but one of the orlistat patients who received a supplement had normal vitamin levels at the time of final measurement.

Gallbladder Ultrasounds

There was no indication that the orlistat-treated subjects had an increased incidence of gallstone development during the year of treatment.

Pharmacokinetic Data

At Week 20 plasma samples were taken for measurement of orlistat and M1 and M3. Orlistat and M1 were detected in three and two placebo patients, respectively. Orlistat was detected in 76 active-treatment

patients and the levels of M1 and M3 were detected in 115 and 101 patients, respectively. In the patients who received orlistat the values for intact orlistat in the plasma ranged from 0.21 - 8.3 ng/ml, the M1 values ranged from 3.0 - 120 ng/ml, and the M3 values from 16 - 353 ng/ml.

SPONSOR'S CONCLUSIONS

The results of this study indicate that obese patients with NIDDM maintained on a hypocaloric diet had significantly greater weight loss, improved glycemic control, and decreased usage of oral hypoglycemic medication when treated with 120mg of orlistat tid for 52 weeks versus treatment with placebo tid for 52 weeks. These results indicate significant clinical benefit for this patient population. Orlistat was well tolerated when administered to obese NIDDM patients at a dose of 120mg tid for 52 weeks.

MEDICAL OFFICER'S CONCLUSIONS

On balance, compared with placebo, the use of orlistat 120mg tid in this population of obese patients with NIDDM was associated with a small reduction in body weight, and modest improvements in glycemic control and other comorbidities. It is unclear why this group of obese patients with NIDDM did not respond as favorably to orlistat as did the patients without diabetes; however, this resistance to weight loss has been observed with other anti-obesity drugs.

9.0 OVERVIEW OF EFFICACY

Because five of the seven phase III studies employed similar study designs and include a homogeneous patient population it is reasonable to pool the data to obtain a more accurate assessment of orlistat's efficacy and safety. The data that are subsequently reviewed represent pooled data from studies BM14119B, BM14119C, NM14161, BM14149, and NM14185.

In this section of the review both ITT and completers datasets were used to assess the effect of orlistat and placebo on weight loss and comorbidities. The ITT populations was defined as randomized patients who received at least one dose of study medication and had body weight measurements before and after randomization. Completers were defined as randomized patients who 1) did not have any protocol violations that might affect efficacy evaluation 2) completed at least 50 weeks or 102 weeks of treatment for one-year or two-year analyses, respectively and 3) had efficacy measurements inside the corresponding time window. These definitions are reasonable. In general, the results of the ITT and completers analyses were similar; therefore, for ease of presentation most of the data presented in this ISE will be from the ITT analyses.

One-Year Data

Demographics

At baseline there were 1561 patients in the 120mg group, 452 in the 60mg group, and 1119 patients in the placebo group. By and large the groups were well matched. Approximately 81% of the subjects were female, the mean age was 44 years (range 18-78 yrs), nearly 92% were Caucasian, the mean body weight was 97 kg, and the average BMI equaled 35 kg/m².

Baseline Risk Factors

The following table illustrates the baseline risk factors for the three groups. In general, this population of obese patients was normotensive and did not have exceedingly high total and LDL cholesterol levels. While some of the baseline values were statistically significantly different among groups, the absolute differences were small. More importantly, the baseline values were included in the statistical model as covariates; thus, any differences at baseline were accounted for statistically.

BASELINE RISK FACTORS (means)				
	Orlistat 120mg	Orlistat 60mg	Placebo	P value
SBP (mmHg)	123	125	124	0.01
DBP (mmHg)	79	80	79	0.2
TC (mmol/L)	5.10	5.21	5.21	0.02
LDL (mmol/L)	3.28	3.31	3.38	0.01
HDL (mmol/L)	1.17	1.17	1.16	0.8
TG (mmol/L)	1.54	1.71	1.55	0.007
Fas Gluc (mmol/L)	5.63	5.60	5.70	0.03
Fas Ins (pmol/L)	94	92	95	0.8

Dietary Intake Data

The daily intake of calories, fat, carbohydrate, and protein did not change significantly from baseline to Week 52 for the placebo or 120mg groups. There were statistically, but not clinically significant differences between the two groups for the change in the intake of some dietary parameters. For example, in the US studies the orlistat group had an increase in total daily calorie intake of 79 kcal when compared with placebo. When reviewing dietary intake data derived from patient records it should be kept in mind that this method is notoriously inaccurate.

Weight Loss (a reminder that initial body weight refers to Week -4 and baseline weight refers to Day 1 of double-blind treatment)

Analysis of the Means

The figure below illustrates the mean percent change in body weight from Week -4 to Week 52 (ITT dataset). All three groups lost approximately 2.5% of initial body weight during the four-week lead-in period. While weight loss plateaued at Week 25 in the placebo group a steady state did not appear until Week 35 in the orlistat 120mg group. The placebo-subtracted mean percent weight loss from baseline to Week 52 was approximately 3% for the orlistat 120mg group.