

2 SYNOPSIS

Abbott Laboratories	Protocol Number: MLAY-02-001
Name of Study Drug: Sibutramine (ABT-991)	Phase of Development:
Name of Active Ingredient: Sibutramine	Date of Protocol Synopsis: 28 December 2006
Protocol Title: Randomized Trial of Obese Non-Diabetic Malaysians using Sibutramine: A Randomized Double-Blind Placebo-Controlled Study of Sibutramine in the Management of Obese Subjects in Malaysia	
<p>Objectives: The primary objective of this study was to evaluate the efficacy and the safety of sibutramine vs. placebo in combination with a hypocaloric diet on weight-loss in overweight and obese Malaysian subjects.</p> <p>The secondary objectives of this study were to evaluate the efficacy of sibutramine vs. placebo in combination with a hypocaloric diet with respect to changes from baseline in other weight, metabolic and quality of life measurements, in overweight and obese Malaysian subjects.</p>	
Investigators: Please refer to Appendix 15.1.4	
Study Centre(s): Please refer to Appendix 15.1.4	
Study Population:	
<p>Number of Subjects to be Enrolled:</p> <p>Planned: Recruitment target: 100</p> <p>Actual:</p> <ul style="list-style-type: none"> Number of randomised: 103 -Treatment group: 54 -Control group: 49 Number of completer: 91 -Treatment group: 46 -Control group: 45 Number of withdrawals: 12 -Treatment group: 8 -Control group: 4 <p>Analyzed:</p> <ul style="list-style-type: none"> For safety evaluation: 103 -Treatment group: 54 -Control group: 49 Intention-To-Treat (ITT): 101 -Treatment group: 54 -Control group: 47 Per Protocol (PP): 64 -Treatment group: 38 -Control group: 26 Completer analysis: 91 -Treatment group: 46 -Control group: 45 	
Methodology: A Phase 3, multi-center, randomized, double-blind study of sibutramine vs. placebo in combination with a hypocaloric diet in overweight and obese Malaysian subjects was conducted. The duration of the study for each of the subject's was approximately 32 weeks, including a screening period of up to 4 weeks, a 24-week treatment period and a 30-day Post-Therapy Follow-up Period.	

Diagnosis and Main Criteria for Inclusion/Exclusion:

A subject was eligible to be enrolled into the study if he or she met the following criteria at Week 0:

1. The subject did not adequately respond (ie, did not achieve or maintain > 5% weight loss) to an appropriate non-pharmacologic weight-reducing regimen (ie, diet and exercise) within 3 months prior to Screening.
2. The subject was either male or female and ≥ 18 and ≤ 65 years of age.
3. The subject had nutritional obesity and $BMI \geq 27 \text{ kg/m}^2$ associated with dyslipidemia or has $BMI \geq 30 \text{ kg/m}^2$. Dyslipidemia was defined as having at least one of the following three conditions: Low-density lipoprotein (LDL)-cholesterol level of $> 3.4 \text{ mmol/L}$ ($> 130 \text{ mg/dL}$), total cholesterol level of $> 5.2 \text{ mmol/L}$ ($> 200 \text{ mg/dL}$), or triglyceride level of $> 1.7 \text{ mmol/L}$ ($> 150 \text{ mg/dL}$).
4. For the female subjects, they were not of childbearing potential or were defined as postmenopausal for at least 2 years or surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy). If the female subject was of childbearing potential, she must be practicing one of the following methods of birth control:
 - condoms, sponge, foams, jellies, diaphragm or intrauterine device (IUD)
 - on contraceptives (oral or parenteral) for the 3-month period prior to Week 0
 - a vasectomized partner
 - total abstinence from sexual intercourse
5. For female subjects, the results of a urine pregnancy test performed at Screening and Week 0 was negative.
6. If female, subject was not breast-feeding.
7. Subject was judged to be in general good health based upon the results of medical history, complete physical examination and clinical laboratory tests.
8. Subject is not taking any over-the-counter or prescription drugs, or herbal products for weight loss during the 4 week period prior to Screening.
9. Subject has voluntarily signed and dated an informed consent form, approved by an Institutional Review Board (IRB)/Independent Ethics Committee (IEC), prior to undertaking any study-specific procedures.

Investigational Product(s):	Sibutramine (ABT-991)
Doses:	10 mg, 15 mg
Mode of Administration:	At Week 0, subjects were instructed to take 1 capsule once daily in the morning with liquid. The capsule could be taken with or without food. Following 4-6 weeks of treatment, the investigator increased the dose to 15 mg if the subject had not achieved a weight loss of $\geq 2 \text{ kg}$ at Week 4 and has tolerated the 10 mg dose according to Figure 9.4.1a. Once the dose was established at Weeks 4, 5 or 6, the dose cannot be changed for the remainder of the study.
Reference Therapy:	Placebo
Dose(s):	Unavailable
Mode of Administration:	Same as test product

<p>Duration of Treatment: 24 weeks of treatment and 32 weeks of documentation</p>
<p>Efficacy: The primary efficacy variable was defined as the change from the baseline to the final evaluation (at 24 weeks or at premature discontinuation of study drug) in body weight.</p> <p>The secondary efficacy variables were defined as the percentage change from baseline to the final evaluation in body weight and the changes from baseline to the final evaluation in the following measurements:</p> <ol style="list-style-type: none"> 1. Other weight measurements <ul style="list-style-type: none"> • BMI calculated as $\text{weight (kg)}/[\text{height(m)}]^2$ at Screening • Waist and hip circumferences • Waist: hip ratio • Total body fat mass, total body lean mass, percent of total body fat mass and percent of total body lean mass (estimated by Bodystat[®] 1500) • Total abdominal fat mass, total abdominal lean mass, percent of total abdominal fat mass and percent of total abdominal lean mass (measured by DEXA scan) 2. Metabolic measurements <ul style="list-style-type: none"> • Cholesterol (Total, Low Density Lipoprotein and High Density Lipoprotein) • Triglycerides • Insulin resistance (R) = $(\text{Insulin} \times \text{Glucose})/22.5$ (Homeostasis model assessment or HOMA) 3. Quality of Life measurement <ul style="list-style-type: none"> • SF 36
<p>Pharmacokinetic:</p>
<p>Pharmacodynamic:</p>
<p>Safety: Physical examination, Blood pressure, Heart rate, Clinical chemistry, 12-Lead ECG, Adverse events.</p>
<p>Statistical methods: The efficacy of treatment was evaluated by the change of the body weight and other measurements after the treatment. ANCOVA model was used to adjust the co-variables (including baseline value and research centre). Binominal variables were described with proportions and logistic model was used to evaluate the effect of treatment after adjusting for the effect of baseline value and research centre.</p>
<p>Efficacy results:</p> <p>101 patients were included in the ITT analysis, 64 patients in the PP analysis and 91 patients in the completers analysis.</p> <p>The results showed that Sibutramine was more effective than the placebo in terms of reductions in BMI and body weight after 24 weeks of treatment.</p> <ul style="list-style-type: none"> • 54 patients who were on sibutramine were included in the ITT analysis. An average of 6.38 ± 4.12 kg weight loss was achieved compared to 1.62 ± 2.41 kg weight loss in the 57 patients in the placebo group; $P < 0.001$. In the sibutramine-treated group, 74.07% of the patients achieved at least a 5% weight loss and 33.33% achieved at least a 10% weight loss whereas in the placebo group, 19.15% of the patients achieved at least a 5% weight loss and 0% achieved at least a 10% weight loss. The difference of patients reached 5% and 10% weight loss between treatment groups were statistically significant.

- The BMI in the treatment group was decreased by 2.59 mg/m^2 and in control group by 0.64 mg/m^2 . The waist circumference was decreased by 5.75cm and 2.11cm for the treatment and the control groups respectively. The measurement for the hip circumference was 4.64cm and 2.07cm for the treatment and the control groups respectively. All the difference of reduction of BMI, waist circumference and hip circumference between the groups were statistically significant. No statistic significant difference of hip ratio was found between treatment groups.
- Sibutramine was effective in reducing the total body fat and the total body lean mass. The total body fat mass was reduced by 4.06 kg in the treatment group and 1.44 kg in the control group ($P=0.0027$). The total body lean mass was reduced by 2.22 kg in treatment group and 0.24 kg in the control group ($p=0.0164$). Both the reductions in the total body fat and lean mass were statistically significant.
- According to ITT analysis, the average percent of total body fat mass was decreased by $2.25\pm 3.79\%$ in the Sibutramine group and by $0.96\pm 3.75\%$ in the placebo group. There was no significant difference between the two groups ($P=0.0689$). However, there was a significant difference in the decrease in percent of total body fat mass in the PP population (2.57% vs 0.66% , $p=0.0158$) and in the Completers population (2.67% vs 1.06% , $p=0.0226$).
- In the ITT analysis population, the average percent of the total body lean mass was increased by $2.55\pm 4.72\%$ in the Sibutramine group and by $1.21\pm 3.82\%$ in the placebo group. There was no significant difference between the two groups ($P=0.0944$). However, there was a significant difference in the decrease in percent of total body lean mass in the PP population (2.57% vs 0.70% , $p=0.018$) and in Completers population (3.01% vs 1.30% , $p=0.0366$).
- Sibutramine was shown to reduce the total abdominal fat mass. The total abdominal fat mass decreased by 580g in the treatment group and 123g in the control group. The decrease in the total abdominal fat mass in the treatment group was significant but not in the control group.
- The difference in the decrease of in the percentage of total abdominal fat mass between two groups was significant. The percentage total abdominal fat mass reduction was 2.60% and 0.27% in the treatment and the control groups. The decrease of percent total abdominal fat mass in the treatment group was significant and the decrease in the control group was not significant. The difference in decrease of percent total abdominal fat mass between two groups was significant ($P=0.0016$).
- The average total abdominal lean mass was decreased by $157.05\pm 382.13\text{g}$ in the Sibutramine group and by $65.34\pm 343.81\text{g}$ in the placebo group. There was no significant difference between the two groups.
- The percentage of the total abdominal lean mass was increased by 2.38% in the treatment group and by 0.32% in the control group. The observed differences of increase of percentage of the total abdominal lean mass between the two groups were

statistically significant (P=0.0054).

- The results also showed sibutramine resulted in a positive trend in decreasing triglyceride, statistically significant decrease of leptin level and statistically significant increase of adiponectin levels. The triglyceride level was decreased by 0.32 mmol/L in the treatment group and by 0.11 mmol/L in the control group after 24 weeks treatment. The difference in the triglyceride levels between the two groups was close to significant in the ITT dataset (p = 0.0546) and, in the completers dataset (p = 0.0545). The leptin level was decreased by 15.77 ng/ml in the treatment group and 5.58 ng/ml in the control group respectively and the difference in the levels of leptin between the two groups was significant in the ITT dataset (p = 0.0020), in the PP dataset (18.54 vs 5.10, p = 0.0023), and in the completer dataset (16.68 vs 5.58, p = 0.0012). The adiponectin level was increased by 0.79 µg/ml in the treatment group and by 0.11 µg/ml in the control group respectively and the difference in the levels between the two groups was significant (p = 0.0205). The analysis of the Completer populations (0.79 vs 0.11, P=0.0177) was consistent with the results from the analysis of the ITT population. However, there was no significant difference (0.85 vs 0.30, P=0.0767) in the change of the adiponectin level between the two groups in the PP population
- Sibutramine had no effect on total cholesterol, LDL, HDL, Apo B TNFa and ghrelin.

Pharmacokinetic: NA

Pharmacodynamic: NA

Safety results:

- 103 subjects were evaluated for the safety profile of Sibutramine and the placebo. There was no significant difference of the study treatment exposure between study groups.
- The incidence of AEs in Sibutramine group was higher than the placebo group (77.78% vs 55.10%). However, most of the AE's occurred were mild and were resolved during the study period.
- The most common adverse events reported in the treatment group were upper respiratory tract infections (nine cases, incidence=16.67%), headaches (eight cases, incidence=14.81%), dry mouth (eight cases, incidence=14.81%) and constipation (six cases, incidence=11.11%);
- The most common adverse events reported in the control group were upper respiratory tract infections (12 cases, incidence=24.49%), headaches (four cases, incidence=8.16%), constipation (four cases, incidence=8.16%), diarrhea (three cases, incidence=6.12%) and rhinitis (three cases, incidence=6.12%).
- Subjects receiving sibutramine were more likely to have giddiness (9.26% vs 0%), tachycardia (9.26% vs 0%) and dry mouth(14.81% vs 4.08%).
- One SAE (left lumbar pain) was reported during the study and was considered as severe but not related to study drug.
- The heart rate in the sibutramine group was increased by 5.3 beats/min (95%C.I.: -3.6~7.0 beats/min) compared with placebo group. However, no clinically significant finding of increase in heart rate was reported. The result of 12-lead ECG also showed no difference of safety in cardiovascular between Sibutramine and placebo.
- There were no clinically significant changes in the clinical chemistry parameters physical examination and other vital signs during the study.
- The study showed that the Sibutramine treatment was safe and well tolerated, compared with placebo.

Conclusions:

The results showed the effectiveness of sibutramine over placebo in terms of weight loss, BMI, waist circumference, hip circumference, total body fat mass, total body lean mass, total abdominal fat mass and total abdominal lean mass among obese subjects.

Weight loss in obese subjects also result in improvements on lipid measurement: positive trend to decrease triglyceride, statistically significant decrease of leptin level and statistically significant increase of Adiponectin levels.

Sibutramine was well tolerated. There were no significant changes of safety assessments. The trial subjects receiving sibutramine were more likely to have symptoms of giddiness, tachycardia and dry mouth. The rates of elevated heart rate associated with sibutramine treatment were high, but without clinically significant findings. The results obtained were consistent with previously published studies.

The study demonstrated that sibutramine can be used effectively and safely in obese non-diabetic patients, at a dose of 10 or 15 mg/day.