Safety and Weight Reduction of Sibutramine in the Treatment of Thai Obese and Overweight Subjects

ABBOTT LABORATORIES

Clinical Study Report

ABT-991/Protocol THAI-03-002

Development Phase:	Phase IV
Investigator or Coordinating Investigator:	**Prof. Apichati Vichayanrat** **Prof. Surat Komindr** **Dr. Chaicharn Deerochanawong**
Date First Subject Dosed:	**22 Dec 2004**
Date Last Subject Completed Dosing:	**12 Jan 2006**
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1 SYNOPSIS

Abbott Laboratories	**Individual Study Table Referring to Part of Dossier:**	**(For National Authority Use Only)**
Name of Study Drug: **Sibutramine (Reductil)**	**Volume:**	
Name of Active Ingredient: **Sibutramine**	**Page:**	

Title of Study:
Safety and Weight Reduction in Sibutramine Treatment of Thai Obese and Overweight Subjects

Investigator: Professor Apichati Vichayanrat , Professor Surat Komindr and Dr. Chaicharn Deerochanawong

Study Sites: 3

Publications: Local journals

Studied Period (Years): First Subject First Visit: 22 Dec 2004 Last Subject Last Visit: 12 Jan 2006	**Phase of Development: Phase IV**

Objective(s):

Primary objective(s)

The primary objective of the study was to evaluate the safety and efficacy of Sibutramine in conjunction with exercise and a hypocaloric diet on weight-loss in obese and overweight Thai subjects.

Secondary objective (s)

The secondary objectives of this study were to evaluate the efficacy of Sibutramine in conjunction with exercise and a hypocaloric diet with respect to changes from the baseline in other metabolic measurements in the obese and overweight Thai subjects.

Methodology:
The study was designed as a Phase IV, multicenter, open-label trial of Sibutramine in conjunction with a hypocaloric diet in obese and overweight Thai subjects. The duration of the study was 48 weeks with a 1-month screening period. Subjects who did not adequately responded to an appropriate non-pharmacologic weight-reducing regimen (i.e., diet and exercise) within 3 months prior to screening were eligible to enter into the study.

Number of Subjects (Planned and Analyzed):

Planned:

Recruitment target: At least 60 subjects

Actual recruited: 93 subjects

Analyzed:
For safety evaluation: 93 subjects
Intention-To-Treat (ITT): 93 subjects
Per Protocol (PP): 67 subjects

Diagnosis and main criteria for inclusion:

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

1. The subject did not adequately respond (*i.e.,* did not achieve or maintain > 5%weight loss) to an appropriate non-pharmacologic weight-reducing regimen (*i.e.,* diet and exercise) within 3 months prior to screening.
2. The subject was either male or female and with age range from ≥ 18 and ≤ 65 years old.
3. The subject had a nutritional obesity and BMI ≥ 30 kg/m^2.
4. For the female subjects, they were not of childbearing potential, 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 were 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 was 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.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:

Reductil® (Sibutramine)

Dose: 10mg, 15mg

Mode of administration:

Each subject was supplied with a standard boxes of 2 blister packs, each pack containing 14 capsules of either 10 or 15 mg Sibutramine.

And additional 3 capsules of either 10 or 15 mg Sibutramine was provided to make the full month supply for each visit through week 48.

Each subject was to take one capsule of either 10 or 15 mg Sibutramine orally daily with or without food and with liquid in the morning. In those subjects who did not adequately respond to the 10 mg dose of Sibutramine (<2kg weight loss after 4 weeks), the dose was increased to 15 mg if the study medication was well tolerated. The dose was not titrated back to the 10 mg dosage.

Duration of Treatment:

48 weeks or at premature discontinuation of the study medication

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:

NA

Criteria for Evaluation

Efficacy:

Primary Efficacy

The primary efficacy variable was defined as the change in the body weight from the baseline to the final evaluation period (at 48 weeks or at premature discontinuation of the study drug).

Secondary Efficacy

The secondary efficacy variables were defined as the percentage change in the body weight from the baseline to the final evaluation period and the changes from baseline to the final evaluation period of the following measurements:

1. Percent change in weight
2. BMI
3. Waist and hip circumference
4. Fasting glucose
5. Fasting lipid levels (total cholesterol, LDL, HDL, triglycerides)
6. Uric acid

Pharmacokinetic:

NA

Safety:

The safety variables examined were:

1. Blood pressure
2. Heart rate
3. Hematology
4. Clinical chemistry – including the renal profile and liver function tests
5. 12 Lead ECG
6. Adverse events

Statistical Methods

Both the efficacy and safety analysis was performed on the set of subjects who received at least one dose of Sibutramine.

Efficacy:

The efficacy (change in body weight and other measurements) and safety (AEs and other safety variables) analyses of the continuous variables were presented descriptively by calculating the summary statistics and the 95% confidence interval. For categorical variables, the absolute and relative frequencies were calculated. Summaries included an endpoint visit defined as the last value observed during the study period as appropriate.

The tests performed were exploratory in nature and where appropriate, Student t-test was carried out for comparing baseline endpoint values to test for significant differences. A two-sided 95%-confidence interval of a continuous variable was also provided.

Pharmacokinetic:

NA

Safety:

AEs were tabulated by the primary system organ class and preferred term, using the MedDRA dictionary. The number and percentage of patients experiencing AEs were presented. Also summaries by severity and relationship to study drug were done. Certain AEs, like serious or severe, leading to premature withdrawal, was listed and described in detail.

The changes from the baseline in vital sign, hematology and clinical chemistry variables were analyzed employing the same analysis methods used for the efficacy variables as described above. In addition, all laboratory values were categorized as low, normal or high based on the laboratory normal ranges. Values outside the normal range were flagged in the data listings. Laboratory values meeting pre-defined criteria for potentially clinically significant values were identified.

Summary/Conclusions

Efficacy Results:

All the 93 study subjects were included in the efficacy evaluation of the Intent-to-Treat population and 37 subjects were excluded in the efficacy evaluation by Per Protocol analysis population.

The data obtained showed that Sibutramine was effective in the reduction of body weight, BMI, waist circumference, hip circumference, WHR, fasting blood glucose level and uric acid level after 48 weeks of treatment.

- The overall weight loss during the 48-week study period was 9.31±5.74 kg (95% CI: 8.13~10.49). There were 78 subjects (83.87%) that achieved at least 5% weight loss and 44 subjects (47.31%) achieved at least 10% weight loss. The reduction was statistically significant.
- After 48 weeks of treatment, there was statistically significant reduction of BMI (3.70±2.20 kg/m^2, 95% CI: 3.24~4.15 kg/m^2), waist circumference (8.90±5.10 cm , 95% CI: 7.85~9.95 cm), hip circumference (7.16±4.27 cm, 95% CI: 6.28~8.04 cm), WHR (0.03±0.03, 95% CI: 0.02~0.03) and fasting blood glucose level (0.43±0.59 mmol/L, 95% CI: 0.31~0.55).
- The efficacy endpoints of body weight, BMI, waist circumference, hip circumference, WHR and fasting blood glucose level were decreased steadily from baseline to week 12, week 24 through week 48.
- There was a significant reduction of uric acid level from baseline to week 48 (15.65±49.73, 95% CI: 2.33~28.97, P=0.022).

No significant changes of fasting lipids level was detected in the study period.

Pharmacokinetic Results:

NA

Safety Results:

The safety evaluation was based on the data obtained from the 93 subjects enrolled in the study.

- The incidence of adverse event reported was 61.29%, four patients discontinued from study due to adverse event.
- Most of the AEs occurred were mild and moderate. Only two subjects (2/93, 2.15%) experienced severe adverse events and they were not related to the study drug.
- No deaths were reported during the study, and three SAEs (perianal abscess, haemorrhagic fever and abdominal pain) were reported in three subjects. All three SAEs were not related to the study medication.

Table (Error! No text of specified style in document.**) 1 - Overall Summary of Adverse Event**

		(N = 93)
Participants having reported		
at least one emergent adverse event	n (%)	57(61.29)
at least one treatment-related emergent adverse event	n (%)	45(48.39)
Participants having experienced		
at least one serious adverse event	n (%)	3(3.23)
at least one treatment-related serious adverse event	n (%)	0(0.00)
Participants withdrawn		
due to an adverse event	n (%)	4(4.30)

due to a serious adverse event	n (%)	1(1.08)
due a treatment-related adverse event	n (%)	2(2.15)
due a treatment-related serious adverse event	n (%)	0 (0.00)
Participants who died	n (%)	0(0.00)

- The most common adverse events reported were dry mouth (31.18%, 29/93), constipation (19.35%, 18/93), headache (10.75%, 10/93), dry throat (9.68%, 9/93%), dizziness (8.60%, 8/93) and pyrexia (8.60%, 8/93), all of which were consistent with the previous publications and the label.

Table (Error! No text of specified style in document.**) 2 - Adverse Event >5%**

Preferred Term	**N(%)**
Dry mouth	29(31.18)
Constipation	18(19.35)
Headache	10(10.75)
Dry throat	9(9.68)
Dizziness	8(8.6)
Pyrexia	8(8.6)

- Both the systolic and diastolic blood pressure measurements were significantly decreased at the end of study. The systolic blood pressure decreased by 4.01±7.97 mmHg (95%C.I.: 2.15~5.87 mmHg, P<0.001) and the diastolic blood pressure decreased by 2.33±4.65 mmHg (95%C.I.: 1.25~3.42 mmHg, P<0.001). The changes in the blood pressure measurements were within the normal range.
- There were no clinical significant changes in the clinical chemistry parameters, 12-lead ECG and other vital signs during the study.
- The study showed that Sibutramine treatment was safe and well tolerated.

Conclusions:

The present study showed that obese subjects treated with Sibutramine had their body weight, BMI, WHR decreased steadily over the duration of the study. The data obtained was consistent with reports published previously.

This study showed that Sibutramine was effective in the treatment of Thai obese and overweight subjects in terms of changes e.g., weight loss, reduced BMI, waist circumference, hip circumference and WHR as compared to baseline.

The safety profile in this study showed that Sibutramine was safe and well tolerated.

This study indicates Sibutramine to be safe and well-tolerated agent leading to reduction of parameters of obesity in obese and overweight Thai subjects, in combination with exercise and a hypocaloric diet.