



## PAPER

# Second phase of a double-blind study clinical trial on Sibutramine for the treatment of patients suffering essential obesity: 6 months after treatment cross-over

G Fanghänel<sup>1</sup>, L Cortinas<sup>1</sup>, L Sánchez-Reyes<sup>1</sup> and A Berber<sup>2\*</sup>

<sup>1</sup>Obesity Research Clinic, Endocrinology Department, Hospital General de México, Mexico City, Mexico; and

<sup>2</sup>Arzneimittelforschung BASF Pharma, Mexico City, Mexico

**OBJECTIVE:** To evaluate the weight gain after Sibutramine 10 mg daily discontinuation. To evaluate the effect of Sibutramine 10 mg daily in patients who were on a diet for 6 months.

**DESIGN:** After a double-blind, placebo-controlled, parallel, prospective phase for 6 months, the treatments were crossed over and the patients continued in double-blind observation for another 6-month period.

**SUBJECTS:** Forty out of 44 patients who were on Sibutramine and 42/44 who were on placebo switched the trial medication. All the patients were obese at the beginning of the trial (body mass index, BMI > 30 kg/m<sup>2</sup>). During the first phase, the weight loss in the Sibutramine group was 7.52 kg (95% confidence intervals (95% CI) 6.15; 8.9) and that in the placebo group 3.56 kg (95% CI 2.41; 4.7) (using last observation carried forward (LOCF)).

**MEASUREMENTS:** Body weight, BMI, waist, medical history, assessment of hunger, satiety and diet compliance, standard laboratory assessments, blood pressure, heart rate and ECG.

**RESULTS:** Thirty out of 40 patients in the Sibutramine/placebo (S/P) group and 32 out of 42 in the placebo/Sibutramine (P/S) group completed the second phase of the trial. During the second part of the trial the S/P gained 3.21 (95% CI 2.15; 4.26) kg, 1.21 (0.82; 1.59) kg/m<sup>2</sup>, and 2.83 (1.55; 4.12) waist cm. The P/S group lost 1.62 (2.62; 0.61), 0.67 (1.09; -0.25) kg/m<sup>2</sup>, and 1.85 (3.18; 0.53) waist cm. Eleven patients in the S/P group suffered 14 adverse events, mainly blood pressure increase ( $n=4$ ); 19 patients in the P/S group had 29 adverse events, mainly dry mouth ( $n=8$ ), constipation ( $n=5$ ) and blood pressure increase ( $n=4$ ). Only one P/S patient withdrew because of an adverse event.

**CONCLUSIONS:** After Sibutramine discontinuation patients had weight gain but they did not reach the baseline body weight. No significant adverse events presented after Sibutramine discontinuation. When Sibutramine was administered to patients after 6 months of diet, the weight plateau was broken. Early Sibutramine administration had better effects than late post-diet administration. Sibutramine was well tolerated by the patients.

*International Journal of Obesity (2001) 25, 741–747*

**Keywords:** obesity treatment; Sibutramine; double blind; placebo controlled; cross-over clinical trial

## Introduction

A minimal weight loss induces significant health benefits in obese patients.<sup>1</sup> The ultimate goal of the treatment of obesity is to decrease the risks associated with the disease by means of long-term weight loss maintenance,<sup>2</sup> but the maintenance

of weight loss is very difficult and most of the patients tend to regain weight.<sup>3,4</sup> The recognition of this problem has led to an approach of long-term treatments for obesity, including drug therapy, in a similar way to other chronic diseases.<sup>2,3,5</sup>

Sibutramine is a brand-new agent for weight loss and weight loss maintenance. Sibutramine is a serotonin and noradrenaline reuptake inhibitor with no effect on the dopamine reuptake system,<sup>6</sup> and has no addictive potential.<sup>7,8</sup> Animal studies show that Sibutramine induces weight loss by enhancing satiety and increasing the metabolic rate.<sup>6,9</sup>

\*Correspondence: A Berber, Arzneimittelforschung BASF Pharma, La Candelaria 186, Colonia Atlantida, CP 04370, Mexico City DF, Mexico.  
E-mail: arturoberber@aol.com

Received 13 April 2000; revised 8 August 2000;  
accepted 19 September 2000

Three clinical trials of the effect of Sibutramine have been extensively reported up to this moment. Weintraub *et al* reported a dose-dependent weight loss induced by Sibutramine over 8 weeks of treatment; the weight loss achieved was 3% for the 5 mg group and 5.1% in the 20 mg group.<sup>10</sup>

In a monocenter trial, Bray *et al*<sup>11</sup> found that Sibutramine produced dose dependent weight loss in obese patients over a 24 week period, with doses ranging from 5 to 30 mg. The weight loss was 3–9% of the baseline body weight and 28–62% of the patients lost at least 5% of the initial body weight. The reported adverse events were dry mouth, anorexia, constipation and insomnia, and were also dose-dependent. The findings were confirmed by a multicenter trial which included these previous results.<sup>12</sup>

Hanotin *et al* described another dose range study for 12 weeks with similar results. Weight loss was dose-dependent. The proportions of patients achieving a weight loss of at least 5% of their initial body weight were 23% for 5 mg, 49% for 10 mg and 55% for 15 mg. The adverse events associated with Sibutramine were dry mouth, insomnia and constipation, and were more frequent in the 15 mg group.<sup>13</sup>

A Mexican trial comparing Sibutramine 15 mg vs placebo in a double-blind model found (using the method of last observation carried forward) that weight loss in the Sibutramine group was 10.27 kg (95% CI 7.66; 13.07), corresponding to 11.8% of the initial body weight, and 37/51 (72.55%) patients losing at least 5% of the initial body weight. The most frequent adverse events were upper respiratory tract infections and constipation.<sup>14</sup>

Antiobesity drugs induce weight loss by the first 6 months of treatment and then reach a plateau.<sup>5,15</sup> After this weight loss period patients on drug treatment tend to gain weight,<sup>15,16</sup> but in the case of Sibutramine<sup>11,12</sup> most of the weight loss is maintained for at least 1 y.

After the drug discontinuation, patients tend to gain weight, and it must be considered as evidence of the efficacy.<sup>2,17</sup> This weight gain was observed after the discontinuation of Sibutramine.<sup>12</sup>

The aim of the second phase of the trial, after cross-over, was to study the effect of Sibutramine withdrawal under placebo-controlled conditions and to explore the adverse events presented after stopping Sibutramine and, additionally, the effect of Sibutramine in patients who had been on diet for 6 months.

During the first phase of this trial 109 obese patients (body mass index, BMI > 30 kg/m<sup>2</sup>) from 16 to 65 y received in double-blind Sibutramine 10 mg or a matching placebo, once a day, *per os* (by mouth), over a period of 6 months. Forty out of 55 patients in the Sibutramine group and 44 out of 54 patients in the placebo group completed the trial. Using the method of last observation carried forward (LOCF), the weight loss in the Sibutramine group was 7.52 kg (95% confidence intervals (95% CI) 6.15; 8.9) and 3.56 kg (95% CI 2.41; 4.7) in the placebo group ( $P < 0.05$  by paired Student's *t*-test). Thirty two Sibutramine patients had 45 adverse events; the most frequent adverse events in the

Sibutramine group were dry mouth ( $n=19$ ), increase in blood pressure ( $n=5$ ), constipation ( $n=5$ ) and tachycardia ( $n=5$ ); 23 placebo patients had 29 adverse events, mainly increase in blood pressure ( $n=11$ ) and dry mouth ( $n=10$ ). Two Sibutramine patients withdrew the trial due to adverse events.

The second phase of the trial consisted of an additional 6 month period of treatment after a treatment cross-over. Only patients who entered the second phase are considered.

## Patients and methods

A double-blind, cross-over, placebo-controlled, parallel group, prospective clinical trial was conducted in order to assess the safety and efficacy of Sibutramine in the treatment of obesity in Mexican patients. The first phase of the trial was reported in *International Journal of Obesity and Related Diseases*. The second phase of the trial after the cross-over is reported here; only the patients who entered the second phase are considered.

Male and female patients from 16 to 65 y with a BMI greater than 30 kg/m<sup>2</sup> were recruited after written informed consent had been obtained. The following patients were not included in the trial: those suffering from endocrine diseases other than type 2 diabetes mellitus, uncontrolled hypertension, autoimmune diseases, ischemic heart disease, arrhythmia, lactating or pregnant women, psychosis, and those requiring drugs acting on the central nervous system, cathartics, thyroid replacement or diuretics.

Patient participation was stopped if they became pregnant, presented with a concomitant severe disease, suffered severe adverse events, withdrew their informed consent or failed to attend the clinical appointments. The subjects were outpatients attending to the Endocrinology Service, Hospital General de México.

Patients were randomized either to the group taking Sibutramine 10 mg once a day, *per os* or to the group taking placebo in the same way. In order to randomize the participants, we prepared a computer list of 120 random numbers in 12 different blocks of 10. For each block the proportion of even/odd numbers by group was 3/2 or 2/3, with no more than three consecutive positions. The patients were assigned a consecutive number as they completed the initial laboratory safety test and an electrocardiogram to confirm the selection criteria. For each number there was a box containing 19 packages with 10 capsules each (two blisters of five capsules), and an opaque sealed envelope with the drug code; all the materials for a patient were identified by the patient number. The materials were prepared by AB, who did not know the identity of the patients. GF received the trial materials without any knowledge of the procedures or order in the random number list.

The first patient entered the trial by March 1998 and the last patient finished the second phase by July 1999.

The appearances of the boxes, packages, blisters and capsules were the same.

Patients were recommended to complete a diet of 30kcal/kg of the ideal body weight, the diet should have about 50% of the energy from carbohydrates, 30% from lipids and 20% from proteins. Patients received a list of recommended food portions and the possible combinations.

Patients received the dietetic advice 15 days before the beginning of the study medications and the dietetic supervision during the treatment phase of the trial.

Clinical control visits were 15 days before the beginning of the study medication, when the study medication began, and then monthly, up to 6 months of treatment. When the patients had completed 6 months of treatment, those taking Sibutramine switched to placebo and vice versa. Patients visited the investigators monthly to assess the end-points and check the safety, up to the end of the second phase. The ancillary therapy remained the same during the second phase of the trial.

The primary end-points for the trial were the body weight and BMI, the secondary end-points were the waist and waist/hip ratio. Appetite, satiety and diet adherence were also evaluated. For appetite, the visual analog scale was a line of 155 mm with 10% divisions from 0% with the quotation 'very hungry' on the left, up to 100% 'without hunger' to the right. In the case of satiety the scale was similar but the 0% mark on the left corresponded to the legend 'extremely full' and the right mark of 100% to 'emptiness sensation'. The scale for compliance with the diet had the legend 'impossible to follow' corresponding to 0% on the left and 'easy to comply' on the right mark of 100%. All the described parameters were evaluated at each visit.

Adverse events were reported as they were detected. Patients were encouraged to call the investigators if they had any question or complaint at any time. Additionally, the patients were asked if 'something unusual had happened since your last visit' in all the visits, in order to collect any possible complaints.

Blood cytology, blood chemistry and urinalysis were performed before the beginning of the medication and after 6 and 12 months of medication. Electrocardiograms were performed at these times too.

The proposed statistical analysis for the end-points included the intragroup comparison of the values at the baseline with those in the last visit by the paired Student's *t*-test. The same kind of analysis was performed with the last observation carried forward (LOCF) of the end-points, where the last observation replaced the missing values. For this analysis, only patients who completed at least 1 month of treatment during the second phase with the corresponding end-point evaluation were considered. Only the data of the patients completing the first phase are considered.

For the rest of the interval measurements, the intragroup comparisons were tested by the paired Student's *t*-test, while the intergroup comparisons were performed using the unpaired Student's *t*-test, and in the case of nominal scales in the intergroup comparisons, the  $\chi^2$  test, with continuity correction in the 2x2 tables, were used.

The protocol was approved by the local investigation and ethics committee, and the Mexican Ministry of Health. The protocol complied with the Mexican regulations and with the European Good Clinical Practice guidelines.

## Results

Forty patients in the group S/P (Sibutramine/placebo) and 44 in the group P/S (placebo/Sibutramine) finished the first phase of treatment. Forty patients in the group S/P and 42 in the group P/S initiated the second phase of the trial. One patient in the group P/S experienced an adverse event when she switched to Sibutramine and withdrew the trial; this case is taken into account for safety analysis but not for the efficacy analysis.

The characteristics of the patient at the beginning of the second phase are shown in Table 1. Evolution of the end-points throughout of the trial is shown in Table 2 for completers and Table 3 for last observation carried forward (LOCF).

The endpoint differences regarding the values after the end of the first phase are shown in Table 4. Patients who changed from Sibutramine to placebo presented a weight gain, while those who switched from placebo to Sibutramine lost weight.

The evolution of percentage of baseline weight and waist during the first and second phase of the study are shown in Figures 1 and 2. Only the patients starting the second phase were considered and the LOCF values were used for the second phase.

By the end of the first phase of the trial 33/40 (82.5%) patients in the group S/P had achieved a significant weight loss  $\geq 5\%$  of baseline body weight, while only 20/41 (48.8%) in the group P/S reached that goal.

After crossing 34/40 (85%) the patients in group S/P increased their body weight, and 32/41 (78%) group P/S patients loss weight; 24/41 (58.5%) lost  $< 5\%$  and 8/41 (19.5%) from 5 to 10% (regarding the weight at the end of the first phase). So, by the end of the second phase 21/40

**Table 1** The characteristics of the patient at the beginning of the second phase

|                               | Group S/P,<br>Sibutramine/placebo | Group P/S,<br>Placebo/Sibutramine |
|-------------------------------|-----------------------------------|-----------------------------------|
| Sex                           |                                   |                                   |
| male                          | 3                                 | 2                                 |
| female                        | 37                                | 39                                |
| Race                          |                                   |                                   |
| euromestizo                   | —                                 | 1                                 |
| indomestizo                   | 40                                | 40                                |
| Age                           | 40.1 ± 10.51                      | 39.0 ± 10.15                      |
| Weight                        | 78.77 ± 15.47                     | 81.7 ± 13.98                      |
| Percentage of baseline weight | 90.11 ± 4.94                      | 95.22 ± 5.16*                     |
| BMI                           | 32.38 ± 4.86                      | 33.41 ± 5.22                      |
| Waist                         | 94.92 ± 11.18                     | 97.05 ± 13.6                      |
| Percentage of baseline waist  | 92.45 ± 6.12                      | 95.59 ± 4.9*                      |

\**P* < 0.05 by unpaired student's *t* test.

**Table 2** Evolution of the endpoints throughout of the second phase of the trial

|                                     | Day 180       | Day 210       | Day 240       | Day 270       | Day 300       | Day 330       | Day 360       |
|-------------------------------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|
| n group A                           | 40            | 39            | 36            | 34            | 32            | 29            | 30            |
| n group B                           | 41            | 41            | 38            | 34            | 36            | 28            | 32            |
| Body weight, Sibutramine            | 78.77 ± 15.47 | 79.63 ± 15.84 | 79.92 ± 16.24 | 80.47 ± 16.49 | 79.73 ± 16.14 | 80.29 ± 17.46 | 80.78 ± 16.9  |
| Body weight, placebo                | 81.7 ± 13.98  | 80.36 ± 13.79 | 79.57 ± 13.84 | 80.05 ± 15.02 | 79.14 ± 13.18 | 80.19 ± 14.41 | 79.38 ± 13.48 |
| Percentage body weight, Sibutramine | 100 ± 0       | 101.49 ± 1.56 | 102.32 ± 2.2  | 102.67 ± 2.96 | 103.06 ± 3.58 | 103.57 ± 3.84 | 103.95 ± 4.01 |
| Percentage body weight, placebo     | 100 ± 0       | 98.35 ± 1.5   | 97.99 ± 2.4   | 98.05 ± 2.8   | 98.48 ± 2.64  | 97.55 ± 3.2   | 97.91 ± 4.42  |
| IMC, Sibutramine                    | 32.38 ± 4.86  | 32.87 ± 4.97  | 33.06 ± 5.17  | 33.07 ± 5.14  | 33.21 ± 5.09  | 33.35 ± 5.26  | 33.3 ± 5.03   |
| IMC, placebo                        | 33.41 ± 5.22  | 32.86 ± 5.14  | 32.67 ± 5.18  | 32.78 ± 5.61  | 32.57 ± 5.08  | 32.8 ± 5.53   | 32.63 ± 5.28  |
| Waist, Sibutramine                  | 94.92 ± 11.18 | 95.95 ± 11.62 | 96.46 ± 12.11 | 97.03 ± 12.39 | 96.28 ± 11.32 | 96.59 ± 12.04 | 96.88 ± 11.9  |
| Waist, placebo                      | 97.05 ± 13.6  | 95.69 ± 13.42 | 95.47 ± 13.8  | 95.04 ± 15.53 | 95.35 ± 14.62 | 95.91 ± 15.03 | 94.83 ± 14.19 |
| Percentage waist, Sibutramine       | 100 ± 0       | 101.28 ± 2.87 | 101.67 ± 3.02 | 102.13 ± 4.37 | 102.11 ± 4.4  | 102.22 ± 3.87 | 102.47 ± 4.28 |
| Percentage waist, placebo           | 100 ± 0       | 98.62 ± 1.97  | 98.15 ± 2.55  | 97.69 ± 3.73  | 98.29 ± 3.33  | 98.23 ± 4.78  | 97.95 ± 4.74  |

**Table 3** Evolution of the LOCF endpoints throughout of the second phase of the trial

|                                     | Day 180       | Day 210       | Day 240       | Day 270       | Day 300       | Day 330       | Day 360       |
|-------------------------------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|
| Body weight, Sibutramine            | 78.77 ± 15.47 | 79.63 ± 15.84 | 80.23 ± 16.13 | 80.85 ± 16.15 | 81.34 ± 16.44 | 81.76 ± 16.74 | 81.98 ± 16.51 |
| Body weight, placebo                | 81.7 ± 13.98  | 80.36 ± 13.79 | 80.02 ± 13.77 | 80.07 ± 14.23 | 80.28 ± 13.94 | 80.18 ± 14.36 | 80.08 ± 14.22 |
| Percentage body weight, Sibutramine | 100 ± 0       | 101.49 ± 1.56 | 102.24 ± 2.22 | 102.6 ± 2.83  | 103.18 ± 3.39 | 103.69 ± 3.82 | 104.04 ± 3.96 |
| Percentage body weight, placebo     | 100 ± 0       | 98.35 ± 1.5   | 97.95 ± 2.39  | 97.93 ± 2.63  | 98.26 ± 2.59  | 98.07 ± 3.24  | 97.99 ± 4.05  |
| IMC, Sibutramine                    | 32.38 ± 4.86  | 32.87 ± 4.97  | 33.11 ± 5.05  | 33.18 ± 5.05  | 33.38 ± 5.21  | 33.51 ± 5.22  | 33.59 ± 5.07  |
| IMC, placebo                        | 33.41 ± 5.22  | 32.86 ± 5.14  | 32.72 ± 5.15  | 32.74 ± 5.31  | 32.83 ± 5.21  | 32.78 ± 5.32  | 32.74 ± 5.28  |
| Waist, Sibutramine                  | 94.92 ± 11.18 | 95.95 ± 11.62 | 96.5 ± 11.87  | 97.15 ± 12.11 | 97.51 ± 12.05 | 97.52 ± 11.95 | 97.76 ± 11.98 |
| Waist, placebo                      | 97.05 ± 13.6  | 95.69 ± 13.42 | 95.23 ± 13.43 | 94.95 ± 14.31 | 95.37 ± 13.83 | 95.39 ± 14.12 | 95.19 ± 13.92 |
| Percentage waist, Sibutramine       | 100 ± 0       | 101.28 ± 2.87 | 101.86 ± 3.02 | 102.34 ± 4.1  | 102.74 ± 4.27 | 102.76 ± 3.89 | 103.01 ± 4.18 |
| Percentage waist, placebo           | 100 ± 0       | 98.62 ± 1.97  | 98.14 ± 2.5   | 97.77 ± 3.46  | 98.25 ± 3.17  | 98.27 ± 4.12  | 98.09 ± 4.29  |

**Table 4** End-point change during the second phase of the trial

|                                | Completers                    |                                | LOCF                          |                               |
|--------------------------------|-------------------------------|--------------------------------|-------------------------------|-------------------------------|
|                                | Group S/P Sibutramine/placebo | Group P/S placebo/Sibutramine  | Group S/P Sibutramine/placebo | Group P/S placebo/Sibutramine |
| Body weight (kg CI 95%)        | + 3.1*<br>(+ 1.83; + 4.36)    | - 1.69****<br>(- 2.94; - 0.44) | + 3.21*<br>(+ 2.15; + 4.26)   | - 1.62**<br>(- 2.62; - 0.61)  |
| Percentage body weight, CI 95% | + 3.95*<br>(+ 2.45; + 5.45)   | - 2.09****<br>(- 3.68; - 0.49) | + 4.05*<br>(+ 2.78; + 5.31)   | - 2.00**<br>(- 3.28; - 0.73)  |
| BMI kg/m <sup>2</sup> , CI 95% | + 1.15*<br>(+ 0.69; + 1.57)   | - 0.7****<br>(- 1.22; - 0.18)  | + 1.21*<br>(+ 0.82; + 1.59)   | - 0.67**<br>(- 1.09; - 0.25)  |
| Waist, CI 95%                  | + 2.31**<br>(+ 0.79; + 3.83)  | - 1.97****<br>(- 3.64; - 0.30) | + 2.83*<br>(+ 1.55; + 4.12)   | - 1.85***<br>(- 3.18; - 0.53) |

\*P < 0.001 by paired Student's t-test; \*\*P < 0.005 by paired Student's t-test; \*\*\*P < 0.01 by paired Student's t-test; \*\*\*\*P < 0.05 by paired Student's t-test.

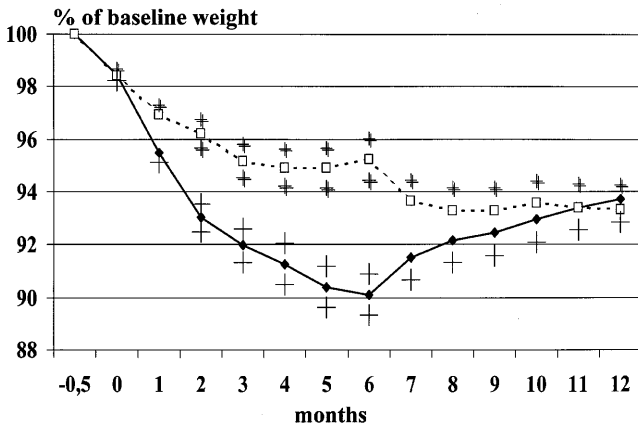
(52.5%) patients in the group S/P had lost ≥ 5% of the baseline body weight and this goal was achieved by 25/41 (61%) patients in the group P/S. The changes in both periods are shown in Figure 3.

The mean values for the parameters appetite, satiety and adherence to the recommended diet (as marked on visual analog scale) were evaluated too. After cross-over the patients in the group S/P presented significant increase in appetite as well as a significant decrease in the diet adherence (except in the month 10). In this group the satiety level decrease significantly in the months 8 and 11. Meanwhile, the patients in the group P/S had decreased appetite in

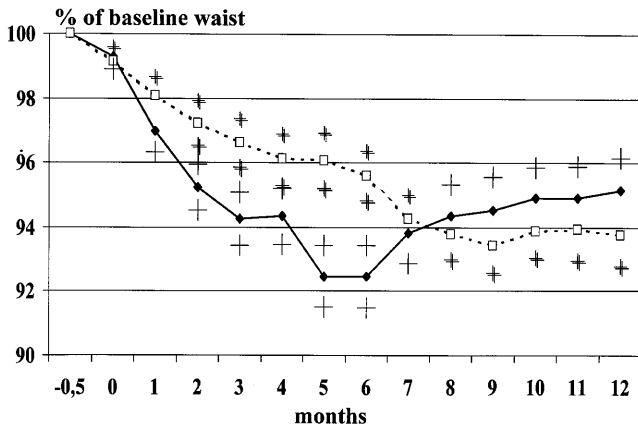
months 8 and 12, increase in the satiety in month 8, and better diet adherence during months 7 and 8.

Regarding the systolic blood pressure, no significant changes were found in the group S/P, instead the group P/S had significant, but small, increases in months 8 and 11 (115.7 ± 7.5 by month 6 vs 118.3 ± 6.6 and 120.5 ± 9.7 respectively; P < 0.05 by paired Student's t-test). No significant changes in diastolic blood pressure were found in both groups.

Group S/P patients had minimal, but significant decrease in heart rate in months 8 and 9 (75.9 ± 4.4 by month 6 vs 74.2 ± 3.4 and 74.1 ± 3.3, respectively; P < 0.05 by paired



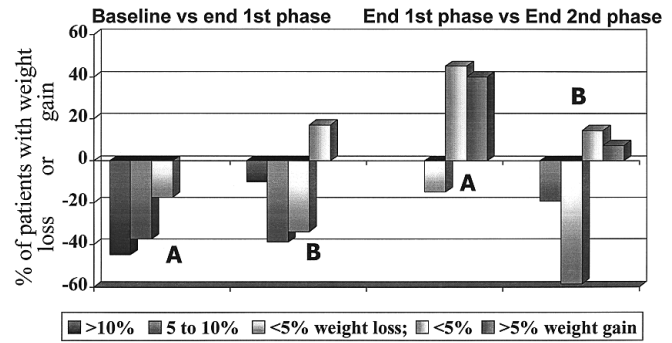
**Figure 1** Evolution of percentage of baseline weight. The bold line represents the evolution of the percentage of starting weight in the Sibutramine/placebo group and the markers to the standard error. The broken line represents the evolution of the percentage of starting weight in the placebo/Sibutramine group and the markers to the standard error.



**Figure 2** Evolution of percentage of baseline waist. The bold line represents the evolution of the percentage of starting waist in the Sibutramine/placebo group and the markers to the standard error. The broken line represents the evolution of the percentage of starting waist in the placebo/Sibutramine group and the markers to the standard error.

Student's *t*-test). Patients in the group P/S had a small, but significant increase in the heart rate 1 month after the beginning of Sibutramine ( $75.3 \pm 4.4$  in month 6 vs  $76.8 \pm 2.9$  in month 7;  $P < 0.05$  by paired Student's *t*-test).

During the second phase of the trial four patients in group S/P presented five episodes of clinically significant increase of blood pressure (systolic  $\geq 140$  and/or diastolic  $\geq 90$  mmHg). Only one patient received an antihypertensive drug (lisinopril) to control blood pressure. On the other hand, four patients in group P/S had six episodes of clinically significant increase of blood pressure, but none of them required antihypertensive medication. Only two patients in group P/S presented transitory heart rate  $\geq 90$  bpm, and they did not require any specific treatment. When baseline and



**Figure 3** Weight loss or gain in the two phases of the trial. The left panel represents the percentage of patients losing  $> 10\%$ ,  $10-5\%$  or  $< 5\%$  or gaining  $10-5\%$  or  $< 5\%$  of the baseline body weight. The right panel depicts the same variations but regarding the body weight at the end of the first phase. The Sibutramine/placebo group is represented with letter A and the placebo/Sibutramine group with letter B.

**Table 5** Values for the laboratory tests express as mean  $\pm$  standard deviation, except the urinalysis median (percentile 25; percentile 75)

|  | Baseline         | End 1st phase     | End 2nd phase     |
|--|------------------|-------------------|-------------------|
| <i>Group S/P (Sibutramine/placebo)</i> |                  |                   |                   |
| Glucose                                | 92.6 $\pm$ 10.5  | 95.0 $\pm$ 80.1   | 91.2 $\pm$ 9.3    |
| Cholesterol                            | 205.5 $\pm$ 34.2 | 193.2 $\pm$ 30.5* | 194.3 $\pm$ 24.2  |
| HDL                                    | 42.0 $\pm$ 9.2   | 49.5 $\pm$ 10.7*  | 49.7 $\pm$ 11.0*  |
| LDL                                    | 121.6 $\pm$ 30.0 | 113.6 $\pm$ 25.7* | 112.8 $\pm$ 26.6* |
| Triglycerides                          | 183.1 $\pm$ 90.7 | 142.3 $\pm$ 64.0* | 143.2 $\pm$ 51.8* |
| Monocytes                              | 1.18 $\pm$ 0.89  | 1.82 $\pm$ 0.85*  | 1.70 $\pm$ 1.09*  |
| Uric acid                              | 4.7 $\pm$ 0.9    | 4.2 $\pm$ 0.6*    | 4.8 $\pm$ 1.0**   |
| Creatinine                             | 0.90 $\pm$ 0.14  | 0.86 $\pm$ 0.15*  | 0.87 $\pm$ 0.14** |
| Proteins                               | 7.4 $\pm$ 0.5    | 7.5 $\pm$ 0.4     | 7.0 $\pm$ 0.4***  |
| Globulin                               | 2.6 $\pm$ 0.4    | 2.6 $\pm$ 0.3     | 2.4 $\pm$ 0.4**   |
| Calcium                                | 9.6 $\pm$ 0.6    | 9.2 $\pm$ 0.8*    | 9.8 $\pm$ 0.5**   |
| TGP                                    | 35.2 $\pm$ 20.5  | 26.7 $\pm$ 10.4*  | 24.5 $\pm$ 11.4*  |
| Urinalysis                             |                  |                   |                   |
| pH                                     | 5 (5; 5)         | 5 (5; 6)*         | 5 (5; 6)          |
| Red cells                              | 0 (0; 0)         | 0 (0; 0)          | 0 (0; 0)*         |
| <i>Group P/S (placebo/Sibutramine)</i> |                  |                   |                   |
| Glucose                                | 106.1 $\pm$ 42.5 | 95.9 $\pm$ 16.3   | 98.8 $\pm$ 19.0   |
| Cholesterol                            | 203.1 $\pm$ 50.8 | 193.6 $\pm$ 46.6  | 192.4 $\pm$ 37.0  |
| HDL                                    | 43.9 $\pm$ 9.5   | 45.6 $\pm$ 10.2   | 47.2 $\pm$ 8.4*   |
| LDL                                    | 118.3 $\pm$ 30.6 | 111.4 $\pm$ 34.7  | 110.7 $\pm$ 24.7  |
| Triglycerides                          | 173.0 $\pm$ 81.8 | 174.3 $\pm$ 107.4 | 187.5 $\pm$ 230.6 |
| Red cells                              | 4.59 $\pm$ 0.36  | 4.69 $\pm$ 0.70   | 4.60 $\pm$ 0.62** |
| Hematocrit                             | 43.0 $\pm$ 3.4   | 43.4 $\pm$ 6.3    | 43.2 $\pm$ 6.2**  |
| Urea                                   | 29.4 $\pm$ 7.4   | 27.6 $\pm$ 8.3    | 27.0 $\pm$ 7.1*   |
| Uric acid                              | 4.9 $\pm$ 1.4    | 4.4 $\pm$ 0.9*    | 5.0 $\pm$ 1.3**   |
| Creatinine                             | 0.91 $\pm$ 0.10  | 0.85 $\pm$ 0.14*  | 0.86 $\pm$ 0.08*  |
| Proteins                               | 7.7 $\pm$ 0.5    | 7.6 $\pm$ 0.4     | 7.1 $\pm$ 0.5***  |
| Globulin                               | 2.8 $\pm$ 0.5    | 2.7 $\pm$ 0.4     | 2.6 $\pm$ 0.6**   |
| Calcium                                | 9.6 $\pm$ 0.7    | 9.0 $\pm$ 1.0*    | 9.6 $\pm$ 0.6     |
| TGP                                    | 29.7 $\pm$ 18.3  | 26.8 $\pm$ 14.3   | 22.0 $\pm$ 9.7*** |

\* $P < 0.05$  vs baseline value;

\*\* $P < 0.05$  vs end of the first phase value.

The items were analyzed by paired Student's *t*-test, except triglycerides, monocytes, eosinophiles, basophiles and urinalysis data, which were analyzed by Wilcoxon test.

**Table 6** Adverse events presented

|  | Group S/P,<br>Sibutramine/Placebo                               | Group P/S,<br>placebo/Sibutramine   |
|--|---|---|
| Significant increase in blood pressure | 4   | 3   |
| Dry mouth                              | 2   | 8   |
| Hyposthesia                            | 2   | —   |
| Constipation                           | 1   | 5   |
| Headache                               | —   | 2   |
| Urinary tract infection                | —   | 2   |
| One case of each of:                   | Corneal ulcer<br>Erisipelas<br>Leg edema<br>Chills<br>Dizziness | Heart rate increase<br>Bad mouth taste<br>Conjunctivitis<br>Bimalleal fracture<br>Articular hand pain<br>Generalized itching and chills<br>Blood pressure and heart rate increase<br>Hoarseness<br>Migraine |

final electrocardiograms were compared no clinical significant changes were detected.

Glucose and lipids values, as well as statistically significant changes in laboratory tests are shown in Table 5. Patients in group S/P had lower cholesterol levels by the end of the first phase and they had persistent decrease in triglycerides and LDL with a concomitant increase in HDL by the end of first and second phase. Patients in group P/S only had HDL increase after the end of the second phase.

Eleven patients in the group S/P suffered 14 adverse events, the most common event being blood pressure increase (four cases). Nineteen patients in the group P/S had 29 adverse events, the most common events being dry mouth (eight cases), constipation (five cases) and blood pressure increase (four cases), including one case with associated increase in heart rate). The complete list of adverse events is given in Table 6. Seven patients in the group S/P were lost to follow-up and three retracted their informed consent. In group P/S one patient withdrew due to an adverse event (generalized itching and chills), four were lost to follow-up and five retracted their informed consent.

## Discussion

In this second phase the two groups are not themselves comparable, but the model provides important clues on obese patient behavior on Sibutramine treatment.

In this trial the cross-over design allows different scenarios to be evaluated in the current consultation: what happened if a patient, who had been on diet and exercise for several months was treated with Sibutramine? Was there a weight rebound after treatment with Sibutramine? Is there any compulsion to continue Sibutramine after treatment?

The response of the patients who were in the placebo group was much less important than that observed if the

patients had just begun Sibutramine after a brief run-in period. During the second phase the patients in the group P/S achieved a 2% weight loss compared with the end of the first phase (only eight out of 41 (19.5%) patients had weight loss between 5 and 10%), instead the patients in the group S/P had achieved a weight loss of about 10% when the first phase finished (15/40 (37.5%) had a weight loss from 5 to 10%, and 18/40 (45%)  $\geq$  10%); meanwhile, nine out of 41 (21.9%) patients in group P/S experienced weight gain during the second phase.

Both groups of patients had about 6% weight loss regardless the treatment order; the weight changes were very small after the treatment cross-over. Yet the patients in the S/P group had persistent benefits on the HDL, LDL and triglyceride levels in contrast to the patients in the P/S group, who only presented an increase in HDL concentration after the cross-over.

The benefits of the weight reduction produced by Sibutramine, during the treatment and after it, should be evaluated in patients suffering co-morbidities such as hypertension and diabetes.

It is important to note that patients in the P/S had reached a weight loss plateau and even had begun to gain weight during the first phase of the trial and probably had resistance to weight loss. On the other hand, patients with 1 month on a very low caloric diet and then treated with Sibutramine, 10mg daily for 1y, had a weight loss of  $5.2 \pm 7.5$  kg.<sup>18</sup>

Resistance to weight loss and weight rebound after 6 months of continuous pharmacotherapy has been described.<sup>2,15,17</sup> This resistance to weight loss may be ascribed to the reduction in the resting metabolic rate.<sup>19,20</sup> Some authors have found that Sibutramine prevents the decline in energy expenditure that follows weight loss.<sup>21,22</sup> This effect may explain the weight loss maintenance during long-term Sibutramine treatment<sup>11,12</sup> and the effect of Sibutramine in the diet-patients who were in a weight plateau.

Thirty-four out of 40 (85%) patients presented weight gain in group S/P, but this weight loss did not reach the baseline levels. Weight gain after the discontinuation of Sibutramine has been described previously.<sup>12</sup> This weight gain must be considered as evidence of the effect of the drug in weight loss maintenance.<sup>2,17</sup>

Patients in group P/S presented good tolerance to the Sibutramine treatment; only one patient withdrew the trial because of adverse events.

Patients in the group S/P had no important complaints when they switched to placebo, and none requested open administration of Sibutramine. This observation is compatible with studies that showed the low abuse potential of Sibutramine.<sup>7,8</sup>

We conclude that after Sibutramine discontinuation there is weight gain in most the patients, but it does not reach the previous baseline body weight. These results stress the need for long-term pharmacotherapy as well as the convenience

of an early pharmacological intervention in the treatment of obese patients.

### Acknowledgements

We want to thank Miss Lucila Velasco for reviewing the manuscript. This Study was supported by Química Knoll de Mexico, Mexico City, Mexico.

### References

- 1 Pi-Sunyer XA. A review of long-term studies evaluating the efficacy of weight loss in ameliorating disorders associated with obesity. *Clin Ther* 1996; **18**: 1006–1036.
- 2 No author listed. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: Executive summary. *Am J Clin Nutr* 1998; **68**: 899–917.
- 3 Stern JS, Hirsch J, Blair SN, Foreyt JP, Frank A, Kumanyika SK, Madans JH, Marlatt GA, St Jeor ST and Stunkard AJ. Weighing the options: criteria for evaluating weight-management programs. The Committee to Develop Criteria for Evaluating the Outcomes of Approaches to Prevent and Treat Obesity. *Obes Res* 1995; **3**: 591–604.
- 4 DePue JD, Clark MM, Ruggiero L, Mediros ML and Pera V Jr. Maintenance of weight loss: a needs assessment. *Obes Res* 1005; **3**: 241–8
- 5 National Task Force on the Prevention and Treatment of Obesity. Long-term Pharmacotherapy in the management of obesity. *JAMA* 1996; **276**: 1907–1915.
- 6 Stock MJ. Sibutramine: a review of the pharmacology of a novel anti-obesity agent. *Int J Obes Relat Metab Disord* 1997; **21**(Suppl 1): S25–S29.
- 7 Cole JO, Levin A, Beake B, Kaiser PE and Schienbaum ML. Sibutramine: A new weight loss agent without evidence of the abuse potential associated with amphetamines. *J Clin Psychopharmacol* 1998; **18**: 231–236.
- 8 Schuh LM, Schuster CR, Hooper JA, Mendel CM. Abuse liability assessment of Sibutramine, a novel weight control agent. *Psychopharmacology (Berl)*. 2000; **147**: 339–346.
- 9 Hansen DL, Toubro S, Stock MJ, Macdonald IA and Astrup A. Thermogenic effects of Sibutramine in humans. *Am J Clin Nutr* 1998; **68**: 1180–1186.
- 10 Weintraub M, Rubio A, Golik A, Byrne L and Scheinbaum ML. Sibutramine in weight control: A dose-ranging, efficacy study. *Clin Pharmacol Ther* 1991; **50**: 33–337.
- 11 Bray GA, Ryan DH, Gordon D, Heidingfelder S, Cerise F and Wilson K. A double-blind randomized placebo-controlled trial of Sibutramine. *Obes Res* 1996 **4**: 263–270.
- 12 Bray GA, Blackburn GL, Ferguson JM, Greenway FL, Jain AK, Mendel CM, Mendels J, Ryan DH, Schwartz SL, Scheinbaum ML, Seaton TB. Sibutramine produces dose-related weight loss. *Obes Res* 1999; **7**: 189–198.
- 13 Hanotin C, Thomas F, Jones SP, Leutenegger E and Drouin P. Efficacy and tolerability of Sibutramine in obese patients: a dose-ranging study. *Int J Obes Relat Metab Disord* 1998; **22** 32–38.
- 14 Martínez-Cuellar GE, Martínez-Ruiz A, Revilla-Monsalve MC, Berber A. Six-month treatment of obesity with Sibutramine 15 mg; a double-blind, placebo-controlled monocenter clinical trial in a Hispanic population. *Obes Res* 2000; **8**: 71–82.
- 15 Goldstein DJ, Potvin JH. Long-term weight loss: the effect of pharmacologic agents. *Am J Clin Nutr* 1994; **60**: 647–657.
- 16 Goldstein DJ, Rampey AH Jr, Enas GG, Potvin JH, Fludzinski LA, Levine LR. Fluoxetine: a randomized clinical trial in the treatment of obesity. *Int J Obes Relat Metab Disord* 1994; **18**: 129–135.
- 17 No authors listed. Guidelines for the approval and use of drugs to treat obesity. A position paper of the North American Association for the Study of Obesity. *Obes Res* 1995; **3**: 473–478.
- 18 Apfelbaum M, Vague P, Ziegler O, Hanotin C, Thomas F, Leutenegger E. Long-term maintenance of weight loss after a very-low-caloric diet: A randomized blinded trial of the efficacy and tolerability of Sibutramine. *A J Med* 1999; **106**: 179–184.
- 19 Ballor DL, Poehlman ET. A meta-analysis of the effects of exercise and/or dietary restriction on resting metabolic rate. *Eur J Appl Physiol* 1995; **71** 535–542.
- 20 Thompson JL, Manore MM, Thomas JR. Effects of diet and diet-plus-exercise programs on resting metabolic rate: a meta-analysis. *Int J Sport Nutr* 1996; **6** 41–61.
- 21 Walsh KM, Leen E, Lean ME. The effects of Sibutramine on resting energy expenditure and adrenaline-induced thermogenesis in obese females. *Int J Obes Relat Metab Disord* 1999; **23**: 1009–1015.
- 22 Hansen DL, Toubro S, Stock MJ, MacDonald IA, Astrup A. The effect of Sibutramine on energy expenditure and appetite during chronic treatment without dietary restriction. *Int J Obes Relat Metab Disord* 1999; **23**: 1016–1024.