**The Effect of Thera-Slim™ on Weight, Body Composition and Select Laboratory Parameters in Adults with Overweight and Mild -Moderate Obesity.**

**Stuart I. Erner, MD and Dennis Meiss, PhD**

Obesity and overweight are increasing at epidemic rates. These conditions are amongst the most common now seen by primary care physicians and are risk factors for many other chronic disorders such as heart disease, hypertension, diabetes, cancer and osteoarthritis.

A recent study by RTI International and the Centers for Disease Control (CDC) estimates that U.S. obesity-attributable medical expenditures reached $75 billion in 2003 and that taxpayers finance about half of these costs through Medicare and Medicaid.[i] The prevalence of obesity is higher amongst minority adolescents and adults although it's not entirely clear as to what specific or combination of cultural, lifestyle, genetic or environmental factors account for the differences. One simple postulate states that in the U.S. today, we've created an environment in which highly palatable foods are accessible to all at low cost and physical activity is not required.[ii]

Etiologic factors causing obesity can be identified. These include genetics, hypothalamic obesity, endocrinopathy, drug-induced weight gain, smoking cessation, sedentary lifestyle and dietary factors. In looking at macronutrient intake in particular, epidemiological data suggests that a high fat diet is associated with obesity, as is over-consumption of non-complex carbohydrates. Dietary fiber appears to be inversely related to body weight in population studies.[iii]

In addition, over the past few years, medical science has recognized the increasing prevalence of metabolic syndrome. Criteria for metabolic syndrome include the presence of three or more of these criteria: central obesity (waist circumference > 40 inches in males; > 35 inches in females); fasting serum triglycerides ≥ 150 mg/dl; blood HDL cholesterol < 40 mg/dl in males, < 50 mg/dl in females; blood pressure ≥ 130/85 mmHg and fasting glucose ≥ 110 mg/dl. Metabolic syndrome has become increasingly common in the United States. Currently it's estimated that 20-25% of Americans meet the criteria for metabolic syndrome. The syndrome is closely associated with insulin resistance and may also be associated with a prothrombotic and proinflammatory state. People with metabolic syndrome are more at risk for coronary heart disease, stroke and peripheral vascular disease.[iv]

Current therapeutic interventions for obesity include: kcal restriction, regular aerobic and anaerobic exercise to induce energy expenditure and optimization of lean body mass to fat ratio, behavioral modification and selective pharmocotherapy (anorectics, fat blockers). Amongst these Kcal restriction appears to still be the most critical intervention especially in the acute and on-going weight loss phases of a typical medically supervised weight loss program. It's also the most difficult part of the therapeutic program to consistently comply with for a variety of reasons including: boredom with food choices, chronic external stressors, social situations with too many hyper caloric temptations,
aggressive marketing of high calorie foods, as well as potential financial constraints when medically supervised " formula" diets are used.[v] Lastly maintenance of weight loss during treatment has also been a chronic problem for many of the aforementioned reasons. Most recently popular lay publications have emphasized the need for restricting

and simple sugars first and foremost in order to achieve satisfactory weight loss in the short and long term. These programs stress the need for adequate protein, fiber and fat intake (low-high). Studies are on-going and have been previously published looking at the pros/cons of each of these approaches with no clear consensus reached amongst various health care professionals.

One of the major problems most people have with these low carbohydrate weight loss regimens is the difficulty complying with rigid and chronic starch and simple sugar restriction. In particular, starchy foods have become staples of the typical American diet. Their availability is ubiquitous and most people truly enjoy their consumption. Starch restriction can lead to reduced consumption of dietary fiber, some B-vitamins and trace elements. There are some individuals who will also experience decreased mood presumably due to decreased serotonin levels. In view of this conundrum, researchers have recently been looking at ways to rectify this dietary dilemma by utilizing starch neutralizers to inhibit dietary starch absorption. In particular, one such agent is phaseolamin. Phaseolamin vulgaris is a botanical extract of white kidney bean that in previous studies appears to particularly block the pancreatic enzyme alpha amylase before it can convert starch into simple sugars which then can potentially increase lipogenesis. Phase 2 ( Phaseolamin 2250) is a relatively new concentrated phaseolamin extract manufactured through a proprietary process from non-GMO white kidney beans that survives undiluted gastric and intestinal solutions, thus preserving it's action on alpha amylase in the intestinal tract.[vi] One gram of the purified extraction can inhibit the digestion of up to 560 gms of dietary starch.[vii] Recent double blinded, placebo-controlled studies of Phase 2 (Phaseolamin 2250) by Vinton (University of Scranton, 2001), Sochim International (2001) and Udani (2003, Northridge Hospital) have been with small groups of subjects and shown variably encouraging results suggesting the need for further study.[viii]

In view of the emerging data regarding Phase 2, we conducted a randomized, controlled trial to determine what effects Thera-Slim™ (Phase 2, fennel seed powder caps) has on overweight and mildly obese adult females and males. We were interested in observing it's effects on body weight, body composition, blood parameters such as fasting lipid profiles, sugar and insulin levels in subject's utilizing Thera-Slim™ in a "real world" environment without strictly controlled variables.

## METHODS

### Study Design

The study was a 24-week, placebo controlled, double-blinded randomized clinical trial with a crossover of the placebo group at 12 weeks performed at a private medical practice in Albany, NY. Informed consent was obtained from all subjects after which they
were assigned either Thera-Slim™ or placebo. Placebo and Thera-Slim™ capsules were identical in appearance and odor. Subjects and the investigator were blinded to the

assigned treatment arm.

3

**Subjects Eligibility (Table 1)**

Subjects were recruited for the Albany, NY region based upon eligibility exclusion criteria.

1. Inclusion Criteria
   a. Age > 25 and< 50 at time of screening
   b. BMI range 24-36
   c. Agree to continued treatment as directed
   d. Agree to periodic follow up
   e. Agree to signed Consent Form
2. Exclusion Criteria
   a. Use of any Of the following drugs within 4 weeks of screening
      - Meridia ( sibutramine)
      - Xenical (orlistat)
      - Metabolife or any other ephedrine-containing product
      - Phenteramine
      - Diethylproprion
      - Phendimetrazine
      - Diuretics ( except if already using to treat hypertension)
   b. Abnormal laboratory parameters ( including at least one of the following):
      - Renal dysfunction ( BUN > 28 and serum creatinine > 1.8)
      - Hepatic dysfunction AST > 57 M, / 39 F; ALT>72 M, / 52 F)
      - Subjects unable to comprehend/follow the study protocol
      - Subjects with active eating disorder including bulimia, anorexia nervosa
      - Subjects with known sensitivities to fennel seed or beans
      - Subjects with significant depression or other psychiatric disease noted on the initial evaluation
      - Subjects with active CAD, CHF, arrhythmia, or uncontrolled hypertension
      - Subjects with severe hepatic or renal disease ( except people with prior diagnosis of fatty liver even if LFTs are elevated)
      - Subjects who are pregnant or breastfeeding
      - Subjects with seizure disorder
      - Subjects with history of cancer within last 5 years prior to evaluation ( except basal or squamous cell cancer of skin)
      - Subjects with anti-coagulation therapy
      - Subjects with alcoholism
      - Subjects with chronic malabsorption
      - Subjects with Inflammatory Bowel Disease ( IBD)
      - Subjects with diverticulosis/diverticulitis

Recruitment was primarily from response to newspaper advertisement. A few subjects were recruited from the private medical practice conducting the study. Those who expressed interest came in in for a pre-screening evaluation reviewed and approved by the clinical investigator. The study population was generally in good health with no active problems except for a few cases of hyperlipidemia ( unspecified) and mild, controlled hypertension. Several subjects had fasting insulin levels greater than 10uU/ml. None of the participants had frank Diabetes Mellitus-Type II.

**Treatment**

Subjects were assigned to Group A or B and were instructed to continue their usual dietary intake making sure to only consume starch-containing foods at any of 2 meals/day. The total amount of starch containing foods was to total anywhere between 100-200 gm/day. At each starch-containing meal subjects were told to take 2 capsules of A or B at the start of that meal. Subjects were furthermore instructed not to consume starchy or "sweet" snacks between meals. They were told to maintain their typical levels of physical activity throughout the 24-week study period. Food record sheets were distributed at each visit and were to be brought in for review at the next 4-week follow up. At the end of each follow-up visit, subjects received a 4-week supply of capsule A or B.

At week 12, the study entered the crossover phase with associated unblinding. Subjects receiving capsule A were informed by the very recently enlightened investigator that they had been receiving a placebo capsule containing cellulose and 250 mg of fennel seed powder. Group B subjects were told that they were receiving Thera-Slim™ capsules (each capsule containing 500mg of Phase 2 phaseolamin and 250 mg fennel seed powder). Subjects then followed the same sequence of events as just outlined. However all participants now realized they were taking active treatment. At week 24 each participant underwent an exit visit and all questions pertaining to their participation in the study were answered by the principle investigator.

**Assessments**

All patients underwent an initial comprehensive medical history and physical exam in conjunction with body composition analysis and lab assessment. Lab studies were all performed by Laboratory Corporation of America. Brief behavioral assessment was performed to rule out eating disorders and depression. See Appendix 1 for an outline of specific, timed assessments/interventions.

**Data Analysis**

Parameters reviewed included body weight, BMI, body composition analysis by bioelectrical impedance (Tanita TBF-215 body composition analyzer), waist/hip circumferences, lipid profiles, fasting glucose and insulin levels. Only data from patients

completing the entire 24 week trial were used in the calculations.
5

**Results**

A total of 60 subjects enrolled in the study. Six withdrew from the study ( 3 each in groups A & B). The withdrawals were all related to inability to continue to fulfill the obligations of follow-up visits, lab work, etc. due to other committments. At the study's conclusion, 27 participants remained in groups A and B with the ration of female:male subjects being an identical 8.5:1 for each group. No drop-outs occurred to side effects nor were there any adverse reactions or abnormal metabolic alterations during the study.

Demographically looking at groups A & B analysis showed the average age of female participants to be 44 in group A and 41 in group B. The average age of male participants was 45 in both groups. The average BMI ( body mass index) in group A and B was 30 for female subjects. The average BMI for males was 31 in group A and 33 in group B.

When pooling date parameters of all subjects in groups A ( placebo-active) and B (active), numerous observations can be noted. (Table 2 ).
Group A had an average weight gain of 1.5lb per subject after 24 weeks. The weight gains during the placebo and cross-over periods were almost identical ( 0.6 vs 0.87 lbs). Group B had an average weight loss of -1.1 lb per subject after 24 weeks. Weight loss was more notable for the first 12 weeks ( -1.4 vs -0.2 lbs) than during the second half of the study. Looking at median weight change, Group A had a median weight gain of 2 lbs vs. a median weight loss of 1 lb for Group B. 18 of 27 subjects gained weight in Group A during the placebo phase. However, 15 of 27 gained weight when switched to active treatment. By the end of the study, 16 of 27 had gained weight in Group A. In contrast 18 of 26 subjects in Group B ( active x24 weeks) lost weight during the first 12 weeks of treatment ( 1 subject had no weight change). 15 of 27 subjects lost weight while on the last 12 weeks of active treatment. Lastly, it was noted that 16 of 27 subjects lost weight during the 24 weeks of the study.

In reviewing the sequential waist and hip circumference measurement, both groups A & B showed minor decreases by study's end with reductions being slightly more prominent in Group B. Body fat changed less than 1% in both groups A and B showing miniscule elevations.

When reviewing lab parameters, both groups showed minor reductions in serum cholesterol levels ( -10 Grp A vs -7 Grp B). However, serum triglyceride levels dropped by almost 3.3x as much in Group B vs Group A by study's conclusion ( -38.1 vs -11.9). HDL levels remained essentially unchanged in both treatment groups while minor reductions in LDL were noted in both groups ( -8.1 Grp A vs -5.2 Grp B). Fasting insulin levels dropped by almost 2% in Groups A & B. Fasting glucose levels remained unchanged in Group A while dropping an average of 2 mg/dl in Group B by the study's conclusion.

One patient developed transient minimal increases in amylase and lipase levels during the 24 week study (amylase121U/L [normal= 0-99]; lipase126U/L [normal=0-59]).
The subject had just returned from a cruise vacation during which time she drank alcohol somewhat frequently in contrast to her usual abstinence. She was otherwise asymptomatic.
The values returned to normal 12 weeks later.

## COMMENT

Obesity is a complex, multi-system disorder for which current medical treatment consists of caloric restriction, behavioral modification, exercise and appropriate pharmacotherapy. In constructing the macronutrient composition of commonly employed low and very low caloric diets, one typically administers high quality protein, low to moderate amounts of fat ( mostly monosaturated) and minimal to moderate amounts of carbohydrates (primarily complex variety). People will often lose weight early in their programs but many inevitably drop-out of treatment prior to obtaining a significant clinical response due to boredom, financial issues (lack of uniform medical insurance coverage), and not infrequently their inability to comply with marked dietary carbohydrate restriction. In the present double blind placebo controlled crossover study we report what effects the administration of Thera-Slim™ ( Phase 2 brand of phaseolamin and fennel seed powder) has on body weight, body composition and various lab parameters of interest in the overweight and obese population.

Numerous observations can be made about the results of the study. Firstly when designing the protocol, it was determined that it would be of interest to see how subjects were effected by Thera-Slim™ in a "real-world" setting. Hence the study design was set up to allow participants to continue their usual dietary and exercise regimens with the only important requirement being that they eat 100-200 gm starchy foods in any 2 meals of their typical day. No specific restrictive dietary protocols were instituted, nor were subjects placed into behavioral modification programs or newly prescribed regimented exercise routines. Analyzing the pooled data shows minimal differences in weight change and body compositions between the placebo and active group. Interestingly a more significant effect on serum triglyceride levels appears to be present both in the group receiving Thera-Slim™ for 24 weeks as well as after the cross-over phase occurred for the placebo group. This triglyceride lowering effect is not to be totally unexpected due to Thera-Slim's™ mechanism of action of variably inhibiting the absorption of dietary starch, hence reducing the amount of ultimately available simple sugar that can be absorbed and converted to fatty acids and triglycerides.

Given previous smaller studies of phase 2 phaseolamin showing some modest weight loss, what are the possible explanations for the minimal weight change observed in this study? The biggest problem noted during the study which may well be confounding the pooled data of all participants was dietary non-compliance. This was made even more troublesome due to a significant part of the study occurring in the summer which is traditionally the most difficult time of year for people to adhere to any

type of consistent dietary regimen due to vacations and more frequent social events. Chart review of most
7

subjects while on placebo or active treatment, revealed that a considerable number were either eating additional starchy foods as snacks or were substituting other simple sugar containing foods as well as hypercaloric foods of high fat/sugar content to "make up" for the restriction of dietary starch intake. This was most notable if a subject was experiencing increased stress levels during particular between visit intervals. Subjects invariably increased intake of hypercaloric foods and sometimes alcohol during week-ends and vacations. Almost 50% of subjects reported periodically skipping their prescribed dose of Thera-Slim™ when eating starch at their meals. None took additional treatment when eating additional starches. Clearly these dietary indiscretions made it harder to know how effective active treatment would have been if they had been more consistent or compliant with the prescribed regimen. In addition, a few subjects reported marked decrease in their typical physical activity hence leading to further reductions in Kcal expenditure when compared to their baselines.

In light of the above situation, data comparison was made between small groups of subjects who either gained or lost more dramatic amounts of weight during the 24 week protocol than most of their counterparts. (Table 3)
In particular, chronically non-compliant subjects were looked at from both groups. Not surprisingly thy gained weight while on placebo or active. However 3 of 4 who initially gained between 6.6 -10 lbs in first 12 weeks while on placebo then had a significant slow down in weight gain while on active ( 1.8-5.2 lbs). Four Group A compliant subjects who lost weight while on placebo continued to lose weight when switched to active. However 3 of 4 of those experienced an accelerated weight loss when on active as compared to placebo.

Non-compliant subjects from Group B who received active from the start typically finished the study with a weight gain. However those who were consistently compliant lost weight throughout the study while eating 100-200gm starch/day ( 6.2-35.2lbs lost). These observations in compliant patients who maintained their typical daily Kcal intake, 100-200gm/day starch consumption and usual activity level are encouraging and clearly point to the fact that the addition of Thera-Slim™ to these subjects regimens was helpful with regards to weight loss while conserving what would be a fairly typical daily intake of starch for most Americans.

The observed results are not surprising in light of Thera-Slim's™ mechanism of action. Unlike anorectic drugs which suppress appetite and/or induce early satiety during meals, using Thera-Slim™ requires proper dietary selection and consistent usage when beginning consumption of starch at a meal.

In looking at other ways in which Thera-Slim™ starch blocker could be shown to be an even more useful, therapeutic agent a number of possibilities come to mind. Obviously, in the future more vigorously controlled studies should be undertaken. In addition, future studies could also look as using higher doses of Thera-Slim™ given the product's tolerability and lack of apparent side effects. Different delivery systems of this agent could also enhance compliance (i.e. sprinkle powder or some additive to popular starch containing foods). Combining Thera-Slim™ with other adjunctive treatments for

weight loss might prove synergistic. For example, it would be intriguing to see if the


combination of the fat blocker Orlistat (Roche Pharmaceutical) with Thera-Slim™ could yield improved outcomes. Likewise combining Thera-Slim™ with an anorectic agent could also lead to additional weight loss and improvement in other health/laboratory parameters. Theoretically, using Thera-Slim™ while patients are following high protein, very low carbohydrate intensive weight loss protocols might diminish the negative impact of unintended starch intake that sometimes occurs on such rigorous protocols. Given the ubiquitous presence of and preference for starch in the Westerner's typical diet as well as somewhat encouraging early data from this and previous trials, further studies with larger number of participants are clearly needed to understand how Phase 2 Phaseolamin products such as Thera-Slim™ can best be utilized for the treatment of overweight/obesity and potentially hypertriglyceridemia, impaired glucose tolerance and insulin resistance.

Lastly, Thera-Slim™ could be studied to discover if it could enhance the maintenance of weight loss seen on any weight reduction protocol. To date the re-introduction of starchy carbohydrates continues to be a significant pit-fall to many overweight/obese individuals who've just recently lost a significant amount of pounds on a carbohydrate restricted weight loss regimen.

Prothera (Pleasanton, CA) provided the Thera-Slim™ and placebo capsules for this study. This clinical study was supported by Prothera and Pharmachem (Kearny, NJ). The principle investigator ( Stuart I. Erner, MD) received research financial support from both Prothera and Pharmachem. Prothera collaborated with Dr. Erner in initial study design.

Table 3: Subject subset with significant weight changes — increased or decreased

GROUP A (placebo to active)

| | weight change, pounds | | |
|---|---|---|---|
| **SUBJECT NO. (m) = male** | **Beginning to mid-study** | **Mid- to end of study** | **TOTALS Beginning to End** |
| 1 | + 8.0 | + 1.8 | + 9.8 |
| 2 (m) | + 6.6 | + 2.0 | + 8.6 |
| 3 | + 7.4 | + 5.2 | + 12.6 |
| 4 | +10.0 | + 15.0 | + 25.0 |
| 5 (m) | - 7.6 | - 5.2 | - 12.8 |
| 6 | + 2.6 | - 9.8 | - 7.2 |
| 7 (m) | - 8.0 | - 9.8 | - 17.8 |
| 8 | - 1.4 | - 6.6 | - 8.0 |

GROUP B (active)

| | weight change, pounds | | |
|---|---|---|---|
| **SUBJECT NO. (m) = male** | **Beginning to mid-study** | **Mid- to end of study** | **TOTALS Beginning to End** |
| 9 | + 10.4 | + 3.4 | + 13.8 |
| 10 | + 6.0 | + 2.6 | + 8.6 |
| 11 | + 8.2 | - 2.6 | + 5.6 |
| 12 | - 6.0 | - 0.2 | - 6.2 |
| 13 | - 19.0 | - 16.4 | - 35.2 |
| 14 | - 6.6 | - 0.6 | - 7.2 |
| 15 | - 3.2 | - 4.2 | - 7.4 |

[i] News from ASBP ( the official newsletter of the American Society of Bariatric Physicians). Jan-Feb. 2004; Pg. 1.

[ii] Crespo, C.J., Arbesman, JA. Obesity in the United States. The Physician and SportsMedicine 2003; 31: 23-26.

[iii] Bray, GA. Evaluation of Obesity. Post Graduate Medicine 2003; 114: 19-27.

[iv] American Heart Association. Google Search: Metabolic Syndrome, 2004

[v] Manson, J.E., Skerrett, P.J. The Escalating Pandemics of Obesity and Sedentary Lifestyle. Archives InterMed 2004; 164: 253.

[vi] Scientific data on file @ Phamachem Labs, Kearney, N.J.

[vii] Anonymous. Clinically studied Phase 2 for non-stimulant carb control. Http://www.Phase 2.com/catalog7.htm. Oct. 19, 2001.

[viii] Studies on file at Pro-Thera, Pleasanton, California. Attention: Dennis Meiss, PhD.