Safey and Efficacy of Banaba—Moringa oleifera—Green Coffee Bean Extracts and Vitamin D3 in a Sustained Release Weight Management Supplement

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This 60-day, 30-subject pilot study examined a novel combination of ingredients in a unique sustained release (Carbopol matrix) tablet consumed twice daily. The product was composed of extracts of banaba leaf, green coffee bean, and Moringa oleifera leaf and vitamin D3. Safety was assessed using a 45-measurement blood chemistry panel, an 86-item self-reported Quality of Life Inventory, bone mineral density, and cardiovascular changes. Efficacy was assessed by calculating a body composition improvement index (BCI) based on changes in dual energy X-ray absorptiometry measured fat mass (FM) and fat-free mass (FFM) as well as between the study group (SG) and a historical placebo group. No changes occurred in any blood chemistry measurements. Positive changes were found in the Quality of Life (QOL) inventory composite scores. No adverse effects were observed. Decreases occurred in FM (p < 0.004) and increases in FFM (p < 0.0009). Relative to the historical placebo group, the SG lost more FM (p < 0.0001), gained more FFM (p = <0.0001), and had a negative BCI of –2.7lb. compared with a positive BCI in the SG of 3.4lb., a 6.1 discordance (p = 0.0009). The data support the safety and efficacy of this unique product and demonstrate importance of using changes in body composition versus scale weight and BMI. © 2016 The Authors Phytotherapy Research Published by John Wiley & Sons Ltd.

Keywords: Moringa oleifera; green coffee bean extract; Lagerstroemia speciosa (banaba); vitamin D.

INTRODUCTION

Approximately two-thirds of the adult American population is either overweight or obese primarily because of a combination of inadequate physical exercise and adherence to unhealthy diets that are high in simple sugars and saturated fats (Vaughan et al., 2014). Over the past 25–30 years, there has been an increase in total energy intake of approximately 570 kcal/day (Duffy and Popkin, 2011).

Numerous diseases are associated with excess weight including coronary artery disease and congestive heart failure, diabetes, hypertension and stroke, muscle wasting, almost all forms of cancer, depression, liver disease, and osteoporosis. As a consequence, large percentages of the population are attempting to lose weight at any given time. In spite of the fact that the health benefits of weight reduction are well known, weight loss via diet and exercise fails in most patients (Arbeeny, 2004; Ferraro et al., 2015). Failure may occur in part because of the indices employed to assess outcomes. Body weight and body mass index (BMI) are commonly used as indicators of weight loss and weight gain. These indices do not differentiate between changes in body fat and lean muscle mass. For example, a 3 lb. loss of body fat with an equal gain in muscle mass will be recorded as no change in body weight when in reality two very beneficial effects were observed, namely, a loss of body fat and a gain in lean muscle mass.

Because of the lack of success in retaining weight loss, many patients turn to complementary and alternative approaches for the management of obesity (Esteghamati et al., 2015). Although many dietary supplements have been designed to support weight management and weight loss, few supplements have been proven to be effective because either the ingredients are ineffective or the wrong indices to assess weight loss were used.

In the current study, the weight management product contains three active ingredients not previously used in combination in a unique sustained tablet delivery system designed to provide release of active ingredients for up to 6h. The product is designed to improve body composition through the depletion of excess body fat while maintaining or increasing fat-free mass (FFM) without adverse effects on bone mineral density (BMD). In an unpublished pilot study, the product was found to improve eating control and helps maintain healthy blood sugar and lipid levels. Furthermore, the ingredients are believed to work in harmony via different and supporting mechanisms, ensuring a high degree of efficacy. The ingredients contained in this product and previous studies supporting these effects are described later.

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Moringa oleifera leaves, seeds, bark, roots, sap, and flowers are widely used in traditional medicine, and the leaves and immature seed pods are used as food products in human nutrition (Mbikay, 2012). Leaf extracts exhibit the greatest antioxidant activity, and various safety studies in animals involving aqueous leaf extracts indicate a high degree of safety. No adverse effects were reported in association with human studies. Five human studies using powdered whole leaf preparations of M. oleifera have been published, which have demonstrated anti-hyperglycemic (anti-diabetic) and anti-dyslipidemic activities (Stohs and Hartman, 2015) that are highly supportive of weight management and weight loss. These activities have been confirmed using extracts as well as leaf powders in animal studies. A rapidly growing number of published studies have shown that aqueous, hydroalcoholic or alcoholic extracts of M. oleifera leaves possess a wide range of additional biological activities including antioxidant, tissue protective (liver, kidneys, heart, testes, and lungs), analgesic, anti-ulcer, anti-hypertensive, radioprotective, and immunomodulatory actions (Stohs and Hartman, 2015). A wide variety of polyphenols and phenolic acids as well as flavonoids, glucosinolates, and possibly alkaloids are believed to be responsible for the observed effects.

Banaba (Lagerstroemia speciosa L.) extracts and decoctions have been used for many years in folk medicine to support weight management and regulate blood sugar levels, with the first published research study being reported in 1940. The hypoglycemic and weight management effects of banaba have been attributed to both corosolic acid (Fig. 1) as well as ellagitannins, which are hydrolysable polymers of ellagic acid (Fig. 2). Studies have been conducted in various animal models, human subjects, and in vitro systems using water-soluble banaba leaf extracts, corosolic acid-standardized extracts, and purified corosolic acid and ellagitannins (Stohs et al., 2012).

Corosolic acid exhibits anti-hyperlipidemic, antioxidant, anti-inflammatory, antifungal, antiviral, anti-neoplastic, and osteoblastic activities in addition to its insulin-like effects. The beneficial effects of banaba and corosolic acid with respect to various aspects of glucose and lipid metabolism as well as weight management appear to involve multiple mechanisms, including enhanced cellular uptake of glucose, impaired hydrolysis of sucrose, and starches, decreased gluconeogenesis, and regulation of peroxisome proliferator-activated receptor-mediated lipid metabolism (Stohs et al., 2012). No adverse effects have been reported in animal studies or controlled human clinical trials. The highest dose of corosolic acid used to date has been 10 mg per day for 30 days and was without adverse effects (Stohs et al., 2012). Tannins are the most abundant secondary metabolites in plants and are without adverse effects at exceedingly high doses. The oral lethal dose for 50% (LD50) of rats and mice of an ellagitannin has been reported to be greater than 1.5 g/kg body weight (Patel et al., 2008).

Chlorogenic acid (Fig. 3) is the major polyphenolic compound present in coffee, and epidemiological studies have shown that high coffee consumption promotes weight loss and reduces the risk of type 2 diabetes. A number of human clinical trials have demonstrated the beneficial effects of green coffee bean extracts containing chlorogenic acid with respect to weight loss and weight management as well as regulation of blood glucose levels (Nardon et al., 2007; Thom, 2007; Onakpoyi et al., 2011). An increase in lean to fat mass (FM) has also been observed with no serious adverse effects being reported. Doses ranging from 180 to 1050 mg of green coffee extract containing approximately 45–50% chlorogenic acid have been used. Various studies in animals have demonstrated the weight loss effects of chlorogenic acid, and decreases in cholesterol, triglycerides, and plasma insulin and leptin levels have been reported.

Multiple mechanisms appear to be involved in these beneficial effects of chlorogenic acid and green coffee extract, including inhibition of the hepatic enzyme glucose-6-phosphatase, modulation of glucose absorption, inhibition of cholesterol and triglyceride biosynthesis, and antioxidant and chemoprotective properties (Onakpoyi et al., 2011). Long-term exposure of human adipocytes has clearly shown that green coffee bean extract enhances the breakdown of fats and the release of free fatty acids (Flanagan et al., 2014). These studies indicate that green coffee extracts containing chlorogenic acid are both effective and safe in weight management and blood glucose and lipid regulation and metabolism, factors essential for weight management.

The average daily intake of chlorogenic acid primarily from coffee consumption has been estimated to be about 150 mg per day, depending upon the kind of coffee and the amount consumed (Ludwig et al., 2014; Grosso et al., 2014). Chlorogenic acid appears to be exceedingly safe with an oral LD50 in mice greater than 2 g/kg (Perez-Vasquez et al., 2014).

The tablets subjects consumed were composed of “Actives,” a diluent, a modified release agent, and lubricant containing a swellable matrix system, “Carbopol 971P.” In the body’s aqueous gastrointestinal environment, the tablet swells significantly, increasing in size and geometry, and the Actives are released slowly over...
METHODS

A total of 30 subjects were enrolled and executed an informed consent form approved by Solutions’ Institutional Review Board. A total of 28 subjects completed the study per protocol. One subject completed the baseline tests but failed to start the study for personal reasons unrelated to the product or protocol. Another subject reported insufficient compliance data. This subject’s data were excluded from the final analyses. The remaining 28 subjects consumed the weight loss product supplement described in Table 1 (CraveCheck SR™, AdvoCare International, Plano, TX, USA) twice daily – before 8:00 AM and between 3:00 and 5:00 PM in the afternoon – thereby providing release of active ingredients for approximately 12 h.

Using a procedure described by Kaats and Preuss (2013) to encourage candid reporting, instead of paying an “incentive fee” for their participation, subjects were paid a daily “tracking fee” of $5.00 per day ($300 total), provided they reported their daily product usage in a “timely manner,” within 48 h after the end of each study day. Using this procedure, the emphasis was placed on candid reporting of product usage and effects to avoid penalizing subjects for not taking the product.

Safety. To assess safety, fasting blood samples were drawn, and the 45-measurement blood chemistry/hematology panel shown in Table 2 was completed at the beginning, mid-point, and end of the 60-day study period. Tests were conducted by an independent testing laboratory, Quest Diagnostics, at drawing stations of the subjects’ choosing. All test results were sent directly to the principal investigator and provided to subjects at the end of the study period. All 28 subjects completed the three blood tests as per protocol. Additionally, comparisons were also made between baseline-ending changes in the study group and the historical placebo group of similar subjects who had also completed the same baseline-ending blood tests over the same study period.

Assessing positive or negative outcomes in the first eight blood tests shown in Table 2 is simply a matter of comparing changes in the respective means using a traditional Student’s t-test. However, assessing changes in the remaining tests required different analyses. Unlike the eight continuous variables, increases or decreases in the remaining measures could reflect either positive or adverse effects depending upon whether or not the changes in the subject’s measurements went from “normal” to “abnormal” or vice versa. Measurements that were in either the normal or abnormal ranges on test 1 or remained in the same ranges on test 2 were deemed irrelevant with regard to safety concerns. Measurements that were in the abnormal range on test 1, but were normal on test 2, were assumed to reflect a positive change. Conversely, measurements that were in the normal range on test 1, but were subsequently in the abnormal range on test 2, were deemed to reflect a negative change or an adverse effect. The appropriate analyses were conducted for all 45 measurements and are shown in the Results section.

As additional measures of safety, subjects completed the 86-item Composite Quality of Life Inventory (QOL) shown in Table 3. Responses to all 86 items were averaged to obtain an overall score for adverse wellness.

The safety analysis also included assessment of changes in heart rates and the ankle–brachial index by conducting simultaneous brachial and ankle blood pressure measurements after the subject remained in a resting prone position for approximately 15 min while completing the dual energy X-ray absorptiometry (DEXA) body composition test. Efficacy was assessed by calculating a body composition improvement index (BCI) based on changes in DEXA-measured FM and FFM derived from the DEXA scans.
shown in the graphics later. All DEXA measurements were performed using a GE Lunar’s DEXA DPX-IQ Bone Densitometer (Madison, WI, USA) with software version DPX-IQ X-Ray Bone Densitometer with SmartScan™ Version 4.7e. All tests used in this study were conducted by a certified technician using the same DEXA technology for baseline and ending measurements.

Although scale weight and the BMI are often used to assesses changes in weight loss interventions and treatment plans, these measures report only changes in total body mass, not the kind of mass (fat and FFM) that was lost or gained. Because the BMI is a ratio of height to weight, and height rarely changes in studies involving adults, as a measure of change, the BMI and scale weight are identical and correlate 1.00. Thus, scale weight and the BMI can be used interchangeably with regard to a measure of change. However, using a DEXA scan to assess changes also provides measurements of the kind of weight, FM, and FFM that was lost or gained — measurements that can be used independently or combined as a BCI index. The BCI is the net result of scoring losses of FM and gains of FFM as positive outcomes and gains of FM and losses of FFM as negative outcomes. The BCI is the net result of combining these positive and negative outcomes. Previous research has found significant differences between the conclusions one would draw about the success or failure of weight loss interventions and treatment plans as opposed to using an index of BCI (Opala et al., 2006; Kaats et al., 2006).

Although included in FFM, because most weight loss interventions often deplete BMD, changes in baseline, mid-study, and ending BMD measurements are also reported. Decreases in BMD could also be considered a measure of safety as well as efficacy. To partition out the potential effects of changes in physical activity, subjects wore a research-quality pedometer during their waking hours and recorded their daily step totals.

### RESULTS

**Blood chemistries.** Table 4 provides the mean values for baseline, mid-study, and ending for the eight continuous variable measurements with _P_ values for comparisons between tests 1 (baseline), 2 (mid-study), and 3 (ending).

No statistically significant changes were found in any of these within-group paired _t_-tests comparisons with respect to total cholesterol, high density lipoprotein (HDL), triglycerides, low density lipoprotein (LDL), LDL:HDL ratio, non-HDL triglycerides, C-reactive protein, and glucose.

Analyses of the remaining 37 blood chemistry measurements required different statistical analyses because increases or decreases could reflect a positive effect, a negative effect, or no effect depending upon what impact the intervention had relative to changes in the “normal” or “abnormal” ranges for the test. As shown
in Fig. 4, 93.7% of the study group had scores in the “normal” range at baseline and remained in the “normal” range on the ending test. Another 2.6% were abnormal at baseline and remained abnormal on the ending test. A total of 1.3% were abnormal at baseline and became normal on the ending test. And finally, 2.4% were normal on the baseline test but were abnormal on the ending test. Thus, 97.6% of the scores remained unchanged or improved. The remaining 2.4% suggesting potentially adverse effects could also be due to statistical artifacts as the result of chance occurrences in taking the 37 measurements. These data are consistent with the findings from the eight continuous variables that, with respect to blood chemistries, there is no evidence of adverse effects. These data were also compared with a random sample of 5000 similar subjects in the investigator’s Longitudinal Database of Medical Biomarkers who had completed the same blood tests during a variety of studies. The average change from normal to abnormal was 4.14% – a percentage significantly ($p < .001$) higher than the same changes found in this study.

The secondary measure of safety was to examine changes in subject responses to the Quality of Life Inventory and sub-scales shown in Table 3 previously. All subjects completed the inventory at baseline, mid-study, and at the end of the study. When completing these items, respondents reported the severity of problem for them by selecting $0 =$ No Problem, $1 =$ A Minor Problem, $2 =$ A Major Problem, or $3 =$ A Severe Problem. Thus, the lower the scores on these scales, the lesser the problem or the greater the improvement during the study period. Results of these analyses are shown in Table 5. As shown in the composite overall scale and all sub-scales, there are consistent improvements from baseline to mid-study and to end-of-study. All of these improvements average ~36% and were statistically significant.

Efficacy. Although the QOL could be classified as a measure of efficacy, the primary outcome measure used in this study was the body composition improvement (BCI©) index that is the net result or sum of scoring gains of FFM and reductions of FM as positive treatment outcomes, and, conversely, losses of FFM and gains of FM as negative treatment outcomes. As shown in Table 7, while there was no significant change in

| TC  | TotC | HDL  | TRIG | LDL  | Ratio | Non-HDL TC | CRP | Gluc |
|-----|------|------|------|------|-------|------------|-----|------|
| Baseline | 201.3 | 59.86 | 124  | 116.7 | 3.532 | 141.4 | 2.328 | 94.214 |
| Mid-study | 201.5 | 58.93 | 125.1 | 117.5 | 3.589 | 142.5 | 2.377 | 93.25 |
| Ending | 198  | 57.43 | 127  | 115.2 | 3.625 | 140.6 | 3.246 | 94.357 |

$1–2 P$ values = 0.965 0.534 0.870 0.788 0.467 0.747 0.928 0.422
$1–3 P$ values = 0.298 0.068 0.592 0.534 0.200 0.736 0.077 0.910
$2–3 P$ values = 0.404 0.320 0.813 0.485 0.661 0.579 0.056 0.279

TotC, total cholesterol; HDL, high density lipoprotein; TRIG, triglycerides; LDL, low density lipoprotein; CRP, C-reactive protein; Gluc, glucose.

Thus, the lower the scores on these scales, the lesser the problem or the greater the improvement during the study period. Results of these analyses are shown in Table 5. As shown in the composite overall scale and all sub-scales, there are consistent improvements from baseline to mid-study and to end-of-study. All of these improvements average ~36% and were statistically significant.

Final safety measures were potential changes in heart rates as well as ankle/brachial blood pressures and the ankle brachial index. These data are shown in Table 6. As shown, ankle and brachial blood pressures were lowered from baseline to end-of-study, although only the changes in the ankle systolic and diastolic reached statistical significance ($p = 0.0335$ and $p = 0.0346$, respectively). However, from a safety standpoint, changes in the resting blood pressures support the safety of the product. No changes were observed with respect to heart rates.

Efficacy. Although the QOL could be classified as a measure of efficacy, the primary outcome measure used in this study was the body composition improvement (BCI©) index that is the net result or sum of scoring gains of FFM and reductions of FM as positive treatment outcomes, and, conversely, losses of FFM and gains of FM as negative treatment outcomes. As shown in Table 7, while there was no significant change in

Figure 4. Analyses of non-linear blood test data.

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Changes in baseline-ending scale weight (−0.2 lb., \( p = 0.718 \)), there were statistically significant decreases in FM (\( p = 0.004 \)) and increases in FFM (\( p = 0.009 \)) resulting in a BCI of 3.4 lb. There were also no significant changes in baseline-mid-study and baseline ending BMD (\( p = 0.735 \)).

As shown in Fig. 5, all of the comparisons between the active study group and the historical placebo group were statistically significant. It is also worth noting that a within-group repeated measures \( t \)-test found a statistically significant scale weight loss of −3.6 lb. (\( p < 0.0001 \)) while the −0.2 lb. scale weight loss in the active study group was statistically insignificant (\( p = 0.716 \)). Additionally, a between-groups \( t \)-test also found that the scale weight loss in the placebo group was statistically greater than that of the active group (\( p < 0.0001 \)).

A total of 94.5% of the study subjects complied with the study protocol based on the compliance procedures that encouraged candid reporting. There were no significant changes in BMD found between baseline to mid-study to end-of-study. An analysis of the pedometer-monitored physical activity levels revealed no significant relationship between physical activity levels and improvements in body composition.

### Table 5. Analyses of self-reported problems with quality of life

| Measurement | Overall problems with quality of life (items 1–86) | Problems with QOL (items 1–51 only) | Problems with eating control (items shown with *) | Problems with depression (items 52–86) |
|-------------|--------------------------------------------------|-------------------------------------|----------------------------------------------|----------------------------------|
| Baseline    | 0.2262                                           | 0.2522                              | 0.3854                                       | 0.2098                          |
| Mid-study   | 0.1649                                           | 0.1747                              | 0.2901                                       | 0.1561                          |
| End-of-study| 0.1459                                           | 0.1601                              | 0.2782                                       | 0.1318                          |
| % improvement baseline-ending | 35.5% | 36.5% | 27.8% | 37.2% |
| Baseline/ending \( P \) values = | \(< 0.0001\) | \(< 0.0001\) | \(< 0.0001\) | 0.0002 |

QOL, quality of life.

### Table 6. Baseline-ending changes in blood pressures

| Resting blood pressures | (Chg) baseline-ending | \( P \) values |
|-------------------------|-----------------------|----------------|
| Arm systolic BP         | −2.32                 | 0.3701         |
| Arm diastolic BP        | −1.18                 | 0.4197         |
| Heart rate              | 1.43                  | 0.4435         |
| Ankle systolic BP       | −4.61                 | 0.0335         |
| Ankle diastolic BP      | −3.71                 | 0.0346         |
| Ankle heart rate        | 2.11                  | 0.2198         |
| Ankle/brachial index    | −0.02                 | 0.2429         |

Chg, Change.

### DISCUSSION

The absence of any significant within-group changes between baseline, mid-study, and end-of-study in the 45-measurement blood chemistry panel, or in the between-group comparisons between the active group and the historical placebo groups, provides compelling support for the safety of the product. Additionally, the consistent and significant positive changes from baseline to mid-study and mid-study to end-of-study in the QOL composite scale and its sub-scales provide further evidence of product safety. Nor were any adverse effects found in the heart rates, resting brachial or ankle blood pressure measurements, or in the brachial/ankle index taken at baseline, mid-study, and end-of-study. Although both systolic and diastolic blood pressures decreased throughout the study, none of these decreases reached statistical significance.

With regard to efficacy, DEXA body composition measurements taken at baseline, mid-study, and end-of-study found statistically significant decreases in FM and increases in FFM resulting in a 3.4 BCI index over the 60 days of the study. The same statistically significant decreases in FM and increases in FFM were also found in comparisons of the study group with the historical placebo group. The subjects’ 94.5% average compliance measurement also supports both the safety and efficacy of the product as does the absence of expected decreases in BMD often found in weight loss studies. An argument could also be made that the consistent and significant improvements found in the QOL and its sub-scales should also be viewed as supporting product efficacy. A study has demonstrated that corosolic acid, the active constituent in banaba leaf extracts, possesses osteoblastic activity that may explain the absence of bone mineral loss in the current study (Shim et al., 2009).

Another important finding from this study is the illustration of the differences in the conclusions one would draw about the success or failure of a weight loss interventions using the BCI or scale weight/BMI. Fig. 2 presents a comparison of within-group or repeated measures changes in body composition between the placebo group and the active study group. The placebo group had a −3.2 lb. reduction in body weight that was significantly greater (\( p < 0.0001 \)) than the non-significant −0.2 lb. weight loss found in the active group. Thus, one could conclude that the placebo group was a modestly successful intervention compared with the unsuccessful intervention of the active group. However, examination of changes in body composition as shown by the BCI

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suggests an opposite outcome because the weight reduction experienced by the placebo group was the result of a −3.1 lb. loss of metabolically active FFM as compared with a 1.6 lb. gain in FFM found in the active group – a 4.7 lb. differential or discordance in changes in FFM.

Because muscle is the primary site at which calories are consumed, any loss of muscle results in a loss of thermogenic ability, while conversely, any gain in muscle enhances the ability to utilize fat as an energy source and decrease FM. The results of this study clearly demonstrate the ability of this unique product over the course of 60 days to increase FFM while decreasing FM, thus leading to a healthy outcome.

The strengths of this study lie in the use of widely recognized multiple measurements of safety and efficacy and the consistent and statistically significant findings between changes from baseline to mid-study and to end-of-study. The 94.5% compliance finding and the 93.3% completion rate of the subjects stand in stark contrast to the 30–40% dropout rates typically reported for weight loss studies. This study also underscores the importance of using the BCI as an outcome measure instead of changes in the BMI or scale weight. In this study, using changes in scale weight as an outcome measure would have led to a conclusion that the product was ineffective as a weight loss supplement – a conclusion in stark contrast to the conclusions one would draw by using changes in body composition, particularly the BCI. Questions could be raised about previous weight loss interventions whose safety and efficacy were rejected, or accepted, by using only changes in body mass as an outcome measure as opposed to using changes in FM, FFM, and BMD. This issue is clearly something that needs further exploration.

The weaknesses of the study are its relatively small number of subjects (n = 28), the failure to use an randomized controlled trial (RCT) protocol with a random selection of placebo subjects, and the relatively short study period (60 days).

CONCLUSIONS

The safety and efficacy of the unique weight management product used in this study contain a novel combination of active ingredients in a unique sustained tablet delivery system that provided release of active ingredients for up to 6 h. The results of this 60-day study demonstrated the product increased FFM while decreasing body fat (FM). The product was designed to suppress appetite, support weight management and weight loss, and help maintain healthy blood sugar and lipid levels. Furthermore, the ingredients are believed to work in harmony via different and supporting mechanisms, ensuring a high degree of efficacy.

The significance and consistency of the measurements of safety and efficacy in this study clearly warrant further study of this combination of ingredients. Additionally, the results obtained using BCI as opposed to body weight and BMI strongly indicate a need for general application of this technique and the need for further comparative studies.

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Conflict of Interest

S.J.S. and H.G.P. have served as consultants for AdvoCare International, the distributor of the product. Dr. Kaats has no conflict of interest.
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