180 Report on AlgaeCal Bone Health Clinical Study

All of the participants have completed the first six months of the program as of August 2007. We asked the following questions of the clinical study Supervisor, Gilbert R. Kaats PhD, to assess the study findings to this point from his practical perspective. The first official report from the study's Principal Investigator, Joel Michaelick PhD, will be available after the 1 year clinical results have been reviewed early in 2008.

QUESTIONS

Q: Is there any particular advantage in using this plant-derived form of calcium as opposed to the laboratory-synthesized forms?

GRK: In our review of the scientific literature, we found a great deal of evidence that plant sources of vitamins and minerals were more effectively utilized by the body than laboratory synthesized vitamins and minerals. For example, an article in the *Journal of Food Chemistry* reported that plant-based minerals are much more easily absorbed by the body. In one study, the data showed that the body was able to use less than 10% of the synthetic minerals contained in the most popular brands of multivitamins. By contrast, the body was able to assimilate between 80 % to 100 % of the minerals derived from plants. Furthermore, there is an extensive body of research suggesting that a number of different vitamins and minerals are needed to optimize bone-health and, at the same time, provide other benefits such as enhancing the body's immune system. In its natural plant form, AlgaeCal contains many of the nutrients thought to contribute to bone health.

An additional benefit is the increased compliance or adherence that may result from the use of a plant-derived form of calcium and bone building nutrients since plant sources appear to have more appeal to the public as "natural" or "purer" forms of nutrients. And this is particularly true of nutritional-savvy consumers.

Q: Going to the "bottom line," does the AlgaeCal Bone Health Plan improve bone health?

GRK: The shortest answer is, "yes, of course!" Although only a few subjects have now completed the one-year tests, analysis of the 6-month test results revealed that instead of the expected decline in BMD, over two-thirds of women over 50 years of age increased their bone densities. Subjects in the 50+ adult group achieved an annualized increase in bone density of over 1% instead of the expected 1% decline for people of this age. The most dramatic improvement was found in a 64-year old woman who improved her bone density at a 10% a year rate and a cancer patient being treated with chemotherapy who also improved his bone density.

The Children and adolescents group increased their bone density over the expected increases, allaying the concern of impeded bone growth expressed by the Surgeon General.

An analysis of the 43-test blood chemistry panels revealed that there were no statistically significant changes in any of the chemistries in children or adults except for higher levels of circulating calcium. Thus, there appears to be no systemic or adverse effects in the blood chemistries or in the self-reported tracking data provided by the study participants.

Q: What does "of course" mean? Wasn't there a chance it would not help bone health?

GRK: Yes, there is always a chance of failure, but in this case, and in my view, that possibility is so remote and the probability of success is so much greater.

Q: What is it about the plan that gave it such a high probability of succeeding?

GRK: Now the answer must get longer. The study began with an exhaustive review of scientific studies conducted on ingredients and behaviors that went beyond calcium, particularly since calcium by itself is likely to have very little effect on bone health. In fact, as one researcher put it, "Calcium and vitamin D are only the 'ante' for improving bone health". There is also another major advantage of going beyond the ante; virtually all of the bone-health ingredients also provide additional health benefits.

Q: What are the additional health benefits of the other bone-health ingredients in the AlgaeCal supplement?

GRK: That is going to require a very long answer to even summarize the hundreds of studies on the health benefits of vitamins D, K-2 and C, magnesium, boron, and strontium. The simplest way of summarizing these health benefits is that, taken together, these studies suggest that these ingredients will enhance immune functioning. I think it would be fair to say that the plan improves both bone health and immune functioning.

Q: Do you think there are sufficient studies to suggest that the bone-health plan could also be called an immune-health plan?

GRK: I wouldn't go so far as to say it is an immune-health plan since there are other nutrients that would be included in an immune-health plan. However, I do think the data are sufficiently compelling to suggest that these other vitamins and minerals can contribute to immune health. And I think the contributions are sufficient to suggest to consumers that there are additional health benefits that go beyond bone health. Certainly the recent studies of vitamin D-3 are consistent with this view.

Q: What about the effects of Vitamin D and claims companies make about it?

GRK: The research on vitamin D3 is a very compelling story. There is substantial evidence that higher levels of Vitamin D3 can not only support bone health, but can also offer a wide range of health benefits.

For example, in June of this year in an article in the *American Journal of Clinical Nutrition* the researchers summarized previous studies that suggest the benefit of Vitamin D-3 for cancer mortality rates including for cancers of the breast, rectum, ovary, prostate, stomach, bladder, esophagus, kidney, lung, pancreas, and uterus, as well as for non-Hodgkin lymphoma and multiple myeloma. In their own a 4-year, double-blind, randomized placebo-controlled trial of 1,179 women, the researchers conclude that taking at least 1,100 IU of vitamin D3 "…substantially reduces all-cancer risk in postmenopausal women".

Other recent studies support the importance of vitamin D-3 for bone-health as well as a number of other health benefits it provides, including enhancements to the immune system. Another study reported that "…most Americans and others are not taking enough vitamin D, a fact that may put them at significant risk for developing cancer, according to a landmark study…" Furthermore, a number of scientists have suggested that we "…should reassess as a matter of high priority dietary recommendations for vitamin D…because current advice is outdated and puts the public at risk of deficiency".

Q: Is Vitamin K2 one of the ingredients that go beyond the "ante" to improve bone health?

GRK: Yes. We have known for some time now that magnesium, boron, and even Vitamin C support bone health. However, we were not aware of a growing body of research that supports the importance of vitamin K2 for bone health. That is why it was included K2 in our clinical trial and in the AlgaeCal formulation.

Subsequent to adding it to the *AlgaeCal* product formulation, in a June 2007 review article in the 50th Anniversary issue of *Thrombosis and Haemostasis*, the reviewers concluded that:

> "Poor vitamin K status must be regarded as a serious risk factor for increased postmenopausal bone loss and for artery calcification, notably in diabetes, end stage renal disease and aging….studies have demonstrated an inverse correlation between dietary vitamin K intake and bone fracture risk…Several clinical trials have demonstrated that supplementary vitamin K may result in decreased bone loss as well as in maintenance of bone strength".

A recent study referred to vitamin K2 as "the coagulation vitamin that became omnipotent…" because of its "Potential new application in dietary supplements and function foods for healthy individuals to prevent bone and vascular disease…."

Q: Magnesium naturally occurs in AlgaeCal. What is the evidence that magnesium provides both bone and immune system benefits?

GRK: Magnesium deficiency has been associated with low bone density. Recent studies of magnesium have reported that it lowers the risk of developing metabolic syndrome. Bone density increased with supplemental magnesium with at least one researcher, which led him to conclude that "...the demand for magnesium is going up and will in the end become a product like calcium". Results of a prospective, placebo-controlled, randomized, one-year double-blind trial of teenage girls "…indicate that regular magnesium supplements during this important age could significantly improve bone mineral density, and could have benefits later in life…" for bone health. Another recent study found "…magnesium intake from food and supplements was associated with increases in bone mineral density in healthy older subjects".

Another study found "people with more magnesium in their blood could reduce their risk of death from cancer by as much as 50 per cent…and was also linked to a 40 percent lower risk of all-cause mortality, and a reduction of similar magnitude for cardiovascular deaths. This researcher also reports that "The research is important because dietary surveys show that a large portion of adults do not meet the RDA for magnesium…" and…"New research indicates that a diet rich in magnesium may lower the risk of colon cancer, supporting previous studies inversely linking intake of the mineral to the disease".

Q: Boron also supports bone and immune health?

GRK: Boron, a natural element in AlgaeCal, appears to play an integral part in bone metabolism, as it supports the functions of calcium, magnesium, and vitamin D, all of which are crucial to promoting dense, healthy bone tissue. In an important study of postmenopausal women who were not on estrogen replacement therapy, scientists examined boron's effect on various measures of bone health. The subjects consumed a boron-deficient diet for 119 days, followed by 48 days of boron supplementation. On the boron-depleted diet, the women demonstrated increased urinary loss of both calcium and magnesium. On the boron-supplemented diet, however, they showed less urinary excretion of calcium and magnesium, as well as increased levels of two hormones associated with healthy bone mass. These findings indicate that adequate boron intake is essential to preserving the body's stores of bone-building calcium and magnesium. Other studies indicate that boron also promotes healthy joints, helps prevent prostate cancer, improves cognitive function, and may offer powerful antioxidant protection.

Q: What led you to include strontium citrate as part of the formulation?

GRK: Over the past few years a number of well designed and often replicated studies have reported reductions in BMD and fracture risks associated with Strontium Renalate, a pharmaceutical version of strontium typified by the dose-related graph shown below.

Other studies have shown dramatic increases in BMD in the spine, femur and total hip (the best predictor of fracture risk) as shown in the charts below:

The data are also consistent that strontium is well tolerated and these studies confirm that strontium "…offers a safe and effective means of reducing the risk of fracture associated with osteoporosis." All of these studies concluded that, as compared to placebo groups, there were no serious adverse events associated with Strontium Ranelate

While there are numerous studies on strontium ranelate, there is virtually no research on strontium citrate—the ingredient used in this study. However, experts are unanimous that ranelatic acid is highly unlikely to improve BMD and that it is strontium that provides the bone-health benefits. Not only is citrate less likely to cause adverse effects, but, unlike renalate, some studies suggest that citrate may facilitate bone health. For example, a recent study of potassium and citric acid found that Potassium citrate balances the high acidity of modern diets that erodes bone density. Researchers report "…significant increases in bone mass with citrate independent of Potassium…we were very surprised with both the magnitude and robustness of the effect of base supplement on BMD".

Q: What is the new study you referred to that bone health may affect weight loss?

GRK: A provocative study entitled "*Do Bones Help Control Metabolism and Weight?*" published in the August issue of *Cell* suggests that while bones are typically thought of as calcified, inert structures, researchers at Columbia University Medical Center have now identified a surprising and critically important novel function of the skeleton. They've shown for the first time that the skeleton is an endocrine organ that helps control our sugar metabolism and weight and, as such, is a major determinant of the development of type 2 diabetes.

The research demonstrates that bone cells release a hormone called osteocalcin, which controls the regulation of blood sugar (glucose) and fat deposition through synergistic mechanisms previously not recognized. Usually, an increase in insulin secretion is accompanied by a decrease in insulin sensitivity. Osteocalcin, however, increases both the secretion and sensitivity of insulin, in addition to boosting the number of insulin-producing cells and reducing stores of fat.

The authors show that an increase in osteocalcin activity prevents the development of type 2 diabetes and obesity in mice. This discovery potentially opens the door for novel therapeutic avenues for the prevention and treatment of type 2 diabetes.

"The discovery that our bones are responsible for regulating blood sugar in ways that were not known before completely changes our understanding of the function of the skeleton, and uncovers a crucial aspect of energy metabolism," said Gerard Karsenty, M.D., Ph.D., chair of the department of Genetics and Development at Columbia University Medical Center, Paul Marks Professor in the Basic Sciences, and senior author of the paper. "These results uncover an important aspect of endocrinology that was unappreciated until now."

But remember, as interesting as this might be, this is an animal study and we will need some demonstration that it has a similar effect on humans before getting too excited.

Q: Is it these studies supporting the nutritional ingredients of the AlgaeCal supplement that led you to add "of course" to your short answer of "Yes"?

GRK: Yes, but it goes further than that. Remember it is a "plan", not just a supplement. The addition of a program to increase physical activity and the value of increasing "health literacy" also led to the "of course." However, even without the physical activity and health literacy, the massive amount of data and studies supporting the nutritional formulation are more than adequate to make an "ingredient claim". In view of the growing concern about America's bone health set forth in the U.S. Surgeon Generals Bone Health Report, I think this evidence is more than sufficient to market this product even without the data from our clinical trials.

Q: Speaking of your clinical trials, how did IHTI get involved with studying the AlgaeCal Bone Health Plan?

GRK: Our involvement with AlgaeCal began when Dean Neuls, AlgaeCal's Founder, contacted us about conducting an independent clinical trial comparing the bio-availability of AlgaeCal's plant-sourced marine calcium with other forms of calcium. He pointed out that he believed that plant sources of vitamins and minerals were more readily absorbed by the body than laboratory derived nutrients and that there was an increasing interest in marine nutrition. In our initial review of the scientific literature, we found a number of studies suggesting that vitamins and minerals from plant sources appeared to be more readily absorbed by the body. We also found that there was an increasing interest in marine nutrition.

Q: Why did you abandon studying the bio-availability of AlgaeCal in favor of a bone-health plan?

GRK: This decision was based on two major considerations: (1) studies that questioned the value of comparing the absorbability of different forms of calcium, and (2) a "call to action" issued by the U.S. Surgeon General.

Q: It seems a number of companies promote their calcium as more bio-available than their competitors. What led you to conclude that bio-availability studies had little value?

GRK: I agree that the claim of increased bio-availability for a particular form of calcium is often seen in marketing materials. The suggestion that the consumer should pay more for a form of calcium that is more easily absorbed by the body because it is more likely to improve bone health seems to make sense. But even if a form of calcium that is more easily absorbed is a better buy, the ultimate question is "Does it lead to better bone health?" That is the real litmus test; and that is why we abandoned testing absorbability or bio-availability and turned our attention to how we could improve the user's bone health using measures of bone mineral density.

Q: How did the U.S. Surgeon General's call to action influence your decision to study a plan, not an ingredient?

GRK: In the SG's first-ever 2004 *Bone Health Report*, it reported that 85% of adolescent girls and 65% of boys do not get enough calcium and bone building nutrients to support normal bone growth, placing "America's bone health in jeopardy." Going beyond adolescents and children, the SG also reported that "…you are never too old or too young to improve your bone health" and issued a "call to action" to the healthcare industry to develop bone-health plans to: (1) improve nutrition, (2) increase physical activity and (3) improve health literacy.

In response to the SG's guidance for products that would "improve nutrition," IHTI scientists conducted an exhaustive review of published studies to identify the nutrients and nutrient amounts that had the highest probability of enhancing bone-health. Once identified, these nutrients were then combined with *AlgaeCal*'s plant-derived calcium (www.algaecal.com) to create an evidence-based bone-health supplement. To "increase physical activity," a practical, well-researched pedometer-based behavior modification program was incorporated into the plan. To "improve health literacy", a reader friendly summary of the scientific literature along with practical steps that can be taken to improve bone health was added to the Plan.

Q: Since IHTI owns a small percentage of AlgaeCal, doesn't that represent a conflict of interest?

GRK: IHTI provides three basic services for the healthcare and nutritional industries: Research & Development (R&D), Independent Clinical Trials, and Product Marketing. Some of our customers, such as AlgaeCal, start with our R & D service to help with the development and modifications of the product and pilot testing. It is the conduct of independent clinical trials reviewed by

independent Institutional Review Boards and executed by independent medical schools (as in AlgaeCal's case) or universities that resolves the conflict of interest.

Q: What was the design of the AlgaeCal study?

GRK: As I said earlier, we were confident that the AlgaeCal study should be based on the support for the ingredients provided by studies conducted by other scientists and organizations. To evaluate the safety and efficacy of the AlgaeCal study, 400 subjects aged 8-80 were recruited into a study to follow the plan and complete a bone density test, a 43- item blood chemistry panel, and self-reported quality of life inventories at baseline, 90 days, 6-months, one-year and 5 years.

Since children & adolescent subjects in this group were unlikely to take capsules, they received the bone building ingredients by eating two highly palatable cookies each day. In addition to the bone building ingredients contained in the cookies, they were prepared with Z-trim's fat-replacer; health-enhancing Enova oil, a product of a joint venture between Japanese Kao Corporation and Archer Daniels Midland; and Fibersol-2 soluble dietary fiber.

To improve physical activity levels, a significant body of scientific research supports the effectiveness of wearing *HealthTech Products'* pedometer and tracking daily step totals. Therefore, a pedometer-based behavior modification plan was added to the program that contained forms for tracking and graphing daily step totals and charts for estimating calorie and glycemic levels of foods.

Q: Did you consider using a double-blinded placebo-control randomized protocol?

GRK: Using placebo protocols always poses challenges to the researcher. We like to use them because the are considered the "gold standard" of scientific research. Thus, placebo studies have more "status" and are easier to get published. But they are not without problems. It is very difficult to get people to participate in a year-long study knowing that they have a 50-50 chance that the product they will be taking is a placebo. So recruiting is a real challenge. Thus, from the outset, questions can be raised about how much the people who do participate in a study of this length typify the consumers who will be using the product. Certainly people who are highly interested in the bone health are not likely to spend a year taking a product that had a 50-50 change would provide no help. Thus, the study population from the outset is likely to be unrepresentative of consumers who will be motivated enough to buy the product. Furthermore, a placebo design is so artificial as compared to the real world conditions under which people will purchase and use the product that it limits the extent to which it can be generalized to the consumers' real world. And even when subjects are enrolled, knowing that they have a 50-50 chance of getting a placebo undermines compliance and adherence to the study design. And all of the difficulties are magnified as the length of the study increases.

Since this is a "plan", not a product, we would also need to have divided subjects into a group who participated in the physical activity program and a control group who did not. And, we would have had to control for the third component of the Surgeon General's call to action, health literacy, by either giving people false information or no information about bone health. That would have, no doubt, put the cost of the study well beyond the resources we had to conduct the study.

Then there are ethical issues. Knowing that for children and adolescents, a significant amount of bone growth occurs in a year and, conversely, a significant decline in bone health for the elderly is likely to occur in a year. Given that the literature review provides such strong evidence of the safety and efficacy of the ingredients and the value of increased physical activity, it is difficult not to want these subjects to benefit from their participation—particularly those who already have deficiencies in their bone health.

Our decision was based on the fact that since there are enormous amounts of normative data for expected changes in bone growth with age against which the results of subjects could be compared, the need for placebo data seemed almost irrelevant. Furthermore, our use of drop-out data and corrections for compliance provide dose-related data further lessening the value of

placebo designs. Then there is the argument that people's belief that the product will help is an inherent part of the benefit of the product and, thus, undermining this belief undermines measuring the real effects of the product.