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FULL*fast* Scientific Review

This report concerns the efficacy of a dietary supplement distributed by Klaumwell Reseach Labs, LLC ("Klaumwell") known as Full*fast* for use in reducing the feelings of hunger (or increasing the feelings of satiety).

I was engaged by Manatt, Phelps & Phillips, LLP, counsel to Klaumwell, to perform certain confidential consulting services in connection with their review of Full*fast*. Specifically, I was requested to review the study on the Full*fast* formula by Rondanelli *et al*, now in press in the International Journal of Obesity, to determine if it provides a scientific basis to support the following claims for Full*Fast*:

- Clinically tested to help reduce the excessive feeling of hunger.
- Helps reduce the excessive feeling of hunger.
- Helps reduce appetite.
- Helps increase the feeling of satiety.
- In a double-blind, placebo-controlled, published clinical study, female volunteers following a weight loss program, used 3 sprays of Full*fast* under the tongue 5 times a day. Around the 5th day they stared to feel less hungry, and they experienced a significantly greater feeling of fullness overall than the placebo group over the 8-week study.
- Formulated to work with your brain to help you feel full.
- Helps you lose more weight than dieting alone.

As discussed in detail below, based upon my review of the Rondanelli study, and my review of the scientific literature concerning the effects of the primary ingredient in the product, in my opinion there is a reasonable scientific basis supporting the claims identified above.

My Background and Experience

I am currently Professor of Psychiatry and Pharmacology at the University of Pittsburgh School of Medicine, Research Director of the UPMC Weight Management Center, and Director of the Basic Neuroendocrinology Program of the Western Psychiatric Institute & Clinic. I received an S.B. in Biology and a Ph.D. in Nutritional Biochemistry & Metabolism from the Massachusetts Institute of Technology (MIT), and was a postdoctoral fellow at the Roche Institute for Molecular Biology. Before coming to the University of Pittsburgh, I was an assistant and then associate professor in the Department of Nutrition & Food Science at MIT. I am a member of the International Advisory Council, *Monell Chemical Senses Center*, and a past member of the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, *National Academy of Sciences*, the Council of the *American Society for Nutritional Sciences*, and a former chairman of the Nervous System Section of the *American Society for Nutritional Sciences*. I am also a member of several professional societies, including the Obesity Society, the American Society for Nutrition, the American Society for Pharmacology & Experimental Therapeutics, the American Physiological Society, the American Society for Neurochemistry, and the Society for Neuroscience. My research interests concern the influence of diet and drugs on the synthesis of neurotransmitters in the

central nervous system, and the pharmacologic treatment of obesity. I have published over 200 articles and reviews.

A copy of my *curriculum vitae* is attached at ***Exhibit A***.

Rondanelli Study

Rondanelli M et al., Satiety and amino-acid profile in overweight women after a new treatment using a natural plant extract sublingual spray formulation. *International Journal of Obesity* advance online publication 15 September 2009; doi: 10.1038/ijo.2009.155, attached as ***Exhibit B***.

The Rondanelli study was a double-blind, placebo-controlled trial in healthy, overweight Italian women (BMI between 25 and 35), who were randomly assigned to receive either a placebo (n=13) or the active formulation (n=14) daily for 8 wk while following a modest weight loss program. The active formulation was a liquid containing a number of plant extracts, manufactured by Medestea Research and Production S.p.A (Torino), and was described as a food supplement rich in 5-hydroxytryptophan (5-HTP). I have been informed that it was the same formula as Full*fast*. The placebo formulation was not described. Both the active formulation and the placebo were self-administered as an oral spray by the subjects. Each dose was given as three sprays into the mouth, to be focused under the tongue. The subjects were instructed to dose (3 sprays) five times each day, at the following times: fasting in the morning, at mid-morning, before lunch, fasting in the afternoon, and before dinner. A dose of three sprays was stated to contain 39 mg of *G.simplicifolia*. As the 5-HTP content of this seed has been estimated to be about 10-20% 5-HTP by weight, each dose probably contained approximately 4-8 mg 5-HTP **(1)**. The daily dose of 5-HTP was thus about 20-40 mg. During the 8-week trial, the subjects were instructed to complete a visual-analog scale (VAS) daily before dinner. The VAS rated hunger/satiety. At baseline, and at the end of the trial, a number of anthropometric measures were made (e.g., BMI, waist circumference, skin fold thicknesses), and 24-hr urine samples were collected to measure the serotonin metabolite, 5-hydroxyindoleacetic acid (5HIAA).

By way of comparison, previous studies showing anorectic and weight loss effects of pure 5-HTP in healthy obese females have used oral doses of between 650 and 900 mg/day. When administered for 5-6 weeks, weight loss was 1.5-2.0 kg **(2;3)**.

In the Rondanelli et al. study, urinary 24-hour 5HIAA excretion was measured as the primary marker for the active treatment (since it contains 5-HTP, and is converted to serotonin, it is metabolized to 5HIAA, and should appear in the urine). A significant increase in urinary 5HIAA was noted in subjects receiving the active product, about 2 mg/24 hr over baseline control values. In the Cecci **(2)** and Cangiano **(3)** studies, urinary 5HIAA increases were much larger, since the 5HTP dose was much larger, and were, respectively, 200 and 500 mg/24 hr. This biochemical result confirms that the 5HTP dose seen by the body in the Rondanelli study is comparatively small, as would be expected.

The most objective measure of success in the Rondanelli et al. study would be the change in BMI. Both groups were instructed to reduce caloric intake moderately (2508 kj/day; 600 kcal/day). Hence, both groups would have expected to lose some weight, and both did experience a modest decline in BMI (table 3). Of note, there was a significant difference in BMI decline between placebo and active treatment groups, indicating that a larger decline was observed in subjects taking the active treatment (table 3). The effect was smaller than that observed in the Cecci **(2)** and Cangiano **(3)** studies, as would be expected, given the large difference in dosing. Feelings of satiety (fullness), based on self-reports (visual analog scales), were significantly greater in subjects on the active treatment than those on the placebo (figure 2). It is also noteworthy that no adverse effects were reported, and the active treatment was well tolerated.

Overall, therefore, the study indicates that the treatment reduced hunger (increased feelings of satiety), and produced a modest reduction in BMI over placebo. I believe the study design and the results described in it are generally acceptable to the scientific community, and thus it is reasonable to assert that the utility of the product, as described in the claims outlined above, is based on/supported by a valid scientific study, published in a peer-reviewed, scientific journal of international stature.

5-hydroxytryptophan (5HTP)

The key ingredient in the preparation is stated to be *G. simplicifolia*, which is a natural source of 5HTP. 5HTP is the intermediate in the serotonin biosynthetic pathway (see box below). The normal substrate for this pathway is L-tryptophan, a dietary amino acid and a constituent of protein. In cells that synthesize serotonin, tryptophan is converted to 5HTP by the enzyme tryptophan hydroxylase (1 in box); 5HTP is then converted to serotonin (5-hydroxytryptamine) by the enzyme aromatic-L-amino acid decarboxylase (2 in box). Serotonin is metabolized to 5-hydroxyindoleacetic acid (5HIAA) via the enzyme monoamine

Tryptophan →(1) **5-hydroxytryptophan (5HTP)** →(2) **Serotonin** →(3) **5-hydroxyindoleacetic acid (5HIAA)**

oxidase (3 in box), and is ultimately excreted in the urine. The initial enzyme (1) is rate-limiting in this reaction, which means that the overall rate of serotonin production can proceed at a rate no faster than that allowed by the speed of this initial enzyme (1) reaction, when tryptophan is the substrate. Normally, the activity of the first enzyme is much less than that of the second enzyme. Both enzymes will make more serotonin, if supplied with an excess of substrate. However, because of the difference in enzyme activity, providing more tryptophan produces a much smaller rise in serotonin synthesis than providing more 5HTP. Since increasing serotonin synthesis leads to the feeling of satiety, ingesting 5HTP would be expected to produce a larger feeling of fullness than ingesting tryptophan, and a greater effect on weight loss, which indeed is what is observed **(2-4)**.

A potentially interesting feature in administering 5HTP is that while the first enzyme is found only in cells that normally produce serotonin, the second enzyme is found in all cells in the body. This means that when tryptophan is given, serotonin is produced only in those cells that normally make it; when 5HTP is given, serotonin is produced in all cells in the body to which it gains access. This may possibly have an advantageous effect, when administering 5HTP in the manner used in the Rondanelli study, since the ingested 5HTP will be converted to serotonin in the mouth, as well as in gut, and in other parts of the body, including the brain. For example, since serotonin is found in taste cells in the tongue and has been linked to taste transduction **(5,6)**, and on sensory neurons further down in the alimentary canal, 5HTP ingestion could produce serotonin effects in the mouth and gut that signal satiety and fullness to the brain via these nerves. The small 5HTP dose delivered by the spray may therefore produce an unusually large (for the dose) effect on fullness, because it can act on the brain indirectly through sensory neurons on the tongue, where it is delivered. Of course, this is speculation, but does not seem unreasonable, since otherwise, the 5HTP effect on the brain produced by the low dose in the spray should be very small. In any case, the bottom line is that the scientific literature *does* support the idea that 5HTP, following its conversion to serotonin, can influence signals either going into or within the brain that alter hunger/appetite, and that the net result of such effects is to moderate hunger/appetite.

In conclusion, the efficacy of Full*fast*, as described in the claims outlined above, is supported by the Rondanelli *et al.*, study and the scientific literature on the effects of the primary ingredient in the product.