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1001 G STREET, N. W.
SUITE 500 WEST
WASHINGTON, D.C. 20001
TEL. 202.434.4100
FAX 202.434.4646
WWW.KHLAW.COM

WRITER'S DIRECT ACCESS

Melvin S. Drozen
(202) 434-4222
drozen@khlaw.com

November 19, 2001

Via Hand Delivery

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Room 1061 (HFA-305)
Rockville, MD 20852

Re: Interim Final Rule for Plant Sterol/Stanol Esters and Coronary Heart Disease Health Claims (reopening of comment period); Docket Nos. 00P-1275 and 00P-1276

Dear Sir or Madam:

We respectfully submit these comments in response to the Food and Drug Admistration's (FDA) reopening of the comment period on the Interim Final Rule for Plant Sterol/Stanol Esters and Coronary Heart Disease Health Claims (CHD) published in the Federal Register on October 5, 2001 (66 Fed. Reg. 50824).

I. Introduction

We submit these comments on behalf of an interested client, a manufacturer of various food products. Our comments address several aspects of the Interim Final Rule and share a common theme, a request for more flexibility. Over the years, numerous studies have demonstrated the efficacy and safety of free and esterified plant sterols and stanols from various sources as a means of reducing dietary cholesterol absorption. We commend FDA for its promulgation of a rule allowing the CHD heath claim for certain applications. However, we believe that, in its present form, the rule is unnecessarily limited in several ways. These limitations are a disservice to consumers, who could benefit from a wide variety of products that would help lower cholesterol, as well as a disservice to the food industry, which could benefit from an opportunity to deliver a wider range of products and obtain ingredients from more suppliers. Providing more food choices in which to enjoy the benefits of these exciting new ingredients should increase the number of consumers taking advantage of the cholesterol-lowering health effects. Furthermore, by broadening the class of ingredients that may be used in conjunction with the CHD health claim, the increased competition will benefit the consumer through price competition and innovation.

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II. Plant Sterols and Stanols, Free and Esterified, and Mixtures Thereof, From Food Plants and Tall Oil, Should All Be Eligible for the CHD Health Claim

As noted above, our client is a food processor, rather than a manufacturer of free or esterified plant stanols or sterols, which, for convenience, we shall collectively refer to as phytosterols in this document. We are aware that several manufacturers have submitted voluminous data regarding efficacy and safety. It is not our goal to independently re-establish either via these comments. Rather, we write to urge FDA to carefully consider such data already submitted by the various manufacturers, and give serious consideration to broadening the rule in several ways. In particular, we believe FDA should broaden the rule in the following ways: 1) allow health claims for free stanols and sterols; 2) include tall oils as a source of all phytosterols; 3) remove the current restrictions on the categories of food eligible to bear the health claim; 4) waive the disqualifying fat level, low saturated fat and minimum nutrient content regulations for small servings sizes of phytosterol-containing foods; and 5) establish a notification program to consider waiving the preceding rules on a case-by-case basis.

A. Free Sterols and Stanols and Phytosterol Mixtures.

It is well established (and recognized by FDA)[1] that the active (cholesterol-lowering) form of phytosterols is the unesterified form. Phytosterol esters hydrolyze in the digestive system to release free phytosterols, and these are responsible for inhibiting the absorption of cholesterol. Although there may have initially been a need to use the ester form of phytosterols to facilitate use in foods (because of their greater fat solubility), this technological limitation has now been overcome by the use of dispersions, for example. This has allowed efficacious use of free phytosterols in a wide variety of foods. Thus, in addition to margarine,[2] the efficacy of a mixture of free stanols and sterols in lowering cholesterol has been demonstrated in a milk based drink;[3] a combination of cereal, snack bar and juice drink;[4] as well as chocolate confectionery.[5]

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1 65 Fed. Reg. 54686, 54688 (Sept. 8, 2000).

2 Jones, P.J. et al., Cholesterol-Lowering Efficacy of a Sitostanol-Containing Phytosterol Mixture with a Prudent Diet in Hyperlipidemic Men. Am. J. Clin. Nut. (1999) 69:1144-50 [hereinafter *Jones*].

3 *See* comments submitted by Novartis Consumer Health, Inc., Nov. 21, 2000.

4 *See* comments submitted by Altus Food Company, a joint venture of The Quaker Oats Company and Novartis Consumer Health, Inc., Nov. 1, 2001.

5 We attach a summary and report of this study of phytosterols in chocolate confectionery as Appendix 1. *See also infra* the discussion in Section IV.C. of these comments.

Because the free form of phytosterols is the active form, we agree with other commentators that the per serving amounts should be expressed as free phytosterols. Thus, the content of esterified phytosterols would be adjusted to reflect the portion of the molecular weight attributable to the unesterified sterol or stanol (the fatty acid moiety is about 40%). This would provide a uniform system that could deal with food products containing mixtures of free and esterified forms, providing consumers with useful information and minimal confusion.

There is some controversy regarding the relative effectiveness of sterols and stanols, with the strongest positions being taken, not surprisingly, by the manufacturers of products that are largely stanols or sterols.[6] In actuality, all of the products are mixtures, but some are heavily weighted to one or the other. Now, products are available with a more even mixture of the two, which, as noted above, have been demonstrated to be efficacious in lowering cholesterol. While we believe it is important to allow health claims based on the per serving contributions of a mixture of sterols and stanols in a mixture, we have little stake in the determination of the relative effectiveness. Rather, we urge FDA to critically evaluate the scientific evidence. If, however, a statistically significant difference in efficacy between sterols and stanols cannot be demonstrated, we agree with some commentators[7] that the consumer will be best served by deeming the two equivalent in efficacy. This will limit a possible source of confusion in the already complicated universe of information a consumer must navigate in order to pursue healthy eating habits.

B. Tall Oil Sources

Although tall oil is recognized as a source of stanol esters in the Interim Final Rule, this source has since been demonstrated to be a safe and effective source of sterols as well. For example, the studies referenced in the section above were conducted with a mixture of sterols and stanols derived from tall oil. Indeed, the tall oil "stanol" product that was the subject of the petition is actually a mixture of sterols and stanols, with the latter predominating. When the tall oil is not hydrogenated, sterols predominate. The safety of tall oil as a source of mixed phytosterols has been demonstrated in the generally recognized as safe (GRAS) notification

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6 *See* 66 Fed. Reg. 50824, 50825 (Oct. 5, 2001); comments submitted by Lipton (Unilever) on Feb. 27, 2001; comments submitted by Arent Fox on behalf of Raisio Benecol Ltd. on Nov. 21, 2000.

7 *See, e.g.*, comments submitted by Novartis Consumer Health, Inc. on Nov. 21, 2000, at p.16.

submitted by Novartis Consumer Health, Inc. ("Novartis"),[8] which FDA did not question.[9] Rather than summarize its findings, we incorporate it by reference. Like our other requests for a broadening of the rule, this request will result in more choices for consumers and food manufacturers as well as the benefits to be realized from increased competition among suppliers of phytosterols.

III. Because More Foods are Now Able to Deliver Phytosterols, the Target Number of Servings Per Day Should Not Be Limited To Two.

The reasons FDA gave for a target recommendation of exactly two servings of foods containing phytosterols are not relevant under the expanded rule that we advocate, which is outlined below. First, the interim final rule noted that "there is not a wide variety of foods that contain plant sterol esters in significant quantities."[10] Secondly, "four servings of plant sterol ester-containing foods per day would not be an appropriate dietary recommendation because such foods are necessarily fat-based."[11] Clearly, with the advent of many additional phytosterol-containing foods that are not necessarily fat-based, these formerly valid concerns are no longer at issue. Thus, there is no reason to deviate from the general assumption of a consumption pattern consisting of three meals and a snack. As is the case for psyllium or soy protein, the target consumption frequency should be one to four times per day, and the label should merely be required to state the daily intake necessary to achieve the effect and the contribution to that amount from the product, without requiring any reference to frequency. Additionally, there is recent evidence that cholesterol can be lowered with only one intake per day.[12] Thus, to require a label suggesting that any specified number of servings are required may unnecessarily discourage and confuse consumers. Frequency recommendations should be allowed, but be optional.

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[8] Notice dated Jan. 28, 2000, GRAS Notice No. GRN 000039. Novartis submitted additional safety data in Nov. 2000.

[9] *See* FDA Response Letter dated Apr. 24, 2000.

[10] 65 Fed. Reg. 54686, 54707 (Sept. 8, 2000).

[11] *Id.*

[12] Plat, J. et al., Effects on serum lipids, lipoproteins, and fat soluble antioxidant concentrations of consumption frequency of margarines and shortenings enriched with plant stanol esters. Eur. J. Clin. Nutr. (2000), 54:671-77.

IV. FDA Should Not Limit the Categories of Foods Eligible to Bear the Stanol/Sterol CHD Health Claim

In section 101.83(c)(2)(iii)(A), FDA limits the products eligible to bear the CHD health claim to spreads and salad dressings containing sterol esters and spreads, salad dressings, snack bars, and dietary supplements in softgel form containing stanol esters. However, in order to ensure that the health benefits offered by phytosterols are accessible to a wide variety of consumers, we believe that FDA should not place limits on the categories of food eligible to bear the CHD health claim. Any food containing phytosterols that meets the requirements prescribed in the Agency's health claim regulations should automatically be eligible to bear the CHD claim. Moreover, to ensure that these health benefits are made available through a wide array of food options, FDA should grant more exemptions from the disqualifying fat, low saturated fat, and minimum nutrient content requirements. As discussed more fully below, this should be accomplished by granting exemptions for all foods with small serving sizes. In any event, FDA should establish a notification system by which a manufacturer may submit data in support of an exemption to any of these rules, which exemption would be deemed granted unless FDA objects.

A. Phytosterols Have Been Shown to be Safe and Effective For Use in a Wide Variety of Foods

As discussed in greater detail below, phytosterols have been shown to be safe and effective when used in a variety of food and dietary supplement applications. Therefore, we urge FDA to reconsider the limitations placed on the products eligible to bear the CHD health claim.

1. GRAS Status of Phytosterols

As discussed above, phytosterols have been shown to be GRAS for use in a variety of food applications in satisfaction of the safety requirement contained in 21 C.F.R. § 101.14(b)(3)(ii). Furthmore, as indicated in the interim final rule, FDA did not object to the GRAS notifications submitted by Lipton and McNeil for plant stanol and sterol esters. Additionally, the variety of foods in which the phytosterols have been shown to be GRAS indicates that there is a sufficient basis for concluding that phytosterols would also be GRAS in all food applications. For example, we attach as Appendix 2 an expert report concluding that a combination of plant sterols and stanols in confectionery, frozen deserts, and meal products are GRAS when consumed at a total dietary intake of 1.8 grams per day.

2. Efficacy of Phytosterols

In addition to being safe, phytosterols have also been shown to be effective at reducing cholesterol when consumed through a variety of foods. Generally, FDA has agreed in the Interim Final Rule, that based on the available scientific documentation, there is significant scientific support for a relationship between the consumption of plant stanol and sterol esters and a reduction in LDL cholesterol levels. Furthermore, as discussed above, the free form of the stanols and sterols has been shown to be equally as effective as the esterified forms of the stanols and sterols at lowering cholesterol levels when consumed in foods.

In particular, FDA agreed that the use of plant stanol esters in spreads and salad dressings is effective for lowering cholesterol.[13] Also, the Agency recognized that the use of plant stanol esters in spreads, salad dressings, snack bars, and softgel form dietary supplements is effective for lowering cholesterol, and thus eligible to bear the CHD health claim.[14] Additionally, as mentioned previously, the efficacy of a mixture of free stanols and sterols in lowering cholesterol has been demonstrated in a milk-based drink; a combination of cereal, snack bar and juice drink; and chocolate confectionery.[15]

There is now sufficient data to show that all phytosterol-containing foods will prove effective at offering the same cholesterol-lowering benefits as the foods discussed above. Stated differently, the food matrix chosen for the phytosterol will have no effect on efficacy. Accordingly, FDA should not limit the categories of foods eligible to bear the CHD claim to only those foods listed in the Interim Final Rule. Therefore, any food containing the phytosterols that meets the requirements prescribed in the Agency's health claim regulations should automatically be eligible to bear the CHD claim. We believe that this approach is also consistent with the recommendations of the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults.[16]

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13 *See* 65 Fed. Reg. 54686, 54701, 54707 (Sept. 8, 2000); *see also Jones,* supra note 2.

14 *See* 65 Fed. Reg. at 54701, 54708.

15 *See supra* notes 2-5 and accompanying text.

16 Available at http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3_rpt.htm.

3. There is No Need for Product-Specific Analytical Methods

We do not believe that there is a need for product-specific analytical methods to quantify the amount of phytosterols contained in separate food categories. In fact, FDA has never required such a method for each category of food eligible to bear health claims. Moreover, neither AOAC International nor the Codex Alimentarius Commission has established such a method.

Rather than establishing product-specific methods, we recommend that industry be allowed to collaboratively establish a general method. In the meantime, industry should be permitted to use reliable methods, such as maintaining production records, which would be subject to inspection, to prove that the foods contain the amount of phytosterols indicated on the label. Such an approach has been employed with the soy protein health claim.

B. FDA Should Waive the Disqualifying Fat Level, Low Saturated Fat, and Minimum Nutrient Content Regulations For Small Serving Sizes of Foods Containing Phytosterols

FDA regulations contain three restrictions that could prevent the use of the CHD health claim for foods containing phytosterols—the disqualifying fat level, the low saturated fat requirement, and the minimum nutrient content requirement, which is otherwise known as the "jelly bean" rule. 21 C.F.R. §§ 101.14(a)(4), 101.62(c)(2) and 101.14(e)(6). These regulations undermine the use of this cholesterol-lowering ingredient thus severely limiting the availability of phytosterol-containing foods, and the benefits they offer, to the public. Because CHD is a widespread and serious health issue, FDA regulations that hinder the market availability of foods containing-phytosterols should be waiveable by the Agency, as discussed below.

In the interest of making the health benefits offered by the phytosterol-containing foods available to the largest possible segment of the public, we believe FDA should apply the disqualifying fat level and the low saturated fat requirement **per packaged serving** for small servings of foods containing phytosterols. By analogy to the 30 grams or less reference amount customarily consumed (RACC) criteria provided in part 101.62 of the Agency's regulations, we believe that a package size of 30 grams or less is an appropriate criterion for exempting foods from the disqualifying fat level and the low saturated fat requirement. We also believe that the "jelly bean" rule should not be applied to this health claim.

1. Disqualifying Fat Level and Low Saturated Fat Requirements

The disqualifying fat level and the low saturated fat requirements are the first two regulations that could hinder the market availability of phytosterol-containing foods bearing the CHD health claim. *See* 21 C.F.R. §§ 101.14(a)(4) and 101.62(c)(2). Due to the strength of the evidence supporting the efficacy of phytosterols in lowering cholesterol, in its Interim Final Rule, FDA decided to waive the disqualifying fat level for spreads and dressings.[17] The Agency recognized that phytosterol-containing foods that are not able to comply with the disqualifying fat level may still offer cholesterol-lowering benefits. As FDA noted, there has been a change in expert opinion regarding total fat intake, risk of CHD, and general health.[18] Furthermore, the Agency stated that "current scientific evidence does not indicate that diets high in unsaturated fat are associated with CHD."[19]

In light of FDA's position regarding fat, we believe that the disqualifying level of total fat (i.e., 13 grams) and low saturated fat criteria (1 gram) per 50 grams should apply to a serving of these foods, not per RACC. We propose a 30 gram package size cutoff. Though in its Interim Final Rule, FDA rejected a similar argument because it did not feel there was any public health rational to justify applying the exception to all foods available in small serving sizes, we believe that the Agency should reconsider. We base our opinion on the belief that health-conscious consumers desiring to lower their cholesterol, to whom the fat content is disclosed, will indeed use these foods as a replacement for similar foods not containing phytosterols. For example, a chocolate bar containing phytosterols could replace another confectionery snack, just as phytosterol-containing spreads replace traditional butter or margarine spreads.

In the Interim Final Rule, FDA indicated its willingness to consider additional exceptions on a case-by-case basis. It is our position that a categorical exception to the disqualifying fat level rule, as well as for the low saturated fat requirement, should be made for products available in small serving sizes, due to the likelihood that these products will replace their conventional counterparts which do not offer cholesterol-lowering benefits. Although the manufacturers of spreads and dressings have been pioneers in the phytosterol health claim area, these products do not have universal appeal. Some consumers may find it more convenient and palatable to obtain the cholesterol-lowering benefits of phytosterols through a product like chocolate, which could

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17 65 Fed. Reg. 54686, 54709 (Sept. 8, 2000).

18 *See* 65 Fed. Reg. at 54710.

19 *Id.*

readily replace other desserts or snacks that the consumer would likely choose in the absence of the phytosterol-containing treat.

2. Minimum Nutrient Content Requirement

The third regulation that could preclude the use of the CHD health claim on phytosterol-containing foods is the minimum nutrient content rule, also known as the "jelly bean" rule. 21 C.F.R. § 101.14(e)(6). This rule prohibits the use of health claims on foods that do not contain at least ten percent of the Reference Daily Intake, or the Daily Reference Value, for vitamin A, vitamin C, iron, calcium, protein, or fiber per reference amount customarily consumed, before the addition of any nutrients. FDA implemented this regulation to ensure that health claims would not be undermined by their use on foods with little or no nutritional value.[20]

In the Interim Final Rule, FDA exempted salad dressings from this minimum nutrient content rule under the rationale that though the minimum nutrient content requirements are important, they are outweighed by the importance of providing consumers with phytosterol-containing foods bearing the CHD claim.[21] An additional factor behind the Agency's decision to exempt salad dressings from the minimum nutrient content requirements was that these dressings will likely be used on foods –such as salads-- rich in nutrients and fiber. The Agency then acknowledged its willingness to consider making exceptions to the minimum nutrient content requirements for other foods on a case-by-case basis.

We believe that FDA's analysis in the interim final rule should necessarily lead to the Agency's adoption of the same flexible and expeditious approach when considering other requests for exemption from the minimum nutrient content requirements. Applying the Agency's own rationale, we believe FDA should waive the minimum nutrient content requirements for any phytosterol-containing food otherwise meeting the CHD claim criteria because such a food will indeed contribute significant nutrition in the form of an appropriate level of phytosterols.

At a minimum, foods packaged in small serving sizes present a particularly compelling case in which the "jelly bean" rule should be waived. In this situation, the food in question is but a small contribution to a meal, and is likely to be consumed primarily for its phytosterols. Moreover, as FDA has recognized, phytosterols contribute "nutritive value."[22] Although not a

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[20] *See* 58 Fed. Reg. 2478, 2521 (Jan. 6, 1993).

[21] *See* 65 Fed. Reg. 54686, 54711 (Sept. 8, 2000).

[22] *See* 65 Fed. Reg. at 54688.

nutrient acknowledged in the "jelly bean" rule, given that the typical American diet is not likely to be deficient in any of the nutrients listed in the rule, phytosterols provide health benefits equal to, if not more important, than the nutrients prescribed in the "jelly bean" rule. Consumption of a small portion of phytosterol-containing food is highly unlikely to lead to a deficiency of any other nutrient.

C. FDA Should Establish A Notification Procedure to Consider Case-By-Case Waivers of the Regulations on Disqualifying Fat Level, Low Saturated Fat, and Minimum Nutrient Content

If FDA will not waive the disqualifying fat level, the low saturated fat requirement, and the "jelly bean" rule for small serving sizes of foods containing phytosterols, we strongly urge the Agency to adopt a notification program to consider waiver of these rules on a case-by-case basis. Furthermore, even if the Agency is willing to waive the disqualifying fat level, the low saturated fat requirement, and the "jelly bean" rule for small serving sizes of foods containing phytosterols, we believe a notification process should be instituted for the Agency to consider waiving the rule for larger serving sizes of phytosterol-containing foods. This process would serve the public by facilitating the timely market placement of a wide range of phytosterol-containing foods offering cholesterol-lowering benefits, without the need to amend the Agency's health claim regulations.

Such a notification program would ideally provide an expedited review process—we would recommend a 120-day review period. To have their foods considered for a waiver of any or all of the rules, manufacturers would submit data establishing why the health benefits offered by their phytosterol-containing foods outweigh the regulatory objectives embodied in the disqualifying fat level, the low saturated fat requirement, and the "jelly bean" rule. If FDA does not object during the 120-day review period, the waiver requested will be deemed granted.

D. The Chocolate Example

A chocolate product is a prime example of a food which, when containing phytosterols, has been proven to offer cholesterol-lowering benefits, but which may not meet the disqualifying fat level, the "low saturated fat" requirement, and the "jelly bean" rule discussed above. To prohibit other foods such as these from bearing the CHD claim because they do not fit strictly within parameters of the Agency's health claims regulations would be a disservice to the many consumers who might otherwise purchase and benefit from these products, substituting them for chocolate products that do not contain phytosterols.

In a March 2001 study (see Appendix 1), hypercholesterolemic patients received a product containing 10 grams of chocolate and 0.6 grams of a phytosterol mixture consisting of approximately 75% free plant sterols and 25% free plant stanols. Thirty subjects (male and

female) received this small serving size product (approximately 11 grams) or a placebo three times per day for 28 days.

Mean total cholesterol levels declined 6.4% relative to baseline values. LDL cholesterol declined by 10.3% relative to baseline values. Both deviations from the baseline are statistically significant. Moreover, there was no statistically significant weight gain among study participants. Similar to findings in prior studies, HDL cholesterol and triglyceride levels did not statistically change over the test period.

As with chocolate, there are most likely many other foods which, although they may not strictly comply with the disqualifying fat level, and the "low saturated fat," and "jelly bean" rule, nevertheless offer the cholesterol-reducing benefits available through the consumption of phytosterols.

V. Conclusion/Summary

In conclusion, given the significant impact that CHD has on the American public, we believe that FDA should employ flexibility to ensure that a wide variety of phytosterol-containing foods offering cholesterol-lowering benefits are made available to the largest possible segment of the public. Though we commend the Agency for its promulgation of a rule allowing the CHD heath claim for certain applications, we believe that, in its present form, the rule is unnecessarily limited. These limitations are a disservice to consumer choice, food industry, product development, and public health generally.

Please let us know if you would like any further information.

Respectfully submitted,

Melvin S. Drozen

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1. Introduction

This report describes the results of a secondary analysis of CLF 9903, including only the subjects randomized to Phytrol 18S or placebo, and only the per protocol population.

The per protocol population was defined as subjects who were randomized, had at least one efficacy data point after baseline, and had:

- average LDL cholesterol at Visits 1 and 2 $\geq$ 3.5 mmol/L
- less than 15% variation in LDL cholesterol between Visits 1 and 2
- triglycerides $\leq$ 4.0 mmol/L at each of Visits 1-3
- 80% compliance (as measured by the ratio of the number of chocolates consumed to the number that should have been consumed between Visits 3 and 5, i.e. 84)
- no more than 3 days off treatment prior to Visit 5
- Visit 5 no more than 6 weeks after Visit 3.

2. Statistical Methods

2.1 Demographics and health status prior to study treatment

Subjects randomized to the two treatment groups were compared with respect to information collected at Visits 1, 2 and 3, which occurred prior to the start of study treatment. This information included demographics, vital signs, findings on physical examination, and laboratory measurements (lipids, hematology and chemistry). The weight, BMI, blood pressure and lipid values obtained at Visits 1, 2 and 3 were averaged to obtain a single baseline value. The statistical significance of any differences between the two groups on categorical variables (e.g. sex, findings on physical examination) was determined using the chi-square test. The statistical significance of any differences between the two groups with respect to continuous variables (e.g. age, weight, height, systolic and diastolic blood pressure, lipids) was determined using the t-test.

2.2 Compliance

Compliance was measured by the ratio of the number of chocolates consumed to the number that should have been consumed between Visit 3 and Visit 5, i.e. 84. This ratio was compared between treatment groups using the Mann-Whitney U test. The proportion of subjects who were 100% compliant was also calculated, and compared between groups using the chi-square test.

2.3 Efficacy

The primary efficacy measurements were the changes in plasma cholesterol (total, LDL and HDL) during the treatment period. Changes in the LDL/HDL ratio and triglyceride levels during treatment were secondary efficacy measurements.

The average of the lipid values obtained at Visits 1, 2 and 3 was used as the baseline value. For total and LDL cholesterol, six outcome variables were analyzed: the absolute cholesterol level at Visit 4 and at Visit 5; the change in the cholesterol level from baseline to each post-

treatment visit; and the percentage (relative) change from baseline to each post-treatment visit. For HDL cholesterol, the LDL/HDL ratio and triglycerides, the average of the values obtained at Visits 4 and 5 was used as the post-treatment value, and four outcome variables were analyzed: the absolute lipid value post-treatment, the change from baseline, and the percentage (relative) change from baseline.

The outcome variables were analyzed using analysis of covariance, with treatment group included as the only main effect. The baseline value was included as a covariate in analysis of the post-treatment values and the absolute changes from baseline. The mean post-treatment values and absolute changes from baseline (and 95% confidence intervals) presented in Tables 4.3.1-4.3.5 are least squares means, adjusted for any difference in the baseline value between the two treatment groups.

2.4 Safety

2.4.1 Adverse Events

All clinical and laboratory adverse events, as defined in the protocol, which occurred between subject enrollment and the end of the study period (Visit 5) were reported. Adverse events which began after the start of study treatment have been considered treatment-emergent. The proportions of subjects reporting any adverse event or any treatment-emergent adverse event were compared between treatment groups using the chi-square test.

2.4.2 Laboratory measurements

The laboratory measurements made at Visit 5 were used as the post-treatment values. If laboratory tests were conducted at Visit 4 but not at Visit 5, the values obtained at Visit 4 were carried forward. The post-treatment value of each laboratory parameter and change from baseline (Visit 1) were compared between treatment groups using analysis of covariance. The baseline value was included as a covariate in all analyses. The significance of the difference from 0 of the change from baseline within each group was determined either by the paired t-test or by Wilcoxon's matched pairs signed ranks test, as appropriate.

2.4.3 Weight and vital signs

The weight, Body Mass Index and blood pressure measurements made at Visit 5 were used as the post-treatment values. If a measurement was not available at Visit 5, the value obtained at Visit 4 was carried forward. These variables were analyzed in the same manner as the laboratory parameters (section 2.4.2).

2.5 Phytosterol Measurements

Three phytosterols (lathosterol, campesterol and sitosterol) were measured at four visits: Visits 2 and 3, prior to treatment; Visit 4, after three weeks of treatment; and Visit 5, after four weeks of treatment.

The values obtained at Visits 2 and 3 were averaged to obtain a baseline value. Six outcome variables were analyzed: the phytosterol level at Visit 4 and at Visit 5; the change in the phytosterol level from baseline to each post-treatment visit; and the percentage (relative) change from baseline to each post-treatment visit. The six outcome variables were analyzed using analysis of variance or covariance, with treatment group included as the only main effect. The baseline value was included as a covariate in the analyses of the post-treatment values and the absolute changes from baseline. The mean post-treatment values and absolute changes from baseline (and 95% confidence intervals) presented in Tables 6.1-6.3 are least squares means, adjusted for any difference in the baseline value between the two treatment groups.

Due to the non-normality of the observations, a second set of analyses was conducted on their ranked values; the significance levels of differences between the two groups given in section 6 were obtained from the analyses of the ranks.

3. STUDY SUBJECTS

3.1 Disposition of subjects

Thirty-five subjects were randomized to each of Phytrol 18S and placebo; four subjects in each group were excluded from the per protocol analysis. All remaining 31 subjects in each group completed the trial.

3.2 Protocol Deviations

Table 3.2.1 shows the protocol deviations which occurred during screening and enrollment. There were a total of 10 violations of the inclusion/exclusion criteria: one in the placebo group, and nine among subjects randomized to Phytrol 18S. The subject (3062) with LDL cholesterol < 3.5 mmol/L at Visit 1 also had average total cholesterol < 5.5 mmol/L at Visits 1 and 2. There were no known protocol violations during the course of the study.

Table 3.2.1 : Protocol deviations, by treatment group

Deviation	Phytrol 18S	Placebo
Average total cholesterol at Visits 1 and 2 < 5.5 mmol/L or > 8.0 mmol/L	7	0
LDL cholesterol < 3.5 mmol/L at Visit 1	1	0
WBC < 3.5 x 10^9/L at Visit 1	1	1

4. EFFICACY ANALYSIS

4.1 Demographic and Other Baseline Characteristics

4.1.1 Demographic Characteristics

Thirty (48%) of the 62 subjects included in the PP population were male (Table 4.1.1). Although this proportion varied from 39% of subjects given Phytrol 18S to 58% of those given placebo, the difference between treatment groups was not statistically significant.

Table 4.1.1: Sex of subjects, by treatment group

Sex	Phytrol 18S		Placebo	
	N	(%)	N	(%)
Male	12	(38.7)	18	(58.1)
Female	19	(61.3)	13	(41.9)

The subjects' age is summarized, by treatment group, in Table 4.1.2. There was no statistically significant difference in age between subjects randomized to the two treatment groups.

Table 4.1.2 : Age (years) of subjects, by treatment group

Group	Mean	95% C.I.	Minimum	Median	Maximum	N
Phytrol 18S	56.2	(52.2,60.3)	31.0	55.0	74.0	31
Placebo	57.8	(54.5,61.0)	42.0	56.0	71.0	31

4.1.2 Weight, Height and Body Mass Index

The subjects' baseline weight and height are shown by sex and treatment group in Tables 4.1.3 and 4.1.4. Baseline BMI is shown, by treatment group, in Table 4.1.5. There was no significant difference between subjects randomized to the two groups with respect to these parameters.

Table 4.1.3 : Baseline weight (kg), by sex and treatment group

Sex/Group	Mean	(95% C.I.)	Minimum	Median	Maximum	N
Males						
Phytrol 18S	77.2	(70.9 , 83.6)	62.3	77.8	101.3	12
Placebo	79.1	(74.2 , 84.0)	64.0	80.0	98.7	18
Females						
Phytrol 18S	72.3	(66.7 , 77.9)	60.0	68.0	107.0	19
Placebo	70.4	(63.8 , 76.9)	57.0	65.0	88.3	13
All Subjects						
Phytrol 18S	74.2	(70.1 , 78.3)	60.0	70.0	107.0	31
Placebo	75.5	(71.4 , 79.5)	57.0	74.0	98.7	31

Table 4.1.4 : Baseline height (cm), by sex and treatment group

Sex/Group	Mean	(95% C.I.)	Minimum	Median	Maximum	N
Males						
Phytrol 18S	178.6	(174.6,182.6)	170.0	178.0	196.0	12
Placebo	177.1	(173.7,180.5)	164.2	179.3	186.0	18
Females						
Phytrol 18S	166.1	(163.0,169.3)	156.0	168.0	176.0	19
Placebo	165.7	(163.6,167.9)	160.0	165.0	172.0	13
All subjects						
Phytrol 18S	171.0	(167.7,174.2)	156.0	172.0	196.0	31
Placebo	172.3	(169.4,175.3)	160.0	172.0	186.0	31

Table 4.1.5 : Baseline Body Mass Index, by treatment group

Group	Mean	(95% C.I.)	Minimum	Median	Maximum	N
Phytrol 18S	25.3	(24.3 , 26.4)	21.6	24.7	34.9	31
Placebo	25.4	(24.3 , 26.4)	21.6	24.2	32.2	31

4.1.3 Blood Pressure

Table 4.1.6 shows the subjects' baseline systolic and diastolic blood pressure (BP). There was no significant difference between treatment groups on either of these variables.

Table 4.1.6 : Baseline blood pressure (mm Hg), by treatment group

Parameter/Group	Mean	(95% C.I.)	Minimum	Median	Maximum	N
Systolic BP						
Phytrol 18S	132.0	(126.7 , 137.2)	106.7	129.3	160.0	31
Placebo	130.4	(125.3 , 135.5)	105.0	128.3	153.7	31
Diastolic BP						
Phytrol 18S	83.4	(80.3 , 86.5)	66.7	82.7	99.3	31
Placebo	82.5	(79.8 , 85.2)	69.3	81.7	96.7	31

4.1.4 Findings on Physical Examination

Table 4.1.7 shows the findings on physical examination at Visit 2. There was no significant difference between treatment groups in the proportion of subjects with abnormal findings on any body system. The abnormal findings are listed, by body system and treatment group, in Table 4.1.8.

Table 4.1.7 : Findings on physical examination at Visit 2, by treatment group

Body System/ Findings	Phytrol 18S		Placebo	
	N	(%)	N	(%)
Lungs				
Normal	31	(100.0)	31	(100.0)
Abnormal	0	(0.0)	0	(0.0)
Heart				
Normal	30	(96.8)	31	(100.0)
Abnormal	1	(3.2)	0	(0.0)
Gastrointestinal				
Normal	31	(100.0)	30	(96.8)
Abnormal	0	(0.0)	1	(3.2)
Neurological				
Normal	20	(64.5)	25	(80.6)
Not done	11	(35.5)	6	(19.4)
Dermatological				
Normal	25	(80.6)	30	(96.8)
Abnormal	3	(9.7)	0	(0.0)
Not done	3	(9.7)	1	(3.2)
Other				
Normal	1	(3.2)	1	(3.2)
Abnormal	0	(0.0)	1	(3.2)
Not done	30	(96.8)	29	(93.5)

Table 4.1.8 : Abnormal findings on physical examination at Visit 2

Body System	Treatment Group	Finding	N
Heart	Phytrol 18S	Murmur and carotid artery murmur	1
Gastrointestinal	Placebo	Stoma	1
Dermatological	Phytrol 18S	Xanthelasmas	1
		Some nevi on chest	1
		Psoriasis all over body	1
Other	Placebo	Scar from bypass surgery	1

4.1.5 Lipid Values

Baseline total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides levels in the two groups are shown in Table 4.1.9, together with the LDL/HDL cholesterol ratio. There was no significant difference between groups with respect to any of the five parameters.

Table 4.1.9: Baseline lipid values by treatment group

Parameter/Group	Mean	(95% C.I.)	Minimum	Median	Maximum	N
Total Cholesterol						
Phytrol 18S	6.76	(6.48 , 7.04)	5.23	6.76	8.40	31
Placebo	6.64	(6.36 , 6.91)	5.60	6.73	7.86	31
LDL Cholesterol						
Phytrol 18S	4.70	(4.46 , 4.94)	3.64	4.69	6.05	31
Placebo	4.57	(4.33 , 4.80)	3.49	4.52	5.77	31
HDL Cholesterol						
Phytrol 18S	1.33	(1.21 , 1.45)	1.07	1.23	2.39	31
Placebo	1.46	(1.33 , 1.58)	0.95	1.35	2.55	31
LDL/HDL Ratio						
Phytrol 18S	3.67	(3.36 , 3.97)	1.65	3.58	5.32	31
Placebo	3.35	(3.04 , 3.65)	1.84	3.52	4.91	31
Triglycerides						
Phytrol 18S	1.60	(1.38 , 1.82)	0.57	1.42	3.60	31
Placebo	1.33	(1.12 , 1.55)	0.57	1.35	2.39	31

4.1.6 Other Laboratory Values

Baseline hematology and chemistry results are shown in section 5.2, together with the post-treatment results. At baseline, there was no significant difference between treatment groups on any of the hematology or chemistry parameters measured.

4.2 Compliance

Compliance has been measured by the ratio of the number of chocolates consumed to the number that should have been consumed, the latter being calculated as three per day for 28 days, i.e. 84.

Table 4.2.1 shows summary statistics for subject compliance expressed as a percentage, and Table 4.2.2 shows the proportion of subjects who were at least 100% compliant, in that they consumed at least 84 chocolates, by treatment group. More than one-half of subjects given the placebo were 100% compliant, as compared with approximately one-third of those given Phytrol 18S. However, there was no statistically significant difference between the two groups.

Table 4.2.1 : Subject compliance (%), by treatment group

Group	Mean	(95% C.I.)	Minimum	Median	Maximum	N
Phytrol 18S	96.7	(94.3,99.0)	85.7	97.6	110.7	31
Placebo	99.4	(96.6,102.2)	84.5	100.0	115.5	31

Table 4.2.2: Subjects who consumed at least 84 chocolates, by treatment group

	Phytrol 18S		Placebo	
	N	(%)	N	(%)
Consumed at least 84 chocolates	11	35.5	16	51.6

4.3 Efficacy Results

Table 4.3.1 shows total cholesterol levels at Visits 4 and 5, the changes from baseline and the relative changes from baseline, by treatment group. Subjects randomized to Phytrol 18S had statistically significant absolute and relative decreases in total cholesterol levels between baseline and both post-treatment visits. At both Visit 4 and Visit 5, there were differences between the two groups in the total cholesterol level, the change in total cholesterol from

baseline, and the relative change in total cholesterol from baseline (Visit 4: $p < 0.005$, $p < 0.005$ and $p < 0.01$, respectively; Visit 5: all $p < 0.005$).

Table 4.3.1: Total cholesterol (mmol/L) post-treatment, by treatment group

Parameter/Group	Mean	(95% C.I.)	Minimum	Median	Maximum	N	Significance of difference from 0
Visit 4							
Phytrol 18S	6.32	(6.16 , 6.48)	5.12	6.31	7.47	30	-
Placebo	6.65	(6.49 , 6.80)	5.22	6.67	7.86	31	-
Visit 5							
Phytrol 18S	6.26	(6.08 , 6.44)	4.58	6.23	7.86	31	-
Placebo	6.67	(6.49 , 6.85)	5.07	6.72	7.99	31	-
Change at Visit 4							
Phytrol 18S	-0.36	(-0.52 , -0.21)	-1.10	-0.38	0.68	30	$p < 0.001$
Placebo	-0.04	(-0.19 , 0.12)	-0.77	-0.06	1.55	31	N.S.
Change at Visit 5							
Phytrol 18S	-0.44	(-0.62 , -0.26)	-1.55	-0.37	0.74	31	$p < 0.001$
Placebo	-0.02	(-0.20 , 0.16)	-0.94	-0.06	1.27	31	N.S.
Relative Change at Visit 4 (%)							
Phytrol 18S	-5.2	(-7.7 , -2.6)	-17.1	-5.0	10.4	30	$p < 0.001$
Placebo	-0.3	(-2.8 , 2.2)	-12.9	-0.8	24.8	31	N.S.
Relative Change at Visit 5 (%)							
Phytrol 18S	-6.4	(-9.3 , -3.5)	-23.0	-5.6	13.0	31	$p < 0.001$
Placebo	0.0	(-2.8 , 2.9)	-15.6	-1.1	20.8	31	N.S.

LDL cholesterol levels at Visits 4 and 5, changes from baseline and relative changes from baseline are shown in Table 4.3.2. Subjects given Phytrol 18S experienced significant absolute and relative decreases in LDL cholesterol levels between baseline and both post-treatment visits. The treated subjects also had lower LDL cholesterol levels at both Visit 4 and Visit 5, and greater decreases and relative decreases in LDL cholesterol than subjects given the placebo (Visit 4: all $p < 0.005$; Visit 5: all $p < 0.001$).

Table 4.3.2: LDL cholesterol (mmol/L) post-treatment, by treatment group

Parameter/Group	Mean	(95% C.I.)	Minimum	Median	Maximum	N	Significance of difference from 0
Visit 4							
Phytrol 18S	4.32	(4.16 , 4.47)	3.08	4.31	5.66	30	-
Placebo	4.68	(4.52 , 4.83)	3.54	4.65	5.64	31	-
Visit 5							
Phytrol 18S	4.15	(3.96 , 4.33)	2.46	4.27	5.56	31	-
Placebo	4.63	(4.44 , 4.81)	3.18	4.63	6.05	31	-
Change at Visit 4							
Phytrol 18S	-0.31	(-0.47 , -0.16)	-1.27	-0.26	0.91	30	$p < 0.001$
Placebo	0.05	(-0.11 , 0.20)	-0.80	0.07	1.38	31	N.S.
Change at Visit 5							
Phytrol 18S	-0.49	(-0.67 , -0.30)	-2.38	-0.41	0.86	31	$p < 0.001$
Placebo	-0.01	(-0.19 , 0.18)	-0.83	0.09	0.92	31	N.S.
Relative Change at Visit 4 (%)							
Phytrol 18S	-6.5	(-10.4 , -2.6)	-24.2	-5.5	21.1	30	$p < 0.005$
Placebo	2.1	(-1.7 , 6.0)	-15.8	1.4	34.4	31	N.S.
Relative Change at Visit 5 (%)							
Phytrol 18S	-10.3	(-14.5 , -6.0)	-49.1	-7.7	23.0	31	$p < 0.001$
Placebo	0.8	(-3.5 , 5.1)	-16.1	1.6	24.4	31	N.S.

Table 4.3.3 shows HDL cholesterol post-treatment, the change from baseline and the relative change from baseline, by treatment group. None of the changes was significantly different from 0, and there was no statistically significant difference between treatment groups with respect to any of the parameters.

The LDL/HDL ratio post-treatment and absolute and relative changes from baseline are summarized in Table 4.3.4. Subjects given Phytrol 18S had significant absolute and relative decreases in their LDL/HDL ratio post-treatment. They also had a lower LDL/HDL ratio post-treatment ($p < 0.05$), and greater absolute and relative decreases in their LDL/HDL ratio from baseline ($p < 0.05$ and $p < 0.005$, respectively) than subjects in the placebo group.

Table 4.3.3: HDL cholesterol (mmol/L) post-treatment, by treatment group

Parameter/Group	Mean	(95% C.I.)	Minimum	Median	Maximum	N	Significance of difference from 0
Post-Treatment							
Phytrol 18S	1.37	(1.31 , 1.44)	0.98	1.26	2.16	31	-
Placebo	1.36	(1.29 , 1.42)	0.81	1.36	2.44	31	-
Change Post-Treatment							
Phytrol 18S	-0.02	(-0.08 , 0.05)	-0.32	-0.05	1.05	31	N.S.
Placebo	-0.04	(-0.10 , 0.03)	-0.28	-0.03	0.30	31	N.S.
Relative Change Post-Treatment (%)							
Phytrol 18S	0.1	(-5.4 , 5.6)	-16.6	-4.1	94.0	31	N.S.
Placebo	-2.6	(-8.0 , 2.9)	-21.6	-2.6	27.0	31	N.S.

Table 4.3.4: LDL/HDL ratio post-treatment, by treatment group

Parameter/Group	Mean	(95% C.I.)	Minimum	Median	Maximum	N	Significance of difference from 0
Post-Treatment							
Phytrol 18S	3.24	(3.03 , 3.45)	1.58	3.34	5.28	31	-
Placebo	3.59	(3.38 , 3.80)	1.93	3.57	5.38	31	-
Change Post-Treatment							
Phytrol 18S	-0.27	(-0.48 , -0.06)	-2.16	-0.16	0.48	31	$p < 0.05$
Placebo	0.09	(-0.12 , 0.30)	-1.01	0.23	1.36	31	N.S.
Relative Change Post-Treatment (%)							
Phytrol 18S	-7.2	(-13.1 , -1.4)	-57.8	-4.1	13.9	31	$p < 0.05$
Placebo	5.3	(-0.6 , 11.2)	-20.5	8.3	33.8	31	N.S.

Table 4.3.5 shows triglyceride levels post-treatment, the change from baseline and the relative change from baseline. None of the changes differed from 0, and there was no significant difference between treatment groups.

Table 4.3.5: Triglycerides (mmol/L) post-treatment, by treatment group

Parameter/Group	Mean	(95% C.I.)	Minimum	Median	Maximum	N	Significance of difference from 0
Post-Treatment							
Phytrol 18S	1.53	(1.28 , 1.79)	0.62	1.28	9.07	31	-
Placebo	1.50	(1.24 , 1.75)	0.55	1.29	2.06	31	-
Change Post-Treatment							
Phytrol 18S	0.06	(-0.19 , 0.32)	-0.45	-0.05	5.47	31	N.S.
Placebo	0.03	(-0.23 , 0.28)	-0.42	-0.05	0.47	31	N.S.
Relative Change Post-Treatment (%)							
Phytrol 18S	1.4	(-7.8 , 10.5)	-27.3	-3.8	151.9	31	N.S.
Placebo	-0.2	(-9.4 , 8.9)	-26.6	-4.9	41.6	31	N.S.

5. Safety Analysis

5.1 Adverse Events

Fifteen (24%) subjects reported a total of 26 adverse events (AEs) after screening (Table 5.1.1). Ten (16%) subjects experienced one or more AEs after starting study treatment, for a total of 21 treatment-emergent events. There was no significant difference between treatment groups with respect to the proportion of subjects who experienced an AE at any time, nor with respect to the proportion of subjects who reported treatment-emergent adverse event(s).

Table 5.1.1: Subjects who experienced adverse event(s), by treatment group

	Phytrol 18S		Placebo	
	N	(%)	N	(%)
Any AE	8	(25.8)	7	(22.6)
Treatment-emergent AE	5	(16.1)	5	(16.1)

There were 23 unique AEs, and 19 unique treatment-emergent AEs, since some subjects reported the same AE more than once (Table 5.1.2).

Table 5.1.2: Numbers of unique adverse events, by treatment group

	Phytrol 18S	Placebo
Any AE	11	12
Treatment-emergent AE	8	11

Table 5.1.3 shows summaries of the 23 unique AEs reported after Visit 1 by treatment group and sex, type (clinical or laboratory) and body system, severity and relationship to study treatment. Fifteen (65%) of the AEs were clinical; six (40%) of these were gastrointestinal. The remaining eight events were clinically significant laboratory AEs. Overall, 19 (83%) of the AEs were mild, three (13%) were moderate and one (4%) was severe; 14 (61%) were recorded as definitely not or probably not related to study treatment, seven (30%) were considered possibly related to study treatment while only two (9%) were recorded as probably related to study treatment. The one severe AE, experienced by a patient taking Phytrol 18S, was recorded as definitely not related to study treatment. The only moderate AE in the placebo group and one of the two moderate AEs in the group randomized to Phytrol 18S were also recorded as definitely not related to study treatment, while the other moderate AE in the Phytrol 18S group was considered possibly related to study treatment. A full listing of the AEs is provided in Appendix 1.

Table 5.1.4 shows summaries of the 19 unique treatment-emergent AEs by treatment group and sex, type (clinical or laboratory) and body system, severity and relationship to study treatment. Thirteen (68%) of the AEs were clinical; six (46%) of these were gastrointestinal. The remaining six events were clinically significant laboratory AEs. Seventeen (89%) of the 19 treatment-emergent AEs were mild and the remaining two were moderate; 10 (53%) were recorded as definitely not or probably not related to study treatment, seven (37%) were considered possibly related to study treatment, while only two (11%) were recorded as probably related to study treatment. The single moderate AE (sleeplessness) among subjects given Phytrol 18S was considered possibly related to study treatment. All treatment-emergent AEs are listed in Appendix 1.

Table 5.1.3: Unique adverse events by treatment group and sex, type/body system, severity and relationship to study treatment

	Phytrol 18S		Placebo	
	N	(%)	N	(%)
Sex				
Male	3	(27.3)	7	(58.3)
Female	8	(72.7)	5	(41.7)
Type/Body System				
Clinical:				
HEENT	1	(9.1)	2	(16.7)
Skin	0	(0.0)	1	(8.3)
Respiratory	1	(9.1)	1	(8.3)
Gastrointestinal	3	(27.3)	3	(25.0)
Renal/urinary	1	(9.1)	0	(0.0)
Neurologic	1	(9.1)	0	(0.0)
Other	1	(9.1)	0	(0.0)
Laboratory	3	(27.3)	5	(41.7)
Severity				
Mild	8	(72.7)	11	(91.7)
Moderate	2	(18.2)	1	(8.3)
Severe	1	(9.1)	0	(0.0)
Related to study treatment				
Definitely not	5	(45.5)	3	(25.0)
Probably not	2	(18.2)	4	(33.3)
Possibly	3	(27.3)	4	(33.3)
Probably	1	(9.1)	1	(8.3)

Table 5.1.4: Unique treatment-emergent adverse events by treatment group and sex, type/body system, severity and relationship to study treatment

	Phytrol 18S		Placebo	
	N	(%)	N	(%)
Sex				
Male	3	(37.5)	7	(63.6)
Female	5	(62.5)	4	(36.4)
Type/Body System				
Clinical:				
HEENT	1	(12.5)	2	(18.2)
Skin	0	(0.0)	1	(9.1)
Respiratory	1	(12.5)	1	(9.1)
Gastrointestinal	3	(37.5)	3	(27.3)
Other	1	(12.5)	0	(0.0)
Laboratory	2	(25.0)	4	(36.4)
Severity				
Mild	7	(87.5)	10	(90.9)
Moderate	1	(12.5)	1	(9.1)
Related to study treatment				
Definitely not	2	(25.0)	2	(18.2)
Probably not	2	(25.0)	4	(36.4)
Possibly	3	(37.5)	4	(36.4)
Probably	1	(12.5)	1	(9.1)

5.2 Laboratory Parameters

5.2.1 Hematology

Hematology results at baseline (Visit 1) and Visit 5, together with the changes from baseline to Visit 5, are shown in Tables 5.2.1-5.2.10. There was no significant difference between treatment groups on any of the hematology parameters measured, either at baseline or at Visit 5. Subjects given placebo had decreased hematocrit ($p < 0.05$, Table 5.2.2), red blood cells ($p < 0.005$, Table 5.2.3), and monocytes ($p < 0.05$, Table 5.2.6) at the end of the treatment period. However, there was no significant difference between the two groups with respect to the changes in hematology parameters during treatment.

Table 5.2.1: Hemoglobin (mmol/L), by treatment group

Parameter/Group	Mean	(95% C.I.)	Minimum	Median	Maximum	N	Significance of difference from 0*
Baseline							
Phytrol 18S	8.56	(8.33 , 8.78)	7.29	8.54	9.66	31	-
Placebo	8.59	(8.38 , 8.80)	7.16	8.66	9.47	31	-
Post-Treatment							
Phytrol 18S	8.51	(8.30 , 8.72)	7.35	8.47	9.84	31	-
Placebo	8.57	(8.34 , 8.81)	6.98	8.60	9.59	31	-
Change Post-Treatment							
Phytrol 18S	-0.04	(-0.15 , 0.07)	-0.63	-0.13	0.74	31	N.S.
Placebo	-0.01	(-0.12 , 0.09)	-0.93	0.06	0.37	31	N.S.

* Wilcoxon matched pairs signed ranks test

Table 5.2.2: Hematocrit (l/l), by treatment group

Parameter/Group	Mean	(95% C.I.)	Minimum	Median	Maximum	N	Significance of difference from 0*
Baseline							
Phytrol 18S	0.41	(0.40 , 0.42)	0.35	0.40	0.49	31	-
Placebo	0.42	(0.41 , 0.43)	0.35	0.42	0.46	31	-
Post-Treatment							
Phytrol 18S	0.41	(0.40 , 0.42)	0.35	0.41	0.49	31	-
Placebo	0.41	(0.40 , 0.42)	0.31	0.41	0.47	31	-
Change Post-Treatment							
Phytrol 18S	0.00	(-0.01 , 0.01)	-0.04	0.00	0.06	31	N.S.
Placebo	-0.01	(-0.01 , 0.00)	-0.06	0.00	0.04	31	$p < 0.05$

* Wilcoxon matched pairs signed ranks test

Table 5.2.3: Red blood cells (10^{12}/l), by treatment group

Parameter/Group	Mean	(95% C.I.)	Minimum	Median	Maximum	N	Significance of difference from 0
Baseline							
Phytrol 18S	4.70	(4.57 , 4.83)	4.06	4.72	5.37	31	-
Placebo	4.70	(4.57 , 4.82)	4.10	4.68	5.27	31	-
Post-Treatment							
Phytrol 18S	4.66	(4.55 , 4.76)	4.12	4.71	5.05	31	-
Placebo	4.60	(4.46 , 4.74)	3.70	4.66	5.25	31	-
Change Post-Treatment							
Phytrol 18S	-0.05	(-0.11 , 0.02)	-0.33	-0.08	0.26	31	N.S.
Placebo	-0.10	(-0.16 , -0.03)	-0.58	-0.08	0.21	31	$p < 0.005$

Table 5.2.4: White blood cells (10^{9}/l), by treatment group

Parameter/Group	Mean	(95% C.I.)	Minimum	Median	Maximum	N	Significance of difference from 0*
Baseline							
Phytrol 18S	6.3	(5.6 , 6.9)	3.3	5.9	12.7	31	-
Placebo	5.8	(5.2 , 6.4)	3.1	5.4	10.1	31	-
Post-Treatment							
Phytrol 18S	6.2	(5.5 , 6.9)	3.3	5.6	12.0	31	-
Placebo	6.0	(5.3 , 6.6)	3.1	5.7	11.2	31	-
Change Post-Treatment							
Phytrol 18S	-0.1	(-0.6 , 0.4)	-3.5	-0.1	4.0	31	N.S.
Placebo	0.2	(-0.2 , 0.6)	-2.0	-0.1	4.5	31	N.S.

* Wilcoxon matched pairs signed ranks test

Table 5.2.5: Lymphocytes (%), by treatment group

Parameter/Group	Mean	(95% C.I.)	Minimum	Median	Maximum	N	Significance of difference from 0
Baseline							
Phytrol 18S	32.8	(30.0 , 35.5)	19.1	32.4	50.3	31	-
Placebo	34.6	(31.9 , 37.3)	21.3	33.3	50.2	31	-
Post-Treatment							
Phytrol 18S	33.1	(30.7 , 35.5)	19.3	33.7	45.2	31	-
Placebo	35.0	(32.7 , 37.4)	19.2	34.1	48.0	31	-
Change Post-Treatment							
Phytrol 18S	0.4	(-2.3 , 3.0)	-16.4	-0.4	21.2	31	N.S.
Placebo	0.4	(-2.5 , 3.3)	-19.9	1.3	22.2	31	N.S.

Table 5.2.6: Monocytes (%), by treatment group

Parameter/Group	Mean	(95% C.I.)	Minimum	Median	Maximum	N	Significance of difference from 0
Baseline							
Phytrol 18S	6.49	(5.93 , 7.05)	3.00	6.40	10.60	31	-
Placebo	6.91	(6.22 , 7.59)	3.00	6.70	10.70	31	-
Post-Treatment							
Phytrol 18S	6.18	(5.66 , 6.70)	3.40	5.80	9.80	31	-
Placebo	6.26	(5.70 , 6.83)	3.50	6.20	10.90	31	-
Change Post-Treatment							
Phytrol 18S	-0.31	(-0.77 , 0.16)	-3.10	-0.10	2.70	31	N.S.
Placebo	-0.64	(-1.27 , -0.01)	-4.70	-0.70	4.60	31	$p < 0.05$

Table 5.2.7: Basophils (%), by treatment group

Parameter/Group	Mean	(95% C.I.)	Minimum	Median	Maximum	N	Significance of difference from 0*
Baseline							
Phytrol 18S	0.64	(0.56 , 0.72)	0.20	0.60	1.00	31	-
Placebo	0.96	(0.50 , 1.42)	0.20	0.70	7.50	31	-
Post-Treatment							
Phytrol 18S	0.69	(0.59 , 0.79)	0.20	0.70	1.20	31	-
Placebo	0.83	(0.73 , 0.93)	0.30	0.80	1.50	30	-
Change Post-Treatment							
Phytrol 18S	0.05	(-0.04 , 0.14)	-0.30	0.00	0.60	31	N.S.
Placebo	-0.14	(-0.60 , 0.32)	-6.50	0.10	0.70	30	N.S.

* Wilcoxon matched pairs signed ranks test

Table 5.2.8: Eosinophils (%), by treatment group

Parameter/Group	Mean	(95% C.I.)	Minimum	Median	Maximum	N	Significance of difference from 0*
Baseline							
Phytrol 18S	2.50	(1.97 , 3.03)	0.70	2.20	7.40	31	-
Placebo	2.76	(2.14 , 3.39)	1.10	2.40	10.00	31	-
Post-Treatment							
Phytrol 18S	2.43	(2.04 , 2.81)	0.60	2.40	5.10	31	-
Placebo	3.08	(2.38 , 3.78)	1.00	2.80	9.70	31	-
Change Post-Treatment							
Phytrol 18S	-0.07	(-0.52 , 0.37)	-4.70	0.20	1.90	31	N.S.
Placebo	0.32	(-0.15 , 0.78)	-2.70	0.10	4.90	31	N.S.

* Wilcoxon matched pairs signed ranks test

Table 5.2.9: Bands (%), by treatment group

Parameter/Group	Mean	(95% C.I.)	Minimum	Median	Maximum	N	Significance of difference from 0
Baseline							
Phytrol 18S	57.6	(54.8 , 60.5)	39.5	58.3	72.9	31	-
Placebo	55.0	(52.0 , 58.0)	37.9	55.3	71.0	31	-
Post-Treatment							
Phytrol 18S	57.6	(55.0 , 60.1)	46.3	57.7	72.6	31	-
Placebo	54.8	(52.2 , 57.4)	38.7	55.4	70.9	31	-
Change Post-Treatment							
Phytrol 18S	-0.0	(-2.9 , 2.8)	-22.2	0.9	15.9	31	N.S.
Placebo	-0.2	(-3.1 , 2.8)	-16.7	-0.5	21.4	31	N.S.

Table 5.2.10: Platelets (10^9/l), by treatment group

Parameter/Group	Mean	(95% C.I.)	Minimum	Median	Maximum	N	Significance of difference from 0*
Baseline							
Phytrol 18S	231.7	(211.1 , 252.3)	118.0	230.0	360.0	31	-
Placebo	237.1	(216.5 , 257.8)	136.0	239.0	335.0	31	-
Post-Treatment							
Phytrol 18S	223.6	(205.5 , 241.6)	101.0	223.0	328.0	31	-
Placebo	234.9	(214.1 , 255.7)	123.0	246.0	330.0	31	-
Change Post-Treatment							
Phytrol 18S	-8.1	(-19.6 , 3.4)	-137.0	-5.0	46.0	31	N.S.
Placebo	-2.2	(-9.7 , 5.2)	-34.0	-6.0	41.0	31	N.S.

* Wilcoxon matched pairs signed ranks test

Table A1.2: Treatment-Emergent Events by Treatment Group (continued)

PLACEBO

Subject Number	Sex	Age	Event	Start Date	Stop Date	Ongoing	Severity	Relationship to Study Drug
3060	M	50	Increased xanthalasma	10JUN99	25JUN99	No	Mild	Probably
3094	M	51	Common cold	07JUL99	16JUL99	No	Moderate	Definitely not
3098	F	53	Headache	08JUL99	09JUL99	No	Mild	Probably not
3111	F	50	Fluid stools	20JUN99	.	No	Mild	Possibly
3111	F	50	Nausea	20JUN99	20JUN99	No	Mild	Possibly
3127	F	56	LDH increased	06JUL99	06JUL99	No	Mild	Possibly
3134	M	52	Diarrhea	05JUL99	06JUL99	No	Mild	Possibly
3134	M	52	Diarrhea	12JUL99	12JUL99	No	Mild	Possibly
3134	M	52	Glucose increased	19JUL99	19JUL99	No	Mild	Definitely not
3137	M	71	Blurred vision	03JUL99	05JUL99	No	Mild	Probably not
3137	M	71	RBC microcytes	05JUL99	05JUL99	No	Mild	Probably not
3137	M	71	Urea increased	12JUL99	12JUL99	No	Mild	Probably not

5.2.2 Chemistry

Chemistry results at baseline (Visit 1) and at Visit 5, together with the changes from baseline to Visit 5, are shown in Tables 5.2.11-5.2.21. There was no significant difference between treatment groups on any of the chemistry parameters measured, either at baseline or at Visit 5. Subjects randomized to Phytrol 18S had a highly significant decrease in creatinine levels during treatment ($p < 0.001$, Table 5.2.12), an increase in uric acid ($p < 0.05$, Table 5.2.13), and a decrease in alkaline phosphatase ($p < 0.05$, Table 5.2.17). Subjects given placebo had a similar decrease in creatinine during treatment ($p < 0.001$), as well as a decrease in glucose levels ($p < 0.005$, Table 5.2.19), and an increase in testosterone levels ($p < 0.05$, Table 5.2.21). However, none of the changes in the chemistry parameters differed significantly between the two groups.

Table 5.2.11: Urea (mmol/L), by treatment group

Parameter/Group	Mean	(95% C.I.)	Minimum	Median	Maximum	N	Significance of difference from 0
Baseline							
Phytrol 18S	5.66	(5.31 , 6.00)	3.83	5.66	8.49	31	-
Placebo	5.66	(5.28 , 6.03)	3.50	5.66	7.99	31	-
Post-Treatment							
Phytrol 18S	6.04	(5.51 , 6.58)	3.33	5.83	8.82	31	-
Placebo	5.87	(5.37 , 6.37)	3.33	5.49	9.32	31	-
Change Post-Treatment							
Phytrol 18S	0.39	(-0.06 , 0.84)	-1.50	0.00	2.99	31	N.S.
Placebo	0.22	(-0.17 , 0.60)	-1.83	0.00	2.83	31	N.S.

Table 5.2.12: Creatinine (μmol/L), by treatment group

Parameter/Group	Mean	(95% C.I.)	Minimum	Median	Maximum	N	Significance of difference from 0
Baseline							
Phytrol 18S	94.9	(90.7 , 99.1)	66.3	98.1	114.0	31	-
Placebo	93.4	(88.6 , 98.2)	51.3	92.8	122.9	31	-
Post-Treatment							
Phytrol 18S	81.2	(76.8 , 85.5)	59.2	81.3	108.7	31	-
Placebo	80.0	(74.6 , 85.5)	46.0	79.6	111.4	31	-
Change Post-Treatment							
Phytrol 18S	-13.7	(-16.5 , -11.0)	-27.4	-14.1	4.4	31	$p < 0.001$
Placebo	-13.3	(-16.3 , -10.4)	-24.7	-15.0	5.3	31	$p < 0.001$

Table 5.2.13: Uric acid (mmol/L), by treatment group

Parameter/Group	Mean	(95% C.I.)	Minimum	Median	Maximum	N	Significance of difference from 0
Baseline							
Phytrol 18S	0.31	(0.29 , 0.34)	0.19	0.31	0.42	31	-
Placebo	0.33	(0.31 , 0.34)	0.23	0.33	0.43	31	-
Post-Treatment							
Phytrol 18S	0.33	(0.30 , 0.35)	0.20	0.33	0.43	31	-
Placebo	0.33	(0.32 , 0.35)	0.26	0.33	0.43	31	-
Change Post-Treatment							
Phytrol 18S	0.01	(0.00 , 0.03)	-0.04	0.01	0.09	31	$p < 0.05$
Placebo	0.01	(-0.00 , 0.02)	-0.04	0.01	0.09	31	N.S.

Table 5.2.14: Total bilirubin (μmol/L), by treatment group

Parameter/Group	Mean	(95% C.I.)	Minimum	Median	Maximum	N	Significance of difference from 0*
Baseline							
Phytrol 18S	9.5	(8.6 , 10.5)	4.1	9.7	16.1	31	-
Placebo	10.2	(8.4 , 12.0)	4.4	9.7	25.1	31	-
Post-Treatment							
Phytrol 18S	8.7	(7.7 , 9.7)	4.8	7.9	16.1	31	-
Placebo	9.7	(8.3 , 11.1)	4.6	8.7	19.5	31	-
Change Post-Treatment							
Phytrol 18S	-0.8	(-1.7 , 0.1)	-8.1	-1.2	4.6	31	N.S.
Placebo	-0.5	(-1.5 , 0.5)	-5.6	0.5	3.2	31	N.S.

* Wilcoxon matched pairs signed ranks test

Table 5.2.15: AST (U/l), by treatment group

Parameter/Group	Mean	(95% C.I.)	Minimum	Median	Maximum	N	Significance of difference from 0*
Baseline							
Phytrol 18S	20.3	(18.9 , 21.8)	14.0	20.0	27.0	31	-
Placebo	20.8	(18.6 , 22.9)	8.0	21.0	35.0	31	-
Post-Treatment							
Phytrol 18S	20.6	(19.1 , 22.2)	13.0	21.0	29.0	31	-
Placebo	20.8	(18.7 , 22.9)	9.0	20.0	32.0	31	-
Change Post-Treatment							
Phytrol 18S	0.3	(-0.8 , 1.5)	-5.0	-1.0	7.0	31	N.S.
Placebo	0.0	(-1.8 , 1.8)	-11.0	-1.0	16.0	31	N.S.

* Wilcoxon matched pairs signed ranks test

Table 5.2.16: ALT (U/l), by treatment group

Parameter/Group	Mean	(95% C.I.)	Minimum	Median	Maximum	N	Significance of difference from 0*
Baseline							
Phytrol 18S	19.6	(17.1 , 22.2)	11.0	19.0	43.0	31	-
Placebo	23.2	(18.2 , 28.2)	10.0	19.0	77.0	31	-
Post-Treatment							
Phytrol 18S	20.5	(17.6 , 23.4)	10.0	18.0	42.0	31	-
Placebo	22.1	(17.3 , 27.0)	8.0	18.0	69.0	31	-
Change Post-Treatment							
Phytrol 18S	0.9	(-0.9 , 2.7)	-7.0	0.0	13.0	31	N.S.
Placebo	-1.1	(-3.8 , 1.6)	-25.0	-2.0	19.0	31	N.S.

* Wilcoxon matched pairs signed ranks test

Table 5.2.17: Alkaline phosphatase (U/l), by treatment group

Parameter/Group	Mean	(95% C.I.)	Minimum	Median	Maximum	N	Significance of difference from 0
Baseline							
Phytrol 18S	158.5	(141.9 , 175.2)	104.0	151.0	298.0	31	-
Placebo	167.8	(150.7 , 184.8)	93.0	163.0	289.0	31	-
Post-Treatment							
Phytrol 18S	153.0	(136.6 , 169.4)	90.0	143.0	289.0	31	-
Placebo	164.3	(148.9 , 179.6)	84.0	162.0	256.0	31	-
Change Post-Treatment							
Phytrol 18S	-5.6	(-9.8 , -1.3)	-42.0	-6.0	24.0	31	$p < 0.05$
Placebo	-3.5	(-8.5 , 1.5)	-54.0	-4.0	16.0	31	N.S.

Table 5.2.18: LDH (U/l), by treatment group

Parameter/Group	Mean	(95% C.I.)	Minimum	Median	Maximum	N	Significance of difference from 0*
Baseline							
Phytrol 18S	334.6	(319.1 , 350.1)	213.0	334.0	423.0	31	-
Placebo	327.2	(314.5 , 339.9)	261.0	325.0	411.0	31	-
Post-Treatment							
Phytrol 18S	341.5	(320.0 , 363.1)	219.0	336.0	485.0	31	-
Placebo	341.0	(322.6 , 359.3)	260.0	334.0	552.0	31	-
Change Post-Treatment							
Phytrol 18S	6.9	(-8.4 , 22.3)	-100.0	3.0	126.0	31	N.S.
Placebo	13.8	(-5.2 , 32.8)	-52.0	3.0	247.0	31	N.S.

* Wilcoxon matched pairs signed ranks test

Table 5.2.19: Glucose (mmol/L), by treatment group

Parameter/Group	Mean	(95% C.I.)	Minimum	Median	Maximum	N	Significance of difference from 0
Baseline							
Phytrol 18S	5.07	(4.89 , 5.25)	4.38	5.00	6.55	31	-
Placebo	5.20	(4.96 , 5.45)	4.05	5.00	6.88	31	-
Post-Treatment							
Phytrol 18S	4.93	(4.76 , 5.10)	3.94	4.88	6.38	31	-
Placebo	4.98	(4.81 , 5.16)	4.00	4.94	5.94	31	-
Change Post-Treatment							
Phytrol 18S	-0.14	(-0.30 , 0.02)	-1.33	-0.11	0.45	31	N.S.
Placebo	-0.22	(-0.36 , -0.08)	-1.33	-0.17	0.56	31	$p < 0.005$

Table 5.2.20: Thyroid stimulating hormone at baseline, by treatment group

Parameter/Group	Mean	(95% C.I.)	Minimum	Median	Maximum	N
Phytrol 18S	1.99	(1.49 , 2.49)	0.42	1.87	8.09	31
Placebo	1.97	(1.64 , 2.31)	0.60	1.86	5.33	31

Table 5.2.21: Testosterone (nmol/L), by treatment group

Parameter/Group	Mean	(95% C.I.)	Minimum	Median	Maximum	N	Significance of difference from 0
Baseline							
Phytrol 18S	18.08	(14.22 , 21.94)	7.46	17.92	27.14	12	-
Placebo	17.51	(15.38 , 19.65)	10.58	16.83	28.14	18	-
Post-Treatment							
Phytrol 18S	19.70	(16.37 , 23.03)	10.06	19.78	25.96	11	-
Placebo	18.92	(16.71 , 21.12)	12.77	18.45	29.25	16	-
Change Post-Treatment							
Phytrol 18S	1.26	(-1.00 , 3.51)	-5.07	1.14	7.46	11	N.S.
Placebo	1.57	(0.07 , 3.06)	-3.64	1.89	6.56	16	$p < 0.05$

5.3 Weight and Blood Pressure

5.3.1 Weight

Table 5.3.1 shows the subjects' weight post-treatment, by sex and treatment group. There was no significant difference between treatment groups at Visit 5, either for all subjects or for male or female subjects. The subjects' change in weight over the treatment period is summarized in Table 5.3.2. None of the changes, whether in male subjects, female subjects, or all subjects, was significantly different from 0, and there was no significant difference between the Phytrol 18S and placebo groups.

Table 5.3.3 shows BMI post-treatment and the change in BMI from baseline. The very small decreases from baseline were not significantly different from 0 in either treatment group, and there was no significant difference between groups with respect to either the post-treatment value or the change from baseline.

Table 5.3.1 : Weight (kg) of subjects post-treatment, by sex and treatment group

Sex/Group	Mean	(95% C.I.)	Minimum	Median	Maximum	N
Males						
Phytrol 18S	76.1	(69.1 , 83.1)	60.0	76.3	101.0	12
Placebo	78.9	(73.9 , 83.9)	64.0	80.0	100.0	18
Females						
Phytrol 18S	72.4	(66.6 , 78.1)	59.0	68.6	107.0	19
Placebo	70.1	(63.7 , 76.4)	57.0	66.0	87.0	13
All Subjects						
Phytrol 18S	73.8	(69.6 , 78.1)	59.0	70.0	107.0	31
Placebo	75.2	(71.2 , 79.2)	57.0	74.0	100.0	31

Table 5.3.2: Change in weight (kg) post-treatment, by sex and treatment group

Sex/Group	Mean	(95% C.I.)	Minimum	Median	Maximum	N
Males						
Phytrol 18S	-1.1	(-3.2 , 0.9)	-9.7	-0.2	2.2	12
Placebo	-0.2	(-0.6 , 0.1)	-2.0	-0.3	1.3	18
Females						
Phytrol 18S	0.1	(-0.4 , 0.5)	-1.6	0.0	2.3	19
Placebo	-0.3	(-0.8 , 0.2)	-1.3	-0.3	2.0	13
All Subjects						
Phytrol 18S	-0.4	(-1.2 , 0.4)	-9.7	0.0	2.3	31
Placebo	-0.3	(-0.6 , 0.0)	-2.0	-0.3	2.0	31

Table 5.3.3 : BMI post-treatment and change from baseline, by treatment group

Parameter/Group	Mean	(95% C.I.)	Minimum	Median	Maximum	N
Post-Treatment						
Phytrol 18S	25.2	(24.1 , 26.3)	19.6	24.7	34.9	31
Placebo	25.3	(24.2 , 26.3)	21.4	24.1	32.1	31
Change from Baseline						
Phytrol 18S	-0.1	(-0.4 , 0.1)	-3.2	0.0	0.8	31
Placebo	-0.1	(-0.2 , 0.0)	-0.6	-0.1	0.7	31

5.3.2 Blood Pressure

Systolic and diastolic blood pressure at Visit 5 are shown in Table 5.3.4. There was no significant difference between treatment groups.

Table 5.3.4 : Blood pressure (mm Hg) post-treatment, by treatment group

Parameter/Group	Mean	(95% C.I.)	Minimum	Median	Maximum	N
Systolic BP						
Phytrol 18S	125.4	(120.0 , 130.8)	100.0	125.0	150.0	31
Placebo	129.5	(124.5 , 134.5)	110.0	130.0	160.0	31
Diastolic BP						
Phytrol 18S	81.0	(77.8 , 84.1)	65.0	80.0	100.0	31
Placebo	81.9	(78.7 , 85.0)	70.0	80.0	100.0	31

Table 5.3.5 shows changes in systolic and diastolic blood pressure from baseline. Subjects given Phytrol 18S experienced significant decreases in both systolic and diastolic blood pressure during treatment. However, there was no significant difference between treatment groups.

Table 5.3.5 : Change in blood pressure (mm Hg) post-treatment, by treatment group

Parameter/Group	Mean	(95% C.I.)	Minimum	Median	Maximum	N	Significance of difference from 0
Systolic BP							
Phytrol 18S	-6.6	(-10.7 , -2.5)	-23.3	-7.3	18.7	31	$p < 0.005$
Placebo	-0.9	(-4.9 , 3.2)	-22.7	0.0	18.3	31	N.S.
Diastolic BP							
Phytrol 18S	-2.4	(-4.2 , -0.7)	-12.7	-3.0	8.7	31	$p < 0.01$
Placebo	-0.6	(-3.1 , 1.8)	-14.7	-1.0	11.7	31	N.S.

5.4 Findings on Physical Examination

None of the subjects had abnormal findings on physical examination at Visit 5 which had not been present at Visit 2.

6. Phytosterols

Table 6.1 shows lathosterol values at baseline and Visits 4 and 5, and the absolute and relative changes from baseline to Visits 4 and 5. There was no difference between the two groups at baseline, and no significant change in lathosterol levels during treatment in the placebo group. Subjects given Phytrol 18S experienced significant absolute and relative increases in lathosterol levels at Visit 5. However, there was no difference between the two groups either in lathosterol levels or in the absolute or relative changes in these levels at Visit 4 or Visit 5.

Table 6.1: Lathosterol values by treatment group

Parameter/Group	Mean	(95% C.I.)	Minimum	Median	Maximum	N	Significance of difference from 0
Baseline							
Phytrol 18S	6.96	(5.89 , 8.04)	2.05	5.75	15.64	29	-
Placebo	6.06	(4.99 , 7.14)	2.12	5.44	11.79	29	-
Visit 4							
Phytrol 18S	6.90	(6.34 , 7.47)	3.09	5.85	14.51	28	-
Placebo	6.82	(6.24 , 7.39)	2.43	5.04	13.11	27	-
Visit 5							
Phytrol 18S	7.58	(6.93 , 8.23)	2.97	6.81	18.02	29	-
Placebo	6.89	(6.21 , 7.57)	2.68	6.15	13.00	27	-
Change at Visit 4							
Phytrol 18S	0.35	(-0.22 , 0.91)	-2.86	0.16	2.83	28	N.S.
Placebo	0.26	(-0.31 , 0.83)	-2.00	-0.20	3.69	27	N.S.
Change at Visit 5							
Phytrol 18S	0.94	(0.29 , 1.59)	-5.03	0.54	5.23	29	$p < 0.01$
Placebo	0.25	(-0.43 , 0.93)	-2.89	0.07	3.36	27	N.S.
Relative Change at Visit 4 (%)							
Phytrol 18S	8.5	(-0.3 , 17.3)	-30.9	3.3	50.9	28	N.S.
Placebo	4.3	(-4.7 , 13.3)	-29.3	-4.2	56.7	27	N.S.
Relative Change at Visit 5 (%)							
Phytrol 18S	17.1	(8.0 , 26.2)	-32.2	9.8	85.9	29	$p < 0.001$
Placebo	5.0	(-4.4 , 14.5)	-24.5	1.2	42.5	27	N.S.

Table 6.2 shows campesterol values at baseline and Visits 4 and 5, and the absolute and relative changes from baseline to Visits 4 and 5. There was no difference between the two groups at baseline, and no significant change in campesterol levels during treatment in the placebo group. Subjects given Phytrol 18S experienced significant absolute and relative increases at both Visit 4 and Visit 5. There were highly significant differences between the two groups with respect to campesterol levels at both post-treatment visits, and in the absolute and relative changes in campesterol levels from baseline to both these visits (all $p < 0.001$).

Table 6.2: Campesterol values by treatment group

Parameter/Group	Mean	(95% C.I.)	Minimum	Median	Maximum	N	Significance of difference from 0
Baseline							
Phytrol 18S	11.35	(9.62 , 13.08)	4.44	10.67	18.38	29	-
Placebo	13.25	(11.52 , 14.98)	3.82	11.64	24.19	29	-
Visit 4							
Phytrol 18S	17.59	(16.74 , 18.43)	8.29	16.06	26.78	28	-
Placebo	12.57	(11.71 , 13.43)	5.34	12.83	25.22	27	-
Visit 5							
Phytrol 18S	17.72	(16.81 , 18.64)	8.21	16.86	24.46	29	-
Placebo	12.78	(11.83 , 13.73)	4.70	11.76	25.00	27	-
Change at Visit 4							
Phytrol 18S	5.39	(4.54 , 6.23)	0.51	5.35	10.06	28	$p < 0.001$
Placebo	0.37	(-0.49 , 1.23)	-3.67	0.67	4.37	27	N.S.
Change at Visit 5							
Phytrol 18S	5.49	(4.58 , 6.41)	0.28	4.98	11.74	29	$p < 0.001$
Placebo	0.55	(-0.40 , 1.50)	-4.47	0.61	3.76	27	N.S.
Relative Change at Visit 4 (%)							
Phytrol 18S	52.7	(42.1 , 63.3)	3.6	46.7	112.9	28	$p < 0.001$
Placebo	6.1	(-4.7 , 16.8)	-29.9	3.8	114.5	27	N.S.
Relative Change at Visit 5 (%)							
Phytrol 18S	54.6	(43.7 , 65.6)	2.0	50.7	150.7	29	$p < 0.001$
Placebo	7.3	(-4.1 , 18.6)	-34.8	6.5	97.8	27	N.S.

Sitosterol levels at baseline and Visits 4 and 5, and the absolute and relative changes from baseline to Visits 4 and 5 are shown in Table 6.3. There was no significant difference between treatment groups at baseline. The placebo group experienced a small but significant absolute increase at Visit 4, while subjects given Phytrol 18S had significant absolute and relative increases at both visits. There were highly significant differences between treatment groups with respect to sitosterol levels at both post-treatment visits, and in the absolute and relative changes in sitosterol levels from baseline to both these visits (all $p < 0.001$).

Table 6.3: Sitosterol values by treatment group

Parameter/Group	Mean	(95% C.I.)	Minimum	Median	Maximum	N	Significance of difference from 0
Baseline							
Phytrol 18S	7.97	(6.83 , 9.11)	3.75	7.79	12.78	29	-
Placebo	8.96	(7.82 , 10.10)	2.11	7.80	16.45	29	-
Visit 4							
Phytrol 18S	14.30	(13.56 , 15.05)	6.78	13.85	22.67	28	-
Placebo	9.13	(8.38 , 9.89)	4.84	8.93	18.29	27	-
Visit 5							
Phytrol 18S	14.65	(13.76 , 15.55)	6.65	13.36	22.22	29	-
Placebo	9.21	(8.28 , 10.14)	4.46	8.64	17.50	27	-
Change at Visit 4							
Phytrol 18S	5.93	(5.19 , 6.68)	0.74	5.59	9.89	28	$p < 0.001$
Placebo	0.76	(0.00 , 1.52)	-1.67	0.94	4.41	27	$p < 0.05$
Change at Visit 5							
Phytrol 18S	6.24	(5.35 , 7.14)	0.61	6.03	13.20	29	$p < 0.001$
Placebo	0.80	(-0.13 , 1.73)	-1.72	0.55	4.67	27	N.S.
Relative Change at Visit 4 (%)							
Phytrol 18S	81.1	(65.3 , 96.9)	9.8	71 7	206.6	28	$p < 0.001$
Placebo	15.1	(-1.0 , 31.2)	-14.9	11.2	208.8	27	N.S.
Relative Change at Visit 5 (%)							
Phytrol 18S	84.5	(67.1 , 101.9)	10.1	76.7	219.5	29	$p < 0.001$
Placebo	15.8	(-2.2 , 33.8)	-26.0	5.8	221.3	27	N.S.

Table 6.4 shows correlations between the percentage change in total and LDL cholesterol at Visit 5, and campesterol and sitosterol levels at baseline, and absolute and relative changes in these levels between baseline and Visit 5. Among subjects given Phytrol 18S, the percentage change in total cholesterol at Visit 5 was positively correlated with the absolute change in sitosterol at Visit 5. In the placebo group, the percentage change in LDL cholesterol at Visit 5 was positively correlated with the absolute change and the relative change in both campesterol and sitosterol at Visit 5. None of the other correlation coefficients calculated was significantly different from 0.

Table 6.4: Correlations between Percent Change in Total/LDL Cholesterol at Visit 5 and Phytosterols at Baseline/Changes in Phytosterols at Visit 5

	Percent change in total cholesterol			Percent change in LDL cholesterol		
	r	Sign.*	N	r	Sign.*	N
Campesterol						
Placebo						
Baseline	-0.101	N.S.	29	-0.057	N.S.	29
Change at Visit 5	0.375	N.S.	27	0.396	$p < 0.05$	27
Percent change at Visit 5	0.375	N.S.	27	0.387	$p < 0.05$	27
Phytrol 18S						
Baseline	0.046	N.S.	29	0.040	N.S.	29
Change at Visit 5	0.239	N.S.	29	0.036	N.S.	29
Percent change at Visit 5	0.213	N.S.	29	0.020	N.S.	29
Both groups						
Baseline	0.032	N.S.	58	0.058	N.S.	58
Change at Visit 5	-0.149	N.S.	56	-0.255	N.S.	56
Percent change at Visit 5	-0.114	N.S.	56	-0.221	N.S.	56
Sitosterol						
Placebo						
Baseline	-0.122	N.S.	29	-0.031	N.S.	29
Change at Visit 5	0.369	N.S.	27	0.495	$p < 0.01$	27
Percent change at Visit 5	0.333	N.S.	27	0.438	$p < 0.05$	27
Phytrol 18S						
Baseline	0.186	N.S.	29	-0.042	N.S.	29
Change at Visit 5	0.384	$p < 0.05$	29	0.125	N.S.	29
Percent change at Visit 5	0.193	N.S.	29	0.133	N.S.	29
Both groups						
Baseline	0.071	N.S.	58	0.019	N.S.	58
Change at Visit 5	-0.126	N.S.	56	-0.220	N.S.	56
Percent change at Visit 5	-0.133	N.S.	56	-0.183	N.S.	56

*Significance of difference of correlation coefficient (r) from 0

Appendix 1 : Adverse Events

Table A1.1: All Adverse Events by Treatment Group

PHYTROL 18S

Subject Number	Sex	Age	Event	Start Date	Stop Date	Ongoing	Severity	Relationship to Study Drug
3007	F	46	Hayfever	10JUN99	.	Yes	Mild	Definitely not
3009	F	44	Headache	02JUN99	05JUN99	No	Mild	Probably not
3009	F	44	Nausea	02JUN99	05JUN99	No	Mild	Probably not
3039	F	54	Urinary tract infection	26MAY99	04JUN99	No	Moderate	Definitely not
3059	F	61	Loose stools after eating chocolate	25MAY99	22JUN99	No	Mild	Probably
3103	F	63	Ataxia	30MAY99	02JUN99	No	Severe	Definitely not
3117	M	58	Sleeplessness	18JUN99	05JUL99	No	Moderate	Possibly
3131	F	64	Uric acid increased	23JUN99	23JUN99	No	Mild	Definitely not
3131	F	64	Urea increased	02AUG99	02AUG99	No	Mild	Possibly
3138	M	70	Feeling of full abdomen	20JUN99	.	Yes	Mild	Possibly
3138	M	70	Glucose decreased	22JUN99	22JUN99	No	Mild	Probably not
3138	M	70	Glucose decreased	29JUN99	29JUN99	No	Mild	Definitely not

Table A1.1: All Adverse Events by Treatment Group (continued)

PLACEBO

Subject Number	Sex	Age	Event	Start Date	Stop Date	Ongoing	Severity	Relationship to Study Drug
3060	M	50	Increased xanthalasma	10JUN99	25JUN99	No	Mild	Probably
3094	M	51	Common cold	07JUL99	16JUL99	No	Moderate	Definitely not
3098	F	53	Headache	08JUL99	09JUL99	No	Mild	Probably not
3111	F	50	Increased SGPT	18MAY99	18MAY99	No	Mild	Definitely not
3111	F	50	Fluid stools	20JUN99	.	No	Mild	Possibly
3111	F	50	Nausea	20JUN99	20JUN99	No	Mild	Possibly
3127	F	56	LDH increased	06JUL99	06JUL99	No	Mild	Possibly
3134	M	52	Glucose increased	16JUN99	16JUN99	No	Mild	Definitely not
3134	M	52	Diarrhea	05JUL99	06JUL99	No	Mild	Possibly
3134	M	52	Diarrhea	12JUL99	12JUL99	No	Mild	Possibly
3134	M	52	Glucose increased	19JUL99	19JUL99	No	Mild	Definitely not
3137	M	71	Blurred vision	03JUL99	05JUL99	No	Mild	Probably not
3137	M	71	RBC microcytes	05JUL99	05JUL99	No	Mild	Probably not
3137	M	71	Urea increased	12JUL99	12JUL99	No	Mild	Probably not

Table A1.2: Treatment-Emergent Events by Treatment Group

PHYTROL 18S

Subject Number	Sex	Age	Event	Start Date	Stop Date	Ongoing	Severity	Relationship to Study Drug
3007	F	46	Hayfever	10JUN99	.	Yes	Mild	Definitely not
3009	F	44	Headache	02JUN99	05JUN99	No	Mild	Probably not
3009	F	44	Nausea	02JUN99	05JUN99	No	Mild	Probably not
3059	F	61	Loose stools after eating chocolate	25MAY99	22JUN99	No	Mild	Probably
3117	M	58	Sleeplessness	18JUN99	05JUL99	No	Moderate	Possibly
3131	F	64	Urea increased	02AUG99	02AUG99	No	Mild	Possibly
3138	M	70	Feeling of full abdomen	20JUN99	.	Yes	Mild	Possibly
3138	M	70	Glucose decreased	22JUN99	22JUN99	No	Mild	Probably not
3138	M	70	Glucose decreased	29JUN99	29JUN99	No	Mild	Definitely not

APPENDIX 1

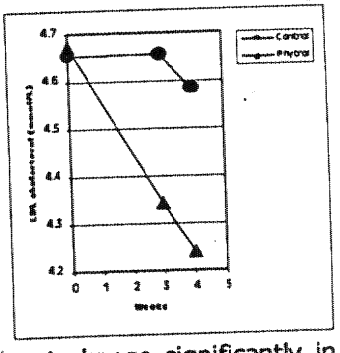
Appendix 1

Summary and Report on a Study of Phytosterols in Chocolate Confectionery

Daily consumption of non-esterified phytosterols from tall oil (Phytrol ™) in a chocolate matrix significantly lowers LDL cholesterol in moderately hypercholesterolemic individuals.

H. Pritchard*, JJP Kastelein[#], A. Stalenhoef[§], J. Jonker[¶]
*University of British Columbia; [#]Academic Medical Center, Amsterdam; [§]Academic Hospital, Nijmegen; [¶]Andromed, Rotterdam

Objective: To investigate the effect of dietary phytosterols on plasma lipid levels when consumed in chocolate. **Methods:** 70 men and women aged 21-70 were recruited to the study who had an LDL cholesterol greater than 3.5mmol/L. Non esterified phytosterols from Tall oil (Phytrol™) (0.6g) were incorporated into 10g chocolate minibars during. Subjects consumed 1 chocolate with each of three meals daily for 28 days. The final dose of total phytosterols was 1.8g/day. Fasting blood lipids were determined at weeks -2, -1 and at randomization and again at week 3 and 4. Control subjects consumed identical chocolates that did not contain the phytosterols. **Results:** 33 individuals in the Phytrol regime and 32 controls completed the study. The reduction of 0.43mmol/L of LDL was highly significant ($p<0.00003$) as determined by paired t-test. This represented a 8.9% reduction. LDL did not change significantly in the control group.



Conclusions: 1.8 g/day of non esterified phytosterols from Tall oil significantly reduce LDL cholesterol when consumed in chocolate.

Daily consumption of non-esterified phytosterols from tall oil (Phytrol™) in a chocolate matrix significantly lowers LDL cholesterol in moderately hypercholesterolemic individuals

H. Pritchard*, JJP Kastelein#, A. Stalenhoef§, J. Jonker¶

*University of British Columbia; #Academic Medical Center, Amsterdam; §Academic Hospital, Nijmegen; ¶Andromed, Rotterdam

Objective:

To investigate the effect of dietary phytosterols on plasma lipid levels when consumed in chocolate

Investigational compound:

- Phytrol™ - Forbes Medi-Tech/Novartis Consumer Health
- Unesterified phytosterols derived from Tall oil

Sitostanol:	*18%*
Sitosterol:	*50%*
Campesterol:	*3%*
Campestanol:	*16%*
Minor sterols:	*6%*
Other:	*2%*

Dosage:

- Mix in Phytrol™ during manufacture of chocolate
- 60 cal/bar (40 from fat)
- 1.8g per day of either placebo or Phytrol™ in 3 divided doses
- Phytosterols portions dispersed in 10g chocolate
- The chocolate containing the phytosterols or placebo consumed with meals 3 times per day

Cohort:

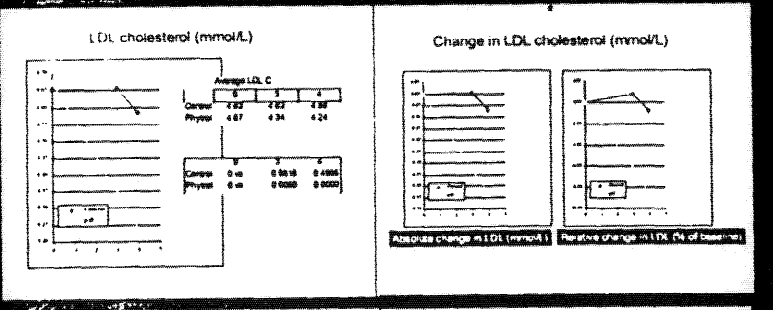
- 70 men and women aged 21-70
- LDL cholesterol greater than 3.5mmol/L

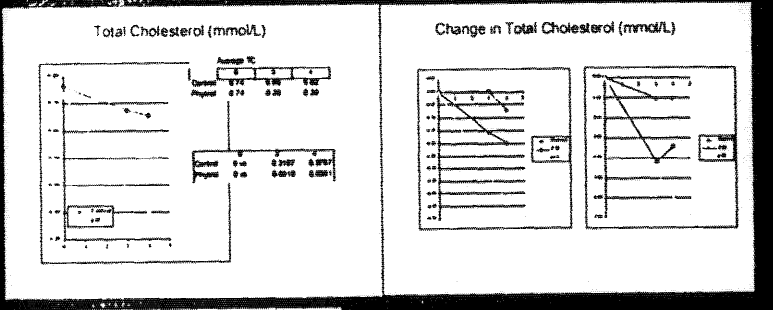
Experimental design

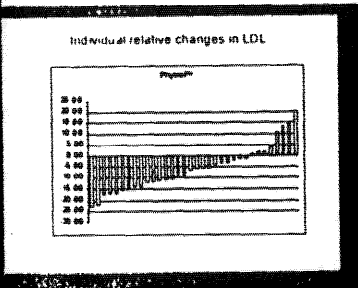
- Double blind, randomized, placebo controlled, parallel arm
- Subjects stratified according to LDL cholesterol levels
- 33 individuals in the Phytrol™ regime and 32 controls completed the study.

Forbes Medi-Tech INC.

Results:





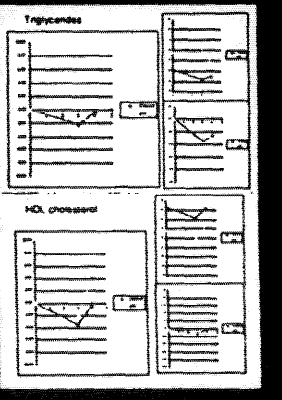


Conclusions:

- 1.8 g/day of non esterified phytosterols from Tall oil significantly reduce LDL cholesterol when consumed in chocolate.

Summary of findings

- Phytrol™ can be incorporated into high quality chocolate suitable for conducting clinical studies
- Consumption of the chocolate by the control group had no significant effect on plasma lipids
- Consumption of 1.8g Phytrol™ per day for 4 weeks by the Phytrol™ treated group significantly decreased both TC and LDL cholesterol
  - Total cholesterol by 6.0% ($p < 0.00009$)
  - LDL cholesterol by 8.83% ($p < 0.00003$)
- No significant effect on HDL cholesterol or Triglyceride levels was observed



FORBES MEDI-TECH INC

PROTOCOL CLF 9903

To Determine The Effect Of Tall Oil Derived Phytosterols (Phytrol™ 18S, Phytrol™ 33S) And Soya Derived Phytosterols (Soya PS – 33S) On The Plasma Lipid Levels Of Hypercholesterolemic Patients

Report on Per Protocol Comparison of Phytrol™ 18S and Placebo

16 March 2001

Elizabeth M. Belsey Ph.D., C.Stat.
SigmaPlus International
2770 S. Horseshoe Drive, Suite 5
Naples, FL 34104
USA

Appendix 2

An Expert Opinion Statement on the GRAS Status of Reducol™ (Phytrol™) Phytosterols Used as an Ingredient of Confectionery, Frozen Dessert, and Rice/Pasta Bowl Prepared Meal Products

An Expert Opinion Statement

GRAS Status of Reducol™ (Phytrol™) Phytosterols Used as an Ingredient of Confectionary, Frozen Dessert and Rice/Pasta Bowl Prepared Meal Products.

The undersigned, an independent recognized expert (hereinafter referred to as Expert), qualified by scientific training and relevant national and international experience to evaluate the safety of food and food ingredients, was requested by Novartis Consumer Health, Inc. on behalf of to determine the Generally Recognized as Safe (GRAS) status of the use of Reducol™ in confectionary products, frozen desserts and rice/pasta bowl prepared meal products. These products are to be manufactured by under license agreement with Novartis Consumer Health, Inc. which owns the marketing rights to Reducol™ in the United States.

Reducol™, originally named Phytrol™, is a tall-oil derived mixture of non-esterified phytosterols and stanols and would be incorporated as an ingredient into confectionary products, frozen desserts and rice/pasta bowl prepared meals at a concentration sufficient to provide a label-recommended composite total intake of 1.8 grams phytosterols and stanols daily through consumption of three servings from among the products (0.6 grams/serving), for the purpose of helping maintain healthy blood cholesterol levels.

Reducol™ is currently manufactured by Forbes Medi-Tech, Inc. at the Quest facility in Houston, Texas. Its use in a vegetable oil-based spread product at a level up to 12% by weight has been previously determined to be GRAS by Novartis Consumer Health, Inc. Novartis Consumer Health, Inc. subsequently submitted to FDA a notification (GRN39) that it had determined that Reducol™ (then termed Phytrol™) phytosterols are GRAS for use in a vegetable oil-based spread. FDA completed a review of the Novartis notification and on April 24, 2000 replied that it had no questions at that time regarding Novartis' determination.

Subsequent to Novartis' GRAS determination and FDA review of their notification, the manufacture of Reducol™ was relocated to the Quest facility in Houston, Texas. This resulted in a change in Reducol™'s profile of constituent phytosterols and necessitated a change in product specifications to accommodate a somewhat higher range of sitosterol content and lower ranges of content for sitostanol, campesterol, and campestanol. The Quest manufacturing process and resultant Reducol™ composition were reassessed by the Expert Panel originally requested by Novartis to evaluate Phytrol™'s GRAS status for use in a vegetable oil-based spread. The Panel, of which this Expert was a member, concluded that the change in manufacture and component specifications were inconsequential with respect to safety and physiologic properties

and that Reducol™, as manufactured at the Quest facility, continued to be GRAS when used in a vegetable oil-based spread at the level previously established.

In conducting the assessment of the GRAS status of the use of Reducol™ in the products, this Expert had available and considered the information and data made available during the previous considerations of Phytrol™'s GRAS status for use in a vegetable oil-based spread. A report providing detailed information regarding confectionary products, frozen deserts and rice/pasta bowl meal product compositions, intended and estimated consumer exposures, as well as, summary safety information updated through July 2001 facilitated the work of this Expert. In this regard, FDA's recent publication of an Interim Final Rule that authorized, with certain conditions, the use of a coronary heart disease health claim for plant sterol esters and plant stanol esters was considered relevant to this review. The Interim Final Rule, which is currently undergoing a second comment period, authorized the health claim for several product forms wherein a single product serving contains at least 0.65 grams of plant sterol esters or 1.7 grams of plant stanol esters. FDA did not raise safety concerns regarding consumer exposure to these levels of plant sterols and stanols arising through possible use of multiple products in which they may be incorporated. FDA's position is considered consistent with and supporting the safety and effectiveness of consuming phytosterols and stanols for the purpose of maintaining healthy cholesterol blood levels. Attention is drawn to the consistency of the proposed use of Reducol™ in the products with that authorized by FDA's health claim regulation.

With respect to critical evaluation of consumer exposure, this Expert considered both the manufacturers' recommendation for total daily Reducol™ intake as well as mean and 90th percentile estimates of Reducol™ exposure among users of the proposed products calculated on the basis of USDA CSFII (1994-96, 1998) data. The manufacturers' recommended consumption of up to the three servings daily from among the confectionary, frozen dessert and rice/pasta bowl prepared meal products (0.6 g/serving), providing a total of 1.8 grams of Reducol™ phytosterols and stanols, was determined to be similar to the intake associated with the recommended use of Reducol™ in a vegetable oil-based spread, as well as, similar in amount to other currently marketed products containing added phytosterols and stanols. This expert, found it reassuring that the magnitude of combined Reducol™ exposure to users of the proposed products, estimated using the CSFII data, demonstrated values less than or similar to the 1.8 grams recommended by the manufacturer (Table 1) and consistent with exposures from the existing array of phytosterol and stanol-containing products. This Expert considers the proposed products to represent an extension of the diversity of product choices available to consumers seeking to include

up to 1.8 grams per day of phytosterols and stanols in their diet for the purpose of maintaining healthy blood cholesterol levels.

Table 1 **Summary of Estimated Composite Daily Intake of Reducol™ Phytosterols from Products in the U.S. by Population Group (1994-1996, 1998 USDA CSFII Data)**

Population Group	Age Group (Years)	% Users	Actual # of Total Users	All-Users Consumption	
				Mean (g)	90th Percentile (g)
Infant	0-2	47.0	1505	036	0.81
Child	3-11	69.7	4289	0.63	1.32
Female Teenager	12-19	60.0	427	0.77	1.60
Male Teenager	12-19	54.2	389	0.96	2.06
Female Adult	20 and Up	49.9	2285	0.64	1.36
Male Adult	20 and Up	50.0	2433	0.85	1.82
Total Population	All Ages	53.2	11328	0.72	1.55

Accordingly, this Expert concluded that consumer exposure to Reducol™ from its use at specified levels in the proposed products is consistent with GRAS status for such use provided the products are clearly labeled to instruct consumers to choose up to three servings per day from among available products to achieve a total daily intake of 1.8 grams phytosterols and stanols.

With regard to other factors related to assessing the safety of the proposed uses, the composition of Reducol™ phytosterols and stanols to be incorporated into the confectionary, frozen dessert and rice/pasta bowl prepared meal products was determined to be the same as that incorporated into the vegetable oil-based spread and which has been determined by Novartis Consumer Health, Inc. to be GRAS with the full knowledge of the FDA. Following critical evaluation, no factors were identified which would suggest incorporation of Reducol™ into confectionary products, frozen desserts and rice/pasta bowl prepared meals, at specified levels, would materially alter its physiologic properties and effectiveness or create new or intensify previous safety considerations, including those regarding vitamin and nutrient availability.

Based on the critical evaluations discussed above and consistent with the authorized uses of phytosterols granted by FDA's Interim Final rule, this Expert has concluded that Reducol™ is generally recognized as safe (GRAS) by scientific procedures when used in the specified confectionary products, frozen desserts and rice/pasta bowl prepared meals for the purpose of helping to maintain a healthy blood cholesterol level, providing it is used in accordance with current good manufacturing practices (21CFR §182.1(b)) in an amount to provide 0.6 grams phytosterols and phytostanols per serving and that the product label instruct consumers to consume up to three servings per day from among all products to achieve a total daily intake of 1.8 grams.

10/15/01

W. Gary Flamm, Ph.D., FACT, F.A.T.S.
President, Flamm Associates