DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: FEB -6 2001

From: Director, Division of Standards and Labeling Regulations, Office of Nutritional Products, Labeling and Dietary Supplements, HFS-820

Subject: 75-Day Premarket Notification for New Dietary Ingredients

To: Dockets Management Branch, HFA-305

New Dietary Ingredient:	Type II Collagen
Firm:	AutoImmune Inc.
Date Received by FDA:	November 20, 2000
90-Day Date:	February 18, 2001

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification for the aforementioned new dietary ingredient should be placed on pubic display in docket number 95S-0316 after February 18, 2001.

Felicia B. Satchell

Felicia B. Satchell

95S-0316

RPT88

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington, DC

DEC 26 2000

Robert C. Bishop, Ph.D.
Chairman and Chief Executive Officer
AutoImmune Inc.
1199 Madia Street
Pasadena, California 91103

Dear Dr. Bishop:

This is to inform you that the notification, dated November 14, 2000, you submitted pursuant to 21 U.S.C. 350b(a)(2) was received and filed by the Food and Drug Administration (FDA) on November 20, 2000. Your notification concerns the substance called "Type II Collagen" that you assert is a new dietary ingredient.

In accordance with 21 C.F.R. § 190.6(c), FDA must acknowledge its receipt of a notification for a new dietary ingredient. For 75 days after the filing date (i.e., after February 3, 2001), you must not introduce or deliver for introduction into interstate commerce any dietary supplement that contains "Type II Collagen."

Please note that the acceptance of this notification for filing is a procedural matter and thus, does not constitute a finding by FDA that the new dietary ingredient or the dietary supplement that contains the new dietary ingredient is safe or is not adulterated under 21 U.S.C. 342. As another procedural matter, your notification will be kept confidential for 90 days after the filing date. After February 18, 2001, your notification will be placed on public display at FDA's Docket Management Branch in docket number 95S-0316. However, any information that is trade secret or otherwise commercial confidential information in the notification will not be disclosed to the public.

Please contact us at (202) 205-4168, if you have any questions concerning this matter.

Sincerely,

Margaret C. Carlson
(Acting) Leader
Dietary Supplements Team
Division of Standards
and Labeling Regulations
Office of Nutritional Products, Labeling
and Dietary Supplements
Center for Food Safety
and Applied Nutrition

- COPY #2 -

AutoImmune Inc.
1199 Madia Street
Pasadena, CA 91103
Phone: (626) 792-1235
FAX: (626) 792-1236

November 14, 2000

Office of Nutritional Products,
Labeling and Dietary Supplements (HFS-800)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C Street, S.W.
Washington, D.C. 20204

NEW DIETARY INGREDIENT NOTIFICATION

Pursuant to 21 U.S.C. § 350b, "New Dietary Ingredients," and Food and Drug Administration (FDA) regulations, 21 C.F.R. § 190.6, "Requirement for premarket notification," we hereby submit this new dietary ingredient notification on behalf of the dietary ingredient Type II Collagen, in the manner established by FDA's regulations.

(1) NAME AND ADDRESS OF MANUFACTURER OF DIETARY SUPPLEMENT THAT CONTAINS THE NEW DIETARY INGREDIENT.

AutoImmune Inc.
1199 Madia Street
Pasadena, California 91103
Telephone: (626) 792-1235
Fax: (626) 792-1236

(2) NAME OF THE NEW DIETARY INGREDIENT THAT IS THE SUBJECT OF THE PREMARKET NOTIFICATION

Type II Collagen (Colloral® Brand)

The new dietary ingredient is Colloral brand Type II Collagen, which is prepared from chicken sternal cartilage. Type II Collagen is the predominant form of collagen in the sternal cartilage and accounts for 40% to 45% of the dry weight of the cartilage. Type II Collagen molecules are trimers of a single type of collagen chain. Each chain contains a large domain that participates with two others to form a triple helix. At both ends of the triple helical domain are telopeptides that have a less defined tertiary structure. In cartilage, the trimers associate in a staggered array to form fibrils. The fibrils are stabilized by enzymatically formed aldehyde-derived cross-links between the triple helices. Enzymatic digestion cleaves these cross-links releasing single triple helices of Type II Collagen.

To obtain the new dietary ingredient, Colloral Type II Collagen is separated from other components of sternal cartilage. The chicken sternum is surrounded by a perichondrium composed predominantly of Type I collagen, which is removed with the enzyme pepsin during an initial preparation step. Proteoglycan, which comprises about 50% dry weight of the sternal cartilage, is removed from the sternal cartilage by preliminary digestion with trypsin. The sternal cartilage also contains small amounts of other types of collagen (Types V, VI, IX and XI) that differ from Type II in their amino acid sequences. These collagens are removed by differential salt precipitation.

(3) DESCRIPTION OF THE DIETARY SUPPLEMENT THAT WILL CONTAIN THE NEW DIETARY INGREDIENT

The dietary supplement that will contain Colloral Type II Collagen is a liquid formulation of Colloral Type II Collagen. The supplement will be packaged in opaque white plastic dropper bottles that will contain enough supplement for one month of dietary supplementation. The supplement is intended for use by individuals requiring dietary support to maintain or improve joint function and health.

(i) The Level of the New Dietary Ingredient in the Dietary Supplement

Each drop of Colloral contains 20 µg of Type II Collagen. The recommended dose is three (3) drops per day (total of 60 µg/day), and the bottle contains approximately 90 drops (one-month supply). Therefore, the total amount of Colloral Type II Collagen in the bottle is 1.8 mg.

(ii) The Conditions of Use Recommended or Suggested in the Labeling of the Dietary Supplement

Individuals will take a daily dose of three (3) drops of Colloral Type II Collagen in the morning. Each drop contains 20 µg of the dietary ingredient. The individual will dispense the daily dose from the dropper bottle into four (4) to six (6) ounces of orange juice (or other suitable fruit juice, except grapefruit juice) and orally ingest it at least 20 minutes prior to breakfast. Smoking is not permitted during this time period. Three (3) drops deliver the recommended 60 µg dose of Colloral.

(4) HISTORY OF USE OR OTHER EVIDENCE OF SAFETY ESTABLISHING THAT THE DIETARY INGREDIENT, WHEN USED UNDER THE CONDITIONS RECOMMENDED, WILL REASONABLY BE EXPECTED TO BE SAFE

Dietary Component

Chicken sternal cartilage, the raw material source for Colloral, is found in the normal diet as the "soft white bone" of chicken sternum. This collagen, along with other selected structural tissue is typically incorporated as an ingredient in home made chicken soup, but is also consumed directly by individuals who enjoy its chewy texture. This collagen is typically eaten in a denatured state as a result of the cooking process. The amino acids of Colloral Type II Collagen are identical to the Type II Collagen that may be ingested after heat processing. The difference between the two lies only in the fact that the Colloral Type II Collagen has not been heat treated, and is therefore in an undenatured, soluble state. It would not be expected that this difference alone would in any way alter the safety of the protein system. However, to insure that this is indeed the case, safety testing was conducted by the Company

Safety Studies

Colloral Type II Collagen has been extensively studied under controlled pre-clinical and clinical trial conditions. Three multiple dosing toxicity studies in rats have been conducted with Colloral Type II Collagen. The first study included visual observation and recovery time only, while the second and third included full necropsy and histopathologic evaluation. In addition, a single mutagenicity study has been conducted and the product's microbial and viral safety profile has also been assessed. Summaries of these studies are presented below.

Animal Safety Studies

90-Day Oral Rat Toxicity; 20 µg /Rat

This first study was conducted at Brigham and Women's Hospital (Boston, MA) with 20 female Lewis rats. The rats were divided into two groups of ten with one group receiving Type II collagen sourced from Sigma Chemical Company (St. Louis, MO), and the other group receiving material sourced from Genzyme (Cambridge, MA). Both sources utilized the same process (Trentham process) for the manufacture of chicken Type II collagen. Each group of rats was administered (by gavage) 20 µg of Type II collagen in 1 mL of phosphate-buffered saline (pH 7.4) three times per week for a period of 90 days. This dose represented a safety margin of >75 times the human dose (considering 250 g rats and a 60 µg dose to a 65 kg individual). On treatment days, the rats were physically examined and observed for behavioral abnormalities. No physical defects or behavioral abnormalities were noted at any time during the three months of treatment. The rats were allowed a recovery. period of approximately 120 days after the 90 days of treatment prior to sacrifice. Observations for all rats at the time of sacrifice were normal.

90-Day Oral Rat Toxicity; 20 and 200 µg /Rat

This second study was conducted at AutoImmune Inc. (Lexington, MA) and consisted of 25 female Sprague Dawley rats that were given doses of Sigma Type II collagen every other day for a period of 90 days. Ten rats were administered (by gavage) 20 µg of type II collagen and ten were given 200 µg. Five additional animals were weighed each week, but did not receive test material, and served as physiological controls. The high dose represents a safety margin of >750 times the human dose (considering 250 g rats and a 60 µg dose for a 65 kg individual). The Type II collagen was solubilized in 0.1 M acetic acid and both doses were administered by gavage in 0.5 mL volume. At the end of the study, the rats were transported to Biodevelopment Laboratories (Cambridge, MA) for evaluation of hematology, clinical chemistry, body and organ weights, and gross and microscopic examination.

No significant differences were observed in weight or growth rate between collagen-treated rats and the untreated controls. In addition, no biologically significant differences in hematology, clinical chemistry, body and organ weights, and gross and microscopic findings were seen. Under the conditions of this study, orally administered Colloral Type II Collagen produced no measurable effects that were considered to be treatment or dose related.

28-Day Oral Rat Toxicity; 0, 80, 800 & 8000 µg /Kg/Day

A four-week study was performed to evaluate the toxicity of AutoImmune's Colloral Type II Collagen in male and female Sprague-Dawley rats. The Colloral was administered once daily by oral gavage to four groups of ten rats. The study consisted of a control group and three treatment groups administered either a low, medium or high dose (80, 800 & 8000 µg/kg/day). The highest dose represents a margin of safety of >7500 times the human dose based on a 250 g rat and a 60 µg dose for a 65 kg individual. The Type II collagen was solubilized in 0.1 M acetic acid and all doses were administered by gavage. The control group received vehicle alone (0.1 M acetic acid) while the treatment groups received the various dosages at approximately equal dosing volumes to the control. Clinical observations, body weights, body weight gain, food consumption, clinical pathology measurements, absolute and relative organ weights, gross necropsy and histopathologic evaluations indicated that there were no treatment-related effects when compared to control animals. A single mammary adenocarcinoma was discovered in one female rat in the high-dose group. While mammary tumors are rare at this age, they do occur spontaneously and their overall incidence increases proportionally with age (1-5% at 12 months and 10-20% at 26 months). This single occurrence may represent a normal variation in the time-to-tumor distribution within a population of female Sprague Dawley rats; and was not considered compound-related by the study pathologist. It was concluded that Colloral Type II Collagen was not toxic when administered at these doses for 28 days to rats.

Ames Bacterial Reversion Assay

An Ames bacterial assay study was conducted to evaluate AutoImmune manufactured Colloral Type II Collagen for its potential to cause a mutation at the histidine operon of *Salmonella typhimurium* (strains: TA98, TA100, TA1535 and TA1537), and at the tryptophan operon of *Escherichia coli* (strain:WP2uvrA). Concentrations ranging from 5 to 5000 µg /plate were tested and compared to solvent control. Colloral Type II Collagen did not induce toxicity, nor did it display any mutagenic effect.

Microbiological and Viral Safety

Microbial organisms may potentially enter the AutoImmune Colloral manufacturing process from raw materials of animal origin (chicken sterna, porcine trypsin and porcine pepsin). The low pH (pH 2.9) of the finished dietary supplement makes it unlikely that any pathogenic bacteria or yeast would survive or propagate. The 0.1 M acetic acid solution used to formulate Colloral has successfully passed the USP 23 <51> Antimicrobial Preservation Effectiveness Test. In addition, Colloral Type II

Collagen and the finished dietary supplement are filtered through a 0.45 micron filter to further reduce any bioburden. The absence of viable cells in the process precludes the possibility of viral replication during manufacture. A viral inactivation study utilizing model viruses including viruses known to infect humans, showed that none of the viruses tested survived the pepsin digestion step of the manufacturing process except porcine parvovirus (PPV). PPV is not known to be infectious to man. Porcine trypsin is the raw material with the greatest risk for contamination with PPV, and it is screened for PPV prior to being included in the Colloral manufacturing process.

Human Studies

Colloral Type II Collagen has been studied in ten separate Phase I and/or Phase II type clinical trials in patients with rheumatoid arthritis. In all studies it was demonstrated that the administration of Colloral Type II Collagen was safe for ingestion at the dose levels intended for use in the dietary supplement. An Integrated Safety Analysis of five of the double-blinded, placebo-controlled, and two of the open-label continuation human studies indicates that there were no differences in the safety parameters measured between subjects administered Colloral and subjects administered a placebo. This analysis is included below. The studies also indicate that Colloral is effective in maintaining joint function and health when administered at the recommended dosage. Summaries of these studies are presented below.

Open-Label Study (AI-200-001)
The initial study was an open-label, single group trial in which ten adult rheumatoid arthritis patients with active disease were administered Colloral Type II Collagen. Dosing consisted of administration of 80 µg Colloral/day for the first four weeks and 400 µg /day for an additional eight weeks. Subjects consumed a liquid formulation of Colloral mixed with juice each morning during the treatment period of three months. The subjects were required to return for monthly visits at which time various safety and efficacy measurements were obtained. Subjects who exhibited an initial positive response and subsequent worsening of disease after being taken off the treatment were allowed additional treatment with study medication on an as needed basis.

There were no adverse events reported by any of the patients in this study. In addition, there were no clinically significant changes noted in any of the hematology values measured during the study. No patients developed IgG antibodies to Colloral administration. Colloral was well tolerated in this study.

Six patients improved (reduced tender and swollen joint counts) after receiving oral Colloral. One of these patients went into disease remission (no tender or swollen joints and no morning stiffness) in the second month of treatment. This remission was sustained for 26 months after treatment discontinuation, after which there is no further data. The four other patients neither improved nor worsened while receiving study medication. Two patients who showed improvement subsequently worsened when therapy was discontinued and then improved again when it was reinstated.

12 Week Randomized, Double-Blinded, Placebo Controlled, Parallel Group Study (Al-200-002)[1]

This trial studied the effect of Colloral in 60 adult rheumatoid arthritis patients with active disease at one study site. Patients were randomized to receive treatment with either active or placebo for a 12 week period. Patients consumed Colloral or placebo mixed with juice prior to breakfast each morning. Dosing for the Colloral treatment group consisted of 80 µg/day for the first 4 weeks and 400 µg /day thereafter. Subjects were required to return for monthly visits at which time various safety and efficacy measurements were obtained.

There were no serious adverse events reported for either Colloral or placebo. All adverse events reported by Colloral-treated subjects were assessed by the investigator as unrelated to therapy, whereas three placebo-treated subjects experienced adverse events which were assessed as possibly related. None of the Colloral-treated patients dropped out of the study due to an adverse event.

In addition, there were no clinically meaningful changes observed in any of the clinical laboratory parameters. None of the patients developed sensitivity to Colloral, as measured by IgG and IgA antibody titer development. Colloral was well tolerated in this study.

Four subjects, all in the placebo group, dropped out of the study before completing three months of treatment due to worsening of their RA. Four patients, all in the Colloral group, achieved complete disease remission defined as no tender joints, no swollen joints, no morning stiffness, no afternoon fatigue, a normal ESR and no disease noted on the physician and patient global scores. It should also be noted that significantly more ($p=0.04$) of the placebo patients required the use of narcotic analgesics to complete the study.

There were statistically significant differences in favor of Colloral over placebo in the number of swollen joints and the number of tender/painful joints experienced by the subjects. Statistically significant differences were also seen in patient global assessments. There were numerical trends in favor of the Colloral group in all other measures of efficacy. None of the baseline features, including presence of antibodies to type II collagen, HLA phenotype, age or sex, were associated with responsiveness in an analysis of variance (ANOVA). The published article describing this study is appended to this submission.

Pediatric, 12 Week, Open-Label Study (Al-200-003)[2]

In addition to adult studies, a ten patient open-label pilot study was conducted in children with severe juvenile rheumatoid arthritis. Dosing consisted of 100 µg/day for four weeks followed by 500 µg/day for an additional eight weeks. The Subjects consumed a liquid formulation of Colloral mixed with juice each morning for a treatment period of three months. The subjects were required to return for monthly visits at which time various safety and efficacy measurements were obtained.

There were no adverse events that were deemed attributable to Colloral therapy. All reported adverse events in the original study were transient and resolved either spontaneously or with appropriate treatment without discontinuation of Colloral therapy. The reported adverse effects included facial flushing, productive cough, stomachache, and rashes.

In addition, there were no clinically meaningful changes in the clinical laboratory parameters measured. None of the patients tested positive for rheumatoid factor or antibodies to collagen prior to or following completion of the three-month treatment period. Colloral was well tolerated in this study.

The juvenile subjects were tested for improvements in joint health and function. The data indicate that the subjects administered Colloral Type II Collagen therapy experienced an improvement in joint health and function. The published article describing this study is appended to this submission.

Six Month, Double-Blinded, Placebo Controlled, Dose-Ranging Study (AI-200-004)[3]

This comprehensive six-month, double-blinded, placebo-controlled trial was concerned with safety, efficacy and dose-ranging of Colloral. A total of 274 patients were enrolled across six investigational sites and randomized into one of five treatment groups (20, 100, 500 or 2500 µg Colloral, or placebo). Safety and efficacy measurements evaluated were similar to those described above, with the addition of a clinical health assessment questionnaire (CLINHAQ).

The 274 patients were randomized to one of the five treatment groups. A total of 228 patients completed the full 6-month treatment period. Of the 46 dropouts, 42 were due to inadequate therapeutic effect and five were due to adverse events (one placebo-treated subject, and four Colloral-treated subjects). None of the adverse events were related to the treatments and the frequency of patient dropout was similar across all treatment groups.

There were no clinically meaningful changes either during the study or at the end of study treatment in hematology, serum chemistry, urinalysis, or vital sign measurements attributable to Colloral therapy. In addition, there were no clinically meaningful changes from baseline to the end of study values between Colloral and placebo for any of the clinical laboratory tests and vital sign measurements. Colloral was well tolerated in this study.

Efficacy was evaluated using three composite measures of response to joint health, in addition to the individual joint health parameters noted in the above study (AI-200-002). The data indicate that the two lower doses (20 µg and 100 µg) of Colloral were significantly better than placebo at improving joint health when

evaluated by linear logistic regression analysis. The published article describing this study is appended to this submission.

Effect of Colloral on the Immune System (AI-200-005)
A 15 patient open-label study of six-month duration involving doses of 20, 100 and 500 µg/day was designed to study the effect of Colloral Type II Collagen on the immune system. Specifically, cytokines found in synovial samples were identified and quantified.

There were no serious adverse events reported during the course of the study. Six of the 14 patients reported adverse events but none were deemed attributed to Colloral therapy by the investigator. There were no clinically meaningful changes in hematology, serum chemistry, or urinalysis during or at the end of the 6-month treatment period. There were no changes in IgG or IgA antibodies from baseline to the end of the study. However, IgM antibodies were found to be higher at the end of the study in five responders, compared to seven non-responders. The clinical meaning of this finding remains unclear. Overall, Colloral was well tolerated in this study.

Gross anatomical evaluation by arthroscopy at the end of the six-month Colloral treatment period showed improvement in eight of 10 patients who had baseline arthroscopic evaluation. The observed improvement constituted a change from either a generalized synovitis with active inflammation comprising proliferation and increased circulation, or active synovitis at baseline, to minor sites within the joint showing synovial circulation at the end of the study.

Multiple synovial tissue specimens were: collected and a modified immunohistochemical method for detecting cytokine-producing cells was used to analyze cytokine synthesis in fixed cryopreserved sections to quantify cytokine expression. The results revealed no differences in cytokine(s) during or following Colloral therapy between responders and non-responders.

Long Term Safety, Open-Label Study (AI-200-006)
An open-label continuation study was initiated to obtain long-term safety data on oral administration of Colloral in adults. Subjects must have successfully completed either the previous AI-200-001, AI-200-002, or AI-200-004 study to be eligible. Each patient initially received a daily dose of 100 µg, but based on the dose ranging study (AI-200-004), patients were reduced to 20 µg/day. At the investigator's discretion, doses could be increased in increments of 20 µg up to a maximum of 100 µg/day. No concomitant DMARD use was permitted.

Subjects were originally seen for safety and efficacy measurements every three months, but this was later changed to every six months. A total of 237 patients were entered into this study, and some of these received Colloral in excess of 4 years. There were no serious adverse events attributable to Colloral administration, and

there were no clinically meaningful changes in clinical laboratory values attributable to the dietary supplement. Dropouts were attributed to perceived inadequate therapeutic effect, and not for safety or tolerance reasons. Additionally, in view of the prohibition of certain other medications, as specified in the protocol, a high patient retention rate reflected favorably on Colloral's long-term tolerability.

Dose Refinement Study (AI-200-007)
A double-blind, placebo-controlled, dose refinement study in which 425 adult patients with active rheumatoid arthritis were randomized to receive either 5, 20 or 60 µg Colloral/day, or placebo, and were treated for 24 weeks. The purpose of this study was to further refine the dose response curve around the best dose of 20 µg/day observed in the prior dose ranging study (AI-200-004), and to evaluate safety of the doses.

When the individual doses of Colloral, all Colloral doses combined, and the placebo were compared, there were no clinically meaningful differences in the incidence of adverse events or serious adverse events. None of the serious adverse events in the Colloral-treated patients were deemed attributable to Colloral therapy. The majority of the reported adverse events were mild to moderate in severity (87.5% compared to 85.8% for all Colloral doses and placebo, respectively). In addition, there were no clinically meaningful changes either during the study or at the end of study treatment in hematology, serum chemistry, urinalysis, IgA and IgG antibodies, or vital sign measurements from baseline between Colloral and placebo. Colloral was well tolerated in this study.

There were no statistically significant differences on the effect of joint function improvement between the three doses of Colloral and placebo. With the exception of the 20 µg dose, there was a trend in favor of Colloral for a higher cumulative joint function response rates compared to placebo, and 60 µg dose of Colloral produced the best response rate. Comparing all doses of Colloral from the -004 and -007 studies, the cumulative joint function improvement response rates appear to present a broad peak within a dose range of 5 µg and 100 µg. A dose of 60 µg/day was the most efficacious Colloral dose observed in this study.

Colloral Therapy After Methotrexate Withdrawal (AI-200-008)
A double-blind, placebo-controlled study was conducted in 203 adult patients with active rheumatoid arthritis, maintained on methotrexate (MTX) therapy. Methotrexate therapy was abruptly withdrawn and patients were randomized to either 20 µg Colloral/day or placebo. The purpose of this study was to evaluate safety and efficacy of Colloral in preventing exacerbation of disease activity after abrupt MTX withdrawal. Patients were treated for a 24-week period

There were no clinically meaningful differences between Colloral and placebo in the incidence of adverse events, or serious adverse events. None of the serious adverse events in the Colloral-treated patients were deemed attributable to Colloral therapy.

The majority of the reported adverse events were mild to moderate in severity (89.0% and 87.4% for Colloral and placebo, respectively). In addition, there were no clinically meaningful changes from baseline either during the study or at the end of study treatment in hematology. serum chemistry, urinalysis, IgA and IgG antibodies, or vital sign measurements between Colloral and placebo. Colloral was well tolerated in this study.

The effectiveness of Colloral therapy was evaluated by comparing the percentage of Colloral and placebo subjects who achieved an improvement in joint function. There was a trend in favor of Colloral 20 µg/day versus placebo, however, this was not statistically significant. The effectiveness of Colloral, as measured in this trial, was compromised by the fact that the best observed dose (60 µg) from the Al-200-007 dose ranging trial was not studied.

Colloral Therapy Compared to Hydroxychloroquine Therapy (Al-200-009)
This was a double-blind, active-controlled study in 287 patients with active rheumatoid arthritis. Patients who had no history of prior hydroxychloroquine (HCQ) therapy were randomized to either 20 µg Colloral/day or 400 mg hydroxy-chloroquine/day, and treated for 24 weeks.

There were no statistically significant differences between Colloral and HCQ in the incidence of adverse events or serious adverse events. However, Colloral-treated patients had a statistically significant lower incidence of "related" adverse events, compared to HCQ-treated patients (27.4% versus 42.6%, respectively, p=0.0091). None of the serious adverse events in the Colloral-treated patients were deemed attributable to Colloral therapy. The majority of the reported adverse events were mild to moderate in severity (84.9% and 84.4% for Colloral and HCQ, respectively).

There were no clinically meaningful changes from baseline either during the study or at the end of study treatment in hematology, serum chemistry, urinalysis, PT and PTT, IgA and IgG antibodies, or vital sign measurements between Colloral and placebo. Colloral was well tolerated in this study.

The proportion of patients achieving improved joint function was less for Colloral-treated patients, compared to HCQ-treated patients. The difference was statistically significant (p=0.045). The improvement in joint function and health for the Colloral 20 µg dose group was consistent with the response in the other studies. The effectiveness of Colloral as measured in this trial was compromised by the fact that the best observed dose (60 µg/day) was not studied.

Open-Label Continuation Study (Al-200-010)
An open-label continuation study was initiated in September 1996 to obtain long-term safety data on Colloral administration in adults. Subjects must have successfully completed AI-200, -007, -008 or –009; or transferred from the Al-200-004 open label continuation trial because of the need for concomitant therapy. Patients not

completing the -007, -008 or –009 studies may still have been eligible if deemed appropriate by the investigator and approved by the sponsor. A total of 599 such patients were enrolled in this continuation study. Each patient initially received a daily dose of 20 µg of Colloral. This dose was subsequently revised to 60 µg/day, based upon analysis of the results of the previous clinical trials. Patients were seen for safety evaluation every six months and were permitted to take concomitant therapy.

Some patients in this study received Colloral in excess of 3 years. There were no serious adverse events attributable to Colloral administration. The adverse event profile appears to be comparable to that observed from the placebo-controlled studies. There were no clinically meaningful changes in clinical laboratory values attributable to Colloral. Additionally, a high patient retention rate (84.6%) reflects favorably on Colloral's tolerability.

Integrated Safety Analysis

An integrated safety analysis of five randomized clinical trials (AI-200-002, -004, -007, -008 and -009) was conducted. All patients with post-baseline data were included in this analysis. In addition, data for the open label, long-term continuation trials (AI-200-006 and -010) are included.

The mean change from baseline, for the hematology laboratory parameters are summarized in the following table. The mean baseline value is given for reference purposes. The mean change from baseline, for the WBC differentials are not shown.

Laboratory Parameter	Overall Colloral (N=810)	Placebo (N=296)	p Value*
Hemoglobin (g/dL)			0.2155
Mean Baseline Value	13.10	13.20	
Mean Change to End of Study	-0.10	-0.20	
Hematocrit (%)			0.5405
Mean Baseline Value	39.80	40.20	
Mean Change to End of Study	-0.40	-0.40	
RBC ($x10^6$/_L)			0.9448
Mean Baseline Value	4.40	4.40	
Mean Change to End of Study	+0.01	+0.02	
WBC ($x10^3$/_L)			0.4300
Mean Baseline Value	8.20	8.30	
Mean Change to End of Study	+0.30	+0.40	
Platelet Count ($x10^3$/_L)			0.0873
Mean Baseline Value	314.00	313.00	
Mean Change to End of Study	+1.40	+8.90	
PT			0.9864
Mean Baseline Value	13.93	10.11	
Mean Change to End of Study	0.00	-0.11	
PTT			0.9864
Mean Baseline Value	24.36	27.70	
Mean Change to End of Study	-0.24	-0.41	

*Wilcoxon rank sum test comparing change from baseline for overall Colloral and placebo

There were no clinically meaningful differences between Colloral and placebo in the mean changes from baseline for the hematology test parameters.

The mean change from baseline, for the serum chemistry laboratory parameters are summarized in the following table. The mean baseline value is given for reference purposes.

Laboratory Parameter	Overall Colloral (N=810)	Placebo (N=296)	p Value*
Total Bilirubin (mg/dL)			0.1440
Mean Baseline Value	0.48	0.48	
Mean Change to End of Study	-0.01	-0.03	
Alkaline Phosphatase (U/L)			0.2504
Mean Baseline Value	77.00	77.50	
Mean Change to End of Study	-1.00	-2.20	
SGOT(U/L)			0.5415
Mean Baseline Value	20.90	21.70	
Mean Change to End of Study	-0.90	-1.40	
SGPT (U/L)			0.4782
Mean Baseline Value	19.80	22.10	
Mean Change to End of Study	-1.00	-3.40	
BUN (mg/dL)			0.6430
Mean Baseline Value	15.50	15.00	
Mean Change to End of Study	-0.30	-0.10	
Creatinine (mg/dL)			0.9285
Mean Baseline Value	0.90	0.80	
Mean Change to End of Study	-0.02	-0.01	
Glucose (mg/L)			0.0530
Mean Baseline Value	103.20	103.20	
Mean Change to End of Study	+1.00	+1.80	
Uric Acid (mg/dL)			0.3385
Mean Baseline Value	4.80	4.70	
Mean Change to End of Study	-0.14	-0.05	
Calcium (mg/dL)			0.0821
Mean Baseline Value	9.10	9.00	
Mean Change to End of Study	+0.05	+0.10	
Phosphorus (mg/dL)			0.1245
Mean Baseline Value	3.60	3.50	
Mean Change to End of Study	-0.03	-0.07	
Total Protein (g/dL)			0.6917
Mean Baseline Value	7.30	7.20	
Mean Change to End of Study	+0.01	-0.01	
Albumin (g/dL)			0.0702
Mean Baseline Value	3.90	3.90	
Mean Change to End of Study	-0.03	-0.06	
Cholesterol (mg/dL)			0.4682
Mean Baseline Value	199.00	198.00	
Mean Change to End of Study	-0.10	-1.90	
Triglycerides (mg/dL)			0.7062
Mean Baseline Value	160.70	150.60	
Mean Change to End of Study	+11.40	+3.72	

*Wilcoxon rank sum test comparing change from baseline for overall Colloral and placebo

There were no clinically meaningful differences in the mean changes from baseline for the serum chemistry laboratory parameters between Colloral and placebo.

The mean change from baseline for the electrolyte laboratory parameters is summarized in the following table. The mean baseline value is given for reference purposes.

Laboratory Parameter	Overall Colloral (N=810)	Placebo (N=296)	p Value*
Sodium (mEq/L)			0.1391
Mean Baseline Value	138.00	137.00	
Mean Change to End of Study	+0.60	+0.90	
Potassium (mEq/L)			0.3639
Mean Baseline Value	4.20	4.10	
Mean Change to End of Study	+0.01	+0.04	
Bicarbonate (mEq/L)			0.6478
Mean Baseline Value	24.80	23.70	
Mean Change to End of Study	+0.10	+0.30	
Chloride (mEq/L)			0.0186
Mean Baseline Value	104.00	104.00	
Mean Change to End of Study	-0.15	+0.24	

*Wilcoxon rank sum test comparing change from baseline for overall Colloral and placebo

There appeared to be no clinically meaningful differences between Colloral and placebo in the mean change from baseline to end of study for electrolyte laboratory parameters.

The mean change from baseline for the specific gravity and pH urinalysis laboratory parameters is summarized in the following table. The mean baseline value is given for reference purposes.

Laboratory Parameter	Overall Colloral (N=810)	Placebo (N=296)	p Value*
Specific Gravity			0.7300
Mean Baseline Value	1.02	1.02	
Mean Change to End of Study	0.00	0.00	
pH			0.9051
Mean Baseline Value	5.50	5.60	
Mean Change to End of Study	-0.18	-0.07	

*Wilcoxon rank sum test comparing change from baseline for overall Colloral and placebo

There were no clinically meaningful differences in the mean changes from baseline for specific gravity and pH urinalysis laboratory parameters between Colloral and placebo.

The mean change from baseline, for the vital sign measurements are summarized in the following table. The mean baseline value is given for reference purposes. Study -002 (N=58) is not included because vital sign measurements were not available.

VITAL SIGN MEASUREMENT	Overall Colloral (N=728)	Placebo (N=266)	p Value*
Systolic Blood Pressure (mmHg)			0.3564
Mean Baseline Value	127.90	127.70	
Mean Change to End of Study	+150	-180	
Diastolic Blood Pressure (mmHg)			0.7262
Mean BasehneValue	77.20	77.70	
Mean Change to End of Study	-0.20	-0.60	
Pulse Rate (bpm)			0.7569
Mean Baseline Value	74.80	75.50	
Mean Change to End of Study	+0.90	+1.10	
Respiratory Rate (rpm)			0.1297
Mean Baseline Value	17.20	17.30	
Mean Change to End of Study	0.10	-0.40	
Oral temperature (F)			0.5592
Mean Baseline Value	98.00	98.00	
Mean Change to End of Study	-0.03	+0.03	

*Wilcoxon rank sum test comparing change from baseline for overall Colloral and placebo

There were no clinically meaningful differences between Colloral and placebo in the mean changes from baseline for any of the vital sign measurements.

The percentage of patients with a change from baseline, i.e., an increase or decrease from baseline to the end of the treatment period, for IgG amd IgA antibodies to Colloral is given in the following table. An increase or decrease from baseline is defined as a greater than 50% increase or decrease from baseline to the last value and the baseline or last value must be greater than 100 U/mL. Studies -002 and -004 are not included in this analysis because these two studies employed a methodology of measurement different from the -007, -008 and -009 studies, resulting in values that could not be incorporated into the analysis. However, by their independent analyses, no statistically significant changes were observed.

ANTIBODY STATUS	Overall Colloral N (%)	Placebo N (%)	p Value*
IgG Antibody	N = 511	N = 191	0.5145
Decrease	28 (5.5)	4 (2.1)	
Unchanged	434 (84.9)	171 (89.5)	
Increased	49 (9.6)	16 (8.4)	
IgA Antibody	N = 512	N = 191	0.1453
Decrease	7 (1.4)	1 (0.5)	
Unchanged	490 (95.7)	181 (94.8)	
Increased	15 (2.9)	9 (4.7)	

*Wilcoxon rank sum test comparing change from baseline for overall Colloral and placebo

There were no differences between Colloral and placebo in the percentage of patients with decreased, unchanged, or increased IgG and IgA antibodies to Colloral from baseline.

The most frequently occurring adverse event for Colloral was infection (15.2%), followed by headache (12.5%) and diarrhea (10.0%), however, these incidence rates between Colloral and placebo were not statistically significant. Abdominal pain was reported by more Colloral-treated patients (5.3%) than by placebo-treated patients (2.4%) (p=0.0345). Although this difference in the incidence of non-specific abdominal pain was statistically significant, it was not considered to be clinically meaningful. Overall, there were no clinically relevant differences in the percentage of patients experiencing adverse events between Colloral and placebo.

No reported serious adverse events were deemed attributable to Colloral administration. The percentage of Colloral patients with reported serious adverse events was comparable to that for placebo (4. 1 % and 4.0%, respectively, p= 1.0000). The most frequently occurring reported serious adverse events for Colloral are hospitalization for joint disorder (0.6%), myocardial infarction (0.5%), and chest pain (0.4%), however, the incidence rates between Colloral and placebo were not statistically significant. Overall, there were no clinically meaningful or statistically significant differences between Colloral and placebo in the percentage of patients with reported serious adverse events.

(5) ADDITIONAL INFORMATION

AutoImmune Inc. doubts that a new dietary ingredient notification is required for Type II Collagen. It is a matter of public knowledge that numerous companies are already selling dietary supplements that are represented to contain this dietary ingredient. Appended to this submission is a partial listing of these companies, including the names of the dietary

supplement products, the structure or function claims associated with the product, and other descriptive information. Additionally, photocopies of advertisements of dietary supplements containing Type II Collagen are also appended to this submission.

Since none of the companies responsible for these products, nor any other company, has submitted a New Dietary Ingredient Notification to FDA for Type II Collagen, and since products containing Type II Collagen are on the market without any evidence of any FDA objections, we infer that it probably has been accepted both within the industry and by FDA that Type II Collagen is not a new dietary ingredient, and that it may be marketed without a New Dietary Ingredient Notification.

However, the earliest evidence that we have seen of marketing of a dietary ingredient of Type II Collagen in the United States is a catalog for Ecological Formulas, Inc., Concord, California, which includes an entry for a dietary supplement named "Rheumatol Forte," which contained the dietary ingredient "Collagen Type II." We have clear evidence that this catalog was in existence on January 30, 1995, and it would be reasonable to infer that the product probably was being marketed before October 15, 1994 [the pertinent date for new dietary ingredient status, 21 U.S.C. § 350b(c)], but we have not been able to find any proof of marketing before January 30, 1995. Accordingly, in order to be certain that our marketing will be in compliance with the law, we have submitted this notification to FDA.

We trust this New Dietary Ingredient Notification submission provides the information that FDA requires. If there are any questions concerning this submission, please call me at (626) 792-1235.

Sincerely yours,

Robert C. Bishop

Robert C. Bishop, Ph.D.
Chairman and Chief Executive Officer
AutoImmune Inc.

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