

# DIATOMIC IODINE TREATMENT FOR FIBROCYSTIC DISEASE

## Special Report of Efficacy and Safety Results

### Study 04

21 March 1995

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STUDY INITIATION: 05 January 1987

STUDY COMPLETION: 26 June 1988

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## ABBREVIATIONS

AE	Adverse event
bpm	Beats per minute
CRF	Case report form
CTM	Clinical trial material
dl	Deciliter
FCD	Fibrocystic disease
g	Gram
IRB	Institutional Review Board
KI	Potassium iodide
lb	Pound
ml	Milliliter
SD	Standard deviation
T <sub>3</sub>	Triiodothyronine
T <sub>4</sub>	Thyroxine
TEAV	Treatment emergent abnormal value
TESS	Treatment emergent signs and symptoms
TSH	Thyroid-stimulating hormone

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**CLINICAL STUDY SYNOPSIS**

- Title:** Diatomic Iodine Treatment of Fibrocystic Disease.
- Investigators:** Donald E. Low, M.D., Virginia Mason Clinic, 909 University Street, Seattle, Washington 98101, U.S.A.
- William R. Ghent, M.D., 275 Bagot Street, Suite 201, Kingston, Ontario K7L 3G4, Canada;  
and
- Lucius D. Hill, M.D., Swedish Hospital, 801 Broadway, Suite 915, Seattle, Washington 98122, U.S.A.
- Objectives:** The primary objectives of this study in patients with fibrocystic disease (FCD) of the breast were as follows:
- To assess, by systematic evaluation of signs and symptoms of FCD, the efficacy of diatomic iodine by investigating the continuing course of FCD in eligible patients; and
  - To obtain long-term safety information about the use of diatomic iodine in patients with FCD.
- The objective of this report is to provide a display and interpretation of key efficacy and safety results of data obtained during this study.
- Study Design:** This investigation was a prospective, double-blind, randomized, parallel, placebo-controlled study designed to compare diatomic iodine to placebo in treatment of the pain as well as the fibrotic and cystic components of FCD. The planned treatment period was seven months. The Protocol specified that a minimum of 100 patients be enrolled, 50 in each treatment group.
- Drug**
- Administration:** Aqueous diatomic iodine was provided to patients in pre-measured, sealed dispensers, each of which provided approximately a two-week supply of clinical trial material (CTM). Placebo dispensers were identical to the active drug dispensers and were filled with an aqueous solution of a nontoxic coloring agent and a bittering agent.
- During the Treatment Phase, patients ingested a single daily oral dose of 10 to 25 ml of aqueous diatomic iodine solution or the placebo solution. The iodine doses contained 1.95 to 4.88 mg of iodine.

**Methods:** The Study included a Screening/Baseline Phase, during which the Investigator assessed eligibility and obtained baseline assessments; a 7-month Treatment Phase, during which each patient took CTM and had efficacy and safety assessments after one month and after three months; and a Follow-up Phase, during which patients received final assessments.

Efficacy assessment consisted of subjective and objective evaluations of changes in FCD signs and symptoms.

Safety evaluation included an Adverse Events (AEs) probe. The checklist that was used elicited information about the following symptoms: Acne, Nausea, Diarrhea, Hair Loss, Hyperthyroid, Hypothyroid, Skin Rash, Iodism, and Other. If deemed necessary, a full evaluation including a physical examination, blood tests, and radiological investigations were performed. Clinical laboratory assessments included thyroid function tests.

## Study

**Population:** There were 106 patients enrolled in the study. Treatment code or patient identification information was unidentifiable for some of these patients resulting in a final data base containing data for 92 patients. This report summarizes data for these 92 patients.

The study population was all female. Age ranged from 25 to 64 years; Body Weight ranged from 100 to 250 lb.

**Results:** Drug Compliance: During the study, about 40% of the patients experienced a shortage of CTM, which caused an interruption in the daily dosing with CTM. The average duration of interruption of treatment was about one month for each treatment group. Due to the potential, important effects of treatment interruption, statistical analysis included assessment of the all-patient population (n = 92) and subgroup analyses for those patients who had one or more days of interruptions in therapy due to CTM shortage (n = 38) and those who were compliant with drug administration throughout the study (n = 54).

Efficacy: In the all-patient population (n = 92), the iodine-treated group Total Breast Examination Score declined from a mean of 37.3 (at Baseline) to a mean of 13.5 (at Month 7), showing a mean change of -23.9; the placebo-treated group score declined from a mean of 35.3 (at Baseline) to a mean of 32.7 (at Month 7), showing a mean change of -2.6. The statistical analysis resulted in a highly significant statistical active-placebo difference for the all-patient population (p < 0.001).

**Table. Analysis of Total Breast Examination Scores**

Comparison Groups	Mean Changes	p-values*
Iodine vs. Placebo	-23.9 vs. -2.6	<0.001
Iodine (C) vs. Placebo (C)	-29.1 vs. -2.6	<0.001
Iodine (C) vs. Iodine (I)	-29.1 vs. -18.7	0.01
Iodine (I) vs. Placebo (C)	-18.7 vs. -2.6	<0.001
Placebo (C) vs. Placebo (I)	-2.6 vs. -2.7	0.99

\* F test

C: Compliant Patients

I: Patients with Treatment Interruptions

In the all-patient population (n = 92), the iodine-treated group Total Breast Examination Score declined from a mean of 37.3 (at Baseline) to a mean of 13.5 (at Month 7), showing a mean change of -23.9; the placebo-treated group score declined from a mean of 35.3 (at Baseline) to a mean of 32.7 (at Month 7), showing a mean change of -2.6. The statistical analysis resulted in a highly statistically significant active-placebo difference for the all-patient population (p < 0.001).

Supporting analysis for the active-placebo difference among patients with no treatment interruption also resulted in statistical significance (mean change for the iodine-treated patients of -29.1; mean change for the placebo-treated patients of -2.6; p < 0.001). When active-treated patients with one or more treatment interruptions are compared to placebo-treated patients with no interruption, the results show a statistically significant difference (mean change for iodine-treated group of -18.7; mean change for placebo-treated group of -2.6; p < 0.001).

When active-treated patients with no treatment interruption are compared to active-treated patients with one or more treatment interruptions, a statistically significant difference is observed. The active-treated patients with no treatment interruption showed a mean change of -29.1; the active-treated patients with one or more interruptions showed a mean change of -18.7. The statistical analysis comparing these groups resulted in a p-value of 0.01.

When placebo-treated patients with no treatment interruption are compared to placebo-treated patients with one or more treatment interruptions, no difference is observed (p = 0.99).

**Safety:** Aqueous diatomic iodine was generally well tolerated by all patients. No serious Adverse Event was reported.

A total of 5 (11%) of the iodine-treated patients and 10 (22%) of the placebo-treated patients reported one or more AEs. Adverse Events reported by iodine-treated patients included the following: acne, constipation, menstrual irregularity, polyuria, loose stools, and weight loss. Adverse Events reported by placebo-treated patients included these events: acne, diarrhea,

indigestion, dry mouth, nausea when taken on empty stomach, headache, and gas. All AEs were transient and classified as minor clinical complaints.

There was no evidence of any influence of treatment with diatomic iodine on Heart Rate, Body Weight, or Thyroid Function.

**Conclusions:** This randomized, double-blinded, placebo-controlled study was designed to examine the effects of seven months of oral treatment with diatomic iodine in FCD females.

The conclusions of this study are as follows:

- Diatomic iodine was generally well-tolerated by all patients, with no serious Adverse Events reported in the study.
- Taking diatomic iodine without interruption for seven months is better than placebo relative to alleviation of symptoms of FCD, as assessed by the Total Breast Score.
- Taking diatomic iodine for a seven-month period, even with an interruption in medication of about a month, is better than taking placebo relative to alleviation of symptoms of FCD, as assessed by the Total Breast Score.
- Taking placebo for a seven-month period without interruption is equivalent to taking placebo for a seven-month period with an interruption of about a month relative to alleviation of symptoms of FCD, as assessed by the Total Breast Score.
- There is no evidence to suggest that treatment with diatomic iodine is associated with any profile of clinical signs or symptoms.

## I. INTRODUCTION

Fibrocystic disease (FCD) of the breast is characterized by lumpy, painful breasts, generally in reproductive-aged women [1]. Initially the syndrome occurs in the premenstrual phase, but it can progress to involve the whole menstrual cycle. Symptoms of FCD can also occur in menopause, particularly if estrogens are used.

Histologically, FCD manifests itself as microcysts, epithelial hyperplasia, apocrine metaplasia, and fibrosis [2]. Fibrosis is the hallmark of the disease. Macrocysts greater than 1 cm in diameter occur in 10% of patients with this syndrome. The latest review by the American Academy of Pathology suggests that up to 80% of North American women may be afflicted with the syndrome at some time during their reproductive lifetime [3]. However, the clinical signs and symptoms of FCD, such as swollen breasts, tenderness, and pain, occur in a small proportion of women with histologic evidence of FCD.

Data support the hypothesis that FCD of the breast is caused by a deficiency of iodine (not iodide) at the level of the terminal and intralobular duct epithelia [4]. Iodine deficiency renders the epithelium in the critical areas more sensitive to circulating estrogens. These cells, therefore, produce more fluid than can be absorbed by the acini, and the acini become distended to form microcysts. The fluid in these microcysts contains high concentrations of potassium. This can stimulate the production of fibrosis, completing the triad of epithelial hyperplasia, cyst formation, and fibrosis, as is found in both the animal model (rat) and in human FCD of the breast.

Research suggests that iodine is taken up by terminal and intralobular duct epithelia and is organified into an iodoprotein component of the estrogen receptor [5]. It is believed that organification of iodine in mammary tissue is a marker for normal estrogen-responsive cells. Ingestion of an appropriate amount of iodine normalizes the function of these critical cells in the breast and restores normal estrogen sensitivity, leading to reversal of the anatomic and symptom complex of FCD.

A series of preclinical and clinical investigations have been conducted to show efficacy and safety of iodine, first in the iodide form, and then in the aqueous form for the treatment of FCD of the breast. For the sake of clarity, diatomic iodine will

be the term used throughout the document to describe the iodine therapy; elemental iodine is a term previously used in this regard.

Four different clinical trials have been performed involving a total of approximately 3,000 patients with FCD; although these are largely Canadian studies, this United States based placebo-controlled study is also included. The results of these clinical trials have been published in the Canadian Journal of Surgery [6]. Studies 01, 02, and 03, which were conducted in Kingston, Ontario, Canada were open-label treatment of patients in a clinic setting where data were collected systematically. Patients treated with Lugol's solution (containing 5% iodine and 10% KI) were designated as Study 01. The patient population in Study 02 was treated with iodized casein, and patients in Study 03 were treated with diatomic iodine.

A positive correlation has been found between animal studies and clinical findings regarding the effects of iodine on FCD. In the laboratory experiments, a standardized iodine-deficient rat model was developed by feeding female rats an iodine-deficient diet and adding perchlorate to the drinking water for short-term or chronic periods [7]. Microscopic changes, such as fibrosis, cysts, and epithelial hyperplasia, which resemble FCD in humans, were produced in those rats. Treatment with oral iodine, but not iodide, resulted in the resolution of the histologic findings.

Based on results obtained to date, derived from several thousand women who are being treated with diatomic iodine (in aqueous form), the present iodine replacement therapy appears to offer a safe and effective treatment of FCD with fewer adverse events (AEs) than occur with other types of therapy (e.g., Danazol). Treatment with diatomic iodine is believed to restore normal function to specific cells in the breast, thereby reducing the pain experienced by the patients, and perhaps reversing the underlying cellular histopathology of FCD.

This prospective, double-blind, randomized, placebo-controlled investigation in FCD patients was designed to compare aqueous diatomic iodine to placebo for the treatment of pain and the fibrotic and cystic components of FCD of the breast. The seven-month treatment period involved an initial dose of 10 ml/day (1.95 mg iodine/day), which could be doubled if no clinical effect was observed.

This study was done at the Virginia Mason Clinic in 1987 and 1988 by Drs. Low, Ghent and Hill under the sponsorship of Iomech Ltd., Toronto, Ontario, Canada. Mimetix, Inc, acquired the licensing of iodine in 1993 and, as sponsor, contacted Cato Research Ltd. to assist in the development. Case Report Forms were obtained by Cato Research Ltd. in 1993 and a data diskette in 1994. This report is prepared to present key efficacy and safety results of the study.

## II. BACKGROUND

### A. OBJECTIVES

The primary objectives of this study were as follows:

- To assess, by systematic evaluation of signs and symptoms of FCD, the efficacy of diatomic iodine by investigating the clinical symptomatology of FCD of the breast; and
- To obtain safety information about the use of diatomic iodine in patients with FCD when treatment is administered for 7 months.

### B. STUDY DESIGN

This investigation was a prospective, double-blind, randomized, placebo-controlled study designed to compare aqueous diatomic iodine to placebo in the treatment of the pain as well as the fibrotic and cystic components of FCD of the breast. The 7-month treatment period involved an initial dose of 10 ml/day (1.95 mg iodine/day), which could be doubled if no clinical effect was observed.

The Protocol required the enrollment of a minimum 100 patients, 50 in each treatment group. Assessments for safety and efficacy were planned for the end of the first month and the third month; final assessments were made at Month 7. An evaluation of clinical results was planned for when the population had completed the seven months of treatment.

**Table A. Planned Doses and Numbers of Patients**

Total Patients	Active	Placebo	Dosage	Length of Treatment
100	50	50	10 ml/day (initial dose)*	7 months

\* Dosage was to be doubled for the duration for the Treatment Phase, if no clinical effect was noted.

The Study included three phases:

- A Screening/Baseline Phase, during which the Investigator assessed eligibility and obtained baseline assessments;
- A Treatment Phase, during which each patient took CTM and had efficacy and safety assessments after one month then after three months; and
- A Follow-up Phase, during which patients received final assessments, including a mammogram.

The study design provided for a mammogram at the end of treatment for completers or dropouts. All patients were to be followed for a maximum of one full year. Also, those patients treated with placebo during the Treatment Phase were to be offered the opportunity to receive diatomic iodine at the end of treatment.

After study initiation in January 1987, some minor modifications to the study conduct were implemented in March 1987 to address patient enrollment and compliance considerations. These modifications are summarized in Appendix I.

#### **C. INFORMED CONSENT AND INSTITUTIONAL REVIEW BOARD (IRB) APPROVAL**

Prior to initiating the study, the protocol was submitted to the IRBs of the Virginia Mason Medical Center and the Swedish Hospital Medical Center. Approval was obtained and the documents are located at the Virginia Mason Medical Center. Written informed consent was obtained from patients prior to their participation in the study.

#### **D. DRUGS AND DOSAGES**

Aqueous diatomic iodine consisted of a saturated solution of iodine in water. This saturated solution was achieved by a patented dosing device, the Iomech Pocket Iodinator®. The aqueous diatomic iodine achieved by the Iodinator®

Background

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results in a concentration of 13.65 mg of total iodine per 70 ml between 2 and 5° C.

After randomization by the clinic pharmacist at the Virginia Mason Medical Center, patients were provided with the Iomech Pocket Iodinator® dosing device or a placebo unit which was identical to the active dosage dispenser except it contained a nontoxic coloring agent and a bittering agent. The dosing device was designed to provide 50 doses of 20 ml, totalling 1,000 ml. The dosing device was not refillable and was to be used until empty at which time it was returned to the dispensing pharmacy. Before dispensing to the patients, the pharmacist recorded the patient's name, the dose date, the dispensing date and the re-order date. The patients were to store the dosing device in the refrigerator at a temperature between 2 and 5° C. After each dose, as prescribed by the physician, the dispenser was stored in the refrigerator again. A color bar series on the side of the dispenser warned users of under-strength solution.

During the Treatment Phase, patients ingested a single daily, oral dose of 10 ml of saturated aqueous diatomic iodine solution or placebo solution. If an inadequate clinical effect was observed, however, a provision in the clinical protocol allowed for the dose to be doubled.

**E. STUDY MANAGEMENT**

Figure 1 presents an abbreviated version of the overall Schedule of Time and Events for this study.

**Figure 1. Schedule of Time and Events**

Assessment	Screening/Baseline Phase	Treatment Phase	Follow-up Phase
Informed Consent	X		
Eligibility Requirements	X		
Mammogram	X <sup>1</sup>		X <sup>2</sup>
Medical History	X		
Physical Examination	X	X <sup>3</sup>	X
Drug Administration		X	
Adverse Events Probe		X	X
Vital Signs <sup>4</sup>	X		X
Clinical Laboratory Assessments: Thyroid Function Tests	X		X
Total Breast Examination Score	X	X	X
Patient's Subjective Score	X	X	X

<sup>1</sup> If not already done within the previous six months, a mammogram was performed.

<sup>2</sup> A mammogram was done at the end of the Treatment Phase or when treatment of dropouts ceased.

<sup>3</sup> If deemed necessary during the Treatment Phase, a Physical Examination, blood tests, and radiological examinations were performed.

<sup>4</sup> Vital Signs included Heart Rate and Body Weight.

**1. Screening/Baseline Phase**

During the Screening/Baseline Phase, the Investigator verified that the patients met the Inclusion/Exclusion Criteria for entry into the study, and obtained baseline assessments.

Inclusion Criteria consisted of diagnosis of FCD (clinical and mammographic findings), mastalgia (constant or cyclical), normal thyroid function, a willingness to undergo pre- and post-treatment mammographic examinations, a willingness to have all previous and subsequent breast

biopsies examined by a designated pathologist, and an age of less than 60 years.

The patient was excluded if there was a history of reduction or "cosmetic" breast surgery, a history of more than two excisional breast biopsies on either breast, a history of significant thyroid abnormality, a history of major psychiatric disorder, or if the patient were pregnant.

Screening/Baseline Phase assessments included the following: a full pretreatment history and physical examination, a pretreatment mammographic examination (if not already done within the previous six months), thyroid function tests ( $T_3$  Uptake, Total  $T_4$ , and TSH levels), Total Breast Examination Score (objective assessment of FCD change and resolution of fibrosis), Patient's Subjective Score (subjective assessment of FCD change), and a recording of baseline signs and symptoms.

## 2. Treatment Phase

Patients were randomized into the active- or placebo-treated group by the clinic pharmacist. CTM was dispensed to each patient according to the randomization scheme, and instructions were given for CTM administration. Compliance was monitored at each visit. All patients were initially seen after one month of treatment; then they were assessed after three months. These assessments consisted of Total Breast Examination Score (objective assessment of FCD change), Patient's Subjective Score (subjective assessment of FCD change), and an Adverse Events Probe. If deemed necessary, a full evaluation including a physical examination, blood tests, and radiological investigations were performed.

## 3. Follow-up Phase

Post-treatment assessments occurred after the completion of treatment and included the following: a mammogram, vital signs (*i.e.*, Heart Rate and Body Weight), thyroid function ( $T_3$  Uptake, Total  $T_4$ , and TSH levels), Total Breast Examination Scores (objective assessment of FCD change), Patient's

Subjective Score (subjective assessment of FCD change), and an Adverse Events Probe.

At the completion of the study, all completers previously receiving placebo became eligible to receive active treatment with diatomic iodine. The Protocol allowed for patients to be followed for a maximum of one year.

#### **4. Study Termination**

Upon the completion of the post-treatment evaluations described in Section 3 above, the study was terminated.

### **F. EVALUATION**

#### **1. Efficacy Evaluation**

In this investigation, the efficacy of diatomic iodine was assessed by the use of objective and subjective measures. The Total Breast Examination Score was an objective assessment by the Investigator of the patient's FCD clinical condition and changes. The Patient's Subjective Score was the patient's assessment of pain associated with the FCD clinical condition.

#### **2. Safety Evaluation**

The safety of diatomic iodine was assessed primarily through examination of the results of the Adverse Events Probe. This checklist, used at each visit during the Treatment Phase and also at Post-Treatment Phase assessment, contained the following eight signs or symptoms: Acne, Nausea, Diarrhea, Hair Loss, Hyperthyroid, Hypothyroid, Skin Rash, Iodism, and Other. If deemed necessary, a full evaluation including a physical examination, blood tests, and radiological investigations were performed. Clinical laboratory assessments included thyroid function tests. In addition, vital signs (Heart Rate and Body Weight) data were examined. Analysis of the data involved comparisons between diatomic iodine-treated patients and placebo-treated patients and the subgroups of patients who were compliant and those who experienced treatment interruptions.

### 3. Adverse Events

Treatment emergent clinical or laboratory abnormalities are, by definition, those abnormalities which were not present prior to treatment or those that represent exacerbation of abnormalities which were present prior to treatment. Treatment emergent signs and symptoms (TESSs) and treatment emergent abnormal values (TEAVs) were examined across time points and by treatment group. The checklist data were examined by category and by treatment group.

### 4. Baseline Assessments

Screening/Baseline Phase assessments were used where baseline assessments were necessary for efficacy or safety evaluations. In addition to Demography, Baseline Phase data were collected on these variables: Physical Examination, Mammogram, Vital Signs (Heart Rate and Body Weight), Thyroid Function Tests ( $T_3$  Uptake, Total  $T_4$ , and TSH levels), subjective (Patient's Subjective Score) and objective (Total Breast Examination Score) evaluations of FCD change.

## G. STATISTICAL METHODOLOGY AND DATA MANAGEMENT

The original CRFs for the Seattle Study are retained by Dr. Hill, and a copy of the CRFs is maintained at the Breast Treatment Centre in Kingston, Ontario, Canada. Under the direction of Dr. Ghent, data were entered into a data diskette. Dr. Ghent was a subinvestigator in the Seattle Study and headed the Breast Treatment Centre in Kingston.

Information was received by Cato Research Ltd. from the Breast Treatment Centre either in a data diskette or in CRFs. A data base was compiled with adequate dosing information for 100 patients. Cato Research Ltd. received notification that there were 6 other patients, not all of whom received drug. Data regarding these 6 patients were on neither diskette nor CRFs.

Comparisons of the CRFs to the data base and review by the Cato Research data managers revealed that for 8 of the 100 patients, the treatment group was

unidentifiable. Due to the time lag between the study conduct and the analysis for this report, it was agreed to suppress these 8 patients from the data base and perform the statistical analysis on the remaining 92 patients.

The results of statistical analysis were considered with and without the inclusion of the 8 patients; the conclusions appear invariant to their inclusion. It follows, therefore, that the suppression of these 8 patients for whom treatment group is unclear does not alter the conclusions resulting from the statistical analysis of this study. For the purpose of this report, intent-to-treat analyses are performed on the complete data set of 92 patients with no data exclusion or imputation for these patients.

All statistical analyses were performed using SAS® Release 6.04. Statistical programs and the data base have been stored in the archives by Cato Research Ltd.

## 1. Demography

Demographic data collected during the Baseline Eligibility Phase were summarized using descriptive statistics.

## 2. Efficacy

Primary efficacy analyses were performed on data from the 92 patients identified. For measurement data (including the Total Breast Examination Score), paired t-tests were used to assess the statistical significance of within group changes from Baseline to Post-Treatment (Month 7) and F tests were used to make between-group comparisons. For dichotomous data, Fisher's Exact Test was used to assess the statistical significance of between-group comparisons.

For this investigation, the primary efficacy parameter was Total Breast Examination Score, an objective assessment of the patient's symptoms of FCD by the Investigator. The secondary efficacy parameter was Patient's Subjective Score, a subjective evaluation of the patient's FCD clinical condition.

**a. Total Breast Examination Scores**

The Total Breast Examination Score is an assessment determined by Investigator evaluation of five symptoms of FCD, assigning scores, and summing the scores.

**(1) Total Score**

The Total Breast Examination Score (or Total Score) ranges from 0 to 66+ and is derived by summing the individual scores from the following five parameters:

<i>Parameter</i>	<i>Range of Scores</i>
Tenderness	0 to 20
Nodularity	0 to 20
Fibrosis	0 to 20
Hyperactivity	0 to 6
Macrocyst	Actual Count

**(2) Individual Parameters**

For each assessment of Tenderness, Nodularity, and Fibrosis, each quadrant of each breast was scored as having the trait or not having the trait, and weighted according to the quadrant:

<i>Quadrant</i>	<i>Score (Weight)</i>
Upper Outside	1
Upper Inside	2
Lower Inside	3
Lower Outside	4

The maximum score is, hence,  $2 \times (1+2+3+4) = 20$  for each of these individual parameters.

For Hyperactivity, the score indicated the absence or presence of the trait. Hyperactivity was scored "present" if the breast exhibited tension characterized by a cone-shaped density behind the areola.

The number of macrocysts that were counted was taken as the individual score for Macrocysts.

### (3) Sensitivity Analyses

For each of three parameters (tenderness, nodularity, and fibrosis), assessments were made in each quadrant and summed across the quadrants for each breast. The scores for each patient for each parameter were available, but the scores were not available by quadrant. In an effort to assess the impact of the weighting scheme, sensitivity analyses were undertaken. Because the quadrant scores were not available, all possible configurations of quadrant scores that would result in the observed breast score were considered. Various configurations were used in analyses, described in the following selections:

- **Minimum Scores**

Quadrant configurations were assumed for each patient that yielded the minimum total breast examination score for that patient.

- **Maximum Scores**

Quadrant configurations were assumed for each patient that yielded the maximum total breast examination score for that patient.

- **Median Scores**

Quadrant configurations were assumed for each patient that yielded the median total breast examination score for that patient.

- **Minimum Reduction Scores**

Quadrant configurations were assumed for each patient that yielded the minimum reduction from baseline in total breast examination score for that patient.

- **Reduction Scores**

Quadrant configurations were assumed for each iodine-treated patient that yielded the minimum reduction from baseline in total breast examination score for that patient, and quadrant configurations were assumed for each placebo-treated patient that yielded the maximum reduction from baseline in total breast examination score for that patient. It is noted that this analysis is harsh, biased against the active-treated group.

### 3. Patient's Subjective Score

Each patient was asked to assess her own symptoms of FCD using the scale provided below. The resulting scores were used as a measure of efficacy in this study.

The Patient's Subjective Score is defined as follows:

Score	Definition
0	(1) Pain level increased in intensity or frequency or (2) Limitation of activity
1	No significant change in intensity or frequency of pain
2	Improvement in pain level: (1) Decrease in intensity or frequency or (2) Improvement in activity level
3	Complete relief of all pain and normal activity resumed.

#### 4. Safety

The 92 patients described above were included in safety analyses. It is noted that there were no AEs for the 8 patients that were excluded from analysis.

The incidence of AEs were summarized using descriptive statistics.

#### 5. Mammography

Mammography results were not available at the time of the preparation of this report. The mammography reports are stored in the Arnold Building at the Virginia Mason clinic in the possession of the radiologist, Dr. McClure Hall.

### III. STUDY ACCOUNTABILITY AND POPULATION

#### A. PATIENT ACCOUNTABILITY

There were 106 patients enrolled in the study. Treatment code or patient identification information was unidentifiable for some of these patients. Some patients did not receive drug, and for some, no data were available. The final data base for analysis contained data for 92 patients, 46 iodine-treated patients and 46 placebo-treated patients. This report summarizes data for these 92 patients. Available data for questionable patients are listed in Appendix IV.18.

Of the 92 patients who received test drug in this study, 46 were randomized to receive diatomic iodine, and 46 were randomized to receive placebo. Of 92 patients, 54 received treatment in compliance with the intended design, and 38 patients experienced treatment interruptions. Patients treated with placebo during the Treatment Phase were offered the opportunity to receive diatomic iodine at the end of the treatment. One such patient received drug.

#### B. DEMOGRAPHY

The study population was all female. Age ranged from 25 to 64 years; Body Weight ranged from 100 to 250 lb. Table B presents a summary of the demographic characteristics of patients reported in this study, displaying the mean and standard deviation (SD) of Age and Body Weight.

**Table B. Demography**

Population	Number of Patients	Mean Age in years (SD)	Mean Body Weight in lbs (SD)
Iodine — All Patients	46	43.0 (5.2)	139.9 (27.7)
Iodine — Compliant	23	43.6 (6.1)	141.2 (34.8)
Iodine — Treatment Interruptions	23	42.5 (4.2)	138.7 (18.9)
Placebo — All Patients	46	41.0 (7.3)	137.1 (24.0)
Placebo — Compliant	31	40.6 (8.0)	135.7 (26.0)
Placebo — Treatment Interruptions	15	41.9 (5.7)	140.1 (19.8)

The active-treated and placebo-treated groups were quite similar relative to Age and Weight. Additional Age and Weight details can be found in Tables 1.0 and 8.0 following text and the data listings provided in Appendix IV.

## C. STUDY ACCOUNTABILITY

### 1. Protocol Modifications

There were several modifications to the original Protocol; and these can be summarized as follows:

- The original Protocol specified that free T<sub>3</sub> was one of the thyroid function tests to be carried out in patients. T<sub>3</sub> uptake was done instead.
- The original Protocol specified that patients be assessed one month after starting the medication, then at two months intervals till the completion of the study. The second to last visit was eliminated.
- The original Protocol specified that patients who had undergone more than two biopsies be excluded. Patients who had three excisional biopsies were included in the study.

- The original Protocol specified that patients with significant thyroid abnormality including adenoma, carcinoma, Grave's disease and thyroiditis be excluded. Patients with a history of adenomas, which were excised and were taking thyroxine but had no identifiable ongoing thyroid pathology, were allowed to participate in the study.

## 2. Administrative Deviations

The original Protocol specified that patients must be less than 60 years old. One patient (#85) in the placebo group was 64 years old when she was enrolled into the study.

## 3. Blinding and Randomization

The clinic pharmacist was responsible for the randomization code; no one else had access to it. The randomization code resides in project files retained by Dr. Hill. The blinding of the identity of the CTM was protected.

## D. TREATMENT COMPLIANCE

As displayed in Table C, of the 46 patients randomized to receive diatomic iodine, 23 had one or more treatment interruptions with an average of 25 days off study drug. Of 46 patients randomized to receive placebo, 15 had treatment interruptions with an average of 26 days off study drug.

**Table C. Treatment Compliance Summary**

Treatment Group	Number of Compliant Patients	Number of Patients with Treatment Interruptions
Iodine	23	23
Placebo	31	15
Total	54	38

**E. DRUG EXPOSURE**

As Table D displays, 23 patients each received the daily dose of 10 to 25 ml of diatomic iodine for an average of 6.5 months each. The remaining 23 active-treated patients received the daily dose of 10 to 25 ml of diatomic iodine for an average of approximately 164 days or approximately 5.5 months.

Among placebo patients, 31 received the daily dose of placebo for an average of 7.0 months each; 15 received the daily dose for approximately 151 days or approximately 5 months.

**Table D. Drug Exposure**

Population	Treatment	Number of Patients	Mean Time On Study (months)	Mean Time Off Study (total days)
<b>All</b>	<b>Iodine</b>	46	6.4	N/A
	<b>Placebo</b>	46	6.6	N/A
<b>Compliant</b>	<b>Iodine</b>	23	6.5	0.0
	<b>Placebo</b>	31	7.0	0.0
<b>With Interruptions</b>	<b>Iodine</b>	23	6.3	25.2
	<b>Placebo</b>	15	5.9	25.9

N/A: Not applicable

Additional information regarding Drug Exposure is provided in Tables 2.1—2.5 following text and in the data listings in Appendix IV.

## IV. EFFICACY EVALUATION

### A. TOTAL BREAST EXAMINATION SCORE

The primary efficacy parameter was Total Breast Examination Score, which was an objective assessment of the patient's symptoms of FCD: Tenderness, Nodularity, Fibrosis, Hyperactivity, and Macrocyst. The Investigator did the individual assessments, assigned the scores, and summed the five individual scores to arrive at a single score.

#### 1. Primary Analysis of Total Breast Examination Score

Means of Total Breast Examination Scores for all patients, for patients with no treatment interruption, and for patients with one or more interruptions in medication are displayed in Table E.

**Table E. Means of Total Breast Examination Scores**

Population	Treatment Group	Baseline Score (SD)	Post-Treatment Score (SD)	Change From Baseline (SD)
All	Iodine (n = 46)	37.3 (16.4)	13.5 (12.7)	-23.9 (18.1)
	Placebo (n = 46)	35.3 (16.4)	32.7 (16.7)	-2.6 (8.9)
Compliant	Iodine (n = 23)	42.0 (14.4)	12.9 (12.6)	-29.1 (18.2)
	Placebo (n = 31)	33.4 (17.7)	30.8 (17.4)	-2.6 (10.0)
With Interruptions	Iodine (n = 23)	32.7 (17.2)	14.0 (13.1)	-18.7 (16.7)
	Placebo (n = 15)	39.2 (12.9)	36.5 (15.2)	-2.7 (6.4)

As Table E indicates, the active-placebo difference is striking in all population groups with the greatest pronounced difference being evident among patients who had no treatment interruptions.

The primary statistical analysis of the Total Breast Examination Score for all patients, for patients with no treatment interruption, and for patients with one or more treatment interruptions is displayed in Table F.

**Table F. Analysis of Total Breast Examination Score**

Comparison Groups	Mean Changes from Baseline	p-values*
Iodine vs. Placebo	-23.9 vs. -2.6	<0.001
Iodine (C) vs. Placebo (C)	-29.1 vs. -2.6	<0.001
Iodine (C) vs. Iodine (I)	-29.1 vs. -18.7	0.01
Iodine (I) vs. Placebo (C)	-18.7 vs. -2.6	<0.001
Placebo (C) vs. Placebo (I)	-2.6 vs. -2.7	0.99

\* F test

C: Compliant Patients

I: Patients with Treatment Interruptions

In the all-patient population (n = 92), the iodine-treated group Total Breast Examination Score declined from a mean of 37.3 (at Baseline) to a mean of 13.5 (at Month 7), showing a mean change of -23.9; the placebo-treated group score declined from a mean of 35.3 (at Baseline) to a mean of 32.7 (at Month 7), showing a mean change of -2.6. The statistical analysis resulted in a highly statistically significant active-placebo difference for the all-patient population ( $p < 0.001$ ).

Supporting analysis for the active-placebo difference among patients with no treatment interruption also resulted in statistical significance (mean change for iodine-treated patients of -29.1; mean change for placebo-treated patients of -2.6;  $p < 0.001$ ). When active-treated patients with one or more treatment interruptions are compared to placebo-treated patients with no interruption, the results show a statistically significant difference (mean change for iodine-treated group of -18.7; mean change for placebo-treated group of -2.6;  $p < 0.001$ ).

When active-treated patients with no treatment interruption are compared to active-treated patients with one or more treatment interruptions, a statistically significant difference is observed. The active-treated patients with no treatment interruption showed a mean change of -29.1; the active-treated

patients with one or more treatment interruptions showed a mean change of -18.7. The statistical analysis comparing these groups resulted in a p-value of 0.01.

When placebo-treated patients with no interruption are compared to placebo-treated patients with one or more treatment interruptions, no difference is observed ( $p = 0.99$ ).

These results are consistent with the following conclusions:

- Taking diatomic iodine without interruption for seven months is better than placebo relative to alleviation of symptoms of FCD, as assessed by the Total Breast Score.
- Taking diatomic iodine for a seven-month period, even with an interruption in medication of about a month, is better than taking placebo relative to alleviation of symptoms of FCD, as assessed by the Total Breast Score.
- Taking placebo for a seven-month period without interruption is equivalent to taking placebo for a seven-month period with an interruption of about a month relative to alleviation of symptoms of FCD, as assessed by the Total Breast Score.

## 2. Sensitivity Analyses of Total Breast Examination Score

The Total Breast Examination Score is a weighted score, weighing each of the four quadrants of the breast from 1 to 4. The Total Breast Examination Score also combines assessments of five characteristics of FCD, with heavier weight given to Tenderness (20 possible points), Nodularity (20 possible points), and Fibrosis (20 possible points) than to Hyperactivity (6 possible points) and Macrocysts (the count of macrocysts detected). In order to ensure the robustness of the analyses against weighing, a series of sensitivity analyses were performed.

For each patient, all possible configurations of symptoms were considered that would result in the score that was reported. Then a uniform weighting was assumed for the quadrants, which yielded a maximum possible score of 8 for Tenderness, Nodularity, and Fibrosis, retaining the Hyperactivity and Macrocyst scores. Various configurations were analyzed:

- Using the minimum scores for all patients, regardless of treatment group;
- Using the medium scores for all patients, regardless of treatment group;
- Using the maximum scores for all patients, regardless of treatment group;
- Using the scores that would produce the minimum reduction from Baseline for all patients, regardless of treatment group; and
- Using the scores that would produce the minimum reduction from Baseline for iodine-treated patients and maximum reduction for placebo-treated patients, which results in an analysis biased against iodine treatment.

The results of these sensitivity analyses are provided in Table G.

**Table G. Summary of Total Breast Examination Score Sensitivity Analyses**

Comparison Groups	66+ Scores	Minimum Scores	Median Scores	Maximum Scores	Minimum Reduction	Reduction*
Iodine vs. Placebo	<0.001	<0.001	<0.001	<0.001	<0.001	0.005
Iodine (C) vs. Placebo (C)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Iodine (C) vs. Iodine (I)	0.01	0.01	0.02	0.04	0.02	0.02
Iodine (I) vs. Placebo (C)	<0.001	<0.001	<0.001	<0.001	<0.001	0.34
Placebo (C) vs. Placebo (I)	0.99	0.87	0.80	0.73	0.65	0.97

\* Calculated using the minimum scores for iodine-treated patients and the maximum scores for placebo-treated patients

C: Compliant Patients

I: Patients with Treatment Interruptions

Note: p-values represent F tests

As Table G shows, the superiority of iodine treatment is preserved in the sensitivity analyses, which provides evidence that the results of the primary analysis are not dependent on the weighing scheme of the Total Breast Examination Score.

Additional details of Total Breast Examination Score Sensitivity Analyses is provided in Tables 16.1—17.0 following text.

Additional details of Total Breast Examination Score results are provided in Tables 10.0—10.5 following text. Data plots are provided in Appendix III, and data listings are located in Appendix IV.

## B. PATIENT'S SUBJECTIVE SCORE

The secondary efficacy parameter was Patient's Subjective Score, which was a subjective assessment by the patient of her symptoms of FCD.

### 1. Analysis of Patient's Subjective Score

Table H provides a summary of the number of patients in each treatment group (all-patient population) whose condition became worse, showed no change, improved, or resolved, based on the Patient's Subjective Score.

**Table H. Summary of Patient's Subjective Score**

Treatment Group	Final Evaluation			
	Worse	No Change	Improved	Resolved
Iodine (n = 46)	1	20	14	11
Placebo (n = 46)	2	29	11	4

Table I displays Patient's Subjective Score results by Compliance Group.

**Table I. Patient's Subjective Score (by Compliance Group)**

Population	Treatment Group	Final Evaluation			
		Worse	No Change	Improved	Resolved
Compliant	Iodine (n = 23)	0	8	9	6
	Placebo (n = 31)	2	19	7	3
With Interruptions	Iodine (n = 23)	1	12	5	5
	Placebo (n = 15)	0	10	4	1

As Tables H and I show, there is a trend, regardless of patient population, toward more favorable response with iodine treatment than with placebo treatment.

Table J displays a summary of the proportions of patients who improved or resolved based on Patient's Subjective Score.

**Table J. Summary of Patient's Subjective Score Results**

Population	Treatment Group	Number (%) of Patients Improved or Resolved
All	Iodine (n = 46)	25 (54%)
	Placebo (n = 46)	15 (33%)
Compliant	Iodine (n = 23)	15 (65%)
	Placebo (n = 31)	10 (32%)
With Interruptions	Iodine (n = 23)	10 (43%)
	Placebo (n = 15)	5 (33%)

As Table J shows, about half of the patients improved or resolved in the iodine-treated group, compared with about a third of the placebo-treated patients.

Table K provides a summary of the results of statistical analysis of Patient's Subjective Score.

**Table K. Analysis of Patient's Subjective Score**

Comparison Groups	Number (%) of Patients Improved or Resolved	p-value*
Iodine vs. Placebo	25 (54%) vs 15 (33%)	0.035
Iodine (C) vs. Placebo (C)	15 (65%) vs 10 (32%)	0.016
Iodine (C) vs. Iodine (I)	15 (65%) vs. 10 (43%)	0.139
Iodine (I) vs. Placebo (C)	10 (43%) vs. 10 (32%)	0.399
Placebo (C) vs. Placebo (I)	10 (32%) vs. 5 (33%)	0.942

\* Fisher's Exact Test

C: Compliant Patients

I: Patients with Treatment Interruptions

As Table K shows, for the all-patient population and for patients with no interruption in medication, there is a statistically significant and greater proportion of iodine-treated patients than placebo-treated patients who subjectively assessed their conditions to have improved or resolved ( $p = 0.035$  and  $p = 0.016$ , respectively).

The results of the analyses on Patient's Subjective Score are consistent with the conclusion that treatment with diatomic iodine is superior to treatment with placebo in the treatment of FCD.

Additional details of Patient's Subjective Score results are provided in Tables 11.0, 12.0 and 12.1 following text. Data plots are provided in Appendix III, and data listings are located in Appendix IV.

## V. SAFETY EVALUATION

Safety evaluations in this study involve the assessment of AEs, Physical Examination, vital signs (*i.e.*, Heart Rate and Body Weight), and clinical laboratory assessments (*i.e.*, thyroid function evaluations).

### A. CLINICAL ADVERSE EVENTS

#### 1. Checklist for Eliciting Clinical Events

A checklist was used that elicited the following symptoms: Acne, Nausea, Diarrhea, Hair Loss, Hyperthyroid, Hypothyroid, Skin Rash, Iodism, and Other.

#### 2. Reported Clinical Events

No serious AE was reported in this study.

Table L displays a summary of the AEs results by treatment group.

**Table L. Adverse Events (Results)**

Treatment Group	Number (%) of Patients Reporting Any Adverse Event
Iodine (n = 46)	5 (11%)
Placebo (n = 46)	10 (22%)

As Table L shows, 5 (11%) of the iodine-treated patients reported an AE; 10 (22%) of the placebo-treated patients reported at least one AE. Although a checklist was used, most of the reported events were recorded as "Other" on the CRF.

It is noted that no AE was reported during the Follow-up period for the placebo-treated patient who received active treatment at the end of the Treatment Phase

Table M displays a summary of the results of the checklist used in this study, indicating the number of patients in each group who reported any clinical event.

**Table M. Number of Patients Reporting Adverse Events**

Checklist Item	Number of Patients Reporting Adverse Events	
	Iodine (n = 46)	Placebo (n = 46)
Acne	1	3
Nausea	0	0
Diarrhea	0	1
Hair Loss	0	0
Hyperthyroid	0	0
Hypothyroid	0	0
Skin Rash	0	0
Iodism	0	0
Other	5	6

As Table M shows, 11 patients (5 iodine-treated and 6 placebo-treated patients) reported clinical events in the "Other" category. With 4 patients (1 iodine-treated and 3 placebo-treated) reporting Acne, this AE became a distant second in checklist frequencies.

Additional details of AE results are provided in Tables 5.0, 6.0, and 7.0 following text. Data listings are located in Appendix IV.

The specific AEs reported as "Other" are displayed in Table N. Patients with AEs with question marks recorded on CRFs were treated as if the events were not in question.

**Table N. Adverse Events Reported as "Other"**

Adverse Events Reported as "Other"	
Iodine (n = 46)	Placebo (n = 46)
Constipation?*	Indigestion
Menstrual irregularity	Dry mouth
Polyuria	Nausea when taken on empty stomach
Loose stools	Headache
Weight loss	Gas?*
	Occasional gas

\* Reported on CRF with question mark

The clinical events that were reported in this study were transient and are classified as minor clinical complaints.

Additional details of AE results are provided in Tables 5.0, 6.0, and 7.0 following text. Data listings are located in Appendix IV.

**B. VITAL SIGNS**

Heart Rate and Body Weight were assessed during this study for safety.

**1. Heart Rate**

Table O displays a summary of the Mean Heart Rate at baseline, Mean Heart Rate at post-treatment, and the Mean Change from Baseline for the all-patient population.

**Table O. Mean Heart Rate (bpm) and Mean Change from Baseline**

Treatment	Baseline	Post-Treatment	Change from Baseline
Iodine	79.9 (n = 46)	76.9 (n = 30)	-4.2 (n = 30)
Placebo	76.4 (n = 46)	76.6 (n = 25)	0.1 (n = 25)

As Table O shows, there is no evidence of any effect of diatomic iodine on Heart Rate.

**2. Body Weight**

Table P displays a summary of the Mean Body Weight at baseline, Mean Body Weight at post-treatment, and the Mean Change from Baseline for the all-patient population.

**Table P. Mean Body Weight (lb) and Mean Change from Baseline**

Treatment	Baseline	Post-Treatment	Change from Baseline
Iodine	139.9 (n = 46)	145.0 (n = 30)	3.0 (n = 30)
Placebo	137.1 (n = 46)	138.8 (n = 25)	4.1 (n = 25)

As Table P shows, there is no evidence of any effect of diatomic iodine on Body Weight.

**C. CLINICAL LABORATORY TESTS (THYROID FUNCTION)**

The potential influence of diatomic iodine on thyroid function was investigated in this study by assessing T<sub>3</sub> Uptake, Total T<sub>4</sub>, and TSH, with measurements at Baseline and Post-Treatment. No clinically significant TEAV or change was recorded in this study. Analysis of thyroid function parameters indicates no evidence that diatomic iodine affects thyroid function.

**1. T<sub>3</sub> Uptake (Normal range: 25.0% - 36.0%)**

No clinically significant change in T<sub>3</sub> Uptake was observed in this study. Table Q displays, by treatment group, the mean of T<sub>3</sub> Uptake at baseline, the mean at post-treatment, and Mean Change from Baseline.

**Table Q. Mean T<sub>3</sub> Uptake (Normal range: 25.0% - 36.0%)**

Treatment	Baseline	Post-Treatment	Change from Baseline
Iodine (n = 45)	28.1	28.4	0.3
Placebo (n = 45)	28.0	28.2	0.2

The mean T<sub>3</sub> Uptake showed small fluctuations that were considered to be clinically insignificant and unrelated to diatomic iodine. The results of the all-patients group are consistent with the results when compliance groups are considered separately.

Additional T<sub>3</sub> Uptake results are provided in Tables 9.1—9.2 and 13.0—13.1 following text. Data listings are provided in Appendix IV.

**2. Total T<sub>4</sub> (Normal range: 4.0 µg/dl - 10.5 µg/dl)**

No clinically significant change in Total T<sub>4</sub> was observed in this study. One patient had a value outside the normal range at post-treatment: patient #48 had a Total T<sub>4</sub> value of 15.4 µg/dl. It should be noted that the Total T<sub>4</sub> value of this patient at Baseline was elevated (11.6 µg/dl). No other patient in this study had any TEAV for Total T<sub>4</sub>.

Table R displays, by treatment group, the mean of Total T<sub>4</sub> at Baseline, the mean at post-treatment, and the Mean Change from Baseline.

**Table R. Mean Total T<sub>4</sub> (Normal range: 4.0 µg/dl - 10.5 µg/dl)**

Treatment	Baseline	Post-Treatment	Change from Baseline
Iodine (n = 45)	6.32	6.79	0.47
Placebo (n = 45)	6.44	6.66	0.26

The mean Total T<sub>4</sub> showed small fluctuations that were considered to be clinically insignificant and unrelated to diatomic iodine. Additional Total T<sub>4</sub> results are provided in Tables 9.1—9.2 and 13.0—13.1 following text. Data listings are provided in Appendix IV.

### 3. TSH (Normal range: 0 µIU/ml - 12 µIU/ml)

No clinically significant change in TSH was observed in this study. One patient had a value outside the normal range at post-treatment: patient #87 had a TSH value of 17.1 µIU/ml. No other patient in this study had any TEAV for TSH.

Table S displays, by treatment group, the mean of TSH at baseline, the mean at post-treatment, and the Mean Change from Baseline.

**Table S. Mean TSH (Normal range: 0 µIU/ml - 12 µIU/ml)**

Treatment	Baseline	Post-Treatment	Change from Baseline
Iodine (n = 45)	2.32	2.89	0.57
Placebo (n = 45)	2.32	2.16	-0.17

The mean TSH showed small fluctuations that were considered to be clinically insignificant and unrelated to diatomic iodine. Additional TSH results are provided in Tables 9.1—9.2 and 13.0—13.1 following text. Data listings are provided in Appendix IV.

#### 4. Summary of Thyroid Function Results

In summary, results of the thyroid function parameters assessed in this study show minor fluctuations that were considered to be clinically insignificant and unrelated to diatomic iodine. The results of these analyses show no evidence of clinically noteworthy influence of iodine on thyroid function.

Summary tables, plots, and data listings provide details of results of thyroid function parameters. Tables 9.1—9.2 and 13.0—13.1 following text display means, standard deviations, and Mean Change from Baseline by treatment group. Data (box) plots are found in Appendix III, and data listings are located in Appendix IV. Appendix V contains statistical analyses of thyroid function. A thorough analysis of these data displays indicates no evidence that iodine has an influence on changes in thyroid function.

#### D. MAMMOGRAPHY

Results of mammography tests were not available at the time of preparation of this report. It was noted by Dr. Hill, however, that seven months was too short a time period to observe changes by mammography.

## VI. DISCUSSION

This prospective, double-blind, randomized, and placebo-controlled investigation in FCD patients was designed to compare aqueous diatomic iodine to placebo in the treatment of pain as well as the fibrotic and cystic components of fibrocystic disease.

### A. ADVERSE EVENTS

Diatomic iodine was generally well-tolerated by all patients, with no serious AEs reported during the study.

No objective physical findings were associated with any of the reported AEs. The remainder of the symptoms reported by the patients were judged by the investigator to be clinically insignificant and not related to diatomic iodine. Analysis of the proportion of patients reporting AEs within each dose group revealed no statistical differences between the iodine- and placebo-treated groups.

### B. VITAL SIGNS

Heart Rate and Body Weight were examined to assess the effect of diatomic iodine on vital signs. Mild fluctuations were observed across all groups and were judged to be clinically insignificant and not related to diatomic iodine.

### C. CLINICAL LABORATORY PARAMETERS

Clinical laboratory assessments involved thyroid function tests (*i.e.*, T<sub>3</sub> Uptake, Total T<sub>4</sub>, and TSH levels). Although mild fluctuations were observed in the thyroid function tests, the variations were considered to be clinically insignificant and not related to diatomic iodine.

### D. EFFICACY EVALUATION

Efficacy assessment consisted of subjective and objective evaluations of FCD change.

In the all-patient population (n = 92), Total Breast Examination Score for the iodine-treated group declined from a mean of 37.3 (at Baseline) to a mean of 13.5 (at Month 7), showing a mean change of -23.9; the placebo-treated group score declined from a mean of 35.3 (at Baseline) to a mean of 32.7 (at Month 7), showing a mean change of -2.6. The statistical analysis resulted in a highly statistically significant active-placebo difference for the all-patient population ( $p < 0.001$ ).

Supporting analysis for the active-placebo difference among patients with no treatment interruption also resulted in statistical significance (mean change for iodine-treated patients of -29.1; mean change for placebo-treated patients of -2.6;  $p < 0.001$ ). When active-treated patients with one or more treatment interruptions are compared to placebo-treated patients with no interruption, the results show a statistically significant difference (mean change for iodine-treated group of -18.7; mean change for placebo-treated group of -2.6;  $p < 0.001$ ).

When active-treated patients with no treatment interruption are compared to active-treated patients with one or more treatment interruptions, a statistically significant difference is observed. The active-treated patients with no treatment interruption showed a mean change of -29.1; the active-treated patients with one or more treatment interruptions showed a mean change of -18.7. The statistical analysis comparing these groups resulted in a p-value of 0.01.

When placebo-treated patients with no treatment interruption are compared to placebo-treated patients with one or more treatment interruptions, no difference is observed ( $p = 0.99$ ).

## E. SAFETY EVALUATION

Safety evaluation included an Adverse Events Probe, a checklist was used to elicit information about the following symptoms: Acne, Nausea, Diarrhea, Hair Loss, Hyperthyroid, Hypothyroid, Skin Rash, Iodism, and Other. If deemed necessary, a full evaluation including a physical examination, blood tests, and radiological investigations was performed. Clinical laboratory assessments consisted of thyroid function tests.

Aqueous diatomic iodine was generally well tolerated by all patients. No serious AE was reported.

A total of 5 (11%) of the iodine-treated patients and 10 (22%) of the placebo-treated patients reported any AE. AEs reported from iodine-treated patients included the following: acne, constipation, menstrual irregularity, polyuria, loose stools, and weight loss. AEs reported from placebo-treated patients included these events: acne, diarrhea, indigestion, dry mouth, nausea when taken on empty stomach, headache, and gas. All AEs were transient and classified as minor clinical complaints.

There was no evidence of any influence of treatment with diatomic iodine on Heart Rate, Body Weight, or Thyroid Function.

## VII. CONCLUSIONS

The conclusions of this study are as follows:

- Diatomic iodine was generally well-tolerated by all patients, with no serious AEs reported in the study.
- Taking diatomic iodine without interruption for seven months is better than placebo relative to alleviation of symptoms of FCD, as assessed by the Total Breast Score.
- Taking diatomic iodine for a seven-month period, even with an interruption in medication of about a month, is better than taking placebo relative to alleviation of symptoms of FCD, as assessed by the Total Breast Score.
- Taking placebo for a seven-month period without interruption is equivalent to taking placebo for a seven-month period with and interruption of about a month relative to alleviation of symptoms of FCD, as assessed by the Total Breast Score.
- There is no evidence to suggest that treatment with diatomic iodine is associated with any profile of clinical signs or symptoms.

## VIII. REFERENCES

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