

APPENDIX D.

**CLINICAL TRIAL REPORT. PROTOCOL PTL-0013/0022.
CLINICAL EVALUATION OF LUBRICOAT 0.5% FERRIC HYALURONATE
GEL FOR THE REDUCTION OF ADHESIONS FOLLOWING PERITONEAL
CAVITY SURGERY, A MULTICENTER STUDY OF SAFETY AND EFFICACY.
MARCH 4, 1999**

CLINICAL EVALUATION OF LUBRICOAT® 0.5% FERRIC HYALURONATE GEL FOR THE REDUCTION OF ADHESIONS FOLLOWING PERITONEAL CAVITY SURGERY, A MULTICENTER STUDY OF SAFETY AND EFFICACY

CLINICAL TRIAL REPORT

Protocol/IDE Numbers: PTL-0013 (United States) and PTL-0022 (Europe)/G950025

Product: LUBRICOAT® 0.5% Ferric Hyaluronate Gel

Form/Route/Dose: Viscous Liquid/Intraperitoneal Instillation/300 mL

Principal Investigators: Multicenter study; 11 sites in the United States and 5 sites in Europe

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Study Start Date: 08 March 1996
(First patient to receive study solution)

Study Stop Date: 18 January 1999
(Last patient to receive "second-look" laparoscopy)

Report Date: 4 March 1999

This clinical study was conducted in accordance with Good Clinical Practice (GCP) and in compliance with all applicable country requirements for the conduct of clinical trials, including the Declaration of Helsinki, and the U.S. Food and Drug Administration.

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APPROVAL

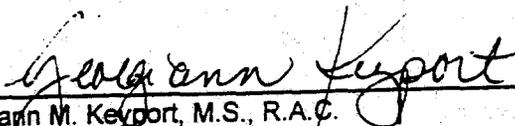
Protocol Numbers: PTL-0013 (United States) and PTL-0022 (Europe)

Protocol Title: Clinical evaluation of LUBRICOAT® 0.5% Ferric Hyaluronate Gel for the reduction of adhesions following peritoneal cavity surgery, a multicenter study of safety and efficacy.

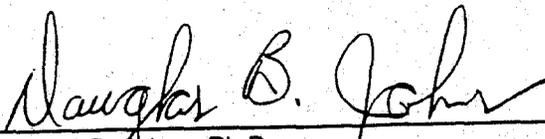
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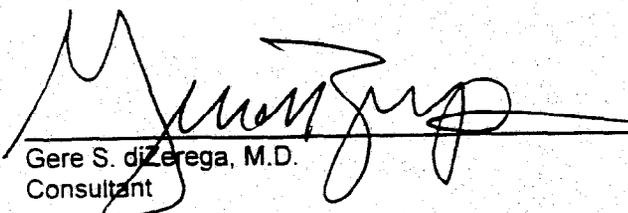
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STUDY ABSTRACT

PROTOCOL NUMBERS: PTL-0013 and PTL-0022

PROTOCOL TITLE:

Clinical evaluation of LUBRICOAT[®] 0.5% Ferric Hyaluronate Gel for the reduction of adhesions following peritoneal cavity surgery, a multicenter study of safety and efficacy.

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OBJECTIVES:

The objectives of this multicenter study were to assess the safety and efficacy of LUBRICOAT[®] 0.5% Ferric Hyaluronate Gel compared with lactated Ringer's solution in preventing or reducing adhesions in patients undergoing peritoneal cavity surgery. This study was conducted in the United States (US) and Europe under two identical protocols: PTL-0013 (US) and PTL-0022 (Europe). As stated in the protocols, the trials in the US and in Europe were to be stopped prior to completion, if the data from

the two trials could be combined to achieve 200 evaluable patients (approximately 100 patients per treatment group). An evaluable patient was defined as one who had completed her scheduled second-look laparoscopy targeted for 6 to 12 weeks from the initial surgical procedure. A total of 303 patients (152 LUBRICOAT[®] and 151 lactated Ringer's solution) were randomized in the two trials; 281 were enrolled, and 265 completed the second-look laparoscopy and were evaluable for efficacy (131 LUBRICOAT[®] and 134 lactated Ringer's solution). This report presents safety and efficacy data on the patients combined from the two trials.

STUDY DATES: 08 March 1996 - 18 January 1999

OVERALL STUDY DESIGN AND METHODS:

The study design was a randomized, third-party blinded, placebo-controlled, multicenter clinical study consisting of two parallel treatment groups (LUBRICOAT[®] 0.5% Ferric Hyaluronate Gel as study device and lactated Ringer's solution as control solution). The study was conducted at 11 centers in the United States (US) and five centers in Europe under identical Protocols: PTL-0013 (US) and PTL-0022 (Europe). A total of 303 (152 in the LUBRICOAT[®] Gel group and 151 in the lactated Ringer's solution group) female patients aged between 18.6 and 45.9 years undergoing peritoneal cavity surgery by laparotomy with a planned second-look laparoscopy were randomized in this study. A single intraperitoneal instillation of 300 mL of LUBRICOAT[®] 0.5% Ferric Hyaluronate Gel or lactated Ringer's solution was administered to the patients in the hospital at the completion of the laparotomy procedure. The four most common surgical procedures were myomectomy, adhesiolysis, ovarian surgery, and tubal surgery. Return visit was conducted approximately 6 to 12 weeks after the initial surgical procedure for a second-look laparoscopic procedure to evaluate efficacy. The primary efficacy variable was an adhesion score using the Adhesion Scoring Method of the American Fertility Society¹ (AFS) applied to 24 anatomical sites including both pelvic and upper abdominal locations (Modified AFS Score). Secondary efficacy variables were the proportion of sites with adhesions, the extent of adhesions, and the severity of adhesions. Adhesions were characterized as *de novo* if the site had no pre-existing adhesions and as reformed if the site had adhesions that were lysed during the initial surgery. Sites with *de novo* adhesions were also characterized as surgical versus non-surgical and pelvic versus abdominal. Adhesions at all surgical sites, pelvic sites only, general surgical sites only, and at each individual anatomical site were also evaluated. Safety assessments were based on the type and incidence of adverse events recorded throughout the study, the pre-operative and post-operative laboratory test values, concomitant medications/conditions, and gross evaluation at second-look laparoscopy.

DISPOSITION OF PATIENTS:

Of the 303 patients randomized in the study, 22 (9 LUBRICOAT[®] Gel and 13 lactated Ringer's solution) did not receive treatment and 281 (143 LUBRICOAT[®] Gel and 138 lactated Ringer's solution) were treated. Of the 281 treated patients, 265 (131 LUBRICOAT[®] Gel and 134 lactated Ringer's solution) completed the study, and 16 (12 LUBRICOAT[®] Gel and 4 lactated Ringer's solution) discontinued from the study. The reasons for discontinuation from the study were: patient's decision (13 patients), physician's decision (one patient), lost to follow-up (one patient), and

¹ The American Fertility Society. The American Fertility Society classification of adnexal adhesions, distal tubal occlusion, tubal occlusion secondary to tubal ligation, tubal pregnancies, Mullerian anomalies, and intrauterine adhesions. Fertil Steril. 49:944-955, 1988.

pregnancy (one patient). Thus, 281 treated patients (143 LUBRICOAT® Gel and 138 lactated Ringers's Solution) were evaluable for safety analysis; the 265 treated patients who completed the study were evaluable for efficacy analysis.

EFFICACY RESULTS:

Treatment with LUBRICOAT® Gel in patients undergoing peritoneal cavity surgery was found to be superior to treatment with lactated Ringer's solution. When all adhesion sites were considered, LUBRICOAT® Gel was found to be significantly ($p < 0.05$) more effective than lactated Ringer's solution in reducing the total number of post-surgical adhesions (based on the Modified AFS score from 24 anatomical sites). Patients treated with LUBRICOAT® Gel had an overall average score that was 45% lower ($p = 0.000$) than that of patients treated with the control solution. The proportion of sites with new adhesions, and the severity and extent of post-surgical adhesions were also significantly ($p < 0.05$) reduced in patients treated with LUBRICOAT® Gel. The gel was also found to be significantly ($p < 0.05$) more effective than the control solution in reducing both *de novo* and reformed adhesions.

The greater reduction in adhesions with LUBRICOAT® Gel was observed regardless of the presence or absence of endometriosis, the use of sutures, the method of adhesiolysis (sharp dissection, blunt dissection, or cautery), or the surgical procedure used.

When only the abdominal sites (i.e., general surgical or upper abdominal sites) were considered, LUBRICOAT® Gel was found to be significantly ($p < 0.05$) more effective than the control solution in reducing the incidence, extent and severity of adhesions, and *de novo* and reformed adhesions. The reduction in *de novo* adhesions was observed at both the surgical and non-surgical sites. The total number of adhesions and the proportion of sites with new adhesions was also significantly ($p < 0.05$) reduced.

When only the pelvic sites were considered, LUBRICOAT® Gel was again found to be significantly ($p < 0.05$) more effective than the control solution in reducing the incidence, extent and severity of adhesions, and *de novo* and reformed adhesions. The reduction in *de novo* adhesions was observed at both the surgical and non-surgical sites. These results prove that LUBRICOAT® Gel is effective in reducing adhesions after peritoneal cavity surgery.

The effect of LUBRICOAT® Gel on reducing adnexal adhesions was shown by a significant reduction in the Standard AFS score compared to lactated Ringer's solution. The minimum score of both the right and left adnexa was reduced by 59% following administration of LUBRICOAT® Gel ($p < 0.005$). In addition, the proportion of patients with minimal scores (Standard AFS score 0-5) increased in the patient group that received LUBRICOAT® Gel and decreased in the lactated Ringer's solution group. Similarly, the proportion of patients with mild, moderate or severe Standard AFS scores (6-10, 11-20, 21-32, respectively) decreased in the group that received LUBRICOAT® Gel and increased in the group that received lactated Ringer's solution.

SAFETY RESULTS:

The safety profile of patients treated with LUBRICOAT® Gel was comparable to that of those treated with lactated Ringer's solution. All patients in both treatment groups reported having at least one adverse event. The most frequently reported patient complaints in both treatment groups were pain (85.3% vs. 80.4%), nausea (42.6% vs. 47.7%), constipation (32.9% vs. 40.6%), headache (31.5% vs. 26.8%), abdominal pain (27.3% vs. 30.4%), and flatulence (24.5% vs. 25.4%). These expected events (given that patients were undergoing anesthesia and surgery) were generally mild to moderate and almost all resolved spontaneously or with treatment. Sixteen patients (11.2%) treated with LUBRICOAT® Gel and 7 (5.1%) patients treated with lactated Ringer's solution experienced adverse events considered by the investigator to be possibly, probably, or definitely related to treatment. These events included abdominal pain/post-operative pain, fever, nausea, and constipation.

Treatment-related serious adverse events were experienced by four patients in the LUBRICOAT® Gel group (two cases of abdominal pain, one case of fever, and one case of post-operative ileus) and one patient in the control group (fever). These patients were treated with medications or additional surgical procedure. There were no discontinuations due to an adverse event and no deaths occurred during the study.

As expected in patients who had undergone recent surgery, normal to low or high shifts in several clinical laboratory parameters occurred in both treatment groups within 3 days of the initial surgery (Visit 1), reflecting factors such as surgical trauma and hemodilution. By Visit 3 (immediately prior to the second-look laparoscopy), most parameters were within normal ranges in both treatment groups. Shifts outside the normal ranges were considered not clinically significant. Elevations in WBCs, primarily due to an increase in the number of neutrophils, first seen at Visit 1 persisted through Visit 2. Subgroup analysis was performed to assess correlation between elevated WBC concentrations and center, continent, fever, infection, adhesion formation (Modified AFS score), duration of hospitalization, surgical time, and blood loss. No correlation was found. No pattern of clinical sequelae (including infection and intraperitoneal adhesions) with patients with elevated WBC and/or neutrophils shifts were identified which were considered to be clinically significant. Since these findings of a low, transient elevation of WBC concentration was not common to any particular center, demographic, or clinical manifestation, it was considered to be a brief, subclinical response without clinical significance.

CONCLUSIONS:

A single intraperitoneal instillation of 300 mL LUBRICOAT® Gel in female patients undergoing peritoneal cavity surgery by laparotomy was safe and effective in improving adhesion outcome:

- The mean total Modified AFS score was significantly ($p < 0.05$) lower in the LUBRICOAT® Gel group than in the lactated Ringer's solution group.
- The minimum Standard AFS score of both the right and left adnexa was significantly ($p < 0.05$) lower in the LUBRICOAT® Gel group than in the lactated Ringer's solution group.
- The proportion of sites with post-surgical adhesions were significantly ($p < 0.05$) fewer in the LUBRICOAT® Gel group than in the lactated Ringer's solution group.
- The severity and extent of post-surgical adhesions were significantly ($p < 0.05$) less in the LUBRICOAT® Gel group than in the lactated Ringer's solution group.
- *De novo* and reformed adhesions were significantly reduced in the LUBRICOAT® Gel group than in the lactated Ringer's solution group.
- The reduction in adhesions was observed whether all sites were considered, only the general surgical sites were considered, or only the pelvic sites were considered.
- The reduction in adhesions was observed regardless of the presence or absence of endometriosis, the use of sutures, the method of adhesiolysis, or the surgical procedure used.
- The safety profile (i.e., adverse event incidence rates, clinical laboratory test results) of patients treated with LUBRICOAT® Gel was comparable to that of those treated with lactated Ringer's solution.

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LIST OF ABBREVIATIONS

AFS	:	American Fertility Society
AHFS	:	American Hospital Formulary System
ALT/SGPT	:	Alanine transaminase/serum glutamic pyruvic transaminase
ANOVA	:	Analysis of variance
AST/SGOT	:	Aspartate transaminase/serum glutamic oxaloacetic transaminase
BUN	:	Blood urea nitrogen
CBC	:	Complete blood count
CTR	:	Clinical Trial Report
CPT	:	Current Procedures Terminology
EC	:	Ethics Committee
FDA	:	Food and Drug Administration
GCP	:	Good Clinical Practice
HA	:	Sodium Hyaluronate
Hgb	:	Hemoglobin
IRB	:	Institutional Review Board
LUBRICOAT® Gel	:	LUBRICOAT® 0.5% Ferric Hyaluronate Gel
OTC	:	Over the counter
PVC	:	Polyvinyl chloride
RBC	:	Red blood cells
US	:	United States of America
WBC	:	White blood cells

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1. INTRODUCTION

Postoperative adhesions, a frequent abdominal surgical complication, may result in patient complaints ranging from abdominal discomfort to bowel obstruction and infertility.¹⁻³ An adhesion, in this report, is defined as fibrous tissue or band(s) interconnecting at least two organs or sites. Adhesions can form following surgery at sites which had no pre-existing adhesions. These are termed "*de novo* adhesions". *De novo* adhesions can form at sites of surgical trauma, a "surgical site *de novo* adhesion", or at sites which had no surgical intervention, a "non-surgical *de novo* adhesion". Pre-existing adhesions which are lysed, i.e. the organ or site is freed from the other structure to which it was attached, can also reform. These are termed "reformed adhesions". Reformed adhesions can be further classified depending on the size (extent) and tenacity (severity) of the original adhesion which was lysed as well as the size (extent) and tenacity (severity) of the adhesion which reforms. Thus, as with *de novo* adhesions, reformed adhesions can be classified according to the extent of surgery or injury which occurred at a particular site.

Numerous products have been used for the purpose of reducing adhesion formation including, saline peritoneal lavage, antibiotic therapy and HYSKON® 32% dextran 70 (Pharmacia Upjohn). Thus far, clinical experience with these treatments has been equivocal. FDA-approved INTERCEED® (TC7) Absorbable Adhesion Barrier (ETHICON, Inc.) and Seprafilm Bioresorbable® Membrane (Genzyme Corporation) have been proven efficacious, but as is inherent with a barrier fabric or film products, the effect is localized and therefore site specific. Interest therefore continues in the development of an intraperitoneal device which functions more broadly as a post-surgical adhesion prophylactic.

Sodium hyaluronate (HA), present throughout the body, is a naturally-occurring polydisperse molecular weight mucopolysaccharide comprised of sodium D-glucuronate and N-acetyl-D-glucosamine which are linked as disaccharides by beta

1-3 linkages. The subunits are joined by beta 1-4 glycosidic bonds. It is hydrolyzed to disaccharide or tetrasaccharide units by the action of the enzyme hyaluronidase. HA has been shown to significantly reduce adhesion formation in animal models⁴ and is believed to function through a physical effect by providing a viscous, lubricious coating on the peritoneal surfaces. In clinical evaluations conducted by ETHICON, Inc., sodium hyaluronate, supplied by Lifecore Biomedical Inc., was found to be safe but only marginally effective, with the greatest effect coming from a reduction in *de novo* adhesions.⁵⁻⁷

LUBRICOAT[®] 0.5% Ferric Hyaluronate Gel (LUBRICOAT[®] Gel) is an aqueous solution of HA which has been ionically cross linked by the addition of a ferric chloride solution. Cross linking between the carboxylate groups on the HA and the trivalent iron (Fe^{+3}) is ionic in nature, resulting in a significant increase in solution viscosity compared to the starting HA solution. The ionically cross linked LUBRICOAT[®] Gel has been found to prevent or reduce adhesion formation in preclinical animal models where HA has little or no effect.⁸

LUBRICOAT[®] Gel is an amber, viscous liquid formulated to a specific viscosity range. It is a sterile, nonpyrogenic gel of a highly purified medium molecular weight hyaluronate adjusted to isotonicity with sodium chloride. For commercial distribution, it has been given the name, INTERGEL* Adhesion Prevention Solution, and is packaged in a single use, 320 mL, polyolefin bellows-type bottle designed to deliver 300 mL of gel. It is provided sterile in a plastic tray with a Tyvek lid, along with a 5 3/4 inch Polyvinyl Chloride (PVC) extension tube to facilitate directing the gel to specific sites. It was packaged in 100 mL Type I borosilicate amber vials with 20 mm flip tear-off seals for this clinical evaluation.

*Trademark of ETHICON, Inc.

A pilot study to assess study methodology and to make a preliminary assessment of the safety of LUBRICOAT® Gel was carried out.⁹⁻¹⁰ The single-center pilot study was conducted in an open-label, randomized, controlled design. Female patients undergoing peritoneal cavity surgery by laparotomy for infertility, with a planned second-look laparoscopy, received either 300 mL of LUBRICOAT® Gel (n=13) or lactated Ringer's solution (n=10) as an intraperitoneal instillate prior to closure. This volume was based on clinical studies conducted with non-cross linked HA solution and was believed to be sufficient to coat the entire surface of the peritoneal cavity. Twenty-one second-look laparoscopies (11 LUBRICOAT® Gel and 10 lactated Ringer's solution) were completed. At second-look laparoscopy, patients treated with LUBRICOAT® Gel had significantly fewer adhesions than patients treated with the control solution. When adhesions did form, they were significantly less extensive and less severe in patients who received LUBRICOAT® Gel. No safety concerns were identified. No unusual lesions were observed grossly upon second-look laparoscopy, and no clinically significant differences in laboratory values, concomitant medications, or adverse events were noted between active and control groups.

This clinical study was planned to assess the efficacy and safety of LUBRICOAT® Gel compared with lactated Ringer's solution in American and European female patients undergoing peritoneal cavity surgery with a planned second-look laparoscopy. As stated in the protocol, the trials in the US and Europe were to be stopped prior to completion, if the data from the two trials could be combined to achieve 200 evaluable patients (approximately 100 patients per treatment group). An evaluable patient was defined as one who had completed her scheduled second-look laparoscopy targeted for 6 to 12 weeks from the initial surgical procedure.

On 30 October 1998, FDA approved the supplement requesting permission to terminate enrollment in these studies. This report presents data on the 281 patients

combined from the trials in the US (PTL-0013, 200 patients) and Europe (PTL-0022, 81 patients). The efficacy and safety results, pooled across all investigators, are displayed in key summary tables within the text of the report. Additional summary tables (referred to as Supplemental Tables) are presented at the end of the text of the report. A set of appendices contain the full documentation for the efficacy and safety variables. The appendices include the study protocol, case report forms, published and unpublished reports, and relevant data listings.

2. OBJECTIVES

The objectives of this multicenter study were to assess the safety and efficacy of LUBRICOAT® Gel in preventing or reducing adhesions in patients undergoing peritoneal cavity surgery.

3. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This multi-center study was conducted by 11 principal investigators in the United States (US) and five principal investigators in Europe, each investigator enrolling between 1 and 44 patients. As originally planned in the protocols, 12 principal investigators in the US were to participate in this study, however, one investigator never enrolled patients. A complete list of principal investigators and sub-investigators from the US and Europe, their study location, and study dates (i.e., the first patient to receive study solution at the site and the last patient to receive second-look laparoscopy at the site) are provided in Appendix 1A. The curricula vitae of the investigators are provided in Appendix 1B.

This study was sponsored by:

LIFECORE BIOMEDICAL, INC.
3515 Lyman Boulevard
Chaska, MN 55318-3051
Tel: 612-368-4300
Fax: 612-368-3411
Contact Person: Georgiann Keyport
Tel: 612-368-6294

The trials in the US and in Europe were monitored by a contract research organization (CRO). The US trial was monitored by:

Quintiles, Inc.
10180 Telesis Court, Suite 200
San Diego, CA 92121
Tel: 619-799-9000
Fax: 619-799-8990
Contact Person: Amy Kovacs
Tel: 619-799-9040
Contact Person for Adverse Events: Gerald L. Klein, MD
Tel: 619-941-4444

The European trial was monitored by:

Quintiles Scandinavia
Global House, 4 Kvaesthusgade
DK 1251 Copenhagen K
Denmark
Tel: 45-33-93-8400
Fax: 45-33-93-8401
Contact Person: Merete Holm-Bentzen, MD
Tel: 45-33-93-8400
Fax: 45-33-93-8401

The Medical Review Officer was:

Gere S. diZerega, MD
Professor of Obstetrics and Gynecology
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1321 N. Mission Rd.
Los Angeles, CA 90033
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Data management and statistical analyses were performed by:

Fred Hoehler, PhD
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Tel: 714-771-7141
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This clinical trial report (CTR) was prepared by:

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Frimpong Clinical Research (FCR) Consulting Services
76 Radcliff Drive
Doylestown, PA 18901
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Fax: 215-340-2731

4. ETHICS COMMITTEE / INSTITUTIONAL REVIEW BOARD

This study complied with the US Food and Drug Administration (FDA) requirements of 21 Code of Federal Regulations (CRF Parts 50 and 56) pertaining to the protection of human subjects. The study was also conducted in conformance with all applicable country requirements regarding ethical committee review and informed consent, including those outlined in the Declaration of Helsinki and its amendments. (See Compliance Statement in Appendix 2.) Each local Ethics Committee/Institutional Review Board (EC/IRB) reviewed and approved the informed consent form before patients were enrolled. The names of the ECs/IRBs

used in this study, their addresses, and the date each EC/IRB approved the study are provided below. The members of each EC/IRB are provided in Appendix 3.

Table 4.1: Institutional Review Boards

Site	Principal		Approved
PTL-0013 (US)			
01	William Yee, MD	MEMORIAL HEALTH SERVICES Research Administration, 2801 Atlantic Ave., Box 142B, Long Beach, CA 90801-1428	19 Feb 1996
02	Richard Paulson, MD	INSTITUTIONAL REVIEW BOARD Darcy V. Spicer, MD, Trailer #25, Unit 1 1200 N. State Street, Los Angeles, CA 90033	21 Dec 1995
03	Christine Cook, MD	UNIVERSITY/LOUISVILLE HEALTH SCIENCES CTR, University Human Studies Committee, Abell Administration Center, 323 East Chestnut Street, Louisville, KY 40202	26 Mar 1996
04	Mark Martens, MD	HUMAN SUBJECTS RESEARCH COMMITTEE 914 South Eighth Street, 600 HFA Building, Minneapolis, MN 55404	20 Feb 1997
05	Theodore C. Nagel, MD	INSTITUTIONAL REVIEW BOARD Administrative Office, 710 East 24th Street, Suite 205, Minneapolis, MN 55404	24 Jun 1996
06	Barry Stewart, MD	SWEDISH MEDICAL CENTER 747 Broadway, Seattle, WA 98122	15 Aug 1996
07	Rafael Valle, MD	NORTHWESTERN UNIVERSITY MEDICAL SCHOOL, Institutional Review Board, 710 N. Lakeshore Drive, Suite 806, Chicago, IL 60611	26 Apr 1996
08	Craig Witz, MD	SOUTHWESTERN TEXAS METHODIST HOSPITAL, 7700 Floyd Curl Drive, San Antonio, TX 78229	10 May 1996
		BAPTIST HEALTH SYSTEM St. Luke's Baptist Hospital, 7930 Floyd Curl Drive, San Antonio, TX 78229	22 May 1996
		SANTA ROSA HEALTH CARE 519 West Houston Street, San Antonio, TX 78207	21 Aug 1996
		UNIVERSITY OF TEXAS Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78274	3 May 1996
09	Michael Kettel, MD	SHARP HEALTH CARE, 8525 Gibbs Drive, Suite 502, San Diego, CA 92123	16 Oct 1996
10	Alan Johns, MD	HARRIS METHODIST FORT WORTH 1301 Pennsylvania, Fort Worth, TX 76104	15 Nov 1996
		COLUMBIA PLAZA MEDICAL CENTER 900 Eighth Avenue, Fort Worth, TX 76104	30 Jan 1997

Site	Principal		Approved
11	Phillip Young, MD	SCRIPPS MEMORIAL HOSPITAL 9888 Genesee Avenue, Mail Code LJ110, P.O. Box 28, La Jolla, CA 92038	13 Nov 1996
12	Russell Malinak, MD	BAYLOR COLLEGE OF MEDICINE Office of Research, One Baylor Plaza, Houston, TX 77030 ST. LUKE'S EPISCOPAL HOSPITAL Institutional Review Board, Mail Code 3-288, Houston, TX 77225	8 Oct 1996 17 Jun 1997
PTL-0022 (Europe)			
21	Per Lundorff, MD, PhD	NORTHERN JUTLAND COUNTY The Ethics Committee for Viborg and Northern Jutland Counties, Amtsgården - Niels Bohrs Vej 30, Postbox 8300 - 92200 Aalborg Øst	18 Jun 1996
23	Hans VanGeldorp, MD, PhD	UNIVERSITY HOSPITAL ROTTERDAM Sophia/Dijkzigt, Dr. Molenwaterplein 40, 3015 GD Rotterdam	17 Oct 1996
25	Sven-Erik Tronstad, MD	Ekonomiavdelningen, V Parken, 4 24 Göteborg	13 Aug 1996
27	Othon Laos, MD	KVINNOKLINIKEN DANDERYDS sjh 182 88 Danderyd	13 Aug 1996
29	Bertil Larsson, MD, PhD	THE NATIONAL BOARD OF HEALTH & WELFARE, (Socialstyrelsen), Medicinetekniska sektionen, 106 30 Stockholm	24 May 1996
* Did not enroll any patients.			

The objectives of the study, procedural details, and the potential risks associated with the use of the study treatments were explained to each patient. A written informed consent was obtained from each patient before their enrollment.

5. INVESTIGATIONAL PLAN

5.1. OVERALL DESIGN AND PLAN OF THE STUDY

5.1.1. Overall Design and Methods

The study was conducted in the US and Europe under identical Protocols: PTL-0013 (US) and PTL-0022 (Europe) (Revision 1). Protocol PTL-0013 and a sample

case report form are found in Appendix 4. Protocol PTL-0022 and a sample case report form are found in Appendix 5. No amendments were made to the protocols.

This was a randomized, third-party blinded, placebo-controlled, multicenter clinical study consisting of two parallel treatment groups. Female patients undergoing peritoneal cavity surgery by laparotomy received a single intraperitoneal instillation of 300 mL of LUBRICOAT® Gel or lactated Ringer's solution at the completion of the laparotomy procedure. The primary indication for surgery included infertility, pain, and/or irregular vaginal bleeding in patients desirous of retaining their fertility. The principal surgical procedures to be performed at the initial laparotomy were to include adhesiolysis, surgical treatment of endometriosis, myomectomy, repair of the Fallopian tube and other pelvic reconstructive surgical procedures, ovarian cystectomy, as well as surgical procedures to facilitate ovulation. A second-look laparoscopic procedure was to be performed approximately 6 to 12 weeks after the initial surgical procedure.

Study blind was maintained by a third party. The study device or control solution, as determined by the randomization schedule, was administered into the peritoneal cavity by a surgical assistant (third party) after the surgeon had completed the primary surgical procedure and had left the operating area. The surgeon then conducted the second-look laparoscopy at the appropriate time interval. Alternatively, the initial surgical procedure and the second-look laparoscopy were carried out by different surgeons if the surgeon conducting the initial surgery instilled the study material.

In the US, a targeted total of 200 (approximately 100 per treatment group) evaluable patients were to be included in the study. A maximum of 350 patients were to be asked to participate, but no more than 250 patients, including those who were not evaluable, were to be entered, with a corresponding maximum of 40 patients for any individual center. In Europe, a targeted total of 120 (60 per treatment group)

evaluable patients were to be included in the study. A maximum of 250 patients were to be asked to participate, but no more than 150 patients, including those who were not evaluable, were to be entered, with a corresponding maximum of 80 patients for any individual center. An evaluable patient was defined as one who had completed her scheduled second-look laparoscopy targeted for approximately 6 to 12 weeks from the initial surgical procedure (minimum of 6 weeks, maximum not to exceed 18 weeks).

The primary efficacy variable was a total adhesion score using the Adhesion Scoring Method of the American Fertility Society¹¹ (AFS) applied to 24 anatomical sites including both pelvic and upper abdominal locations (termed the Modified AFS Score). Secondary efficacy variables included the proportion of sites with adhesions, the extent of adhesions, and the severity of adhesions. Adhesions were characterized as *de novo* if the site had no pre-existing adhesions and as reformed if the site had adhesions that were lysed during the initial surgery. Sites with *de novo* adhesions were also characterized as surgical versus non-surgical and pelvic versus abdominal. Adhesions at all surgical sites were also evaluated. Safety assessments were based on the type and incidence of adverse events recorded throughout the study, the pre-operative and post-operative laboratory test values, concomitant medications/conditions, and gross evaluation at second-look laparoscopy.

5.1.2. Plan of the Study

Detailed descriptions of the study procedures and evaluations are found in the study protocols (Appendices 4 and 5). A summary of the plan of the study is provided in this section. The schedule of evaluations and procedures is shown in Table 5.1.

Table 5.1: Schedule of study evaluation/procedures
 Protocols PTL-0013 and PTL-0022

EVALUATIONS/PROCEDURES	SCHEDULE OF EVALUATIONS				
	PRE-OP	INITIAL OPERATIVE	INITIAL POST-OP	POST-OP DAY 7-28	SECOND-LOOK*
Informed Consent	X				
Inclusion/Exclusion	X	X			
Background Information (Demog., Med. & Surg. History)	X				
Physical Exam (& Vital Signs)	X		X ^b	X ^b	
Concomitant Medications	X	X	X ^c	X ^{c,d}	X ^d
Blood Chemistries	X		X	X	X
Hematology	X		X	X	X
Urine Pregnancy Test	X				X
Confidential Patient Follow-Up	X				
Device Label Check		X			
Adhesion Assessment		X			X
Suture Use, Surg. Intervention		X			
Endometriosis Evaluation		X			X
Abdominal Drawings		X			X
Adverse Events		X	X	X	X
Patient Status				X	X
Principal Investigator Signature & Comment	X	X	X	X	X

* Concomitant Medications, Blood Chemistries, Hematology, and Pregnancy Test/Urinalysis were to be completed prior to undergoing a second-look laparoscopy.
^b A limited physical examination prior to discharge and at the Days 7 to 28 visits was for the purpose of performing an abdominal auscultation and percussion for assessment of the presence of ascites.
^c Dispense Daily Patient Diary.
^d Collect Daily Patient Diary.

Patients who agreed to participate in the study were to complete the following evaluations and procedures:

5.1.2.1. Pre-Operative Procedures

- Inclusion criteria
- Exclusion criteria
- Demographics/Medical history
- Surgical history
- Physical examination/Vital signs
- Concomitant medications
- Laboratory evaluation(s)
- Comments/Principal Investigator signature

Within the 2 weeks prior to the initial surgical procedure, general background information including surgical history, current medications (prescription, non-prescription, and iron or iron-containing supplements) and checklists for inclusion/exclusion (including witnessed informed consent) were to be obtained.

Each patient was to have her vital signs (oral temperature, body weight and height, respiration rate, blood pressure and pulse) measured and undergo a physical examination. Since these examinations (vital signs and physical examination) represented standard pre-operative practice, they could be performed prior to the patient's signing of the consent form, as long as the examinations were performed within the 3 weeks prior to the initial surgical procedure.

Serum electrolytes, hematology (CBC with differential), blood chemistries and a urine pregnancy test were also to be performed within the 2 weeks prior to the initial surgical procedure.

5.1.2.2. Initial Operative Procedure

- Adhesion assessment
- Surgical intervention/Suture use/Presence and treatment of Endometrial Tissue

- Operative procedures/Endometriosis/Transfusions
- Abdominal diagrams
- Device label check
- Concomitant medications
- Adverse events
- Comments/Principal Investigator signature

Approximately 2 hours prior to the scheduled initial surgery, the patient was to be assigned the next available study number. At the time of initial surgical procedure and prior to any adhesiolysis, the investigator was to assess the presence of adhesions at each of 24 anatomical sites listed below, with the exception of the anterior peritoneum incision, i.e. the laparotomy incision, which was to become a site of assessment at second-look:

Table 5.2: Anatomical Sites

Anatomical Site	Descriptor
caudal anterior peritoneum	caudal with respect to the fundus of the uterus
cephalad anterior peritoneum right	cephalad with respect to the fundus of the uterus & right of midline
cephalad anterior peritoneum left	cephalad with respect to the fundus of the uterus & left of midline
anterior peritoneum incision	the laparotomy incision for this procedure
small bowel	
anterior uterus	
posterior uterus	
omentum	
large bowel right	right of midline
large bowel left	left of midline
rectosigmoid portion of the large bowel	
cul-de-sac	posterior cul-de-sac, medial to the uterosacral ligaments
right pelvic sidewall	lateral to right ureter
left pelvic sidewall	lateral to left ureter
right ovary- lateral aspect	
right ovary- medial aspect	
right ovarian fossa	portion of the broad ligament normally in contact with the right ovary
left ovary- lateral aspect	
left ovary- medial aspect	
left ovarian fossa	portion of the broad ligament normally in contact with the left ovary
right tube	tube proximal to ampulla
right ampulla	including the infundibulum and fimbriae
left tube	tube proximal to ampulla
left ampulla	including the infundibulum and fimbriae

An adhesion, in this study, was defined as fibrous tissue or band(s) interconnecting at least two organs or sites. If an adhesion was present, this information was to be captured on the appropriate case report forms. If an adhesion was lysed, i.e. the

organ or site was completely freed from the other structure, this information was also to be recorded, along with the method of adhesiolysis. The severity and extent of the adhesion(s) were to be assessed utilizing the following classifications:

<u>Severity</u>	<u>Description</u>
Mild	filmy avascular adhesion
Severe	dense, organized, cohesive, vascular adhesion

<u>Extent</u>	
Localized	less than $\frac{1}{3}$ of the site covered
Moderate	$\frac{1}{3}$ to $\frac{2}{3}$ of the site covered
Extensive	more than $\frac{2}{3}$ of the site covered

However, the extent of adhesions was not to be determined for the small bowel, omentum, and large bowel right and left, since their size precluded adequate visualization or evaluation.

Areas of additional surgical intervention, and/or use of sutures as well as the presence of endometriosis (along with the American Fertility Society classification and method of treatment) were also to be recorded. The investigator was to list the actual surgical procedures performed, the types of sutures used, estimate the amount of blood loss and operative time, note any transfusions, and record all concomitant medications used.

All adhesions seen prior to adhesiolysis were to be sketched (at the time of the initial surgical procedure, or shortly thereafter -within 24 hours) with careful attention paid to clearly identifying the anatomical site of attachment, extent, and severity for each adhesion. Any adhesions not lysed was to be so indicated on ASSESSMENT OF ADHESIONS I as well as the ABDOMINAL DIAGRAM-I(s) in the case report form. Although the drawings were two-dimensional, they could be used to depict adhesions in other planes, including anterior to posterior, by careful labeling of each adhesion. All incisional lines were also to be recorded on the appropriate diagrams. The study device or control solution, as determined by the randomization schedule, was to be administered into the peritoneal cavity by the surgeon or surgical

assistant (depending on the method of blinding being employed) after the surgeon had completed the primary surgical procedure, achieved complete hemostasis, aspirated all irrigants, and had removed all packs and sponges, providing the intraoperative exclusions did not apply. The principal investigator was to identify the surgeon and surgical assistant (if applicable, depending on the method of blinding) on the DEVICE LABEL CHECK case report form.

5.1.2.3. Initial Post-Operative Procedures

- Laboratory evaluations
- Adverse events
- Concomitant medications
- Abdominal auscultation and percussion
- Comments/Principal Investigator signature

Prior to the patient's discharge from the hospital or within 3 days of the initial surgery, serum electrolytes, hematology (CBC with differential) and blood chemistries were to be performed.

The investigator was to record any adverse experiences noted by the patient and/or observed by the staff, i.e., post-operative pain, nausea, infection, etc. The patient was to be examined for the presence of significant accumulation of abdominal fluid or ascites, by abdominal auscultation and percussion in all four quadrants. The date of discharge was to be noted.

The patient was to be provided with a diary to document medications taken following discharge and to comment on their general status.

5.1.2.4. Post-Operative Day 7 to Day 28 Evaluations

- Laboratory evaluations
- Adverse events
- Concomitant medications
- Abdominal auscultation and percussion
- Comments/Principal Investigator signature

Serum electrolytes, hematology (CBC with differential) and blood chemistries were to be performed at the initial post-operative visit at Days 7 to 28.

The investigator was to record any adverse experiences noted by the patient and/or observed by the staff, i.e., post-operative pain, nausea, infection, etc. The patient was also to be examined for the presence of significant accumulation of abdominal fluid or ascites, by abdominal auscultation and percussion in all four quadrants.

The patient's diary was to be retrieved and a new one provided. Prior to completing this visit, the patient was to be interviewed regarding any ongoing or new adverse experience(s).

5.1.2.5. Second-Look Laparoscopy

- Laboratory evaluations (prior to surgery)
- Adverse events
- Concomitant medications
- Adhesion assessment
- Abdominal diagrams

- Gross Observations
- Comments/Principal Investigator signature

The patients were to undergo a second-look laparoscopy targeted for 6 to 12 weeks following the laparotomy (minimum of 6 weeks, maximum not to exceed 18 weeks).

Prior to the surgery, serum electrolytes, hematology (CBC with differential), blood chemistries, and a urine pregnancy test were to be performed.

The patient's diary was to be retrieved, and the patient was to be interviewed regarding any ongoing or new adverse experience(s).

The second-look laparoscopy procedure was to be videotaped. During the surgical procedure, the investigator was to perform a gross examination of the peritoneal cavity, note any unusual lesions or the presence of ascites, and was to repeat the assessment of the presence, severity and extent of adhesions at the same 24 anatomical sites. Specific adhesion sites were to be indicated on the abdominal drawings and recorded on the case report form. If any tissues or biopsies were taken during this procedure, the histology information was to be recorded.

5.1.2.6. Clinical Laboratory Evaluations

Standard clinical laboratory tests were to be performed at baseline (within 2 weeks prior to the initial surgical procedure), immediately prior to the patient's discharge from the hospital or within 3 days of the initial surgery, 7 to 28 days after the initial surgery, and immediately prior to the second-look laparoscopic procedure. All laboratory values were to be compared to their corresponding reference ranges. Clinically significant values below or above the normal range were to be flagged by the investigator. The following laboratory tests were to be performed:

- Blood Chemistry: BUN, creatinine, phosphorus, calcium, uric acid, total protein, albumin, total bilirubin, SGOT (AST), SGPT (ALT), alkaline phosphatase, sodium, potassium, and chloride.
- Hematology: hemoglobin, hematocrit, RBC, and WBC with differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils)

5.1.2.7. Adverse Events

All adverse events and/or intercurrent illnesses which occurred during the study were to be recorded on the case report forms. The onset date, severity (mild, moderate, or severe), potential relationship (none, possible, probable, definite) to the device as determined by the investigator, and outcome (resolved with treatment, resolved spontaneously, persisted) were to be recorded. Any additional actions taken were also to be recorded as none, OTC/non-prescription therapy, prescription therapy, or hospitalization.

A serious adverse event was an adverse event that:

- resulted in death
- was life threatening
- resulted in or prolonged hospitalization
- resulted in severe or permanent disability
- involved cancer, a congenital anomaly, or an overdose.

All serious adverse events, whether considered related or not related to treatment, were to be reported promptly by telephone to the sponsor.

5.1.2.8. Patient Diary

Patients were provided with a DAILY PATIENT DIARY to document medications taken following discharge and to comment on their general status. Patients were to bring the diary with them to each return visit.

5.2. DESCRIPTION AND DISCUSSION OF THE DESIGN AND CHOICE OF CONTROL GROUP

This was a multicenter, third-party blinded, clinical study utilizing a parallel group design in which equal numbers of patients were to be randomly assigned to one of two treatment groups within each center. This balanced group design was to permit a valid comparison between LUBRICOAT® Gel (study device) and lactated Ringer's solution (control solution).

The practice of leaving a volume of crystalloid, especially lactated Ringer's solution, in the peritoneal cavity following gynecologic pelvic surgery has been well accepted.¹²⁻²⁰ Numerous clinical studies have compared liquid therapies such as dextran or solutions of pharmaceutical agents to lactated Ringer's solution,²¹⁻²³ saline,^{24,25} or buffered salt solutions.²⁶ While none of these have directly compared the use of crystalloid to no treatment, such studies have been carried out in preclinical animal models with lactated Ringer's solution, and have demonstrated a beneficial effect of lactated Ringer's solution in reducing adhesions.^{27,28}

The sample size of 200 evaluable patients was based on statistical methods and is discussed further in Section 5.7.3.; "Statistical Determination of Sample Size".

5.3. PATIENT SELECTION

5.3.1. Inclusion Criteria/Pre-operative

To be included in the study were:

1. female patients 18 to 45 years of age requiring peritoneal cavity surgery via laparotomy with preservation of fertility (patients with endometriosis could be included)
2. patients who were able to be scheduled for the Day 7 to Day 28 post-surgical laboratory determinations
3. patients who were scheduled for a second-look laparoscopy as part of their treatment plan targeted for 6 weeks to 12 weeks after the initial surgical procedure (minimum of 6 weeks, maximum not to exceed 18 weeks)
4. patients giving written, witnessed, informed consent to participate in the study (This informed consent was to be given prior to any study-mandated determinations or procedures to be performed with the exception of the physical examinations as discussed previously).

The period of inclusion at each investigational site is provided below in Table 5.3.

Table 5.3: Inclusion Period by Investigational Site

Site Number	Investigator	Investigational Site Address	Inclusion Period	
			Start Date	End Date
PTL-0013 (US)				
02	Mevin Thornton, MD	Univ. Infertility Associates Long Beach, CA 90806, US	8 Mar 1996	13 Feb 1997
03	Christine Cook, MD	Dept. Of OB/GYN Univ. of Louisville Louisville, KY 40292, US	17 Sep 1996	31 Oct 1998
04	Mark Martens, MD	OB/GYN, HCMC Minneapolis, MN 55415, US	4 Mar 1997	10 Apr 1998
05	Theodore Nagel, MD	Reproductive Health Assoc. St. Paul, MN 55102, US	30 Oct 1996	—
06	Barry Stewart, MD	Pacific Gynecology Spec. PC Seattle, WA 98104, US	9 Oct 1996	28 Jul 1998
07	Rafael Valle, MD	Northwestern Medical Faculty Found. Chicago, IL 60611, US	9 Aug 1996	26 Oct 1998
08	Craig Witz, MD	Univ. Of Texas Health Sc. Center of San Antonio San Antonio, TX 78284, US	15 Jul 1996	3 Sep 1998
09	Michael Kettel, MD	San Diego Fertility Center La Jolla, CA 92037, US	25 Nov 1996	11 Sep 1998
10	Alan Johns, MD	Texas Health Care Fort Worth, TX 76180, US	23 Dec 1996	21 Sep 1998
11	Phillip Young, MD	Fertility Institute San Diego, CA 92121, US	17 Dec 1996	23 Oct 1998
12	Russell Malinak, MD	Baylor College of Medicine Houston, TX 77030, US	24 Mar 1997	24 Aug 1998
PTL-0022 (Europe)				
21	Per Lundorff, MD, PhD	Dept. of OB/GYN Viborg, Denmark	27 Aug 1996	7 Oct 1997
23	Hans VanGeldorp, MD, PhD	GYN and Reprod. Surgery Univ. Hospital Rotterdam Rotterdam, The Netherlands	4 Feb 1997	17 Jul 1997
25	Sven-Erik Tronstad, MD	Dept. of OB/GYN Skovde Hospital Skovde, Sweden	15 Oct 1996	29 Jul 1997
27	Othon Lalos, MD	Dept. Of OB/GYN Univ. Hospital Uwea Uwea, Sweden	15 Nov 1996	2 Sep 1997
29	Bertil Larsson, MD, PhD	Karolinska Institutet Danderyd Hospital Danderyd, Sweden	29 Oct 1996	27 May 1997

5.3.2. Exclusion Criteria/Pre-operative

To be excluded from the study were:

1. pregnant (including ectopic pregnancy) or lactating patients
2. patients undergoing tubal sterilization, reversal of sterilization, or tubal implantation
3. patients currently receiving cancer therapy including drugs and radiation, i.e. within the last 4 weeks
4. patients who had lymphatic ($WBC \geq 12.5 \text{ K/mm}^3$), hematologic or coagulation disorders ($Hgb \leq 8.0 \text{ g/dL}$), or patients who were taking anticoagulants
5. patients with a history of hemochromatosis
6. patients with hepatic disorders ($AST \geq 25 \text{ mg/dL}$ [$SGOT/SGPT \geq 50 \text{ IU/L}$]) or renal disorders ($creatinine \geq 1.5 \text{ mg/dL}$)
7. patients who were taking oral or parenteral hypoglycemic agents for diabetes
8. patients whose pre-operative laboratory values were outside 20% of the normal range and considered clinically significant
9. patients who were immunocompromised or possessed autoimmune disorders
10. patients who were unable to process large fluid loads, such as patients with congestive heart failure

5.3.3. Exclusion Criteria/Intra-operative

To be excluded from the study were:

1. patients receiving any peritoneal instillate containing corticosteroids, NSAID's, or HYSKON® (Dextran) during the procedure (irrigants which might or might not contain heparin and /or antibiotics could be used if completely aspirated)
2. patients in whom any absorbable hemostat was left in the

3. abdominal/peritoneal cavity (i.e., Surgicel[®], Avitene[®], Gelfoam[®], etc.) patients receiving any adhesion prevention adjuvant (INTERCEED[®][TC7] Absorbable Adhesion Barrier, GoreTex[®] Surgical Membrane)
4. patients who would need to receive post-operative hydrotubation
5. patients who presented with pelvic or abdominal infection
6. patients who would undergo peritoneal grafting as part of their operative procedure
7. patients in whom fibrin glue or other thrombogenic agents were used
8. any surgical procedure at the time of the initial laparotomy that involved opening of the gastrointestinal or urinary tract
9. patients with 12 or more of the 24 anatomical sites involved with adhesions as noted during the initial operative procedure
10. patients who had one or more of their anatomical sites removed during the initial operative procedure

5.3.4. Removal of Patients from the Study

Patients were to be discontinued from the study for any of the following reasons:

- Adverse effect/complication
- Lost to follow-up
- Noncompliance
- Pregnancy
- Patient's decision
- Protocol violation
- Did not meet entrance requirements
- Intra-operative exclusion
- Physician's decision
- Patient death

The reason for any discontinuation from the study was to be documented in the

case report form. Any patient who failed to return for the Day 7 to Day 28 laboratory determination and/or the second-look laparoscopy was to be contacted and interviewed if possible as to her reason for not returning and her medical status ascertained relative to the effects of the study device. All attempts to contact the patient was to be documented on the case report form.

5.4. TREATMENTS

5.4.1. Treatments Administered

- LUBRICOAT® 0.5% Ferric Hyaluronate Gel, three separate vials each containing 100 mL; Lot numbers: X9504-5, X9610-1, and X9704-5 OR
- lactated Ringer's solution, one package containing at least 300 mL; Lot numbers: 9504114 and 9701371.

5.4.2. Identity of Investigational Products

LUBRICOAT® 0.5% Ferric Hyaluronate Gel (study device) was formulated, manufactured, and packaged by Lifecore Biomedical, Inc., Minneapolis, Minnesota. The gel was packaged in 100 mL Type I borosilicate amber vials with 20 mm flip tear-off seals. Commercial lactated Ringer's solution (control solution) was purchased, inspected, and tested by Lifecore Biomedical, Inc. The study device and control solution were each packaged in sealed cartons so that there was one carton for each patient appropriately labeled with the protocol number and patient number (from the randomization schedule).

The study device and control solution were provided to each center without charge by Lifecore Biomedical, Inc. A list of the formulation components of LUBRICOAT® Gel and lactated Ringer's solution are found in Appendix 6.

5.4.3. Method of Assigning Patients to Treatment

Patients were assigned to one of two parallel treatment groups (LUBRICOAT® Gel or lactated Ringer's solution) at 11 study centers in the US and 5 in Europe according to a computer-generated randomization scheme prepared by Lifecore Biomedical, Inc., prior to study initiation. Based on this randomization scheme, the assigned study solution for each patient was packaged and labeled in a double-blind manner. Patient numbers were pre-printed on the labels and assigned sequentially beginning with the lowest number as patients were accepted into the study. Patient numbers assigned to each site are presented in Appendix 7. Not all the assigned patient numbers were used at some sites. The reasons for not using assigned patient numbers are presented in Appendix 7 and include: product was not used and returned to sponsor (most common reason), either because product expired, was not stored properly, was not refrigerated on delivery, or was not warmed at the correct temperature; vial was broken during shipment; product was unblinded by mistake; patient withdrew consent; or surgery was canceled.

The randomization scheme showing treatment assignment is found in Data Listings 1.1. and 1.2.

5.4.4. Dosage and Administration

A single dose of 300 mL of LUBRICOAT® Gel or lactated Ringer's solution was administered into the peritoneal cavity following the initial laparotomy. The single dose of 300 mL of study device was selected based on data from a pilot study⁴ and on the mode of action of the gel. The gel was intended to coat the raw surfaces left behind at the time of surgery, thus, allowing these surfaces to heal without adhering to other surfaces.

5.4.5. Blinding

The treatment assignments remained unknown to all patients, investigators, ancillary study personnel, and monitors throughout the study to minimize any bias. The investigators were blinded by a third party. The study device or control solution, as determined by the randomization schedule, was to be administered into the peritoneal cavity by a surgical assistant (third party) after the surgeon had completed the primary surgical procedure and had left the operating area. The surgeon then conducted the second-look laparoscopy at the appropriate time interval. Alternatively, the initial surgical procedure and the second-look laparoscopy were carried out by different surgeons, if the surgeon conducting the initial surgery instilled the study material.

The bottles containing the LUBRICOAT® Gel or the lactated Ringer's solution were packaged in identical protective cartons. Each bottle contained a two-part, tear-off label with identical information on the label: protocol number, quantity of solution, directions for use, route of administration, storage instructions, the caution statement required by Federal Law, and a blank space for patient identification number and initials. One part of the label remained affixed to the bottle, the tear-off portion of the label was removed and attached to the patient's case report form when the study gel or solution was dispensed. The tear-off portion of the label also contained a blinded area (silver paint) concealing the identity of the study device or control solution, and the control lot number. This blinded area could be unblinded by the investigator, in an emergency, by rubbing off the silver paint. The randomization code, which consisted of a patient's identifier and the treatment assigned, was kept in confidence at Lifecore Biomedical, Inc.

5.4.6. Prior and Concomitant Medications

Beginning with the pre-operative phase, all baseline and concomitant medications (with the exception of IV hydrating solutions, anaesthetics, and muscle relaxants administered during the surgical procedure) were to be recorded on the case report forms. Details pertaining to drug name, dose, route of administration, start and discontinuation dates, and indication for use were to be recorded.

5.4.7. Treatment Compliance

Compliance with the study treatments was ensured since the administration of the single dose of 300 mL of LUBRICOAT® Gel or lactated Ringer's solution into the peritoneal cavity was performed by the surgeon or surgical assistant in the hospital depending on the method of blinding employed.

5.5. APPROPRIATENESS AND CONSISTENCY OF MEASUREMENTS

The protocol design used in this study was similar to that demonstrated to be adequate and appropriate in a previous pilot study.⁴ In the pilot study, the surgical methodology, reliability and safety of the method of LUBRICOAT® Gel administration to patients undergoing peritoneal cavity surgery were found to be feasible and safe.

In this clinical study, patients were evaluated for their potential to have reformed and *de novo* adhesions throughout the peritoneal cavity following a surgical procedure. Since all sites in the pelvis and abdomen are candidates for development of these adhesions, it was appropriate to assess the 24 anatomical sites for adhesion formation.

Safety assessments including clinical laboratory tests were based on standard

procedures.

5.6. MONITORING PROCEDURES AND DATA QUALITY ASSURANCE

The following measures were taken to assure consistent, accurate, and complete data:

- At the time the study was initiated, the monitor thoroughly reviewed the protocol and case report forms with the investigator and their staff in addition to all regulations, device accountability, record keeping, and report requirements.
- During the course of the study, the Sponsor was available to discuss by telephone, questions regarding adverse experiences, removal of patients from the study, conduct of the study, etc.
- Periodic monitoring visits were conducted as necessary. At the time of each monitoring visit, the monitor reviewed the case report forms of each patient in the study to make certain that all items had been completed and that the data provided were accurate and obtained in the manner specified in the protocol. The patients' clinical records were reviewed to confirm that (1) the case report form data were consistent with the surgeon's clinical records, (2) the background clinical and laboratory data and concurrent medications were documented in the case report forms, and (3) that there was an accurate account of the use of the study device in surgery. The patient's clinical records were reviewed to determine whether recording of adverse effects had been omitted on the case report forms. If this was found to be so, then the case report forms were returned to the investigator and corrected to include this information.
- The protocol required investigators to complete the drawings related to adhesions and surgical procedures within 24 hours of the operation. Following the second-look laparoscopy procedure, these data were carefully reviewed by the monitor, and then forwarded along with the videotape of the

second-look procedure and a copy of the operative dictation notes to an independent masked Medical Review Officer, who reviewed the videotape and drawings to ensure the data had been accurately represented and transcribed on the key case report forms. Any questions from this medical review were directed to the monitor for discussion with the surgeon. The surgeon had final authority in resolving any discrepancies. The final drawings were considered the primary source document.

5.7. STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

Two-sided p values are reported and p values less than 0.05 are considered to be statistically significant.

5.7.1. Analysis Groups

The following population groups were analyzed:

- The intent-to-treat (ITT) population consisted of all patients who received LUBRICOAT® Gel or lactated Ringer's solution. The ITT population was also the safety population (n=281).
- The efficacy evaluable population was a subset of the ITT population consisting of all patients who received a second-look laparoscopic evaluation (n=265).

Patients who were randomized but did not receive treatment were described, but not otherwise analyzed.

5.7.2. Demographic, Pretreatment and Surgical Variables

Age, race, height, weight, previous and concomitant medications (categorized by

AHFS codes), presence of endometriosis, surgical procedures (categorized by CPT codes), estimated blood loss, operative time, baseline adhesion scores and length of hospital stay were summarized. Differences between the treatment groups were compared using Fisher's Exact test for the categorical data and Student's t-test for the continuous data. These analyses were performed for the efficacy evaluable population and for the patients who did not receive a second-look laparoscopic evaluation.

5.7.3. Efficacy Variables

Primary Efficacy Variable

The primary efficacy variable was an adhesion score using the Adhesion Scoring Method of the American Fertility Society⁵ (AFS) applied to 24 anatomical sites (i.e., the Modified AFS Score) including both pelvic and upper abdominal locations (i.e., general surgical sites). Adhesions occurring at each of the 24 potential adhesion sites were scored as:

- None (no adhesion)
- Mild (a filmy avascular adhesion) or
- Severe (a dense organized cohesive vascular adhesion).

The extent of adhesions were graded as:

- None (no adhesion)
- Localized (< 1/3 of the site covered),
- Moderate (1/3 - 2/3 of the site covered) or
- Extensive (> 2/3 of the site covered).

The extent of adhesions were not scored for the small bowel, omentum and left and

right large bowel since their size precludes adequate visualization. These sites were assigned a classification of Moderate in order to determine the total adhesion score.

For each adhesion site, the adhesion score was derived from severity and extent scores as follows:

No Adhesion		0
Severity: Mild	Extent: Localized	1
Severity: Mild	Extent: Moderate	2
Severity: Mild	Extent: Extensive	4
Severity: Severe	Extent: Localized	4
Severity: Severe	Extent: Moderate	8
Severity: Severe	Extent: Extensive	16

Scores from all potential adhesion sites were averaged to yield the Modified AFS score (0 to 16 range). Adhesions were characterized as *de novo* if the site had no pre-existing adhesions and as reformed if the site had adhesions that were lysed during the original surgery. Sites with *de novo* adhesions were also characterized as surgical versus non-surgical. In addition, adhesion sites were categorized by the presence or absence of endometriosis, use of sutures and the method of adhesiolysis (sharp dissection, blunt dissection, cautery, laser).

Treatment group comparisons were performed for the efficacy evaluable population using Student's t-test. The analyses were performed for all sites, for pelvic and abdominal site groupings, and for each anatomical site. The pelvic sites included the caudal anterior peritoneum, anterior and posterior uterus, cul-de-sac, right and left pelvic sidewall and all tube, ampulla and ovarian sites. The abdominal sites included the right and left cephalad anterior peritoneum, small bowel, omentum, right and left large bowel, rectosigmoid and the anterior peritoneum incision.

For the primary efficacy variable (Averaged Modified AFS Score from all the adhesion sites), overall analyses were performed using factorial analysis of

covariance (ANCOVA). A preliminary analysis included the following factors.

Treatment:	LUBRICOAT® Gel versus lactated Ringer's solution
Center:	Small centers were combined into "pseudo-centers" such that no "center" had less than 5 patients per group
Treatment x Center:	Interaction between treatment and center
Baseline Level:	Baseline modified AFS score as a continuous covariate
Treatment x Baseline:	Interaction between treatment and baseline level

The purpose of this initial analysis was to examine homogeneity of slopes for the continuous covariate (Baseline modified AFS score). If slopes were homogeneous (as indicated by a nonsignificant Treatment x Baseline interaction - p value > 0.10), the Treatment x Baseline interaction was removed from the model and the final model included only the first four factors.

Protocol-defined ANCOVA analyses were performed on the Efficacy population and on the ITT population. For the ITT population, patients with no second-look laparoscopic evaluation were defined as treatment failures and given the worst possible score (modified AFS score = 16). Because this distribution was expected to be extremely skewed, data were transformed to ranks and the mean rank scores were presented and analyzed.

Secondary Efficacy Variables

The proportion of sites with adhesions were analyzed as a secondary efficacy variable. This was a mean proportion based on the number of sites with adhesions divided by the number of possible adhesion sites. As described above, adhesions were characterized as *de novo* versus reformed, surgical versus non-surgical and pelvic versus abdominal.

Additional secondary variables were the extent and severity of all categories of adhesions. Severity was scored on a three-point scale where 0 = None, 1 = Mild and 3 = Severe. Extent was scored on a four-point scale where 0 = None, 1 = Localized, 2 = Moderate and 3 = Extensive. A mean score for all 24 sites was calculated for each patient.

Treatment group comparisons were performed for the efficacy evaluable population using Student's t-test.

5.7.4. Safety Variables

Safety variables included the proportions of patients reporting adverse events categorized using COSTART terms. Laboratory values were presented as mean change from baseline and as transition tables showing the proportions of patients above, below and within the normal range before and after treatment.

Adverse event data were analyzed by using Fisher's Exact test. Mean laboratory values were analyzed using Student's t-test. Laboratory value transition tables were analyzed using 2x9 Fisher's Exact tests on the 2 groups and 9 cells of each transition table. These analyses were performed on the safety population, which as noted above, was the same as the ITT population.

5.7.5. Determination of Sample Size

Power calculations were performed using the method described by Lachin²⁹ using an alpha level of 0.05 and a beta level of 0.20 (80% power). Preliminary analysis of a Phase I study indicated a mean adhesion score of 1.7 (Standard deviation: 1.4) for the treated group and 5.7 (Standard deviation: 2.7) for the lactated Ringer's solution group. For the US enrollment, assuming that at worst case 20% of the treatment group and 10% of the lactated Ringer's solution group were lost to follow-

up, scoring these patients as treatment failures would yield a mean adhesion score of 4.6 (Standard deviation: 5.9) for the treated group and 6.7 (Standard deviation: 4.1) for the lactated Ringer's solution group. Assuming a standard deviation of 5.0, 180 patients would be required. Thus the 200 evaluable patients (approximately 250 total patients) appeared to provide sufficient power to reject the null hypothesis if the observed trends were maintained.

For the European enrollment, assuming a standard deviation of 2.7, a difference as small as 1.5 would require a total of 104 patients. Thus, the 120 evaluable patients would provide sufficient power to reject the null hypothesis.

5.8. CHANGES IN THE PLANNED ANALYSES

Several analyses were performed in addition to those planned in the protocol. The following subgroup analyses were performed based on the surgical procedure used: patients with myomectomy, patients without myomectomy, patients with adhesiolysis, patients with tubal procedures, patients with ovarian procedures, patients with dermoid or endometrioma ovarian procedures, patients with dermoid ovarian procedures, and patients with endometrioma ovarian procedures. Differences between the treatment groups within these subgroups were compared using Student's t-test.

In addition to the Modified AFS score which is derived from 24 anatomical sites, adhesion outcome in the two treatment groups for the efficacy evaluable population was analyzed based on the Standard AFS Score.¹¹ The Standard AFS scoring method, the most widely utilized scoring system for description of pelvic adhesions, is based on the classification of adhesions on an organ-by-organ basis utilizing the extent to which an organ is covered by adhesions (<1/3, 1/3-2/3, >2/3). In addition, the type of adhesion severity (either filmy and avascular or dense and vascular) involving the organ is classified. This scoring system is limited to the adnexa

thereby taking into account only the ovaries and Fallopian tubes. Differences between the treatment groups were compared using Student's t-test and the Fisher's Exact test.

Analysis of Covariance (ANCOVA) as described in Section 5.7.1.3, were performed on subgroups of American and European patients. In addition ANCOVA of the entire efficacy population was performed after log transformation of the modified AFS scores. In order to handle scores of zeros, one was added to each modified AFS score prior to log transformation.

For a comprehensive review of scoring methods and clinical outcomes, see a report on "Adhesion Reduction and Clinical Outcome" in Appendix 14.

5.9. INTERIM ANALYSIS

An interim analysis was specified in the protocol. After at least 120 evaluable patients had completed the US study (Protocol PTL-0013), the possibility of combining the US data with data from a concurrent European study (Protocol PTL-0022) was to be considered. The European study was expected to have enrolled approximately 80 evaluable patients by that time. Combinability of the data were to be assessed based on three factors:

- There was to be no significant interaction between location (US versus Europe) and treatment efficacy.
- The US and European populations were to be similar on demographic and pre-treatment variables and the level of medical care.
- The US and European lactated Ringer's solution groups were to be similar on second-look adhesion scores. This variable could serve as a proxy for subtle differences in medical treatment. The 95% confidence intervals of the difference between the US and European lactated Ringer's solution groups were to be presented.

Detailed description of the factors for assessing combinability of the data is found in the study Protocols in Appendices 4 and 5.

Due to apparent differences in the baseline number of adhesions in patients in the US and Europe, the combinability analysis was initiated early, i.e. when 200 patients were entered (not all had completed second-look laparoscopy). The FDA was notified of the early assessment plans on 10 September 1997. An interim analysis report on 170 completed patients (88 LUBRICOAT® Gel and 82 lactated Ringer's solution) was submitted to the FDA on 12 March 1998. A Supplemental Report was submitted on 27 May 1998.

On 11 August 1998, the FDA requested another analysis be performed on a larger sample in order to determine the combinability of the data. This analysis was to include at least all of the European patients and either the first 120 US patients or all of the US patients who had completed the study to that point. On 29 September 1998, the second interim analysis report on 213 completed patients (109 LUBRICOAT® Gel and 104 lactated Ringer's solution) was submitted to the FDA.

On 30 October 1998, the FDA approved the supplement requesting permission to terminate enrollment in these studies. A final combinability assessment was completed. The results of the interim analyses and the final combinability analysis are summarized in Section 8.1 and the reports are found in Appendix 9.

Note that, because the criterion for study termination was combinability rather than the significance of the difference between LUBRICOAT® Gel and lactated Ringer's solution, *p* values were not adjusted.

6. STUDY POPULATION RESULTS

For all results, key summary tables are presented in the text of this report and are numbered by section number in the order of their appearance in that section (e.g., the first in-text table appearing in this section will be numbered Table 6.1, the second table will be numbered Table 6.2, etc). Additional summary tables, referred to as Supplemental Tables, are presented at the end of the text. All supplemental tables cited in the text are cross-referenced to their corresponding table number.

6.1. RANDOMIZED PATIENTS AND THEIR DISPOSITION

6.1.1. Randomized Patients

As of 31 July 1998, a total of 303 patients were randomized at 11 centers in the US and 5 in Europe under Protocols PTL-0013 and PTL-0022, respectively. The number of patients randomized at each center ranged from 1 to 53. The distribution of randomized patients is shown by treatment group and investigational center in Table 6.1.

Table 6.1: Number and percent of patients randomized at each center
 Protocols PTL-0013 and PTL-0022

Center No.	LUBRICOAT® Gel		lactated Ringer's Solution		Total	
	N	%	N	%	N	%
<u>PTL-0013 (US)</u>						
02	27	17.8	26	17.2	53	17.5
03	6	3.9	6	4.0	12	10.0
04	4	2.6	3	2.0	7	2.3
05	1	0.7	-	-	1	0.3
06	6	3.9	9	6.0	15	5.0
07	5	3.3	6	4.0	11	3.6
08	7	4.6	7	4.6	14	4.6
09	12	7.9	11	7.3	23	7.6
10	14	9.2	13	8.6	27	8.9
11	20	13.2	19	12.6	39	12.9
12	7	4.6	10	6.6	17	5.6
Total	109	71.7	110	72.8	219	72.3
<u>PTL-0022 (Europe)</u>						
21	14	9.2	15	9.9	29	9.6
23	11	7.2	9	6.0	20	6.6
25	7	4.6	8	5.3	15	5.0
27	5	3.3	3	2.0	8	2.6
29	6	3.9	6	4.0	12	4.0
Total	43	28.3	41	27.2	84	27.7
All Centers	152	100.0	151	100.0	303	100.0

Cross Reference: Supplemental Table 1

6.1.2. Patient Disposition

Of the 303 randomized patients, 22 did not receive treatment and 281 were treated. The disposition of patients who were randomized but not treated is summarized in Table 6.2. These patients were removed from all remaining tables and analyses. They are listed in Data Listings 1.1 and 1.2.

Table 6.2: Disposition of randomized patients who were not treated: number (%) of patients
 Protocols PTL-0013 and PTL-0022

	LUBRICOAT® Gel	lactated Ringer's Solution	Total
Total randomized but not treated	9 (100.0)	13 (100.0)	22 (100.0)
Reason for not receiving treatment			
Did not meet intra-operative criteria	9 (100.0)	11 (84.6%)	20 (91.0)
Lost to follow-up*	0 (0.0)	1 (7.7)	1 (4.5)
Physician decision	0 (0.0)	1 (7.7)	1 (4.5)

* Patient was scheduled for surgery but canceled and went to another hospital for treatment.
 Cross Reference: Data Listings 1.1 and 1.2.

The reason(s) for not treating patients who were randomized are provided in Table 6.3.

Table 6.3: List of randomized patients who were not treated
 Protocols PTL-0013 and PTL-0022

Patient Identification	Site No.	Treatment	Reason for Not Being Treated
PTL-0013 (US)			
	2	lactated Ringer's Solution	Salpingo-oophorectomy was performed
	2	lactated Ringer's Solution	Patient refused second-look procedure and went to another hospital
	2	lactated Ringer's Solution	Interceed was used
	2	lactated Ringer's Solution	Twelve or more of the 24 anatomical sites involved with adhesions
	2	LUBRICOAT® Gel	Left salpingo-oophorectomy was performed
	2	lactated Ringer's Solution	Twelve or more of the 24 anatomical sites involved with adhesions, left ovary and fallopian tubes were removed
	2	LUBRICOAT® Gel	Surgical Septrafilm used
	2	lactated Ringer's Solution	Patient had serious papillary cystadenoma and ovarian cancer present
	2	LUBRICOAT® Gel	Extensive adhesions, patient potentially had ovarian cancer
	3	lactated Ringer's Solution	Insulin dependent diabetic
	6	lactated Ringer's Solution	Twelve or more of the 24 anatomical sites involved with adhesions
	8	LUBRICOAT® Gel	Salpingo-oophorectomy was performed
	9	lactated Ringer's Solution	Twelve or more of the 24 anatomical sites involved with adhesions
	11	lactated Ringer's Solution	Twelve or more of the 24 anatomical sites involved with adhesions
	11	LUBRICOAT® Gel	Patient diagnosed with ovarian cancer
	11	lactated Ringer's Solution	Patient did not have a uterus
	12	lactated Ringer's Solution	Twelve or more of the 24 anatomical sites involved with adhesions
	12	LUBRICOAT® Gel	Twelve or more of the 24 anatomical sites involved with adhesions
	12	LUBRICOAT® Gel	GI resection during surgery to excise endometriosis
PTL-0022 (Europe)			
	25	LUBRICOAT® Gel	Twelve or more of the 24 anatomical sites involved with adhesions
	25	LUBRICOAT® Gel	Twelve or more of the 24 anatomical sites involved with adhesions

Table 6.3: List of randomized patients who were not treated (continued)
 Protocols PTL-0013 and PTL-0022

Patient Identification	Site No.	Treatment	Reason for Not Being Treated
PTL-0022 (Europe) - Continued			
██████████	29	lactated Ringer's Solution	Twelve or more of the 24 anatomical sites involved with adhesions

Cross Reference: Data Listings 1.1 and 1.2.

Of the 281 randomized patients who received treatment, 265 completed the study, and 16 did not complete the second-look procedure and were discontinued from the study. The disposition of randomized patients who received treatment is summarized by treatment group in Table 6.4.

Table 6.4: Disposition of randomized patients who received treatment: number (%) of patients
 Protocols PTL-0013 and PTL-0022

	LUBRICOAT® Gel	lactated Ringer's Solution	Total
Total randomized and treated	143 (100.0)	138 (100.0)	281 (100.0)
Completed study	131 (91.6)	134 (97.1)	265 (94.3)
Discontinued from study ^a	12 (8.4)	4 (2.9)	16 (5.7)

^a Treated patients who did not complete the second-look procedure.
 Cross Reference: Data Listings 1.1 and 1.2.

A list of treated patients who discontinued from the study and the reasons for discontinuation are provided in Table 6.5. Demographics and other baseline characteristics for these patients are provided in Supplemental Tables 2.3, 3.3, 4.1.3 and 4.2.3.

Table 6.5: List of patients who discontinued from the study and the reason for discontinuation
 Protocols PTL-0013 and PTL-0022

Patient Identification	Site No.	Treatment	Reason for Discontinuation
<u>PTL-0013 (US)</u>			
[REDACTED]	2	LUBRICOAT® Gel	Patient Decision - patient had no complaints but refused second-look
[REDACTED]	2	lactated Ringer's Solution	Patient Decision - patient had some lower quadrant pain but refused second-look due to out-of-state move
[REDACTED]	2	LUBRICOAT® Gel	Patient Decision - patient had mild supra-pubic pain but refused second-look due to move
[REDACTED]	2	lactated Ringer's Solution	Patient Decision - patient thought she had not fully recovered from first surgery, had returned to work, but refused second-look
[REDACTED]	2	LUBRICOAT® Gel	Physician Decision - failed laparoscopy due to patient obesity
[REDACTED]	5	LUBRICOAT® Gel	Patient Decision - patient had no complaints but refused second-look
[REDACTED]	11	LUBRICOAT® Gel	Pregnant
[REDACTED]	11	LUBRICOAT® Gel	Patient Decision - patient had no complaints but refused second-look
[REDACTED]	11	LUBRICOAT® Gel	Patient Decision - patient had a pleural effusion after the surgery, did not want any more complications, and refused second-look
[REDACTED]	11	LUBRICOAT® Gel	Patient Decision - patient refused second-look and refused to complete her medication diaries
[REDACTED]	12	LUBRICOAT® Gel	Patient Decision - patient had no complaints but refused second-look due to personal reasons
[REDACTED]	12	lactated Ringer's Solution	Patient Decision - patient refused second-look because she thought surgery involving her belly button would make her infertile. She brought her minister with her to Dr. Malinak's office and even he was unable to educate her regarding this matter.
<u>PTL-0022 (Europe)</u>			
[REDACTED]	21	lactated Ringer's Solution	Patient Decision - patient was feeling well and did not want a second-look
[REDACTED]	21	LUBRICOAT® Gel	Patient Decision - patient was feeling well and did not want a second-look
[REDACTED]	21	LUBRICOAT® Gel	Patient Decision - patient was feeling well and did not want a second-look
[REDACTED]	23	LUBRICOAT® Gel	Lost to Follow-up - patient did not return verbal or written messages to schedule the second-look

Cross Reference: Data Listings 1.1 and 1.2.

6.2. PATIENT EVALUABILITY

All of the randomized patients who received treatment, 281, were evaluable for safety and the intent-to-treat analyses. The 265 treated patients who completed the study (i.e., had second-look laparoscopic data available) were evaluable for efficacy analysis. Table 6.6 presents a summary of patients evaluable for safety and efficacy analyses by treatment group.

Table 6.6: Summary of patient evaluability: number of patients
Protocols PTL-0013 and PTL-0022

	LUBRICOAT® Gel	lactated Ringer's Solution	Total
Evaluable for safety analyses	143	138	281
Evaluable for efficacy analysis	131	134	265

Cross Reference: Table 6.4.

6.3. PROTOCOL DEVIATIONS

Patients with notable protocol deviations are listed in Appendix 8.

6.3.1. Entry Criteria Deviations

All inclusion and exclusion criteria were met with the exception of age at entry, pre-operative laboratory values, and number of sites with adhesions.

As specified in the protocol, patients were to be between the ages of 18 and 45 years at study entry. Two patients in the lactated Ringer's solution group (██████████) were 45.9 and 45.1 years at study entry.

As specified in the protocol, patients whose WBC ≥ 12.5 K/mm³, Hgb ≤ 8.0 g/dL, SGOT or SGPT ≥ 50 IU/L, or those whose pre-operative laboratory values were

outside 20% of the normal range and considered clinically significant were to be excluded from the study. Nine (6.3%) patients in the LUBRICOAT® Gel group (#s [REDACTED]) and ten (7.2%) in the lactated Ringer's solution group ([REDACTED]) had pre-operative laboratory values which fell outside the ranges specified in the protocol (See Data Listing 8.1 for individual patient data).

Patients who had 12 or more of the 24 anatomical sites involved with adhesions as noted during the initial operative procedure were to be excluded from the study. Seven patients in the LUBRICOAT® Gel group ([REDACTED] 3, [REDACTED]) and seven patients in the lactated Ringer's solution group ([REDACTED]) were noted to have more than 11 adhesions during the initial operative procedure (See Data Listing 6.1 for individual patient data).

Since all patients with entry criteria deviations were otherwise suitable for the study, they were neither dropped from the study nor were their data excluded from analyses for these reasons.

6.3.2. Study Procedure Deviations

Minor deviations from the study procedures, as specified in the protocol, occurred during the study. These deviations included patients who were missing laboratory data, patients who failed to properly document medications in their diaries, those who did not return the Medications Diary at the time specified by the protocol, those who had blood drawn outside the time window allowed by the protocol, or those who completed the second-look procedure outside of the time window allowed by the protocol.

7. PREVIOUS AND CONCOMITANT MEDICATIONS

Various previous and concomitant medications were taken before and during the study, but the classes of medications used by 70% or more of patients in each treatment group were: anti-infective agents (77.1% LUBRICOAT® Gel vs. 80.6% lactated Ringer's solution), autonomic drugs (81.7% LUBRICOAT® Gel vs. 79.1% lactated Ringer's solution), central nervous system agents (100% in each group), and gastrointestinal drugs (85.5% LUBRICOAT® Gel vs. 86.6% lactated Ringer's solution). The use of previous and concomitant medications was not statistically significantly different between the two treatment groups. Previous and concomitant medications are summarized in Supplemental Table 3.1 to 3.3 and listed by patient in Data Listings 4.1 and 4.2.

8. EFFICACY RESULTS

8.1 COMBINABILITY

8.1.1 Interim Analyses Results

As previously discussed in Section 5.9, an interim analysis was specified in the protocol. After at least 120 evaluable patients had completed the US study, the possibility of combining the US data with data from a concurrent European study was to be considered. Due to apparent differences in the baseline number of adhesions in patients in the US and Europe, the combinability analysis was initiated early; an analysis based on 170 completed patients (88 LUBRICOAT® Gel and 82 lactated Ringer's solution) was performed and submitted to the FDA on 12 March 1998. The report is found in Appendix 9. A summary of the results is as follows:

A significant effect of LUBRICOAT® Gel in improving the adhesion outcome in patients undergoing laparotomy compared to microsurgical technique plus

lactated Ringer's solution was demonstrated for the combined US and European data sets. In addition, the patient populations in the US and Europe were found to be similar if baseline condition and/or surgical procedures were taken into account, i.e., trends for the different subpopulations (myomectomy or patients with few adhesions at baseline versus adhesiolysis, or patients with a high adhesion average at baseline) were similar with respect to adhesion reduction associated with LUBRICOAT® Gel treatment versus lactated Ringer's solution.

It was concluded based on the results that the two data sets were considered combinable because the surgical procedures: (a) were common to both studies, (b) were anticipated and allowed by the protocol, (c) differed only in the proportion of surgical procedures in the US and European population, and (d) produced similar trends in efficacy.

On 11 August 1998, the FDA requested another interim analysis to be performed on a larger sample in order to assess the combinability of the data sets. The second interim analysis, based on 213 completed patients (109 LUBRICOAT® Gel and 104 lactated Ringer's solution), was submitted to the agency on 29 September 1998. This second report is found in Appendix 9. A brief summary of the results is as follows:

As found in the first interim analysis based on 170 completed patients, a significant effect of LUBRICOAT® Gel in improving the adhesion outcome in patients undergoing laparotomy compared to microsurgical technique plus lactated Ringer's solution was demonstrated for the combined US and European data sets.

Three conditions of combinability were prospectively identified in the protocol. The first condition, there should be no significant interaction between location (US vs. Europe) and treatment efficacy, was met. The second condition, US and

European populations were to be similar on demographic and pretreatment variables, did differ in several areas, including race, operative time, length of hospital stay, time to second look, and baseline adhesion score. Differences in race, length of hospital stay, and time to second look were expected, and the differences were not considered clinically significant as these differences would not be expected to have an effect on the outcome. Baseline adhesion score, and the third condition of combinability (the US and European lactated Ringer's solution groups were to be similar on second-look adhesion scores), were also different, but logically follow considering the differences in the proportion of the surgical procedures used in the US versus those used in Europe. More detailed analyses of these possible confounding variables indicate that the effect of treatment was significant and the interaction of treatment and continent was non-significant.

Therefore, it was concluded that the data sets were combinable and INTERGEL* Adhesion Prevention Solution (LUBRICOAT® Gel) significantly reduces adhesions compared to microsurgical technique plus lactated Ringer's solution in patients undergoing peritoneal cavity surgery by laparotomy. Thus, a request to terminate enrollment was submitted to the FDA and approved on 30 October, 1998.

8.1.2. Combinability

The primary criterion for combinability is that subgroup membership should not greatly affect the magnitude of the treatment effect. This is commonly indicated by the absence of a statistically significant ($p < 0.05$) interaction between the treatment effect (LUBRICOAT® Gel versus lactated Ringer's solution) and the subgroup. Four subgroup factors were investigated;

1. Continent (US versus Europe)
2. Center
3. Patients undergoing a myomectomy
4. Patients undergoing adhesiolysis

The first factor (Continent) was of interest because of the usual concerns regarding the combinability of data from different countries and is thoroughly discussed in the protocol. The second (Center) is always a concern in multicenter clinical trials, and the third and fourth factors were suggested by previous combinability analyses. Numbers of patients in these subgroups is shown in Appendix 10, Table 1.

A secondary criterion requires comparison of the subgroups on demographic and pre-treatment variables. In contrast to the interaction criterion described above, absence of statistically significant differences is not required. Rather, variables that show statistically significant differences should be considered as possible sources of non-homogeneity that might preclude combination.

In general, combinability was assessed using factorial analyses where one factor indicated treatment (LUBRICOAT® Gel versus Lactated Ringer's solution) and the other factor indicated group (continent, center, myomectomy, adhesiolysis). An interaction term indicating the extent to which the treatment effect differed in the two groups was also included. For continuous variables, this was implemented using the SAS GLM procedure. For categorical variables, this was implemented using the SAS GENMOD procedure with a logit link. Categorical variables that had counts in only one cell could not be analyzed using GENMOD and were, therefore, analyzed using separate two-sided Fisher exact tests combining cells in a fashion analogous to the treatment, continent and interaction effects. Refer to Appendix 10 for details of each analysis.

8.1.2.1. Primary Combinability Criterion - Effects of Continent

Analyses of the effect of continent were carried out, and the results are presented in Table 8.1. The modified AFS scores at second-look laparoscopy are lower for patients treated with LUBRICOAT Gel than for those who received lactated Ringer's solution for both the US and Europe (US, 1.44 vs. 2.48; Europe, 0.91 vs. 1.95 respectively). The overall effect of treatment (LUBRICOAT® Gel versus lactated Ringer's solution) was highly significant ($p = 0.001$) while the overall effect of continent (US versus Europe) approached significance ($p = 0.076$) and the interaction of the two factors was not significant ($p = 0.989$). If baseline level is included in the model, the effects of treatment, baseline level and continent are all highly significant ($p < 0.001$), but the interaction term is not ($p = 0.662$). Similar results were obtained for analyses of mean number of adhesions.

Because the interaction between treatment and continent did not approach significance, the US and European data are combinable.

TABLE 8.1: Primary Efficacy Variables (by Continent)
 Protocol PTL-0013 and PTL-0022 (Combinability Analysis)

Variable	----- USA -----				----- Europe -----				p values		
	Active		Control		Active		Control		Treatment	Group	Interaction
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)			
Modified AFS Score											
Baseline	93	0.83 (1.51)	95	0.69 (1.42)	38	1.66 (1.91)	39	2.00 (1.96)	0.651	<0.001	0.268
2nd Look	93	1.44 (1.67)	95	2.48 (2.88)	38	0.91 (1.13)	39	1.95 (2.18)	0.001	0.076	0.989
Least Squares Means		1.55		2.67		0.62		1.50			
ANOVA	Source		Stage 1	Final							
	Treatment		0.038	<0.001							
	Group		<0.001	<0.001							
	Treatment*Group		0.420	0.662							
	Baseline		<0.001	<0.001							
	Treatment*Baseline		0.183	.							
Number of Adhesions											
Baseline	93	2.58 (3.67)	95	2.19 (3.46)	38	6.26 (4.55)	39	6.56 (4.96)	0.933	<0.001	0.517
2nd Look	93	6.80 (5.17)	95	7.78 (5.43)	38	5.37 (3.96)	39	7.59 (5.28)	0.022	0.245	0.373
Least Squares Means		7.23		8.39		4.16		6.25			
ANOVA	Source		Stage 1	Final							
	Treatment		0.430	0.014							
	Group		<0.001	<0.001							
	Treatment*Group		0.935	0.478							
	Baseline		<0.001	<0.001							
	Treatment*Baseline		0.184	.							

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 p values determined using factorial ANOVA

8.1.2.2. Primary Combinability Criterion - Center

For analysis of centers, it was necessary to combine small centers into "pseudo centers". This procedure is discussed more fully in Section 8.4.6. Mean modified AFS scores for each center are shown in Table 8.2. In order to adjust for initial differences, baseline adhesion score was included as a continuous covariate and the analysis was performed in two stages. In the first stage, the factors included treatment, center, treatment x center interaction, baseline level and treatment x baseline level interaction. The treatment x baseline level interaction was included in order to test for homogeneity of slopes. Since the treatment x baseline level interaction was not statistically significant ($p=0.58$), it was removed from the model and the final model included only the first four factors. The effect of treatment was statistically significant ($p < 0.001$) as were the effects of center ($p = 0.032$) and baseline level ($p < 0.001$). However, the treatment x center interaction was not significant ($p = 0.787$). The nonsignificant treatment x center interaction indicates that the centers are combinable.

Separate analyses were performed on the US and European data, and are presented in Appendix 10, Tables 7.2.2 and 7.2.3. For both continents, the effect of treatment was statistically significant (US: $p = 0.001$, Europe: $p = 0.026$) as was the effect of baseline modified AFS score (US: $p < 0.001$, Europe: $p = 0.034$) while nonsignificant p-values were obtained for center (US: $p = 0.34$, Europe: $p = 0.91$) and the treatment x center interaction (US: $p = 0.51$, Europe: $p = 0.87$). Again, the nonsignificant treatment x center interaction indicates that the centers are combinable within each subgroup as well.

TABLE 8.2.: Modified AFS Score by Center -All Patients
 Protocol PTL-0013 and PTL-0022 (Combinability Analysis)

	Lubricoat Gel				lactated Ringer's Solution			
	N	Pre	Post	LS Mean	N	Pre	Post	LS Mean
All Patients	131	1.07	1.28	.	134	1.07	2.33	.
US Center 02	21	0.89	1.39	1.48	18	0.61	2.85	3.08
Center 03	6	0.09	1.49	1.98	5	1.77	4.66	4.31
Centers 04 and 12	8	0.11	0.83	1.31	11	0.33	1.08	1.45
Center 06	6	2.32	1.86	1.24	8	0.63	1.73	1.95
Center 07	5	0.92	1.47	1.55	6	0.17	2.17	2.62
Center 08	6	0.20	1.12	1.55	7	0.00	1.32	1.86
Center 09	12	0.77	0.86	1.01	10	0.21	2.71	3.14
Center 10	14	0.02	2.22	2.75	13	0.45	2.41	2.71
Center 11	15	1.88	1.48	1.07	17	1.64	3.24	2.96
Europe Center 21	12	0.99	0.77	0.82	14	1.96	2.28	1.84
Center 23	10	1.81	0.97	0.61	9	1.11	1.40	1.38
Center 25	5	1.31	0.52	0.40	8	3.03	2.20	1.22
Centers 27 and 29	11	2.42	1.18	0.51	8	2.07	1.74	1.24

ANALYSIS OF VARIANCE (Including Baseline Interaction Term)

Source: Treatment p = 0.0055
 Source: Center p = 0.0340
 Source: Treatment*Center p = 0.8114
 Source: Baseline Level p = 0.0000
 Source: Treatment*Baseline p = 0.5839

ANALYSIS OF VARIANCE (Final)

Source: Treatment p = 0.0002
 Source: Center p = 0.0322
 Source: Treatment*Center p = 0.7873
 Source: Pre-treatment Level p = 0.0000

8.1.2.3. Primary Combinability Criterion - Myomectomy

The modified AFS scores at second-look laparoscopy are lower for patients treated with LUBRICOAT Gel than for those who received lactated Ringer's solution for both the myomectomy and non-myomectomy groups (myomectomy, 1.30 vs. 2.23; non-myomectomy, 1.25 vs. 2.55 respectively), as shown in Appendix 10, Table 7.3. The overall effect of treatment (LUBRICOAT® Gel vs. lactated Ringer's solution) was highly significant ($p < 0.001$) while the overall effect of group (myomectomy vs. non-myomectomy) was not significant ($p = 0.652$) and the interaction of the two factors was not significant ($p = 0.515$). If baseline level is included in the model, the effects of treatment and baseline level are highly significant ($p < 0.001$) and the effect of group (myomectomy vs. non-myomectomy) is marginally significant ($p = 0.032$) but the interaction term is still not significant ($p = 0.889$). Similar results were obtained for analyses of mean number of adhesions. Because the interaction between treatment and group (myomectomy vs. non-myomectomy) did not approach significance, myomectomy and non-myomectomy patient populations are combinable.

8.1.2.4. Primary Combinability Criterion - Adhesiolysis

The modified AFS scores at second-look laparoscopy are lower for patients treated with LUBRICOAT Gel than for those who received lactated Ringer's solution for both the adhesiolysis and non-adhesiolysis groups (adhesiolysis, 1.58 vs. 2.94; non-adhesiolysis, 0.98 vs. 1.75 respectively), as shown in Appendix 10, Table 7.4. The overall effect of treatment (LUBRICOAT® vs. lactated Ringer's solution) was highly significant ($p < 0.001$) while the overall effect of group (adhesiolysis vs. non-adhesiolysis) was also significant ($p = 0.001$), but the interaction of the two groups was not significant ($p = 0.264$). If baseline level is included in the model, the effects of treatment and baseline level are highly significant ($p < 0.001$) while the effect of

group (adhesiolysis vs. non-adhesiolysis) is not significant ($p = 0.763$) and the interaction term is not significant ($p = 0.247$). Similar results were obtained for analyses of mean number of adhesions. Because the interaction between treatment and group (adhesiolysis vs. non-adhesiolysis) did not approach significance, adhesiolysis and non-adhesiolysis patient populations are combinable.

8.1.2.5. Secondary Combinability Criteria - Continent

As shown in Appendix 10 Tables 2-7, the following significant demographic and pre-treatment differences between the US and Europe were observed.

Race:	There were more Caucasians in Europe and more Blacks and Hispanics in the US.
Medications:	Use of several categories of medications differed for US and European patients.
Laboratory Values:	Statistically but not clinically significant differences were commonly observed.
Surgical Procedures:	Myomectomy was more common in US patients while adhesiolysis was more common in European patients.
Operative factors:	US patients had longer operative times and shorter times to hospital discharge and shorter times to second-look laparoscopy.
Baseline AFS score:	US patients had lower baseline adhesion scores than European patients.

The racial differences were expected as were the shorter time to discharge from hospital in the US. The later factor results from differences in the nature of medical care rather than any important difference in treatments characteristics. The difference in medications are also attributable to preference differences, but as discussed in the previous combinability analyses, would not be expected to have

any influence on adhesion formation.

US patients had lower baseline adhesion (modified AFS) scores and, not unexpectedly, were less likely to have had adhesiolysis. US patients were more likely to receive myomectomy. Thus, there is some indication that, as a group, US patients were somewhat different from European patients. However, the fact that both putative subgroups had similar beneficial effects of LUBRICOAT® Gel as discussed above, indicates that they are combinable for analysis of the safety and effectiveness of LUBRICOAT® Gel.

8.1.2.6. Secondary Combinability Criteria - Center, Myomectomy and Adhesiolysis

Myomectomy was compared with non-myomectomy and adhesiolysis was compared with non-adhesiolysis on demographic and pre-treatment variables, and the results are presented in Appendix 10, Tables 2-7. Because of the relatively small sample size per center, additional analyses were not carried out. However, in general, the differences observed were predictable.

8.1.2.7. Further Examination of Baseline

The relationship between baseline AFS score and Second-Look AFS score for all US patients in the LUBRICOAT® Gel group and for all US patients in the lactated Ringer's solution group are shown in Appendix 11, Figure 1. Figure 2 shows comparable data for the European patients. Because the data tend to be skewed with a large number of patients at the low end of the range and a smaller number of patients with extreme values, Figures 3 and 4 show the same data with log transformed modified AFS scores. These data graphically confirm that:

1. Baseline modified AFS score predicts second-look modified AFS

- score, i.e. a higher initial score predicts a higher final score.
2. Baseline modified AFS score is lower in US patients.
 3. Second-look modified AFS score is higher in US patients.
 4. LUBRICOAT® Gel reduces second-look modified AFS score (in both subgroups) regardless of the aforementioned effects.

Statistical analyses of covariance (ANCOVA) with all interaction terms included and with nonsignificant interaction terms removed (other than the treatment x continent interaction which was forced into the model) along with plots of the data are shown in Appendix 11 for the following factors;

1. Baseline modified AFS score (log-transformed)
2. Blood loss (log-transformed)
3. Operative Time
4. Time to hospital discharge (log-transformed)
5. Time to second-look laparoscopy (log-transformed)
6. Race (caucasian versus other)
7. Myomectomy (myomectomy versus no myomectomy)

Significance levels for the final model with each factor are given below:

	Treatment	Continent	Interaction	Other Variable	
1.	<0.001	<0.001	0.942	Baseline AFS:	<0.001
2.	<0.001	0.513	0.944	Blood Loss:	<0.001
3.	<0.001	0.369	0.873	Operative Time:	<0.001
4.	<0.001	0.054	0.752	Time to Discharge:	0.367
5.	<0.001	0.139	0.710	Time to 2nd look:	0.112
6.	<0.001	0.614	0.564	Race:	0.004
7.	<0.001	0.023	0.692	Myomectomy:	0.076

When any individual factor was added into the model, it was often statistically significant (i.e. baseline modified AFS score, blood loss, operative time, race) and sometimes produced a significant continent effect (i.e. baseline modified AFS score, myomectomy) but the treatment effect was always statistically significant ($p < 0.001$) and the interaction effect was never statistically significant ($p > 0.50$).

All of these factors were, then, entered into a single model. Also included were the operative-time x continent and the discharge-time x continent interactions which had approached significance in the initial statistical models ($0.05 < p < 0.10$).

As shown in Appendix 11 Table 8.1, the treatment effect was highly significant ($p < 0.001$), the continent effect was not significant ($p = 0.095$) and none of the interaction terms were significant ($p > 0.25$). When nonsignificant factors were removed from the model in a backwards elimination procedure, the final model contained baseline modified AFS score, blood loss, time to second look and race (Appendix 11 Table 8.2). The treatment effect was statistically significant ($p < 0.001$), the continent effect was marginally significant ($p = 0.034$) and the treatment x continent interaction was not significant ($p = 0.610$).

8.1.2.8. Conclusion

No statistically significant interactions between the effect of treatment and any subgroup were observed.

There are a number of statistically significant baseline differences between subgroups based on continent (US versus Europe) and on surgical treatment with myomectomy or adhesiolysis. However, there is no reason to believe that these baseline differences have any effect on treatment efficacy. Therefore, the data are combinable.

8.2. EFFICACY DATA SET ANALYZED

All 265 (131 LUBRICOAT® Gel and 134 lactated Ringer's solution) patients who completed the second-look laparoscopic procedure were included in the efficacy analysis, with the exception of the intent-to-treat analysis which utilized all 281 patients who received treatment.

8.3. DEMOGRAPHIC AND BASELINE FEATURES OF PATIENTS AND COMPARABILITY OF TREATMENT GROUPS

8.3.1. Demographics, Height, Weight, and Vital Signs

Patients in the two treatment groups were comparable with respect to race, age, height, weight, and vital signs with no statistically significant differences between the two groups (Table 8.3).

8.3.2. Operative Characteristics

Operative characteristics, including blood loss, operative time, days to discharge, days to second-look laparoscopy, presence of adhesions, and presence of endometriosis, were similar in the two treatment groups with no statistically significant differences between the groups (Table 8.4).

8.3.3. Surgical Procedures

Similar surgical procedures were performed in the two treatment groups with no statistically significant differences between the groups (Table 8.5). Myomectomy, adhesiolysis, ovarian surgery, and tubal surgery were the four most common procedures.

Table 8.3: Demographics, Height, Weight, and Vital Signs
 Protocols PTL-0013 and PTL-0022

Variable	Lubricoat Gel			lactated Ringer's Solution			p*
	n	N	%	n	N	%	
Race							
Caucasian	74	131	56.5%	82	134	61.2%	0.456
Black	28	131	21.4%	23	134	17.2%	0.437
Oriental	4	131	3.1%	4	134	3.0%	1.000
Hispanic	20	131	15.3%	22	134	16.4%	0.867
Other	5	131	3.8%	3	134	2.2%	0.497

Variable	N	Mean	(SD)	Range	N	Mean	(SD)	Range	P
Age (years)	131	33.8	(5.8)	18.8 to 44.9	134	34.2	(5.4)	18.6 to 45.9	0.637
Temperature (F)	125	98.1	(0.8)	95.9 to 99.9	131	98.3	(0.6)	96.0 to 99.7	0.079
Pulse (bpm)	128	75.1	(11.2)	45 to 110	132	74.8	(10.9)	50 to 109	0.811
Respiration (min)	114	18.3	(3.7)	10 to 32	113	19.2	(6.1)	10 to 64	0.174
Systolic BP (mmHg)	131	120.1	(14.5)	92 to 162	133	119.9	(13.9)	80 to 168	0.900
Diastolic BP (mmHg)	131	73.7	(11.1)	47 to 108	133	73.7	(10.6)	42 to 104	0.998
Height (in)	130	64.5	(2.5)	57.0 to 71.0	134	64.6	(2.9)	57.0 to 71.7	0.690
Weight (lbs)	131	150.1	(30.9)	104 to 252	134	150.2	(31.8)	100 to 264	0.994

*p values determined using the Fisher exact test or Student's t test
 Cross-Reference: Supplemental Table 2.2.

Table 8.4: Operative Characteristics
 Protocols PTL-0013 and PTL-0022

Variable	Lubricoat Gel			Lactated Ringer's Solution			p*
	n	N	%	n	N	%	
Adhesions	70	131	53.4%	71	134	53.0%	1.000
Endometriosis	23	131	17.6%	29	134	21.6%	0.441
Stage I	9	23	39.1%	9	29	31.0%	0.571
Stage II	4	23	17.4%	11	29	37.9%	0.132
Stage III	4	23	17.4%	5	29	17.2%	1.000
Stage IV	6	23	26.1%	4	29	13.8%	0.307
Transfusions	8	131	6.1%	4	134	3.0%	0.251

Variable	N	Mean	(SD)	Range	N	Mean	(SD)	Range	P
Blood Loss (mL)	131	214	(214)	2 to 1500	134	224	(284)	2 to 2200	0.742
Blood Units	131	0.15	(0.66)	0.00 to 4.00	134	0.08	(0.49)	0.00 to 4.00	0.324
Operative Time (hrs)	131	1.86	(0.82)	0.75 to 5.00	134	1.80	(0.85)	0.75 to 5.00	0.533
Days to Discharge	131	3.0	(1.6)	0 to 12	134	3.0	(1.7)	0 to 10	0.909
Days to 2nd Look	131	60.4	(26.2)	26 to 245	134	58.7	(21.4)	31 to 145	0.561

*p values determined using the Fisher exact test or Student's t test
 Cross-Reference: Supplemental Table 4.1.2.

Table 8.5: Surgical Procedures
 Protocols PTL-0013 and PTL-0022

Variable	Lubricoat Gel			Lactated Ringer's Solution			p*
	n	N	%	n	N	%	
APPENDECTOMY	1	131	0.8%	0	134	0.0%	0.494
LAPAROTOMY	131	131	100.0%	134	134	100.0%	1.000
ABLATION ENDOMETRIOSIS	13	131	9.9%	18	134	13.4%	0.446
CYSTOTOMY REPAIR	1	131	0.8%	1	134	0.7%	1.000
OMENECTOMY	0	131	0.0%	1	134	0.7%	1.000
LAPAROSCOPY	2	131	1.5%	4	134	3.0%	0.684
HYSTEROSCOPY	5	131	3.8%	6	134	4.5%	1.000
HYSTEROSCOPY / LYSIS	3	131	2.3%	0	134	0.0%	0.119
HYSTEROSCOPY / RESECTION	1	131	0.8%	0	134	0.0%	0.494
EXCISION VAGINAL CYST	0	131	0.0%	1	134	0.7%	1.000
COLPOSCOPY	0	131	0.0%	1	134	0.7%	1.000
ENDOMETRIAL BIOPSY	1	131	0.8%	0	134	0.0%	0.494
DILATION AND CURETTAGE	3	131	2.3%	1	134	0.7%	0.367
MYOMECTOMY	88	131	67.2%	92	134	68.7%	0.895
CHROMOPERTUBATION	2	131	1.5%	7	134	5.2%	0.172
UTERINE SUSPENSION	2	131	1.5%	1	134	0.7%	0.619
UTERINE SUSPENSION / NEURECTOMY	0	131	0.0%	1	134	0.7%	1.000
SALPINGO-OOPHORECTOMY	1	131	0.8%	0	134	0.0%	0.494
ADHESIOLYSIS	66	131	50.4%	65	134	48.5%	0.806
TUBAL REVERSAL	2	131	1.5%	2	134	1.5%	1.000
FIMBRIOPLASTY	4	131	3.1%	9	134	6.7%	0.255
SALPINGOSTOMY	17	131	13.0%	13	134	9.7%	0.442
PARATUBAL CYSTECTOMY	8	131	6.1%	4	134	3.0%	0.251
OVARIAN RESECTION	4	131	3.1%	1	134	0.7%	0.210
OVARIAN CYSTECTOMY -SIMPLE	12	131	9.2%	13	134	9.7%	1.000
OVARIAN CYSTECTOMY -DERMOID	3	131	2.3%	8	134	6.0%	0.217
OVARIAN CYSTECTOMY -ENDOMETRIOMA	13	131	9.9%	10	134	7.5%	0.519
OVARIAN SUSPENSION	0	131	0.0%	1	134	0.7%	1.000

*p values determined using the Fisher Exact test
 Cross-Reference: Supplemental Table 4.2.2.

8.3.4. Baseline Adhesion Assessment

For all sites, there were no statistically significant differences between the two treatment groups for any of the baseline adhesion variables, including the mean number of sites at baseline with adhesions, the number of adhesions which were lysed, and the number of surgical sites (which includes adhesiolysis, surgical treatment of endometriosis, and other surgical procedures) (Table 8.6).

Baseline adhesion data for all subsets (including pelvic sites, general surgical sites, and individual anatomical sites) are presented in the supplemental tables. As found for all sites, the two treatment groups within each subset were generally comparable with regard to the mean number of sites at baseline with adhesions, the number of adhesions which were lysed, and the number of surgical sites.

Table 8.6: Baseline Adhesion Data - All Sites
 Protocols PTL-0013 and PTL-0022

Variable	Lubricat Gel				lactated Ringer's Solution				p*
	N	Mean	(SD)	Range	N	Mean	(SD)	Range	
Baseline									
Adhesions	131	3.65	(4.27)	0 to 15	134	3.46	(4.41)	0 to 14	0.727
Total Possible	131	22.82	(0.77)	18 to 23	134	22.66	(1.12)	18 to 23	0.157
Proportion ^b	131	0.161	(0.187)	0.00 to 0.65	134	0.156	(0.201)	0.00 to 0.78	0.853
Severity Score(0-3) ^b	131	0.38	(0.49)	0.0 to 1.9	134	0.35	(0.47)	0.0 to 1.7	0.517
Extent Score(0-3) ^c	131	0.29	(0.39)	0.0 to 1.5	134	0.30	(0.40)	0.0 to 1.6	0.917
Modified AFS Score(0-16) ^d	131	1.07	(1.67)	0.0 to 6.8	134	1.07	(1.70)	0.0 to 6.7	0.994
Adhesions Lysed	131	3.07	(3.84)	0 to 15	134	2.92	(4.05)	0 to 14	0.756
Surgical Sites	131	5.53	(3.46)	2 to 16	134	5.48	(3.55)	2 to 15	0.895
Mild Adhesions	131	1.11	(1.95)	0 to 8	134	1.37	(2.49)	0 to 11	0.348
Severe Adhesions	131	2.53	(3.54)	0 to 14	134	2.09	(3.14)	0 to 11	0.280
Localized Adhesions	131	1.50	(2.34)	0 to 10	134	1.25	(2.01)	0 to 9	0.351
Moderate Adhesions	131	1.34	(2.15)	0 to 9	134	1.35	(2.28)	0 to 10	0.957
Extensive Adhesions	131	0.82	(1.95)	0 to 8	134	0.87	(1.91)	0 to 9	0.837

* p values determined using Student's t test

^b Proportion of sites with adhesions=number of sites with adhesions divided by the number of possible adhesion sites.

^c Severity was scored on a 3-point scale with 0=none, 1=mild, and 3=severe.

^d Extent was scored on a 4-point scale with 0=none, 1=localized, 2=moderate, and 3=extensive.

^e An aggregate score derived from the severity and extent of adhesion scores from 24 anatomical sites. The score ranged from 0 to 16 with 0 indicating no adhesions to 16 indicating severe and extensive adhesions.

Cross Reference: Supplemental Table 5.1.1.1.

8.3.5. Baseline Laboratory Values

The baseline clinical laboratory mean values were not significantly different between the two treatment groups (Supplemental Table 7.1).

8.4. ADHESION OUTCOME AT SECOND-LOOK LAPAROSCOPY - PER PROTOCOL ANALYSES

Section 8.4 presents the results of all efficacy analyses specified in the protocol (i.e. per protocol analyses). Additional efficacy analyses not specified in the protocol are presented in Section 8.5.

8.4.1. All Sites

8.4.1.1 Primary Efficacy Variable - Modified AFS score

As previously discussed in Section 8.3.4, the mean number of sites at baseline with adhesions, the number of adhesions which were lysed, and the number of surgical sites were comparable between the two groups. However, at second-look, patients treated with LUBRICOAT® Gel had a mean overall Modified AFS score that was 45% lower than that of patients treated with lactated Ringer's solution (Table 8.7). This difference was statistically significant ($p=0.000$).

The significantly greater reduction in adhesions with LUBRICOAT® Gel based on the Modified AFS score was observed for *de novo* adhesions, (including surgical and non-surgical sites), reformed adhesions, and all surgical site adhesions. At second-look, patients treated with LUBRICOAT® Gel had a mean *de novo* Modified AFS score 49% lower ($p=0.000$), a mean reformed Modified AFS score 43% lower ($p=0.002$), and a mean surgical site Modified AFS score 44% lower ($p=0.000$) than the mean scores of patients treated with lactated Ringer's solution (Table 8.8).

The reduction in *de novo* adhesions with LUBRICOAT® Gel was observed at both the surgical sites and at the non-surgical sites. In patients treated with LUBRICOAT® Gel, the mean *de novo* Modified AFS score at the surgical sites was 49% lower ($p=0.001$) and the mean score at the non-surgical sites was 49% lower ($p=0.000$) than the mean scores of patients treated with lactated Ringer's solution.

The results of the adhesion outcome at second-look for all adhesion sites demonstrate that treatment with LUBRICOAT® Gel is effective in reducing post-surgical adhesions, including *de novo* and reformed adhesions.

Table 8.7: Baseline and Second-Look Adhesion Data - All Sites
 Protocol PTL-0013 and PTL-0022

Variable	Lubricoat Gel				Lactated Ringer's Solution (LRS)				p*	% Mean Difference [(LRS-LUBRICOAT')/LRS]x100
	N	Mean	(SD)	Range	N	Mean	(SD)	Range		
Baseline										
Adhesions	131	3.65	(4.27)	0 to 15	134	3.46	(4.41)	0 to 14	0.727	
Total	131	22.82	(0.77)	18 to 23	134	22.66	(1.12)	18 to 23	0.157	
Proportion ^a	131	0.161	(0.187)	0.00 to 0.65	134	0.156	(0.201)	0.00 to 0.78	0.853	
Severity Score(0-3) ^b	131	0.38	(0.49)	0.0 to 1.9	134	0.35	(0.47)	0.0 to 1.7	0.517	
Extent Score(0-3) ^c	131	0.29	(0.39)	0.0 to 1.5	134	0.30	(0.40)	0.0 to 1.6	0.917	
Modified AFS Score(0-16) ^d	131	1.07	(1.67)	0.0 to 6.8	134	1.07	(1.70)	0.0 to 6.7	0.994	
Adhesions Lysed	131	3.07	(3.84)	0 to 15	134	2.92	(4.05)	0 to 14	0.756	
Surgical Sites	131	5.53	(3.46)	2 to 16	134	5.48	(3.55)	2 to 15	0.895	
Mild Adhesions	131	1.11	(1.95)	0 to 8	134	1.37	(2.49)	0 to 11	0.348	
Severe Adhesions	131	2.53	(3.54)	0 to 14	134	2.09	(3.14)	0 to 11	0.280	
Localized Adhesions	131	1.50	(2.34)	0 to 10	134	1.25	(2.01)	0 to 9	0.351	
Moderate Adhesions	131	1.34	(2.15)	0 to 9	134	1.35	(2.28)	0 to 10	0.957	
Extensive Adhesions	131	0.82	(1.95)	0 to 8	134	0.87	(1.91)	0 to 9	0.837	
Second Look										
Adhesions	131	6.38	(4.88)	0 to 18	134	7.72	(5.37)	0 to 22	0.034	17
Total Possible	131	23.24	(1.71)	16 to 24	134	23.04	(2.16)	13 to 24	0.405	-
Proportion	131	0.279	(0.215)	0.00 to 0.89	134	0.340	(0.237)	0.00 to 0.92	0.027	18
Severity Score(0-3) ^b	131	0.51	(0.46)	0.0 to 1.9	134	0.76	(0.64)	0.0 to 2.7	0.001	33
Extent Score(0-3) ^c	131	0.47	(0.45)	0.0 to 1.9	134	0.64	(0.58)	0.0 to 2.6	0.006	27
Modified AFS Score(0-16) ^d	131	1.28	(1.55)	0.0 to 6.6	134	2.33	(2.70)	0.0 to 13.5	0.000	45

* p values determined by Student's t test

^a Proportion of sites with adhesions=number of sites with adhesions divided by the number of possible adhesion sites.

^b Severity was scored on a 3-point scale with 0=none, 1=mild, and 3=severe.

^c Extent was scored on a 4-point scale with 0=none, 1=localized, 2=moderate, and 3=extensive.

^d An aggregate score derived from the severity and extent of adhesion scores from 24 anatomical sites. The score ranged from 0 to 16 with 0 indicating no adhesions to 16 indicating severe and extensive adhesions.

Cross-Reference: Supplemental table 5.1.1.1.

Table 8.8: DeNovo^a, Surgical Site and Reformed^b Adhesions - All Sites
 Protocols PTL-0013 and PTL-0022

Variable	Lubricoat Gel				lactated Ringer's Solution (LRS)				p*	% Mean Difference [(LRS-LUBRICOAT)/LRS]x100
	N	Mean	(SD)	Range	N	Mean	(SD)	Range		
DeNovo Adhesions	131	4.80	(4.44)	0 to 18	134	5.72	(4.54)	0 to 19	0.098	16
Total Possible	131	20.18	(4.39)	9 to 24	134	20.13	(4.80)	5 to 24	0.931	-
Proportion	131	0.239	(0.206)	0.00 to 0.88	134	0.292	(0.227)	0.00 to 0.94	0.046	18
Severity Score	131	0.42	(0.42)	0.0 to 1.7	134	0.65	(0.61)	0.0 to 2.6	0.001	35
Extent Score	131	0.39	(0.41)	0.0 to 1.8	134	0.55	(0.54)	0.0 to 2.5	0.008	29
Modified AFS Score(0-16)	131	1.00	(1.30)	0.0 to 5.8	134	1.97	(2.51)	0.0 to 12.8	0.000	49
Surgical site Adhesions	131	2.49	(2.56)	0 to 12	134	3.23	(3.10)	0 to 13	0.035	23
Total Possible	131	6.39	(3.44)	1 to 17	134	6.35	(3.53)	3 to 16	0.928	-
Proportion	131	0.365	(0.304)	0.00 to 1.00	134	0.464	(0.293)	0.00 to 1.00	0.008	21
Severity Score(0-3)	131	0.73	(0.73)	0.0 to 3.0	134	1.04	(0.82)	0.0 to 3.0	0.001	30
Extent Score(0-3)	131	0.60	(0.62)	0.0 to 3.0	134	0.89	(0.73)	0.0 to 3.0	0.001	33
Modified AFS Score(0-16)	131	1.88	(2.51)	0.0 to 16.0	134	3.38	(3.73)	0.0 to 16.0	0.000	44
Surgical site DeNovo Adhesions	131	0.73	(0.86)	0 to 4	134	1.04	(1.01)	0 to 5	0.007	30
Total Possible	131	2.40	(0.98)	1 to 6	134	2.50	(1.10)	1 to 8	0.456	-
Proportion	131	0.290	(0.328)	0.00 to 1.00	134	0.389	(0.352)	0.00 to 1.00	0.018	25
Severity Score(0-3)	131	0.59	(0.82)	0.0 to 3.0	134	0.90	(0.97)	0.0 to 3.0	0.005	34
Extent Score(0-3)	131	0.45	(0.62)	0.0 to 3.0	134	0.72	(0.81)	0.0 to 3.0	0.003	38
Modified AFS Score(0-16)	131	1.41	(2.52)	0.0 to 16.0	134	2.79	(3.95)	0.0 to 16.0	0.001	49
Non-surgical site DeNovo Adhesions	131	4.08	(3.92)	0 to 16	134	4.68	(3.90)	0 to 17	0.211	13
Total Possible	131	17.77	(3.91)	8 to 22	134	17.63	(4.28)	4 to 22	0.775	-
Proportion	131	0.232	(0.210)	0.00 to 0.93	134	0.278	(0.229)	0.00 to 0.94	0.089	17
Severity Score(0-3)	131	0.40	(0.41)	0.0 to 1.6	134	0.61	(0.61)	0.0 to 2.6	0.001	34
Extent Score(0-3)	131	0.38	(0.42)	0.0 to 1.9	134	0.52	(0.54)	0.0 to 2.6	0.018	27
Modified AFS Score(0-16)	131	0.95	(1.27)	0.0 to 5.8	134	1.85	(2.49)	0.0 to 12.5	0.000	49
Reformed Adhesions	66	3.14	(2.69)	0 to 12	65	4.14	(3.32)	0 to 13	0.060	24
Total Possible	66	6.09	(3.29)	1 to 15	65	6.02	(3.90)	1 to 14	0.905	-
Proportion	66	0.492	(0.343)	0.00 to 1.00	65	0.690	(0.346)	0.00 to 1.00	0.001	29
Severity Score(0-3)	66	1.02	(0.84)	0.0 to 3.0	65	1.54	(1.05)	0.0 to 3.0	0.002	34
Extent Score(0-3)	66	0.88	(0.77)	0.0 to 2.7	65	1.37	(0.88)	0.0 to 3.0	0.001	36
Modified AFS Score(0-16)	66	2.87	(3.13)	0.0 to 12.0	65	5.06	(4.83)	0.0 to 16.0	0.002	43

* p values determined using Student's t test

^a Only sites without adhesions at the initial surgery were capable of having *de novo* adhesions at the second-look laparoscopic procedure.

^b Only sites with adhesions that were lysed at the initial surgery were capable of reformed adhesions at the second-look laparoscopic procedure.

Cross-Reference: Supplemental Table 5.1.1.2.

8.4.1.2. Secondary Efficacy Variables - Proportion, Severity, and Extent of Adhesions - All Sites

Proportion of Sites with Adhesions

The proportion of sites with new adhesions for all sites in the LUBRICOAT® Gel group was significantly ($p=0.027$) lower at second-look than the proportion of sites with new adhesions in the lactated Ringer's solution group. The mean proportion of sites with new adhesions was 18% lower in the LUBRICOAT® Gel group (Table 8.7).

Severity and Extent of Adhesions

The severity and extent of post-surgical adhesions were also reduced in the LUBRICOAT® Gel group compared to the lactated Ringer's solution group. The mean severity of post-surgical adhesions was 33% lower ($p=0.001$) and the mean extent of adhesions was 27% lower ($p=0.006$) in the LUBRICOAT® Gel group than in the lactated Ringer's solution group (Table 8.7).

8.4.2. Pelvic Sites

8.4.2.1 Primary Efficacy Variable - Modified AFS Score

Supplemental Table 5.1.2.1. presents a summary of the adhesion outcome data for the pelvic sites and Supplemental Table 5.1.2.2. presents the results for *de novo*, reformed, and surgical sites.

As observed for all sites, LUBRICOAT® Gel was significantly more effective than lactated Ringer's solution in reducing pelvic site adhesions based on the Modified AFS score. Although baseline pelvic site adhesion data were comparable between the two groups, patients treated with LUBRICOAT® Gel had a

significantly ($p=0.002$) lower mean Modified AFS score at second-look than those treated with lactated Ringer's solution.

The gel was also more effective than lactated Ringer's solution based on the Modified AFS Score in reducing surgical site adhesions ($p=0.002$), reformed adhesions ($p=0.011$), and *de novo* adhesions ($p=0.001$), including surgical site *de novo* adhesions ($p=0.003$) and non-surgical site *de novo* adhesions ($p=0.004$).

These results demonstrate that LUBRICOAT® Gel is effective in reducing post-surgical adhesions in the pelvis, including *de novo* and reformed adhesions.

8.4.2.2. Secondary Efficacy Variables - Proportion, Severity, and Extent of Adhesions

Proportion of Adhesions

The proportion of sites with new adhesions at the pelvic sites was reduced in the LUBRICOAT® Gel group, although the p-value did not reach significance ($p=0.077$) (Supplemental Table 5.1.2.1.).

Severity and Extent of Adhesions

As observed for all adhesion sites, the severity and extent of post-surgical adhesions at the pelvic sites were significantly lower in the LUBRICOAT® Gel group ($p=0.005$ and $p=0.021$, respectively) (Supplemental Table 5.1.2.1.).

8.4.3. General Surgical Sites

8.4.3.1. Primary Efficacy Variable - Modified AFS Score

Supplemental Table 5.1.3.1. presents a summary of adhesions outcome data for the general surgical sites and Supplemental Table 5.1.3.2. presents a summary of the data for *de novo*, reformed, and surgical sites.

Similar to the results obtained for all sites, patients treated with LUBRICOAT® Gel had a mean Modified AFS Score that was significantly ($p=0.000$) lower than that of patients treated with lactated Ringer's solution. The gel was more effective than lactated Ringer's solution based on the Modified AFS Score in reducing surgical site adhesions ($p=0.001$), reformed adhesions ($p=0.007$), and *de novo* adhesions ($p=0.000$), including surgical site *de novo* adhesions ($p=0.012$) and non-surgical site *de novo* adhesions ($p=0.000$).

These results demonstrate that LUBRICOAT® Gel is effective in reducing post-surgical adhesions throughout the abdomen including *de novo* and reformed adhesions.

8.4.3.2. Secondary Efficacy Variables - Proportion, Severity, and Extent of Adhesions

Proportion of Adhesions

Similar to the results observed for all sites, the proportion of sites with new adhesions at the general surgical sites was significantly ($p=0.008$) lower in the LUBRICOAT® Gel group than in the lactated Ringer's solution group (Supplemental Table 5.1.3.1.).

Severity and Extent of Adhesions

Similar to the results observed for all sites, the severity and extent of post-surgical adhesions for the general surgical sites were significantly ($p < 0.001$) lower in the LUBRICOAT® Gel group than in the lactated Ringer's solution group (Supplemental Table 5.1.3.1.).

8.4.4 Individual Anatomical Sites

8.4.4.1. Primary Efficacy Variable - Modified AFS Score

Treatment group comparisons were also performed for each of the 24 anatomical sites with the potential for forming post-operative adhesions. As observed for all sites, a reduction in adhesions with LUBRICOAT® Gel following peritoneal cavity surgery was found for each individual anatomical site based on the Modified AFS Score (Supplemental Table 5.2.2.). Statistically significant ($p < 0.05$) greater reduction in adhesions with LUBRICOAT® Gel was found for 14 of the 24 anatomical sites, and the differences between the treatment groups approached statistical significance ($p > 0.05 < 0.10$) for 4 additional sites. The remaining 6 sites showed a positive trend.

8.4.4.2. Secondary Efficacy Variable - Proportion of Sites with Adhesions

The proportion of adhesions was significantly (< 0.05) reduced in patients treated with LUBRICOAT® Gel for 6 of the 24 anatomical sites with trends in favor of the LUBRICOAT® Gel group for 9 additional sites (Supplemental Table 5.3.2.).

8.4.5. Analyses by Surgical Technique

Additional subgroup analyses were performed by the following site groupings based on the presence of endometriosis and surgical technique used, i.e. sites

with sutures, sites lysed using sharp dissection, sites lysed using cautery, sites lysed using laser, and sites lysed using blunt dissection. The overall results are presented in Supplemental Tables 5.1.14.1 to 5.1.20.1. The results for *de novo*, surgical site, and reformed adhesions are presented in Supplemental Tables 5.1.14.2 to 5.1.20.2.

A significant reduction in adhesions with LUBRICOAT® Gel was observed at sites with endometriosis ($p=0.041$) as well as those without endometriosis ($p=0.000$), and at sites where sutures were used ($p=0.004$). A greater reduction in adhesions with LUBRICOAT® Gel was observed, regardless of the method of adhesiolysis, i.e. sharp dissection, blunt dissection, or cautery (lasers were used too infrequently to comment). Blunt dissection had the highest reformation rates (lactated Ringer's solution = 91%, LUBRICOAT® Gel = 63%), followed by sharp dissection (lactated Ringer's solution = 75%, LUBRICOAT® Gel = 61%), and cautery (lactated Ringer's solution = 69%, LUBRICOAT® Gel = 41%).

8.4.6. Modified AFS Score by Center

The primary efficacy variable (modified AFS Score at Second Look) was analyzed using factorial Analysis of Covariance (ANCOVA) with treatment group (LUBRICOAT® versus Lactated Ringer's solution) and center as categorical factors and baseline modified AFS score as a continuous covariate.

Centers with small numbers of patients were combined into "pseudo-centers" as shown in Table 8.9. US centers were only combined with US centers and European centers were only combined with European centers. Small centers were combined such that the resulting pseudo-centers and all other centers had at least 5 patients per group. Thus, for the efficacy population, Center 4 (Ns = 4 for LUBRICOAT® Gel and 3 for Lactated Ringer's solution) was combined with Center 12 (Ns = 4 for LUBRICOAT® Gel and 8 for Lactated Ringer's solution) and

Center 27 (Ns = 5 for LUBRICOAT® Gel and 3 for Lactated Ringer's solution) was combined with Center 29 (Ns = 6 for LUBRICOAT® Gel and 5 for Lactated Ringer's solution). For the Intent-to-Treat population, Center 5 (N = 1 for LUBRICOAT® Gel) was added into the pseudo-center containing Centers 4 and 12.

Table 8.9: Combining Centers for Factorial Analysis
 Protocols PTL-0013 and PTL-0022

Protocol No.	Center No.	No. of Completed Patients	New Center
PTL-0013	03	11	Center
	07	11	Center
	04	7	Combined Center (i.e. "pseudo-center")
	12	12	
	06	14	Center
	08	13	Center
	09	22	Center
	10	27	Center
	11	32	Center
	02	39	Center
PTL-0022	27	8	Combined Center (i.e. "pseudo-center")
	29	11	
	25	13	Center
	23	19	Center
	21	26	Center

8.4.6.1. Modified AFS score - By Center

Factorial analysis of variance was performed on the Modified AFS score derived from all adhesion sites for all completed patients (i.e., US and European data combined). Supporting data is provided in Appendix 12. Modified AFS Scores were used with no transformation. In order to adjust for initial differences, baseline adhesion score was included as a continuous covariate and the analysis

was performed in two stages. In the first stage, the factors included treatment, center, treatment x center interaction, baseline level and treatment x baseline level interaction. The treatment x baseline level interaction was included in order to test for homogeneity of slopes. Since the treatment x baseline level interaction was not statistically significant ($p=0.58$), it was removed from the model and the final model included only the first four factors. The results are shown in Supplemental Table 5.4.1.

The overall effect of treatment was statistically significant ($p = 0.0002$) as was the effect of baseline level ($p < 0.0001$). The overall center effect was also statistically significant ($p = 0.032$) but the interaction between treatment and center was not ($p=0.79$). Examination of least squares (LS) means indicated that the LUBRICOAT® Gel group had fewer second-look adhesions than the Lactated Ringer's solution group in all but one of the centers (Center 10). A detailed discussion of the center differences is found in the combinability discussion in Section 8.1.2.

Factorial analyses of variance were also performed on the subset of all completed US patients and the subset of all completed European patients. Results similar to those obtained for all patients were obtained for these subsets (Supplemental Tables 5.4.2 and 5.4.3). For each subset, the overall treatment effect was statistically significant (US: $p = 0.001$, Europe: $p = 0.026$). Effects of baseline level were also significant (US: $p < 0.0001$, Europe: $p = 0.034$). Effects of center and treatment x center interactions were not statistically significant ($ps > 0.30$).

8.4.6.2. Modified AFS Score (Log-Transformed Data) - By Center

Because the distribution of Modified AFS scores was somewhat skewed with most patients showing low scores but a few patients showing relatively high

scores, a factorial analysis of variance was performed on the log-transformed Modified AFS score derived from all adhesion sites for all completed patients (i.e. US and European data combined). This analysis was performed as described in Section 8.4.6.1 above). *For results see Supplemental Table 5.4.4*

Results were similar to those obtained from nontransformed data. The overall treatment effect was significant ($p = 0.0002$) as was the effect of center ($p = 0.003$) and the effect of baseline level ($p < 0.0001$). The Treatment x Center interaction was not statistically significant ($p = 0.70$).

8.4.6.3. Modified AFS Score in the ITT Population (Rank-Transformed Data)

An Intent-to-Treat (ITT) analysis was performed in which all treated patients, who did not receive a second-look laparoscopy, were defined as treatment failures and given the worst possible Modified AFS score. Because of the extreme skewness produced by this procedure, analysis of variance was performed after rank-transformation. Demographics and other baseline characteristics for these patients are provided in Supplemental Tables 2.1, 3.1, 4.1.1 and 4.2.1.

For results see Supplemental Table 5.4.5

Results were similar to those obtained from untransformed and log-transformed data for completed patients. The overall treatment effect was statistically significant ($p = 0.017$) as was the effect of center ($p = 0.027$) and the effect of baseline level ($p < 0.0001$). The treatment x center interaction was not statistically significant ($p=0.82$).

8.4.6.4 General Assessment of Effect of Treatment on the Modified AFS Score

Regardless of population or method of analysis, LUBRICOAT® Gel produced significantly lower Modified AFS scores than Lactated Ringer's solution. The effect of center was always at least marginally significant when US and European centers were both in the analysis but was absent when the US and European centers were analyzed alone. However, it is most important to note that the treatment x center interaction never approaches statistical significance indicating that, although some centers may have higher overall adhesion scores than others, treatment with LUBRICOAT® Gel reduces adhesion scores and the data are combinable.

8.5. EFFICACY ANALYSES NOT SPECIFIED IN THE PROTOCOL

8.5.1. Analyses by Surgical Procedure

Additional efficacy analyses, not specified in the protocol, were performed for the following subgroups of patients based on the surgical procedure performed: patients with myomectomy, patients without myomectomy, patients with adhesiolysis, patients with tubal procedures, patients with ovarian procedures, patients with dermoid or endometrioma ovarian procedures, patients with dermoid ovarian procedures, patients with endometrioma ovarian procedures, patients with endometriosis excision, and patients with endometriosis excision or endometrioma ovarian procedures. The overall results are found in Supplemental Table 5.1.4.1 to 5.1.13.1. The results for *de novo*, surgical site, and reformed adhesions are presented in Supplemental Tables 5.1.4.2 to 5.1.13.2.

The results were similar to those obtained for all patients. Treatment with LUBRICOAT® Gel following peritoneal cavity surgery resulted in a reduction in adhesions compared to treatment with lactated Ringer's solution within each subgroup (the mean Modified AFS score was lower in the LUBRICOAT® Gel group in all subgroups). Statistically significant ($p < 0.05$) differences between the treatment groups (based on the Modified AFS score) were observed for patients with myomectomy, patients without myomectomy, patients with adhesiolysis, patients with tubal procedures, and patients with ovarian procedures. Trends favoring LUBRICOAT® Gel were also observed for all of the other procedures, despite the relatively small number of cases.

8.5.2. Standard AFS Score

In addition to the Modified AFS score which is derived from 24 anatomical sites, adhesion outcome in the two treatment groups was analyzed based on the Standard AFS Score. As previously described in Section 5.8, the Standard AFS scoring method is limited to the adnexa, thereby taking into account only the ovaries and Fallopian tubes.

The effect of LUBRICOAT® Gel on reducing adnexal adhesions was shown by a significant reduction in the Standard AFS score compared to lactated Ringer's solution (Supplemental Table 5.6.1). The minimum score of both the right and left adnexa was significantly ($p = 0.000$) reduced by administration of LUBRICOAT® Gel (1.89 vs. 4.60; a 59% reduction). In addition, the proportion of patients with minimal scores (Standard AFS score 0-5) increased in the patient group that received LUBRICOAT® Gel (from 83.2% at baseline to 90.8% at second-look) (Supplemental Table 5.6.2). In contrast, the proportion of patients who received lactated Ringer's solution who had minimal Standard AFS scores decreased at second-look (from 81.3% at baseline to 75.4% at second-look). Similarly, the proportion of patients with mild, moderate or severe Standard AFS

scores (6-10, 11-20, 21-32, respectively) decreased in the group that received LUBRICOAT® Gel and increased in the group that received lactated Ringer's solution.

TABLE 8.10: Standard AFS Score (Minimum of Right and Left)
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Variable	Lubricoat Gel				Lactated Ringer's Solution				P	
	N	Mean	(SD)	Range	N	Mean	(SD)	Range		
Mean Values										
Baseline	131	2.44	(5.32)	0 to 32	134	2.85	(6.04)	0 to 32	0.553	
Second Look	131	1.89	(3.61)	0 to 24	134	4.60	(7.95)	0 to 32	0.000	
Variable	n N %			n N %			P			
Proportions										
Baseline	0-5 (minimal)	109 / 131	83.2%	109 / 134	81.3%	0.749				
	6-10 (mild)	13 / 131	9.9%	8 / 134	6.0%	0.262				
	11-20 (moderate)	7 / 131	5.3%	13 / 134	9.7%	0.245				
	21-32 (severe)	2 / 131	1.5%	4 / 134	3.0%	0.684				
Second Look	0-5 (minimal)	119 / 131	90.8%	101 / 134	75.4%	0.001				
	6-10 (mild)	8 / 131	6.1%	13 / 134	9.7%	0.364				
	11-20 (moderate)	3 / 131	2.3%	13 / 134	9.7%	0.018				
	21-32 (severe)	1 / 131	0.8%	7 / 134	5.2%	0.066				

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 p values determined using Student's t test and the Fisher exact test
 Cross reference Supplemental Table 5.6.2.