



DEPARTMENT OF HEALTH & HUMAN SERVICES

P960057
Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

MAY 27 1998

Mr. Michael T. Hingson
Manager, Regulatory Affairs
Gliatech, Inc.
23420 Commerce Park Road
Cleveland, Ohio 44122

Re: P960057
ADCON[®]-L Adhesion Barrier Gel
Filed: December 23, 1996
Amended: January 11, February 14, March 26, August 13,
September 11, October 29, November 12 and December 19,
1997, February 13, 18, and 19, March 6, 23, and 24 and
April 8, and May 4, 1998

Dear Mr. Hingson:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for ADCON[®]-L Adhesion Barrier Gel. This device is indicated for use during single level, posterior lumbar laminectomy or laminotomy procedures where nerve roots are exposed to inhibit postsurgical peridural fibrosis. We are pleased to inform you that the PMA is approved subject to the "Conditions of Approval" (enclosed). You may begin commercial distribution of the device upon receipt of this letter.

The sale, distribution and use of this device are restricted to prescription use in accordance with 21 CFR 801.109.

The labeling for your device is incomplete since it includes interim results of the U.S. clinical trial being conducted under G940001. Therefore, in addition to the postapproval requirements in the enclosure, you must complete the 370 subject U.S. clinical trial being conducted under G940001 and provide postapproval supplements to your PMA which include the following information:

1. Within thirty days of the receipt of the approval order, you must provide a description of the twelve month longer term clinical outcome data that you will collect on the 370 subjects enrolled in your U.S. clinical trial (G940001).
2. The final report for your U.S. clinical trial (G940001) must be provided within three months of study completion.
3. Revised draft labeling that replaces the results of the interim analyses for the U.S. clinical trial with the final study results at six months, and that reflects longer term clinical outcome at twelve months must be provided.

Expiration dating for this device has been established and approved for a two year when stored at room temperature (59-77°F). This is to advise you that the protocol you used to establish this expiration dating is considered an approved protocol for the purpose of extending the expiration dating as provided by 21 CFR 814.39(a)(8).

CDRH will notify the public of its decision to approve your PMA by making available a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at <http://www.fda.gov/cdrh/pmapage.html>. Written requests for this information can also be made to the Dockets

Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the Federal Food, Drug, and Cosmetic Act (the act).

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

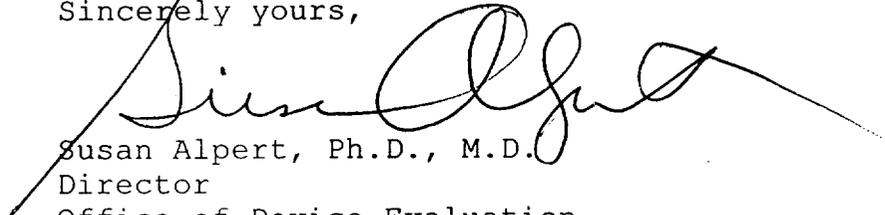
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All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Kevin Lee, M.D., at (301) 594-1296.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Susan Alpert", with a long horizontal flourish extending to the right.

Susan Alpert, Ph.D., M.D.
Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

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Issued: 3-4-98

CONDITIONS OF APPROVAL

APPROVED LABELING. As soon as possible, and before commercial distribution of your device, submit three copies of an amendment to this PMA submission with copies of all approved labeling in final printed form to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration (FDA), 9200 Corporate Blvd., Rockville, Maryland 20850.

ADVERTISEMENT. No advertisement or other descriptive printed material issued by the applicant or private label distributor with respect to this device shall recommend or imply that the device may be used for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the act under the authority of section 515(d)(1)(B)(ii) of the act, all advertisements and other descriptive printed material issued by the applicant or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects and contraindications.

PREMARKET APPROVAL APPLICATION (PMA) SUPPLEMENT. Before making any change affecting the safety or effectiveness of the device, submit a PMA supplement for review and approval by FDA unless the change is of a type for which a "Special PMA Supplement-Changes Being Effectuated" is permitted under 21 CFR 814.39(d) or an alternate submission is permitted in accordance with 21 CFR 814.39(e). A PMA supplement or alternate submission shall comply with applicable requirements under 21 CFR 814.39 of the final rule for Premarket Approval of Medical Devices.

All situations which require a PMA supplement cannot be briefly summarized, please consult the PMA regulation for further guidance. The guidance provided below is only for several key instances.

A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification.

A PMA supplement must be submitted if the device is to be modified and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective.

A "Special PMA Supplement - Changes Being Effectuated" is limited to the labeling, quality control and manufacturing process changes specified under 21 CFR 814.39(d)(2). It allows for the addition of, but not the replacement of previously approved, quality control specifications and test methods. These changes may be implemented before FDA approval upon acknowledgment by FDA that the submission is being processed as a "Special PMA Supplement - Changes Being Effectuated." This acknowledgment is in addition to that issued by the PMA Document Mail Center for all PMA supplements submitted. This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source.

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of a PMA supplement before implementation of the change and include the use of a 30-day PMA supplement or annual postapproval report. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence with the applicant that the alternate submission is permitted for the change. Before such can occur, FDA and the PMA applicant(s) involved must agree upon any needed testing protocol, test results, reporting format, information to be reported, and the alternate submission to be used.

POSTAPPROVAL REPORTS. Continued approval of this PMA is contingent upon the submission of postapproval reports required under 21 CFR 814.84 at intervals of 1 year from the date of approval of the original PMA. Postapproval reports for supplements approved under the original PMA, if applicable, are to be included in the next and subsequent annual reports for the original PMA unless specified otherwise in the approval order for the PMA supplement. Two copies identified as "Annual Report" and bearing the applicable PMA reference number are to be submitted to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. The postapproval report shall indicate the beginning and ending date of the period covered by the report and shall include the following information required by 21 CFR 814.84:

(1) Identification of changes described in 21 CFR 814.39(a) and changes required to be reported to FDA under 21 CFR 814.39(b).

(2) Bibliography and summary of the following information not previously submitted as part of the PMA and that is known to or reasonably should be known to the applicant:

(a) unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and

(b) reports in the scientific literature concerning the device.

If, after reviewing the bibliography and summary, FDA concludes that agency review of one or more of the above reports is required, the applicant shall submit two copies of each identified report when so notified by FDA.

ADVERSE REACTION AND DEVICE DEFECT REPORTING. As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit 3 copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850 within 10 days after the applicant receives or has knowledge of information concerning:

(1) A mix-up of the device or its labeling with another article.

(2) Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and

(a) has not been addressed by the device's labeling or

(b) has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.

(3) Any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved PMA that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the applicant's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the applicant. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report described under "Postapproval Reports" above unless specified otherwise in the conditions of approval to this PMA. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.

REPORTING UNDER THE MEDICAL DEVICE REPORTING (MDR) REGULATION. The Medical Device Reporting (MDR) Regulation became effective on December 13, 1984. This regulation was replaced by the reporting requirements of the Safe Medical Devices Act of 1990 which became effective July 31, 1996 and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to the FDA whenever they receive or otherwise become aware of information, from any source, that reasonably suggests that a device marketed by the manufacturer or importer:

- (1) May have caused or contributed to a death or serious injury; or
- (2) Has malfunctioned and such device or similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for this PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Conditions of Approval" for a PMA, the manufacturer shall submit the appropriate reports required by the MDR Regulation within the time frames as identified in 21 CFR 803.10(c) using FDA Form 3500A, i.e., 30 days after becoming aware of a reportable death, serious injury, or malfunction as described in 21 CFR 803.50 and 21 CFR 803.52 and 5 days after becoming aware that a reportable MDR event requires remedial action to prevent an unreasonable risk of substantial harm to the public health. The manufacturer is responsible for submitting a baseline report on FDA Form 3417 for a device when the device model is first reported under 21 CFR 803.50. This baseline report is to include the PMA reference number. Any written report and its envelope is to be specifically identified, e.g., "Manufacturer Report," "5-Day Report," "Baseline Report," etc. Any written report is to be submitted to:

Food and Drug Administration
Center for Devices and Radiological Health
Medical Device Reporting
PO Box 3002
Rockville, Maryland 20847-3002

Copies of the MDR Regulation (FOD # 336&1336) and FDA publications entitled "An Overview of the Medical Device Reporting Regulation" (FOD # 509) and "Medical Device Reporting for Manufacturers" (FOD #987) are available on the CDRH WWW Home Page. They are also available through CDRH's Fact-On-Demand (F-O-D) at

800-899-0381. Written requests for information can be made by sending a facsimile to CDRH's Division of Small Manufacturers Assistance (DSMA) at 301-443-8818.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device generic name: Peridural Fibrosis (adhesion barrier) Inhibitor

Device trade name: ADCON®-L Adhesion Control in a Barrier Gel

Applicant's name and Address: Gliatech Inc.
23420 Commerce Park Road
Cleveland, OH 44122

Date of Panel Recommendation: December 12, 1997

Pre market Approval Application (PMA) Number: P960057

Date of Notice of Approval to the Applicant: MAY 27 1998

II. INDICATIONS FOR USE

ADCON®-L *Adhesion Control in a Barrier Gel* is indicated for use during single level, posterior lumbar laminotomy and laminectomy procedures (see SUMMARY OF CLINICAL STUDIES) where nerve roots are exposed to inhibit postsurgical peridural fibrosis.

III. DEVICE DESCRIPTION

ADCON®-L *Adhesion Control in a Barrier Gel* is a resorbable flowable gel composed of porcine-derived gelatin, and a complex sugar of the polyglycan family in a phosphate buffered saline solution. The polyglycan is a long-chain polymer containing repeating units of poly-sulfo-alpha-(1→6)-D-glucan (a specially processed dextran sulfate). The product is resorbed within approximately four weeks of application.

IV. CONTRAINDICATIONS

Do not use ADCON®-L in patients with current infection or contamination of the operative site. The warnings and precautions can be found in the ADCON®-L labeling .

V. ALTERNATIVE PRACTICES OR PROCEDURES

Free-fat grafting is a procedure currently in clinical use for prevention of postoperative peridural fibrosis.

VI. MARKETING HISTORY

ADCON®-L has not been previously marketed in the United States. ADCON®-L obtained CE marking and is sold in many of the 15 countries that have adopted the European Medical Devices Directive. ADCON®-L is also sold in Switzerland, Canada, the Czech Republic, South Africa, Iceland, Israel, Norway, New Zealand and Australia. ADCON®-L has not been withdrawn from any market for reasons of safety or effectiveness.

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VII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

PIVOTAL EUROPEAN STUDY

ADCON[®]-L was investigated in a pivotal European clinical trial having a total of 298 patients (147 ADCON[®]-L-treated and 151 untreated control patients). There were no statistically significant differences in the rates of adverse events between the ADCON[®]-L-treated group and the untreated control group.

Adverse events (cumulative) experienced by greater than or equal to 1% of the ADCON[®]-L-treated patients at 6 and 12 months included redness, swelling, motor deficit, tenderness, sensory deficit, new or increased radiculitis, back spasm, headache, pseudomenigocele, wound infection, skin rash, and deep thrombophlebitis. Adverse events experienced by less than 1% of the ADCON[®]-L-treated patients at 6 and 12 months included: (ADCON[®]-L) bowel deficit, cauda equina syndrome, peridural hematoma, wound necrosis, skin rash, shock, temperature spike and transient alopecia. The time course distribution of adverse events showed no statistically significant difference between the ADCON[®]-L-treated and control groups at 1, 3, 6, and 12 months (see SUMMARY OF CLINICAL STUDIES).

U. S. STUDY

An interim analysis at 6 months of a supportive U.S. multicenter clinical investigation of ADCON[®]-L demonstrated no statistically significant differences in the rates of adverse events between the ADCON-L-treated group and the untreated control group.

Adverse events (cumulative) experienced by greater than or equal to 1 % of the ADCON[®]-L-treated group included reherniation, sciatica, spasm, low back pain, wound infection, numbness, and cerebrospinal fluid leak. Adverse events experienced by less than 1% of the ADCON[®]-L patients at 6 months included: elevated temperature, headaches, urinary retention, wound pain and , and urinary tract infection (see SUMMARY OF CLINICAL STUDIES).

SURGICAL REINTERVENTIONS

In the pivotal European study, secondary surgical interventions occurred in 8 % (12/147) of the ADCON[®]-L-treated group. The most common reason for reoperation for the ADCON[®]-L-treated group was reherniations 58 % (7/12).

In the U. S. study, secondary surgical interventions occurred in 5 % (6/114) of the ADCON[®]-L-treated group at the time of interim analysis. The most common reasons for reoperation for the ADCON[®]-L-treated group were reherniations and sciatic pain (3%, 3/114).

There were no differences between the ADCON[®]-L-treated group and the untreated control group with regard to healing of the operative site and incidence of complications or adverse events (see SUMMARY OF CLINICAL STUDIES).

VIII. SUMMARY OF PRECLINICAL STUDIES

MICROBIOLOGICAL

ADCON[®]-L is terminally sterilized by autoclave using a validated sterilization cycle. All lots of ADCON[®]-L are sampled and tested for sterility (current USP <1211>) and bacterial endotoxin (current USP <85>).

NONCLINICAL STUDIES

The safety of ADCON®-L was evaluated in accordance with tests described in the "Tripartite Biocompatibility Guidance" (April 24, 1987). These investigations were performed according to Good Laboratory Practice regulations (Title 21, Code of Federal Regulations, Part 58). Additional studies were performed to assess product safety and effectiveness as a resorbable device. These studies included: acute systemic toxicity, hypersensitivity, and rat and rabbit laminectomy studies. The rat and rabbit laminectomy studies represent pivotal, longitudinal studies. These studies were designed to represent clinical usage and provide safety and effectiveness information for ADCON®-L in a preclinical model (see Tables 1 and 2 for a summary of the results of the nonclinical studies).

Table 1
Biocompatibility Testing of ADCON®-L

TEST	RESULTS
Ames Mutagenicity Study of a Saline Extract	Nonmutagenic
<i>In Vitro</i> Hemolysis Study (Direct Contact)	Nonhemolytic
<i>In Vitro</i> Cytotoxicity Study (Agarose Overlay)	No evidence of cytotoxicity
Modified USP Systemic Toxicity Study in Mice (Extract)	Not systemically toxic to mice
Acute Subcutaneous Toxicity Study with ADCON®-L in Rats	Not systemically toxic to the rat Minor splenic extra medullary hematopoiesis evident deemed due to inflammatory response at the implant site as a result of product resorption
Modified Intracutaneous Toxicity Study in the Rabbit (7 days)	Signs of moderate tissue reaction at 7 days consistent with the resorption process
Muscle Implantation Study (with histopathology) in the Rabbit (14 days)	Classified as a severe irritant at 14 days consistent with the resorption process
Sensitization Studies	
Dermal Sensitization Study (Modified Landsteiner Method) in the Guinea Pig	Signs of delayed dermal sensitization consistent with the resorbable process
Hypersensitivity Study in a Guinea Pig Injection Model	Classified as a non-sensitizer or, at worst, a mild or potential sensitizer consistent with the resorbable properties of the product
Evaluation of Wound Healing and Peridural Fibrosis after Implantation of ADCON®-L and GT402 in Rabbit Laminectomy	ADCON®-L and GT402 implant sites exhibited normal wound healing responses with no adverse tissue or biological responses
Evaluation of Wound Healing and Peridural Fibrosis after Implantation of ADCON®-L, GT402 and GT003 in Rat Laminectomy	ADCON®-L, GT402 and GT003 implant sites exhibited normal wound healing responses with no adverse tissue or biological responses

Table 2
Pivotal ADCON®-L Effectiveness Studies
Laminectomy Animal Models
Conducted according to GLP Regulations

SPECIES	Investigational Treatment	Control	Evaluation Time points	Findings
Rabbit (N=80)	ADCON®-L	GT402 solution or No-treatment sham	2, 6, 13, 26 Weeks	ADCON®-L inhibited epidural scar to a greater extent than GT402 solution or no-treatment sham.
Rat (N=128)	ADCON®-L	GT003 GT402 solution or No-treatment sham	2, 6, 13, 26 Weeks	ADCON®-L inhibited epidural scar to a greater extent than GT402 solution, GT003 or no-treatment sham.

SHELF LIFE

Samples of eight (8) lots of ADCON®-L were stored at ambient room temperature for at least 36 months. At various times, the material was tested for GT402 content, sterility, package integrity and % dry weight. To at least 36 months, the material remained within specification.

Samples of two (2) ADCON®-L commercial lots are being stored at 5°C, 25°C and 30°C. At various times, the material is being tested for physical appearance, package integrity, GT402 content, and sterility. All material has been tested at a minimum of six months, and the material has remained within specification. The above mentioned lots will continue to be tested for up to 36 months.

The ADCON®-L kit was subjected to an Accelerated Aging Test Protocol representing three years of simulated aging followed by distribution simulation tests in accordance with ASTM 4169. The contents of the ADCON®-L kit were then tested for sterility to confirm the integrity of the ADCON®-L packaging. The contents of the ADCON®-L kit remained sterile following the package integrity testing.

Based on the obtained stability data, ADCON®-L is presently assigned a two (2) year expiration date when stored at room temperature (59°-77°F).

PYROGENICITY

ADCON®-L was tested using the rabbit pyrogen test (USPXXII). The results indicated that ADCON®-L was non-pyrogenic.

ENDOTOXIN LEVEL

The market release specification of the endotoxin is ≤ 2.8 E.U./g, which is the amount allowed for products which come in contact with the cerebrospinal fluid. The value is in accordance with the FDA "GUIDELINE ON VALIDATION OF THE LIMULUS AMEBOCYTE LYSATE TEST AS AN END-PRODUCT ENDOTOXIN TEST FOR HUMAN AND ANIMAL PARENTERAL DRUGS, BIOLOGICAL PRODUCTS, AND MEDICAL DEVICES".

IX. SUMMARY OF CLINICAL STUDIES

SUMMARY

The pivotal European study was conducted at nine sites in three European countries (Belgium, Netherlands, and Switzerland) from November, 1992, to August, 1995. An interim report at 6 months of an ongoing U. S. study was also provided.

EUROPEAN STUDY

Study Design

A randomized, double-masked, concurrently controlled clinical investigation was performed at nine sites in three countries in Europe to evaluate the safety and effectiveness of ADCON[®]-L *Adhesion Control in a Barrier Gel* as a therapy for the inhibition of peridural fibrosis. A total of 298 male and female patients between 17 and 60 years of age were randomized to receive either ADCON[®]-L (147 patients) or no treatment (151 patients) following first-time, unilateral, single-level, posterior lumbar discectomy. Patients were evaluated for extent of peridural fibrosis and for activity-related pain over a 6 month period (clinic visits at 1, 3 and 6 months following surgery).

Effectiveness Assessments

The primary outcome measure was the extent of peridural fibrosis as assessed with the use of magnetic resonance imaging (MRI) scans. An MRI protocol was established prior to the start of the study for all centers to follow. Each scan had images obtained both before and after the injection of gadolinium DTPA. Each MRI series consisted of five contiguous non-overlapping 4-mm scans centered on the operative intervertebral space. The middle slice ("Operative Site") was cut through the middle of the disc space. The slice just cranial or cephalad was cut through the region closely approximating the location where the affected nerve root sleeve separated from the long axis of the cauda equina thecal sac. The slice just caudal completed the area of the operated disc space. The most-cranial slice and most-caudal slice overlapped the adjacent vertebral bodies and were used for visual orientation purposes; these two slices were not included in the scar score analyses. Each of the three middle MRI slices was divided into four spatial quadrants centered on the thecal sac.

A scar score was assigned to each quadrant as follows: a score of "0" if the quadrant area showed no fibrosis or only a trace amount; a score of "1" if the quadrant was $> 0\%$ and $\leq 25\%$ filled with fibrosis; a score of "2" for $>25\%$ and $\leq 50\%$ fibrosis; a score of "3" for $>50\%$ and $\leq 75\%$ fibrosis; and a score of "4" for $> 75\%$ fibrosis. A neuroradiologist was masked to patient treatment and reviewed the films and assigned the scar scores. The patient's score was recorded as the most extensive scar score on any of the 12 quadrants. Success was defined as demonstrating that the ADCON[®]-L group had statistically significantly less peridural fibrosis as compared to the untreated control group utilizing a Cochran-Mantel-Haenszel (CMH) procedures stratified by center at 6 months.

Activity-related pain was the secondary outcome measure. A self-assessment questionnaire was used to describe the effect of activities of daily living on pain after surgery. The method to score and analyze the data was based on the National Low Back Pain Study (U.S.A). The questionnaire included five activities of daily living associated radiculopathy with scores ranging from 0 to 3.2, with 3.2 being the maximum score, i.e., the most severe pain. Success was defined as a statistically significant difference between the means of the weighted activity-related pain (wARP) in favor of the ADCON[®]-L-treated group as compared to the untreated control group at 6 months.

Additional assessments included the maximum straight-leg-raising (SLR) angle for the operative and nonoperative side, and the amount of low back pain and radicular pain as measured by a visual analog scale. Success criteria were not defined for these outcome measures.

Safety Assessment

All adverse events were monitored and recorded including the date of onset, along with severity, relationship to device, action taken, and outcome. Severity was graded as mild, moderate, severe, or life-threatening. The relationship was classified as not related, definitely related, or unknown. There were no statistically significant differences between treatment groups with regard to incidence of redness, swelling, and tenderness of the operative site or incidence of adverse events (see ADVERSE EVENTS).

Twelve Month Data

The pivotal study was designed for 6 months, and additional data were collected at 12 months for all available patients at the request of FDA. Clinical assessments (i.e., WARP, maximum SLR angle for the operative and nonoperative sides, and the amount of low back pain and radicular pain as measured by a visual analog scale) were performed by physicians masked to patient treatment status. MRI scans (with and without gadolinium enhancement) were also obtained twelve months postoperatively. MRIs were evaluated by a neuroradiologist masked to patient treatment status.

Results

The distribution of gender, age, preoperative clinical findings, operative level and disc pathology were comparable between the ADCON[®]-L-treated and control groups (Table 3).

Table 3.
Patient Characteristics (European Study-Evaluable Patients)

Characteristics	Treatment group		p-value
	ADCON®-L (N=128)	Control (N=141)	
Gender [number (%)]			1.0 ^a
Male	79 (62)	88 (62)	
Female	49 (38)	53 (38)	
Age (years)			
Mean (standard deviation)	38.2 (10)	39.9 (9)	0.13 ^b
Preoperative clinical signs [mean (SD)]			
Radicular pain ^c	7.8 (2)	8.0 (2)	0.40 ^b
Low back pain ^c	6.0 (3)	5.4 (3)	0.10 ^b
SLR ^d sign	50.0 (21)	52.4 (22)	0.37 ^b
Operative level [number (%)]			0.04 ^a
L4/L5	38 (30)	59 (42)	
L5/S1	90 (70)	82 (58)	
Surgical procedure [number (%)]			0.95 ^a
Laminectomy	2 (2)	4 (3)	
Laminotomy	22 (17)	25 (18)	
Hemilaminectomy	49 (38)	53 (38)	
Hemilaminotomy	55 (43)	58 (41)	
Other (Foraminotomy)	0 (0.)	1 (1)	
Disc pathology [number (%)]			0.27 ^a
Sequestration	57 (45)	53 (38)	
Extrusion	43 (34)	61 (43)	
Protrusion	28 (22)	27 (19)	

^a Two-tailed Fisher's Exact test for comparison of distributions between treatment groups

^b Two-tailed t-test for comparison of means between treatment groups

^c Visual Analog Scale (0-10 cm)

^d Straight Leg Raise

Six months following discectomy, those patients treated with ADCON®-L demonstrated a statistically significant reduction in peridural fibrosis (i.e., there was a statistically significant downward shift in the distribution of scar score in the ADCON®-L-treated group than in the control group at 6 months) when compared to those patients in the untreated control group (Table 4). Additionally, patients treated with ADCON®-L had a statistically significantly lower severity of wARP at 6 months while performing five specific activities associated with radiculopathy (Table 5) as compared to the untreated control group at 6 months, using a two-tailed t-test. Comparison of the ADCON®-L-treated group to the control group using a CMH test demonstrated no statistically significant difference for SLR on the operative side at 6 months, or for low back pain and radicular pain at 6 months (Table 6, 7 and 8).

Table 4
Distribution of Scarring at 6 Months
(Evaluable Patients)

	Extent of scar ^a					p-value ^b
	None	>0% to ≤25%	>25% to ≤50%	>50% to ≤75%	>75% to ≤100%	p=0.01
Control ^c	1 %	3 %	17 %	29 %	50 %	
ADCON [®] -L ^c	3 %	10 %	13 %	36 %	38 %	

^a Most extensive scar on any of the twelve quadrants on the MRI scan

^b Two-tailed test for comparison of distributions between treatment groups using the CMH procedure stratified by center

^c There were 127 patients in the ADCON[®]-L group, and 139 patients in the control group at 6 months.

Table 5
Weighted Activity-Related Pain (wARP) Scores^a at 6 Months

	ADCON-L	Control	p-value ^b
Preoperative baseline mean score	2.49 (N=128)	2.51 (N=141)	0.74
Mean score after treatment	1.24 (N=87) ^c	1.58 (N=83) ^c	0.03
Percent of improvement from baseline ^d	50 %	37 %	

^a Linear combinations based on National Low Back Pain Study (U.S.) (BenDebba, M, et al: A Simple Procedure for Assessing the Impact of Low Back Pain on Activities of Daily Living, 8th World Congress on Pain, 58, 1996.) Weighted sum of activities that caused an increase in pain. Maximum overall score is 3.2. Activities included bending, riding/driving in a car, sitting < 15 min, sitting > 15 min, and lifting heavy objects > 10 lbs.

^b Two-tailed t-test for comparison of means between treatment groups

^c Excluding patients who did not have pain at 6 months

^d Percent of improvement from baseline = [(preoperative baseline mean score - mean score after treatment) / preoperative baseline mean score] x 100

Table 6
Straight Leg Raise Test (SLR) on Operative Site at 6 Months

	6 Months			p-value*
	Improvement	No Improvement	Worse	
ADCON [®] -L(N=119)	112 (94 %)	5 (4 %)	2 (2 %)	0.07
Control (N=134)	116 (87 %)	14 (10 %)	4 (3 %)	

* Two-tailed CMH procedure stratified by center

Table 7
Most Serious Low Back Pain at 6 Months

	Worse	No change	Better	p-value*
ADCON [®] -L (N=126)	12 (10 %)	4 (3 %)	110 (87 %)	0.09
Control (N=141)	21 (15 %)	10 (7 %)	110 (78 %)	

* Two-tailed CMH procedure stratified by center

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Table 8
Most Severe Radicular Pain at 6 Months

	Worse	No change	Better	p-value ^a
ADCON [®] -L (N=126)	4 (3 %)	2 (2 %)	120 (95 %)	0.94
Control (N=141)	5 (3 %)	1 (1 %)	135 (96 %)	

^aTwo-tailed CMH procedure stratified by center

Results of 12 Month Data Analyses

The scar scores were significantly less (i.e., there was a statistically significant downward shift in the distribution of scar scores) in the ADCON[®]-L group than in the control group at 6 months. At 12 months, in 86 % of the original patients, 28 % of ADCON[®]-L-treated patients had extensive scar scores, as compared to 41 % of the control patients (Table 9).

In approximately 17 % (22/130) of the control patients and 19 % (21/113) of the ADCON[®]-L treated patients, scar scores changed by one grade between 6 months and 12 months. In approximately 5 % (7/130) of the control patients and 2 % (2/113) of the ADCON[®]-L-treated patients, the scar score changed more than one grade from 6 to 12 months. Approximately 2 % (2/130) of the control patients had scar scores that were worse at 12 months than at 6 months. The decrease in the scar score of more than one grade was attributed to some consolidation, remodeling or vascularization of scar.

The statistically significant difference in wARP was not maintained at 12 months (Table 10). However, both groups continued to improve.

There was no statistically significant difference in SLR raise results on operative side between the ADCON[®]-L-treated group and the untreated control group at 12 months (Table 11). There was no statistically significant difference in low back pain at 12 months between the two groups (Table 12).

Table 9
Distribution of Scarring at 12 Months (Evaluable Patients)

	Extent of scar ^a					p-value ^b
	None	>0% to ≤25%	>25% to ≤50%	>50% to ≤75%	>75% to ≤100%	
Control (N=130)	0 (0 %)	12 (9 %)	28 (22 %)	37 (28 %)	53 (41 %)	0.01
ADCON [®] -L (N=116)	5 (4 %)	13 (11 %)	30 (26 %)	36 (31 %)	32 (28 %)	

^a Most extensive scar on any of 12 quadrants on the MRI scan.

^b Two-tailed test for comparison of distributions between treatment groups using the CMH procedure stratified by center.

Table 10

Weighted Activity-Related Pain (wARP)^a at 12 Months

	ADCON [®] -L	Control	p-value ^b
Preoperative baseline mean score	2.49 (N=128)	2.51 (N=141)	0.74
Mean score after treatment	1.32 (N=71) ^c	1.58 (N=66) ^c	0.13
Percent of improvement from baseline ^d	47 %	37 %	

^a Linear combinations based on National Low Back Pain Study (U.S.) (BenDebba, M, et al: A Simple Procedure for Assessing the Impact of Low Back Pain on Activities of Daily Living, 8th World Congress on Pain, 58, 1996.) Weighted sum of activities that caused an increase in pain. Maximum overall score is 3.2. Activities included bending, riding/driving in a car, sitting < 15 min, sitting > 15 min, and lifting heavy objects > 10 lbs.

^b Two-tailed t-test for comparison of means between treatment groups

^c Excluding patients who did not have pain at 12 months

^d Percent of improvement from baseline = [(preoperative baseline mean score - mean score after treatment) / preoperative baseline mean score] x 100

Table 11

Straight Leg Raise (SLR) Test on Operative Side at 12 Months

Improvement	Improvement	No Improvement	Worse	p-value [*]
ADCON [®] -L (N=111)	106 (95 %)	3 (3 %)	2 (2 %)	0.13
Control (N=125)	110 (88 %)	13 (10 %)	2 (2 %)	

*Two-tailed CMH test procedure stratified by center

Table 12

Low Back Pain at 12 Months

	Worse	No Change	Better	p-value [*]
ADCON [®] -L (N=106)	17 (16 %)	2 (2 %)	87 (82 %)	0.71
Control (N=141)	15 (13 %)	8 (7 %)	97 (81 %)	

* Two-tailed CMH procedure stratified by center

Adverse Events

ADCON[®]-L was investigated in a pivotal European clinical trial having a total of 298 patients (147 ADCON[®]-L - treated and 151 untreated control patients). All adverse events are listed in Table 13. There were no statistically significant differences in the rates of adverse events between the ADCON[®]-L-treated group and the untreated control group (Table 13).

The time course distribution of adverse events showed no statistically significant difference between the ADCON[®]-L-treated and control groups at 1, 3, 6, and 12 months.

Table 13
All Adverse Events (cumulative)
Experienced by either ADCON[®]-L-Treated or Control Patients at 6 and 12 Months

Event Description	6 Months			12 Months		
	ADCON [®] -L (N=147)	Control (N=151)	p-value *	ADCON [®] -L (N=147)	Control (N=151)	p-value *
Redness	30 (20.4 %)	39 (25.8 %)	0.28	30 (20.4 %)	39 (25.8 %)	0.28
Swelling	23 (15.6 %)	30 (19.9 %)	0.37	23 (15.6 %)	30 (19.9 %)	0.37
Motor deficit	12 (8.2 %)	12 (7.9 %)	1.00	12 (8.2 %)	13 (8.6 %)	1.00
Tenderness	12 (8.2 %)	11 (7.3 %)	0.83	12 (8.2 %)	11 (7.3 %)	0.83
Sensory deficit	10 (6.8 %)	16 (10.6 %)	0.31	11 (7.5 %)	17 (11.3 %)	0.32
New or increased radiculitis	8 (5.4 %)	10 (6.6 %)	0.81	10 (6.8 %)	12 (7.9 %)	0.83
Back spasm	8 (5.4 %)	8 (5.3 %)	1.00	9 (6.1 %)	9 (6.0 %)	1.00
Headache	4 (2.7 %)	1 (0.7 %)	0.21	7 (4.8 %)	3 (2.0 %)	0.21
Pseudo-meningocele	2 (1.4 %)	0 (0.0 %)	0.24	2 (1.4 %)	0 (0.0 %)	0.24
Temperature spike	1 (0.7 %)	0 (0.0 %)	0.49	2 (1.4 %)	0 (0.0 %)	0.24
Skin rash	1 (0.7 %)	1 (0.7 %)	1.00	1 (0.7 %)	2 (1.3 %)	1.00
Peridural hematoma	1 (0.7 %)	0 (0.0 %)	0.49	1 (0.7 %)	0 (0.0 %)	0.49
Transient alopecia	1 (0.7 %)	0 (0.0 %)	0.49	1 (0.7 %)	0 (0.0 %)	0.49
Wound necrosis	1 (0.7 %)	1 (0.7 %)	1.00	1 (0.7 %)	1 (0.7 %)	1.00
Bowel deficit	1 (0.7 %)	0 (0.0 %)	0.49	1 (0.7 %)	0 (0.0 %)	0.49
Cauda equina syndrome	1 (0.7 %)	0 (0.0 %)	0.49	1 (0.7 %)	0 (0.0 %)	0.49
Wound infection	0 (0.0 %)	2 (1.3 %)	0.50	0 (0.0 %)	2 (1.3 %)	0.50
Deep thrombophlebitis	0 (0.0 %)	2 (1.3 %)	0.50	0 (0.0 %)	2 (1.3 %)	0.50
Septicemia	0 (0.0 %)	1 (0.7 %)	1.00	0 (0.0 %)	1 (0.7 %)	1.00
Shock	0 (0.0 %)	1 (0.7 %)	1.00	1 (0.7 %)	1 (0.7 %)	1.00
Pulmonary embolism	0 (0.0 %)	1 (0.7 %)	1.00	0 (0.0 %)	1 (0.7 %)	1.00
Disc space infection	0 (0.0 %)	1 (0.7 %)	1.00	0 (0.0 %)	1 (0.7 %)	1.00
Wound dehiscence	0 (0.0 %)	1 (0.7 %)	1.00	0 (0.0 %)	1 (0.7 %)	1.00
Wound keloid	0 (0.0 %)	1 (0.7 %)	1.00	0 (0.0 %)	1 (0.7 %)	1.00

* Two-tailed Fisher's Exact Test

Surgical Reinterventions

In the pivotal European study, secondary surgical interventions occurred in 8 % (12/147) of the ADCON[®]-L-treated group and in 5 % (8/151) of the untreated control group. The most common reason for reoperation for the ADCON[®]-L-treated group and control group was reherniations, i.e., 58 % (7/12), and 38 % (3/8) respectively (Table 14).

Table 14
Surgical Reinterventions

Reason for reoperation	ADCON [®] -L (N=147)	Control (N=151)	p-value*
Reherniation at same level	7 (5 %)	3 (2 %)	0.21
Disc fragments	4 (3 %)	1 (1 %)	0.21
Other ^a	1 (1 %)	4 (3 %)	0.37
Total	12	8	0.36

*Two-tailed Fisher's Exact Test

^a ADCON[®]-L: hip problem; Control: negative re-exploration for persistent, worsened pain (1), extreme fibrosis (1), spinal stenosis at a different level (1), herniation at a different level (1)

U. S. STUDY

Study Design

A randomized, double-masked, concurrently controlled multicenter trial is being conducted to evaluate the safety and effectiveness of ADCON[®]-L at 6 months postoperatively. The protocol calls for 365 patients to be randomized in a 1:1 ratio to either ADCON[®]-L treatment or no treatment (control). Approximately 332 patients are expected to be evaluated for safety and effectiveness at study completion.

Interim analyses were based on approximately half of the patients originally planned for entry into the study. The planned sample size and the sample size justification for the study are described in the protocol. The interim analyses were conducted on all data available for database entry by March 10, 1997.

Effective Assessments

The protocols for the MRIs and the WARP measure were the same as those used in the European study. Results from surgery with ADCON[®]-L are to be compared to surgery without ADCON[®]-L. Clinical assessments performed by evaluators masked to patient treatment status are to be conducted preoperatively, and at 1, 2, and 6 months postoperatively. MRI films (with and without gadolinium enhancement) are to be obtained 6 months postoperatively. MRIs are to be evaluated by a neuroradiologist masked to patient treatment.

Other Clinical Assessments

At each clinical evaluation (preoperative and 1, 2, and 6 months postoperative) patients are to complete a Roland-Morris Activities Performance Questionnaire containing 24 statements that describes radicular symptoms in relation to daily activities, work, and recreation. The severity of radicular pain over the prior week is indicated by the patient on a standardized visual analog scale (VAS).

Results (Interim Analyses)

The distribution of gender, age, preoperative clinical findings, operative level and disc pathology were comparable between the ADCON[®]-L-treated and control groups (Table 15).

Table 15
Patient Characteristics (Evaluable Patients)

Characteristics	Treatment Group		p-value
	ADCON [®] -L (N=88)	Control (N=77)	
Gender [number (%)]			0.75 ^a
Male	58 (65.9)	48 (62.3)	
Female	30 (34.1)	29 (37.7)	
Age (years)			0.80 ^b
Mean (standard deviation)	42.7 (9.5)	43.1 (7.4)	
Preoperative clinical signs [mean (SD)]			
Radicular pain ^c	7.9 (1.6)	7.9 (1.5)	0.87 ^b
wARP score ^d	2.2 (0.9)	2.3 (0.8)	0.97 ^b
Total Roland Morris score ^e	14.8 (5.6)	15.7 (4.9)	0.26 ^b
Operative Level [number (%)]			0.55 ^b
L4/L5	35 (39.8)	31 (40.3)	
L5/S1	44 (50.0)	34 (44.2)	
Data not yet collected	9 (10.2)	12 (15.6)	
Disc pathology [number (%)]			0.60 ^a
Protrusion	9 (10.2)	7 (9.1)	
Extrusion	31 (35.2)	31 (40.3)	
Free fragment	23 (26.1)	21 (27.3)	
Protrusion and other	3 (3.4)	0 (0.0)	
Extrusion and fragment	22 (25.0)	17 (22.1)	
Data not collected	0 (0.0)	1 (1.3)	
Surgical procedure [number (%)]			0.42 ^f
None (besides discectomy)	13 (14.8)	7 (9.1)	
Only hemilaminectomy	15 (17.0)	16 (20.8)	
Only facetectomy	0 (0.0)	1 (1.3)	
Only laminotomy	11 (12.5)	9 (11.7)	
Only foraminotomy	12 (13.6)	15 (19.5)	
Other	1 (1.1)	3 (3.9)	
Hemilaminectomy and other	5 (5.7)	5 (6.5)	
Laminotomy and other	18 (20.5)	8 (10.4)	
Foraminotomy and other	13 (14.8)	13 (16.9)	

^a p-value for comparison of distribution between treatment groups (two-tailed Fisher's Exact test).

^b p-value for comparison of means between treatment groups (two-tailed test based on analysis of variance with treatment group and center as factors).

^c Visual Analogue Scale(0-10cm); N=86 for ADCON[®]-L group; N=75 for control group.

^d N=80 for ADCON[®]-L group; N=75 for control group.

^e N=83 for ADCON-L group; N=74 for control group.

^f Two-tailed Fisher's Exact test for comparison of distributions between treatment groups. Three groups were combined into one for this analysis; Only facetectomy, Other, and Hemilaminectomy and other.

Interim analyses demonstrated that the scar scores were statistically significantly less (i.e., there was a statistically significant downward shift in the distribution of scar scores) in the ADCON[®]-L-treated group than in the control group at 6 months (Table 16). Additionally, there was a statistically significant difference in the Roland-Morris score for sciatic pain at 6 months in favor of the ADCON[®]-L-treated group over the control group (Table 17). There was no statistically significant difference for the means of wARP and radicular pain between the two groups at 6 months (Tables 18, 19).

Table 16
Distribution of Scarring at 6 Months
(Evaluable Patients)

	Extent of scar ^a					p-value ^b
	None	> 0 to ≤ 25%	>25%to≤ 50%	>50% to ≤75%	>75% to ≤ 100 %	
Control (N=65)	0 (0 %)	2 (3 %)	4 (6 %)	9 (14 %)	50 (77 %)	0.03
ADCON®-L (N=76)	0 (0 %)	4 (5 %)	8 (11 %)	23 (30 %)	41 (54 %)	

^a Most extensive scar on any of the twelve quadrants on the MRI scan

^b Two-tailed test for comparison of distributions between treatment groups using the CMH procedure stratified by center

Table 17
Total Roland-Morris Score^a at 6 Months (Evaluable Patients)

Total Roland-Morris Score	Treatment Group		p-value ^b
	ADCON®-L	Control	
Preoperative baseline mean score (standard deviation)	14.7 (5.5) (N=114)	15.2 (4.9) (N=109)	0.46
Mean after treatment at 6 months (standard deviation)	2.24 (4.27) (N=86)	3.76 (5.43) (N=74)	0.03
Percent of improvement from baseline ^c	85 %	75 %	

^a Roland-Morris Scale is composed of a questionnaire containing 24 statements that describe typical ways in which radicular symptoms may interfere with daily activities, work and recreation . A patient who has absolutely no radiculopathy-related impairment would have a score of “0”, and a maximally-affected patient would have a score of “24”.

^b Two-tailed test for comparison of means between treatment group (analysis of variance with treatment group and center as factors)

^c Percent of improvement from baseline [(preoperative baseline mean score - mean score after treatment at 6 months) / preoperative baseline mean score] x 100

Table 18

Weighted Activity-Related Pain (wARP) Scores^a at 6 Months

	ADCON®-L	Control	p-value ^b
Preoperative baseline mean score	2.21 (N=103)	2.31 (N=103)	0.53
Mean score after treatment	1.43 (N=49 ^c)	1.47 (N=49 ^c)	0.65
Percent of improvement from baseline ^d	35 %	36 %	

^a Linear combinations based on National Low Back Pain Study (U.S.) (BenDebba, M, et al: A Simple Procedure for Assessing the Impact of Low Back Pain on Activities of Daily Living, 8th World Congress on Pain, 58, 1996.) Weighted sum of activities that caused an increase in pain. Maximum overall score is 3.2. Activities included bending, riding/driving in a car, sitting < 15 min, sitting > 15 min, and lifting heavy objects > 10 lbs.

^b Two-tailed t-test for comparison of means between treatment groups

^c Excluding patients who did not have pain at 6 months

^d Percent of improvement from baseline = [(preoperative baseline mean score - mean score after treatment) / preoperative baseline mean score] x 100

Table 19
Radicular Pain^a at 6 Months (Evaluable Patients)

Total Score on VAS	Treatment Group		p-value ^b
	ADCON [®] -L	Control	
Preoperative baseline mean score (standard deviation)	7.90 (1.55) (N=86)	7.86 (1.52) (N=75)	0.87
Mean after treatment at 6months (standard deviation)	1.46 (2.35) (N=85)	1.83 (2.60) (N=74)	0.32
Percent of improvement from baseline ^c	82 %	77 %	

^a Radicular pain was measured on the Visual Analog Scale.

^b Two-tailed test for comparison of means between treatment group (analysis of variance with treatment group and center as factors)

^c Percent of improvement from baseline = [(preoperative baseline mean score - mean score after treatment at 6 months) / preoperative baseline mean score] x 100

Adverse Events

An interim analysis of a supportive U. S. multicenter clinical investigation of ADCON[®]-L demonstrated no statistically significant differences in the rates of adverse events between the ADCON[®]-L-treated group and the untreated control group (Table 20).

Table 20
All Adverse Events (Cumulative) Experienced by either ADCON[®]-L-Treated or Control Patients

Event Description	ADCON [®] -L (N=114)	CONTROL (N=109)	p-value [*]
Sciatica	4 (3.5 %)	4 (3.7 %)	1.00
Spasm	3 (2.6 %)	2 (1.8 %)	1.00
Low back pain	3 (2.6 %)	6 (5.5 %)	0.32
Wound infection	2 (1.8 %)	3 (2.8 %)	0.68
Numbness	2 (1.8 %)	1 (0.9 %)	1.00
Cerebrospinal fluid leak	2 (1.8 %)	0 (0.0 %)	0.5
Wound pain	1 (0.9 %)	0 (0.0 %)	0.51
Allergic reaction	0 (0.0 %)	1 (0.9 %)	1.00
Elevated temperature	1 (0.9 %)	0 (0.0 %)	0.51
Headache	1 (0.9 %)	0 (0.0 %)	0.51
Insomnia	0 (0.0 %)	1 (0.9 %)	1.00
Lower extremity pain	0 (0.0 %)	1 (0.9 %)	1.00
Urinary retention	1 (0.9 %)	1 (0.9 %)	0.76
Weakness	0 (0.0 %)	1 (0.9 %)	1.00
Urinary tract infection	1 (0.9 %)	2 (1.8 %)	0.62
Total patients with at least one event	23 (20.2 %)	22 (20.2 %)	0.57
Total patients with multiple events	4 (3.5 %)	3 (2.8 %)	0.53

* Two-tailed Fisher's Exact Test

Surgical Reinterventions

In the U. S. study, 5 % (6/114) of the ADCON[®]-L-treated group and 3 % (3/109) of the untreated control group underwent reoperation for reherniation or disc fragments (Table 21).

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Table 21
Surgical Reinterventions

Reason for reoperation	ADCON®-L (N=114)	Control (N=109)	p-value*
Reherniation at same level	3 (3 %)	1 (1 %)	0.62
Disc fragments	3 (3 %)	2 (2 %)	1.00
Total	6	3	0.32

* Two-tailed Fisher's Exact Test

X. GENDER ANALYSIS

The gender of the subjects was reported in both European and U.S. studies. There appear to be no effects of gender on the safety and effectiveness of ADCON®-L.

XI. CONCLUSIONS DRAWN FROM THE CLINICAL STUDIES

European Study

Six months following discectomy, those patients treated with ADCON®-L demonstrated a statistically significant reduction in peridural fibrosis (i.e., there was a statistically significant downward shift in the distribution of scar scores in the ADCON®-L-treated group at 6 months) when compared to those patients in the untreated control group (Table 4). Additionally, patients treated with ADCON®-L had a statistically significantly lower severity of wARP at 6 months while performing five specific activities associated with radiculopathy as compared to the untreated control group at 6 months, using the two-tailed t-test (Table 5). The ADCON®-L-treated group and untreated control group improved 50 % and 37 % respectively as compared to baseline preoperative wARP scores. Additional data collected at 12 months continued to demonstrate the safety and effectiveness of ADCON®-L. There was a statistically significant difference between the ADCON®-L-treated and control groups in the reduction of peridural fibrosis (Table 9). At 12 months, there was no statistically significant difference between the means of the wARP for both groups (Table 10). However, both ADCON-L treated and untreated group continued to improve in wARP.

U.S. Study

Interim analyses of the ongoing U. S. Study demonstrated that the scar scores were statistically significantly less (i.e., there was a statistically significant downward shift in the distribution of scar scores) in the ADCON®-L-treated group than in the control group at 6 months (Table 16). Additionally, there was a statistically significant difference in the Roland-Morris score for sciatic pain at 6 months in favor of the ADCON®-L-treated group over the control group. The ADCON®-L-treated group and the untreated control group improved 85 % and 75 % respectively as compared to preoperative Roland-Morris baseline scores (Table 17).

In light of the clinical results from the European and U.S. studies, it is reasonable to conclude that the benefits of using the device for the target population outweigh the risk of illness or injury when used as indicated in accordance with the directions for use.

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XII. PANEL RECOMMENDATION

On December 12, 1997, the Orthopedic and Rehabilitation Devices Panel discussed this PMA and recommended approval with the following conditions:

1) Labeling revisions

- Limit use to one level, posterior laminectomy or laminotomy surgery instead of generalizing to all lumbar surgery;
- Include a statement that transient foreign body formation may occur;
- Remove all claims for pain relief;
- Insert a table regarding scar formation of European study at six months;
- Use full chemical name of the device; and include a contraindication regarding subarachnoid exposure;
- Include the following two sentences: "Although substantial fibrosis occurred in ADCON[®]-L-treated and control groups, there was a slight benefit in the ADCON[®]-L-treated group upon statistical analysis." "Long term clinical benefit in terms of pain has not been shown.";

2) Reanalyze the peridural fibrosis of the anterior quadrant where the ADCON[®]-L was placed, and evaluate the correlation between the peridural fibrosis and the WARP at six months and twelve months; and

3) Submit validation of intraobserver reliability of a radiologist.

XIII. CDRH DECISION

CDRH concurred with the panel's recommendation with the following modifications and exceptions: The panel recommended the insertion of the following two sentences: "Although substantial fibrosis occurred in ADCON[®]-L-treated and control groups, there was a slight benefit in the ADCON[®]-L-treated group upon statistical analysis". "Long term clinical benefit in terms of pain has not been shown". It was also said that the label should remove all claims for pain relief. CDRH believes the Panel's recommendation to remove all claims for pain relief is inconsistent with the data presented in the PMA. The ADCON[®]-L-treated group had less peridural fibrosis at 6 and 12 months, and less WARP at 6 months than the control group. While the statistically significant difference in WARP between the ADCON[®]-L and control groups was not maintained at 12 months, the study was not designed for 12 months and both groups continued to improve. Therefore, the label will reflect the results of the WARP scale at 6 and 12 months.

In an amendment received by FDA on February 14, 1998, the analysis of the correlation between the peridural fibrosis and the WARP at 6 months and 12 months was done. The sponsor had done logistic regression analysis for assessing the probability of having pain in the presence or absence of extensive peridural fibrosis. This analysis showed significant probability of having pain in the presence of extensive scar at 6 and 12 months [odds ratios at 6 months (N=165) and 12 months (N=132) were 0.7 and 0.6 respectively]. However, the logistic regression analysis for predicting the probability of having pain in the presence of an I scar score was not a quantitative analysis. The data in the original PMA demonstrated no difference in the WARP between ADCON[®]-L-treated and the control group at 12 months quantitatively. Gliatech submitted the clinical utility index analysis at 6 and 12 months to FDA. It included all the parameters (non-extensive scarring, increased WARP, improved low back pain, and improved straight leg raise test) for success. However, in this analysis, the relevance of clinical improvement was not addressed.

Gliatech Inc. submitted validation of intraobserver reliability of a radiologist to FDA. The results indicated a 0.94 weighted kappa for all slices, a 0.93 weighted kappa for the middle 3 slices, and weighted kappas ranging between 0.9 and 0.99 for all individual quadrants of the MRI scans.

The sponsor's manufacturing facility was inspected on February 20 and March 12, 1998 and was found to be in compliance with the device Good Manufacturing Practice Regulations.

FDA issued an approval order on May 27, 1998. The approval order includes the following conditions of approval:

The labeling for the firm's device is incomplete since it includes interim results of the U.S. clinical trial being conducted under G940001. Therefore, in addition to the postapproval requirements in the enclosure, the firm must complete the 370 subject U.S. clinical trial being conducted under G940001 and provide postapproval supplements to your PMA which include the following information:

1. Within thirty days of the receipt of the approval order, the firm must provide a description of the twelve month longer term clinical outcome data that the firm will collect on the 370 subjects enrolled in the U.S. clinical trial (G940001).
2. The final report for the U.S. clinical trial (G940001) must be provided within three months of study completion.
3. Revised draft labeling that replaces the results of the interim analyses for the U.S. clinical trial with the final study results at six months, and that reflects longer term clinical outcome at twelve months must be provided.

The PMA was granted expedited review on February 6, 1997 because the use of the device was thought to have a potential benefit public health by acting as a barrier to epidural adhesion formation after lumbar disectomy, of which there are approximately 400,000 related procedures performed annually.

XIV. APPROVAL SPECIFICATIONS

Directions for Use: See the labeling .

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions and Adverse Events in the labeling.

ADCON[®]-L

Adhesion Control in a Barrier Gel

Caution: Federal law restricts this device to sale by or on the order of a physician (or properly licensed practitioner).

DESCRIPTION:

ADCON-L *Adhesion Control in a Barrier Gel* is a resorbable flowable gel composed of porcine derived gelatin, and a complex sugar of the polyglycan family in a phosphate buffered saline solution. The polyglycan is a long-chain polymer containing repeating units of poly-sulfo-alpha-(1→6)-D-glucan (a specially processed dextran sulfate). The product is resorbed within approximately four weeks of application.

INDICATIONS:

ADCON-L *Adhesion Control in a Barrier Gel* is indicated for use during single-level, posterior, lumbar laminectomy or laminotomy procedures (see Clinical Investigations Section) where nerve roots are exposed to inhibit postsurgical peridural fibrosis.

CONTRAINDICATIONS:

Do not use ADCON-L in patients with current infection or contamination of the operative site.

PRECAUTIONS:

General

Use caution when administering ADCON-L in patients who are allergic to products containing porcine protein. The safety and effectiveness of ADCON-L for uses other than single-level, unilateral, posterior, lumbar laminectomy, or laminotomy have not been established.

Use caution when administering ADCON-L in the presence of dural nicks.

Foreign body reaction may occur.

Sterile contents. For single patient use only. Unused contents should be discarded. ADCON-L must not be resterilized.

Do not use the ADCON-L tube or applicator if the pouches have been opened, torn or punctured. Store at room temperature 59°-77°F (15°-25°C). Do not freeze or expose to extreme heat.

Use in Specific Populations

Pregnancy: The safety and effectiveness of ADCON-L have not been established in pregnant women.

Nursing mothers: It is not known if ADCON-L is excreted in human milk.

The safety and effectiveness of ADCON-L have not been established in lactating women.

Children: The safety and effectiveness of ADCON-L have not been established in children.

ADVERSE EVENTS:

Pivotal European Study

ADCON-L was investigated in a pivotal European clinical trial having a total of 298 patients (147 ADCON-L treated and 151 untreated control patients). Common adverse events are listed in Table 1. There were no statistically significant differences in the rates of adverse events between the ADCON-L treated group and the untreated control group.

Table 1
Adverse Events (cumulative) Experienced by $\geq 1\%$ of either ADCON-L treated or Control Patients through 6 and 12 Months

Pivotal European Clinical Study

Event Description	6 Months			12 Months		
	ADCON-L (N=147)	Control (N=151)	p-value*	ADCON-L (N=147)	Control (N=151)	p-value*
Redness	30 (20.4%)	39 (25.8%)	0.28	30 (20.4%)	39 (25.8%)	0.28
Swelling	23 (15.6%)	30 (19.9%)	0.37	23 (15.6%)	30 (19.9%)	0.37
Motor deficit	12 (8.2%)	12 (7.9%)	1.00	12 (8.2%)	13 (8.6%)	1.00
Tenderness	12 (8.2%)	11 (7.3%)	0.83	12 (8.2%)	11 (7.3%)	0.83
Sensory deficit	10 (6.8%)	16 (10.6%)	0.31	11 (7.5%)	17 (11.3%)	0.32
New or increased radiculitis	8 (5.4%)	10 (6.6%)	0.81	10 (6.8%)	12 (7.9%)	0.83
Back spasm	8 (5.4%)	8 (5.3%)	1.00	9 (6.1%)	9 (6.0%)	1.00
Headache	4 (2.7%)	1 (0.7%)	0.21	7 (4.8%)	3 (2.0%)	0.21
Temperature spike	1 (0.7%)	0 (0.0%)	0.49	2 (1.4%)	0 (0.0%)	0.24
Pseudo-meningocele	2 (1.4%)	0 (0.0%)	0.24	2 (1.4%)	0 (0.0%)	0.24
Wound infection	0 (0.0%)	2 (1.3%)	0.50	0 (0.0%)	2 (1.3%)	0.50
Skin rash	1 (0.7%)	1 (0.7%)	1.00	1 (0.7%)	2 (1.3%)	1.00
Deep thrombophlebitis	0 (0.0%)	2 (1.3%)	0.50	0 (0.0%)	2 (1.3%)	0.50

* Two-tailed Fisher's Exact Test

Adverse events experienced by less than 1% of the study group at 6 and 12 months included: (ADCON-L) bowel deficit, cauda equina syndrome, peridural hematoma, wound necrosis, transient alopecia, and (Control) septicemia, shock, disc space infection, wound necrosis, pulmonary embolism, wound keloid, and wound dehiscence.

The time course distribution of adverse events showed no statistically significant difference between the ADCON-L treated and Control groups at 1, 3, 6 and 12 months.

U.S. Study

An interim analysis of a supportive U.S. multicenter clinical investigation of ADCON-L demonstrated no statistically significant differences in the rates of adverse events between the ADCON-L treated group and untreated control group (Table 2).

Table 2
Adverse Events (cumulative) Experienced by $\geq 1\%$ of either ADCON-L treated or Control Patients
U.S. Study at 6 Months

Event Description	ADCON-L (N=114)	Control (N=109)	p-value*
Sciatica	4 (3.5%)	4 (3.7%)	1.00
Spasm	3 (2.6%)	2 (1.8%)	1.00
Low back pain	3 (2.6%)	6 (5.5%)	0.32
Wound infection	2 (1.8%)	3 (2.8%)	0.68
Numbness	2 (1.8%)	1 (0.9%)	1.00
Cerebrospinal fluid leak	2 (1.8%)	0 (0.0%)	0.50
Urinary tract infection	1 (0.9%)	2 (1.8%)	0.62

* Two-tailed Fisher's Exact Test

Adverse events experienced by less than 1% of the study group at 6 months included: (ADCON-L) elevated temperature, headaches, urinary retention, wound pain, and (Control) allergic reaction, insomnia, lower extremity pain, numbness, urinary retention and weakness.

SURGICAL REINTERVENTIONS:

In the pivotal European study, secondary surgical interventions occurred in 8% (12/147) of the ADCON-L treated group and in 5% (8/151) of the untreated control group. The most common reason for reoperation in the ADCON-L-treated group and control group was reherniations, i.e., 58% (7/12), and 38% (3/8), respectively (Table 3). In the U.S. study, 5% (6/114) ADCON-L patients and 3% (3/109) control patients underwent reoperation for reherniation or disc fragments (Table 4).

Table 3
Surgical Reinterventions (Pivotal European Study)

Reason for reoperation	ADCON-L (N=147)	Control (N=151)	p-value*
Reherniation at same level	7 (5%)	3 (2%)	0.21
Disc fragments	4 (3%)	1 (1%)	0.21
Other ^a	1 (1%)	4 (3%)	0.37
Total	12	8	0.36

* Two-tailed Fisher's Exact Test

^a ADCON-L: hip problem; Control: negative re-exploration for persistent, worsened pain (1), extreme fibrosis (1), spinal stenosis at a different level (1), herniation at a different level (1).

Table 4
Surgical Reinterventions (U.S. Study)

Reason for reoperation	ADCON-L (N=114)	Control (N=109)	p-value*
Reherniation at same level	3 (3%)	1 (1%)	0.62
Disc fragments	3 (3%)	2 (2%)	1.00
Total	6	3	0.32

* Two-tailed Fisher's Exact Test

INSTRUCTIONS FOR USE:

A. Assembly of Components

1. Remove the pouches containing the ADCON-L tube and the applicator from the box.
2. Inspect the pouches to insure they are not damaged or open.

THE OUTSIDES OF THE POUCHES ARE NOT STERILE.

The ADCON-L tube and the inner bag containing the applicator are sterile unless the pouches have been torn, punctured or opened. NOTE: If a pouch has been damaged or opened, place both pouches back in the box and return the box to the manufacturer.

3. To maintain product sterility, peel back the corner(s) of each pouch and individually present the ADCON-L tube and the inner bag containing the applicator to the designated person in the sterile field. Dispose of the pouches.
4. Grasp the neck of the ADCON-L tube and break off the tip of the tube.
5. Wipe the top of the ADCON-L tube with dry, sterile gauze or cloth.
6. With a twisting motion, slide the hub of the applicator over the opening of the ADCON-L tube until it is securely fitted onto the tube. Gently tug on the applicator. If the hub is properly fitted on the tube, it should not pull off.
7. Dispense ADCON-L directly into the surgical site by squeezing the end of the tube.
8. After use, properly dispose of the ADCON-L tube and the applicator.

B. Surgical Procedure

Follow accepted procedures for single-level, posterior, lumbar laminectomy or laminotomy surgery. Irrigate the site, obtain hemostasis and remove all fluids and hemostatic materials prior to placement of ADCON-L.

C. Placement of ADCON-L

Immediately prior to closure of soft tissue incisions, apply the ADCON-L gel in the areas described below:

1. Coat the exiting nerve root along both its dorsal and ventral surfaces, and within the vertebral foramen.
2. Instill ADCON-L gel around the cephalic extent of the nerve root, getting under the exposed surface of the lamina by about 1 cm cephalad.
3. Place gel into the space between the dural sac and the posterior longitudinal ligament, both cephalad and caudal to the annular incision.

4. If the ligamentum flavum has been removed, apply ADCON-L gel over the posterior aspect of the dura in this region. If the ligament is intact, apply ADCON-L gel over its ventral and dorsal surfaces.
5. Apply ADCON-L gel into the site of the laminectomy/laminotomy to fill the depth of the site to the level of the ventral surface of the vertebral lamina. If excess ADCON-L gel spills onto tissue other than the intended application site, remove the gel with a sterile gauze.

Do not irrigate the surgical site once ADCON-L has been applied. Irrigation may remove ADCON-L from the application site.

DETAILED DEVICE DESCRIPTION:

ADCON-L contains the following: absorbable gelatin, poly-sulfo-alpha-(1→6)-D-glucan (a specially processed dextran sulfate), sodium chloride, dibasic sodium phosphate, monobasic potassium phosphate, potassium chloride, and water for injection.

HOW SUPPLIED:

ADCON-L is provided sterile as a kit (5 gram tube of ADCON-L gel and an applicator). Each ADCON-L kit contains 5 grams ADCON-L gel in a collapsible aluminum tube and an 18 cm polyvinylchloride (PVC) applicator designed to facilitate administration of the gel at the site of application. Both the ADCON-L tube and PVC applicator are separately packaged within Tyvek® pouches. The ADCON-L tube and the inner bag containing the applicator are sterile.

STORAGE AND HANDLING:

ADCON-L should be stored at room temperature 59°-77°F (15°-25°C). Do not freeze or expose to extreme heat. DO NOT RESTERILIZE.

CLINICAL INVESTIGATION:

Study Design

The pivotal trial was a randomized, double-masked, concurrently-controlled clinical investigation, which was performed at nine sites in three countries in Europe to evaluate the safety and effectiveness of ADCON-L *Adhesion Control in a Barrier Gel* as a therapy for the inhibition of peridural fibrosis with the primary outcome measure of extent of postoperative peridural fibrosis and a secondary outcome measure of weighted activity-related pain.

A total of 298 male or female patients between 17 and 60 years of age were randomized to receive either ADCON-L (147 patients) or no treatment (151 patients) following first-time unilateral, single level, posterior lumbar discectomy. Patients were evaluated for extent of peridural fibrosis and for activity related pain over a 6 month period (clinic visits at 1, 3 and 6 months following surgery).

Effectiveness Assessments

The primary outcome measure was the extent of peridural fibrosis as assessed with the use of magnetic resonance imaging (MRI) scans. Each MRI series consisted of five contiguous non-overlapping 4-mm scans centered on the operated intervertebral space. Each of the three middle MRI slices was divided into four spatial quadrants centered on the thecal sac for a total of twelve quadrants. Success was defined as demonstrating that the ADCON-L group had statistically significantly less peridural fibrosis as compared to the control group utilizing a Cochran-Mantel Haenszel test at 6 months.

The secondary outcome measure, weighted activity-related pain, was evaluated with a self-assessment questionnaire to describe the effect of activities of daily living on pain after surgery. Success was also defined as a statistically significant difference between the means of the weighted activity-related pain in favor of the ADCON-L treated group as compared to the untreated control group at 6 months.

The pivotal study was designed for 6 months, and additional data were collected at 12 months from available patients.

Results

The distribution of gender, age, preoperative clinical findings, operative level and disc pathology were comparable between the ADCON-L treated and untreated control group (Table 5).

Table 5
Patient Characteristics (Pivotal European Study-Evaluable Patients)

Characteristic	Treatment Group				p-value
	ADCON-L (N = 128)		CONTROL (N = 141)		
Gender [Number (%)]					1.0 ^a
Male	79	(62%)	88	(62%)	
Female	49	(38%)	53	(38%)	
Age (years)					
Mean (Standard Deviation)	38.2	(10)	39.9	(9)	0.13 ^b
Preoperative Clinical Signs [Mean (SD)]					
Radicular Pain ^c	7.8	(2)	8.0	(2)	0.40 ^b
Low Back Pain ^c	6.0	(3)	5.4	(3)	0.10 ^b
SLR ^d Angle (degrees)	50.0	(21)	52.4	(22)	0.37 ^b
Operative Level [Number (%)]					0.04 ^a
L4/L5	38	(30%)	59	(42%)	
L5/S1	90	(70%)	82	(58%)	
Surgical Procedure [Number (%)]					0.95 ^a
Laminectomy	2	(2%)	4	(3%)	
Laminotomy	22	(17%)	25	(18%)	
Hemilaminectomy	49	(38%)	53	(38%)	
Hemilaminotomy	55	(43%)	58	(41%)	
Other (Foraminotomy)	0	(0%)	1	(1%)	
Disc Pathology [Number (%)]					0.27 ^a
Sequestration	57	(44%)	53	(38%)	
Extrusion	43	(34%)	61	(43%)	
Protrusion	28	(22%)	27	(19%)	

^a Two-tailed test for comparison of distributions between treatment groups.

^b Two-tailed t-test for comparison of means between treatment groups.

^c Visual Analogue Scale (0-10 cm).

^d Straight Leg Raise.

Six months following discectomy, those patients with ADCON-L demonstrated a statistically significant reduction in peridural fibrosis when compared to those patients in the untreated control group (Table 6). Additionally, patients treated with ADCON-L had a statistically significantly lower severity of weighted activity related pain at six months while performing five specific activities associated with radiculopathy (Table 7) as compared to the untreated control group at 6 months, using the two-tailed t-test.

Additional data collected on the same study patients at 12 months continued to demonstrate the safety and effectiveness of ADCON-L. There was a statistically significant difference between the ADCON-L treated and control groups in the reduction of peridural fibrosis (Table 6). At 12 months, there was no statistically significant difference between the means of the weighted activity-related pain scores for both groups (the pivotal study had a 6 month endpoint).

Safety Assessment

All adverse events were monitored and recorded including the date of onset, severity, relationship to device, action taken, and outcome. Severity was graded as mild, moderate, severe, or life-threatening. The relationship between the event and the device was classified as not related, definitely related, or unknown. There were no statistically significant differences between treatment groups with regard to incidence of redness, swelling, and tenderness of the operative site and incidence of adverse events (see ADVERSE EVENTS SECTION).

Table 6
Distribution of Scarring at 6 and 12 Months
(Pivotal European Study-Evaluable Patients)

	Extent of Scar ^a					p-value ^b
	None	>0% to ≤25%	>25% to ≤50%	>50% to ≤75%	>75% to ≤100%	
6 Months ^c						
Control	1%	3%	17%	29%	50%	0.01
ADCON-L	3%	10%	13%	36%	38%	
12 Months ^d						
Control	0%	9%	22%	28%	41%	0.01
ADCON-L	4%	11%	26%	31%	28%	

^a Most extensive scar on any of the 12 quadrants on the MRI scan.

^b Two-tailed test for comparison of distributions between treatment groups using the Cochran-Mantel-Haenszel procedure stratified by center.

^c There were 127 patients in the ADCON-L group, and 139 patients in the control group at 6 months.

^d There were 116 patients in the ADCON-L group, and 130 patients in the control group at 12 months.

Table 7
Weighted Activity-Related Pain Scores ^a
Pivotal European Study at 6 Months

	ADCON-L	Control	p-value ^b
Preoperative baseline mean score	2.49 (N=128)	2.52 (N=141)	0.74
Mean score after treatment	1.24 (N=88) ^c	1.58 (N=84) ^c	0.03
Percent of improvement from baseline ^d	50%	37%	

^a Linear combinations based on National Low Back Pain Study (U.S.) (BenDebba, M. et al: A Simple Procedure for Assessing the Impact of Low Back Pain on Activities of Daily Living, 8th World Congress on Pain 58, 1996).

Weighted sum of activities that caused an increase in pain. Maximum total score is 3.2. Activities included bending, riding/driving in a car, sitting ≤ 15 min, sitting > 15 min, and lifting heavy objects >10 lbs.

^b Two-tailed t-test for comparison of means between treatment groups.

^c Excluding patients who did not have pain at 6 months.

^d Percent of improvement from baseline equals (preoperative baseline mean score minus mean score after treatment) divided by the preoperative baseline score times 100.

U.S. Study

This is a randomized, double-masked, concurrently controlled multicenter trial to evaluate the safety and effectiveness of ADCON-L. Results from surgery with ADCON-L were compared to surgery without ADCON-L. Clinical assessments performed by evaluators masked to patient treatment status were conducted preoperatively, and at 1, 2 and 6 months postoperatively. The MRI films (with and without gadolinium enhancement) were obtained at 6 months postoperatively. MRIs were evaluated by a neuroradiologist masked to patient treatment.

A planned interim analysis demonstrated that the patients treated with ADCON-L had a statistically significant reduction in peridural fibrosis when compared to control patients at 6 months (Table 8). Additionally, there was a statistically significant difference in the Roland-Morris Score for sciatic pain at six months in favor of the ADCON-L treated group over the control group (Table 9).

Table 8
Distribution of Scarring at 6 Months
(U.S. Study-Evaluable Patients)

	Extent of Scar ^a					p-value ^b
	None	>0 to ≤25%	>25% to ≤50%	>50% to ≤75%	>75% to ≤100%	
Control (n=65)	0%	3%	6%	14%	77%	0.03
ADCON-L (n=76)	0%	5%	11%	30%	54%	

^a Most extensive scar on any of the twelve quadrants on the MRI scan.

^b Two-tailed test for comparison of distributions between treatment groups using the Cochran-Mantel-Haenszel procedure stratified by center.

Table 9
Total Roland-Morris Score^b at 6 Months (U.S. Study-Evaluable Patients)

Total Roland-Morris Score	Treatment Group		p-value ^a
	ADCON-L	Control	
Preoperative baseline mean score (Standard Deviation)	14.7 (5.5) (N=114)	15.2 (4.9) (N=109)	0.46
Mean after treatment at 6 months (Standard Deviation)	2.2 (4.3) (N=86)	3.8 (5.4) (N=74)	0.03
Percent of improvement from baseline ^c	85%	75%	

^a Two-tailed test for comparison of means between treatment group (analysis of variance with treatment group and center as factors).

^b Roland Morris Disability Questionnaire is composed of a questionnaire containing 24 statements that describe typical ways in which symptoms may interfere with daily activities, work and recreation. A patient who has absolutely no radiculopathy-related impairment would have a score of "0", and a maximally-affected patient would have a score of "24".

^c Percent of improvement from baseline equals (preoperative baseline mean score minus mean score after treatment at 6 months) divided by the preoperative baseline mean score times 100.