

**A PHASE II STUDY OF THE SAFETY AND EFFICACY OF TOPICAL LIPOSOME-  
ENCAPSULATED DICLOFENAC ANALGESIC (LEDA) IN PATIENTS WITH  
OSTEOARTHRITIS OF THE KNEE**

**STATISTICAL SUMMARY REPORT**

PROTOCOL NUMBER: LEDA.C.001  
REPORT PREPARED BY: Peter Shabe, Biostatistician  
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This study was performed in compliance with EN 540 and good clinical practice (GCP), including archival of essential study documents.

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## LIST OF ABBREVIATIONS

ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
CBC	Complete Blood Count
CRF	Case Report Form
dL	deciliter(s)
ECG	electrocardiogram
IRB	Institutional Review Board
kg	kilogram(s)
LEDA	Liposome-Encapsulated Diclofenac Analgesic
ml	milliliter(s)
mm	millimeter(s)
NSAID	Non-Steroidal Anti-Inflammatory Drug
OA	Osteoarthritis
OTC	Over The Counter
T.I.D.	Three Times Daily
VAS	Visual Analog Scale
WBC	White Blood Count
WOMAC	Western Ontario, McMaster Osteoarthritis Index

## **STATEMENT OF ETHICS**

### **INSTITUTIONAL REVIEW BOARD**

The protocol and all subsequent amendments were submitted to either the investigator's IRB or a central IRB (Western Institutional Review Board, Seattle WA) for review. The IRB was to conform to all requirements listed in the Code of Federal Regulations. The investigator provided documentation to the sponsor, of both the federal certification of the local IRB and the IRB approval of the protocol and any amendments, prior to the investigator initiating the protocol or amendment.

### **ETHICAL CONDUCT OF THE STUDY**

The investigators were contractually bound to ensure that this study was conducted in complete conformance with the principles of the Code of Federal Regulations (21CFR, Parts 50, 56, and 312) regarding human research.

### **PATIENT INFORMATION AND CONSENT**

The investigator was to obtain written informed consent from each participating patient prior to entering that patient into the study. The consent form was to be approved by the IRB and was to contain a description of the study's aims, methods, anticipated benefits, and potential risks. This document was to be written in a language understandable to the consenting adult. The consent form was to be modified so as to incorporate any unique requirements due to ethnic, cultural or racial circumstances at that study site.

All patients were to provide written informed consent for their participation. It was incumbent upon the investigator to inform the patient that he/she was free to refuse to enter the study and to withdraw from the study at any time, for any reason, and that such refusal would not compromise the care they are rendered. The CRFs for this study contained a section for documenting informed patient consent and the investigator was to complete it, and maintain the original consent form. A copy of the signed consent form was to be given to the patient.

### **REGULATORY CONSIDERATIONS**

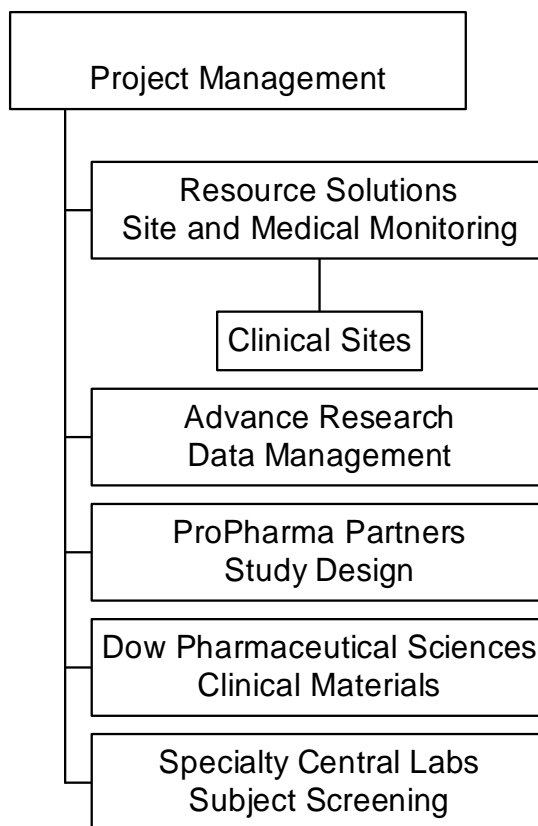
The investigators were to ensure that this study was conducted in complete conformance with the principles of the Code of Federal Regulations regarding human research.

The investigators were to have this protocol reviewed and approved by an appropriate IRB prior to initiating the study. This IRB was to conform to all requirements listed in the Code of Federal Regulations. The investigators were to provide documentation to the sponsor, of the IRB approval of the protocol, prior to the investigator initiating the protocol.

## INVESTIGATORS AND ADMINISTRATIVE STRUCTURE

Site Code	Site Name	Principal Investigator
01	University of Alabama, Birmingham	Dr. Larry Moreland
02	Northern California Medical Associates (Santa Rosa, CA)	Dr. Jack Waxman
03	Osteoporosis Medical Center (Beverly Hills, CA)	Dr. David Silver
04	Robin K. Dore, MD Inc. (Anaheim, CA)	Dr. Robin Dore
05	Michael Lovy, MD (private practice, Tacoma, WA)	Dr. Michael Lovy
06	Sarasota Arthritis Center (Sarasota, FL)	Dr. Jeffrey Kaine
07	Physicians Pharmaceutical Study Services (Everett, WA)	Dr. Reynold Karr
08	Arthritis Education and Treatment Center (Grand Rapids, MI)	Dr. Jan Ciejka
09	Palo Alto Medical Clinic (Palo Alto, CA)	Dr. Arthur Bobrove
10	Wallace Rheumatic Study Center (Los Angeles, CA)	Dr. Daniel Wallace
11	Research Testing Laboratories (Huntington, NY)	Dr. Louise Donikyan
12	Research Testing Laboratories (Hackensack, NJ)	Dr. Louise Donikyan

## ADMINISTRATIVE STRUCTURE



## INTRODUCTION

Diclofenac, a phenylacetic acid derivative, is a non-steroidal anti-inflammatory agent (NSAID) that is commercially available as diclofenac sodium delayed-release (enteric-coated) tablets and as diclofenac potassium tablets. This drug has been used by millions of patients worldwide for nearly 20 years and is licensed for sale in the United States for use as an analgesic for post-operative pain, dysmenorrhea, osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. Diclofenac has pharmacological actions similar to those of other NSAIDs as the drug exhibits anti-inflammatory, analgesic, and antipyretic activities which appear to be principally associated with its ability to inhibit prostaglandin synthesis.

The adverse event profile of orally administered diclofenac is similar to that of other NSAIDs and includes gastrointestinal, genitourinary, renal, and hematological toxicities. In addition, diclofenac is reputed to have a slightly higher incidence of liver enzyme elevation compared to many other NSAIDs (Catalano, 1986). With oral diclofenac, the overall incidence of side effects has been reported to be about 30% (Biscarini, 1996). The majority of side effects seen with diclofenac and other NSAIDs are gastrointestinal disturbances such as dyspepsia as well as gastrointestinal ulcerative lesions. On average, about 10-12% of patients taking NSAIDs will develop dyspepsia (Hardin et al, 1992; Goldenberg and Cohen, 1986) and it has been reported that up to 20% of regular NSAID users can be expected to develop an ulcer during the course of therapy (Hardin et al, 1992).

Due to the frequency and severity of NSAID-associated side effects, especially gastrointestinal bleeding, considerable interest has been focused on developing new, better-tolerated formulations of NSAIDs. In this regard, the topical method of delivery may be potentially effective in relieving regional pain syndromes while avoiding the serious side effects associated with oral NSAIDs. For patients with only one or a few painful joints or muscles, it seems appropriate to target the site where analgesia is required, thereby avoiding unnecessary systemic exposure. Importantly, compared to oral delivery, a topical formulation would be expected to result in lower blood levels and since the risk of major adverse events such as gastrointestinal bleeding is dose and blood level related, topical NSAIDs should be safer than their oral equivalents (Griffin, 1998).

We have developed a new formulation of diclofenac using multi-lamellar liposomes. Referred to as Liposome-Encapsulated Diclofenac Analgesic (LEDA), this topically applied formulation may provide a superior approach to the safe and effective treatment of patients with mono- or pauci-articular osteoarthritis, and other localized musculoskeletal pain syndromes.

A pre-clinical study utilizing a formulation closely approximating the LEDA formulation has been performed in guinea pigs. This study demonstrated the potential for LEDA in treating regional pain with relatively minimal uptake of diclofenac into the systemic circulation. In guinea pigs, the biodistribution of [<sup>14</sup>C] radio-labeled diclofenac formulated in liposomes was compared to that formulated in Voltaren Emulgel<sup>®</sup>, an alcoholic topical diclofenac gel (1%) currently marketed in Europe. Radioactivity recovered from the subcutaneous tissue and muscle beneath the site of application was significantly higher with LEDA than that recovered from the same tissues in guinea pigs treated with Voltaren Emulgel<sup>®</sup>. There was an approximately 4-12 fold increase in radio-labeled material recovered from the subcutaneous and muscle tissues of

LEDA treated animals. Conversely, lower levels of radioactivity relative to Voltaren Emulgel<sup>®</sup> treated guinea pigs were found in all of the other tissues analyzed as well as plasma and urine. The data from this non-clinical study suggest that the topical application of liposomal encapsulated diclofenac resulted in a lower level of systemic exposure and higher local delivery of diclofenac.

The total topical dose of LEDA evaluated in this study (60 mg daily) was less than the approved oral dose of diclofenac (100-150 mg daily), and was similar to the dose of topical diclofenac Voltaren Emulgel<sup>®</sup> (up to 80 mg daily) which is sold over-the-counter (OTC) in European countries. Thus, it was expected that topical treatment with LEDA would have less systemically associated safety risk than oral diclofenac and topical Voltaren Emulgel<sup>®</sup> due to the lower dose and reduced systemic exposure.

LEDA should provide clinical benefit in several clinical settings for the treatment of musculoskeletal pain. Treatment with LEDA is expected to reduce the severity of pain associated with arthritis, simple backache, sprains and strain, and sunburn. The intended use for LEDA will be similar to that for several currently marketed topical products such as those containing the NSAID methyl-salicylate in combination with capsaicin, and oral products such as ibuprofen and naproxyn which are all currently licensed for OTC sale as a treatment for minor musculoskeletal pain.

## **STUDY OBJECTIVES**

The primary study objectives were to evaluate the safety and efficacy of topically applied Liposome Encapsulated Diclofenac Analgesic (LEDA), in patients with osteoarthritis (OA) of the knee. The primary efficacy endpoint is change from baseline in the WOMAC Pain Subscale. Secondary outcomes are changes from baseline in the WOMAC Stiffness Subscale, the WOMAC Physical Function Subscale, the total WOMAC score, change from baseline in patient and physician global assessments, change in pain (from baseline) resulting from a 50-foot walk, and dropout rates.

The test therapy was a 20mg diclofenac equivalent of Liposome-Encapsulated Diclofenac Analgesic, applied topically three times daily. The Control therapy was a diclofenac-free, liposome cream also applied topically three times daily

## **INVESTIGATIONAL PLAN**

### **OVERALL STUDY DESIGN AND PLAN**

Approximately 160 adult patients (males and females) with OA of the knee were to be enrolled by 12-16 centers. LEDA or Control was to be administered from squeeze tubes, in the amount of 2 inches of cream delivering approximately 20 mg of diclofenac (or Control) T.I.D., in a randomized, double-blind manner.

Patients were to “wash out” of all oral anti-inflammatory medications and analgesics for at least 3 days (5 days for long half-life NSAIDS) prior to starting study treatment and remain off these and all other pain medications for the duration of the study. Blinded study treatment was applied topically using the hand or fingers over the local area of pain in the osteoarthritic study knee. Treatment was to be administered three times per day (TID) for 14 days. Blood was to be collected for determination of serum diclofenac concentrations at day 14. Safety evaluations

consisted of visual inspection of the study drug application site, complete blood counts, liver enzymes, serum creatinine, and recording of adverse events. Efficacy evaluations consisted of the WOMAC osteoarthritis instrument, patient and physician global assessments, pain resulting from a 50-foot walk, and physical examination of the study joint. Since no pain “rescue” medications were allowed according to the protocol, and the duration of the study was relatively short, dropout rates due to lack of efficacy were also to be evaluated.

## **SELECTION OF STUDY POPULATION**

### **Inclusion Criteria**

The following criteria were required for entry into the study:

1. Males and females, at least 18 years of age.
2. Able and willing to provide informed consent.
3. Having a clinical diagnosis of osteoarthritis of the knee
4. Moderate to severe pain (WOMAC Pain Subscale score at least 10 (of a maximum of 20, using 0-4 for scoring each of the five questions) in the affected joint after washout of oral analgesics and/or any oral anti-inflammatory drug for three days (five days for long half-life NSAIDs, i.e. any NSAID labeled for once per day dosing).
5. Symptoms present for at least 3 months prior to enrollment.

### **Exclusion Criteria**

The following criteria were exclusionary to participation in this study:

1. Pregnancy or lactation
2. A history of an allergic reaction, or a renal or hepatic toxicity to any NSAID.
3. A history of active gastrointestinal ulceration, or gastrointestinal bleeding within one year.
4. A history of chronic liver disease, or chronic renal disease
5. Serum creatinine, blood urea nitrogen, ALT, AST, or alkaline phosphatase above the upper limit of normal for the clinical laboratory used for the study site.
6. Hemoglobin less than 12.0 gm/dL, WBC less than  $3 \times 10^3 / \text{mm}^3$ , platelets less than  $1 \times 10^5 / \text{mm}^3$ .
7. Unwillingness to use adequate contraception from seven days prior to the first study treatment day, through the duration of the study. Adequate contraception includes abstinence, barrier methods combined with spermicidal agents, hormonal methods, post-menopausal state, or surgical sterilization.
8. A history of use of any illegal drugs for three months prior to the first study treatment day.
9. Regular consumption of greater than 2 fluid ounces of beverage ethanol per day. Subjects must refrain from consumption of greater than 2 fluid ounces of beverage ethanol per day for seven days prior to the first study treatment day, through the duration of the study.
10. Participation in any study involving another experimental agent within one month prior to the first study treatment day.

## **DATA QUALITY ASSURANCE**

During monitoring visits, the completed CRFs were reviewed at the site against patient source documents prior to collecting and sending the CRFs to Advance Research Associates, Inc., an independent data management group. Data from the CRFs were entered into a database. Once all discrepancies had been resolved to the satisfaction of the sponsor, the CRFs for all of the patients were compared to the database to assure that no other systematic errors had been introduced into the database. The database was released for analysis once all these activities

were satisfactorily completed. At that point, the database was locked, and no additional changes to the database were allowed.

A pre-approved Statistical Analysis Plan outlining the Tables, Listings, and Graphs for this report was used as the blueprint for the analysis programs. The Analysis Plan included definitions and formulas for all data derived for the analyses, as well as outlined the statistical methods to be followed when performing statistical tests for Treatment Group differences. Each program went through two levels of review and quality assurance. The first level of review was performed jointly between the programmer writing the program and the statistician that wrote the analysis plan. Using the Analysis Plan as the guide, the programmer and the statistician reviewed the assumptions made to generate the summary and reviewed the content and format of the output generated by the program. At that point, the program output was ready to be included in the Statistical Summary Report. However, an additional level of quality assurance is provided by including another independent review by a programmer who has not worked on the programs before. Once the final review is complete, the programs are considered fully verified.

The Tables, Listings, and Figures all include a statement in the footer describing the status of the database and the programs.

## **STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE**

### **STATISTICAL AND ANALYTICAL PLANS**

SAS statistical analysis software (Version 8.2, The SAS Institute, Inc) was used to perform all statistical analyses.

No special data handling conventions were used for missing values. If a patient was missing data for a given analysis, that patient was not included in that analysis.

No adjustments to the data were intended for dealing with missing values or patients who withdrew prior to completing the study. A final statistical analysis plan was developed prior to locking of the CRF database. The statistical plan included mock-ups of the tables, listings, and figures for the statistical report, as well as documentation of the data derivations and statistical methods utilized.

### **DEFINITION OF PATIENT EVALUABILITY FOR EACH ANALYSIS**

All patients receiving at least one application of either the LEDA or Control are included in the Safety analyses.

Patients who did not have a baseline WOMAC Pain Subscale Score of 10 or greater were excluded from the efficacy analyses.

### **GROUPINGS OF PATIENTS IN THE ANALYSES**

All evaluable patients were included in all analyses. Patients are summarized within the treatment group they were assigned, as well as all patients combined.

## DATA DERIVATION RULES AND ASSUMPTIONS

The primary objective for determining efficacy of LEDA for treating pain associated with osteoarthritis of the knee is to compare the Day 1 WOMAC Osteoarthritis Index Pain Subscale scores with the Day 14 score and to evaluate the difference between the LEDA treated patients and the Control treated patients.

The change-from-baseline in the patient's WOMAC Pain Subscale is calculated as follows:

Change from baseline score = score post-treatment – score pre-treatment

and serves as the metric for measuring knee pain and comparing rates of pain reduction between treatment groups. Negative values indicate a reduction in pain, positive values indicate a worsening in pain. A change of –20% or greater, indicating a considerable reduction in pain, is a clinically significant result.

Secondary measures of efficacy include:

- WOMAC Stiffness Subscale score, WOMAC Physical Function Subscale score, and Total WOMAC score,
- Percent of patients with at least a 20% reduction in the WOMAC Pain Subscale, in the WOMAC Function Subscale, in the WOMAC Stiffness Subscale, and in the total WOMAC Score,
- Investigator Global Assessment,
- Patient Global Assessment,
- Pain from 50 foot walk, as measured on a 100mm Visual Analogue Scale (VAS),
- Dropout evaluation

Change from baseline scores will be calculated for each of the continuous variables using the formula:

Change from baseline score = score post-treatment – score pre-treatment

Negative values indicate an improvement in a patient's condition, positive values indicate a worsening in their condition. A change of –20% or greater, indicating a considerable improvement in the patient's disease condition, is a clinically significant result.

Adverse events were followed over the course of the study. All patients receiving at least one dose of LEDA or Control were included in all summaries of adverse events. All reported events were coded to a standard set of terms using the MedDRA adverse event dictionary. Adverse events will be listed and summarized for patients within each treatment group. The frequency of each event for each body system are summarized by severity and by relatedness with the study treatment. Since some patients may report the same event several times (e.g., headache), the first occurrence of the worst reported case of the event is used for the purposes of analysis.

## DETERMINATION OF SAMPLE SIZE

The table below indicates that the study should have enrolled at least 64 patients in each treatment group to be able to detect a 10 point difference between the groups, assuming that both treatment groups have a common standard deviation of 20. Assuming that roughly 20% of the

patients may be lost to follow-up, 160 total patients (80 LEDA patients and 80 Control patients) should be enrolled in the study.

Minimum Number of Patients Needed in the <i>each</i> Treatment Group To Detect the Specified Difference in Means			
Comparing Two Independent Sample Means Using a Two-sided T-Test with an $\alpha = 0.05$ Level of Significance and a $1 - \beta = 0.80$ Level of Statistical Power			
Common Standard Deviation	Difference in Means		
	5 vs 10	5 vs 15	5 vs 20
15	143	37	17
20	253	64	29
25	394	100	45

## CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

No changes were made to the conduct of the study, nor in the original Analysis Plan for this study. Some minor changes were made to the protocol and documented in protocol amendment submissions to the IND application. None of the changes affected the conduct of the study or the planned analysis of its results.

## STUDY PATIENTS

### DISPOSITION OF PATIENTS

A total of 191 patients were enrolled and treated at twelve (12) centers participating in this study. Ninety five (95) patients were randomized to receive LEDA and ninety-six (96) were randomized to receive the Control. Twenty eight (28) of these patients (15 LEDA patients and 13 Control patients) were excluded from all efficacy analyses because they did not meet the criteria of a baseline WOMAC Pain Subscale score of 10 or greater to be eligible to enroll in this study. However, since these patients did receive study medication (LEDA or Control), they are included in the summaries of Adverse Events. See [Table 1](#) for details.

### PROTOCOL DEVIATIONS

Several patients did not satisfy the study enrollment criteria of having a baseline WOMAC Pain Subscale score of 10 or greater (moderate to severe osteoarthritis pain). These patients were randomized and received the study treatment. Since these patients violated the key enrollment criteria for the study, the patients are excluded from all efficacy analyses. However, since they were randomized and did receive treatment, these patients are included in the safety analyses.

## EFFICACY EVALUATION

### DATA SETS ANALYZED

All patients who enrolled in the study and were treated are included in all safety analyses. Only patients with at least a baseline WOMAC Pain Subscale score of 10 or greater are included in the efficacy analyses.

### DEMOGRAPHICS AND OTHER PATIENT CHARACTERISTICS

Sixty-six per cent (66%) of all patients treated were female. On average, patients were 64 years of age and had osteoarthritis in their study knee for 7.1 years. There were no material differences between the treatment groups in any of the patient demographics and baseline disease characteristics. See [Table 2](#) for details.

### MEASUREMENTS OF TREATMENT COMPLIANCE

All patients were asked to return their tubes. No significant deviations in the application of the cream or in using the tubes were reported. Eight (8) of the LEDA patients and 12 of the Control patients reported interruptions in their treatment. Most of these patients missed only one or two of the 42 total applications prescribed according to the protocol, usually because of personal reasons. Two patients (1 LEDA patient and 1 Control patient) stopped applying the treatment because of lack of efficacy. See [Table 1](#) for details.

### EFFICACY RESULTS AND TABULATIONS OF INDIVIDUAL PATIENT DATA

The following results were found for each of the primary and secondary efficacy parameters studied:

WOMAC Pain Subscale – The primary efficacy variable for this study, the WOMAC Pain Subscale, was collected on Study Day 1 immediately before treatment started and again on Study Day 14, the last day of the treatment period. The LEDA patients showed **highly statistically significant improvement** in their Pain Subscale scores (mean percent improvement from baseline scores of 33.0%, with  $p < 0.01$ ). Though the difference between the two groups did not achieve statistical significance, the LEDA treatment group demonstrated a reduction of 4.1 points versus a reduction of 3.7 points for the Control treatment group. See [Table 6](#) and [Figures 1 and 2](#) for details. See [Table 7](#) for details from each Study Center.

WOMAC Stiffness Subscale – Data for a secondary efficacy variable for the study, the WOMAC Stiffness Subscale, were also collected on Day 1 and Day 14. The LEDA patients showed **highly statistically significant improvement** in their Stiffness Subscale scores (mean percent improvement from baseline scores of 30.5%, with  $p < 0.01$ ). Though the difference between the two groups did not achieve statistical significance, the LEDA group demonstrated a reduction of 1.6 points versus a reduction of 1.4 points for the Control treatment group. See [Table 8](#) and [Figures 3 and 4](#) for details. See [Table 9](#) for details for each Study Center.

WOMAC Physical Function Subscale – A secondary efficacy variable for the study, the WOMAC Physical Function Subscale, was also collected on Day 1 and Day 14. The LEDA patients showed **highly statistically significant improvement** in their Physical Function Subscale scores (mean percent improvement from baseline scores of 28.9%, with  $p < 0.01$ ).

Though the difference between the two groups did not achieve statistical significance, the LEDA group demonstrated a reduction of 12.1 points versus a reduction of 11.3 points for the Control treatment group. See [Table 10](#) and [Figures 5 and 6](#) for details. See [Table 11](#) for details for each Study Center.

**Total WOMAC Score** – As with the Pain and Stiffness Subscales, the LEDA patients showed **highly statistically significant** improvements in their Total WOMAC scores (mean percent improvement from baseline scores of 30.1%, with  $p < 0.01$ ). Though the difference between the two groups did not achieve statistical significance, the LEDA group demonstrated a reduction of 17.8 points versus a reduction of 16.4 points for the Control treatment group. See [Table 12](#) for details. See [Table 13](#) for details for each Study Center. See [Tables 16 through 21](#) for the results summarized for each individual question on the WOMAC questionnaire.

**At Least 20% Improvement in WOMAC Subscales** – Patients were classified as showing at least a 20% improvement in each of the WOMAC Subscales. In total, 75.0% of the LEDA treatment group (60 of 80 LEDA patients) had at least a 20% improvement in one or more of the WOMAC Subscales. See [Table 14](#) for details. See [Table 15](#) for details for each Study Center.

**Investigator Global Assessment** – Using the same question posed to the patients to rate the overall effect of the arthritis on their daily activities, Investigators rated the effect of the patients arthritis using a five-point scale anchored with No Effect and Extreme. Investigator responses showed **highly statistically significant** improvements in the LEDA patients' disease condition ( $p < 0.01$ ). Though the difference between the two groups did not achieve statistical significance, the LEDA group demonstrated a mean improvement of 24.6% in the Investigator's rating of their disease condition. See [Tables 24, 25 and 26](#), plus [Figures 9 and 10](#), for details.

**Patient Global Assessment** – Patients were asked to rate the overall effect of the arthritis on their daily activities using a five-point scale from No Effect to Extreme. The LEDA patients indicated **highly statistically significant** improvements in their disease condition ( $p < 0.01$ ). Though the difference between the two groups did not achieve statistical significance, the LEDA group demonstrated a mean improvement of 22.4% in Patient's rating of their disease condition. See [Table 22](#) and [Figures 7 and 8](#) for details.

**Pain from 50-foot Walk VAS** – Patients were asked to indicate on a 100mm Visual Analog Scale (VAS) their pain level after walking 50 feet. The ends of the VAS were anchored with "No Pain" and "Worst Possible Pain". The LEDA patients indicated **highly statistically significant** reductions in the amount of pain after walking 50 feet ( $p < 0.01$ ). Though the difference between the two groups did not achieve statistical significance, the LEDA group demonstrated a mean improvement in their pain score of 20.0%. See [Table 23](#) and [Figures 11 and 12](#) for details.

**Pain Rescue Medications** – Although prohibited in the protocol, pain medication such as oral and topical anti-inflammatory agents (prescription and OTC), and analgesics were taken by some of the study participants during the treatment period. These medications were recorded and classified according to their potential for providing pain relief. The indication of use for each medication was evaluated to further classify pain relief medication as Cardiac Prophylaxis (such as aspirin), Arthritis Diet Supplements (such as glucosamine), pain relief medication indicated as used for non-arthritis symptoms, and pain relief medication indicated as used for arthritis symptoms. The number of Control patients involved in this violation was greater than the number of LEDA patients, the difference achieving **statistical significance** ( $p < 0.04$ ). In

addition, considerably more Control patients than LEDA patients were taking one or more of the classes of pain relief agents during the treatment period. The difference between the two groups is **highly statistically significant** ( $p < 0.01$ ) with 56.6% of the Control patients taking pain rescue medication during the treatment period. See [Table 27](#) for details.

## STATISTICAL/ANALYTICAL ISSUES

All data was analyzed using traditional statistical methodology and hypothesis tests. As such, no special statistical or analytical methodologies were necessary.

## HANDLING OF DROPOUTS OR MISSING DATA

No special data handling methods were used to replace data that was missing. All data collected was summarized.

## EXAMINATION OF SUBGROUPS

All patients were included in the summaries. No subgroups of patients were identified for separate analysis.

## EFFICACY CONCLUSIONS

A total of 163 patients (80 LEDA patients and 83 Control patients) were evaluable for efficacy. In all cases, the LEDA patients showed **highly statistically significant improvement** in their disease condition over baseline. There was a positive trend in favor of LEDA-treated patients in the primary efficacy endpoint and all secondary efficacy endpoints versus the Control patients. Although statistical significance was not achieved for the difference between the two groups, it is the belief of the statistician that this positive trend indicates that statistical significance would have been achieved had the sample population been increased.

In total, 75.0% of patients in the LEDA-treated patients demonstrated a **clinically significant improvement** of greater than 20% in one or more subscale categories.

## SAFETY EVALUATION

### EXTENT OF EXPOSURE

The total topical dose of LEDA which was evaluated in this study (60 mg daily) is less than the approved oral dose of diclofenac (100-150 mg daily), and is similar to the dose of topical diclofenac Voltaren Emulgel<sup>®</sup> (up to 80 mg daily) which has been sold OTC in Europe.

### ADVERSE EVENTS

A total of 191 patients received treatment (95 LEDA patients and 96 Control patients) and were followed for safety. Fifty five (55) of these patients reported a total of 79 adverse events (28 events reported by 22 LEDA patients and 51 events reported by 33 Control patients). There were 3 events reported by LEDA patients and 7 events reported by Control patients that were considered to be Possibly or Probably related to the patient's treatment. Only seven (7) of all events (one (1) event reported by a LEDA patient and six (6) events reported by Control patients) were considered to be Severe. There was one (1) Control patient who died as a result of a myocardial infarction (MI) that was determined to be unrelated to the study treatment. In

addition to the MI, another three (3) events were considered serious (moderate posterior nose bleed, lymph node metastatic cancer, and hospitalized due to fall) but were not determined to have been associated with the therapy. See [Tables 28, 29 and 30](#) for details.

### **DEATHS, OTHER SERIOUS ADVERSE EVENTS**

One Control patient (Patient 12-229 JRM) experienced a myocardial infarction (MI) four (4) days after starting treatment that resulted in the patient's death. The event was determined to be related to an intercurrent illness and not to the treatment. See [Listing 16](#) for details.

### **VITAL SIGNS, PHYSICAL FINDINGS, OTHER SAFETY OBSERVATIONS**

Temperature, weight, and pulse were collected only at the Screening visit. Blood Pressure was collected at the Screening Visit, Day 1, and Day 14 of treatment. There were no differences between patients in each treatment group for any of the Vital Signs measured at the Screening Visit, nor were there any differences between treatment groups in Systolic or Diastolic Blood Pressure at Day 1 or Day 14. In addition, changes from baseline in Systolic or Diastolic Blood Pressure at Day 14 were not statistically significant. See [Tables 7 and 8](#) for details.

### **SAFETY CONCLUSIONS**

The most common safety concern with oral NSAIDs is gastrointestinal upset. With LEDA, the expectation was that GI upset would be greatly reduced due to the topical application of the drug. This expectation was confirmed as there were **zero (0) GI-related adverse events** associated with the study drug. Of the 95 patients using the LEDA cream, only three (3) had events related to the safety of the product. These events were determined to be minor and were classified as skin redness at the study joint, tingling in foot and slight dizziness.

Based on the data presented in this study, LEDA demonstrated efficacy in the studied endpoints and resulted in no significant safety concerns.

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