CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206976Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 206976
Supplement #:	SN044
Drug Name:	LICART (Diclofenac epolamine) topical system
Indication(s):	Treatment of minor sprains, strains and contusions
Applicant:	Institut Biochimique SA (IBSA)
Date(s):	Submission: June 25, 2018 PDUFA: December 25, 2018 Primary Review Due: November 16, 2018
Review Priority:	Standard (Class 2)
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Kate Meaker, M.S.
Concurring Reviewers:	David Petullo, M.S. - Team Leader
Medical Division:	Division of Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Clinical Team:	Christina Fang, M.D. – Clinical Reviewer Joshua Lloyd, M.D. – Clinical Team Leader
Project Manager:	Sandy Truong, PharmD.

Regulatory Pathway: Resubmission to address Complete Response for original submission

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1. OVERVIEW

This application is a resubmission in response to a Complete Response letter issued on March 24, 2017. The clinical reason given in the letter was:

> *The product used in the clinical studies was manufactured at a different facility than the to-be-marketed product. You have not provided adequate information (refer to the Biopharmaceutics section below) to bridge these two products in order to establish the safety and effectiveness of the to-be-marketed product.*
>
> *Information needed to resolve the deficiency*
> *Conduct at least one adequate and well-controlled clinical efficacy trial to demonstrate the safety and effectiveness of the to-be-marketed product manufactured at the proposed commercial manufacturing site,* (b) (4) *We recommend that you discuss the design of this study with the Division in advance.*

The CR letter was discussed at a Type A meeting on October 5, 2017. The manufacturing site of the products used in the clinical studies (Teikoku Seiyaku) was still manufacturing the Licart (b) (4) for IBSA (marketed in Switzerland). In the original submission for Licart, the applicant planned to switch manufacturing to the (b) (4) After receiving the CR letter, the applicant decided to continue production of Licart at the Teikoku Seiyaku site until after approval. A post-marketing supplement regarding switching manufacturing sites could be submitted later. The Agency agreed that documentation that the materials, processes, and equipment at the Teikoku Seiyaku were unchanged from the clinical batches and the registration batches, along with comparative dissolution studies, would be sufficient to address the clinical deficiency. That information was submitted in this resubmission. There was no new clinical study data to be reviewed.

My review of the original submission focused on results from two Phase 3 studies that were conducted to support the efficacy of LICART (b) (4) (DHEP+Heparin) for the treatment of acute pain due to minor sprains, strains, and contusions. The studies, FHp03 and FHp11, were factorial designs, with both an active-control (Flector patch) and a placebo-control comparator arms. Study FHp03 enrolled subjects with a severe ankle sprain, and Study FHp11 enrolled subjects with a mild to moderate contusion to the upper or lower limb (shoulder, arm, hand, leg or foot). Pain on movement was the primary efficacy measure and change from baseline to Day 3 was the primary efficacy endpoint in both studies.

In both studies the primary comparison was to test superiority of Licart vs. Flector for the reduction of pain on movement from baseline to Day 3. If superiority was shown, each of the active treatment arms (Licart and Flector) would be tested for superiority vs. placebo. Analysis of Covariance (ANCOVA) models were used to perform the tests. The results showed that Licart was statistically superior to both Flector and to placebo for the reduction of pain on movement.

The resubmission did not contain any new clinical study data. This review covers only the revised label submitted with the resubmission, based on the analyses and conclusions from my original review (February 10, 2017).

2. LABEL REVEIW

The two Phase 3 studies reviewed to support efficacy should be described individually, with details on the type and severity of injury, length of treatment, sample size, efficacy outcome, and the conclusion that the Licart group was superior to placebo. From my statistical point of view, it would also be acceptable to include a comment that Licart showed superiority to Flector Patch.

In the label dated September 20, 2018, the applicant proposed the following indication statement: "LICART (b) (4) is indicated for the topical treatment of acute pain due to minor strains, sprains, and contusions."

I agree with the proposed indication.

(b) (4)

(b) (4)

(b) (4)

The above description and results for the two studies are not consistent with wording or presentation for products with this indication. (b) (4) The clinical team will decide on the preferred wording and level of detail.

The clinical study description should be changed to include only the two clinical studies which were designed with pain on movement as the primary endpoint. (b) (4)

FLECTOR PATCH is also owned by the applicant, and they plan to continue to market it. Both efficacy studies included comparisons to that active-control arm, with an appropriate closed testing method to control the overall level of significance. However, in these two studies FLECTOR PATCH (b) (4) which indicated BID dosing rather the once a day. (b) (4) However, if the results are presented it should be made clear that FLECTOR PATCH (b) (4)

(b) (4) Also, Figure 1 should consolidate the two sources (CRF, Diary) for each treatment arm.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KATHERINE B MEAKER
11/16/2018

DAVID M PETULLO
11/16/2018
I concur.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA Serial Number: NDA 206-976 / 0009

Drug Name: LICART (b) (4) (Diclofenac 1.3% (b) (4)

Indication(s): Treatment of minor sprains, strains and contusions

Applicant: Institut Biochimique SA (IBSA)

Date(s): Received: May 26, 2016
PDUFA: March 24, 2017

Review Priority: Standard

Biometrics Division: Division of Biometrics II

Statistical Reviewer: Kate Meaker, M.S.

Concurring Reviewers: David Petullo, M.S. - Team Leader

Medical Division: Division of Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Clinical Team: Christina Fang, M.D. – Clinical Reviewer
Joshua Lloyd, M.D. – Clinical Team Leader

Project Manager: Spiros Nichols, PharmD, MBA, R.Ph

Keywords: NDA review**,** clinical studies;;

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1. EXECUTIVE SUMMARY

This application contains three Phase 3 studies intended to show efficacy of LICART (b) (4) (DHEP+Heparin) for the treatment of acute pain due to minor sprains, strains, and contusions. Two of the studies, FHp03 and FHp11, were factorial designs, with both an active-control (Flector patch) and a placebo-control comparator arms. Study FHp03 enrolled subjects with a severe ankle sprain, and Study FHp11 enrolled subjects with a mild to moderate contusion to the upper or lower limb (shoulder, arm, hand, leg or foot). Pain on movement was the primary efficacy measure, and change from baseline to Day 3 was the primary efficacy endpoint. The third study (18-12-98) was a placebo-controlled study which enrolled subjects with a severe ankle sprain. However, the primary objective of this study was to show a reduction in edema or swelling. Pain was a secondary outcome and was not evaluated on movement. The results of this study were considered supportive and are not discussed in this review. Thus the focus of my review will be studies FHp03 and FHp11

In both studies reviewed to support efficacy the primary comparison was to test superiority of Flector-H vs. Flector for the reduction of pain on movement from baseline to Day 3. If superiority was shown, each of the active treatment arms (Flector-H and Flector) would be tested for superiority vs. placebo. The results showed that Flector-H was statistically superior to both Flector and to placebo for the reduction of pain on movement.

I encountered two issues during my review of this application. The first involved data quality, particularly regarding collection of discontinuation information. Study FHp03 listed the number of discontinuations, but did not provide reasons in the data sets. Study FHp11 only reported discontinuations for centers in Germany but approximately 63% of the subjects enrolled were at centers in the Czech Republic. I considered the impact of this missing information on the results and decided it was not big enough to change the conclusions (low number of recorded dropouts; daily diary data was available for most discontinued subjects for imputation).

The second concern was that there were notable differences in the magnitude of the treatment effect across the five European countries in the two main efficacy studies. However, the direction and size of the between-group comparisons was similar, suggesting the relative efficacy of the three treatments was consistent across populations.

In the clinical overview, the Applicant reported that the clinical studies show Licart (Flector-H) (b) (4) has better efficacy and a similar safety profile as Flector (Flector) patch. Based on my review of studies FHp03 and FHp11, there is sufficient evidence to conclude the Flector-H patch has superior efficacy than the Flector patch. The safety review is being done by Dr. Yang, the clinical reviewer, so I will defer to her review regarding the safety profile.

2. INTRODUCTION

2.1 Overview

This application is for a gel topical analgesic (b) (4) containing diclofenac epolamine (DHEP) and heparin. DHEP is a salt of diclofenac, a non-steroidal anti-inflammatory drug marketed since 1990. The applicant, Institut Biochimique SA or IBSA, is filing this NDA using a 505(b)(2) pathway referencing NDA 21-234, Flector® (diclofenac epolamine) Patch, which is owned by IBSA. Flector Patch is a topical formulation of DHEP which was approved in 2007 and is marketed in the US by Alpharma Pharmaceuticals LLC, a subsidiary of Pfizer. The proposed indication is for the topical treatment of acute pain due to minor strains, sprains, and contusions. This is the same indication as Flector Patch. The proposed name for the current product is Licart® (b) (4)

Heparin is an anticoagulant used for local treatment of minor injuries, contusions, and bruises. The applicant contends that the heparin in Licart (b) (4) is infused in the gel of the (b) (4), and improves absorption of the DHEP into the skin, without actually being absorbed by the skin itself. This rational will be addressed by other scientific reviewers. The clinical staff agrees that this is not a combination drug because heparin is not absorbed subcutaneously.

Licart is a 10x14 cm (b) (4) that according to the applicant provides continuous release of DHEP over 24 hours. In the clinical studies patients replaced the patch each morning. The active-comparator, Flector (Flector Tissugel® 1%), is designed to provide continuous release over 12 hours, and the approved label directions direct patients to replace the patch every 12 hours to the most painful area.

The applicant's first interaction with DAAAP regarding this product was the pre-IND meeting on May 10, 2011. The clinical studies they proposed to submit to support efficacy had already been completed. The summary information in the meeting package did not provide sufficient detail to make a decision on the adequacy of the studies. The Agency advised the sponsor to submit the protocols and statistical analysis plans, which they did in 2012.

This NDA was initially submitted on March 4, 2015 (SN0000). Information requests were sent regarding the need for efficacy datasets and subgroup analyses. The SAS datasets for the clinical studies were submitted on March 25, 2015 (SN0001) and the subgroup analyses were submitted on April 13, 2015 (SN0006). The Agency issued a Refuse-to-file (RTF) letter to IBSA on April 29, 2015.

One concern in the RTF letter was that all clinical trials were conducted outside of the US, with advice that the applicant "must provide a justification as to how the results of these trials can apply to the US population. Include in your justification factors such as demographics, diagnostic criteria used in the studies, and standard of care for the injuries studied." The rationale was provided and discussed at the Post Action meeting (August 25, 2015) and was acceptable to the Agency.

This application contains three Phase 3 studies intended to demonstrate the efficacy of LICART (b) (4) for the treatment of acute pain due to minor sprains, strains, and contusions. Two of the studies were factorial designs, with both an active-control (Flector patch) and a placebo-control comparator arms. Study FHp03 enrolled subjects with a severe ankle sprain, and Study FHp11 enrolled subjects with a mild to moderate contusion to the upper or lower limb (shoulder, arm, hand, leg or foot). Pain on movement was the primary efficacy measure, and change from baseline to Day 3 was the primary efficacy endpoint.

The third study (18-12-98) was a placebo-controlled study which enrolled subjects with a severe ankle sprain. It was designed to show reduction in edema (swelling) as the primary efficacy outcome, and subjects were not instructed to move the injured joint to assess pain. Dr. Yang referred to this as assessing spontaneous pain, rather than pain on movement. The results from this study are not discussed in my review.

The focus of my review will be Studies FHp03 and FHp11, the two studies which had pain on movement as primary efficacy endpoints. In both studies the primary comparison was to test superiority if Flector-H vs. Flector for the reduction of pain on movement from baseline to Day 3 on treatment. If superiority was shown, each of the active treatment arms (Flector-H and Flector) would be tested for superiority vs. placebo. Analysis of Covariance (ANCOVA) models were used to perform the tests.

2.2 Data Sources

All data was submitted electronically by the applicant to the CDER electronic data room (edr) in SAS transport format. Information requests (IRs) were needed to acquire SAS code, documentation, and explanations to access the information I needed. The safety datasets were updated for the resubmission. Efficacy datasets had been submitted in March, 2015, and were not updated for the resubmission. Information on dropouts due to adverse events was recorded in the safety datasets, which I needed to link back to the efficacy datasets. Due to inconsistent subject ID coding and variable names in the efficacy datasets, I requested an updated dataset with all disconsolation information merged. Instead the applicant sent SAS code to generate the combined data and merge adverse event records.

The final study reports for the electronic submission are archived under the network path location: \\Cdsesub1\evsprod\NDA206976\0000. The efficacy data sets were submitted in response to an Information Request letter dated March 23, 2015 and are archived at \\Cdsesub1\evsprod\NDA206976\00001. The ISS and corresponding safety datasets are archived at: \\Cdsesub1\evsprod\NDA206976\0009.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The two studies, FHp03 andFHp11, reviewed to support efficacy were conducted 10 or more years prior to being submitted. The datasets were not in standard formats, did not have consistent variable names, and were not well organized or documented. Tables in the study reports were not linked to the source data sets. A substantial amount of time was required to recreate the necessary records to confirm the calculation of pain endpoints and the LOCF imputation which the applicant had performed.

The applicant provided SAS code to assist with identifying adverse events that corresponded with dropouts. For study FHp03, discontinuation reasons were not included in the submitted datasets; for study FHp03, discontinuation reasons were not captured for centers in the Czech Republic.

3.2 Evaluation of Efficacy

3.2.1 Study 06EU/FHp03

The applicant refers to this as Study S-11, but that identifier is confusing given the numbering of the other Phase 3 study. Therefore in my review I will refer to it as study FHp03.

Study Design and Endpoints

Study FHp03 was a multicenter, randomized, double-blind, parallel group design. It included three treatment arms: Flector-H patch; Flector patch, and placebo patch. It was conducted in 2007 at 3 sites in Italy, 4 sites in Poland, and 6 sites in Ukraine.

Eligible subjects were adults, ages 18-65 who experienced a severe ankle sprain within 48 hours prior to enrollment in the study. The severity of the ankle sprain was determined by pain on movement (at least 50 mm on a 0-100mm visual analog scale), along with presence of swelling, Patients that required orthopedic or surgical treatment were excluded. Prior treatment with ice packs was acceptable, but no other previous treatment was allowed.

After screening and randomization (Visit 1), subjects had the first patch applied in the office by the clinician. Subjects were instructed to keep the patch on continuously, and to change the patch in the morning each day. Subjects returned to the clinic on Days 3 and 7. Pain on movement, pain at rest, and pain when leaning on injured leg were recorded using a 0-100 mm VAS scales twice daily (am/pm) in a log book, along with use of rescue and other relevant information. The log book pain assessments were collected at the clinic visits and were used in the planned efficacy analyses.

The primary efficacy variable was defined as change from baseline to Day 3 for pain on movement. Change from baseline to Day 7 for Pain on movement was a secondary endpoint. An ANCOVA model with treatment as the factor and baseline as the covariate was used for all between group comparisons. The pre-specified primary comparison was superiority of Flector-H to Flector patch. Comparisons of each active arm to placebo were secondary.

Subjects were randomized at a 1:1:1 ratio to the three treatment groups. A total of 430 were randomized to receive study treatment (142 Flector-H; 146 Flector; 142 placebo). The primary efficacy variable was change from baseline to Day 3 for pain on movement (100mm VAS), and the primary comparison of interest was superiority of the Flector-H patch to the Flector patch. The applicant assumed a difference between the two active treatment groups of 6.5 mm with a standard deviation of 16, using an $\alpha = 0.05$ two-sided test, and power of 90%. The calculation was based on information from previous studies. The enrolment of 420 patients (140 per group) would allow for a dropout rate of approximately 10% and provide at least 128 patients per group.

Patient Disposition, Demographic and Baseline Characteristics

A total of 430 subjects were randomized and received study treatment. As shown in Table 1, only seven discontinued overall. One did not receive treatment. Three were lost to follow-up at the Day 3 clinic visit, while a fourth had no pain data recorded in the clinic visits or logbook. These five were excluded from the applicant's efficacy analyses as defined in the protocol. Two others discontinued after Day 3 but prior to Day 7. There was no documentation as to why these two patients discontinued treatment. Last observation carried forward (LOCF) was applied to include these in all analyses.

Table 1: Patient Disposition (Study FHp03)

	Flector-H	**Flector**	**Placebo**
Randomized	142 (100%)	146 (100%)	142 (100%)
Received Study Treatment	142 (100%)	145 (99%)	142 (100%)
Discontinued Prior to Day 3 No Pain Scores Recorded	0	1 (1%) 1 (1%)	2 (1%)
Protocol Defined Intent-to-Treat	142 (100%)	143 (98%)	140 (99%)
Discontinued between Day 3 and Day 7 LOCF imputation applied from Day 3 or later logbook pain scores if available. No reasons for discontinuation were given in datasets.	1 (1%)	0	1 (1%)

Source: Reviewer, ADSL.xpt and LOGBOOK.xpt datasets
All percentages are calculated based on Randomized N per group as denominator.

Baseline Demographics

The three treatment groups were well balanced with respect to relevant demographic and baseline characteristics as shown in Table 2.

Table 2: Demographic and Baseline Injury Characteristics

All Treated	**Flector-H N=142**	**Flector N=145**	**Placebo N=142**
Age (years)			
Mean (SD)	35 (13)	35 (13)	35 (13)
Range	18 – 65	18 – 64	18 – 63
Gender			
Female	61 (43%)	57 (39%)	57 (40%)
Male	81 (57%)	88 (61%)	85 (60%)
Race			
Caucasian	141 (99%)	142 (98%)	140 (99%)
Black	0	1 (1%)	0
Asian	1 (1%)	1 (1%)	0
Other	0	1 (1%)	2 (1%)
Country			
Italy	11 (8%)	13 (9%)	12 (8%)
Poland	87 (61%)	86 (59%)	84 (59%)
Ukraine	44 (31%)	47 (32%)	46 (32%)
Weight (kg)			
Mean (SD)	75 (14)	77 (14)	76 (15)
Range	48 – 110	45 – 118	42 – 119
BMI (kg/m^2)			
Mean (SD)	25 (4)	25 (4)	25 (5)
Range	18 – 34	17 – 39	17 – 40
Baseline Ankle Sprain Characteristics			
Baseline Pain (100 mm VAS)			
Mean (SD)	72 (12)	73 (12)	71 (12)
Range	46 – 96	46 – 99	45 – 100
Injury Severity			
Grade I	83 (59%)	79 (54%)	81 (57%)
Grade II	59 (41%)	67 (46%)	61 (43%)
Injury Pretreated (Ice or water)			
Yes	22 (15%)	15 (10%)	14 (10%)
No	120 (85%)	131 (90%)	128 (90%)

Source: Reviewer, Base.xpt dataset

Statistical Methodologies

The protocol specified that the primary efficacy analyses would use the Intent-to-Treat (ITT) population, defined as all randomized subjects who received at least one dose of treatment and had at least one on-treatment pain assessment. The protocol also specified that Last Observation Carried Forward (LOCF) imputation would be applied to all missing values during the treatment period. Neither excluding subjects without on-treatment assessments nor LOCF are the currently preferred approaches, but did not impact the results or conclusions in this study.

The statistical analyses described in the protocol used an analysis of variance (ANOVA) model with treatment as the single term in the model. The clinical study report presented results using an analysis of covariance (ANCOVA) model with treatment and baseline pain terms in the model. In both cases, the single primary comparison was a superiority test of Flector-H to Flector. Comparisons of each of the active treatment groups to placebo on the primary endpoint were planned as secondary analyses. The same ANCOVA model was used. There was no adjustment for multiplicity.

The applicant reported results for other secondary outcomes: pain at rest; pain on leaning; and perimalleolar edema (swelling) which are not of interest to the clinical reviewer, Dr. Fang. She requested results on the percentage of subjects who used rescue (paracetamol) as the only other efficacy outcome to report.

Results and Conclusions

For the efficacy endpoints, the primary analyses used the intent-to-treat (ITT) population, which included all randomized patients who received at least one dose of study medication and for whom there was at least one post-baseline efficacy assessment. The preferred ITT population would include all randomized and treated patients. Six subjects were randomized and not included in the ITT population (4 in Flector group; 2 in placebo group). One patient in the Flector group did not receive treatment. The other five had no post-baseline efficacy measures. I deemed this not to have an impact of the efficacy conclusions.

Table 3 presents the applicant's results, along with additional endpoints of interest to the clinical reviewer, Dr. Fang. Using either the ANOVA or ANCOVA model, the conclusions were the same and the results almost identical. On the primary efficacy endpoint, at Day 3 on treatment, the Flector-H treatment group was statistically significantly better than the Flector treatment group (p=0.002) and both active treatment groups were superior to placebo. The magnitudes of the treatment differences were also consistent at Day 7. There was no notable difference in the proportion of subjects who used rescue.

Table 3: Efficacy Analysis Results

ITT Subjects		Flector-H N=142	Flector N=142	Placebo N=140
Pain on Movement Unadjusted Mean (SD)	Baseline	72 (12)	73 (12)	71 (12)
	Day 3	48 (18)	54 (18)	58 (17)
	Day 7	18 (14)	24 (18)	27 (21)
	Baseline to Day 3:	-24 (16)	-19 (17)	-14 (13)
	Baseline to Day 7:	-54 (16)	-49 (19)	-44 (20)
Primary Efficacy: [a] **Change from Baseline to Day 3 for Pain on Movement (ANCOVA model)**	Adjusted Mean	-24	-19	-14
	Diff.: Flector-H. vs. Flector	-5		
	(p-value)	0.002		
	Diff. vs. placebo	-11	-5	
	(p-value)	<0.001	0.005	
Secondary Efficacy: [a] **Change from Baseline to Day 7 for Pain on Movement (ANCOVA model)**	Adjusted Mean	-54	-49	-45
	Diff.: Flector-H. vs. Flector	-5		
	Diff. vs. placebo	-9	-4	
Secondary: Proportion Who Took Rescue (paracetamol)	Baseline to Day 3: Yes (%)	98 (69%)	103 (73%)	104 (74%)
	Baseline to Day 7: Yes (%)	104 (73%)	109 (77%)	107 (76%)

Source: Reviewer, CSR Tables T18.1.1, T19.1, T23.3; Logbook.xpt; Rescue.xpt

[a] The adjusted means and p-values were obtained from ANCOVA model including effects for treatment and baseline pain.

Based on these results, study FHp03 does provide evidence to support the efficacy of Flector-H patch for the treatment of pain from severe ankle sprains.

3.2.2 Study 05DCz/FHp11

The applicant refers to this as Study S-10, but again that identifier is confusing given the numbering of the other Phase 3 study. I will refer to this as study FHp11.

Study Design and Endpoints

Study FHp11 was a multicenter, randomized, double-blind, parallel group design. It included three treatment arms: Flector-H patch; Flector patch, and placebo patch. It was conducted from June 2006 through May 2007 at 9 sites in Germany and 9 sites in the Czech Republic.

Eligible subjects were adults, ages 18-65, who experienced a mild-to-moderate muscle contusion to the upper or lower limbs within 72 hours prior to enrollment in the study. Eligibility was limited to Caucasians, presumably because one of the applicant's endpoints of interest involved recording colors present in the skin to assess disappearance of bruising. A mild contusion was defined as localized tenderness with near-normal associated joint range of movement. Moderate muscle contusion was defined as swollen and tender muscle mass, with at least 75% normal range of motion. The injury could not require orthopedic or surgical treatment, but treatment with ice packs during the first two days on study was acceptable. The maximum size of the superficial hematoma (area of bruised skin and soft tissue) was 10x14 cm, the dimensions of the treatment patch.

At the screening visit, each subject identified the most painful "specific standardized movement" of the injured limb, which was documented by the clinician. The subject had to report a minimum pain score of 50 on the 0-100 VAS scale at screening for the identified movement, and was instructed to repeat the same movement before recording pain in the patient logbook twice (am/pm) each day during the study. The size and colors present in the hematoma and use of rescue (paracetamol) medication were recorded daily

After the screening and randomization (Visit 1), subjects had the first patch applied in the office by the clinician. Subjects were instructed to keep the patch on continuously, and to change the patch in the morning each day. Subjects returned to the clinic on day 8 and Day 15. The logbook pain assessments were collected at the clinic visits and were used in the planned efficacy analyses.

The primary efficacy variable was defined as change from baseline to Day 3 for pain on movement. Time until disappearance of the superficial hematoma (defined as first day only yellow or normal skin tone colors were present) was a secondary endpoint pre-specified in the protocol.

An ANCOVA model with treatment and center as factors, and baseline as the covariate, was used for between group comparisons on the pain outcomes. The pre-specified primary comparison was superiority of Flector-H to Flector patch. Comparisons of each active arm to placebo were secondary.

For the efficacy endpoint, the primary analyses used the ITT population, which included all randomized patients who received at least one dose of study medication and for whom there was at least one post-baseline efficacy assessment. This not the preferred ITT definition, which would include all randomized. Only one subject, in the placebo group, withdrew consent after being randomized but before using the patch. That subject was not included in the ITT population.

Subjects were randomized in a 1:1:1 ratio to the three treatment groups. A total of 355 subjects were randomized to receive study treatment (121 Flector-H; 115 Flector; 119 placebo). The primary efficacy variable was Change from baseline to Day 3 for pain on movement (100mm VAS), and the primary comparison of interest was superiority of the Flector-H patch to the Flector patch. The applicant assumed a difference between the two active treatment groups of 7.5 mm with a standard deviation of 18, using an $\alpha = 0.05$ two-sided test, and power of 80%. This information was from previous studies conducted by the applicant. The enrolment of 330 patients (110 per group) would allow for a dropout rate of approximately 15% and provide at least 92 patients per group. In the protocol, the sample size calculation was also performed for the "time to hematoma disappearance" endpoint, but this was not mentioned in the study report. Although this endpoint was pre-specified, it was deemed not have any clinical relevance, this endpoint is not discussed in my review.

Patient Disposition, Demographic and Baseline Characteristics

A total of 355 subjects were randomized and received study treatment. As shown in Table 4, one subject in the placebo group did not have on-treatment pain measures (withdrew consent after randomization). All other randomized subjects were included in ITT population for the efficacy analyses.

There were no notable differences across the three groups for the reasons given for discontinuation. "Other" reasons included lost study patches, patches applied to other injury, no fun, and unspecified.

Table 4: Patient Disposition (Study FHp11)

	Flector-H	**Flector**	**Placebo**
Randomized (All received treatment)	121 (100%)	115 (100%)	119 (100%)
Withdrew Consent (Day 1) No On-treatment Pain Scores Recorded	0	0	1 (1%)
Protocol Defined Intent-to-Treat	121 (100%)	115 (100%)	118 (99%)
Discontinued During Treatment			
Adverse Event	0	2 (2%)	2 (2%)
Lack of Efficacy	0	1 (1%)	0
Patient reported "Recovered/No pain"	4 (3%)	4 (3%)	2 (2%)
Other	1 (1%)	1 (1%)	6 (5%)
Total Discontinued	5 (4%)	8 (7%)	10 (8%)

Source: Reviewer, ADSL.xpt dataset and CSR Table 10.1.1 and Table 11.1.2
All percentages are calculated based on Randomized N per group as denominator.

It was noted that all subjects that discontinued from the study were enrolled at centers in Germany with none noted as discontinuing at sites in the Czech Republic. Since study was conducted 10 years ago, the value of inspecting sites was limited and there was little information to be gained from investigating this difference in discontinuation rates.

Baseline Demographics

The three treatment groups were well balanced with respect to relevant demographic and baseline characteristics as shown in Table 5.

Table 5: Demographic and Baseline Injury Characteristics

All Treated	**Flector-H N=121**	**Flector N=115**	**Placebo N=118**
Age (years)			
Mean (SD)	39 (15)	40 (14)	38 (14)
Range	18 – 75	18 – 66	18 – 65
Gender			
Female	46 (38%)	39 (34%)	41 (35%)
Male	75 (62%)	76 (66%)	77 (65%)
Race			
Caucasian	121 (100%)	115 (100%)	118 (100%)
Country			
Czech Republic	78 (64%)	72 (63%)	73 (61%)
Germany	43 (36%)	43 (37%)	47 (39%)
Weight (kg)			
Mean (SD)	77 (15)	77 (14)	78 (17)
Range	47 – 140	40 – 110	49 – 140
BMI (kg/m^2)			
Mean (SD)	25 (4)	25 (3)	26 (4)
Range	16 – 39	17 – 39	19 – 42
Baseline Injury Characteristics			
Baseline Pain (0-100 mm VAS)			
Mean (SD)	68 (11)	67 (11)	68 (12)
Range	34 – 99	35 – 95	47 – 100
Injury Location			
Upper Limb (Arm/Hand)	31 (26%)	34 (30%)	34 (29%)
Lower Limb (Leg/Foot)	90 (74%)	81 (70%)	84 (71%)
Injury Severity			
Mild	32 (26%)	30 (26%)	31 (26%)
Moderate	89 (74%)	85 (74%)	87 (74%)
Injury Pretreated			
Yes	1 (1%)	3 (3%)	1 (1%)
No	120 (99%)	112 (97%)	117 (99%)

Sources: CSR Tables T05 and T07

Statistical Methodologies

The protocol pre-specified that the primary efficacy analyses would use the ITT population which was defined as all randomized subjects who received at least one dose of treatment and had at least one on-treatment pain assessment. The protocol also specified that last observation carried forward (LOCF) imputation would be applied to all missing values during the treatment period. Neither excluding subjects without on-treatment assessments nor LOCF are the currently preferred approaches, but did not impact the results or conclusions in this study.

The statistical analyses described in the protocol used an analysis of variance (ANCOVA) model with treatment as factor and baseline pain as the covariate in the model. The clinical study report presented results using an ANCOVA model with treatment, center, and baseline pain terms in the model. The protocol listed several potential variables to be considered in exploratory analyses, including center, country, area of injury, age, weight, etc. The study report did not provide details on when the decision to report the alternative model with center added was made.

The single primary comparison was a superiority test of Flector-H to Flector. Comparisons of each of the active treatment groups to placebo on the primary endpoint were planned as secondary analyses. The same ANCOVA model was used. There was no adjustment for multiplicity.

The applicant reported results for secondary outcomes (time to superficial hematoma disappearance, day-by-day pain reduction, and global assessments) which are not of interest to the clinical reviewer, Dr. Fang. She is interested in the percentage of subjects who used rescue (paracetamol).

Results and Conclusions

Table 6 presents my results from the ANCOVA model planned in the protocol. On the primary efficacy endpoint, at Day 3 on treatment, the Flector-H treatment group was statistically significantly better than the Flector treatment group ($p<0.001$) and both active treatment groups were superior to placebo. The applicant's results, using an ANCOVA model which included CENTER, are discussed in Table 7. Analyses conducting using an ANCOVA model with or without CENTER as a factor did not change the conclusion that Flector-H was significantly different from Flector.

The proportion of subjects who used rescue medication was slightly lower in the Flector-H treatment group than for the other groups, but it was not noteworthy. Rescue use overall was much lower in this study than in study FHp03.

Table 6: Efficacy Analysis Results (Study FHp11)

ITT Subjects		Flector-H N=121	Flector N=115	Placebo N=118
Pain on Movement Unadjusted Mean (SD)	Baseline	68 (11)	67 (11)	69 (12)
	Day 3	49 (21)	56 (17)	64 (16)
	Day 8	25 (17)	32 (20)	40 (20)
	Day 15	9 (13)	13 (15)	17 (17)
	Baseline to Day 3:	-18 (18)	-10 (13)	-4 (15)
	Baseline to Day 8:	-42 (17)	-35 (21)	-28 (22)
	Baseline to Day 15:	-59 (16)	-54 (19)	-51 (20)
Primary Efficacy: [a] **Change from Baseline to Day 3 for Pain on Movement (Planned ANCOVA model: Trmt + Baseline Pain)**	Adjusted Mean	-18	-10	-4
	Diff.: Flector-H. vs. Flector	-8		
	(p-value)	<0.001		
	Diff. vs. placebo	-14	-6	
	(p-value)	<0.001	0.007	
Secondary: Proportion Who Took Rescue (paracetamol)	Baseline to Day 15: Yes (%)	12 (10%)	17 (15%)	20 (17%)

Source: Reviewer, CSR Tables T12.1.1, T18; Painlog.xpt, Rescue.xpt

[a] The adjusted means and p-values were obtained from ANCOVA model including effects for treatment and baseline pain.

Because almost two-thirds of the subjects were enrolled in the Czech Republic, and none of those centers reported any dropouts, I investigated any potential efficacy differences by country. As shown in Table 7, the mean change from Baseline to Day 3 was larger in Germany than in Czech Republic across all the treatment groups. There was a significant effect due to country ($p<0.001$) but no significant interaction between treatment and country ($p=.81$). When adjusted for Country in the ANCOVA model, the results of the between-group comparisons were consistent with the primary analysis in Table 6. The Flector-H treatment group was statistically significantly better than the Flector treatment group ($p<0.001$) and both active treatment groups were superior to placebo.

Table 7: Efficacy Analysis Results by Country (Study FHp11)

ITT Subjects		**Flector-H**	**Flector**	**Placebo**
Czech Republic		**N=78**	**N=72**	**N=73**
Pain on Movement Unadjusted Mean (SD)	Baseline	67 (10)	66 (9)	66 (10)
	Day 3	50 (22)	59 (14)	64 (15)
	Baseline to Day 3:	-16 (18)	-7 (12)	-2 (14)
Germany		**N=42**	**N=43**	**N=45**
Pain on Movement Unadjusted Mean (SD)	Baseline	69 (13)	68 (13)	72 (13)
	Day 3	48 (21)	53 (20)	63 (16)
	Baseline to Day 3:	-22 (16)	-15 (14)	-9 (17)
Change from Baseline to Day 3 for Pain on Movement [a] (ANCOVA model: Trmt + Country + Base Pain)	Adjusted Mean	-19	-11	-5
	Diff.: Flector-H. vs. Flector	-8 <0.001		
	Diff. vs. placebo	-14 <0.001	-6 0.006	

Source: Painlog.xpt

[a] The adjusted means and p-values were obtained from ANCOVA model including effects for treatment, country, and baseline pain.

Based on the efficacy results, study FHp11 does provide evidence to support the efficacy of Flector-H patch for the treatment of pain from mild to moderate muscle contusions. The questionable differences in dropout rates between subjects enrolled in Germany and subjects enrolled in Czech Republic (no dropouts) is an uncertainty. However, there was no significant difference in the treatment effect between countries, i.e. the direction and magnitude of the treatment effect was not different.

3.3 Evaluation of Safety

Dr. Fang completed the safety review for this study. She did not request any additional safety analyses.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Age, Gender, and Country

I examined the primary efficacy endpoint in studies FHp03 and FHp011 for differences due to age, sex, and country. Results are shown in Tables 8 and 9. As discussed in the demographics sections (Tables 2 and 5), almost all the subjects were Caucasian, so I did not report subgroup results by race. There were very few subjects over 65 years of age. Both efficacy studies were conducted at sites in Europe.

Table 8: Subgroup Analyses: Age, Gender and Country (Study FHp03) – Reviewer's Results

Change from Baseline to Day 3	**Study FHp03**		
Pain on Movement	DHEP-Heparin	DHEP alone	Placebo
N Mean (SD)	N=142	N=142	N=140
Age group			
≤ 65 years	N=142 -25 (16)	N=142 -19 (17)	N=117 -14 (13)
> 65 years	N=0	N=0	N=0
Sex			
Female	N=61 -26 (15)	N=57 -20 (17)	N=57 -13 (11)
Male	N=81 -23 (17)	N=85 -18 (17)	N=83 -14 (14)
Country			
Italy	N=11 -32 (17)	N=11 -27 (26)	N=12 -13 (19)
Poland	N=67 -27 (18)	N=65 -19 (19)	N=62 -14 (15)
Ukraine	N=64 -20 (11)	N=66 -18 (12)	N=66 -13 (9)

Source: Reviewer

Table 9: Subgroup Analyses: Age, Gender and Country (Study FHp11) – Reviewer's Results

Change from Baseline to Day 3 Pain on Movement	**Study FHp11**		
	DHEP-Heparin	DHEP alone	Placebo
N	N=121	N=115	N=119
Mean (SD)			
Age group			
≤ 65 years	N=114	N=114	N=117
	-18 (18)	-10 (13)	-4 (15)
> 65 years	N=5	N=1	N=0
	-15 (11)	-8	
Sex			
Female	N=46	N=39	N=41
	-15 (15)	-11 (12)	-6 (16)
Male	N=73	N=76	N=76
	-20 (19)	-10 (14)	-4 (15)
Country			
Czech Republic	N=77	N=72	N=73
	-16 (18)	-7 (12)	-2 (14)
Germany	N=42	N=43	N=44
	-22 (16)	-15 (14)	-9 (17)

Source: Reviewer

The only notable difference in the subgroup tables is that the size of the mean pain reduction differed across the countries. Within each country, the Flector-H group had a larger change from baseline than the other two groups.

These are descriptive analyses only and are not intended for inferential purposes. The Flector-H treatment group consistently showed more pain reduction from baseline to Day 3 than the Flector or placebo treatment groups.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

There statistical issues identified in this review included studies which were conducted without Agency input, and were conducted over 10 years prior to review. The data was difficult to work with because there was no consistency in variable names, dataset contents, or organization. Considerable data manipulation was required to complete my review.

One particular concern with the data sets submitted was the inconsistent recording of discontinuation codes and reasons, and the number of days on treatment. The applicant provided SAS code in response to my information request to assist in this. Study FHp03 had dropouts identified, but no reasons were coded in the data sets. Since the study report for FHp11 had listings giving some details for dropouts at the sites in Germany, I was able to match the discontinuation reasons in the data sets to each subject and could get a complete accounting for all subjects that discontinued. There were no dropouts indicated in either the listings or the datasets for centers in the Czech Republic. These studies were conducted 10 years before the application was submitted, so site inspections were not expected to yield much clarification and were not conducted

The applicant provided LOCF imputation, which is not the preferred method. However, in these studies there were very few dropouts before Day 3 so almost all the subjects who discontinued had sufficient information to conduct the efficacy analyses without impacting the conclusions. Also, for discontinuation reasons such as Recovered/NoPain, the LOCF values did not make a difference.

The results of the two phase 3 studies were consistent, Flector-H was superior to Flector with respect to reduction in pain, and both active arms (Flector-H and Flector) were superior to placebo for reduction of pain from baseline to Day 3. Since different types of injuries were treated in each study, the size of the treatment effect was different. This was not unexpected.

Dr. Yang requested I look at use of rescue medication (paracetamol tablets) in each study. The use of rescue was lowest in the Flector-H group and supports the primary efficacy results

5.2 Conclusions and Recommendations

This application contains two prospectively planned, multicenter, randomized, double-blind, active- and placebo- controlled clinical studies to provide evidence of efficacy for Flector-H patch for the treatment of pain due to acute sprains or mild-to-moderate contusions. Both studies were conducted in Europe, but rationale was provided to relate the enrolled subjects to similar patients in the United States.

The quality of the collection of data regarding subjects who discontinued from the studies was the only notable concern in my review. The number of subjects known to have discontinued, and the amount of missing data, were not sufficient to impact the results or conclusions. The possible impact of the unknown potential dropouts in the Czech Republic centers cannot be clearly measured.

Based on the consistent results from Studies FHp03 and FHp11, there is sufficient evidence to support Flector-H for the treatment of acute pain due to minor sprains, strains, and contusions.

5.3 Labeling Recommendations

In the label, these two studies should be described individually, with details on the type and severity of injury, length of treatment, sample size, efficacy outcome, and the conclusion that the Flector-H group was superior to placebo. From my statistical point of view, it would also be acceptable to include a comment that Flector-H showed superiority to Flector. The Figures the applicant has proposed should not be included in the label.

The proposed trade name for the Flector-H patch is LICART (b) (4)

The applicant proposed the following indication statement:
"LICART (b) (4) *is indicated for the topical treatment of acute pain due to minor strains, sprains, and contusions."*

The following is the current proposed language for the Clinical Studies section:

14 CLINICAL STUDIES
14.1 Minor Soft Tissue Injuries (Sprain, Contusion)
(b) (4)

Following this page, 1 Page Withheld in Full as (b)(4)

(b) (4)

The above description and results for the two studies are not consistent with wording or presentation for products with this indication. (b) (4)

FLECTOR PATCH is also owned by the applicant, and they plan to continue to market it. Both efficacy studies included comparisons to that active-control arm, with an appropriate closed-testing method to control the overall level of significance. If the clinical review staff accept making comparative claims to FLECTOR PATCH, it is acceptable from my point of view.

(b) (4)

The clinical study description should be changed to include (b) (4)

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/s/

KATHERINE B MEAKER
02/10/2017

DAVID M PETULLO
02/10/2017
I concur.