CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-234

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

SECONDARY REVIEW

NDA:	21-234
Name of drug:	Diclofenac Epolamine Patch
Indication:	Treatment of pair [redacted]
Applicant:	Institut Biochimique SA (IBSA)
Submission Date:	July 27, 2006
Review Priority:	Priority
Biometrics Division:	Division of Biometrics II
Statistical reviewer:	Barbara Elashoff
Statistics team leader:	Dionne L. Price, Ph.D.
Medical Division:	Division of Anesthesia, Analgesia, and Rheumatology Products
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Keywords: NDA review, clinical studies, missing data

1 BACKGROUND

NDA 21-234 was originally submitted to the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products on 18 December 2000. As a result of numerous deficiencies, the applicant received a non-approval letter on 18 October 2001. The letter included the following:

> *1. The submitted studies fail to demonstrate efficacy of Diclofenac Epolamine Patch (DHEP) for the treatment of the pain ——— On this basis, the submission is not approvable.*
>
> ***a.** Study 49459-01 failed to demonstrate efficacy based on the primary efficacy variables of pain intensity difference (PID), sum of pain intensity difference (SPID), pain on pressure difference (POPD) and sum of pain pressure difference (SPOPD) for days 3, 7, and 14.*
> ***b.** Study 49459-02 failed to demonstrate efficacy. Several deficiencies in this study are noted.*
>
> ***i.** For study 49459-02, when the significant imbalance in body weight (an important potential confounding variable in a study with a large percentage of injuries to weight bearing areas) is incorporated in the analysis of the primary endpoint of time to pain resolution, no significant treatment difference was detected (p=0.072). Mean weight in the placebo group was 4.5 kg higher than the DHEP treated group.*
> ***ii.** The primary endpoint, days to pain resolution is a derivative of the secondary endpoint, daily pain score. The originally submitted analysis of daily pain score was based on a post hoc decision to use 24-hour rather than nominal days on therapy. When the nominal day is used there is not statistically significant difference on way study day. The nominal study day is more relevant in view of the impact of activity and weight bearing on pain following injury. Time of measurement in relation to daily sleep/rest cycle is a critical issue that should be addressed in study design and analysis.*
> ***iii.** All secondary efficacy variables failed to show any significant difference between the treatment groups in study 49459-02. Therefore, study 49459-02 fails to provide adequate evidence of efficacy of the patch, especially in light of failed study 49459-01.*
> ***iv.** Consistency of results for secondary endpoints of average daily pain and patient as well as investigator reported global response to therapy are necessary to fully interpret the clinical benefit proposed based on the derived endpoint of median time to pain resolution.*

The applicant submitted a response on 28 March 2002. However, the response did not adequately address the deficiencies. Currently, Institut Biochimique SA (IBSA) has provided two clinical studies to support the approval of diclofenac epolamine patch. Study 00GB/Fp05 is referred to as the UK/German Study throughout my review. Similarly, Study 05-05-98 is referred to as the French Study.

2 REVIEW

The two clinical studies were reviewed by the primary statistical reviewer, Ms. Barbara Elashoff. During the review cycle, Ms. Elashoff relocated and subsequently terminated her employment with the Food and Drug Administration. She completed her review prior to leaving. However, the review was completed in advance of numerous team meetings regarding the drug. During the meetings, the clinical team requested that additional analyses be conducted. Thus, my secondary review will include the requested analyses in addition to a summary of my findings.

2.1 UK/GERMAN STUDY

Design

In the UK/German Study, four-hundred and eighteen patients (achieving a pain score of five or more on an 11-point scale) were randomized to diclofenac epolamine patch or placebo. Patients were instructed to apply a patch to the injured site twice a day for a two-week period. The level of pain, time of patch removal, use of any rescue medication, and occurrence of adverse events were to be recorded in a dairy upon removal of each patch. The use of topically applied medications, ice bandages, and analgesics was prohibited during the study.

The primary efficacy variable was the time to pain resolution where resolution was defined as the attainment of four consecutive pain scores of two or less. According to the applicant, "[a] blinded examination of the data indicated that patients often reached low pain scores and immediately discontinued the study due to injury resolution, thus failing to reach the designated success endpoint despite a favorable response to treatment." In addition, the applicant stated that the criterion for resolution was arbitrary and not meaningful in a study wherein patients discontinued as soon as attaining a low pain score. Thus, the statistical analysis plan was modified by a statistician blinded to the randomization code. The modified plan specified the mean post-treatment pain score as the primary efficacy variable.

Statistical Methodologies and Patient Disposition

The primary analysis employed an analysis of variance (ANOVA) model with treatment as a factor in the model. Moreover, the mean pain score was divided by the baseline score to account for possible variations in baseline pain. The method of multiple imputation was used as a strategy to handle missing data. Details of the applicant's multiple imputation strategy are provided in the appendix of my review. The applicant performed two secondary analyses. The first analysis used a repeated measures ANOVA model with a last observation carried forward (LOCF) strategy. The second analysis

utilized a generalized estimating equation (GEE) model on all available data. The applicant did not provide additional details regarding the secondary analyses. Ms. Elashoff did not focus on the analyses conducted by the applicant due to a large amount of missing data. While I shared Ms. Elashoff's concern regarding the amount of missing data, I believed further exploration of the methods and reasons for discontinuations was worthwhile.

I initially considered the applicant's proposed multiple imputation strategy. In general, a multiple imputation technique predicts the missing data from correlated non-missing data. When implementing a multiple imputation strategy, observed data are used to construct predictive distributions for the missing data. The missing values are subsequently replaced by random draws from the predictive distributions. An underlying assumption of a multiple imputation strategy is that data is missing at random. Since missing values in pain trials are often informative, there is a general concern regarding the appropriateness of methods such as multiple imputation and LOCF. Specifically in pain trials, patients may experience some relief from pain due to the treatment but may also experience intolerable side effects caused by the treatment. Thus, these patients may have a good score at the time of withdrawal that does not reflect the unfavorable outcome.

As shown in Table 1, there were a substantial number of discontinuations. However, the largest proportion of discontinuations was due to a favorable outcome, namely injury resolution. Moreover, only 3% of study participants discontinued due to adverse events with a greater proportion of patients in the placebo arm experiencing adverse events. I was somewhat concerned that perhaps adverse events could be masked under some of the other categories used to classify discontinuations such as "another therapy" or "withdrawal" (see Table 1). However, the medical team believed it was unlikely that the categories masked unreported adverse events. Ms. Elashoff noted that the applicant presented a second, modified disposition table (see appendix). The applicant's rationale for the modifications is provided below.

> The study discontinuation categories are, for several reasons, slightly different from those proposed in the protocol and for which data were captured in the Exit Visit – Reason for Discontinuation CRF. First, one of the original Reason for Discontinuation categories (Study Admission Problems such as inappropriate enrollment, non-compliance with the protocol schedule, or a need for a concurrent medication prohibited by the protocol) seemed not only excessively broad but somewhat confusing since the latter two examples of a "study admission problem" should more accurately be termed "post admission problems", if indeed the requirement for a rescue medication could even be considered a "problem". Secondly, the original listing also included "Discontinued in Favor of Another Therapy" which not only fails to identify the other therapy but may have captured patients who required a "concurrent medication prohibited by the protocol". An example of the latter include patients 21-015 and 18-338 (both of whom took concurrent pain medications prohibited by the protocol at the time of patch discontinuation and exit from the study) who were originally classified as "Discontinued in Favor of Another

Therapy" which was changed to "Withdrew Unresolved" (i.e. withdrew with a pain score of 3 or more). Thirdly, the new listing more accurately characterizes the actual reasons the patients discontinued the study. To illustrate, there were 17 patients originally designated "Discontinued Due to Injury Resolution" but were reclassified as "Completed 14 Days of Therapy" since they had applied a patch for at least 14 days, as were another 28 patients who were also treated for 14 days but were originally classified as "Study Admission Problems".

Ms. Elashoff's analyses were conducted using the protocol-defined reasons for discontinuation (Table 1). Thirty-one of the 418 randomized patients did not have diary data and were excluded from the applicant's primary and secondary analyses. The disposition of those patients is shown in Table 2.

Table 1: Patient Disposition
(Source: Statistical review of Ms. Barbara Elashoff)

	Placebo	Diclofenac	Combined
Patients Randomized	211	207	418
Completed 14 Days	35	21	56
Injury Resolution	68	92	160
Another Therapy	22	20	42
Adverse Event	8	4	12
Study Admission Problems	51	46	97
SAE or Death	0	0	0
Withdraw	23	22	45
No Reason Given*	4	2	6

*Patients with no discontinuation reason given in dataset. Placebo: 83, 148, 429, 440; Patch: 145, 755.

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Table 2: Patient disposition for the 31 patients without dairy data

Patient ID	Reason for Discontinuation	Additional explanation provided	Treatment
30	Study Admission Problems		Placebo
82	Withdraw	Lost to follow-up	Placebo
83		Lost to follow-up	Placebo
107	Withdraw		Placebo
127	Withdraw	Lost to follow-up	Placebo
133	Study Admission Problems		Diclofenac
140	Study Admission Problems		Placebo
142	Study Admission Problems		Placebo
145			Diclofenac
148			Placebo
202	Study Admission Problems		Diclofenac
203	Study Admission Problems		Diclofenac
204	Study Admission Problems	Contusion on the digits*	Placebo
247	Study Admission Problems		Diclofenac
288	Study Admission Problems		Diclofenac
298	Study Admission Problems		Placebo
309	Study Admission Problems		Placebo
427	Study Admission Problems		Placebo
429			Placebo
437	Study Admission Problems		Diclofenac
438	Study Admission Problems		Placebo
440			Placebo
446	Discontinued/Another Therapy		Diclofenac
496	Withdraw	Pt did not show up for visit 2, refused further treatment	Diclofenac
499	Withdraw	Did not bring back daily dairy and dropped out	Diclofenac
524	Study Admission Problems		Placebo
544	Study Admission Problems	Patient lost to follow-up	Placebo
564	Study Admission Problems		Diclofenac
576	Study Admission Problems		Placebo
755			Diclofenac
770	Withdraw	Lost to follow-up	Placebo

Results

The applicant's results are provided in Table 3. Due to the division's initial concerns regarding the appropriateness of the applicant's analyses, Ms. Elashoff conducted several additional analyses. She utilized ANOVA models with a factor for treatment to examine the change in pain from baseline to day 14 as well as the mean pain at day 14. She used a LOCF imputation technique for patients discontinuing due to injury resolution and a baseline observation carried forward (BOCF) strategy for patients discontinuing for all other reasons. Ms. Elashoff found that patients in the diclofenac arm had significantly lower pain at the end of the study as compared to patients in the placebo group. However, her results did not indicate a significant difference between treatment groups in the change in pain from baseline.

I began to further explore the data when the medical team requested the analyses be repeated using a LOCF strategy for all discontinuations. I discovered that the NDA submission contained several dairy datasets. I used the adjusted diary dataset (adjdiary.xpt) because the data contained patch numbers that correlated with the study days. The sponsor stated, "Assessments were performed twice daily at the time that each patch was removed. These assessments are characterized in the database by patch numbers (0 to 28) rather than days (0 to 14). Patch numbers have been adjusted to insure an exact correlation with days from the start of treatment." I performed an analysis of covariance with factors for treatment and center and baseline as a covariate. By accounting for the baseline values, the precision of the analysis was increased and therefore preferred by me. In my analysis, the screening value was carried forward for the 31 patients who did not have diary data. Like Ms. Elashoff, I used the protocol-defined reasons for discontinuation in my analyses. My results, shown in Table 4, indicate a greater analgesic effect for patients in the diclofenac group compared to the placebo group.

Table 3: Efficacy Evaluable Population: Primary Outcome Variable
(Source: Applicant's Table 8, Final Study Report)

Parameter*	Diclofenac Epolamine Patch	Placebo Patch	p-value†
Primary Outcome Variable			
Multiple Imputation Strategy	0.4 ± 0.2	0.5 ± 0.3	0.009
LOCF Analysis	0.4 ± 0.3	0.5 ± 0.3	<0.001
GEE Model Analysis	0.6	0.6	0.008

* Mean ± standard deviation provided where appropriate.
† P-values derived from multiple imputation ANOVA, repeated measures ANOVA, or GEE analysis, respectively.
LOCF= last observation carried forward, GEE=general estimating equations.

Table 4: Analysis of change from baseline to day 14

		Diclofenac Patch (n=207)	Placebo Patch (n=211)	
Baseline				
	Mean (Std deviation)	7.3 (1.3)	7.5 (1.3)	
Change from Baseline to Day 14				
*Imputation Strategy 1**				
	LS Mean (SE)	**-3.5 (0.2)**	**-2.8 (0.2)**	
	LS Mean difference			-0.7 (-1.3,-0.07)
	p-value			0.029
*Imputation Strategy 2***				
	LS Mean (SE)	**-5.0 (.2)**	**-4.2 (.2)**	
	LS Mean difference			-0.8 (-1.3,-0.2)
	p-value			0.007

p-values derived via an ANCOVA model with factors for treatment and center and baseline as a covariate.
*Imputation Strategy 1 = LOCF for all pts discontinuing due to injury resolution and BOCF for all other discontinuation reasons.
**Imputation Strategy 2 = LOCF for all pts discontinuing.

Ms. Elashoff performed a test of the pain scores at the end of treatment and a test of the change in scores from baseline. In addition, I performed an analysis of covariance of the change from baseline. All of the analyses were post-hoc and were valid. However in a post-hoc setting, it was difficult to determine which analysis was most satisfactory since the differences from the analyses were possibly random. The analysis of covariance would have been the preferred, pre-specified analysis.

Differences in conclusions may have also arisen from the use of different datasets by Ms. Elashoff and me. Ms. Elashoff used the unadjusted diary data that did not correlate the patch number with study day. Ms. Elashoff preferred not to use the adjusted data based on her concern that the applicant had possibly manipulated the data inappropriately. The applicant additionally submitted a dataset comparing the unadjusted and adjusted data. Based on my evaluation of the data, I believed the adjusted data was appropriate for the analyses.

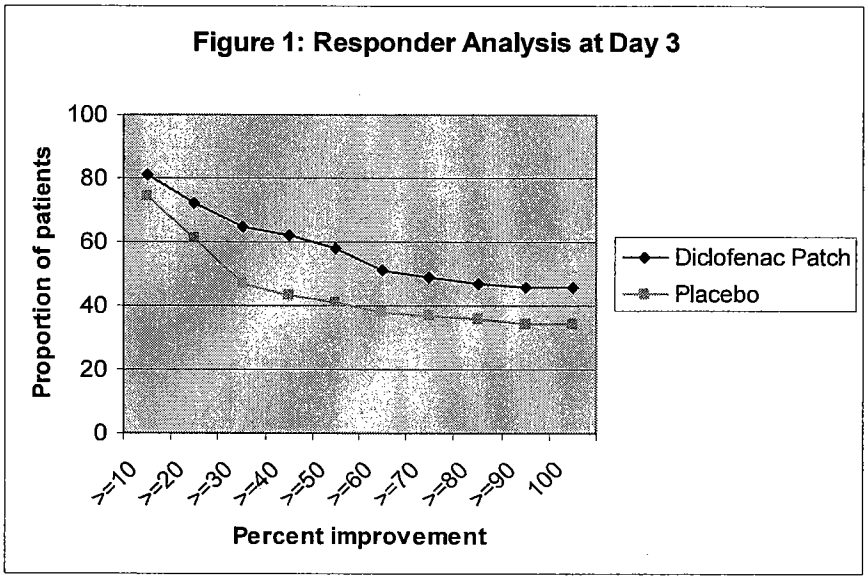
Since the clinical meaningfulness of the difference in means may be difficult to determine, the medical team also requested that responder analyses at day 3 and day 14 be conducted. In the responder analysis, the proportion of patients achieving a response based on numerous cut-offs was calculated. All patients who discontinued due to injury resolution were classified as responders, and all other discontinuations were classified as non-responders. The analyses at day 3 and day 14 are shown in Tables 5 and 6 and graphed in Figures 1 and 2. A larger proportion of patients in the diclofenac group showed a decrease in pain from baseline compared to placebo across all cut-offs.

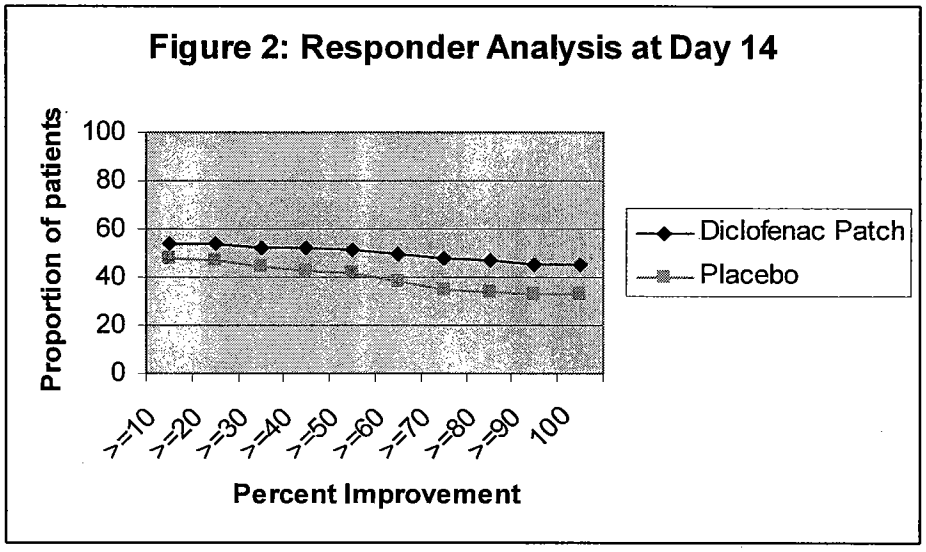
Table 5: Responder Analysis at Day 3

Percent Improvement	Diclofenac n=207 n(%)	Placebo n=211 n (%)
10%	168 (81%)	155 (74%)
20%	149 (72%)	130 (61%)
30%	134 (65%)	100 (47%)
40%	128 (62%)	90 (43%)
50%	119 (58%)	86 (41%)
60%	106 (51%)	81 (38%)
70%	102 (49%)	77 (37%)
80%	98 (47%)	75 (36%)
90%	95 (46%)	71 (34%)
100%	95 (46%)	71 (34%)

Table 6: Responder Analysis at Day 14

Percent Improvement	Diclofenac n=207 n(%)	Placebo n=211 n (%)
10%	112 (54%)	101 (48%)
20%	111 (54%)	99 (47%)
30%	108 (52%)	92 (44%)
40%	107 (52%)	91 (43%)
50%	106 (51%)	88 (42%)
60%	103 (50%)	80 (38%)
70%	99 (48%)	74 (35%)
80%	97 (47%	71 (34%)
90%	94 (45%)	70 (33%)
100%	94 (45%)	70 (33%)





2.2 FRENCH STUDY

Design

In the French Study, one-hundred and thirty-four patients (achieving a pain score of 50mm or greater on a 100 mm visual analog scale (VAS)) were randomized to diclofenac epolamine patch or placebo. Patients were instructed to apply a patch once a day for seven consecutive days. Patients evaluated their pain on days 0, 3, and 7 during clinic visits.

Ms. Elashoff observed that the primary efficacy variable was not clearly defined. She attributed the difficulty in understanding the variable to an awkward translation (from French to English). In Ms. Elashoff's review, she additionally referenced page numbers within the study report to support her observation. Subsequently, Ms. Elashoff interpreted the protocol-defined primary endpoint to be the patient assessed VAS on day 7.

Statistical Methodologies and Results

Ms. Elashoff's primary analysis employed an ANOVA model with treatment and investigator as factors in the model. Five patients did not have data at day 7. Ms. Elashoff performed analyses with and without the inclusion of these patients. The analysis including all randomized patients is preferred and is shown in Table 7. The results indicate an analgesic effect of diclofenac compared to placebo at days 3 and 7.

Table 7: Mean VAS as Day 3 and Day 7
(Source: Statistical Review of Ms. Elashoff's)

		Diclofenac Patch (n=68)	Placebo Patch (n=66)	
VAS at **Day 3**				
	LS Mean (SE)	17.8 (3.2)	30.5 (3.5)	
	LS Mean difference			-12.7
	p-value			0.001
VAS at **Day 7**				
	LS Mean (SE)	12.1 (2.8)	21.4 (3.1)	
	LS Mean difference			-9.3
	p-value			0.004

p-values derived via an ANOVA model with terms for treatment and center.

Ms. Elashoff found a statistically significant treatment-by-center interaction suggesting the treatment effect varied across the 24 centers. Thus, Ms. Elashoff additionally investigated the treatment effects for the eight centers enrolling five or more patients (see page 29 of Ms. Elashoff's review). While an exploration of the effect across the centers was desirable, my concern regarding the apparent interaction was diminished because the majority of the centers enrolled less than four patients. The distribution of patients per investigator and treatment is illustrated in Table 8. The analyses used to explore the heterogeneity of the effect weighted each center equally. I felt that such an analysis was not optimal when considering the number of centers enrolling less than four patients.

Table 8: Listing of numbers of patients assigned to each center/investigator

Investigator	Diclofenac Patch	Placebo
	1	2
	1	0
	1	1
	4	4
	1	0
	7	8
	1	2
	5	4
	5	5
	1	0
	0	2
	1	0
	4	4
	1	0
	12	12
	1	1
	2	1
	1	1
	2	2
	0	1
	2	1
	12	12
	1	0
	2	3

I additionally explored the statistical report for insight into the applicant's analyses and results. The report stated,

> The main criteria was the difference between the VAS measured by the patients at time of the inclusion (day 0) and the VASs measured during the 7 days following this inclusion, on the self-evaluation form until day 3 and in the presence of the physician at day 3 day 7. An analysis had to be first carried out using an analysis of variance (ANOVA) for repeated measurements. If a global effect of treatment was evidenced in the ANOVA, the value of each time of measurement could be compared with non-parametric tests. The last value had to be reported for latest times in case of drop out (end point analysis).

The applicant's results (included in the appendix) additionally suggested an analgesic effect of diclofenac. Of note, the applicant's analysis did not include a center effect in the model. However, the applicant did explore a model including a center effect and an interaction term in the model. A statistically significant treatment-by-center interaction ($p=0.30$) was not found.

I evaluated the change in pain from baseline to days 3 and 7 as well as the proportion of responders. My analysis of change employed an ANCOVA model with factors for treatment and baseline pain as a covariate. By accounting for the baseline values, the precision of the analysis of covariance was increased and therefore preferred by me. My results are shown in Table 9 and support the conclusions of Ms. Elashoff and the applicant. I did not include a center effect in the model because of the limited numbers of patients in most of the centers. However for consistency, I also employed a model including a center effect (see appendix). The overall conclusions remained the same. The responder analyses are provided in Table 10 and Table 11 and graphed in Figures 3 and 4. A larger proportion of patients in the diclofenac group showed a decrease in pain from baseline compared to placebo patients (for all cut-offs).

Table 9:Change from Baseline Analyses

		Diclofenac Patch (n=68)	Placebo Patch (n=66)	
Baseline				
	Mean (Std deviation)	66.9 (10.6)	70.0 (11.8)	
Change from Baseline to **Day 3**				
	Mean (Std deviation)	-49.9 (21.7)	-40.5 (22.0)	
	LS Mean (SE)	-50.8 (2.5)	-39.6 (2.6)	
	LS Mean difference			-11.2 (-18.4,-4.0)
	p-value			0.003
Change from Baseline to **Day 7**				
	Mean (Std deviation)	-56.0 (19.2)	-50.7 (20.1)	
	LS Mean (SE)	**-57.0 (2.2)**	**-49.8 (2.3)**	
	LS Mean difference			-7.2 (-13.6,-0.9)
	p-value			0.027

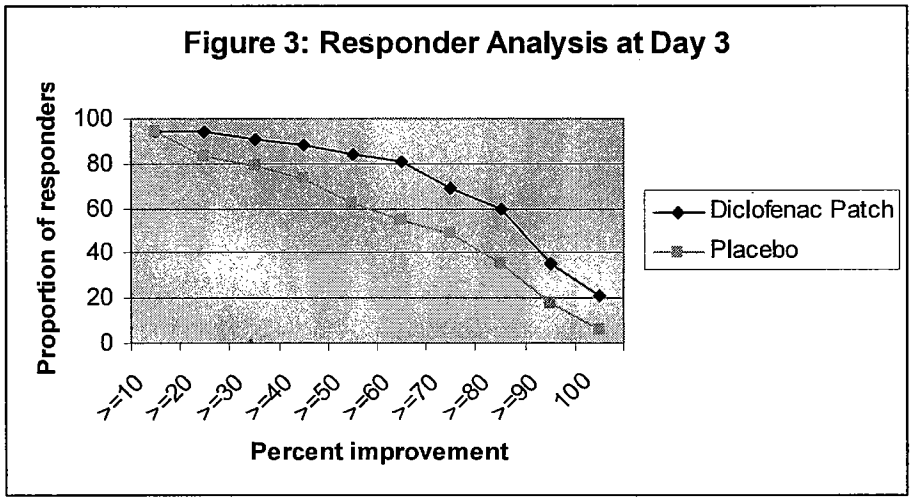
Analysis conducted using ANCOVA with treatment as a factor and baseline pain as a covariate in the model.

Table 10: Responder Analysis at Day 3

Improved by:	Diclofenac Patch (n=68)	Placebo (n=66)
10%	64 (94%)	62 (94%)
20%	64 (94%)	55 (83%)
30%	62 (91%)	52 (79%)
40%	60 (88%)	48 (73%)
50%	57 (84%)	41 (62%)
60%	55 (81%)	36 (55%)
70%	47 (69%)	32 (49%)
80%	41 (60%)	23 (35%)
90%	24 (35%)	12 (18%)
100%	14 (21%)	4 (6%)

Table 11:Responder Analysis at Day 7

Improved by:	Diclofenac Patch (n=68)	Placebo (n=66)
10%	63 (93%)	63 (96%)
20%	63 (93%)	63 (96%)
30%	63 (93%)	61 (92%)
40%	62 (91%)	59 (89%)
50%	62 (91%)	55 (83%)
60%	60 (88%)	48 (73%)
70%	57 (84%)	40 (61%)
80%	52 (77%)	33 (50%)
90%	38 (56%)	23 (35%)
100%	24 (35%)	13 (20%)



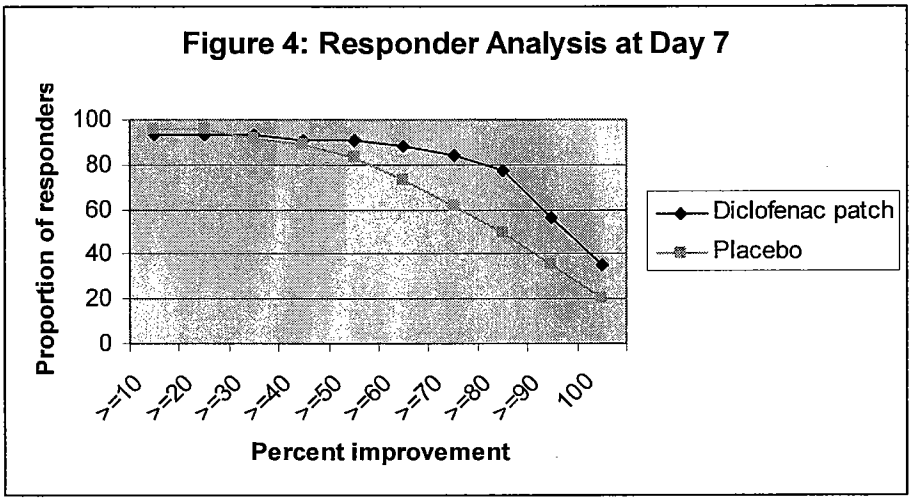


Figure 4: Responder Analysis at Day 7
Proportion of responders
100
80
60
40
20
0
>=10
>=20
>=30
>=40
>=50
>=60
>=70
>=80
>=90
100
Percent improvement
Diclofenac patch
Placebo

3 CONCLUSIONS AND RECOMMENDATIONS

IBSA has submitted two studies to support the use of the diclofenac epolamine patch for the treatment —— The applicant's primary analyses employed statistical techniques for longitudinal data to incorporate the repeated assessments of pain taken over time. The techniques used are not generally favored by the Division of Anesthesia, Analgesia, and Rheumatology Products in pain trials where interest focuses on the ability of patients to remain on treatment and attain a treatment benefit for a specified duration of time. In contrast, pain ——— may possibly resolve with or without treatment. In this setting, the ability of a patient to remain on treatment for a specified time course may be of less importance. Moreover, few patients in the submitted studies withdrew due to adverse events alleviating the common concern in pain trials that treatment may reduce pain but be of little benefit to the patient as a result of intolerable side effects. Thus, the analysis techniques used by the applicant have merit in this setting. However in the UK/German Study, the techniques were not conducted on the desired intent-to-treat population including all randomized patients. Evaluation of the studies was complicated by the lack of clarity among the datasets and analyses. Based on our understanding of the submitted documents, Ms. Barbara Elashoff and I performed several post-hoc analyses to provide additional insights into the data. In my opinion, our analyses of the two studies support the efficacy of the diclofenac patch for the treatment ——

The totality of the evidence from the current submission as well as the original NDA must be considered. Two efficacy studies were submitted in the original NDA. According to the statistical review and evaluation of the original NDA conducted by Dr. Suktae Choi, one study failed to show a difference between treatment and placebo. The second study used an inappropriate primary outcome, namely, the time to pain resolution. In addition, the secondary endpoints in the second trial failed to support the efficacy of the treatment. The applicant has reanalyzed the data from the studies submitted under the original NDA using the mean pain as the primary endpoint. A multiple imputation strategy was employed in the re-analyses. The re-analyses were not formally reproduced or reviewed in-depth by Ms. Elashoff or me; however on the surface, there appears to be some evidence of an analgesic effect.

Based on the totality of the efficacy data, I believe that IBSA has provided evidence that the diclofenac patch provides some reduction in pain ——

4 APPENDIX

4.1 UK/GERMAN STUDY

Multiple Imputation

The following description of the multiple imputation strategy was provided by the applicant in Attachment 5 of the clinical study report.

The method of multiple imputation will be used for the primary analysis of pain scores. This imputation does not depend on the assigned treatment group and can, therefore, be performed prior to breaking the randomization code. Multiple imputation was performed in two stages using the SAS Version 8.2 MI procedure.

1. Limited imputations were performed using the Markov Chain Monte Carlo (MCMC) method to produce a pattern of monotone missingness in the 29 pain scores from Day 0 (baseline) to Day 14. That is, values were imputed only prior to the last available value. No other variables were included in the imputation model. Starting values were obtained using the EM algorithm which required 256 iterations for convergence. The method was based on a single chain with a Jeffreys prior and a random number seed of 101. Imputed values less than 0 were given a score of 0 and imputed values greater than 10 were given a score of 10. A total of 20 imputations were performed.

2. A second set of imputations were derived for the remaining missing data using the imputed values from Stage 1. The regression method was used with a random number seed of 102. All other parameters remained the same. A total of 20 final imputation sets were produced. Imputed values less than 0 were given a score of 0 and imputed values greater than 10 were given a score of 10. With 20 imputations and a missing data rate of 0.828 (318 of 384 patients had missing data the last assessment of Day 14) the minimum efficiency of estimates is given by $(1 + 0.828/20)^{-1} = 96\%$.

The primary efficacy analysis will be based on the mean pain score obtained over the 14 day period. This mean post-treatment score will be divided by the baseline score to adjust for baseline level. When the randomization code becomes available, diclofenac and control patients will be compared in the 20 imputed datasets using analysis of variance (ANOVA) implemented by the SAS GLM procedure. These results will be combined and an overall analysis that adjusts for variability of imputed values will be obtained from the SAS MIANALYZE procedure.

Patient Disposition

The table below shows the patient disposition using the modified reasons for discontinuation.

Patient Disposition using modified reasons for discontinuation (Source: Statistical review of Ms. Barbara Elashoff)

	Placebo	Diclofenac	Combined
Patients Randomized	211	207	418
Completed 14 Days	56	45	101
Injury Resolution	94	112	206
Adverse Event	9	4	13
Fracture Discovered	0	1	1
Hospitalization	2	0	2
Not entered	1	0	1
Withdrawn: Lost to Follow Up	8	7	15
Withdrawn: Patient Moved	0	1	1
Withdrawn: Unresolved (pain score>=3)	41	37	78

4.2 FRENCH STUDY

The following tables show the applicant's results and have been copied directly from the clinical study report.

Table 9: VAS Spontaneous Pain (ANOV/LOCF))

Source of variance	Sum of squares	Mean square	F	Degrees of freedom	p-value
Between subjects					
Treatment	75488	75488	11.75	1 / 131	0.0008
Error	841515	6424		131	
Within subjects					
Time	1103443	73563	213.88	15 / 1965	<0.0001
Time * Treatment	12759	851	2.47	15 / 1965	0.002
Error	675848	344			

Table 8: VAS Spontaneous Pain

Global spontaneous pain measured by the patient: # patients, mean (s.d.), median (min-max).	Flector Tissugel ® (n=68)	Placebo (n=66)
Self-evaluation form		
Day 0 consultation	N=69, 66.9 (10.6), 66.0 (50-92)	N=66, 70.0 (11.8), 67.5 (50-100)
1 hour after 1st application	N=65, 60.9 (19.4), 65.0 (0-100)	N=66, 65.5 (15.7), 66.5 (27-97)
2 hours after 1st application	N=64, 58.0 (18.8), 66.0 (0-100)	N=65, 64.1 (16.2), 65.0 (27-98)
3 hours after 1st application	N=63, 53.5 (19.9), 54.0 (0-100)	N=63, 61.1 (16.9), 64.0 (22-90)
4 hours after 1st application	N=61, 48.9 (19.9), 50.0 (0-84)	N=64, 61.2 (16.8), 62.0 (21-94)
5 hours after 1st application	N=58, 46.6 (20.4), 49.5 (0-83)	N=61, 59.3 (16.2), 60.0 (22-94)
6 hours after 1st application	N=54, 46.8 (22.0), 46.5 (0-98)	N=59, 57.4 (16.7), 57.0 (20-95)
Day 0, 8 pm	N=64, 48.2 (22.1), 47.0 (0-100)	N=65, 59.6 (17.6), 57.0 (15-90)
Day 1, 8 am	N=65, 39.7 (21.1), 39.0 (0-79)	N=66, 50.1 (20.6), 51.5 (4-90)
Day 1, noon	N=65, 33.4 (19.6), 29.0 (0-87)	N=65, 46.1 (17.9), 44.0 (2-85)
Day 1, 8 pm	N=65, 27.4 (16.5), 26.0 (0-66)	N=66, 44.9 (20.9), 39.5 (0-84)
Day 2, 8 am	N=65, 24.8 (17.5), 24.0 (0-75)	N=66, 39.0 (19.9), 38.5 (0-89)
Day 2, noon	N=64, 21.1 (15.9), 19.0 (0-70)	N=66, 35.5 (19.5), 30.5 (0-79)
Day 2, 8 pm	N=65, 18.6 (15.0), 17.0 (0-66)	N=64, 35.7 (22.0), 30.0 (0-90)
Day 3, 8 am	N=65, 14.3 (16.2), 10.0 (0-84)	N=65, 28.8 (21.8), 25.0 (0-75)
Evaluation in the presence of the physician		
Day 3 Consultation	N=65, 14.5 (16.2), 10.0 (0-84)	N=65, 28.8 (21.8), 25.0 (0-75)
Day 7 Consultation	N=64, 7.9 (11.6), 4.0 (0-60)	N=65, 18.4 (18.5), 12.0 (0-80)

Analysis of change form baseline conducted via an ANCOVA model including center as a term in the model.

Change from Baseline Analyses

		Diclofenac Patch (n=68)	Placebo Patch (n=66)	
Baseline				
	Mean (Std deviation)	66.9 (10.6)	70.0 (11.8)	
Change from Baseline to **Day 3**				
	LS Mean (SE)	**-50.3 (3.2)**	**-38.1 (3.5)**	
	LS Mean difference			-12.2(-19.3,-5.1)
	p-value			0.001
Change from Baseline to **Day 7**				
	LS Mean (SE)	**-55.8(2.8)**	**-47.3(3.1)**	
	LS Mean difference			-8.5 (-14.8, -2.2)
	p-value			0.01

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Dionne Price
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Thomas Permutt
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Statistical Review and Evaluation

NDA: 21-234
Drug name: Diclofenac Epolamine Patch
Dosage Form: Adhesive Patch
Strength: 1.3% diclofenac epolamine
Route/Admin: Topical, Dermal
Sponsor: Institut Biochimique SA (IBSA)
Proposed Indication: Treatment of Pain
Date Submission: July 27, 2006
Documents Reviewed:

Electronic submission

- All the pdf files in directory "//clinstat/"
- All the SAS transport files in directory "//crt/french/" and "//crt/ukgerman/"

Medical Reviewer: Robert A. Levin, M.D.
Statistical Reviewer: Barbara Elashoff

1. Background and Introduction

The sponsor submitted two studies in support of the efficacy of Diclofenac Patch for treatment in 2001. They were not found to be supportive of efficacy. In the current submission, the sponsor has submitted two more double-blind randomized, placebo-controlled studies, the UK/German Study and the French Study, for the indications of pain relief

2. UK/German Study (00GB/Fp05)

2.1 Summary

Study 00GB/Fp05 was a multi-center, double-blind, placebo-controlled, parallel group study that evaluated the safety and efficacy of Diclofenac Epolamine Patch vs. placebo for pain relief from minor soft tissue injury. This two-week study enrolled 418 patients (ages 18 to 65 years) with minor soft tissue injury within 7 days of study entry at 14 centers (all located in Great Britain and Germany) during 2002 and 2003. The primary efficacy variable was pain. The primary efficacy analysis, as described in the protocol, was changed after the study ended since most patients dropped out before they achieved "success" as defined in the protocol. By Day 7 of this two-week study, 50% of the patients had dropped out. By Day 14, >80% of the patients had dropped out. Using a slight variation of the protocol-specified primary efficacy analysis, the difference between treatment groups in time to pain relief was statistically significantly different. The high dropout rate coupled with a large amount of missing diary data precluded an estimation of the magnitude of pain relief. The study provides only weak evidence for efficacy of the drug.

2.2 Study Design

The UK/German Study was a 14-center, double-blind, placebo-controlled, parallel group study carried out from 2/21/2002 to 1/5/2004 in Great Britain and Germany. After a screening and baseline evaluation, the patients were randomized to either Diclofenac Epolamine Patch or to placebo for a 2-week double-blind period. The patients were to replace the patch twice daily. The study included two clinic visits (Day 0 and Day 14). The protocol stated that the patients should not use other topical medications, ice bandages or analgesics.

Patients having spontaneous pain of at least 5 on a 0-10 category pain scale were eligible for enrollment. Randomization took place at Visit 1 (baseline) and the first patch was applied the same day. The patients self-administered the patch every 12-hours. Each day, at the time of patch replacement, patients recorded the severity of their pain in their diary cards on an 11-point scale. Any rescue medication taken during the previous 12 hours was also recorded on the diary cards. Any other symptoms, including adverse events, were reported as well.

The patients were telephoned every day to confirm completion of the diary and study drug compliance.

The patients were evaluated during the exit session. The patients completed a local patch tolerability assessment, and the investigator evaluated both patch tolerability and the patient's overall response to therapy, each on a 5-point scale (none, poor, fair, good and excellent).

2.3 Primary and Secondary Efficacy Endpoints

Primary Endpoints

The protocol stated that the primary efficacy variable was to be: post-treatment pain caused by normal activity and movement assessed by the patient on a visual analog scale (VAS) twice a day for 14 days or until pain resolution. It was to be expressed as a proportion of the baseline pain score. The primary analysis of the endpoint was time to attainment of four consecutive pain scores of 2 or less. This analysis was not ideal because patients often reached low pain scores and immediately discontinued the study due to injury resolution. Therefore, after the study data were collected, a new analysis was proposed (by a statistician blinded to treatment assignments) which involved a one-way Analysis of Variance (ANOVA) of the mean post-treatment pain score expressed as a proportion of the baseline pain score. The Markov Chain Monte Carlo (MCMC) method was used to impute missing values.

In addition to the new ANOVA with MCMC imputation method, two new secondary analyses were performed also: 1) a repeated measures ANOVA and 2) a Generalized Estimating Equation (GEE) of the mean post-treatment pain score. For the repeated measures ANOVA, the sponsor used the method of Last Observation Carried Forward (LOCF) to impute missing values. Class variables for treatment and day of treatment were included in the model as was Baseline pain score as a continuous variable. For the GEE, no imputation method was used. The model included a class variable for treatment, and continuous variables for baseline pain score, treatment day and treatment day squared.

Table 1: Sponsor's Analysis Methods

	Analysis	Imputation Method	Model Variables/Covariates
Primary	ANOVA	Markov Chain Monte Carlo	Treatment
Secondary	Repeated Measures ANOVA	LOCF	Treatment Baseline pain score Treatment Day
Secondary	GEE	None	Treatment Baseline pain score Treatment Day Treatment Day Squared

For the primary analysis, the sponsor generated four different sets of imputations to assess the sensitivity of the imputation model to variance assumptions.

Imputation methods, in general, use information from completed subjects to predict how patients would have performed had the stayed in the study. This is obviously difficult when so few subjects actually completed the study. In the current study, more than 50% had dropped out by Day 7, and by Day 14 the dropout rate reached >80%. It is inappropriate to interpret results from an analysis of means from a study with a dropout rate of >80%, whether or not an imputation method has been used in the analysis. Therefore, this review will focus primarily on descriptive statistics, graphs and time-to-event analyses.

Secondary Endpoints

Secondary endpoints included:

- Investigator's global assessment at the exit visit (0-4 scale)
- Swelling at the site of injury (0-3 scale)
- Effect of injury on the active range of motion – for joint injury patients only (0-3 scale)

2.4 Results

Study conduct

Four-hundred eighteen (Placebo: 211, Diclofenac: 207) patients were randomized to 14 centers. There were no diary data for 31 patients (7.4%), see Tables 2 and 3 below. The discontinuation reasons for these 31 patients recorded in the dataset of the exit CRF were "Study Admission Problems" and "withdrew". Six patients had no reason given. Six patients did return the diary (133, 140, 142, 437, 438 and 446), but are not included in the diary dataset, (perhaps because they did not fill the diary card in). The sponsor states on page 20 of the study report that 7.2% and 8.6% of the patients in the Diclofenac and Placebo groups, respectively, failed to complete a diary, "thereby necessitating their exclusion from the efficacy evaluable study population due to an absence of information on injury-associated pain following the start of therapy."

Table 2: Patients That Are Not Included In Diary Dataset

Patient ID	Treatment Group	Investigator Name	Inv #	Start Date	Stop Date	Screening/ Baseline Pain Score
30	Placebo		21	15-Apr-02	3-Feb-03	8
82	Placebo		23	3-Apr-02	12-Apr-02	5
83	Placebo		23	16-Apr-02	23-Oct-02	7
107	Placebo		23	2-Sep-02	12-Sep-02	8
127	Placebo		24	30-Aug-02	11-Oct-02	9
133	Diclofenac EP		24	31-Oct-02	15-Nov-02	10
140	Placebo		24	30-Jan-03	10-Feb-03	6
142	Placebo		24	3-Mar-03	17-Mar-03	8
145	Diclofenac EP		24	20-Mar-03		8
148	Placebo		24	7-Feb-03		9
202	Diclofenac EP		16	29-Apr-02	13-May-02	6
203	Diclofenac EP		16	23-Sep-02	7-Oct-02	6
204	Placebo		16	25-Jun-02	25-Jun-02	6
247	Diclofenac EP		11	24-Sep-02	1-Oct-02	7
288	Diclofenac EP		17	10-Feb-03	13-Feb-03	9
298	Placebo		17	20-Nov-02	25-Nov-02	6
309	Placebo		18	4-Mar-02		9
427	Placebo		24	21-May-03	3-Jun-03	7
429	Placebo		24	1-May-03		7
437	Diclofenac EP		24	17-Jun-03	23-Jun-03	5
438	Placebo		24	6-Aug-03	19-Aug-03	7
440	Placebo		24	4-Jun-03		7
446	Diclofenac EP		24	25-Aug-03	28-Aug-03	7
496	Diclofenac EP		12	4-Dec-02	5-Dec-02	5
499	Diclofenac EP		12	6-Feb-03	26-Feb-03	6
524	Placebo		13	14-May-03	30-May-03	7
544	Placebo		14	19-Feb-03	8-Mar-03	8
564	Diclofenac EP		14	6-Mar-03	5-May-03	8
576	Placebo		14	31-Mar-03	7-May-03	10
755	Diclofenac EP		13	21-Jul-03	24-Sep-03	8
770	Placebo		15	11-Sep-03	26-Sep-03	8

Table 3: Exit Visit Data from Patients That Are Not Included in Diary Dataset

Patient ID	Days of Trt	Did Patient Return Zip-lock bag?	How many zip-lock baggies returned	Did Patient Return Diary?	Did Patient return unused patches?	How many patches returned?	Days Treated with Patch	Discontinuation Reason	Comment 1	Exit: Explain
30	999.99	No		No	No		999.99	Study Admission Problems	Pt lost to follow-up. Contacted by phone, but did not return for visit 2. No diary or meds recovered.	
82		No		No	No			Withdraw		Lost to follow up
83								None		Lost to follow up
107	6	Yes	8	No	Yes	22	6	Withdraw		
127								Withdraw		Lost to follow-up.
133	14	Yes	25	Yes	Yes	5	14	Study Admission Problems		
140	10	Yes	17	Yes	Yes	13	10	Study Admission Problems		
142	11	Yes	22	Yes	Yes	8	11	Study Admission Problems		
145								None		
148								None		
202	14	No		No	No		14	Study Admission Problems		
203	9	No		No	No		9	Study Admission Problems		
204								Study Admission Problems		Contusion on the digits
247	7	No		No	Yes	18	7	Study Admission Problems		
288	4	Yes	9	No	Yes	21	4	Study Admission Problems		
298	6	Yes	11	No	Yes	19	6	Study Admission Problems		
309		No		No	No			Study Admission Problems		
427	9	No		No	Yes	15	9	Study Admission Problems		
429								None		
437	7	Yes	12	Yes	Yes	18	7	Study Admission Problems		
438	14	Yes	26-1 lost.	Yes	Yes	3	14	Study Admission Problems		
440								None		
446	2	No		Yes	Yes	27	2	None		
496								Withdraw		Patient did not show up for visit 2, refused further treatment
499								Withdraw		Did not bring back daily diary and dropped out!
524	15	No		No	No		15	Study Admission Problems		
544								Study Admission Problems		Patient lost to follow up
564		No		No	No			Study Admission Problems	Drop-out	
576	10.5	Yes	21	No	Yes	8	11	Study Admission Problems		
755								None		
770								Withdraw	Visit N.D.	Lost of follow up

Of the 418 randomized patients, 50% discontinued by Day 7. By Day 14, 87.2% and 82.1% of the Diclofenac and placebo groups, respectively, had dropped out.

The sponsor submitted two different datasets with discontinuation information. The first dataset (in the "raw" folder) closely resembled the Exit Case Report Form. The choices of reasons for ending the study treatment were:

1. Completed 14 days.
2. Injury Resolved. The injury resolved to the extent that the test article was of no further benefit.
3. Another Therapy: The injury was unresponsive to the test article, and the patient elected to discontinue treatment in favor of an alternate therapy.

4. Adverse Event: An adverse event occurred which was possibly / probably test article related.
5. Study Admission Problems: Study admission problems such as inappropriate enrolment, non-compliance with the protocol schedule, or a need for a concurrent medication prohibited by the protocol.
6. SAE or Death: an explanation of the cause of death is required with immediate reporting to the sponsor.
7. Withdraw: The patient wishes to withdraw from this study for another reason (explain).

Table 4 below summarizes the information from the sponsor's "raw" exit dataset.

Table 4: Patient Disposition (Information Summarized from "Raw" Exit Dataset)

	Placebo	Diclofenac	Combined
Patients Randomized	211	207	418
Completed 14 Days	35	21	56
Injury Resolution	68	92	160
Another Therapy	22	20	42
Adverse Event	8	4	12
Study Admission Problems	51	46	97
SAE or Death	0	0	0
Withdraw	23	22	45
No Reason Given*	4	2	6

*Patients with no discontinuation reason given in dataset. Placebo: 83, 148, 429, 440; Patch: 145, 755.

Table 5 below summarizes the information from the other exit dataset in the folder labeled "analyses". The information is quite different.

Table 5: Patient Disposition (Information Summarized from "Analyses" Exit2 Dataset)

	Placebo	Diclofenac	Combined
Patients Randomized	211	207	418
Completed 14 Days	56	45	101
Injury Resolution	94	112	206
Adverse Event	9	4	13
Fracture Discovered	0	1	1
Hospitalization	2	0	2
Not entered	1	0	1
Withdrawn: Lost to Follow Up	8	7	15
Withdrawn: Patient Moved	0	1	1
Withdrawn: Unresolved (pain score>=3)	41	37	78

The number of patients with "injury resolution" given as a discontinuation reason is greater by 46 patients in the "analyses" Exit2 dataset. The number of patients who completed 14 days is also different. The sponsor explained these differences on page 21 of the study report by

stating that the new listings of discontinuation reasons "more accurately characterizes the actual reasons the patients discontinued the study."

Demographics and Baseline Characteristics
The treatment groups were similar with respect to baseline symptom severity and the demographic characteristics: race, age, and gender, see Table 6 below.

Table 6: Summary of Patient Demographic and Background Characteristics
(Sponsor's Table 4)

Parameter*	Diclofenac Epolamine Patch (DEP)	Placebo Patch (PP)	p Value
Age (years)	37.7 ± 14.3 (18-82)	40.1 ± 14.8 (15-85)	0.094
Height (cm)	171.2 ± 9.5 (150-193)	171.3 ± 10.1 (146-197)	0.888
Weight (kg)	74.6 ± 14.1 (47-150)	76.0 ± 14.4 (46-125)	0.294
Body Mass Index (kg/m²)	25.5 ± 4.8 (16-48)	26.0 ± 4.9 (16-49)	0.331
Sex			
Male	100 (48.3%)	106 (50.2%)	0.697
Female	107 (51.7%)	105 (49.8%)	
Race			
Caucasian	207 (100%)	209 (99.1%)	0.499
Asian	0 (0.0%)	2 (0.9%)	
Medication/Concomitant Pathology	58 (28.0%)	68 (32.5%)	0.338
Drug Hypersensitivity	7 (3.4%)	13 (6.2%)	0.252
Injury Characteristics			
Time to Injury (days)	1.4 ± 1.6 (0-7)	1.4 ± 1.8 (0-8)	0.893
Injury Location			
Right	123 (59.4%)	114 (54.3%)	0.323
Left	84 (40.6%)	96 (45.7%)	
Ankle	43 (20.8%)	40 (19.0%)	
Shoulder	42 (20.3%)	39 (18.5%)	
Knee	32 (15.5%)	33 (15.6%)	
Foot	27 (13.0%)	25 (11.8%)	
Calf/Shin (lower leg)	19 (9.2%)	15 (7.1%)	
Wrist/Hand	11 (5.3%)	17 (8.1%)	0.663
Elbow	11 (5.3%)	14 (6.6%)	
Arm	9 (4.3%)	10 (4.7%)	
Thigh/Femur (upper leg)	7 (3.4%)	5 (2.4%)	
Hip	3 (1.4%)	7 (3.3%)	
Back	3 (1.4%)	2 (0.9%)	
Thorax	0 (0.0%)	4 (1.9%)	
Diagnosis			
Contusion	89 (43.0%)	89 (42.2%)	
Strain	69 (33.3%)	61 (28.9%)	0.601
Sprain	46 (22.2%)	56 (26.5%)	
Other	3 (1.4%)	5 (2.4%)	
Bruising	68 (32.9%)	67 (31.9%)	0.917
Swelling			
None	54 (26.1%)	45 (21.3%)	
Mild	86 (41.5%)	95 (45.0%)	0.416
Moderate	65 (31.4%)	68 (32.2%)	
Severe	2 (1.0%)	3 (1.4%)	
Active Range of Motion			
Full	25 (12.1%)	44 (20.9%)	
Restricted	170 (82.1%)	159 (75.4%)	0.013
Immobile	12 (5.8%)	8 (3.8%)	
Joint Stability	187 (94.9%)	190 (96.4%)	0.621
Skin Examination			
Normal	128 (61.8%)	139 (65.9%)	
Erythema	73 (35.3%)	67 (31.8%)	0.714
Abrasion/Laceration	6 (2.9%)	5 (2.4%)	
Mean Pain Score	7.3 ± 1.4 (5-10)	7.5 ± 1.3 (5-10)	0.115
Categorical Pain Score			
5	18 (8.7%)	14 (6.6%)	
6	46 (22.2%)	39 (18.5%)	
7	50 (24.2%)	44 (20.9%)	0.101
8	55 (26.6%)	71 (33.6%)	
9	24 (11.6%)	25 (11.8%)	
10	14 (6.8%)	18 (8.5%)	

* Mean ± standard deviation (plus range in parenthesis) provided for continuous variables, and number of patients with the percentage of total in parenthesis for categorical variables. P values derived from analysis of variance or Fisher's exact test.

Parameter*	Diclofenac Epolamine Patch (DEP)	Placebo Patch (PP)	p Value†
Treatment Days			
1-3	14 (6.8%)	23 (10.9%)	
4-6	57 (27.5%)	40 (19.0%)	
7-9	51 (24.6%)	43 (20.4%)	0.138
10-12	21 (10.1%)	31 (14.7%)	
13-16	54 (26.1%)	62 (29.4%)	
> 16	1 (0.5%)	0 (0.0%)	
NA	9 (4.3%)	12 (5.7%)	
Mean =	8.7 ± 4.1 (1-17)	9.1 ± 4.1 (1-15)	0.343
Total =	1723	1811	
Patches Applied			
1-5	14 (6.8%)	18 (8.5%)	
6-10	37 (17.9%)	34 (16.1%)	
11-15	52 (25.1%)	39 (18.5%)	0.596
16-20	33 (15.9%)	34 (16.1%)	
21-25	17 (8.2%)	18 (8.5%)	
26-30	42 (20.3%)	49 (23.2%)	
NA	12 (5.8%)	19 (9.0%)	
Mean =	16.4 ± 8.0 (1-29)	16.9 ± 8.5 (2-30)	0.497
Total =	3198	3245	
Patch Adherence Problems‡	6 (2.9%)	5 (2.4%)	

* Mean ± standard deviation (plus range in parenthesis) provided for continuous variables, and number of patients with the percentage of total in parenthesis for categorical variables. Exception is Total which equals the total number of days or patches. NA = not available.

† P values derived from Fisher's exact test.

‡ DEP = 14-559 (lost during night), 14-713 (hot weather), 15-606 (removed during sleep), 21-017 (wrist felt fine, didn't stick at work), 24-157 (came off during sleep), 25-162 (not sticking properly, curling); PP = 15-627 (lost during night), 21-020 (fell-off while sleeping), 24-127 (came off), 24-432 (came off due to sweat on feet), 24-440 (no PM patch, coming off at home).

The mean baseline pain scores including the 31 patients that had no diary data were similar to the mean scores excluding these patients.

Table 7: Baseline Means: Including and Excluding 31 Patients With No Diary Data

	Patch		Placebo	
	n	mean	n	Mean
Including 31 patients with no diary data	207	7.30	211	7.51
Excluding 31 patients with no diary data	195	7.31	192	7.52

Sponsor's Primary Endpoint Analyses

The sponsor's primary endpoint analyses are not meaningful due to the high (>80%) rate of dropout. As described above, the sponsor used a variety of imputation methods for the missing data.

Sponsor's Secondary Analyses

Most of the sponsor's secondary analyses are not meaningful due to the high rate of dropout. However, using a time to event approach may be valid in this context. The sponsor performed 5 such analyses: the number of days until a score of 0, <=1, <=2, or 4 consecutive scores of <=2 (with and without censoring at 15.5 days). In the protocol, the sponsor chose to specify an unusual method of censoring for the primary analysis. A score of 15.5 days was assigned to all patients who did not reach the injury resolution endpoint (4 consecutive scores of <=2). It does not make sense to impute a censoring time after the study duration. The sponsor also used the usual method of censoring with the injury resolution endpoint of 4 consecutive scores <=2. Table 8 below summarizes the results of these analyses.

Table 8: Time to Event (Pain Relief) Analyses

Sponsor's Table
(Attachments page 520, Table 9.9: Life Table Analyses – Evaluable Population)

	Diclofenac			Control			
Variable	**end/N**	**Median**	**(95% CI)**	**end/N**	**Median**	**(95% CI)**	**p**
Days to reach endpoint							
Endpoint: score of 0	89/192	12.0	9.0 to 13.0	72/192	14.0	11.0 to .	0.060
Endpoint: score of <=1	108/192	9.0	6.5 to 11.0	89/192	10.5	9.0 to 13.0	0.020
Endpoint: score of <=2	141/192	5.5	4.5 to 6.5	115/192	7.5	6.5 to 8.5	0.007
Endpoint: 4 consecutive scores <=2	94/192	10.0	8.0 to 12.0	70/192	13.5	10.0 to .	0.010
Endpoint: 4 consecutive scores <=2*	94/192	.	11.5 to .	70/192	.	. to .	0.014

DIRECTORY: D:\DICLOFEN\OSTUDY\DATA\ FILE: TTIME.PRT D: 07FEB2006 T:14FEB2006
p values determined using the Log-Rank test.
end/N: Patients reaching endpoint / All Patients.
*: All censored patients considered censored at 15.5 days.

The first analysis shows a marginally statistically significant difference (p=.06) between times to success (Diclofenac 12 days vs. Placebo 14 days). The second, third and fourth analyses show statistically significant differences in the median times to success across treatment groups. Finally, in the last analysis (time to 4 consecutive scores of <=2, with censoring at 15.5 days *for all patients who did not reach the injury resolution endpoint*) not enough patients achieved success to compare medians. As mentioned above, this method of censoring has no statistical basis. Using the usual method of censoring with the injury resolution endpoint of 4 consecutive scores <=2, the estimate of the median time to pain relief for Diclofenac is 10 days and for Placebo is 13.5 days, (p=0.010). Even though this was the primary analysis, the findings of statistical significance provide less than definitive evidence due to the high rate of missing diary data and dropouts seen in the study.

Reviewer's Analyses

The reviewer's analyses will focus on descriptive statistics and graphs due to the large amount of missing data in this study. Additionally, a simple difference in the mean scores between treatment groups using a conservative imputation method was performed to conform to other analyses reviewed in this area of disease in the Division of Anesthesia, Analgesia, and Rheumatology Products.

Figure 1 and Table 5 below show the percentage of patients with a recorded value over time (Patch number). Ten percent of patients had already dropped out (or had no diary data) by the end of Day 1, 20% by Day 4 (Patch #7) and 50% by the end of Day 7 (Patch #15). This study cannot be used to determine the efficacy of Diclofenac Patch in sustained pain relief because very small numbers of patients were still in the study towards the middle of the second week (Day 10: Diclofenac 28%, Placebo 33%) and almost none remained until the end of the second week (Day 14: Diclofenac 13%, Placebo 18%).

Figure 1: Percent of Patients With Recorded CPS Pain Score for Each Patch Number

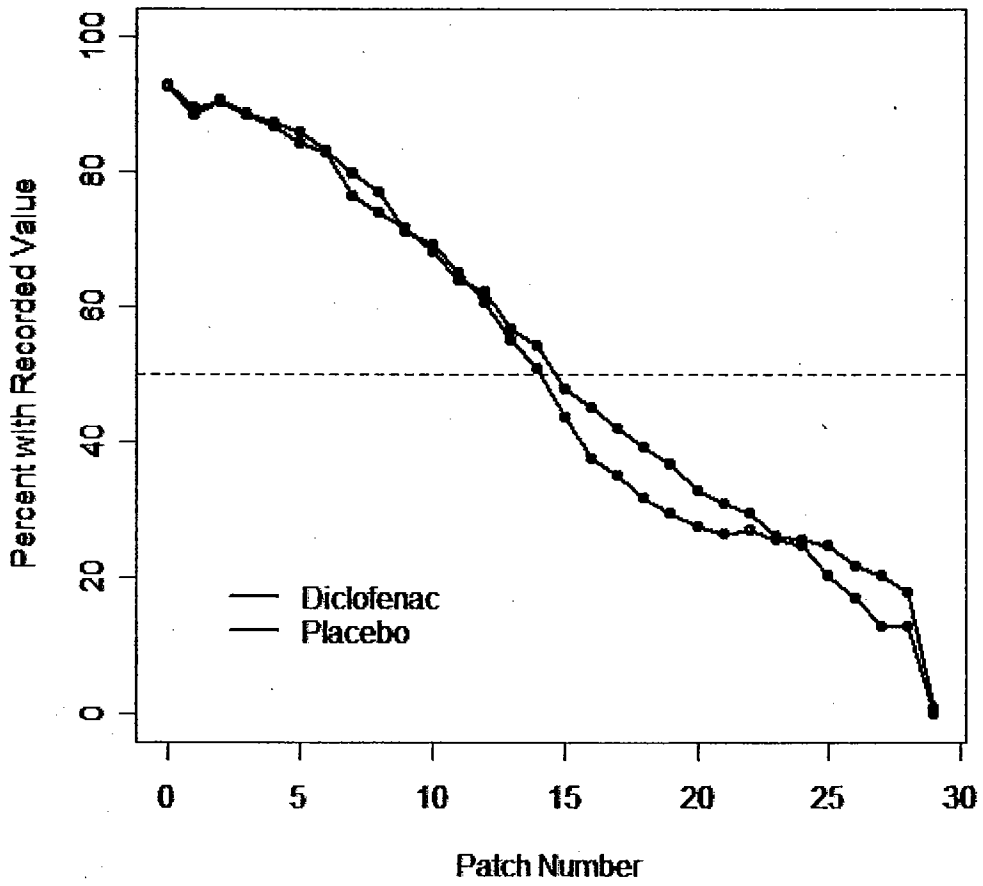
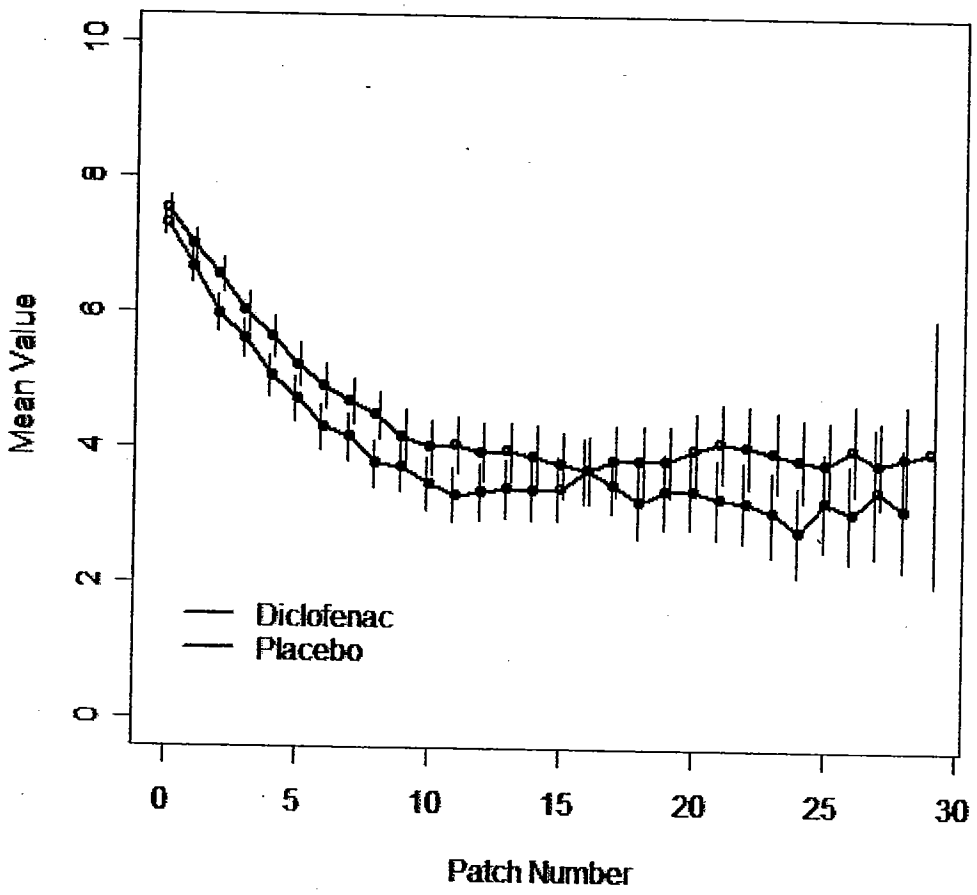


Table 9: Percent of Patients with a Recorded CPS Pain Score for Each Patch Number

Patch #	Diclofenac EP Patch	Placebo
0	92.42	92.75
1	88.15	89.37
2	90.52	90.34
3	88.63	88.41
4	87.20	86.47
5	85.78	84.06
6	82.94	82.61
7	79.62	76.33
8	76.78	73.91
9	71.09	71.50
10	69.19	68.12
11	64.93	63.77
12	60.66	62.32
13	54.98	56.52
14	50.71	54.11
15	43.60	47.83
16	37.44	44.93
17	35.07	42.03
18	31.75	39.13
19	29.38	36.71
20	27.49	32.85
21	26.54	30.92
22	27.01	29.47
23	25.59	26.09
24	24.64	25.60
25	20.38	24.64
26	17.06	21.74
27	12.80	20.29
28	12.80	17.87
29	0.00	0.97

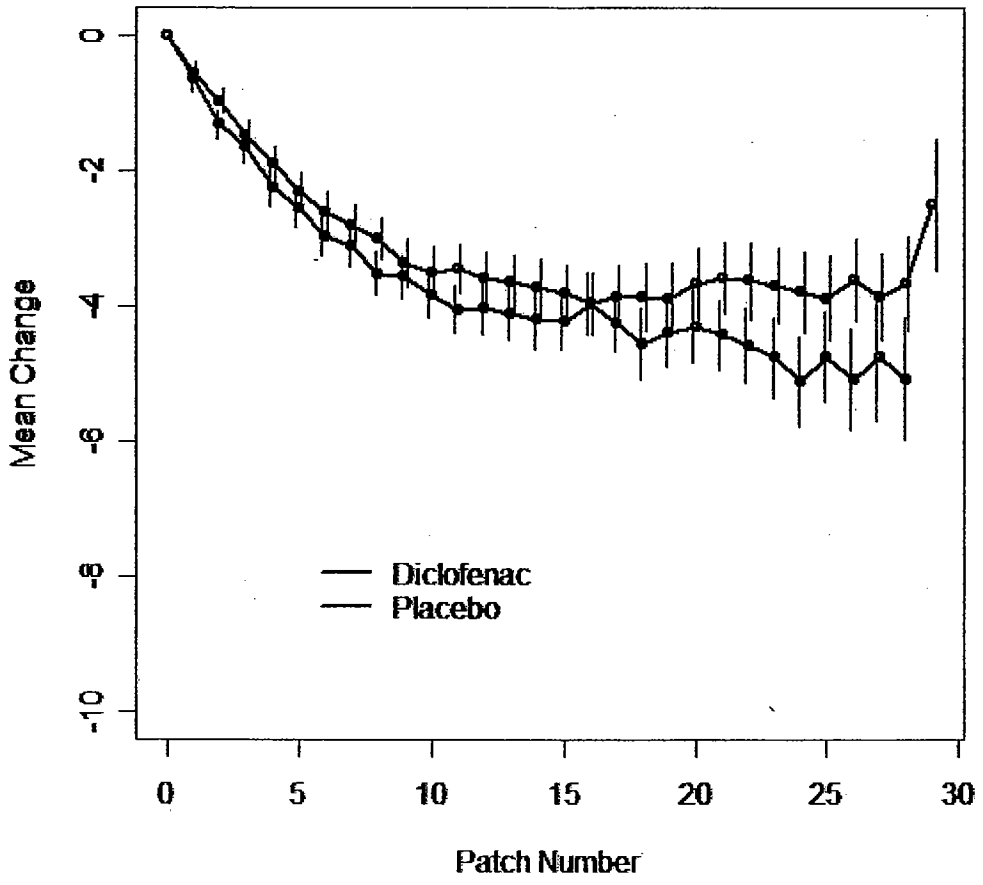
Mean CPS scores decreased over time from about 7.5 units to about 3-4 units (see Figure 2). However, the mean scores (even as early as Day 4) are biased due to the informative dropout. By Day 14, >80% of the patients have dropped out, therefore, caution should be used in reading the mean scores towards the end of the study.

Figure 2: Mean CPS Pain Scores with 95% Confidence Intervals



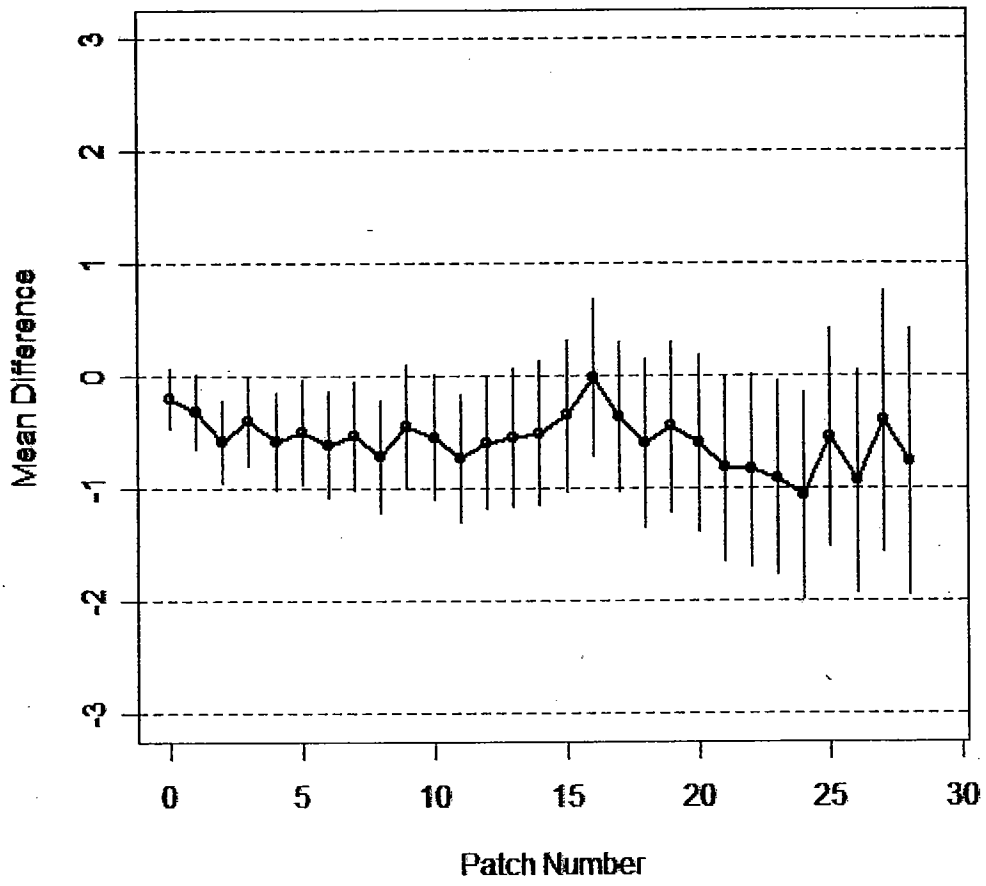
Since the placebo group had slightly higher baseline scores, the change from baseline scores are presented in Figure 3. The two treatment groups first start to separate at Patch #2 (which is the score recorded in the morning of the day after baseline).

Figure 3: Mean Change from Baseline CPS Pain Scores with 95% Confidence Intervals



The differences between placebo and Diclofencac in mean CPS scores over time were between -1 and 0 units on a 10-point scale (Diclofenac superior). Again, these differences are subject to bias due to the large amount of informative dropout (see Figure 4).

Figure 4: Difference between Treatment Groups in Mean CPS Pain Scores with 95% Confidence Intervals

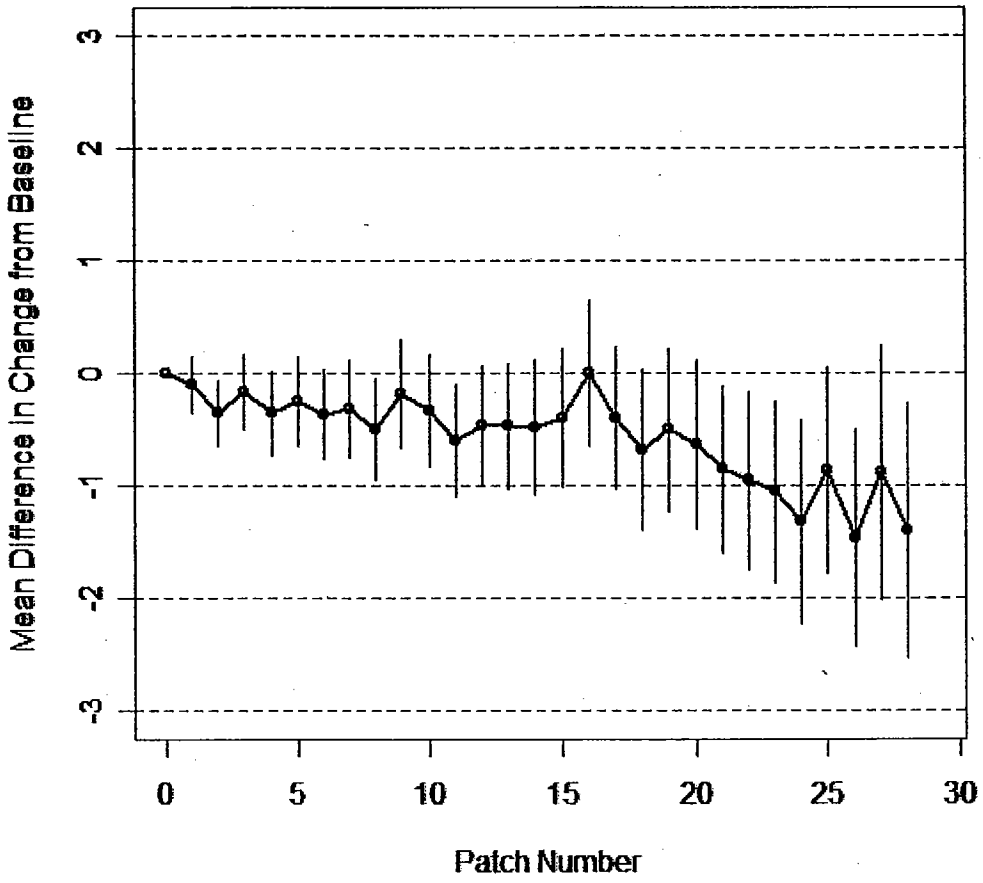


Mean differences in change from baseline are presented in Table 6 and graphed in Figure 5. The mean differences between treatment groups in change from baseline were between 0.6 units and zero (Diclofenac superior) from Patch 1 to Patch 20 (the first 10 days). After Patch 20, the differences are greater, but more subject to bias.

Table 10: Mean Differences in Change from Baseline

Patch #	Mean Difference in Change from Baseline	Patch #	Mean Difference in Change from Baseline
1	-0.099	16	-0.005
2	-0.357	17	-0.393
3	-0.171	18	-0.688
4	-0.356	19	-0.506
5	-0.254	20	-0.631
6	-0.369	21	-0.850
7	-0.315	22	-0.956
8	-0.505	23	-1.056
9	-0.188	24	-1.323
10	-0.332	25	-0.862
11	-0.597	26	-1.461
12	-0.458	27	-0.884
13	-0.471	28	-1.398
14	-0.482		
15	-0.399		

Figure 5: Difference between Treatment Groups in Mean Change from Baseline CPS Pain Scores with 95% Confidence Intervals

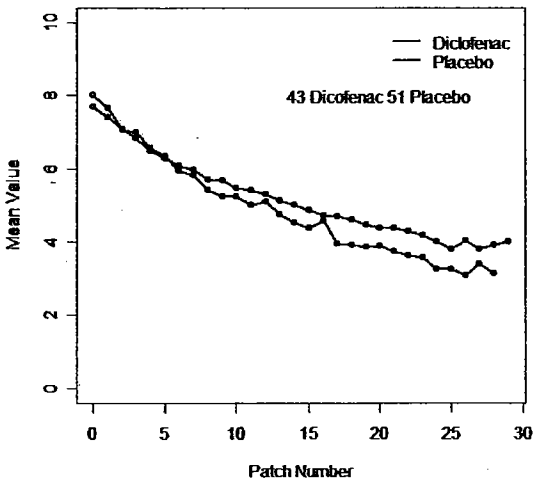


In order to understand the pattern of the scores prior to dropout day, the dataset was divided into 7 cohorts based on the last patch for which a patient recorded a score:

Last patch =1, 2, or 3
Last patch =4, 5, 6, or 7
Last patch =8, 9, 10, or 11
Last patch =12, 13, 14, or15
Last patch =16, 17, 18, or 19
Last patch =20, 21, 22, or 23
Last patch =24, 25, 26, 27, 28, 29 or 30

A graph of the mean score for each treatment group within each dropout cohort is provided below (Figures 6a-6g). The patients who dropped out the earliest had the quickest decline in mean scores and those who completed at least 24 patches had the slowest decline in mean scores.

Fig 6a: Last Patch 24, 25, 26, 27, 28, 29 or 30



APPEARS THIS WAY
ON ORIGINAL

Fig 6b: Last Patch 20, 21, 22, or 23

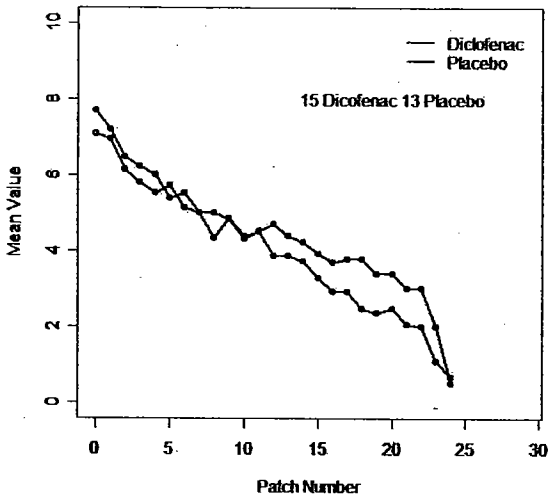


Fig 6c: Last Patch 16, 17 18 or 19

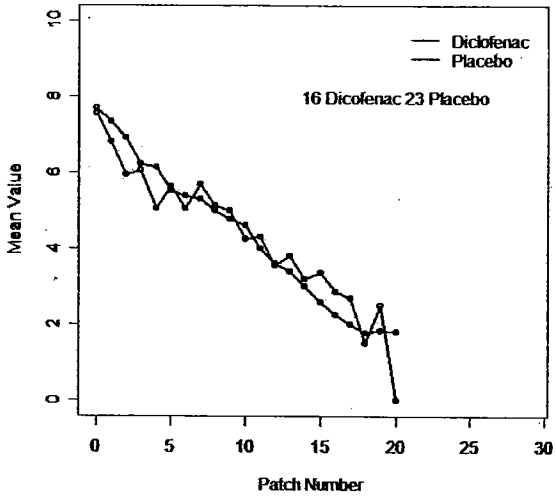


Fig 6d: Last Patch 12, 13, 14, or 15

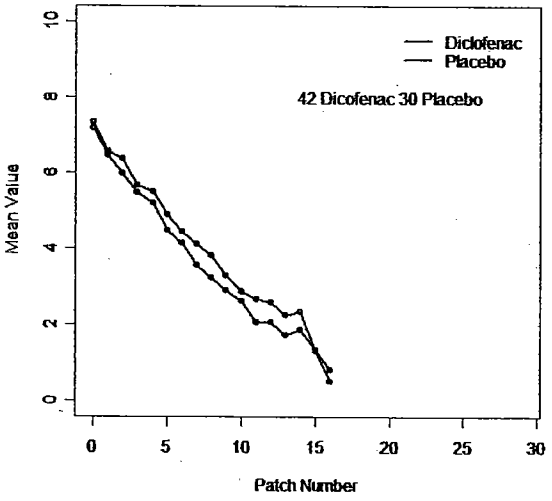


Fig 6e: Last Patch 8, 9, 10, or 11

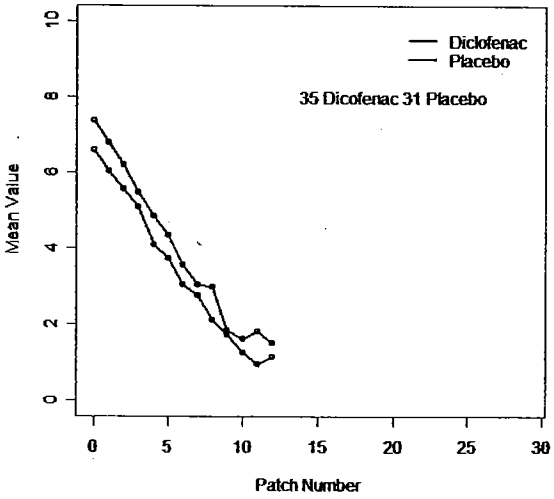


Fig 6f: Last Patch 4, 5, 6 or 7

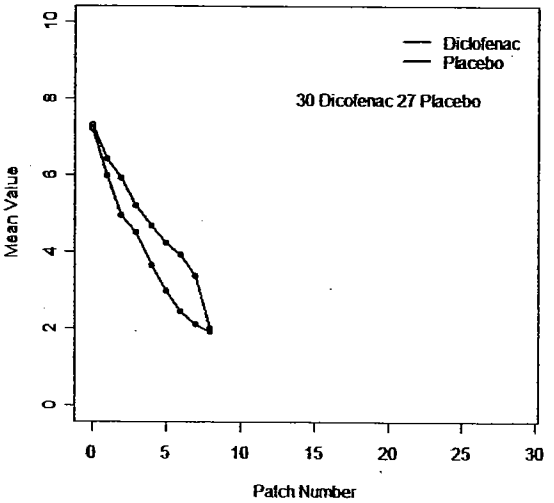
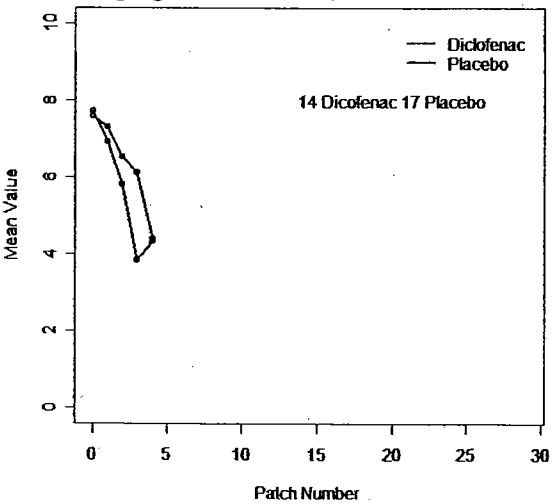


Fig 6g: Last Patch 1, 2 or 3



Descriptive Statistics: Responder Analysis

The percentages of patients who "responded" are presented in Table 11 below where:

a. patients who discontinued due to injury resolution were automatically counted as "responders" (no matter what their last value was); and
b. patients who discontinued for other reasons were counted automatically counted as "non-responders" (no matter what their last value was).
c. Patients who completed without injury resolution were counted if they met a percent improvement criteria.

The table below shows the results of this responder analysis, using a range of definitions for treatment success in the "completed without injury resolution" subgroup.

Table 11: Responder Analysis

Improved by:	Diclofenac n-195 n (%)	Placebo n=192 n (%)
10%	150 (76.9)	141 (73.4)
20%	149 (76.4)	138 (71.9)
30%	145 (74.4)	129 (67.2)
40%	144 (73.8)	125 (65.1)
50%	142 (72.8)	123 (64.1)
60%	137 (70.3)	114 (59.4)
70%	130 (66.7)	106 (55.2)
80%	124 (63.6)	101 (52.6)
90%	114 (58.5)	99 (51.6)

The percentages of patients that improved by 10% were high in both the treatment and placebo groups (77% and 73%, respectively). The percent responders in the placebo group drops off gradually, as the definition of response increases from 10% improvement to 90% improvement. The percent responders in the treatment group, however does not drop off as quickly. It remains as high as 70% of all Diclofenac patients until the definition of response is greater than 60% improvement.

Reviewer's Analyses with Imputed Values

An analysis comparing the mean scores of patients at the end of the study was performed with imputed data for dropouts whereby:

a. patients who discontinued due to injury resolution (using the data from the Exit CRF, or the "raw" Exit dataset), received a score equal to their last score; and
b. patients who discontinued for any other reason received a score equal to their baseline score.
c. patients who completed received their last score.

The results are shown in Table 12 below.

Table 12: Endpoint Analysis

N=418	**Diclofenac n=207**	**Placebo n=211**	**Difference / p-value**
Endpoint (imputed)	2.90±0.23	3.60±0.25	-0.699 / 0.03663
Change from Baseline (imputed)	-4.40±0.22	-3.91±0.23	-0.486 / 0.1222

The analyses in Table 12 include the cohort of 31 patients with no diary data. Since none of these patients discontinued due to injury resolution, the baseline score obtained during the screening visit was used to impute the last value the patient recorded. In general, it is not preferable to impute data from baseline to the end of the study from as high a percentage as 7.4% of the patients. However, this imputation method was used to conform to other analyses reviewed in this area of disease in the Division of Anesthesia, Analgesia, and Rheumatology Products.

The mean difference in the endpoint value was a little more than half a point (which is similar to that found by looking at the raw means with no imputation). The difference was statistically significant when tested at an alpha-level of 0.05.

The mean difference in the change from baseline value was a little less than half a point (which is also similar to that found by looking at the raw means with no imputation). The difference was not statistically significant tested at an alpha-level of 0.05.

Due to the differences seen at baseline between the two treatment groups, an analysis with baseline included in the model would be preferable. However, since the imputation method also used baseline to impute some values, the interpretation of such a model would be difficult.

2.5 Conclusions of UK/German Study

The primary efficacy analysis, as described in the protocol, was not performed because most patients discontinued before they achieved "success" as defined in the protocol (4 consecutive scores equal to 2 or less with censoring at 15.5 days for all patients who did not reach the injury resolution endpoint). If one uses conventional censoring methods where the patient is censored at the time of dropout, then the protocol-specified primary efficacy variable (time to pain relief) shows a statistically significant difference between the two treatment groups (Diclofenac: 10.0 days, Placebo: 13.5 days, p=0.010).

This review investigated whether the study also showed a difference between treatment groups in a) pain relief sustained over time; and b) pain relief at the end of the study. Due to an inordinately high rate of dropouts from Day 7 to Day 14, this study was not able to quantify either of these types of pain relief. However, a reviewer's responder analysis was supportive evidence of a greater percentage of patients in the Diclofenac group than in the placebo group achieving 60%, 70%, 80% and 90% improvement. Additionally, in a reviewer's endpoint analysis using an imputation method in order to include all 418 patients, the mean difference between the two treatment groups in last pain score was 0.699 units on a 0-10 scale with a p-value=0.03663. In a reviewer's change from baseline analysis using the same imputation

method, the mean difference between the two treatment groups was 0.486 with a p-value=0.1222. These analyses imputed a relatively large amount of data from baseline to the end of study, therefore, they should be viewed with caution.

In summary, this study demonstrated a statistically significant difference in time to pain relief. There may also be a small difference in the scores of pain over time between treatment groups, however the treatment effect was not able to be estimated using accepted statistical methods due to the large dropout rate. There were data quality issues regarding the missing diary data and conflicting information regarding the reasons for discontinuation. The study therefore provides marginal evidence of efficacy of the drug.

3 French Study (Protocol n° 05-05-98)

The French study was a multi-center, double-blind, placebo-controlled, parallel group study that evaluated the safety and efficacy of Flector Tissugel vs. placebo for pain relief from minor ankle sprain. This one-week study enrolled 134 patients (ages 18 to 65 years) with minor ankle sprain within 48 hours of injury at 24 centers (all located in France) from June 1998 to May 1999. The primary efficacy variable was pain on active mobilization. The analysis was not clearly described in the protocol, due to translation problems between French and English. Using the VAS at D7 as the outcome variable, a model with treatment and center as class variables, an analysis of variance found a statistically significant difference between treatment and placebo. There was also a statistically significant treatment-by-center interaction effect that makes it difficult to estimate the magnitude of the treatment effect.

3.1 Study Design

The French study was a multi-center, double-blind, placebo-controlled, parallel group study carried out from June 30, 1998 to May 14, 1999 in France. After a screening and baseline evaluation, the patients were randomized to either Flector Tissugel or placebo for a 1-week double-blind period. The patients were required to apply the treatment drug once per day on the sprain for seven consecutive days. The study included three visits (Day 0, 3 and 7).

Patients having a pain evaluation score of $\geq$50 mm on a 100 mm Visual Analog Scale (VAS) were eligible for enrollment. The sprain must not have been treated prior to study entry and not require an orthopedic or surgical treatment. Randomization took place at Visit 1 (Day 0 or baseline) and the first treatment was applied the same day. On Days 0, 1, 2, and 3 patients recorded VAS scores in their diary cards. On Day 0, patients recorded a VAS score at 1, 2, 3, 4, 5, and 6 hours after application. On Days 1, and 2, patients recorded a VAS score at 8am, noon, and 8pm. On Day 3, patients recorded a VAS score at 8 am and during the investigator's visit. On Day 7, patients recorded a VAS score only during the investigator's office visit.

Table 13: Study Diary Card and Clinic Visit Schedule

	Day 0	Day 1	Day 2	Day 3	Day 7
Patient Diary recording	In physician's office 1 hour post 2 hours post 3 hours post 4 hours post 5 hours post 6 hours post 8 pm	8 am Noon 8 pm	8 am Noon 8 pm	8 am In physician's office	 In physician's office
Physician assessments	In physician's office			In physician's office	In physician's office

At the two subsequent investigator visits (Day 3 and Day 7), the patient completed the VAS score and recorded ice applications, use of Paracetamol rescue medication, compliance and adverse events. Both the physician and patient recorded assessments of local and global tolerability and judgments of therapy efficacy. Additionally, the physician assessed pain (at rest, on passive stretch and on palpation) on a 4-point scale (absent, slight, moderate, severe), possibility of single foot leaning and periarticular edema (mm).

3.2 Primary and Secondary Efficacy Endpoints

Primary Endpoints

It was difficult to understand exactly what the primary endpoint was because the translation of the protocol from French to English was awkward. In the sample size calculation section (Section 13.1, page 113), the protocol stated "Choice of primary criterion: VAS at D7". Whereas, on page 115, in the section titled "Efficacy variables", the first sentence described an analysis for VAS in a way that implies that all the physician visits (D0, D3 and D7) were to be included in the ANOVA: "the measured parameter VAS at the physician site, oedema:=two-factor analysis of variance model between treatment groups (treatments/time) et [sic] one factor anova (time) within treatment groups." In the study report, the sponsor used all the VAS results, physician assessed and patient assessed (including those that the patient did at home) in the analyses.

This reviewer interpreted the protocol-defined primary endpoint to be the VAS (assessed by the patient), at the physician's office on Day 7.

The protocol specified that Last Observation Carried Forward (LOCF) should be used to impute missing data for subjects who stopped treatment for reasons of "failure", "worsening", "healing", or "disappearance of the symptoms" (as described in the protocol).

Secondary Endpoints

Secondary endpoints included:

- Consumption of paracetamol (rescue medication)
- Status of skin

- Functional disability
- Possibility of single foot leaning
- Pain on pressure
- Pain on passive-stretch
- Pain at rest
- Pain on palpation

3.3 Results

Study Conduct

One-hundred thirty-four (Placebo: 66, Flector Tissugel: 68) patients were randomized to 24 centers. Of these, seven patients (5.2%) discontinued the study before completion. All patients were included in the intent-to-treat analysis.

Table 14: Summary of Patient Disposition
(Reviewer's Table summarized from dataset "db05098.xpt")

	Placebo	Diclofenac	Combined
Patients Randomized	66	68	134
Adverse Event	1	0	1
Inefficacy	2	0	2
Inefficacy, worsening	1	0	1
Lost to Follow Up	0	3	3
Non-observance	1	0	1
Other	0	1	1

Demographics and Baseline Characteristics

The treatment groups were similar with respect to baseline symptom severity and the demographic characteristics: race, age, and gender, weight, height, body mass index, ice application before enrollment, and ankle sprain history (see below).

Table 15: Summary of Patient Demographic and Background Characteristics
(Reviewer's Table)

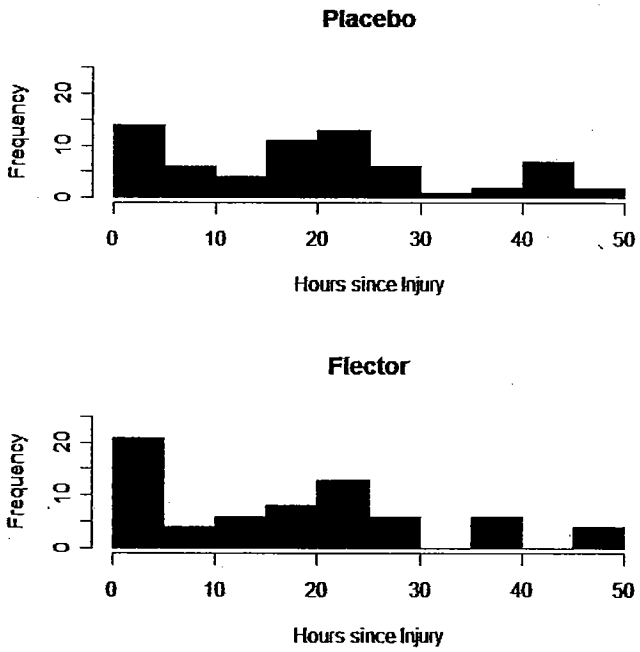
	Flector Tissugel (n=68)	Placebo (n=66)
Race:		
Age: mean (S.D)	33.3 (13.9)	29.7 (11.6)
Gender: M/F	33/35	39/27
Weight:		
Males: mean(S.D)	75.4 (11.0)	77.7 (19.2)
Females: mean (S.D)	62.8 (126)	57.1 (9.2)
Height		
Males: mean (S.D.)	178 (11.0)	177 (19.2)
Females: mean (S.D.)	163 (7.1)	164 (7.9)
Body Mass Index		

Males: mean(S.D.)	23.9 (3.3)	24.8 (5.6)
Females: mean (S.D.)	23.6 (5.1)	21.1 (3.0)
Ice Application: No/Yes	43/25	39/27
Ankle sprain enrollment delay: mean hours (min-max)	17.3 (1.0-48.0)	19.9 (0.5-48.0)
Site of injury: Left/Right	30/38	31/34
Circumference difference (injured ankle vs healthy ankle in mm) Mean (SD) Median (min-max)	 13.3 (10.7) 10.0 (-10-40)	 16.2 (13.4) 13.5 (0-60)

Ankle Sprain Enrollment Delay

The mean difference in number of hours from ankle sprain to enrollment was 2.6 hours (Flector 17.3 hours; Placebo 19.9 hours). Figure 7 is a histogram of the number of hours for each treatment group. There do not appear to be any outliers and the distribution seems similar across treatment groups.

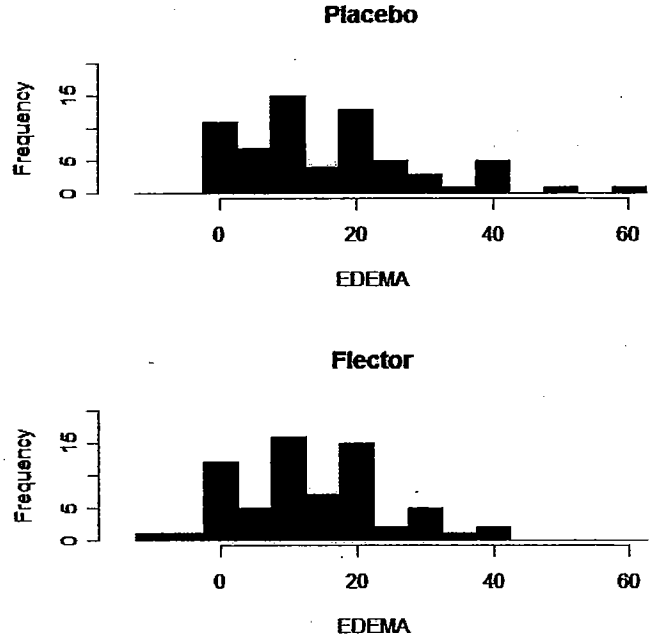
Figure 7: Enrollment Time in Hours Since Ankle Sprain



Baseline Edema

Baseline edema was defined as the difference between the circumference of the injured ankle and the healthy ankle at the baseline visit. The difference between treatment groups in the mean value of edema was 2.9 mm, with the placebo group having a greater mean. Additionally, some patients on Flector had greater circumferences on the healthy ankle than on the injured ankle. For this reason, baseline edema was included in some reviewer's exploratory models and not found to be a significant factor explaining pain.

Figure 8: Baseline Edema in mm
(Circumference of Injured Ankle-Circumference of Healthy Ankle)



Sponsor's Primary Endpoint Analyses
The sponsor compared the two treatment groups in decrease in VAS at each timepoint using a Wilcoxon nonparametric test, see Table 16 below. The results show a p-value<0.05 between treatment groups from hour 4 to the end of the study, with the exception of Day 1 at 8 am. The sponsor claimed statistical significance for these timepoints, but did not adjust for multiple comparisons.

Table 16: Sponsor's Primary Analyses

Decrease (%) in spontaneous pain measured by the patient: mean ± s.d. median (min-max).	Flector Tissugel ® (n=68)	Placebo (n=66)	P-value*
Last known value			
1 hour after 1 st application	-7.7 (26.2), -2.0 (-100 to 67)	-5.9 (18.3), -2.7 (-60 to 37)	0.9
2 hours after 1 st application	-11.6 (26.4), -7.9 (-100 to 67)	-7.8 (20.5), -4.9 (-60 to 45)	0.5
3 hours after 1 st application	-18.3 (27.9), -14.5 (-100 to 67)	-11.3 (22.2), -6.8 (-66 to 55)	0.1
4 hours after 1 st application	-23.9 (27.5), -16.9 (-100 to 42)	-11.1 (22.6), -11.2 (-67 to 62)	0.02
5 hours after 1 st application	-26.6 (28.2), -23.3 (-100 to 42)	-13.0 (22.0), -11.6 (-66 to 62)	0.02
6 hours after 1 st application	-27.5 (30.9), -23.7 (-100 to 63)	-14.8 (23.7), -12.9 (-66 to 64)	0.02
Day 0, 8 pm	-26.4 (31.4), -21.3 (-100 to 67)	-13.6 (24.7), -12.7 (-79 to 55)	0.02
Day 1, 8 am	-38.3 (30.8), -38.5 (-100 to 23)	-28.3 (28.1), -28.7 (-94 to 43)	0.08
Day 1, noon	-47.5 (29.1), -48.9 (-100 to 10)	-33.5 (25.5), -35.8 (-97 to 23)	0.005
Day 1, 8 pm	-55.8 (27.0), -59.1 (-100 to 5)	-35.3 (30.9), -41.1 (-100 to 37)	0.0001
Day 2, 8 am	-59.4 (29.0), -64.6 (-100 to 17)	-44.5 (27.8), -46.3 (-100 to 41)	0.002
Day 2, noon	-64.7 (27.0), -70.5 (-100 to 0)	-49.4 (27.1), -51.0 (-100 to 17)	0.0006
Day 2, 8 pm	-68.6 (26.3), -75.5 (-100 to 0)	-50.0 (32.0), -57.4 (-100 to 43)	0.0002
Day 3, 8 am	-71.8 (25.5), -75.8 (-100 to 0)	-56.8 (28.3), -65.7 (-100 to 8)	0.001
Day 3 Consultation	-74.7 (29.3), -84.2 (-100 to 40)	-59.4 (30.7), -69.1 (-100 to 19)	0.0006
Day 7 Consultation	-84.3 (24.8), -93.2 (-100 to 0)	-74.0 (25.8), -79.9 (-100 to 27)	0.002

** Wilcoxon non parametric test on the rank of the value.*

Reviewer's Primary Endpoint Analysis

As discussed above, the translation of the protocol from French to English was awkward. This reviewer interpreted the protocol-defined primary endpoint to be *VAS assessed by the patient at the physician's office on Day 7.*

Five patients were not included in the reviewer's analysis because they did not have pain scores at Day 7. These 5 patients are listed in Table 17 below. (Intent-To-Treat analyses were also performed including these 5 patients, see Table 1 in the Appendix).

Table 17: Patients Not Included in Reviewer's Analysis

Patient ID	Treatment	Center	Patient Assessment VAS Day 0	Physician Assessment Pain at Rest Day 0	Physician Assessment Pain on Passive Stretch Day 0	Physician Assessment Pain on Pressure Day 0
45	Flector	Le Van	75	2	2	0
54	Flector	Tisal	79	3	2	0
173	Flector	Coudreuse	73	3	3	0
38	Placebo	Bauer	75	3	2	0
73	Flector	Schmitt	51	2	1	0

Table 18: Day 7 ANOVA with treatment and investigator in model
Least Squares Means ± SE

Day 7

N=129	Flector	Placebo	Difference / p-value
VAS at Day 7	6.925±2.546	17.280±2.776	10.355/ 0.0005

At Day 7, the Flector group was statistically significantly superior to the Placebo group on the 100 mm Visual Analog Scale for pain on movement, with a mean score of 10 mm less than the Placebo group, p=0.0005.

A treatment-by-investigator interaction was tested at the alpha-level of 0.15. It was statistically significantly different from zero. Another model, including baseline VAS, was performed to test the robustness of this interaction effect (see Model 4 in Table 19 below).

Table 19: Models Investigating Interaction Term

Model	Outcome	Terms	p-value		LS Means	SE	Diff	p-value
1	VAS Day 7	Treatment	0.0001	Flector	6.93	2.55	10.36	0.0005
		Investigator	0.5996	Placebo	17.28	2.78		
2	VAS Day 7	Treatment	0.2860					
		Investigator	0.2969					
		Treatment by Inv Interaction	[redacted]					
3	VAS Day 7	Treatment	0.0008	Flector	7.36	2.56	9.91	0.0008
		Investigator	0.6535	Placebo	17.27	2.76		
		Baseline VAS	0.1769					
4	VAS Day 7	Treatment	0.5669					
		Investigator	0.2834					
		Baseline VAS	0.4358					
		Treatment by Inv Interaction	[redacted]					

The treatment effects for each of the 8 centers with 5 or more patients were plotted in Figure 9 below.

Figure 9: Treatment Effects by Investigator for Centers with >=5 Patients

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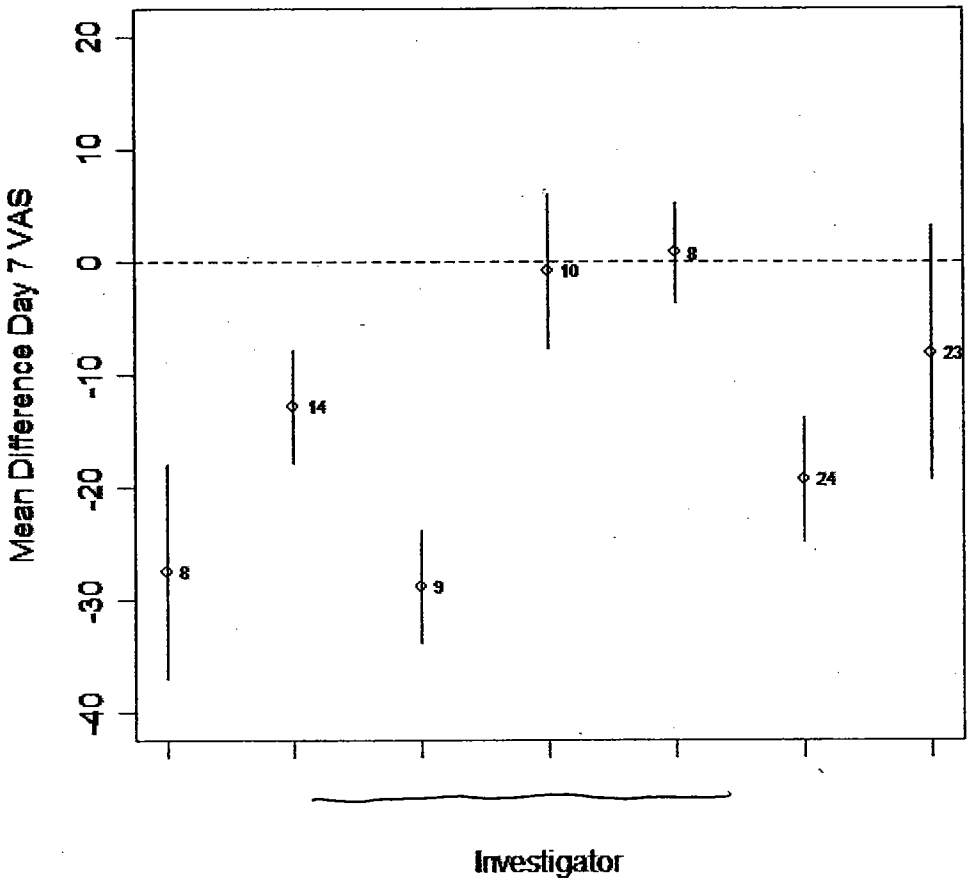

Figure X shows that ___ and ___ had a large treatment effect, while ___ and ___ had no treatment effect. The statistically significant treatment-by-investigator interaction makes it difficult to estimate the magnitude of the treatment effect.

Reviewer's Secondary Endpoint Analyses

Day 3 VAS

The results of the VAS on Day 3 were similar to Day 7, see table below.

Table 18: Day 3 ANOVA with treatment and investigator in model
Least Squares Means +/- SE

Day 3

N=130	Flector	Placebo	Difference / p-value
VAS at Day 3	12.93±2.987	27.153±3.259	14.223/ 0.0001

Percent Improved

In Section 8.1 of the protocol titled "Evaluation Criteria for Efficacy", it was stated that, "At the end of treatment, subjects will be considered 'improved' and therapy efficient, if the relative evolution shows a diminution of the VAS value of at least 20 mm minimum between study entry and end of the study." Therefore, one of the secondary endpoints analyzed is percent "improved" based on a 20 mm difference between baseline and end of study.

Table 20: Percent of Patients Improved by >=20 mm

	Day 3	Day 7
Flector	62/68 = 91%	63/68 = 93%
Placebo	53/66 = 80%	61/66 = 92%

The difference between the two treatment groups at Day 7 was negligible (1%). The difference between the two treatment groups was greater (11%) at Day 3.

Ice Application

The application of ice during the study was recorded by the patient at the D3 and D7 visits. There was no difference between the two treatment groups in number of patients using ice or number of occurrences of ice being applied among the people who used it.

Investigator Assessed Pain Scores

The investigator-assessed pain scores were rated on a scale of 0-3 (0: absent, 1: slight, 2: moderate, 3: severe). The pain scores were low for the Flector group, with mean values close to 0 and 1. The mean Placebo scores were slightly higher (0.6-1.7 units). After adjusting for investigative site, the treatment effects were 0.379 units for pain at rest, 0.435 units for pain on passive stretch and 0.387 units for pain on pressure (Flector superior).

Table 21: Day 3 ANOVA with treatment and investigator in model
Least Squares Means +/- SE

Day 3

N=130	**Flector**	**Placebo**	**Difference / p-value**
Pain at rest	0.240±0.093	0.619±0.101	0.379/ 0.0004
Pain on passive stretch	1.025±0.116	1.46±0.126	0.435/ 0.0012
Pain on pressure	1.336±0.130	1.723±0.142	0.387/ 0.0093

The pain scores at Day 7 were slightly lower for both groups, but the treatment effect sizes were similar, with the exception of pain on pressure. The treatment effect for pain on pressure on Day 7 (0.677 units) was almost twice that of Day 3 (0.387 units).

Table 22: Day 7 ANOVA with treatment and investigator in model
Least Squares Means +/- SE

Day 7

N=129	Flector	Placebo	Difference / p-value
Pain at rest	0.024±0.085	0.398±0.093	0.374/ 0.0002
Pain on passive stretch	0.617±0.132	1.208±0.144	0.591/ 0.0001
Pain on pressure	0.805±0.130	1.482±0.142	0.677/ 0.0001

3.4 Conclusions

The analysis of the primary efficacy variable was not clearly described in the protocol, due to translation problems between French and English. Using the VAS at D7 as the outcome variable, a model with treatment and center as class variables, an analysis of variance found a statistically significant difference between treatment and placebo. There was also a statistically significant treatment-by-interaction effect that makes it difficult to estimate the magnitude of the treatment effect. Despite the interaction effect, this study provides evidence of efficacy of Diclofenac Patch for the indication of [redacted]

4 Overall Conclusions

The sponsor submitted two double-blind randomized, placebo-controlled studies, the UK/German Study and the French Study, for the indications of pain relief [redacted] ity. The results of the French Study were definitive evidence of efficacy. The evidence of efficacy in the UK/German Study was marginal, although in the right direction. Overall, the studies are consistent with a real, but small, treatment effect.

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Appendix

For the French study, Intent-To-Treat analyses were performed for the primary efficacy variable including the 5 patients with no data at Day 7. The results were similar to those obtained using the evaluable population.

Appendix Table 1: Day 7 ANOVA with treatment and investigator in model Least Squares Means ± SE

Day 7

N=134	Flector	Placebo	Difference / p-value
VAS at Day 7	12.076±2.816	21.384±3.089	-9.308/ 0.0041

At Day 7, the Flector group was statistically significantly superior to the Placebo group on the 100 mm Visual Analog Scale for pain on movement, with a mean score of 10 mm less than the Placebo group, p=0.0005.

The results were similar at Day 3, see table below.

Appendix Table 2: Day 3 ANOVA with treatment and investigator in model Least Squares Means +/- SE

Day 3

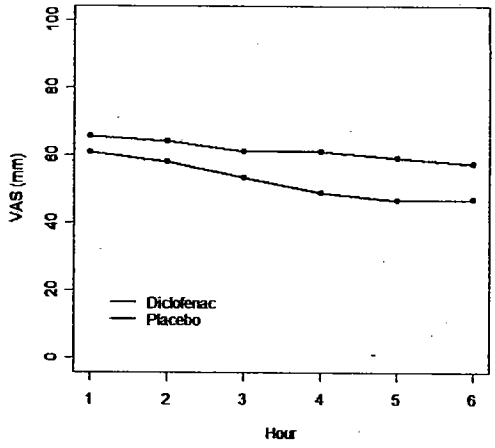
N=134	Flector	Placebo	Difference / p-value
VAS at Day 3	17.760±3.158	30.471±3.47	-12.712/ 0.0005

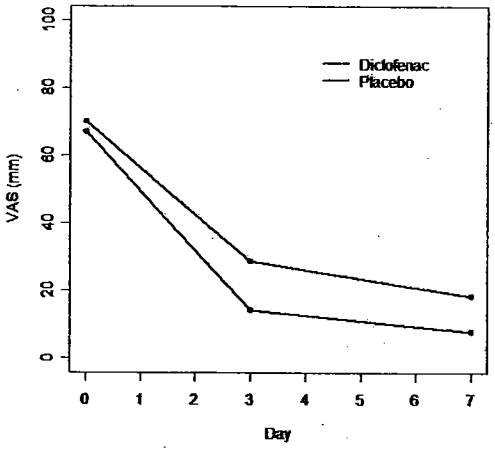
A treatment-by-investigator interaction was tested at the alpha-level of 0.15. It was statistically significantly different from zero. Another model, including baseline VAS, was performed to test the robustness of this interaction effect (see Model 4 in Table X below).

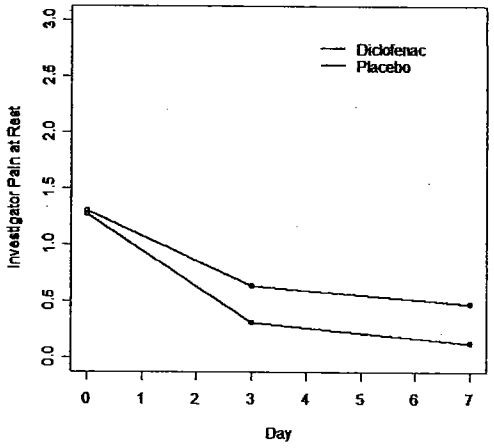
Appendix Table 3: ITT Models Investigating Interaction Term

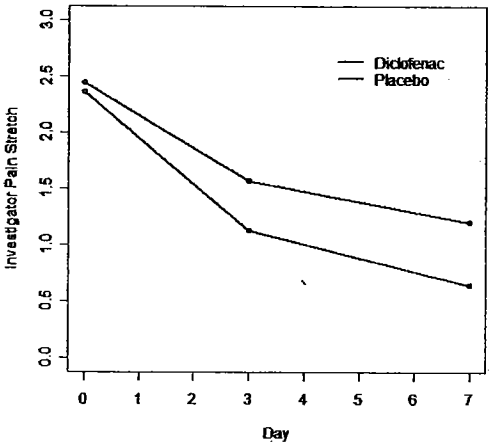
Model	Outcome	Terms	p-value		LS Means	SE	Diff	p-value
1	VAS Day 7	Treatment	0.0041	Flector	12.08	2.82	9.3	0.0041
		Investigator	0.0229	Placebo	21.38	3.09		
2	VAS Day 7	Treatment	0.1003					
		Investigator	0.0034					
		Treatment by Inv Interaction	0.0091					
3	VAS Day 7	Treatment	0.0084	Flector	12.56	2.79	8.49	0.0084
		Investigator	0.0388	Placebo	21.05	3.05		
		Baseline VAS	0.0504					
4	VAS Day 7	Treatment	0.1116					
		Investigator	0.0081					
		Baseline VAS	0.3550					
		Treatment by Inv Interaction	0.0218					

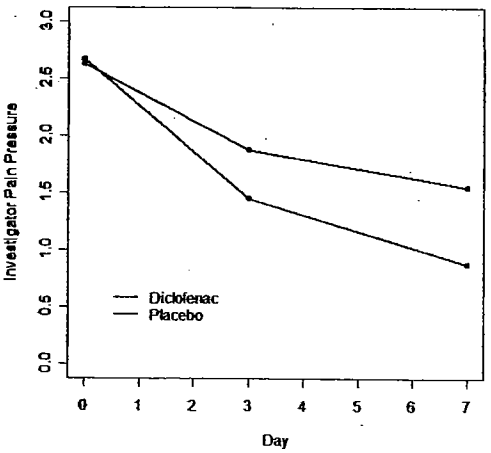
Appendix Figures











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/s/

Dionne Price
1/12/2007 04:49:40 PM
BIOMETRICS
Please see my secondary review in DFS

First cycle 9/21/01

Statistical Review and Evaluation

NDA #: 21-234

Drug Name

Established Name: Diclofenac Epolamine Salt 1.3% Adhesive Patch

Proprietary Name: Diclofenac Epolamine Patch

Dosage Form: Adhesive Patch

Strength: 1.3% w/w **Route/Admin:** Topical, Dermal

Sponsor: Institut Biochimique SA (IBSA)

Proposed Indication: Treatment of Pain

Date Submission: 12/12/2000

Documents Reviewed:

Electronic submission

- All the pdf files in directory "//clinstat/"
- All the SAS transport files in directory "//crt/datasets/"

Hard copy - NDA original amendment submitted in Aug 16, 2001.

Medical Reviewer: Joseph Stauffer, M.D.

1 Background and Introduction

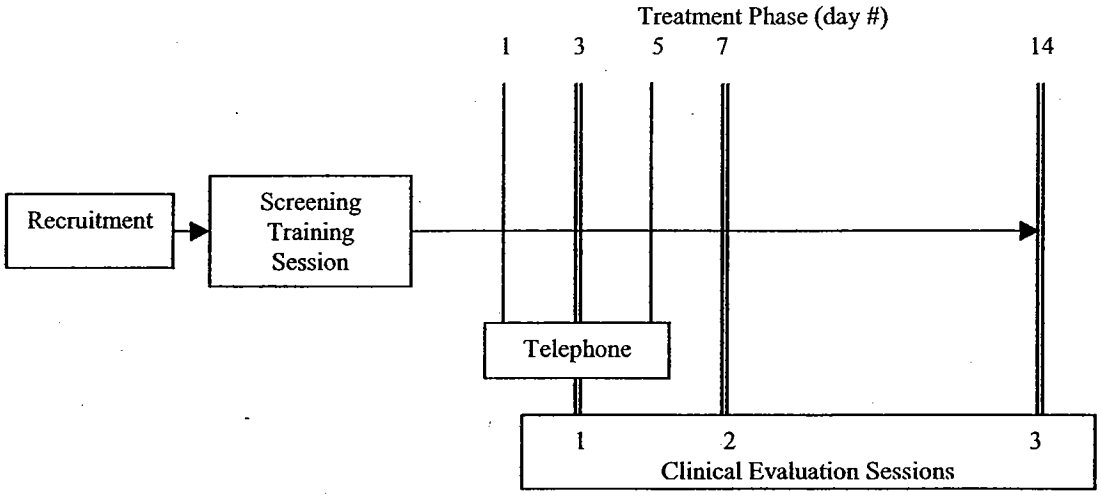
Sponsor submitted two double-blinded randomized, placebo controlled studies (Study 1 and Study 2) for Diclofenac Patch for the indication of pain relief

2 Study 1

2.1 Protocol Synopsis

Design

This was a double-blind, balanced random assignment, placebo (vehicle) controlled, parallel design trial of two weeks continuous-use in 213 patients with minor sports injury. Half of the patients were randomized to receive the active agent and half received placebo (vehicle). Placebo patches are identical in appearance and utilize the same formula as the active patches, without the active principal, diclofenac epolamine. The following diagram presents an overview of the study design, including: recruitment, screening evaluation/training, two-week treatment phase, telephone follow-up calls and the three clinical evaluation sessions.



During the Training Session, the baseline Measures of Spontaneous Pain VAS and Pain on Pressure were recorded using algometer (Day 1).
Subjects were asked to complete the measures of pain relief, and functionality, twice daily (at patch application) on Treatment Days 1-14. Dosage in this study was standard for all patients. The research Coordinator telephoned the subjects on treatment days 1 and 5 to confirm that there was no problems with compliance and completion of the daily diary. During the three Clinical Evaluation Sessions on treatment days 3, 7, and 14, the subject returned to the clinic for measures of Spontaneous Pain VAS and Pain on Pressure using the algometer.

Objectives
The purpose of this placebo-controlled clinical study was to test the analgesic efficacy and safety of a two-week treatment with Diclofenac Epolamine Patch in minor sports injury (sprain, strain, contusion)

Endpoints
Primary Efficacy Variables

- Spontaneous Pain VAS (10 cm, from "no pain" to "severe pain")
- Pain on Pressure (algometer reading compared to contralateral side)

These variables were recorded during all clinical sessions for baseline, Day 3, 7, and 14 clinic visit.

Secondary Efficacy Variables

- Spontaneous Pain, Visual Analog Scale (baseline and diary)
- Relief from Spontaneous Pain, 5-Point Verbal Scale (diary)
- Relief from Pain on Pressure/Movement, 5-Point Verbal Scale (diary)
- Functional Improvement, 5-Point Verbal Scale (diary)
- Patient assessment of local tolerability, 5-point verbal scale (day 3,7,14 clinic visit)
- Investigator assessment of local tolerability, 5-point verbal scale (day 3,7,14 clinic visit)
- Patient Assessment of the Global Response to Therapy, 5-point verbal scale (day 3,7,14 clinic visit)

2.2 Sponsor's statistical analyses and results

Disposition of subjects

At the time of study closure 222 patients had been randomized. Of these, 202 patients completed the protocol as planned, while 20 patients were dropped from the study before completion of the protocol. Nine of these drop-outs have been excluded from the intent-to-treat analysis, because no data exist for these patients beyond the clinic visit at study enrollment.

Demographics and Baseline Characteristics

Table 3 of appendix summarizes the characteristics of the patient demographics at baseline for the ITT patients. A summary of patient's race was not submitted. Table 2 summarizes the baseline values of the primary efficacy variables. Without the race information, the treatment groups were well balanced.

Sponsor's Statistical analysis and Results of Efficacy

The primary efficacy variables were designated in the protocol as: the investigator recorded pain experienced in the course of normal activities (VAS), and pain on pressure (algometer reading of the injured site minus the contralateral site). Each of these was collected at days 1, 3, 7, and 14. The value at the post-baseline day was to be subtracted from that of baseline (initial value in clinic or at home) for each measure creating a pain intensity difference (PID) for each post-baseline day and patient. PIDs were to be analyzed by a two-way analysis of variance with factors of treatment group and research study center at days 3, 7, and 14. The PID and Pain on Pressure Difference (POPD) scores were calculated and analyzed in a similar manner. A summed pain intensity difference (SPID) was to be computed for each day and treatment group for the PIDs and SPIDs as a weighted (by previous time interval) sum of the PID scores. The SPIDs were also to be analyzed by the two-way ANOVA at days 3, 7, and 14. The SPID and Summed Pain on Pressure Difference (SPOPD) scores were calculated and analyzed in a similar manner. For the secondary efficacy variables, two-way ANOVA and Cochran-Mantel-Haenszel test stratified by center were used.

Following table summarizes the sponsor's analysis results of the primary efficacy variables for ITT patients.

Variable	Day	Active			Placebo			P-Value
		N	LSmean	Stderr	N	LSmean	Stderr	
PID	Day 3	106	2.69	0.18	106	2.27	0.18	0.108
	Day 7	106	4.00	0.20	106	3.66	0.20	0.228
	Day 14	106	5.25	0.18	106	4.87	0.18	0.132
SPID	Day 3	106	8.40	0.53	106	7.26	0.53	0.132
	Day 7	106	24.58	1.23	106	22.13	1.23	0.161
	Day 14	106	61.30	2.27	106	56.15	2.27	0.109
POPD	Day 3	105	1.22	0.36	105	1.59	0.36	0.463
	Day 7	105	2.44	0.36	105	2.61	0.36	0.747
	Day 14	105	3.89	0.38	104	3.87	0.38	0.970
SPOPD	Day 3	105	4.13	1.03	105	5.24	1.03	0.451
	Day 7	105	14.04	2.26	104	15.91	2.27	0.560
	Day 14	105	41.26	4.60	104	42.79	4.62	0.814

As shown in the table, none of the primary analysis results show statistical significance. Moreover, for the analyses of POPD and SPOPD, each active treated group is worse than each placebo treated group. Therefore, this study does not support the efficacy of the drug.

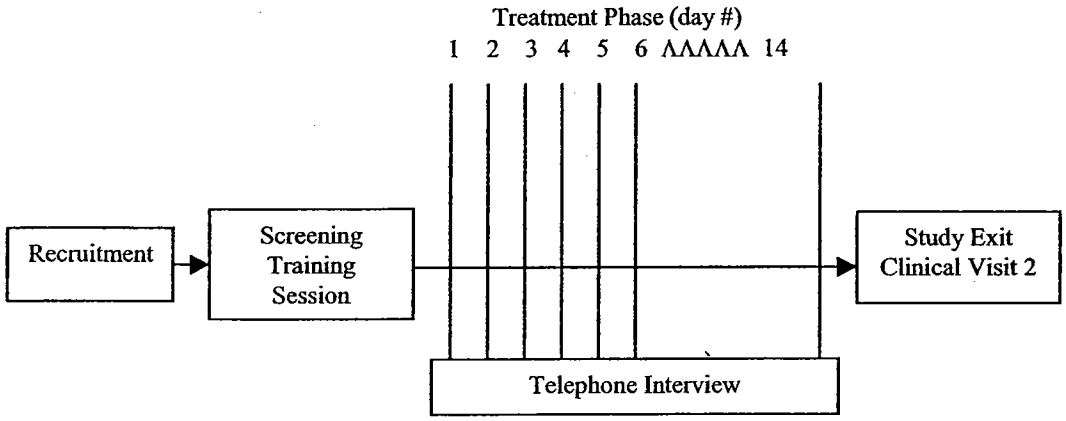
Analysis results of the primary and the secondary variables are summarized in Table 5 and Table 6 of appendix respectively.

3 Study 2

3.1 Protocol Synopsis

Design

This was a double-blind, balanced random assignment, placebo (vehicle) controlled, parallel design trial of two weeks continuous-use in 372 intent-to-treat patients with minor sports injury. Approximately half of the patients were randomized to receive the active agent and half received placebo (vehicle). The following diagram presents an overview of the study design, including: recruitment, screening evaluation/training, two-week treatment phase, telephone follow-up calls and the three clinical evaluation sessions.



During the Training Session, the baseline Measures of the 0-10 Category pain scale was recorded. Patients were asked to complete the measures of pain and adverse events twice daily (at patch application on Treatment Days 1-14. Additionally, patients were instructed to complete their evaluation of global response to treatment and assessment of local tolerability at the exit visit. The research coordinator telephoned each patient on a daily basis during the treatment phase (at least 6 days per week). These daily contacts are to confirm that there no problems with compliance and completion of the daily diary.

Objectives

The purpose of this placebo-controlled clinical study was to test the analgesic efficacy and safety of a two-week treatment with Diclofenac Epolamine Patch in minor sports injury (sprain, strain, and contusion).

Endpoints

Primary Efficacy Variables

- Time to Pain Resolution

The primary efficacy variable described in the protocol was the Time to Pain Resolution based on the daily pain assessments using the 0 – 10 Category Pain (10 cm, from "no pain" to severe pain). Daily measure of pain was recorded at the clinic office at baseline and daily at the time of each patch removal. The pain was considered to be resolved if

the pain level fell to "2" or less on the 0-10 category pain scale for two consecutive days (4 consecutive measures at 12-hour intervals).

This variable was based on the study day at which either pain resolution occurred and the study patch was no longer needed or the patient discontinued wearing the patch and pursued an alternative treatment. Additionally, the patient was required to discontinue wearing the study patch if pain resolution had not occurred at the end of the 14th study day.

In the event that the patient never recorded two consecutive days of pain levels of "2" or less, then the Time to Pain Resolution was set to 15 days since pain resolution did not occur within 14 days of treatment. Additionally, if a patient discontinued wearing the patch due to a lack of perceived efficacy, then the Time to Pain Resolution was set to 15 days.

The actual implementation of the Time to Pain Resolution used the time that had elapsed from the initial patch application to the time at which the patient recorded the fourth Spontaneous Pain of "2" or less. In the event that the patient never recorded four 12-hour intervals of pain levels of "2" or less, then the Time to Pain Resolution was set to 15 days since the pain resolution did not occur within 14 days of treatment. Additionally, if a patient discontinued wearing the patch due to a lack of perceived efficacy, then the Time to Pain Resolution was set to 15 days. Some patients did not provided either the date or the time at which the end point was realized. In that event the time was estimated from the diary date sequence number.

Secondary Efficacy Variables

- Investigator's Assessment of the Global Response to Therapy 5-point verbal scale
- Patient's Assessment of the Global Response to Therapy 5-point verbal scale

3.2 Study Results

Disposition of subjects

At the time of study closure, 411 patients had been randomized. Of these, 365 patients completed the protocol as planned, while 46 patients were dropped from the study before completion of the protocol. Thirty-nine of these dropouts were excluded from the intent-to-treat analysis because no data exist for these patients beyond the clinic visit at study enrollment. Although data from the remaining 7 dropouts are incomplete, those patients are included in the intent-to-treat analyses, but excluded from the per-protocol analyses. Therefore, 372 patients are included in the intent-to-treat analyses and 365 patients are included in the per-protocol analysis.

Patient Demographics and Baseline

The two treatment groups were inbalanced in body weight with a mean difference of 10 lbs and p-value of 0.01 for both ITT and Per-Protocol patients. The primary efficacy variable was reanalyzed with a body weight adjustment and reported in Reviewer's Comments. For the races, 336(93%) patients were unknown and only 24 (7%) patients were observed. For other variables, about 5% of the data are missing for each variable.

Sponsor's statistical analyses and results for efficacy

The primary efficacy variable, Time to Pain Resolution, was analyzed using a Wilcoxon survival test as specified in the protocol, stratified by research study center. Significance was declared at the ϑ=0.05 level. The analysis results showed the p-values to be less than 0.05 for

both ITT and PP patients. Following table summarizes the analysis results of the primary efficacy endpoints. Note that these sponsor's analyses were not adjusted for body weight.

Efficacy analysis results of primary endpoints

Population	Treatment group	Median time (days)	95% CI. for median time	P-value
ITT	Active	9.0	(7.8, 10.5)	0.016
	Placebo	12.3	(10.3, >15)	
PP	Active	8.8	(7.5, 10.3)	0.009
	Placebo	12.4	(10.3, >15)	

Secondary analysis results are summarized in Table 9 of appendix, none of them show the significant difference between treatment groups.

In addition, Average pain score was compared between treatment groups for each study day, which was a primary efficacy analysis in study 1. The analysis results are summarized in Table 7 of appendix. But in these analyses, a definition of "day" of using 24 hour time window was used. In other words, instead of nominal days specified in the CRF, any measurement in 24 hours from baseline was considered as day 1, and any measurement between 24 hour and 48 hours was considered as day 2, and so on. This method was not specified in either protocol nor final report. Moreover, missing data due to dropout were imputed by zero. But LOCF was specified as an imputation method in the protocol. Agency asked the sponsor to reanalyze them using "nominal day" and LOCF. The results were summarized in Table 8 of appendix. As shown in the table, none of them show the significant difference between treatment groups.

Reviewer's comments

As noted above, there was a significant difference in body weight between the two treatment groups. So, the sponsor's efficacy analyses including previous table may not valid. This reviewer reanalyzed the primary endpoint adding body weight as a covariate to check the sensitivity of the analysis results to the inbalanced body weight. Since body weight is a continuous variable, a Cox's proportional hazard model with maximum likelihood estimates was used. The analysis results are summarized in the following table.

Reanalysis results adding body weight as a factor, using Cox's Model

Population	Independent factors	P-value for treatment comparison
ITT	Treatment group, Investigator, Body Weight	0.072
	Treatment group, Investigator	0.019
PP	Treatment group, Investigator, Body Weight	0.045
	Treatment group, Investigator	0.011

As shown in the table, p-values from Cox's model without body weight are similar to the ones from sponsor's Wilcoxon test. But when the analysis is adjusted for body weight, we find increase in the p-values for both ITT and PP population. The between group difference looses significance when the between group difference in body weight is taken into account. Moreover, all the results of secondary efficacy variables failed to show separation of the test drug treated patients from placebo treated patients as shown in Table 8 and 9 of appendix. Therefore, this study does not show a enough evidence of the drug efficacy, especially in the light of the failed study 1. The clinical significance of 9 vs. 12 days of median time to

resolution (and the definition itself) is not convincing in an acute condition such as sports injury.

In addition, this reviewer reanalyzed average pain score adding body weight as a covariate, but none of the days showed a significant difference between treatment groups.

4 Conclusion

Results from two studies (Study 1 and Study 2) with 2-week duration are submitted ——— ——— . For Study 1, the primary efficacy endpoints failed to show the significant difference between the treatment groups for all 4 primary efficacy variables and all the post baseline visits (See Table 5 of appendix). For Study 2, sponsor's analysis results show a separation of test drug's efficacy from placebo's based on their primary efficacy endpoint – Time to Pain Resolution. However, there was a significant inbalance in body weight with the mean difference of 10 lbs. Additional analysis was performed by this reviewer, comparing two treatment groups with body weight as an additional factor. This analysis result shows no significant separation of efficacy of drug treated group from placebo treated group. Details of this analysis result are shown in Reviewer's comments above. In addition, all the analysis results of secondary efficacy variables failed to show significant separation of the test drug treated patients from placebo treated patients as shown in Table 8 and 9 of appendix. Therefore, Study 2 does not provide enough evidence of the drug efficacy, especially in the light of failed study 1.

Suktae Choi, Ph.D.
Mathematical Statistician

Concur: Stan Lin, Ph.D.
Team Leader

Cc: Archival NDA 21-234
HFD-550/Gould/Stauffer/Goldkind
HFD-725/Choi/S.Lin/Huque/Anello
HFD-725/Division File/Chron

Appendix

Table 1. Summary of Patient Enrollment and Validity

		ACTIVE	PLACEBO	TOTAL
Study 1	Patients Enrolled	110	112	222
	Patients Excluded from Safety/Intent-to-Treat	4	5	9
	Patients Included In Safety/Intent-to-Treat	106	107	213
	Patients Excluded from Per-Protocol	4	3	7
	Patients Included In Per-Protocol	102	104	206
Study 2	Patients Enrolled	205	206	411
	Patients Excluded from Safety/Intent-to-Treat	14	25	39
	Patients Included In Safety/Intent-to-Treat	191	181	372
	Patients Excluded from Per-Protocol	3	4	7
	Patients Included In Per-Protocol	188	177	365

Table 2: Baseline measurements of the primary efficacy variables; ITT

	VARIABLE	ACTIVE	PLACEBO	P-VALUES
Study 1	Baseline VAS			
	Mean	6.20	6.29	0.578 [a]
	SD	1.02	1.10	
	Range	3.8 – 8.8	3.6 – 9.5	
	Baseline POP			
	Mean	5.62	5.81	0.688 [a]
	SD	3.72	3.32	
	Range	-14.0 – 12.2	-2.0 – 14.0	
Study 2	Categorical Pain on day 0			
	4	1 (1%)	0 (0%)	0.986 [b]
	5	51 27(%)	56 (31%)	
	6	60 (31%)	45 (25%)	
	7	46 (24%)	42 (23%)	
	8	22 (12%)	31 (17%)	
	9	9 (5%)	2 (1%)	
	10	2 (1%)	3 (2%)	
	Unknown	0	2	

a. P-values for treatment comparisons from a 2-way ANOVA with factors of site and treatment
b. P-values from Cochran-Mantel-Haenszel test for row mean scores, adjusted for site

Table 3: Patient Demographics; Study 1, ITT

Variable	Descriptive Statistics	ACTIVE	PLACEBO	TOTAL	P-Values
Number of Patients		106	107	213	
Age (yrs)	Mean	31.15	29.90	30.52	0.446 [a]
	SD	11.83	9.94	10.91	
	Range	18.0-78.0	18.0-62.0	18.0-78.0	
Sex	Male	78 (74%)	70 (65%)	148 (69%)	0.191 [b]
	Female	28 (26%)	37 (35%)	65 (31%)	
Weight (lbs)	Mean	166.45	168.38	167.42	0.669 [a]
	SD	35.26	32.16	33.67	
	Range	102.0-295.0	100.0-270.0	100.0-295.0	
Height (inches)	Mean	69.2	68.77	68.98	0.423 [a]
	SD	3.80	3.92	3.86	
	Range	59.0-78.0	60.0-77.0	59.0-78.0	
	Not Respond	3	2	5	
Temperature	Mean	98.24	98.21	98.22	0.593 [a]
	SD	0.74	0.75	0.74	
	Range	96.0-99.5	96.2-100.0	96.0-100.0	
	Not Reported	1	4	5	
Systolic Blood Pressure	Mean	124.18	124.23	124.21	0.890 [a]
	SD	16.22	13.54	14.90	
	Range	94.0-165.0	101.0-163.0	94.0-165.0	
Diastolic Blood Pressure	Mean	76.87	77.07	76.97	0.935 [a]
	SD	8.90	10.40	9.66	
	Range	52.0-100.0	51.0-100.0	51.0-100.0	
Heart Rate	Mean	67.49	68.49	67.99	0.473 [a]
	SD	12.15	10.99	11.57	
	Range	48.0-125.0	48.0-104.0	48.0-125.0	
Location of Injury	Foot	8 (8%)	5 (5%)	13 (6%)	0.250 [b]
	Ankle	28 (26%)	30 (28%)	58 (27%)	
	Calf	6 (6%)	4 (4%)	10 (5%)	
	Knee	14 (13%)	14 (13%)	28 (13%)	
	Thigh	7 (7%)	6 (6%)	13 (6%)	
	Finger	2 (2%)	5 (5%)	7 (3%)	
	Hand	2 (2%)	0 (0%)	2 (1%)	
	Wrist	8 (8%)	2 (2%)	10 (5%)	
	Forearm	2 (2%)	1 (1%)	3 (1%)	
	Elbow	6 (6%)	4 (4%)	10 (5%)	
	Groin	1 (1%)	1 (1%)	2 (1%)	
	Other	22 (21%)	35 (33%)	57 (27%)	
Diagnosis	Sprain	40 (38%)	44 (41%)	84 (39%)	0.559 [b]
	Strain	42 (40%)	32 (30%)	74 (35%)	
	Contusion	20 (19%)	25 (23%)	45 (21%)	
	Sprain/Strain	1 (1%)	1 (1%)	2 (1%)	
	Sprain/Contusion	0 (0%)	1 (1%)	1 (0%)	
	Strain/Contusion	1 (1%)	2 (2%)	3 (1%)	
	Other	2 (2%)	2 (2%)	4 (2%)	

a. P-values for treatment comparisons from a 2-way ANOVA with factors of site and treatment
b. P-values from Cochran-Mantel-Haenszel test for row mean scores, adjusted for site

Table 4: Patient Demographics; Study 2, ITT

Variable	Descriptive Statistics	ACTIVE	PLACEBO	TOTAL	P-Values
Number of Patients		191	181	372	
Age (yrs)	N	181	172	353	0.611 [a]
	Mean	32.65	33.06	32.85	
	SD	9.49	10.70	10.08	
	Range	18.3-56.5	18.1-70.8	18.1-70.8	
Sex	Male	117 (64%)	124 (72%)	241 (68%)	0.093 [b]
	Female	65 (36%)	48 (28%)	113 (32%)	
	Unknown	9	9	18	
Race	White	14 (70%)	10 (63%)	24 (67%)	0.640 [b]
	Black	5 (25%)	5 (31%)	10 (28%)	
	Hispanic	1 (5%)	0 (0%)	1 (3%)	
	Asian	0 (0%)	0 (0%)	0 (0%)	
	Other	0 (0%)	1 (6%)	1 (3%)	
	Unknown	171	165	336	
Weight (lbs)	N	178	170	348	0.010 [a]
	Mean	165.76	175.69	170.61	
	SD	36.37	39.14	38.02	
	Range	95.0-297.0	103.0-302.0	95.0-302.0	
Heart Rate	N	188	175	363	0.551 [a]
	Mean	71.73	71.03	71.39	
	SD	10.52	10.56	10.53	
	Range	44.0-108.0	46.0-105.0	44.0-108.0	
Systolic Blood Pressure	N	187	176	363	0.138 [a]
	Mean	117.66	119.95	118.77	
	SD	13.85	14.80	14.34	
	Range	88.0-175.0	86.0-186.0	86.0-186.0	
Diastolic Blood Pressure	N	187	176	363	0.318 [a]
	Mean	74.43	75.38	74.89	
	SD	9.46	10.66	10.06	
	Range	51.0-101.0	50.0-120.0	50.0-120.0	
Temperature	N	178	170	348	0.472 [a]
	Mean	97.96	97.88	97.92	
	SD	0.85	0.86	0.85	
	Range	95.1-99.7	94.4-99.9	94.4-99.9	

a. P-values for treatment comparisons from a 2-way ANOVA with factors of site and treatment
b. P-values from Cochran-Mantel-Haenszel test for row mean scores, adjusted for site

Table 5: Primary efficacy Variable analysis; Study 1

Variable	Day	Active			Placebo			P-Value [a]
		N	LSmean	Stderr	N	LSmean	Stderr	
ITT								
PID	Day 3	106	2.69	0.18	106	2.27	0.18	0.108
	Day 7	106	4.00	0.20	106	3.66	0.20	0.228
	Day 14	106	5.25	0.18	106	4.87	0.18	0.132
SPID	Day 3	106	8.40	0.53	106	7.26	0.53	0.132
	Day 7	106	24.58	1.23	106	22.13	1.23	0.161
	Day 14	106	61.30	2.27	106	56.15	2.27	0.109
POPD	Day 3	105	1.22	0.36	105	1.59	0.36	0.463
	Day 7	105	2.44	0.36	105	2.61	0.36	0.747
	Day 14	105	3.89	0.38	104	3.87	0.38	0.970
SPOPD	Day 3	105	4.13	1.03	105	5.24	1.03	0.451
	Day 7	105	14.04	2.26	104	15.91	2.27	0.560
	Day 14	105	41.26	4.60	104	42.79	4.62	0.814
Per-Protocol								
PID	Day 3	102	2.68	0.19	104	2.28	0.18	0.126
	Day 7	102	4.03	0.20	104	3.69	0.20	0.237
	Day 14	102	5.33	0.17	104	4.93	0.17	0.104
SPID	Day 3	102	8.40	0.54	104	7.30	0.54	0.151
	Day 7	102	24.72	1.25	104	22.30	1.24	0.172
	Day 14	102	62.00	2.26	104	56.73	2.23	0.099
POPD	Day 3	102	1.14	0.36	104	1.60	0.36	0.369
	Day 7	102	2.40	0.36	104	2.62	0.36	0.660
	Day 14	102	3.89	0.38	104	3.87	0.38	0.971
SPOPD	Day 3	102	3.91	1.04	104	5.26	1.03	0.357
	Day 7	102	13.65	2.27	104	15.91	2.25	0.481
	Day 14	102	40.86	4.63	104	42.79	4.58	0.768

a. P-values for treatment comparisons from a 2-way ANOVA with factors of site and treatment

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Table 6: Secondary efficacy Variable analysis; Study 1

Variable	Day	Active			Placebo			P-Value [a]
		N	LSmean	Stderr	N	LSmean	Stderr	
ITT								
SPID	Day 3	105	10.08	0.63	106	7.93	0.63	0.017
	Day 7	105	26.40	1.29	106	21.83	1.29	0.013
	Day 14	105	56.07	2.23	106	49.30	2.22	0.033
TOTPAR	Day 3	104	8.47	0.38	105	6.87	0.38	0.003
	Day 7	104	19.27	0.75	105	16.36	0.75	0.007
	Day 14	104	37.78	1.34	105	33.45	1.33	0.023
TOTPMR	Day 3	105	7.87	0.37	105	6.82	0.37	0.046
	Day 7	105	18.34	0.72	105	16.05	0.72	0.027
	Day 14	105	36.55	1.29	105	32.66	1.29	0.034
SFIS	Day 3	105	8.15	0.37	105	7.01	0.37	0.029
	Day 7	105	18.87	0.73	105	16.39	0.73	0.017
	Day 14	105	37.06	1.33	105	33.07	1.33	0.035
Per-Protocol								
SPID	Day 3	102	9.81	0.64	103	8.07	0.63	0.053
	Day 7	102	25.99	1.30	103	22.21	1.29	0.041
	Day 14	102	55.59	2.23	103	50.22	2.22	0.090
TOTPAR	Day 3	101	8.42	0.38	102	6.99	0.38	0.009
	Day 7	101	19.24	0.76	102	16.61	0.76	0.015
	Day 14	101	37.85	1.34	102	33.99	1.34	0.043
TOTPMR	Day 3	102	7.87	0.37	102	6.96	0.37	0.086
	Day 7	102	18.41	0.73	102	16.34	0.73	0.046
	Day 14	102	36.77	1.29	102	33.27	1.29	0.056
SFIS	Day 3	102	8.13	0.38	102	7.08	0.38	0.051
	Day 7	102	18.91	0.74	102	16.59	0.74	0.027
	Day 14	102	37.25	1.34	102	33.54	1.34	0.052

a. P-values for treatment comparisons from a 2-way ANOVA with factors of site and treatment

Table 7: Average pain score by 24-hour day with ZeroCF; Study 2

	Day	Active			Placebo			P-Value
		N	LSmean	Stderr	N	LSmean	Stderr	
ITT	Day 0	191	6.34	0.09	181	6.32	0.09	0.920[a]
	Day 1	191	5.93	0.05	181	5.92	0.06	0.981[b]
	Day 2	191	4.77	0.11	181	4.88	0.11	0.445[b]
	Day 3	191	3.89	0.13	181	4.16	0.13	0.116[b]
	Day 4	191	3.18	0.15	181	3.50	0.15	0.116[b]
	Day 5	191	2.63	0.15	181	2.94	0.16	0.137[b]
	Day 6	191	2.14	0.15	181	2.59	0.16	0.030[b]
	Day 7	191	1.76	0.15	181	2.24	0.16	0.023[b]
	Day 8	191	1.43	0.15	181	1.96	0.15	0.009[b]
	Day 9	191	1.19	0.15	181	1.66	0.15	0.018[b]
	Day 10	191	0.98	0.14	181	1.52	0.15	0.005[b]
	Day 11	191	0.77	0.14	181	1.34	0.14	0.002[b]
	Day 12	191	0.71	0.13	181	1.16	0.13	0.011[b]
	Day 13	191	0.62	0.12	181	0.99	0.13	0.025[b]
	Day 14	191	0.54	0.12	181	0.85	0.12	0.057[b]
Per-Protocol	Day 0	188	6.33	0.09	177	6.34	0.09	0.936[a]
	Day 1	188	5.92	0.05	177	5.92	0.06	0.990[b]
	Day 2	188	4.76	0.11	177	4.89	0.11	0.369[b]
	Day 3	188	3.86	0.13	177	4.15	0.13	0.091[b]
	Day 4	188	3.15	0.15	177	3.48	0.15	0.094[b]
	Day 5	188	2.57	0.16	177	2.92	0.16	0.095[b]
	Day 6	188	2.09	0.15	177	2.57	0.16	0.020[b]
	Day 7	188	1.71	0.15	177	2.21	0.16	0.015[b]
	Day 8	188	1.37	0.15	177	1.94	0.16	0.005[b]
	Day 9	188	1.13	0.15	177	1.63	0.15	0.011[b]
	Day 10	188	0.92	0.14	177	1.50	0.15	0.003[b]
	Day 11	188	0.72	0.14	177	1.32	0.14	0.001[b]
	Day 12	188	0.64	0.13	177	1.14	0.13	0.004[b]
	Day 13	188	0.55	0.12	177	0.98	0.13	0.009[b]
	Day 14	188	0.47	0.12	177	0.83	0.12	0.021[b]

a. P-values for treatment comparisons from a 2-way ANOVA with factors of site and treatment
b. P-values from a 2-way ANCOVA with factors of treatment and investigator as factors and baseline severity as the covariate

Table 8: Average pain score by nominal study day with LOCF; Study 2

	Day	Active			Placebo			P-Value
		N	LSmean	Stderr	N	LSmean	Stderr	
ITT	Day 0	191	6.34	0.09	181	6.32	0.09	0.920[a]
	Day 1	191	6.13	0.04	181	3.13	0.04	0.993[b]
	Day 2	191	5.13	0.10	181	5.17	0.11	0.775[b]
	Day 3	191	4.31	0.12	181	4.43	0.12	0.427[b]
	Day 4	191	3.57	0.13	181	3.85	0.14	0.128[b]
	Day 5	191	1.13	0.14	181	3.33	0.15	0.296[b]
	Day 6	191	2.77	0.14	181	3.04	0.15	0.164[b]
	Day 7	191	2.54	0.14	181	2.78	0.15	0.218[b]
	Day 8	191	2.30	0.14	181	2.56	0.15	0.185[b]
	Day 9	191	2.12	0.14	181	2.39	0.15	0.159[b]
	Day 10	191	1.96	0.14	181	2.30	0.15	0.075[b]
	Day 11	191	1.87	0.14	181	2.20	0.15	0.081[b]
	Day 12	191	1.82	0.14	181	2.09	0.14	0.159[b]
	Day 13	191	1.78	0.14	181	2.01	0.15	0.222[b]
	Day 14	191	1.72	0.14	181	1.92	0.15	0.306[b]
Per-Protocol	Day 0	188	6.33	0.09	177	6.34	0.09	0.936[a]
	Day 1	188	6.13	0.04	177	6.12	0.04	0.856[b]
	Day 2	188	5.12	0.10	177	5.17	0.11	0.680[b]
	Day 3	188	4.28	0.12	177	4.43	0.13	0.367[b]
	Day 4	188	3.54	0.13	177	3.84	0.14	0.103[b]
	Day 5	188	3.09	0.14	177	3.32	0.15	0.250[b]
	Day 6	188	2.72	0.14	177	3.03	0.15	0.115[b]
	Day 7	188	2.50	0.15	177	2.77	0.15	0.161[b]
	Day 8	188	2.26	0.14	177	2.55	0.15	0.137[b]
	Day 9	188	2.08	0.14	177	2.38	0.15	0.116[b]
	Day 10	188	1.91	0.15	177	2.29	0.15	0.049[b]
	Day 11	188	1.83	0.14	177	2.20	0.15	0.054[b]
	Day 12	188	1.78	0.14	177	2.08	0.15	0.111[b]
	Day 13	188	1.73	0.14	177	2.00	0.15	0.156[b]
	Day 14	188	1.67	0.14	177	1.91	0.15	0.214[b]

a. P-values for treatment comparisons from a 2-way ANOVA with factors of site and treatment
b. P-values from a 2-way ANCOVA with factors of treatment and investigator as factors and baseline severity as the covariate

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Table 9: Secondary efficacy Variable analysis; Study 2

Population	Variable	Category	ACTIVE	PLACEBO	TOTAL	P-values [a]
ITT	Number of patients		191	181	372	
	Patients' Assessment	None	16 (8%)	15 (8%)	31 (8%)	0.118
		Poor	14 (7%)	11 (6%)	25 (7%)	
		Fair	32 (17%)	55 (30%)	87 (23%)	
		Good	67 (35%)	57 (31%)	124 (33%)	
		Excellent	62 (32%)	43 (24%)	105 (28%)	
	Investigators' Assessment	None	13 (7%)	15 (8%)	28 (8%)	0.158
		Poor	16 (8%)	13 (7%)	29 (8%)	
		Fair	39 (21%)	51 (29%)	90 (24%)	
		Good	63 (33%)	56 (31%)	119 (32%)	
		Excellent	59 (31%)	43 (24%)	102 (28%)	
Per-Protocol	Number of patients		188	177	365	
	Patients' Assessment	None	16 (9%)	14 (8%)	30 (8%)	0.143
		Poor	14 (7%)	11 (6%)	25 (7%)	
		Fair	31 (16%)	54 (31%)	85 (23%)	
		Good	65 (35%)	55 (31%)	120 (33%)	
		Excellent	62 (33%)	43 (24%)	105 (29%)	
	Investigators' Assessment	None	13 (7%)	15 (9%)	28 (8%)	0.174
		Poor	16 (9%)	12 (7%)	28 (8%)	
		Fair	38 (20%)	50 (29%)	88 (24%)	
		Good	62 (33%)	55 (32%)	117 (32%)	
		Excellent	58 (31%)	42 (24%)	100 (28%)	

a. P-values from Cochran-Mantel-Haenszel test stratified by research study center

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