CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-202

STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: NDA 22-202

Drug Name: Zipsor (diclofenac potassium) Soft Gelatin Capsules

Indication(s): For the relief of mild to moderate acute pain

Applicant: Xanodyne Pharmaceuticals, Inc.

Date(s): Submitted: September 21, 2007
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Review Priority: Standard

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Keywords: NDA review, clinical studies, sensitivity analyses

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Two multiple-dose studies, XP21L-301 and XP21L-302, in patients with pain following bunionectomy surgery demonstrated a statistically significant difference in pain intensity between diclofenac potassium 25 mg soft gelatin capsules and placebo.

Two single-dose studies, CL-000395 and CL-000400, in patients with pain following dental surgery demonstrated a statistically significant difference in pain intensity between each dose of 25 mg, 50 mg, and 100 mg diclofenac potassium and placebo.

Two multiple-dose studies CL-000396 and CL-000401 in patients with pain following knee arthroscopy surgery failed to show a statistically significant difference in pain intensity when comparing 25 mg and 50 mg diclofenac potassium to placebo.

Overall, the evidence of efficacy was replicated in two well-controlled, multiple-dose, bunionectomy pain studies. As supportive evidence, the efficacy was also replicated in two well-controlled, single-dose, dental pain studies.

1.2 Brief Overview of Clinical Studies

The applicant submitted the results and data from six efficacy studies of diclofenac potassium soft gelatin capsule in patients with pain from bunionectomy, dental surgery, or knee arthroscopy surgery. Studies XP21L-301 and XP21L-302 were multi-dose trials of identical design in patients with bunionectomy pain. Studies CL-000395 and CL-000400 were single-dose trials of identical design in patients with dental pain. Studies CL-000396 and CL-000401 were multi-dose trials of identical design in patients with pain following knee arthroscopy surgery. Because the applicant's analyses of studies CL-000396 and CL-000401 failed to show statistically significant differences between the active drug and placebo, I focused on studies XP21L-301, XP21L-302, CL-000395, and CL-000400 only in my review.

In study XP21L-301, two-hundred and one patients were randomized to diclofenac 25 mg (n = 102) or placebo (n = 99) in 1:1 ratio. In study XP21L-302, two-hundred patients were randomized to diclofenac 25 mg (n = 99) or placebo (n = 101) in 1:1 ratio.

The primary objective of the two studies was to show efficacy of therapy with diclofenac 25 mg when compared to placebo. The primary efficacy outcome variable of the two studies was the average pain intensity scores (11-point numerical pain rating scale ranging from 0 to 10) over 48 hrs during the multi-dose period. Therefore, the score ranges from 0 to 10 continuously. The average score was prespecified as the primary endpoint to be used in statistical inference.

The secondary efficacy variables included the following:

- Time to re-medication (single dose period)
- Onset of perceptible and meaningful pain relief (single dose period)
- Total pain relief over 8 hours (TOTPAR8) (single dose period)
- Summed pain intensity difference over 8 hours (SPID8) (single dose period)
- Subjects' global assessment of study medication (multi-dose period).

In study CL-000395, two-hundred and sixty-five patients were randomized to diclofenac 25 mg (n = 63), diclofenac 50 mg (n = 68), diclofenac 100 mg (n = 66), and placebo (n = 68) in 1:1:1:1 ratio. In study CL-000400, two-hundred and forty-nine patients were randomized to diclofenac 25 mg (n = 63), diclofenac 50 mg (n = 62), diclofenac 100 mg (n = 63), and placebo (n = 61) in 1:1:1:1 ratio.

The primary objective of the two studies was to show efficacy of therapy with diclofenac 25 mg, 50 mg, or 100 mg when compared to placebo. The primary efficacy outcome variable of the studies was the summed pain intensity difference over 6 hours (SPID6). The score ranges from 0 (= no pain) to 3 (= worst possible pain) discretely. The score was pre-specified as the primary endpoint to be used in statistical inference.

The secondary efficacy variables were

- Time to rescue medication
- Time to onset of perceptible and meaningful PR
- TOTPAR
- Overall global evaluation score.

1.3 Statistical Issues and Findings

For the efficacy analyses of studies XP21L-301 and XP21L-302, the applicant based their inferences on the full analysis set (FAS) with the worst observation carried forward (WOCF). The applicant's FAS population for these studies was defined as all randomized patients who received at least one dose of study medication. The analysis population and the conservative imputation method are acceptable.

There were no statistically significant interactions between treatment and center or baseline pain. In study XP21L-301, sites 2 and 7 were pooled for analysis because site 7 had fewer than 8 patients and site 2 was the next smallest as pre-specified in the statistical analysis plan.

As a sensitivity analysis, a LOCF analysis was conducted and gave results similar to the WOCF analysis. The primary analysis conducted on the FAS population and the per protocol (PP) analysis were consistent. No adjustment for multiplicity was made for the secondary endpoints analyses.

For the efficacy analyses of studies CL-000395 and CL-000400, the applicant based their inferences on the FAS with the last observation carried forward strategy. The applicant's FAS population for these studies was defined as all randomized patients who received at least one dose of study medication and at least one post baseline pain assessment. However, since the intention-to-treat (ITT) population including all randomized patients is more appropriate as the primary analysis set, I conducted the same analysis as the sponsor based on the ITT population as a sensitivity analysis. Although LOCF may not be considered conservative, because there were very few dropouts (less than 1%) and patients only received a single dose, it is acceptable. For adjustment for multiple comparisons (diclofenac 25 mg vs. placebo, 50 mg vs. placebo, and 100 mg vs. placebo), the applicant proposed Dunnett's method which is considered acceptable.

There were no statistically significant interactions between treatment and baseline pain. The analyses conducted on varying populations (i.e. ITT, FAS, and PP) were consistent. No adjustment for multiplicity was made for the secondary endpoints analyses.

2. INTRODUCTION

2.1 Overview

2.1.1 Drug class and regulatory history

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) used to treat arthritic conditions, mild to moderate pain, dysmenorrhea, and a variety of other painful conditions.

The applicant states the following regarding the drug and regulatory history:

> Diclofenac potassium soft gelatine capsule (DPSGC) is designed to ensure rapid and consistent delivery of diclofenac for prompt relief of mild to moderate pain. It contains the same active ingredient as the approved reference drug, Cataflam® (diclofenac potassium immediate-release tablets, 50 mg) and is administered by the same route. The primary difference between DPSGC and the reference product is the change from a tablet dosage form to a proprietary liquid formulation in a soft gelatin capsule that provides rapid and consistent absorption of diclofenac using the patented ProSorb® technology. The Food and Drug Administration (FDA) has approved numerous diclofenac products, including:
>
> • Voltaren® (diclofenac sodium) 25, 50, and 75 mg Delayed Release Tablets (NDA 19-201, approved in 1988);
>
> • Voltaren® (diclofenac sodium) 0.1% Ophthalmic Solution (NDA 20-037, approved in 1991);
>
> • Cataflam® (diclofenac potassium) 25 and 50 mg Immediate Release Tablets (NDA 20-142, approved in 1993);

- Voltaren-XR® (diclofenac sodium) 100 mg Extended Release Tablets (NDA 20-254, approved in 1996);
- Arthrotec® (diclofenac sodium/misoprostol) 50, 75 mg/0.2 mg Delayed Release Tablets (NDA 20-607, approved in 1997);
- Solaraze® (diclofenac sodium) 3% Gel (NDA 21-005, approved in 2000); and
- Flector® (diclofenac epolamine) 1.3% patch (NDA 02-1234, approved in 2007).

In addition, FDA has approved at least nine generic versions of Voltaren Delayed Release Tablets and six generic versions of Cataflam Immediate Release Tablets. Most recently, FDA approved Mutual Pharmaceutical's abbreviated new drug application (ANDA) 75-470 for Diclofenac Potassium Tablets on February 21, 2002.

In addition to the existing data on diclofenac, Xanodyne's clinical trial program provides supplemental evidence of the safety and efficacy of DPSGC in the treatment of mild to moderate pain. These clinical trials were designed in consultation with the FDA Division of Anti-inflammatory, Analgesic and Ophthalmologic Products (meetings 06 April 2001; 11 February 2003) and the Division of Anesthetic, Analgesic, and Rheumatology Products (12 June 2006), which suggested that replicate studies should be conducted in postsurgical pain populations using a 25 mg dose.

2.1.2 Proposed Indication for Zipsor™

Zipsor™ (diclofenac potassium) Soft Gelatin Capsule is indicated for the relief of mild to moderate (b) (4) pain.

2.2 Data Sources

The original electronic SAS data submission of September 11, 2007 can be found on the FDA, CDER electronic document room (EDR).

Data sets:

\\Cdsesub1\evsprod\NDA022202\0000\m5\datasets

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

XP21L-301 and XP21L-302 were of identical design and were multi-center, double-blind, multiple-dose studies of the safety and efficacy of diclofenac 25 mg compared to placebo in patients with bunionectomy pain. The studies consisted of 2 dosing periods: a

single dosing period (on Day 1) followed by a multiple dose period (through Day 4). When subjects first reported a pain intensity score of at least 4 on an 11-point numerical pain rating scale (0=no pain, 10=worst pain imaginable) between 4 am and 10 am on Day 1, they were randomized to diclofenac 25 mg or placebo in 1:1 ratio. The re-medication dose was given 8 hours after the initial dose or earlier when needed and marked the start of the 48-hour multiple dosing period, during which subjects took their study medication every 6 hours.

CL-000395 and CL-000400 were of identical design and were multi-center, double-blind, single-dose studies of the safety and efficacy of diclofenac 25 mg, 50 mg, or 100 mg compared to placebo in patients with dental pain. Patients were randomized to diclofenac 25 mg, 50 mg, 100 mg, or placebo in 1:1:1:1 ratio.

Schematics of the study designs for studies XP21L-301, XP21L-302, CL-000395, and CL-000400 are presented in the appendix (Figure 13). Six investigators enrolled subjects from US sites and participated in the clinical study XP21L-301. Four investigators enrolled subjects from US sites and participated in the clinical study XP21L-302. Six investigators enrolled subjects from US sites and participated in the clinical study CL-000395. Seven investigators enrolled subjects from US sites and participated in the clinical study CL-000400.

The primary efficacy endpoint for studies XP21L-301 and XP21L-302 was the average of 48-hour pain intensity measured on an 11-point numerical pain rating scale (NPRS). The primary efficacy endpoint for studies CL-000395 and CL-000400 was the summed pain intensity difference (SPID) during 6 hours.

3.1.2 Patient Disposition and Demographics

About 2%, 5%, 1%, and 1% of the patients discontinued from studies XP21L-301, XP21L-302, CL-000395, and CL-000400, respectively as shown in the appendix (Table 17). Because the dropout rates were low as expected from these short term acute pain studies, issues of handling missing data were not critical in assessing efficacy data.

Patient demographics are presented in the appendix by treatment groups for the studies XP21L-301, XP21L-302, CL-000395, and CL-000400, respectively (Table 18). There were no noticeable imbalances among treatment groups with respect to demographic variables of age, race, and weight.

Table 18 also shows baseline values for the pain variables by treatment groups for the studies XP21L-301, XP21L-302, CL-000395, and CL-000400, respectively. Distributions of the pain variables at baseline were comparable among treatment groups.

3.1.3 Statistical Methodologies

In studies XP21L-301 and XP21L-302, the average 48-hour pain intensity was compared between diclofenac 25 mg and placebo using an analysis of covariance (ANCOVA) model with terms for treatment, site and baseline value as covariate. The worst observation carried forward (WOCF) (including baseline observation) was used as the imputation strategy for missing data in the primary analysis. The last observation carried forward (LOCF) analysis was conducted as a sensitivity analysis. As the primary analysis population, the full analysis set (FAS) was defined as all randomized patients who received at least one dose of study medication.

In studies CL-000395 and CL-000400, SPID6 was compared between diclofenac 25 mg, 50 mg, or 100 mg and placebo using an ANCOVA model with terms for treatment and baseline value as covariate. LOCF was used as the imputation strategy for missing data in the primary analysis. Dunnett's method was used to adjust for multiple comparisons. As the primary analysis population, the full analysis set (FAS) was defined as all randomized patients who received at least one dose of study medication and at least one post baseline pain assessment.

3.1.4 Results and Conclusions

Tables 1 - 16, 19 - 22 and Figures 1 – 12 present the statistical analyses done by the applicant and me. The following are results of the analyses.

Study XP21L-301:

Data from the study demonstrated the superiority of diclofenac 25 mg to placebo in terms of the primary endpoint, average pain intensity over 48 hours. In their analysis, the applicant used ANCOVA model with terms for treatment, site and baseline pain as covariate on FAS population with WOCF. The numbers in my analysis are slightly different from those in the submission because I could not reproduce the numbers provided by the applicant. However, the overall conclusions are the same. My sensitivity analysis with LOCF in the appendix also showed a statistically significant difference between diclofenac 25 mg and placebo.

The superiority of diclofenac 25 mg to placebo was also shown in the analyses of the secondary efficacy variables of SPID48, use of rescue medication, and time to re-medication. In the analysis of time to onset of pain relief, there was a statistically significant difference between diclofenac 25 mg and placebo in meaningful pain relief although not in perceptible pain relief. However, it should be noted that no multiplicity adjustments were done on the analyses of secondary endpoints.

In the analysis of time to event, the median time and its confidence limits cannot be estimated when the survival distribution function does not provide information on those parameters. When this is the case, the parameter is denoted as 'ne'.

Table 1 Reviewer's Primary Endpoint Analysis: Study XP21L-301 FAS with WOCF

average pain intensity over 48 hrs	**DICLOFENAC (N=102)**	**PLACEBO (N=99)**
LS Means (SE)	2.8 (0.20)	5.6 (0.20)
Difference from placebo (SE) 95% CI	2.8 (0.23) (2.37, 3.30)	
P-value*	**<0.0001**	

*LSMeans and p-values calculated from ANCOVA model: Y = trt +site+baseline.

Table 2 Reviewer's Secondary Endpoint Analysis: Study XP21L-301 FAS with WOCF

SPID over 48 hrs	**DICLOFENAC (N=102)**	**PLACEBO (N=99)**
LS Means (SE)	205 (9.1)	77 (9.4)
Difference from placebo (SE) 95% CI	128 (10) (107, 150)	
P-value*	**<0.0001**	

*LSMeans and p-values calculated from ANCOVA model: Y = trt +site+baseline.

Table 3 Reviewer's Secondary Endpoint Analysis of Rescue Medication Use: Study XP21L-301 FAS

	DICLOFENAC (N=102)	**PLACEBO (N=99)**
N, % of rescue medication use	44 (43%)	90 (91%)
P-value*	**<0.0001**	

* P-value calculated from CMH test with site as strata.

Table 4 Secondary Endpoint Analysis of Time to Onset of Pain Relief: Study XP21L-301 FAS

	DICLOFENAC (N=102)	**PLACEBO (N=99)**
Time to Perceptible Pain Relief (min):		
Median time*	26	22
95% CI*	(18.6 – 31.3)	(16.6 – 35.8)
Log-rank p-value**	0.235	
Cox-phreg p-value**	0.357	
Time to Meaningful Pain Relief (min):		
Median time*	70	106
95% CI*	(61.2 – 92.0)	(84.7 – ne)
Log-rank p-value**	**0.008**	
Cox-phreg p-value**	**0.012**	

*Median time and CI based on Kaplan-Meier analysis. 'ne' stands for 'not estimable'.
** P-values calculated from Log-rank test and Cox regression model with terms for treatment and baseline score as covariate.

Figure 1 Kaplan-Meier Plot of Time to Perceptible Pain Relief: Study XP21L-301 FAS

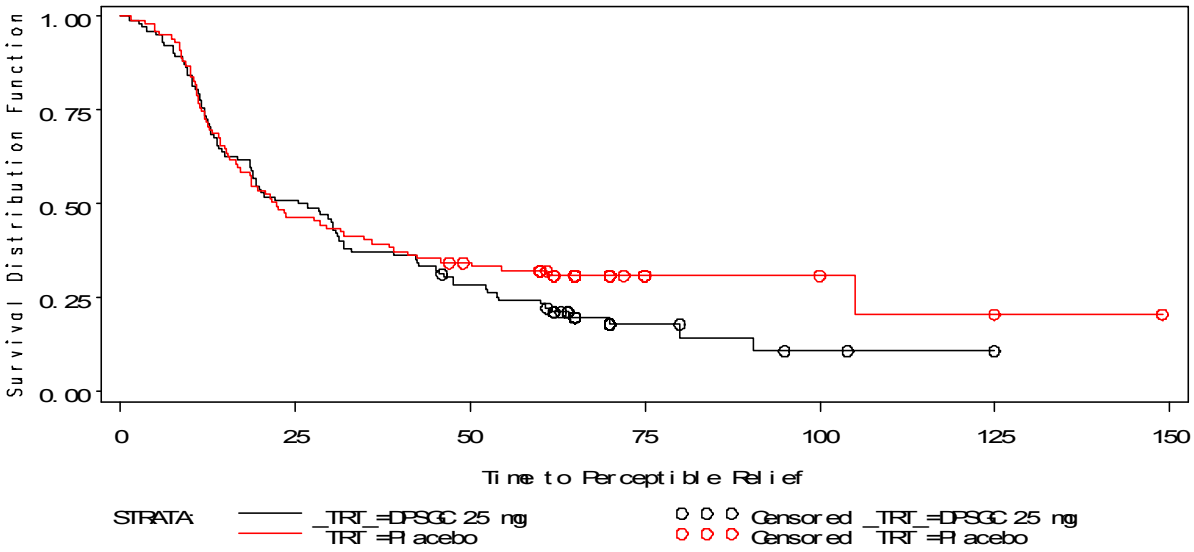


Figure 2 Kaplan-Meier Plot of Time to Meaningful Pain Relief: Study XP21L-301 FAS

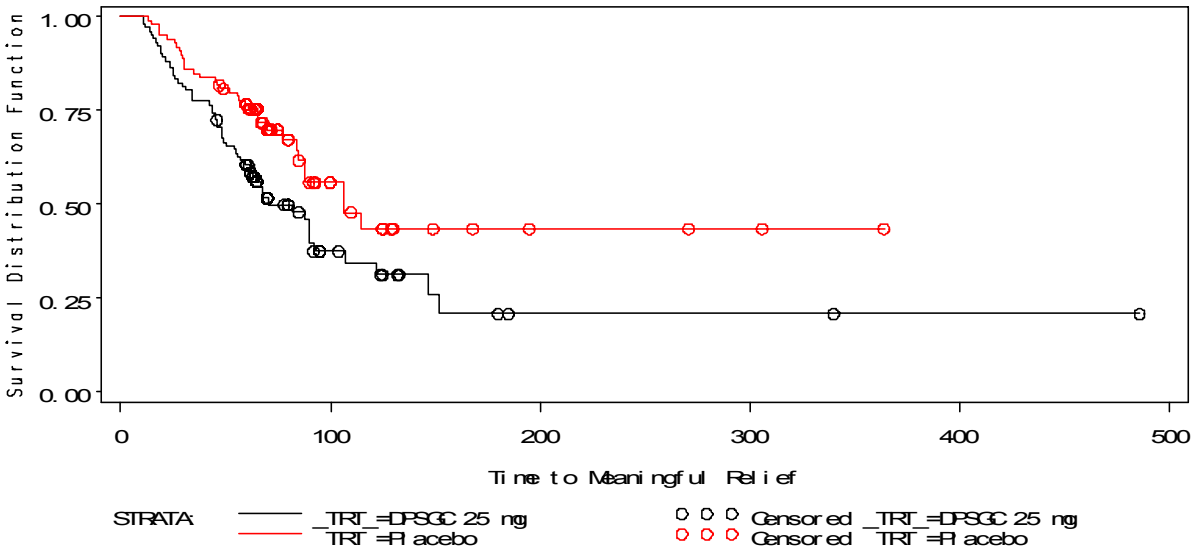
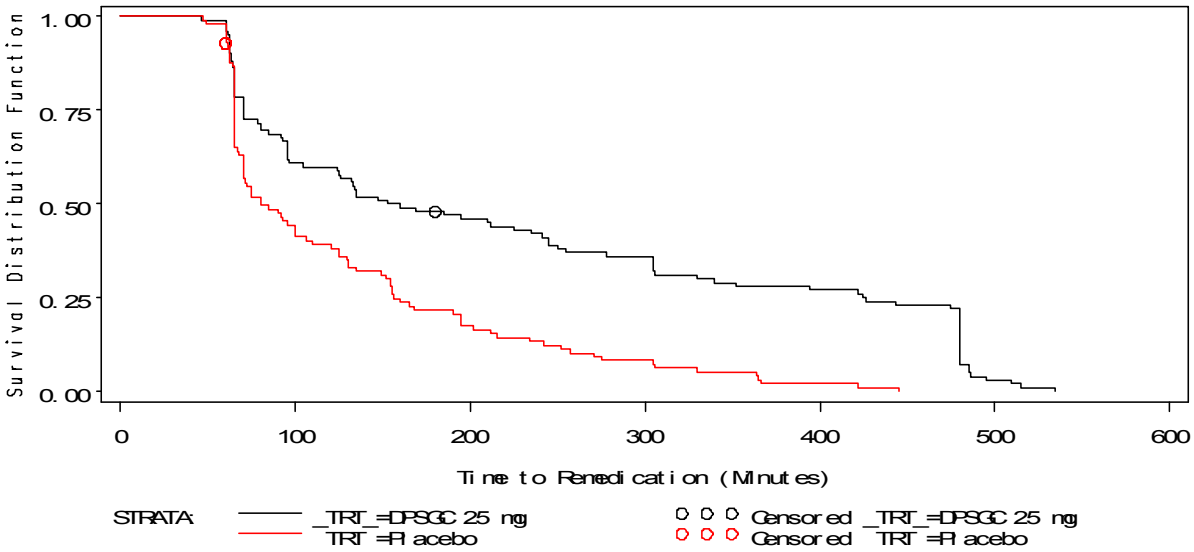


Table 5 Secondary Endpoint Analysis of Time to Re-medication: Study XP21L-301 FAS

	DICLOFENAC (N=102)	**PLACEBO (N=99)**
Time to re-medication (min):		
Median time*	157	80
95% CI*	(124.0 – 245.0)	(70.0 – 110.0)
Log-rank p-value**	**<0.001**	
Cox-phreg p-value**	**<0.001**	

*Median time and CI based on Kaplan-Meier analysis. 'ne' stands for 'not estimable'.
** P-values calculated from Log-rank test and Cox regression model with terms for treatment and baseline score as covariate.

Figure 3 Kaplan-Meier Plot of Time to Re-medication: Study XP21L-301 FAS



Study XP21L-302:

Data from the study demonstrated the superiority of diclofenac 25 mg to placebo in terms of primary endpoint, average pain intensity over 48 hours. In their analysis, the applicant used ANCOVA model with terms for treatment, site and baseline pain as covariate on FAS population with WOCF. The numbers in my analysis are slightly different from those in the submission because I could not reproduce the numbers provided by the applicant. However, the overall conclusions are the same. My sensitivity analysis with LOCF in the appendix also showed a statistically significant difference between diclofenac 25 mg and placebo.

The superiority of diclofenac 25 mg to placebo was also shown in the analyses of the secondary efficacy variables of SPID48, use of rescue medication, and time to re-medication. In the Cox regression analysis of time to onset of pain relief, there was a statistically significant difference between diclofenac 25 mg and placebo both in the meaningful pain relief and the perceptible pain relief. However, it should be noted that no multiplicity adjustments were done on the analyses of secondary endpoints.

Table 6 Reviewer's Primary Endpoint Analysis: Study XP21L-302 FAS with WOCF

average pain intensity over 48 hrs	**DICLOFENAC (N=99)**	**PLACEBO (N=101)**
LS Means (SE)	3.3 (0.19)	5.8 (0.19)
Difference from placebo (SE) 95% CI	2.5 (0.27) (1.98, 3.05)	
P-value*	**<0.0001**	

*LSMeans and p-values calculated from ANCOVA model: Y = trt +site+baseline.

Table 7 Secondary Endpoint Analysis: Study XP21L-302 FAS with WOCF

SPID over 48 hrs	**DICLOFENAC (N=99)**	**PLACEBO (N=101)**
LS Means (SE)	203 (9.1)	87 (9.1)
Difference from placebo (SE) **95% CI**	116 (13) (91, 141)	
P-value*	**<0.0001**	

*LSMeans and p-values calculated from ANCOVA model: Y = trt +site+baseline.

Table 8 Secondary Endpoint Analysis of Rescue Medication Use: Study XP21L-302 FAS

	DICLOFENAC (N=99)	**PLACEBO (N=101)**
N, % of rescue medication use	57 (58%)	93 (92%)
P-value*	**<0.0001**	

* P-value calculated from CMH test with site as strata.

Table 9 Secondary Endpoint Analysis of Time to Onset of Pain Relief: Study XP21L-302 FAS

	DICLOFENAC (N=99)	**PLACEBO (N=101)**
Time to Perceptible Pain Relief (min):		
Median time*	43	36
95% CI*	(33.6 – 53.3)	(29.8 – 60.4)
Log-rank p-value**	0.673	
Cox-phreg p-value**	**0.045**	
Time to Meaningful Pain Relief (min):		
Median time*	91	ne
95% CI*	(85.0 – 119.7)	(118.0 – ne)
Log-rank p-value**	**0.035**	
Cox-phreg p-value**	**0.016**	

*Median time and CI based on Kaplan-Meier analysis. 'ne' stands for 'not estimable'.
** P-values calculated from Log-rank test and Cox regression model with terms for treatment and baseline score as covariate.

Figure 4 Kaplan-Meier Plot of Time to Perceptible Pain Relief: Study XP21L-302 FAS

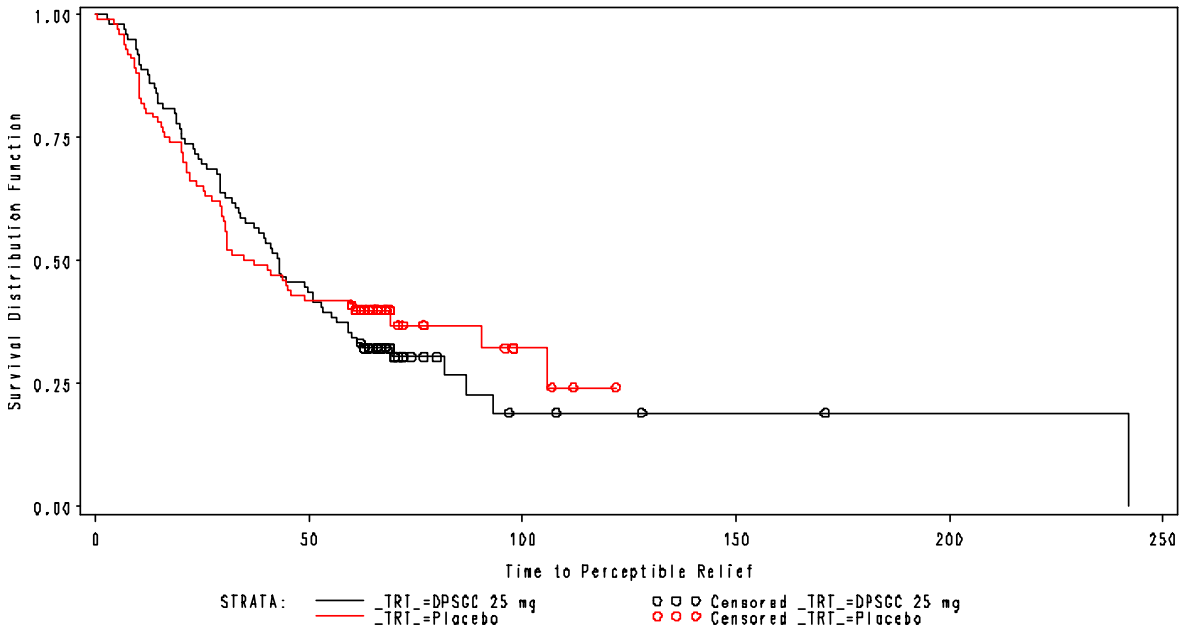


Figure 5 Kaplan-Meier Plot of Time to Meaningful Pain Relief: Study XP21L-302 FAS

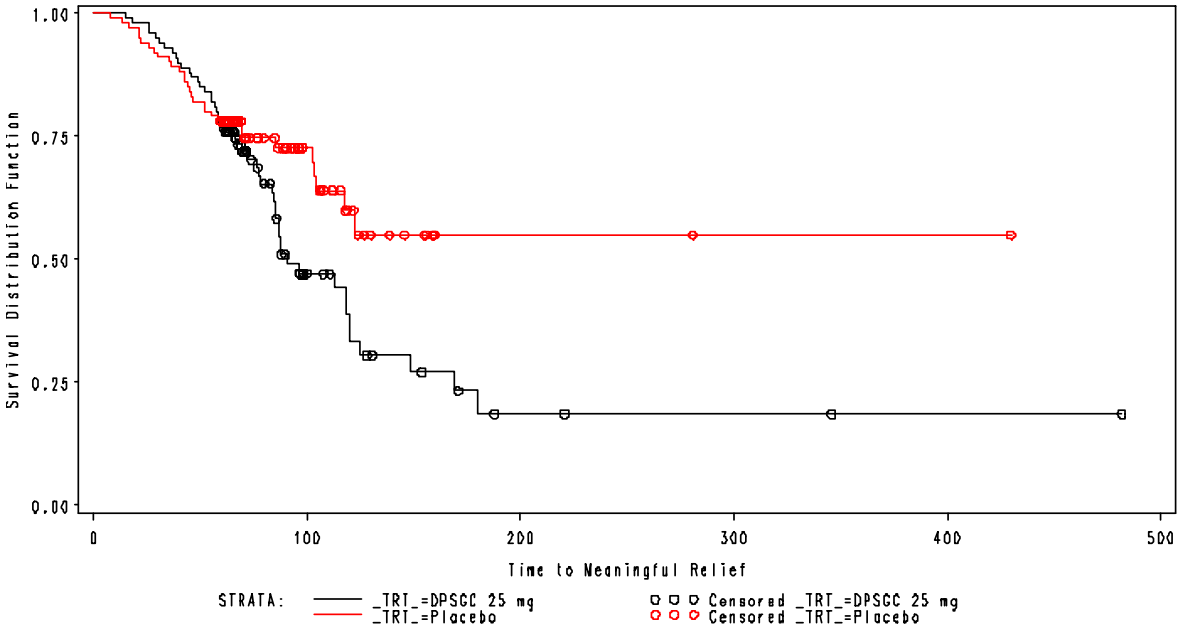
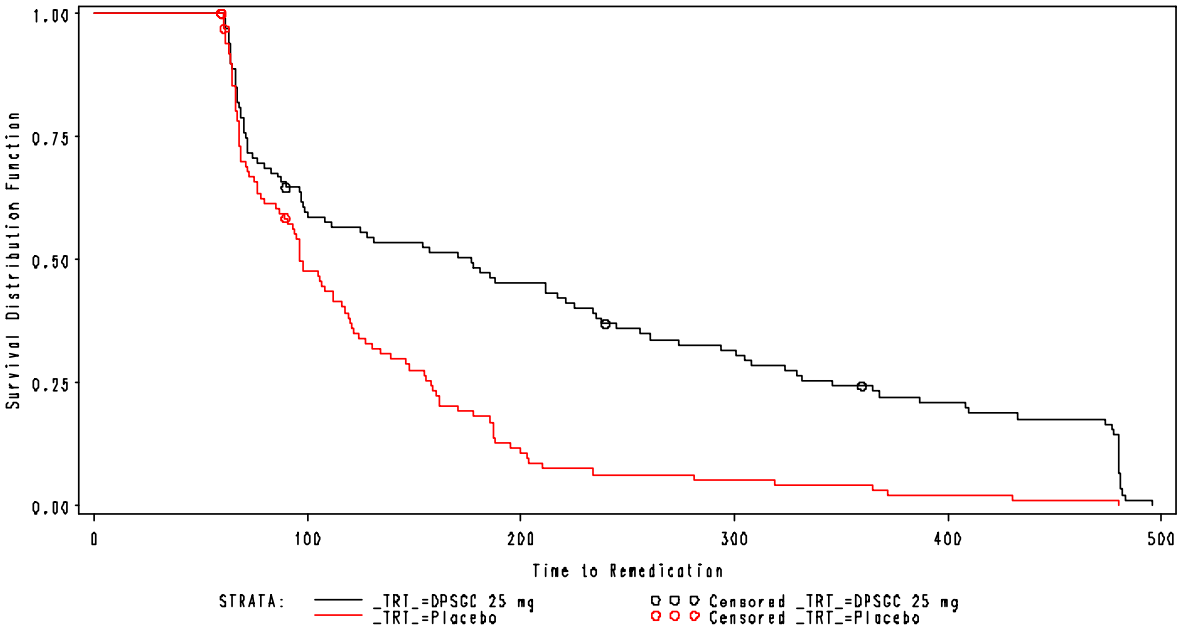


Table 10 Secondary Endpoint Analysis of Time to Re-medication: Study XP21L-302 FAS

	DICLOFENAC (N=99)	**PLACEBO (N=101)**
Time to re-medication (min):		
Median time*	177	96
95% CI*	(99.0 – 225.0)	(87.0 – 1180.0)
Log-rank p-value**	**<0.001**	
Cox-phreg p-value**	**<0.001**	

*Median time and CI based on Kaplan-Meier analysis. 'ne' stands for 'not estimable'.
** P-values calculated from Log-rank test and Cox regression model with terms for treatment and baseline score as covariate.

Figure 6 Kaplan-Meier Plot of Time to Re-medication: Study XP21L-302 FAS



Study CL-000395:

Data from the study demonstrated the superiority of diclofenac 25 mg, 50 mg, or 100 mg to placebo in terms of the primary endpoint, summed pain intensity differences over 6 hours. In their analysis, the applicant used ANCOVA model with terms for treatment and baseline pain as covariate on FAS population with LOCF.

The superiority of diclofenac 25 mg to placebo was also shown in the analyses of the secondary efficacy variable of time to rescue medication. In the Cox regression analysis of time to onset of pain relief, there was a statistically significant difference between diclofenac 25 mg, 50 mg, or 100 mg and placebo both in the meaningful pain relief and the perceptible pain relief.

Table 11 Primary Endpoint Analysis: Study CL-000395 FAS with LOCF

SPID6 hrs	**DICLOFENAC 25 MG (N=63)**	**DICLOFENAC 50 MG (N=68)**	**DICLOFENAC 100 MG (N=66)**	**PLACEBO (N=68)**
LS Means (SE)	4.3 (0.53)	5.7 (0.53)	7.7 (0.53)	0.2 (0.53)
Difference from placebo (SE)	4.1 (0.76)	5.5 (0.76)	7.6 (0.75)	
95% CI	(2.58, 5.57)	(3.98, 6.97)	(6.07, 9.04)	
Dunnett-adjusted P-values*	**<0.0001**	**<0.0001**	**<0.0001**	

*LSMeans and p-values calculated from ANCOVA model: Y = trt + baseline.

Table 12 Reviewer's Secondary Endpoint Analysis of Time to Onset of Pain Relief: Study CL-000395 FAS

	DICLO 25 MG (N=63)	**DICLO 50 MG (N=68)**	**DICLO 100 MG (N=66)**	**PLACEBO (N=68)**
Time to Perceptible Pain Relief (min):				
Median time*	22	22.5	19.5	24.5
95% CI*	(16.0 – 27.0)	(17.0 – 26.0)	(16.0 – 22.0)	(17.0 – 46.0)
Cox-phreg p-value**	**0.003**	**0.003**	**<0.001**	
Time to Meaningful Pain Relief (min):				
Median time*	45	53	43	242
95% CI*	(43.0 – 59.0)	(45.0 – 59.0)	(39.0 – 50.0)	(221.0 – ne)
Cox-phreg p-value**	**<0.001**	**<0.001**	**<0.001**	

*Median time and CI based on Kaplan-Meier analysis. 'ne' stands for 'not estimable'.
**P-value calculated from Cox regression model with terms for treatment and baseline score as covariate.

Figure 7 Kaplan-Meier Plot of Time to Perceptible Pain Relief: Study CL-000395 FAS

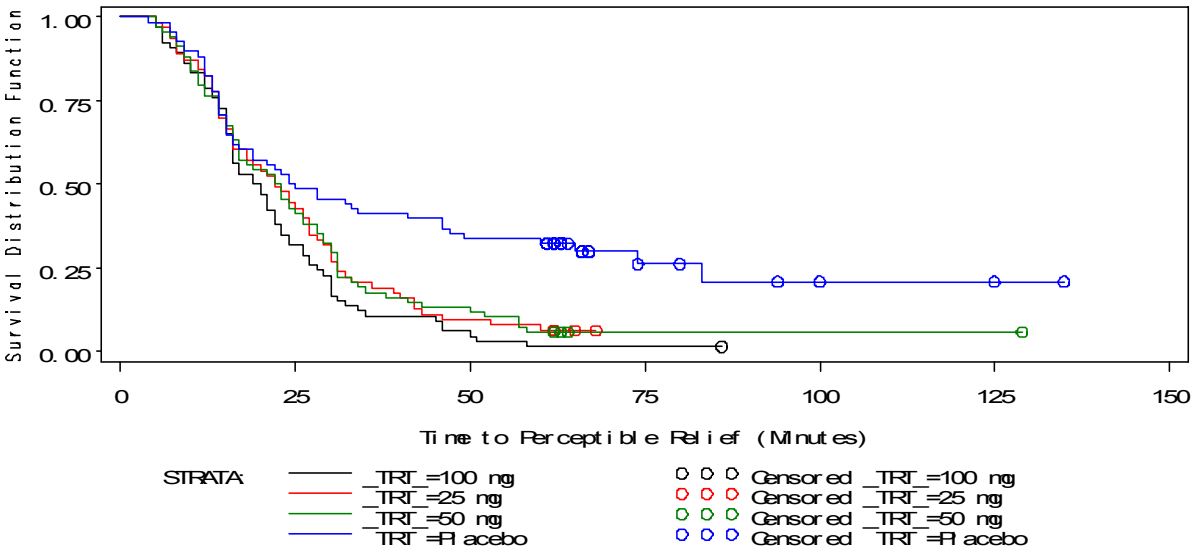


Figure 8 Kaplan-Meier Plot of Time to Meaningful Pain Relief: Study CL-000395 FAS

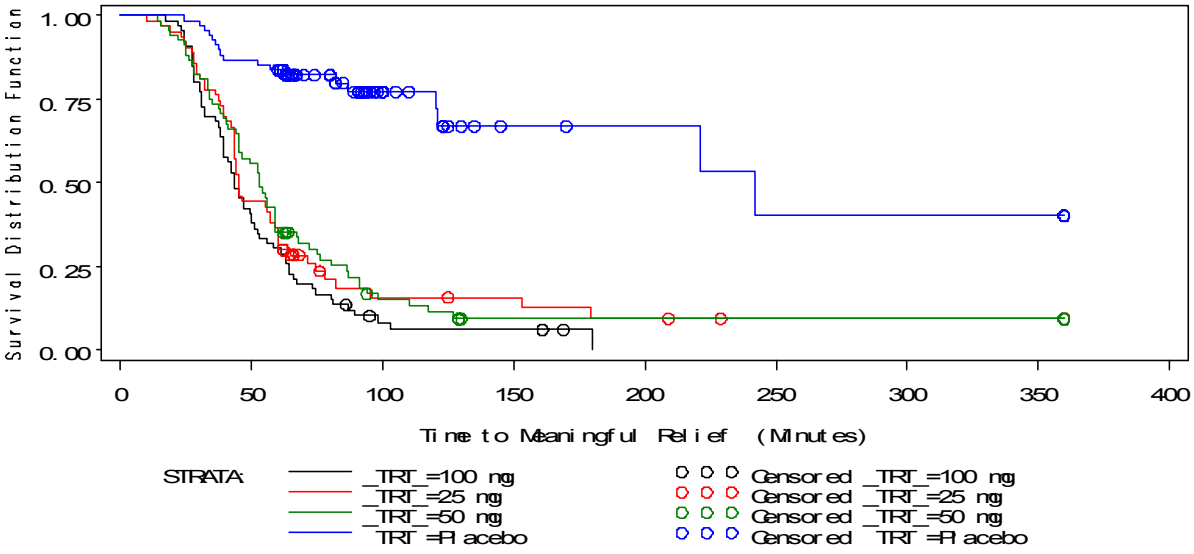
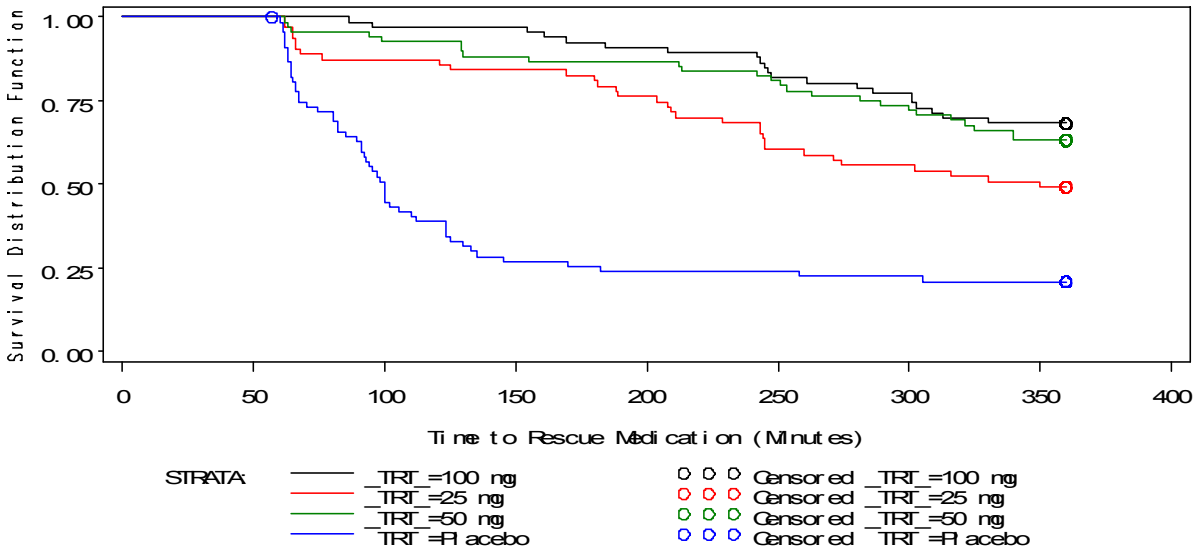


Table 13 Reviewer's Secondary Endpoint Analysis of Time to Rescue Medication: Study CL-000395 FAS

	DICLO 25 MG (N=63)	DICLO 50 MG (N=68)	DICLO 100 MG (N=66)	PLACEBO (N=68)
Time to Rescue Medication (min):				
Median time*	350	ne	ne	100
95% CI*	(245.0 – ne)	(ne – ne)	(ne – ne)	(91.0 – 123.0)
Cox-phreg p-value**	**<0.001**	**<0.001**	**<0.001**	

*Median time and CI based on Kaplan-Meier analysis. 'ne' stands for 'not estimable'.
**P-value calculated from Cox regression model with terms for treatment and baseline score as covariate.

Figure 9 Kaplan-Meier Plot of Time to Rescue Medication: Study CL-000395 FAS



Study CL-000400:

Data from the study demonstrated the superiority of diclofenac 25 mg, 50 mg, or 100 mg to placebo in terms of primary endpoint, summed pain intensity differences over 6 hours. In their analysis, the applicant used ANCOVA model with terms for treatment and baseline pain as covariate on FAS population with LOCF.

The superiority of diclofenac 25 mg to placebo was also shown in the analyses of the secondary efficacy variable of time to rescue medication. In the Cox regression analysis of time to onset of pain relief, there was a statistically significant difference between diclofenac 25 mg, 50 mg, or 100 mg and placebo both in the meaningful pain relief and the perceptible pain relief.

Table 14 Primary Endpoint Analysis: Study CL-000400 FAS with LOCF

SPID6 hrs	**DICLOFENAC 25 MG (N=63)**	**DICLOFENAC 50 MG (N=62)**	**DICLOFENAC 100 MG (N=63)**	**PLACEBO (N=61)**
LS Means (SE)	4.0 (0.57)	5.9 (0.57)	6.4 (0.57)	-0.3 (0.58)
Difference from placebo (SE) **95% CI**	4.3 (0.82) (2.68, 5.89)	6.2 (0.82) (4.62, 7.85)	6.7 (0.82) (5.12, 8.33)	
Dunnett-adjusted P-values*	**<0.0001**	**<0.0001**	**<0.0001**	

*LSMeans and p-values calculated from ANCOVA model: Y = trt + baseline.

Table 15 Reviewer's Secondary Endpoint Analysis of Time to Onset of Pain Relief: Study CL-000400 FAS

	DICLO 25 MG (N=63)	DICLO 50 MG (N=62)	DICLO 100 MG (N=63)	PLACEBO (N=61)
Time to Perceptible Pain Relief (min):				
Median time*	25	17	21	30
95% CI*	(20.0 – 30.0)	(14.0 – 24.0)	(17.0 – 27.0)	(25.0 – ne)
Cox-phreg p-value**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Time to Meaningful Pain Relief (min):				
Median time*	52	47.5	52	ne
95% CI*	(42.0 – 77.0)	(37.0 – 55.0)	(44.0 – 60.0)	(98.0 – ne)
Cox-phreg p-value**	**<0.001**	**<0.001**	**<0.001**	

*Median time and CI based on Kaplan-Meier analysis. 'ne' stands for 'not estimable'.
**P-value calculated from Cox regression model with terms for treatment and baseline score as covariate.

Figure 10 Kaplan-Meier Plot of Time to Perceptible Pain Relief: Study CL-000400 FAS

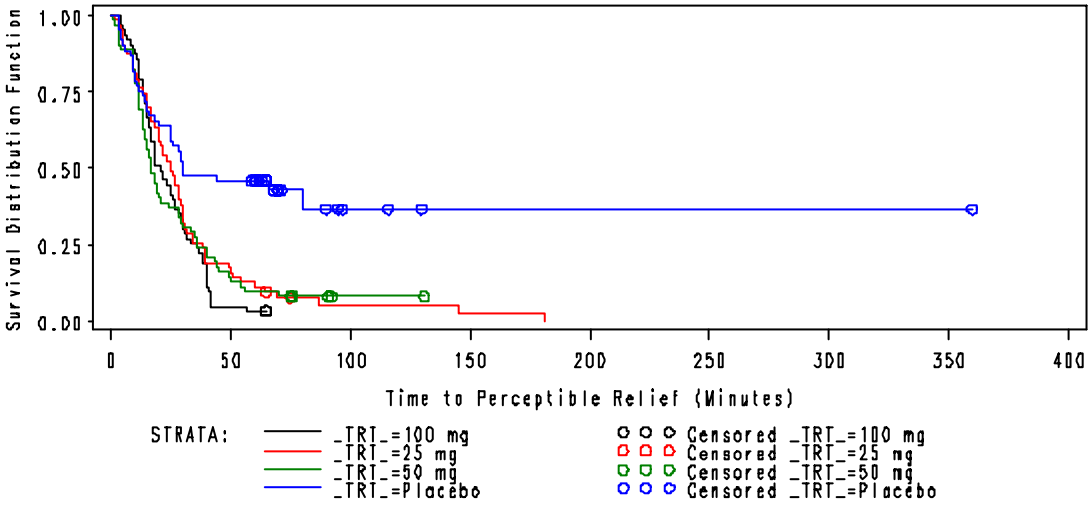


Figure 11 Kaplan-Meier Plot of Time to Meaningful Pain Relief: Study CL-000400 FAS

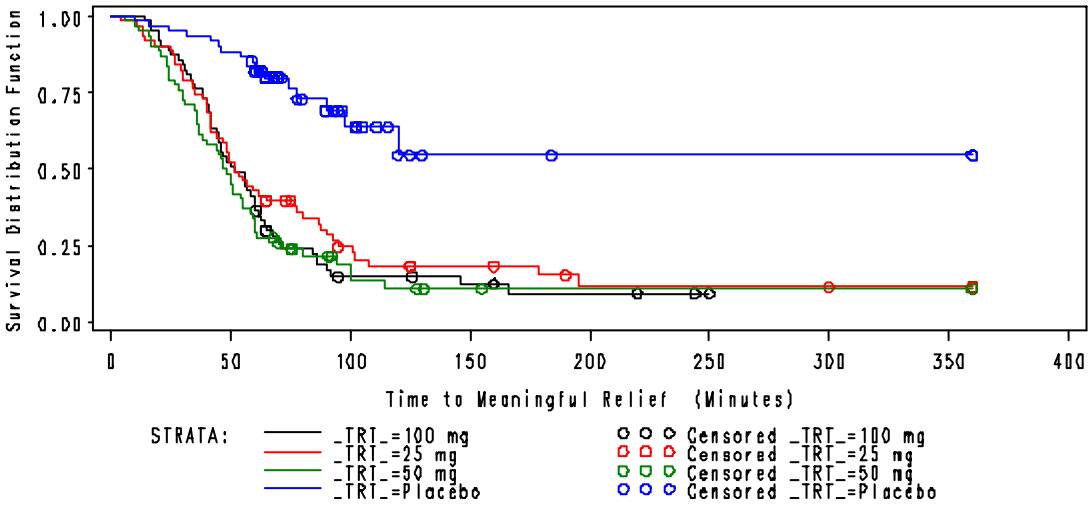
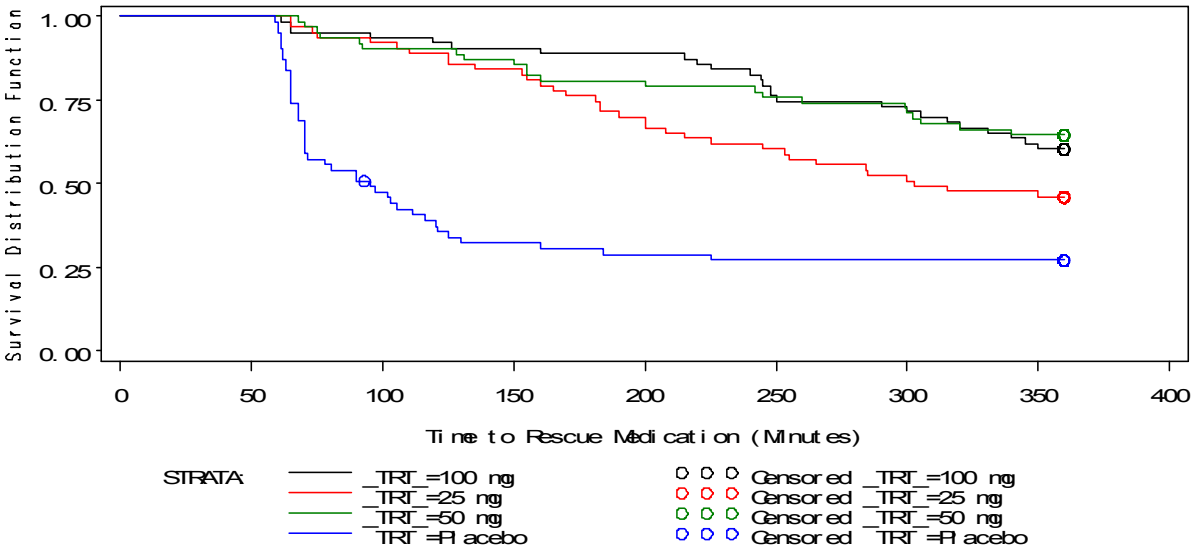


Table 16 Reviewer's Secondary Endpoint Analysis of Time to Rescue Medication: Study CL-000400 FAS

	DICLO 25 MG (N=63)	**DICLO 50 MG (N=62)**	**DICLO 100 MG (N=63)**	**PLACEBO (N=61)**
Time to Rescue Medication (min):				
Median time*	303	ne	ne	95
95% CI*	(225.0 – ne)	(ne – ne)	(345 – ne)	(70.0 – 120.0)
Cox-phreg p-value**	**<0.001**	**<0.001**	**<0.001**	

*Median time and CI based on Kaplan-Meier analysis. 'ne' stands for 'not estimable'.
**P-value calculated from Cox regression model with terms for treatment and baseline score as covariate.

Figure 12 Kaplan-Meier Plot of Time to Rescue Medication: Study CL-000400 FAS



3.2 Evaluation of Safety

Safety analyses were done by the clinical reviewer, Christina Fang, M.D.

No statistical problems or issues were found.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

I explored the heterogeneity of the treatment effect across gender, age and race group ('White' vs. 'Non-White') by inclusion of interaction terms in the ANCOVA model. In Study XP21L-301, there were no statistically significant interactions between treatment and gender or age in the primary efficacy outcome variables. However, there were statistically significant interactions between treatment and race. I am not concerned with the interactions because the differences between treatment groups were statistically significant favoring diclofenac treatment in each race. In Study XP21L-302, there were no statistically significant interactions between treatment and gender or age or race group in the primary efficacy outcome variables. Subgroup analyses were conducted by me and presented in the appendix (Tables 21 and 22). In the subgroup analysis, age group was classified by 'age of less than 65' or 'age of at least 65'.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

5.1.1 Statistical Issues

For the efficacy analyses of studies XP21L-301 and XP21L-302, the applicant based their inferences on the full analysis set (FAS) with the worst observation carried forward (WOCF). The applicant's FAS population for these studies was defined as all randomized patients who received at least one dose of study medication. The analysis population and the conservative imputation method are acceptable.

There were no statistically significant interactions between treatment and center or baseline pain. In study XP21L-301, sites 2 and 7 were pooled for analysis because site 7 had fewer than 8 patients and site 2 was the next smallest as pre-specified in the statistical analysis plan.

As a sensitivity analysis, a LOCF analysis was conducted and gave results similar to the WOCF analysis. The primary analysis conducted on the FAS population and the per protocol (PP) analysis were consistent. No adjustment for multiplicity was made for the secondary endpoints analyses.

For the efficacy analyses of studies CL-000395 and CL-000400, the applicant based their inferences on the FAS with the last observation carried forward strategy. The applicant's FAS population for these studies was defined as all randomized patients who received at least one dose of study medication and at least one post baseline pain assessment. However, since the intention-to-treat (ITT) population including all randomized patients is more appropriate as the primary analysis set, I conducted the same analysis as the sponsor based on the ITT population as a sensitivity analysis. Although LOCF may not be considered conservative, because there were very few dropouts (less than 1%) and patients only received a single dose, it is acceptable. For adjustment for multiple comparisons (diclofenac 25 mg vs. placebo, 50 mg vs. placebo, and 100 mg vs. placebo), the applicant proposed Dunnett's method which is considered acceptable.

There were no statistically significant interactions between treatment and baseline pain. The analyses conducted on varying populations (i.e. ITT, FAS, and PP) were consistent. No adjustment for multiplicity was made for the secondary endpoints analyses.

5.1.2 Collective Evidence

The data from the four studies – two multiple dose studies XP21L-301, XP21L-302, and two single dose studies CL-000395 and CL-000400 – provided substantial evidence of

analgesic efficacy of diclofenac potassium 25 mg soft gelatin capsules. Studies XP21L-301 and XP21L-302 demonstrated a statistically significant difference between diclofenac potassium 25 mg and placebo in terms of average pain scores over 48 hours in patients with bunionectomy pain. Studies CL-000395 and CL-000400 demonstrated a statistically significant difference between diclofenac potassium 25 mg, 50 mg, and 100 mg and placebo in patients with dental pain in terms of the summed pain intensity differences over 6 hours. These studies also showed a statistically significant difference in the time to onset of analgesia between diclofenac potassium 25 mg, 50 mg, and 100 mg and placebo.

5.2 Conclusions and Recommendations

Based on the data from two multiple-dose studies XP21L-301 and XP21L-302, I concluded that patients randomized to diclofenac demonstrated a greater improvement in pain intensity compared to patients randomized to placebo

Also based upon the data from two single-dose studies CL-000395 and CL-000400, I conclude that patients receiving diclofenac 25 mg, 50 mg or 100 mg experienced a greater analgesic effect compared to patients randomized to placebo.

Two multiple-dose studies CL-000396 and CL-000401 in patients with pain following knee arthroscopy surgery failed to show a statistically significant difference on pain intensity at each dose of 25 mg and 50 mg diclofenac potassium soft gelatin capsule compared to placebo.

Overall, the evidence of efficacy was replicated in two well-controlled, multiple-dose, bunionectomy pain studies XP21L-301 and XP21L-302. As a supportive evidence, the efficacy was also replicated in two well-controlled, single-dose, dental pain studies CL-000395 and CL-000400.

5.3 Review of Clinical Studies of Proposed Label

Following is the text portion in the Clinical Study section from 'PROPOSED LABELING TEXT' regarding results from the four efficacy studies:

4 pp withheld in full immed. after this page as (b)(4) draft labeling.

APPENDIX

Table 17 Patient Disposition by Treatment Group

Study XP21L-301:

	Diclofenac	Placebo	Total
Randomized	102	99	201
Treated	102	99	201
Discontinued	1 (1%)	2 (2%)	3 (1.5%)
Reason for Discontinuation			
AE	0	0	0
LOE	0	1	1
Consent Withdrawal	0	1	1
Other	1	0	1

Study XP21L-302:

	Diclofenac	Placebo	Total
Randomized	99	101	200
Treated	99	101	200
Discontinued	3 (3%)	6 (6%)	9 (4.5%)
Reason for Discontinuation			
AE	1	1	2
LOE	0	2	2
Consent Withdrawal	1	2	3
Other	1	1	2

Study CL-000395:

	Diclofenac 25 mg	Diclofenac 50 mg	Diclofenac 100 mg	Placebo	Total
Randomized	63	68	66	68	265
FAS	63	68	66	68	265
Completers	63	68	66	67	264
Discontinued	0	0	0	1	1
Reason for Discontinuation:					
AE	0	0	0	0	0
LOE	0	0	0	0	0
Consent Withdrawal	0	0	0	0	0
Other	0	0	0	1	1

Study CL-000400:

	Diclofenac 25 mg	Diclofenac 50 mg	Diclofenac 100 mg	Placebo	Total
Randomized	63	62	63	61	249
FAS	63	62	63	61	249
Completers	63	62	63	60	248
Discontinued	0	0	0	1	1
Reason for Discontinuation:					
AE	0	0	0	0	0
LOE	0	0	0	0	0
Consent Withdrawal	0	0	0	1	1
Other	0	0	0	0	0

Table 18 Patient Demographics and Baseline Efficacy Variable (FAS Subjects)

Study XP21L-301:

	TREATMENT		
	DICLOFENAC (N=102)	**PLACEBO (N=99)**	**TOTAL (n=201)**
Gender n (%)			
Male	14 (14%)	13 (13%)	27 (13%)
Female	88 (86%)	86 (87%)	174(87%)
Race n (%)			
Asian	4 (4%)	5 (5%)	9 (5%)
Black	23 (23%)	19 (19%)	42 (21%)
Caucasian	61 (60%)	56 (57%)	117 (58%)
Hispanic	13 (13%)	16 (16%)	29 (14%)
Other	1 (1%)	3 (3%)	4 (2%)
Age (years)			
Mean ± SD	45 ± 11	45 ± 12	45 ± 12
Median	46	47	46
Range	18 - 65	18 - 65	18 - 65
Weight (kg)			
Mean ± SD	71 ± 12.3	74 ± 14.8	72 ± 13.6
Median	68	72	69
Range	51 – 103	49 – 108	49 – 108
Pain Intensity NPRS Score			
Mean ± SD	6.9 ± 1.75	7.3 ± 1.86	
Median	7.0	7.0	
Range	4.0 – 10.0	4.0 – 10.0	

Study XP21L-302:

	TREATMENT		TOTAL (n=200)
	DICLOFENAC (N=99)	PLACEBO (N=101)	
Gender n (%)			
Male	13 (13%)	15 (15%)	28 (14%)
Female	86 (87%)	86 (85%)	172(86%)
Race n (%)			
Asian	2 (2%)	2 (2%)	4 (2%)
Black	8 (8%)	15 (15%)	23 (12%)
Caucasian	66 (67%)	57 (56%)	123 (62%)
Hispanic	21 (213%)	26 (26%)	47 (24%)
Other	2 (2%)	1 (1%)	3 (2%)
Age (years)			
Mean ± SD	41 ± 13	40 ± 12	40 ± 12
Median	42	42	42
Range	18 - 65	18 - 63	18 - 65
Weight (kg)			
Mean ± SD	72 ± 15.2	73 ± 12.1	72 ± 13.7
Median	69	72	71
Range	47 – 108	52 – 103	47 – 108
Pain Intensity NPRS Score			
Mean ± SD	7.5 ± 1.56	7.4 ± 1.42	
Median	8.0	8.0	
Range	4.0 – 10.0	4.0 – 10.0	

Study CL-000395:

	TREATMENT				TOTAL (n=265)
	DICLO 25 MG (N=63)	**DICLO 50 MG (N=68)**	**DICLO 100 MG (N=66)**	**PLACEBO (N=68)**	
Gender n (%)					
Male	28 (44%)	34 (50%)	21 (32%)	28 (41%)	111 (42%)
Female	35 (56%)	34 (50%)	45 (68%)	40 (59%)	154 (58%)
Race n (%)					
Asian	1 (2%)	6 (9%)	5 (8%)	1 (2%)	13 (5%)
Black	4 (6%)	8 (12%)	5 (8%)	9 (13%)	26 (10%)
Caucasian	51 (81%)	45 (66%)	49 (74%)	54 (79%)	199 (75%)
Hispanic	6 (10%)	5 (7%)	5 (8%)	2 (3%)	18 (7%)
Other	1 (2%)	4 (6%)	2 (3%)	2 (3%)	9 (3%)
Age (years)					
Mean ± SD	24 ± 5	24 ± 5	23 ± 4	23 ± 4	23 ± 4
Range	18 - 46	18 - 42	18 - 44	18 - 36	18 - 46
Weight (kg)					
Mean ± SD	70 ± 13.3	72 ± 17.9	71 ± 19.1	73 ± 18.3	72 ± 17.3
Range	46 – 100	45 – 118	44 – 136	49 – 126	44 – 136
Pain Intensity					
None	0	0	0	0	
Mild	0	1 (2%)	0	0	
Moderate	46 (73%)	58 (85%)	50 (76%)	44 (65%)	
Severe	17 (27%)	9 (13%)	16 (24%)	24 (35%)	

Study CL-000400:

	TREATMENT				TOTAL (n=249)
	DICLO 25 MG (N=63)	**DICLO 50 MG (N=62)**	**DICLO 100 MG (N=63)**	**PLACEBO (N=61)**	
Gender n (%)					
Male	28 (44%)	31 (50%)	27 (43%)	29 (48%)	115 (46%)
Female	35 (56%)	31 (50%)	36 (57%)	32 (52%)	134 (54%)
Race n (%)					
Asian	8 (13%)	5 (8%)	4 (6%)	6 (10%)	23 (9%)
Black	9 (14%)	11 (18%)	6 (10%)	4 (7%)	30 (12%)
Caucasian	44 (70%)	43 (69%)	46 (73%)	43 (71%)	176 (71%)
Hispanic	1 (2%)	2 (3%)	7 (11%)	8 (13%)	18 (7%)
Other	1 (2%)	1 (2%)	0	0	2 (1%)
Age (years)					
Mean ± SD	24 ± 5	26 ± 5	24 ± 5	24 ± 5	24 ± 5
Range	18 - 47	18 - 43	18 - 42	19 - 39	18 - 47
Weight (kg)					
Mean ± SD	74 ± 16.8	76 ± 19.8	71 ± 14.0	72 ± 16.1	73 ± 16.8
Range	46 – 135	42 – 150	45 – 108	45 – 114	42 – 150
Pain Intensity					
None	0	0	0	0	
Mild	0	0	1 (2%)	0	
Moderate	40 (64%)	41 (66%)	41 (65%)	42 (69%)	
Severe	23 (37%)	21 (34%)	21 (33%)	19 (31%)	

Table 19 Reviewer's Sensitivity Analysis on Primary Efficacy Endpoint: Study XP21L-301 FAS with LOCF

average pain intensity over 48 hrs	**DICLOFENAC (N=102)**	**PLACEBO (N=99)**
LS Means (SE)	2.7 (0.19)	5.6 (0.20)
Difference from placebo (SE) 95% CI	2.9 (0.23) (2.45, 3.36)	
P-value*	**<0.0001**	

*LSMeans and p-values calculated from ANCOVA model: Y = trt +site+baseline.

Table 20 Reviewer's Sensitivity Analysis on Primary Efficacy Endpoint: Study XP21L-302 FAS with LOCF

average pain intensity over 48 hrs	**DICLOFENAC (N=99)**	**PLACEBO (N=101)**
LS Means (SE)	3.1 (0.19)	5.6 (0.18)
Difference from placebo (SE) 95% CI	2.5 (0.26) (1.99, 3.01)	
P-value*	**<0.0001**	

*LSMeans and p-values calculated from ANCOVA model: Y = trt +site+baseline.

Table 21 Reviewer's Subgroup Analysis on Primary Efficacy Endpoint: Study XP21L-301 FAS with WOCF

average pain intensity over 48 hrs LS Means (SE)	**DICLOFENAC (N=102)**	**PLACEBO (N=99)**	**P-value***
Female (n=174)	2.8 (0.21)	5.7 (0.21)	**<0.0001**
Male (n=27)	2.5 (0.47)	5.4 (0.48)	**0.0003**
White (n=117)	2.5 (0.21)	5.9 (0.22)	**<0.0001**
Non-White (n=84)	3.0 (0.32)	5.0 (0.35)	**<0.0001**
Age <65 (n=199)	2.8 (0.20)	5.7 (0.20)	**<0.0001**
Age >65 (n=2)	ne	ne	

*LSMeans and p-values calculated from ANCOVA model: Y = trt +site+baseline.
'ne' stands for 'not estimable'.

Table 22 Reviewer's Subgroup Analysis on Primary Efficacy Endpoint: Study XP21L-302 FAS with WOCF

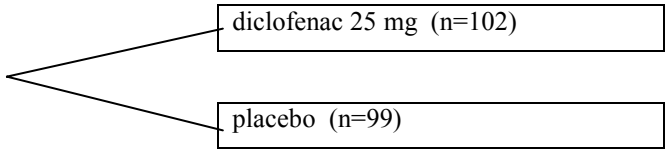
average pain intensity over 48 hrs LS Means (SE)	**DICLOFENAC (N=99)**	**PLACEBO (N=101)**	**P-value***
Female (n=172)	3.3 (0.21)	5.8 (0.21)	**<0.0001**
Male (n=28)	2.6 (0.63)	5.3 (0.64)	**0.0125**
White (n=123)	3.4 (0.24)	5.9 (0.26)	**<0.0001**
Non-White (n=77)	3.1 (0.36)	5.8 (0.31)	**<0.0001**
Age <65 (n=199)	3.3 (0.20)	5.8 (0.19)	**<0.0001**
Age >65 (n=1)	ne	ne	

*LSMeans and p-values calculated from ANCOVA model: Y = trt +site+baseline.
'ne' stands for 'not estimable'.

Figure 13 Schematic of Study Design

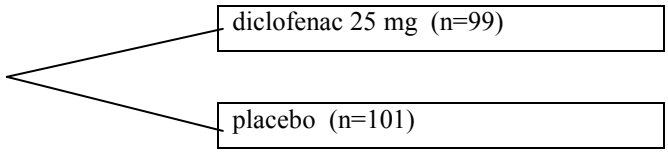
Study XP21L-301:

(N=201)
Randomized 1:1



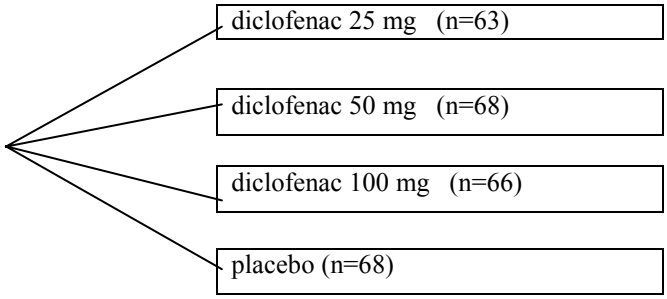
Study XP21L-302:

(N=200)
Randomized 1:1



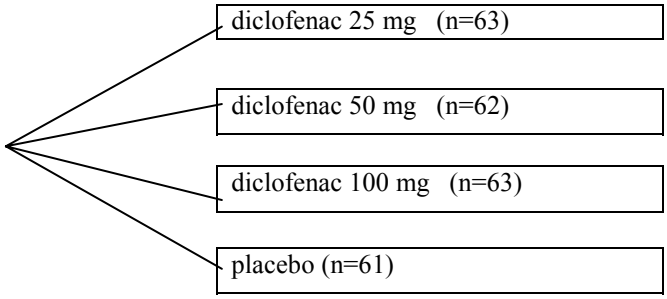
Study CL-000395:

(N=265)
Randomized 1:1:1:1



Study CL-000400:

(N=249)
Randomized 1:1:1:1



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