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APPLICATION NUMBER:

22-202

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Submission Number	22-202
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Reviewer Name	Christina Fang, M.D.
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Established Name	Diclofenac potassium
(Proposed) Trade Name	Zipsor™ Soft Gelatin Capsules
Therapeutic Class	NSAID
Applicant	Xanodyne Pharmaceuticals Inc.
Priority Designation	3S
Formulation	Immediate-release soft gelatin capsules 25 mg
Dosing Regimen	One oral capsule (25 mg) four times a day
Indication	Relief of mild to moderate pain
Intended Population	Adult patients with acute pain

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1. RECOMMENDATIONS/RISK BENEFIT ANALYSIS

1.1 Recommendation on Regulatory Action

Diclofenac Potassium Soft Gel Capsules (DPSGC) 25 mg for relief of mild to moderate pain is recommended for a regulatory action of approvable.

The recommendation for approvable is based on an acceptable benefit/risk ratio according to my review of clinical efficacy and safety data submitted in NDA 22-202 and pending toxicology studies to address safety concerns with the impurities exceeding the ICH qualification threshold.

The analgesic efficacy of DPSGC 25 mg for relief of mild to moderate pain is supported by replicable positive findings from the studies of post-operative pain. The strength of evidence in support of analgesic efficacy of DPSGC 25 mg includes a clear demonstration of multiple-dose efficacy in bunionectomy studies (Study 301 and 302) and single-dose efficacy in bunionectomy and dental studies (Study 395 and 400).

DPSGC 25 mg has a similar safety profile to Cataflam®, the approved immediate-release formulation of diclofenac, and is considered reasonably safe to be administered four times a day for the short-term duration necessary for treating acute pain conditions.

1.2 Risk Benefit Analysis

The benefit of treatment with DPSGC 25 mg has been shown in terms of clinically meaningful treatment differences from placebo.

In comparing multiple-dose effects of DPSGC 25 mg to placebo, DPSGC 25 mg was shown to be twice as effective in the primary efficacy measurement. The size of treatment difference was about three units on an 11-point scale in terms of the average and time-specific pain intensity (PI) recorded at three hours after dosing and at the end of the 6-hour dosing interval during 48 hours. Substantially smaller proportions of DPSGC treated patients than placebo patients took rescue medications: about 45% less on the first treatment day, 40% less on the second day, and 25% on the third and fourth day. About 35% more DPSGC patients than placebo patients had a response of 'good' to 'excellent' in patient global assessment.

In comparing single-dose effects of DPSGC 25 mg to placebo, substantially greater proportions of DPSGC 25 mg treated patients than placebo patients reported onset of pain relief, at least 20% more in terms of perceptible relief and at least 50% more in terms meaningful relief and at least 45% more had a response of 'good' to 'excellent' in patient global assessment in the two single-dose dental studies. At least 20% more patients treated with DPSGC 25 mg than placebo were identified as responders to the study drug in the initial-dose evaluation in bunionectomy studies.

An analgesic duration of 5-6 hours has been demonstrated in the 48-hour multiple-dose evaluation of rescue interval in bunionectomy studies and single-dose evaluation of time to rescue in dental studies.

DPSGC 25 mg treatment is relatively safe as shown by data collected from the 12 clinical studies. Among the 1114 subjects exposed to any DPSGC treatment and 468 to at least four days of multiple-dose DPSGC treatment, there were no deaths or serious treatment-related adverse events (AEs) and only two cases of DPSGC treatment-related dropout due to AEs. The most commonly reported AEs were GI symptoms including abdominal pain, nausea, and vomiting and nervous system symptoms including headache and dizziness. The incidences of AEs were <15% in the single-dose studies and about 40% to 55% in the multiple-dose studies. The proportions reporting AEs in general and reporting individual events in particular, were similar across

treatment groups (DPSGC 25, 50, and 100mg and placebo) in the single-dose studies, and basically similar between the treatment groups or somewhat higher in the placebo group than the active treatment groups (DPSGC 25 and 50 mg) in the multiple-dose studies. The noticeably higher rates of AE reports in the DPSGC groups than placebo group were abdominal pain and elevation of liver enzymes, which appeared to be dose-related. Elevation of liver enzymes (ALT and/or AST) to ≥3 x ULN was reported in seven DPSGC treated patients (four from normal and two from above normal at baseline) with no increase in total bilirubin. Spontaneous resolution was reported in those who had follow up laboratory tests. There were no reports of liver enzyme elevation to >8 x ULN.

Subpopulation safety analyses did not suggest treatment differences with respect to gender or race. Pediatric patients (age 8 to 16 years) reported more CNS AEs, and less GI AEs than adult patients based on cross study comparison of single-dose safety data.

No new safety issues or signals with DPSGC treatment could be identified in the safety database.

1.3 Recommendations for Postmarketing Risk Management Activities

None.

1.4 Recommendation for other Postmarketing Study Commitments

A multiple-dose study in pediatric patients is recommended. The Applicant proposed a Phase 4 multiple-dose study of acute pain in 150 patients in the age group of 12 to 17 years to obtain pediatric safety data on the short-term use of DPSGC 25 mg (refer to the submission dated April 18, 2008).

2. INTRODUCTION AND REGULATORY BACKGROUND

2.1 Product Information

Diclofenac Potassium Soft Gelatin Capsule (DPSGC) is a liquid formulation of diclofenac potassium encapsulated in soft gelatin capsules. The characteristic feature of the new formulation is the patented technology, ProSorb®, which uses selected dispersing agents to facilitate more rapid, consistent, and complete absorption of diclofenac from the gastrointestinal tract.

The established name of the product is diclofenac potassium and the proposed trade name, Zipsor™ Soft Gelatin Capsule. The active ingredient of the product, diclofenac, is a benzeneacetic acid derivative and a member of the non-steroidal anti-inflammatory drug (NSAID) class. DPSGC 25 mg is proposed to be used four times a day in adult patients for relief of mild to moderate pain.

2.2 Table(s) of Currently Available Treatment(s) for Proposed Indication(s)

Several drugs of the NSAID class are currently available for treating mild to moderate pain.

2.3 Availability of Proposed Active Ingredient in the United States

Diclofenac containing products currently available in the United States include oral formulations (immediate release, delayed release, and extended release products), ophthalmic solutions, and topically applied gel and patch as listed below:

• 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)
• Flector® (diclofenac epolamine) 1.3% patch (NDA 21-234, approved in 2007)
• Voltaren® (diclofenac sodium) 1% Gel (NDA 22-122, approved in 2007)
Generic versions of some of the diclofenac products are also available.

Major safety concerns with the use of diclofenac, especially with a higher dose for a prolonged exposure, are risks of cardiovascular, gastrointestinal, renal, and hepatic toxicities.

2.4 Important Issues with Consideration to Related Drugs

The most recent safety findings concerning the use of NSAID drugs are their cardiovascular toxicities, for which all NSAID drugs are now required to have cardiovascular box warnings in their labels.

2.5 Summary of Presubmission Regulatory Activity Related to this Submission

In responding to the Applicant's request for a discussion on drug development plan when the initial relative bioavailability data became available, the Division expressed concerns with single-dose and multiple-dose analgesic duration of DPSGC 25 mg because of its similar Cmax and one-half AUC in comparison to Cataflam® 50 mg and concerns about safety of DPSGC 50 mg because of its 80% higher Cmax in comparison to Cataflam® 50 mg (refer to the meeting minutes for the meeting held on February 11, 2003).

When a brief summary of results of the five efficacy studies using three time a day dosing regimen was presented to the Division, it was noticed that the single-dose effects were not evaluated beyond six hours in dental studies; a high placebo response was shown in the initial dose evaluation in knee arthroscopy studies; and the active-controlled bunionectomy study had an open-label design. The Division pointed out that the data from these studies did not appear to support an eight-hour dosing interval and recommended additional efficacy studies to define and support an appropriate dosing regimen (refer to the meeting minutes for the meeting held on March 16, 2004).

The Division agreed that it is reasonable for DPSGC to have the same analgesic indication (for relief of mild to moderate pain) as Cataflam® if the duration of acute analgesic effects could be replicated in the studies of the proposed dosing regimen; and agreed that the safe use of DPSGC could be supported by bridging safety information from the other diclofenac products if the maximum and the total between dosing exposure and daily exposure would not exceed exposures to the tablet formulation (refer to the Special Protocol Assessment response letter dated August 30, 2004).

In the follow up discussion of the SPA, the Division encouraged the Applicant to explore study methodology for evaluation of analgesic effects in the bunionectomy model and emphasized the importance of an analysis of time-specific measurements to obtain useful information on the analgesic effects during each dosing interval and each dosing day and the inclusion of the end-of-dosing response to make data more supportive of proposed dosing interval (refer to the meeting minutes for the meeting held on October 12, 2004).

With regard to the changes in the composition and manufacturing process for the to-be-marketed formulation in comparison to the formulations used in earlier PK and efficacy studies, the Division recommended the Applicant to compare the composition of these different formulation, assess the impact of formulation change, and to provide *in vitro* dissolution data or *in vivo* bioequivalence data to link the formulations with justification

for the method chosen. With regard to the evaluation of multiple-dose efficacy the Division required the primary efficacy measurement to cover at least 48 hours. The Division acknowledged the acceptance of two adequate and well-controlled clinical studies in providing evidence for efficacy, a safety database of 4-5 days of exposure in more than 400 patients, and the defer of pediatric studies. (b) (4)

[redacted]

2.6 Other Relevant Background Information

DPSGC has not been marketed in any country.

3. ETHICS AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Integrity

The quality of the overall submission is considered reasonable in general in terms of data organization, retrieval, and completeness. Additional data/analysis queries asked for exposure details in three of the five multiple-dose studies and analyses of dose response in the two single-dose dental studies.

3.2 Compliance with Good Clinical Practices

The steps to ensure compliance with Good Clinical Practices (GCP) included approval of protocols, informed consent forms, and all the amendments by the Institutional Review Boards (IRBs) before the initiation of the study, documentation of the Investigators' willingness to adhere to the protocol and to conduct the study in accordance with local legal requirements and the ICH guidelines for GCP, and writing and processing informed consent in accordance with the US 21 CFR part 50 and the ICH Guidelines.

A high rate of report of protocol violations in the two pivotal efficacy studies (301 and 302) was identified early during the NDA review. Most of these violations were related to an uncovered stopwatch. Five sites in the two studies were selected for DSI inspections based on the proportion and nature of protocol violations. The results of the inspections showed that four of the five sites inspected (site 1 with Dr. Steven Duckor as the Investigator, site 3 with Dr. Dennis Riff as the Investigator, site 12 with Dr. Stephen Daniels as the Investigator, and site 13 with Dr. Michael H Golf as the Investigator) had no significant regulatory violations. In most cases where the stopwatch was uncovered, the elapsed time was not in the view of patients.

Site 14 (where Dr. Mark E. McDonnell served as the Investigator) was the only site identified with protocol violations and record keeping deficiencies. The list included an uncovered stopwatch in all 54 patients; one occasion of mistimed dosing and two missing assessments in one patient; missing pre rescue pain assessment three times in one patient and one time in another patient; delayed 3-hour mid dosing assessment by 20 to 80 minutes in seven patients; missing records in the CRF (case report form) about three adverse events (AEs) that were documented in AE report forms; and missing CRF records about four occasions of use of rescue in three patients whose rescue information were already documented in the post dose rescue medication forms. In comparison to the total amount of data collected (about 900 doses taken by 54 patients who provided pain scores at about 2200 total time points) the amount of protocol violation is not considered as having a major impact on the study outcomes.

3.3 Financial Disclosures

The financial disclosure form signed by the Applicant certified that no financial arrangement with the listed clinical investigators (a complete list of all clinical investigators involved in Phase 2/3 studies was attached to

the form) had been made whereby study outcomes affects compensation as defined in 21 CFR 54.2(a); certified that each listed investigator was required to disclose to the Applicant whether the investigator had a proprietary interest in this product or a significant equity in the Applicant as defined in 21 CFR 54.2(b) did not disclose any such interests; and certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

4. SIGNIFICANT EFFICACY OR SAFETY FINDINGS RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry Manufacturing and Controls

According to the CMC review by Dr. Hill, the CMC portion of the application is generally considered adequate and acceptable to support a market approval of the product with some issues identified: an issue with impurities pending toxicology studies and an issue with relative bioavailability between the registration batch and the batch used in some of the clinical studies, pending pharmacokinetic evaluation.

Six impurities, impurities (b) (4) had been identified in DPSGC, of which impurities (b) (4) were process impurities, (b) (4) were known (b) (4), and (b) was a (b) (4) the Xanodyne's (b) (4) of diclofenac potassium. Impurity specifications for (b) (not more than (b) (4)), (b) (NMT (b) (4), and (b) (NMT (b) (4) exceeded the ICH safety qualification threshold (NMT 0.5%) and thus, need to be decreased or evaluated in toxicology studies.

Various DPSGC formulations had been produced with their designation grouped into three major series: 1000, 1200, and 1300/1400 (to-be marketed formulation), of which PDS1304 in the 1300 series was used in Phase 3 bunionectomy studies, and PDS1027 in the 1000 series was used in the other Phase 3 studies and all the Phase 2 studies. Relative bioavailability was studied between 1000 and 1200 series but not between the older 1000/1200 series and to-be-marketed 1300/1400 series. The Applicant submitted comparative dissolution data instead and requested for a waiver of relative bioavailability study.

From a CMC standpoint the applicant has provided adequate formulation development data to support the manufacture of the registration batches.

Stability data support an expiry period of 30 months for DPSGC capsules to be stored in HDPE bottles, at 25°C/60%RH and 15 months in blisters, at 25°C/60%RH.

4.2 Clinical Microbiology (if applicable)

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

The NDA submission does not contain animal studies of DPSGC. The Applicant was informed of the need to address safety concerns with the three impurities exceeding the ICH qualification threshold and required to conduct minimal genetic toxicology screen (*in vitro* point mutation assay and chromosome aberration assay) with the isolated impurity and conduct 28-day repeat dose toxicology study. The Applicant responded by submitting their timelines for the proposed studies. The data from these new toxicology studies are still pending.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The mechanism of action for diclofenac, the active ingredient in DPSGC, like that of other NSAIDs, is not completely understood but may be related to regulation of prostaglandin synthesis via prostaglandin synthetase. The mechanism involves an inhibition of cyclooxygenase (COX-1 and COX-2) pathways.

4.4.2 Pharmacodynamics

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models.

There was a multiple-dose (8-day), open-label, active-controlled (diclofenac liquid 12.5 mg and Cataflam® 50 mg) parallel study of DPSGC 25 mg and 50 mg in patients with bunionectomy post operative pain, designed to explore pharmacodynamic (PD) and pharmacokinetic (PK) relationships. The study enrolled only 12 to 14 patients in each treatment group. The study did not provide useful information on a PD/PK relationship because analgesic effects of the product could not be adequately measured due to the lack of placebo control and a too small sample size and multiple-dose PK could not be adequately assessed due to high inter subject variability as a result of small sample size coupled with a parallel study design (refer to the PK review by Dr. Fadiran for detail).

4.4.3 Pharmacokinetics

There were four single-dose PK studies of a crossover design: a study of relative bioavailability between DPSGC 50 mg and Cataflam® 50 mg (Study AAI-US-142), a study of dose proportionality between DPSGC 25 mg and 50 mg and relative bioavailability between DPSGC doses and Cataflam® 50 mg (Study OA-170), a study of food effect of DPSGC 25 mg and 50 mg (Study AAI-US-119), and a study of relative bioavailability between different formulations of DPSGC 25 mg: 1000 series, 1200 series, and a liquid formulation (Study OA-171).

Based on the results of statistical analyses of PK parameters for DPSGC doses in comparison to Cataflam® 50 mg summarized in the table below, DPSGC 25 mg had similar Cmax, half of the AUC, twice as fast Tmax, and similar T1/2 as Cataflam® 50 mg in Study 170. DPSGC 50 mg had about 80% higher Cmax, similar AUC, twice as fast Tmax, and similar T1/2 as Cataflam® 50 mg in both studies. The two DPSGC doses were dose proportional.

Table 4-1 Results of Statistical Analysis of PK Comparison between DPSGC and Cataflam

LSMeans	Study 142 (N=24)		Study 170 (N=54)		
PK Parameters	**DPSGC 50 mg**	**Cataflam 50 mg**	**DPSGC 50 mg**	**DPSGC 25 mg**	**Cataflam 50 mg**
Cmax (ng/ml)	1773	992	1882	***1025***	***1060***
AUC0-t (ng.hr/ml)	1161	1078	1161	***557***	***1096***
AUC0-∞ (ng.hr/ml)	1195	1087	1179	***582***	***1112***
Tmax (h)	0.60	1.28	0.48	***0.45***	***0.93***
T1/2 (h)	0.96	0.85	1.60	***1.18***	***1.29***

Source: Table 3 on page 27 of the report for Study 142 and Table 14.2.3 on page 64 and Table 14.2.4.2 on pages 66 to 68 of the report for Study 170.

The results of statistical analyses of PK parameters for DPSGC doses administered under fed (high-fat breakfast) and fasted (overnight fast) conditions are summarized in the table below. A high-fat meal decreased Cmax to half, delayed Tmax to twice as long, and did not change AUC or T1/2 as compared to the PK

parameters obtained under fasted conditions. In another words, a high-fat meal taken with DPSGC 25 mg produced a PK profile equivalent to that of Cataflam® 25 mg.

Table 4-2 Results of Statistical Analysis of PK Comparison of DPSGC Given Fed and Fasted

LSMeans	DPSGC 25 mg		DPSGC 50 mg	
PK Parameters	**Fed**	**Fasted**	**Fed**	**Fasted**
Cmax (ng/ml)	562	1069	1015	2155
AUC0-t (ng.hr/ml)	656	665	1375	1479
AUC0-∞ (ng.hr/ml)	700	677	1415	1506
Tmax (h)	1.02	0.49	1.28	0.51
T1/2 (h)	1.11	1.06	1.07	1.10

Source: Tables 5 and 6 on pages 31 and 32 of the report for Study 119.

[*Reviewer's comments*
In Phase 3 bunionectomy studies patients were instructed to withhold solid food from midnight until 1.5 hours after the initial dose and were not given dietary restrictions during the repeated dosing period. There were no dietary restrictions in the single-dose dental studies and patients were probably not expected to be able to eat solid food for a couple hours after a major dental operation.]

In PK Study 171 formulations in series 1000 and 1200 were shown to be bioequivalent.

[*Reviewer's comments*
The information is not useful from a clinical point of view since the formulations in the 1200 series had not been used in any of the Phase 2 and 3 studies.]

In response to the Applicant's request for a waiver of a relative bioavailability study between the registration batch and the older formulations, based on the comparative dissolution data showing (b) (4) % dissolution at (b) (4) for all formulation series, the dissolution profiles were judged to be similar between the new and old series. Therefore, a waiver is recommended by the PK review team.

5. SOURCES OF CLINICAL DATA AND REVIEW STRATEGY

5.1 Tables of Clinical Studies

Study # Dates, Phase	Study Design	Sites	Treatments	N: enrolled/ Completed	Study Population Demographics	Use of Data	Review section
XP21L-301 8/06-10/06 Phase 3	Randomized, double-blind, parallel, placebo-controlled	6 US	DPSGC 25 mg Placebo Second dose as needed or at H8 post initial dose followed by q6 hr for 4 days	102/101 99/98 T: 201/199	Bunionectomy pain 27 M/174 F Mean age 45.2 yr (18.0-65.0)	Positive outcome in support of efficacy ISS: repeated exposure	5.3 7.2-7.5
XP21L-302 9/06-1/07 Phase 3	Randomized, double-blind, parallel, placebo-controlled	4 US	DPSGC 25 mg Placebo Second dose as needed or at H8 post initial dose followed by q6 hr for 4 days	99/96 101/95 T: 200/191	Bunionectomy pain 28 M/ 172 F Mean age 40.4 yr (18.0-65.0)	Positive outcome in support of efficacy ISS: repeated exposure	5.3 7.2-7.5
CL-000395 12/01-3/02 Phase 3	Randomized, double-blind, parallel, placebo-controlled	6 US	DPSGC 25 mg DPSGC 50 mg DPSGC 100 mg Placebo Single dose	63/63 68/68 66/66 68/67 T: 265/264	Post-op dental pain 111 M/154 F Mean age 23.3 yr (18.0-46.2)	Positive outcome in support of efficacy ISS: single-dose exposure	5.3 7.2-7.5

CL-000400 1/02-4/02 Phase 3	Randomized, double-blind, parallel, placebo- controlled	7 US	DPSGC 25 mg DPSGC 50 mg DPSGC 100 mg Placebo Single dose	63/63 62/62 63/63 61/61 T: 249/249	Post-op dental pain 115 M/134 F Mean age 24.4 yr (18.0-46.8)	Positive outcome in support of efficacy ISS: single-dose exposure	5.3 7.2-7.5
CL-000396 2/02-7/02 Phase 3	Randomized, double-blind, parallel, placebo- controlled	13 US	DPSGC 25 mg DPSGC 50 mg Placebo 5 days dosing (2 doses on Day 1, tid on Days 2-5)	67/64 61/60 62/59 T: 190/183	Post arthroscopy knee pain 122 M/67 F Mean age 45.6 yr (18.5-78.6)	Results not in support of single-dose efficacy ISS: repeated exposure	5.3 7.2-7.5
CL-000401 4/02-9/02 Phase 3	Randomized, double-blind, parallel, placebo- controlled	13 US	DPSGC 25 mg DPSGC 50 mg Placebo 5 days dosing (2 doses on Day 1, tid on Days 2-5)	64/64 63/60 65/64 T: 192/188	Post arthroscopy knee pain 112 M/80 F Mean age 46.4 yr (18.3-82.1)	Results not in support of single-dose efficacy, some multiple-dose effects ISS: repeated exposure	5.3 7.2-7.5
CL-002000 7/03-9/03 Phase 2	Randomized, open-label, parallel	1 US	Diclofenac 12.5 mg liquid DPSGC 25 mg DPSGC 50 mg Cataflam 50 mg 1 tab or 1mL q8h In-patient: for 24 h Out-patient: for 7 days	14/14 13/13 14/14 12/12 T: 53/53	Post bunionectomy pain 4 M/ 49 F Mean age 39.8 yr (18.8-71.7)	ISS: repeated exposure	7.4
CL-000424 3/02-6/02 Phase 2	Randomized, parallel, double-blind, single-dose	2 US	DPSGC 25 mg DPSGC 50 mg Single dose	47/47 50/49 T: 97/96	Orthodontal pain 41 M/ 56 F Mean age 13.3 yr (8.1-16.9)	ISS: single-dose exposure in pediatric population	7.6
AAI-US-142 11/02-12/02 Phase 1	Open-label, randomized, crossover	1 US	DPSGC 50 mg Cataflam 50 mg Single dose	24/ 21 24/ 21 T: 24/ 21	Healthy Volunteers 15 M/ 6 F Mean age 29.0 yr (20-44)	ISS: single-dose exposure	4.4 7.5
AAI-US-119 9/02-10/02 Phase 1	Open-label, randomized, crossover	1 US	DPSGC 25 mg DPSGC 50 mg Single dose (fed vs. fasted states)	24/ 24 23/ 23 T: 47/ 47	Healthy Volunteers 38 M/ 9 F Mean age 28.6 yr (19-44)	ISS: single-dose exposure	4.4 7.5
OA-170 5/04-7/04 Phase 1	Open-label, randomized, 3- way crossover	1*	DPSGC 25 mg DPSGC 50 mg Cataflam 50 mg Single dose (fasted)	54/ 54 54/ 54 54/ 54 T: 54/ 54	Healthy Volunteers 29 M/ 25 F Mean age 30.8 yr (18-28.5)	ISS: single-dose exposure	4.4 7.5
OA-171 5/04-6/04 Phase 1	Open-label, randomized, 3- way crossover	1*	DPSGC 25 mg (new process) Diclofenac K liquid 25 mg DPSGC 25 mg (old process) Single dose (fasted)	24/ 24 24/24 24/ 24 T: 24/ 24	Healthy Volunteers 15 M/ 9 F Mean age 34.5 yr (19-36)	ISS: single-dose exposure	4.4 7.5

*Studies conducted in Germany

5.2 Review Strategy

There were 13 clinical studies submitted in the NDA, 12 studies of the Diclofenac Potassium Soft Gel Capsules (DPSGC) and one study of the liquid formulation at 6.25, 12.5, and 25 mg dose levels. The data from the study of the liquid formulation are included in the efficacy and safety review. Of the 12 clinical studies listed in the table above six were adequately designed and well controlled Phase 3 studies, two were Phase 2 studies (one was not blinded and one had no control group), and four were Phase 1 pharmacokinetic studies. The six adequately designed and well-controlled studies of postoperative pain are reviewed for efficacy. Each of the two multiple-dose bunionectomy studies of DPSGC 25 mg is reviewed separately. The two single-dose dental studies of DPSGC 25 mg, 50 mg, and 100 mg used same protocol and are grouped together in the individual study review. The two multiple-dose knee arthroscopy studies of DPSGC 25 mg and 50 mg are summarized briefly because of the lack of adequate assessment of multiple-dose effects and the study outcomes that do not support single-dose efficacy. Data from all 12 studies will be used for safety review.

5.3 Discussion of Individual Studies

5.3.1 Bunionectomy Study 301

5.3.1.1 Protocol

Study XP21L-301 was planned as a randomized, double-blind, placebo-controlled, parallel, multiple-dose (4-day) study of Diclofenac Potassium Soft Gelatin Capsules (DPSGC) 25 mg in patients with postoperative pain following bunionectomy surgery.

Eligible subjects were to have been adult patients scheduled to undergo primary unilateral first metatarsal bunionectomy surgery with osteotomy and internal fixation and no collateral procedures; with sufficient baseline pain intensity score of ≥4 on an 11-point (0 to 10) numerical scale at rest; without any clinically significant condition or a significant laboratory abnormality (refer to the complete list of the eligibility criteria attached as the last item in the Appendix of study review).

Within 21 days prior to surgery, patients were to have been screened for eligibility and given informed consent. Following the completion of the primary unilateral metatarsal bunionectomy on Day 0, patients were to receive the routine standard of care until discharge to the study unit on the same day.

Upon arrival in the study unit, patients were to have been evaluated for continuing eligibility for the study. Eligible patients were to remain in the study unit and to have limited physical activity. Post operative pain management to be allowed included hydrocodone/APAP (5mg/500mg) to be taken 1-2 tablets every 4 to 6 hours as needed for pain with the total daily dosage not to exceed 8 tablets, up to four hours prior to randomization, and the use of ice packs on Day 0 and Day 1 (up to three hours after the last analgesic dose before randomization).

Patients were to have been instructed to assess their pain intensity (PI) using an 11-point (0-10) numerical scale (NPRS) every 30 minutes upon awakening the next morning on Day 1. Patients with PI at rest that reached ≥4 were to have been randomized to one of the two treatment groups to receive the initial dose of the study medication. The planned pain measurements included baseline PI at rest (no activity of the affected toe for at least 10 minutes prior to pain assessment), PI and pain relief (PR, on a 5-point categorical scale) at rest and at 10, 15, 20, 30, 45, and 60 minutes and 1.5, 2, 2.5, 3, 4, 5, 6, 7, and 8 hours after the initial dose or until the request of remedication. Two stop watches were planned to record the onset of the first perceptible and meaningful pain relief. Rescue medication was not to have been allowed after the initial dose. Patients were to have been encouraged to delay their request for remedication until one hour after the initial dose.

The planned remedication dose (upon request or at six hours after the initial dose) was to have been identified as the start of the 48-hour assessment period and was to have been followed by repeated dosing every six hours thereafter. PI was to have been assessed immediately prior to and 3 hours after every dose of study medication until midnight on Day 4. Rescue medication, hydrocodone/APAP (5mg/500mg), was to have been allowed during the multiple-dose evaluation period. Patients were to have been encouraged to delay their request for rescue medication until at least one hour after each dose of study medication. Patients taking rescue medication were to record pain assessment at the time of rescue, take the subsequent doses of study medication on schedule, and continue the remaining pain assessments.

The plan for the inpatient 48-hour multiple-dose evaluation included 48-hour pain assessments at mid dosing interval (three hours after dosing) and at the end of the dosing interval (six hours after dosing), report of the time and the amount of rescue intake, and patient global assessment of study medication. Patients were to receive the 10^{th} dose of the study medication before discharge on Day 3.

During the outpatient multiple-dose evaluation period, patients were to have been instructed to take their study medication on a fixed time schedule at 6 am, 12 noon, 6 pm, and 12 midnight (±1 hour), to respond to an interactive voice response system (IVRS) prior to each dose of the study medication and at three hours after the 6 am, 12 noon, and 6 pm doses to provide PI data, and to record the use of rescue medication and PI scores prior to taking rescue.

The planned primary efficacy endpoint was the average pain intensity over the 48-hour inpatient multiple-dose period. The planned secondary efficacy endpoints for the multiple-dose evaluation included total number and percentage of patients requiring rescue medication, total number of rescue doses, and quantity of rescue medication on each postoperative day; mean rescue interval, calculated from the rescue intervals during each 6-hour dosing interval for postoperative Days 1-4 (except the first six hours while rescue was not permitted); number of patients discontinuing due to inadequate pain relief; patient global assessment of study medication at discharge and on Day 5 or early termination. The planned secondary efficacy endpoints for the single-dose evaluation included time to remedication following the initial dose on Day 1; onset of perceptible and meaningful pain relief (double stopwatch) on Day 1; number and percentage of patients achieving clinically significant analgesic efficacy (defined as having both ≥ 30% reduction in baseline pain intensity by NPRS and meaningful relief as indicated by the stopwatch method) after the administration of the first dose of the study medication on Day 1; the onset and duration of obtaining a ≥ 30% reduction in pain intensity after the administration of the first dose of the study medication on Day 1; pain intensity, pain intensity difference, and pain relief measured at 10, 15, 20, 30, 45, and 60 minutes as well as 1.5, 2, 2.5, 3, 4, 5, 6, 7, and 8 hours after the initial dose and the derived total scores, Sum of Pain Intensity Differences (SPID) and Total Pain Relief (TOTPAR); and number of patients obtaining mild to no pain (NPRS ≤ 2) after the administration of the first dose of study medication on Day 1.

Safety monitoring was planned to consist of reports of adverse events (AEs) during the study and serious AEs until 15 days after the last dose of the study medication, vital signs at screening visit, prior to the initial dose, and at completion or early termination visit; physical examination and laboratory tests at screening visit and at completion or early termination visit; a urine pregnancy test for female of child-bearing potential at screening, on the day of surgery or prior to the first dose on Day 1, and on Day 5.

Population for analysis

The planned primary population for efficacy analysis was to be the full analysis population (same as the safety population) consisting of all randomized patients who received study drug regardless if they had post dose NPRS scores or not.

The planned evaluable (per protocol) population was a subset of the full analysis population that had no major protocol violations that could influence the efficacy evaluation.

Efficacy analysis

- The planned primary efficacy parameter, the arithmetic average of pain intensity over 48 hours, was to be analyzed using an Analysis of Covariance (ANCOVA) model with factors for treatment, center, and baseline pain intensity score (based on the Pain Intensity NPRS Score).
- Other planned continuous variables were to be analyzed by an Analysis of Covariance (ANCOVA) model with factors for treatment and center.
- Planned categorical efficacy parameters, such as global assessment of study medication, were to be analyzed using the Cochran-Mantel-Haenszel (CMH) test with the site as a stratification factor.

- Planned time-to-event variables were to be summarized for each treatment group using the Kaplan-Meier survival curves and analyzed by using the Logrank test with additional analysis using a Cox proportional hazard model.

Missing data management
Missing data at a particular time point were to have been imputed by the Worst Observation Carried Forward (WOCF) with the additional analyses by using LOCF and observed cases.

Sample size
The planned sample size was 86 patients per treatment group based on an estimated effect size of 1.5 unit (SD=3) on an 11-point scale in the average PI over 48 hours, using a two-sided, two-sample comparison of means at the 5% level of significance, to provide over 90% power to detect a treatment difference from placebo. A total of 200 patients were to have been enrolled to achieve 172 evaluable patients.

The original protocol was dated May 22, 2006 and amended on July 24, 2006. The amended protocol was reviewed by IRB before the study initiation on August 18, 2006. The major amendments were the change of primary efficacy parameter from 6-hour SPID to the average PI during the 48 hours from the start of remedication, the widening of the observation period following the initial dose from 6 hours to 8 hours, and the replacement of rescue medication by remedication in assessment of single-dose duration. The study described above included the content of the amended protocol.

The major components of the protocol are also summarized in the table below.

Table 5.3.1-1 Protocol

Study #	XP21L-301
Objectives	To study single-dose and multiple-dose efficacy, tolerability, and safety of Diclofenac Potassium Soft Gelatin Capsules (DPSGC) 25mg in patients with postoperative pain following bunionectomy surgery.
Design	Randomized, double-blind, single-dose (up to 8 hours) followed by multiple-dose (every 6 hours until midnight on Day 4), placebo-controlled, parallel study at six U.S. centers
Sample population	Healthy male and non-pregnant female; 18 to 65 years of age; scheduled to undergo primary unilateral first metatarsal bunionectomy surgery (osteotomy and internal fixation) with no collateral procedures; had sufficient baseline pain intensity score of ≥4 on a 0-10 numerical scale at rest (refer to the complete list of the eligibility criteria in Appendix at the end of study review)
Baseline	Moderate to severe pain by a categorical scale and ≥50 mm on a 100-mm VAS within the required time periods
Treatment	A single dose of DPSGC 25 mg or placebo initially followed by repeated dosing every 6 hours starting from the time of request of remedication (up to 8 hours post initial dose) until midnight on Day 4
Rescue and concomitant medication	**Rescue medication**: No rescue was permitted in the time interval after the initial dose of study medication before remedication. Patients were encouraged to delay requesting for remedication until at least 1 hour after the initial dose of study medication. Rescue medication, hydrocodone/APAP (5 mg/500 mg, 1 to 2 tablets every 4 to 6 hours as needed for pain, not to exceed 8 tablets daily) was allowed during the multiple-dose period. Hydrocodone/APAP was also allowed for initial post surgical pain until at least 4 hours before the initial dose of study medication **Anesthetics** allowed: local anesthesia block (e.g., 3% mepivacaine), intravenous sedation a suitable combination of the following agents: propofol, midazolam or diazepam, nitrous oxide, or fentanyl; Not allowed: succinylcholine, corticosteroids, other sedatives or hypnotic agents, and local anesthetics; **Ice packs** not allowed during the treatment with study medication; can be used only for initial post surgical pain for up to 3 hours following the last analgesic dose taken prior to randomization
Raw efficacy data	Initial dose: PI (on a 11-point numerical scale, NPRS) and PR (on a 5-point categorical scale) at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 hours post initial dose or until request of remedication; time to first perceptible PR and time to meaningful PR by using two stopwatches; time to remedication Multiple-dose: PI immediately prior to and 3 hours after every repeated dose of study medication until midnight of each day and at the time of each rescue; time to taking each rescue and amount of rescue; global assessment at the end of 48 hours and last visit.
Efficacy parameter	***Primary:*** average pain intensity over the 48-hour inpatient multiple-dose period ***Secondary:*** • Time to re-medication following initial dose on Day 1; • Onset of perceptible and meaningful pain relief (double stopwatch) on Day 1; • Number and percent of subjects achieving clinically significant analgesic efficacy (defined as both ≥ 30% reduction in baseline pain intensity using NPRS and meaningful relief as indicated by the stopwatch method) after the administration of the first dose of the study medication on Day 1; • Total number and percentage of subjects requiring rescue medication, total number of rescues, and quantity of rescue medication on each postoperative day; • Mean rescue interval, calculated from the rescue intervals during each 6-hour dosing interval for postoperative Days 1-4, during the multiple dose period (Days 1-4). The rescue interval was defined as the difference between the dosing time and either the time that a rescue medication was taken (if any) or the time of the next study medication administration, whichever was less; • The onset and the duration of obtaining a ≥ 30% reduction in pain intensity after the administration of the first dose of the study medication on Day 1; • Number of subjects discontinuing due to inadequate pain relief; • Pain intensity, pain intensity difference, and pain relief measured at 10, 15, 20, 30, 45, and 60 minutes as well as 1.5, 2, 2.5, 3, 4, 5, 6, 7, and 8 hours after the initial dose. Sum of Pain Intensity Differences (SPID) and Total Pain Relief (TOTPAR) were also evaluated; • Patient global assessment of study medication at discharge and on Day 5 or early termination; and • Number of subjects obtaining mild to no pain (NPRS ≤ 2) after the administration of the first dose of study medication on Day 1
Statistical analysis	ITT: randomized patients taking ≥1 dose of study medication and completed ≥1 post dose efficacy evaluation Primary analysis: median time by Kaplan-Meier estimate; pair wise comparison by log-rank test and p-values evaluation by a Step-down procedure
Safety monitoring	Vital signs at screening, baseline, and 0.5, 1, 2, 4, and 6 hours post dose; adverse events (AEs) report

5.3.1.2 Results

Demographic and other baseline characteristics

The study sample population consisted of 201 patients enrolled who received the study medication, with an age range of 18 to 65 years and a mean of 46 years. Of the 201 patients, 58% were Caucasian, 21% were African American, 14% were Hispanic, 5% were Asian, and 87% were female. The treatment groups were approximately balanced with regard to demographic characteristics such as age, gender, race, height, and weight and with regard to the use of ice packs and analgesics (hydrocodone/acetaminophen) before randomization. The level of baseline pain intensity (PI) was balanced across treatment groups with a group mean of approximately 7 on an 11-point (0 to 10) numerical scale.

Table 5.3.1-2 Demographics and Baseline Characteristics

Study 301 Characteristics	DPSGC 25 mg (N=102)	Placebo (N=99)	Total (N=201)	p-value (a)
Age (years)				
Mean (SD)	45.0 (11.22)	45.4 (11.83)	45.2 (11.50)	0.7944
Median	46.0	47.0	46.0	
Minimum, Maximum	18.0, 65.0	18.0, 65.0	18.0, 65.0	
Gender, n (%)				
Male	13 (13.1)	14 (13.7)	27 (13.4)	0.9017
Female	86 (86.9)	88 (86.3)	174 (86.6)	
Race, n (%)				
Caucasian	61 (59.8)	56 (56.6)	117 (58.2)	0.6417 (b)
Black	23 (22.5)	19 (19.2)	42 (20.9)	
Hispanic	13 (12.7)	16 (16.2)	29 (14.4)	
Asian	4 (3.9)	5 (5.1)	9 (4.5)	
Other	1 (1.0)	3 (3.0)	4 (2.0)	
Height (cm)				
Mean (SD)	165.2 (7.81)	165.2 (7.93)	165.2 (7.85)	0.9679
Median	165.1	164.0	165.0	
Minimum, Maximum	149.9, 192.0	143.5, 191.0	143.5, 192.0	
Weight (kg)				
Mean (SD)	70.9 (12.33)	73.7 (14.79)	72.3 (13.63)	0.1457
Median	68.0	71.7	69.4	
Minimum, Maximum	50.8, 102.7	49.4, 108.0	49.4, 108.0	
Used ice packs before randomization, n (%)	95 (93.1%)	92 (92.9%)	187 (93.0%)	0.9538
Used hydrocodone before randomization, n (%)	101 (99.0%)	99 (100.0)	200 (99.5%)	0.3233
Baseline pain NPRS score Mean (SD)	6.89 (1.746)	7.29 (1.859)	7.09 (1.809)	0.4416

SD = standard deviation; Min = minimum; Max = maximum

a From 1-way ANOVA for continuous variables, chi-square test for categorical variables, and Cochran-Mantel-Haenszel with site as strata for baseline pain NPRS score.

b Test performed for Caucasian versus non Caucasian.

Reference: Appendix Tables 14.1.4.1 and 14.2.9.1 and Appendix Listing 16.2.3.

Source: Table 4 on page 55 of the report for Study 301.

Patient disposition

Of the 201 patients who received study medication, almost all completed the study except three who dropped out. One patient in the DPSGC treatment group discontinued for personal reasons. Two patients in the placebo group withdrew their consent and one of them was due to lack of efficacy.

Table 5.3.1-3 Patient Disposition

Study 301 Patient Disposition n (%)	DPSGC 25 mg (N=102)	Placebo (N=99)	Total (N=201)
Randomized	102	99	201
All Treated Patients	102	99	201

Completed treatment Period	101	97	198
Discontinued	**1 (1.0)**	**2 (2.0)**	**3 (1.5)**
Lack of Efficacy	0	1 (1.0)	1 (0.5)
Adverse Event	0	0	0
Withdrew Consent	0	1 (1.0)	1 (0.5)
Other	1 (1.0)	0	1 (0.5)

Source: Figure 1 and Table 3 on pages 51 and 52 of the report for Study 301.

Protocol violations

There was a high rate of report of protocol violations, 74% in the DPSGC group and 80% in the placebo group. More than 50% of patients in either group had stopwatch uncovered, which was the most frequent reason for protocol violation. In response to this reviewer's request for clarification, an additional analysis submitted on March 25, 2008 indicated that time-to-relief data were reported by all the patients who reported relief; median times to perceptible and meaningful relief were slightly longer when the stopwatch was covered than uncovered with the differences not statistically significant; the response to treatment was not differentially affected by the use of a covered or an uncovered stopwatch in the two treatment groups.

Fewer cases of protocol violations were reported in each of the other categories listed in the table below. Most of them were balanced in the two treatment groups except that study medication extra dose and missing dose were reported more frequently in the placebo group than in the DPSGC group. The magnitude of such differences is not considered as having a major impact on treatment differences taking the total number of doses into consideration (about 1600 doses taken by about 100 patients per treatment group during the course of study).

Table 5.3.1-4 Summary of Protocol Violations

Study 301 **Protocol violations**	**DPSGC 25 mg** **(N=102)**	**Placebo** **(N=99)**	**Total** **(N=201)**
Total number of patients with violations	75 (74%)	79 (80%)	154 (77%)
# of patients with stopwatch uncovered	56 (55%)	54 (55%)	110 (55%)
Total number of violations	94	115	208
1. Uncovered stopwatch	56	54	110
2. Others	38	61	99
Study medication-extra dose	4	15	19
Study medication-missing dose	3	9	12
Study medication-dosing time	4	6	10
Study medication-lost	4	1	5
Rescue medication-extra dose	3	5	8
Rescue medication- dosing time	2	1	3
Eligibility criteria	3	3	6
Pre-randomization analgesics	3	3	6
Day 5 visit off schedule	4	2	6
Missing assessment	2	4	6
Assessment off schedule	1	4	5
Use of ice packs	1	4	5
Use of prohibited medication	1	3	4
Randomization out of order	3	0	3
Missing lab	0	1	1

Source: Appendix listing 16.2.26 of the report for Study 301 and tables in the submission dated March 25, 2008.

Exposure

The exposure information is summarized in the table below. More than 90% of patients in both treatment groups had at least 16 doses, which is equivalent to four days of continuous exposure, as scheduled. At least 10% of patients had ≥20 doses or five days of multiple-dose exposure. Drug exposure was similar in the two treatment groups.

Table 5.3.1-5 Exposure during the Multiple-Dose Period

Study 301 Exposure	DPSGC 25 mg (N=102)	Placebo (N=99)	DPSGC 25 mg (N=102)	Placebo (N=99)
# Doses Taken, n (%)	Distribution		Cumulative	
1	0	0	102 (100%)	99 (100%)
2	0	2 (2%)	102 (100%)	99 (100%)
3	0	0	102 (100%)	97 (98.0%)
4	0	0	102 (100%)	97 (98.0%)
5	0	0	102 (100%)	97 (98.0%)
6	1 (1%)	0	102 (100%)	97 (98.0%)
7	0	0	101 (99.0%)	97 (98.0%)
8	0	0	101 (99.0%)	97 (98.0%)
9	0	0	101 (99.0%)	97 (98.0%)
10	0	0	101 (99.0%)	97 (98.0%)
11	0	0	101 (99.0%)	97 (98.0%)
12	1 (1.0%)	0	101 (99.0%)	97 (98.0%)
13	0	2 (2.0%)	100 (98.0%)	97 (98.0%)
14	1 (1.0%)	2 (2.0%)	100 (98.0%)	95 (96.0%)
15	3 (2.9%)	1 (1.0%)	99 (97.1%)	93 (93.9%)
16	29 (28.4%)	21 (21.2%)	96 (94.1%)	92 (92.9%)
17	40 (39.2%)	44 (44.4%)	67 (65.7%)	71 (71.7%)
18	11 (10.8%)	8 (8.1%)	27 (26.5%)	27 (27.3%)
19	3 (2.9%)	9 (9.1%)	16 (15.7%)	19 (19.2%)
20	4 (3.9%)	1 (1.0%)	13 (12.7%)	10 (10.1%)
>20	9 (8.8%)	9 (9.1%)	9 (8.8%)	9 (9.1%)

Reference: Appendix Tables 14.3.6 and 14.3.7
Source: Table 22 on page 97 of the report for Study 301.

Efficacy results

Primary efficacy endpoint: mean average PI (48-hour inpatient post first remedication dose)

The mean scores for the average of PI measured at mid (three hours post dose) and end of the 6-hour dosing interval during the 48 hours after the first dose of remedication are presented in the table below. The treatment difference in LS-means of the average PI was 2.89 units and was highly statistically significant.

Table 5.3.1-6: Average 48-Hour Pain Intensity NPRS Score during Multiple-Dose Period

Study 301 Average PI	Placebo (N=99)	DPSGC 25 mg (N=102)	p-value(a)
Mean (SD)	5.56 (2.026)	2.49 (1.967)	
Median	5.65	1.85	
Min-Max	0.50-10.00	0.00-7.83	
LS-Mean	5.60	2.71	< 0.0001
Difference in LS-Means	2.89		
95% CI for difference in LS-Means	2.43, 3.35		

WOCF = worst observation carried forward; SD = standard deviation; Min = minimum; Max = maximum;
LS-mean = least squares means
a From ANCOVA with factors for treatment and site, and with baseline pain intensity as covariate.
Reference: Appendix Table 14.2.1.1
Source: Table 6 on page 61 of the report for Study 301.

Multiple-dose effects (48-hour inpatient): time-specific pain intensity scores

The results of statistical comparisons (with no adjustments to the Type I error to account for multiple endpoints) of time-specific pain measurements are summarized in the table below. DPSGC 25 mg performed statistically significantly better than placebo during the entire 48-hour inpatient evaluation period. The effect size of the statistically significant treatment difference in PI (measured by the 11-point numerical scale at mid and end of the 6-hour dosing interval) ranged from -3.3 to -3.7 units in the first 24 hours and from -2.2 to -2.7 units in the second half of the 48-hour period. The graphs of the mean PI (NPRS) scores plotted against time during the

inpatient 48-hour period (refer to Figure 1 in Appendix) provide a visual impression of the effect size of the treatment difference over 48 hours.

Table 5.3.1-7 Summary of Time-Specific PI - 48 Hours after the First Remedication Dose

Study 301 Efficacy parameter	Time (stat. sign. diff: DPSGC > placebo)	Effect size (units) corresponding to stat. sign. differences				Refer to Appendix
		Hour 0	Hour 3 to 24	Hour 27 to 45	Hour 48	
PI	0 to 48 hours	-1.72	-3.28 to -3.73	-2.18 to -2.66	-1.9	Table 5.3.1A-1 Figure 5.3.1A-1

Multiple-dose effects (48-hour inpatient): SPID and peak PID

The LS-mean scores for SPID and peak PID are summarized in the table below. The effect size of the treatment difference was 119 in SPID (206 for DPSGC versus 87 for placebo) and was 1.3 in peak PID (6.5 for DPSGC versus 5.2 for placebo). These treatment differences were statistically significant at $p< 0.0001$ for each comparison.

Table 5.3.1-8 Summary of SPID and Peak PID during the 48-Hour Multiple Dose Period

Study 301 Summation and Peak PID: 48-Hour Inpatient	Placebo (N=99)	DPSGC 25 mg (N=102)	Effect size	p-value	Refer to Appendix
SPID, LS-Mean	86.56	206.00	119.44	< 0.0001	Table 5.3.1A-2
Peak PID, LS-Mean	5.15	6.47	1.33	< 0.0001	Table 5.3.1A-3

Multiple-dose effects (48-hour inpatient): use of rescue medication

The data on the use of rescue medication during the 48-hour multiple-dose period are summarized in the table below. The proportion of patients who used rescue medication was significantly lower in the DPSGC group than the placebo group: 49% less on the first day, 43% less on the second day, and 24% less on the third treatment day prior to discharge. The number of administrations of rescue and the number of tablets taken (both representing use pattern among rescue users) were less in the DPSGC group in comparison to the placebo group. The treatment differences were close to borderline statistical significance at p-value of 0.05 on the first day. The effect size of the difference was decreasing with the length (days) of treatment. Rescue interval (defined by the time interval between dosing with study medication and dosing with rescue) ranged from 5 to 5.8 hours for patients on DPSGC and was significantly different from placebo on each treatment day.

Table 5.3.1-9: Summary of Rescue Data during the 48-Hour Multiple Dose Period

Study 301 Rescue Data: 48-Hour Inpatient	Placebo (N=99)	DPSGC 25 mg (N=102)	Effect size	p-value	Refer to Appendix
Rescue use- proportion of patients (%)					Table 5.3.1A-4
Day 1	87.9%	39.2%	-48.7%	< 0.0001	
Day 2	64.6%	21.6%	-43.0%	< 0.0001	
Day 3 (up to discharge)	29.3%	4.9%	-24.4%	< 0.0001	
Rescue use- # administration among users, mean (SD)					
Day 1	2.37 (1.221)	1.93 (1.047)	-0.44	0.0497	
Day 2	2.17 (1.121)	2.09 (1.269)	-0.08	0.7782	
Day 3 (up to discharge)	1.07 (0.258)	1.00 (0.000)	-0.07	0.5591	
Rescue use- # tablets among users, mean (SD)					
Day 1	3.78 (2.020)	3.03 (2.106)	-0.75	0.0553	
Day 2	3.28 (1.804)	2.95 (1.889)	-0.33	0.4710	
Day 3 (up to discharge)	1.62 (0.677)	1.40 (0.548)	-0.22	0.4962	
Rescue interval, LS-mean (min): overall	258.77	325.77	67.00	< 0.0001	Table 5.3.1A-5
Day 1	193.59	300.36	106.77	< 0.0001	
Day 2	288.74	336.44	47.70	< 0.0001	
Day 3 (up to discharge)	312.78	347.27	34.49	0.0001	

Multiple-dose effects (48-hour inpatient): patient global assessment

The patient global assessment of study medication at the end of 48-hour period before discharge is summarized in the table below. The mean response to DPSGC treatment was between very good and excellent (mean score

of 4.2) and that to placebo treatment was between fair and good (mean score of 2.8). The treatment difference was statistically significant. The proportion of patients with 'good' to 'excellent' response was 92% in the DPSGC groups versus 59% in the placebo group. The proportion of patients with 'very good' and 'excellent' responses was 79% in the DPSGC groups versus 34% in the placebo group.

Table 5.3.1-10: Summary of Patient Global Assessment of Study Drug at Discharge

Study 301 Patient's global assessment at discharge (%)	Placebo (N=99)	DPSGC 25 mg (N=102)	Effect size	p-value	Refer to Appendix
Poor (score=1)	25.3%	1.0%	-24.3%		Table 5.3.1A-6
Fair (score=2)	15.2%	5.9%	-9.3%		
Good (score=3)	24.2%	13.7%	-10.5%		
Very Good (score=4)	19.2%	27.5%	8.35%		
Excellent (score=5)	15.2%	51.0%	35.8%		
Patient's global at discharge-mean response	2.84	4.23	1.39	< 0.0001	

Initial dose effects (8-hour inpatient): time-specific pain measurements

The results of statistical comparison of time-specific pain measurements are summarized in the table below. DPSGC 25 mg performed statistically significantly better than placebo from 1 to 8 hours in PR and at 2.5 hours and from 4 to 8 hours in PID using both WOCF and LOCF analyses. The effect size of the statistically significant treatment difference in PR (measured by a 5-point scale) started as 0.63 units at Hour 1, reached a maximum of 0.98 units at Hour 2.5, and decreased to 0.55 units at Hour 8. The effect size of the statistically significant treatment difference in PID (PI measured by an 11-point scale) started as 1.39 units at Hour 2.5, reached a maximum of 1.57 units at Hour 4, and decreased to 1 unit at Hour 8.

Table 5.3.1-11 Summary of Time-Specific Pain Measurements - 8 Hours after the Initial Dose

Study 301 Efficacy parameter	Time (stat. sign. diff: DPSGC > placebo)	Effect size (units) corresponding to stat. sign. differences			Refer to Appendix
		Start	Maximum	End	
PR	1 to 8 hours	0.63	0.98	0.55	Table 5.3.1A-7, Figure 5.3.1A-2
PID	2.5 and 4 to 8 hours	1.39	1.57	1	Table 5.3.1A-8, Figure 5.3.1A-3

Initial dose effects (8-hour inpatient): summation of pain scores and peak relief

Time-weighted summation of pain scores and peak pain relief over the first eight hours of evaluation of the initial dose are briefly summarized in the table below with details presented in the Appendix. Statistically significant differences from placebo were shown in all three parameters listed.

Table 5.3.1-12 Summary of SPID, TOTPAR, and Peak PR - 8 Hours after the Initial Dose

Study 301 8-Hour Initial Dose: Pain Parameters	Placebo (N=99)	DPSGC 25 mg (N=102)	Effect size	p-value	Refer to Appendix
SPID, LS-mean	3.83	11.40	7.57	< 0.0001	Table 5.3.1A-9
TOTPAR, LS-mean	2.47	7.98	5.51	< 0.0001	Table 5.3.1A-10
Peak pain relief, mean	1.44	2.19	0.75	0.0006	Table 5.3.1A-11

Initial dose effects (8-hour inpatient): onset

Median time to the onset of perceptible and meaningful pain relief and proportion of patients achieving the onset are summarized in the table below. The proportion of patients with either perceptible or meaningful relief was statistically significantly higher in the DPSGC group than in the placebo group, 82 versus 70% for perceptible and 57 versus 35% for meaningful pain relief. The median time to onset of perceptible relief was between 20 and 30 minutes in both groups. The difference in median time to onset of meaningful relief between the two groups was 36 minutes and was statistically significant. Although 55% of patients in both treatment groups had their stopwatch uncovered when the onset was recorded, the treatment effects were not differentially affected by the use of a covered or an uncovered stopwatch in the two treatment groups.

Table 5.3.1-13 Summary of Onset Data - 8 Hours after the Initial Dose

Study 301 8-Hour Initial Dose - Onset	Placebo (N=99)	DPSGC 25 mg (N=102)	Effect size	p-value	Refer to Appendix
Proportion of patients achieving perceptible pain relief	69.7%	82.4%	12.7%	0.0380	Table 5.3.1A-12
Median onset to perceptible pain relief (minutes)a	22.18	26.01	3.83	0.2348	
Proportion of patients achieving meaningful pain relief	35.4%	56.9%	21.5%	0.0025	
Median onset to meaningful pain relief (minutes)a	106.30	70.22	-36.08	0.0080	

Initial dose effects (8-hour inpatient): duration

The duration was defined as the median time to request of remedication during the first eight hours after the initial dose. As shown in the table below the median time to remedication was about 2.6 hours for DPSGC and 1.3 hours for placebo and the treatment difference was statistically significant.

Table 5.3.1-14 Summary of Duration - 8 Hours after the Initial Dose

Study 301 8-Hour Initial Dose - Duration	Placebo (N=99)	DPSGC 25 mg (N=102)	Effect size	p-value	Refer to Appendix
Median time to re-medication (minutes)a	80.00	156.50	76.5	< 0.0001	Table 5.3.1A-13

Initial dose effects (8-hour inpatient): responder analyses

As summarized in the table below at least 20% more patients in the DPSGC group than in the placebo group were classified as responders by each of the three criteria, i.e., those who achieved ≥ 30% reduction in pain, achieved clinically significant analgesic efficacy defined as having both ≥ 30% reduction in baseline pain and meaningful relief by stopwatch, and experienced mild to no pain after the initial dose.

Median time to onset of ≥ 30% reduction was 1.0 hour in patients on DPSGC versus 2.5 hours in patients on placebo. Mean duration of ≥ 30% reduction in pain was 3.7 hours in patients on DPSGC versus 2.3 hours in patients on placebo. The treatment differences in terms of the five parameters used in the responder analyses were all statistically significant.

Table 5.3.1-15 Summary of Responder Analysis - 8 Hours after the Initial Dose

Study 301 8-Hour Initial Dose - Responder Analyses	Placebo (N=99)	DPSGC 25 mg (N=102)	Effect size	p-value	Refer to Appendix
Proportion of patients achieving ≥ 30% reduction in pain	40.4%	60.8%	20.4%	0.0043	Table 5.3.1A-14
Median time to onset of ≥ 30% reduction in pain (minutes)	150	60	-90	0.0376	
Mean (LS) duration of ≥ 30% reduction in pain (minutes)	137.64	220.14	82.51	0.0132	
Proportion achieving clinical sign. efficacy after first dose	29.3%	52.9%	23.6%	0.0008	Table 5.3.1A-15
Proportion experiencing mild to no pain after first dose	23.2%	44.1%	20.9%	0.0019	

Multiple-dose effects (outpatient):

The mean scores for the average PI measured at the mid and end of the 6-hour dosing interval after discharge are summarized by day in the table below. The levels of pain and the effect sizes of treatment differences were much lower than the results obtained from the 48-hour inpatient comparisons. The treatment differences were statistically significant.

Table 5.3.1-16: Summary of Average Pain Intensity by Day during the Outpatient Period

Study 301 Outpatient - Mean average PI	Placebo (N=99)	DPSGC 25 mg (N=102)	Effect size	p-value	Refer to Appendix
Day 3	3.18	1.41	-1.77	< 0.0001	Table 5.3.1A-16
Day 4	2.51	1.23	-1.28	< 0.0001	
Day 5	1.96	1.16	-0.8	0.0011	

Multiple-dose effects (outpatient): use of rescue medication

The data on the use of rescue medication during the outpatient period are summarized in the table below. The proportion of patients who used rescue medication was significantly lower in the DPSGC group than in the

placebo group on the third and fourth treatment day (at least 25% less). The differences in the use pattern among rescue users (the number of administrations of rescue and the number of tablets taken) were small and were not statistically significant.

Table 5.3.1-17: Summary of Rescue Data during the Outpatient Period

Study 301 Rescue Data: Outpatient	Placebo (N=99)	DPSGC 25 mg (N=102)	Effect size	p-value	Refer to Appendix
Rescue use- proportion of patient n (%)					Table 5.3.1A-17
Day 3 (after discharge)	39.4%	12.7%	-26.7%	< 0.0001	
Day 4	38.4%	9.8%	-28.6%	< 0.0001	
Day 5	9.1%	6.9%	-2.2%	0.5502	
Rescue use- # administration among users					
Day 3 (after discharge)	1.46	1.62	0.16	0.4595	
Day 4	1.92	2.30	0.38	0.3340	
Day 5	1.44	1.57	0.13	0.8167	
Rescue use- # tablets among users					
Day 3 (after discharge)	1.85	2.00	0.15	0.6755	
Day 4	2.39	2.30	-0.09	0.8313	
Day 5	1.67	1.57	-0.1	0.8610	

Multiple-dose effects (outpatient): patient global assessment

The patient global assessments of study medication at the end of study are summarized in the table below. The mean response to DPSGC treatment was between very good and excellent (mean score of 4.3) and to placebo treatment was between fair and good (mean score of 2.8). The treatment difference was statistically significant. The proportion of patients with 'good' to 'excellent' response was 91% in the DPSGC groups versus 58% in the placebo group. The proportion of patients with 'very good' and 'excellent' responses was 79% in the DPSGC groups versus 33% in the placebo group.

Table 5.3.1-18: Summary of Patient Global Assessment of Study Drug at the End of Study

Study 301 Patient's global assessment at end of study (%)	Placebo (N=99)	DPSGC 25 mg (N=102)	Effect size	p-value	Refer to Appendix
Poor (score=1)	29.3%	4.9%	-24.4%		Table 5.3.1A-18
Fair (score=2)	12.1%	2.9%	-9.2%		
Good (score=3)	24.2%	11.8%	-12.4%		
Very Good (score=4)	19.2%	19.6%	0.4%		
Excellent (score=5)	14.1%	59.8%	45.7%		
Patient's global at discharge-mean response	2.77	4.28	1.51	< 0.0001	

Discontinued due to lack of efficacy

There was only one placebo patient who discontinued due to inadequate pain relief.

Table 5.3.1-19 Number and Percent of Subjects Who Discontinued Due to Inadequate Pain Relief

Study 301 Response Definition	Statistics	Placebo (N=99)	DPSGC 25 mg (N=102)	P-value #
Discontinued Due to Inadequate Pain Relief	Yes [N (%)]	1 (1.0)	0	0.3173

Note: # P-value from Cochran-Mantel-Haenszel test with site as stratification factor. NC = Not Calculable
Source: Table 14.2.8.1 on page 211 of the report for Study 301.

5.3.1.3 Summary of Findings and Discussions

Study conduct

The treatment groups in Study 301 were basically balanced with regard to the demographic characteristics and baseline pain intensity. Dropouts only accounted for 1.5% (3/201) of the study population. The main contributor to the high rate of protocol violation was stopwatch uncovered, which occurred in 55% of the study population in both treatment groups and had no differential impact on treatment effects of the study medication.

Extra dose and missing dose of study medication were the next most frequent protocol violations and were reported in seven patients on DPSGC versus 24 patients on placebo. The magnitude of the difference was relatively small in comparison to the total number of doses, about 1600 taken by about 100 patients per treatment group during the course of the study. Most patients (94% on DPSGC and 93% on placebo) received at least 16 doses of study medication or four days of continuous treatment.

Efficacy
Multiple-dose effects were supported by demonstration of statistically significant treatment differences in the primary efficacy parameter and almost all of the secondary efficacy parameters, especially during the 48 hours of inpatient evaluation. Most of these statistically significant treatment differences are also considered clinically meaningful because of their effect sizes. The effect size of the treatment difference between DPSGC and placebo was about three units by an 11-point scale in primary efficacy parameter, the average PI from the mid and end of the 6-hour dosing interval measurements during the 48-hour inpatient period. The magnitude of the effect size of the treatment differences can be illustrated by the distance between the two pain curves of time-specific measurements over the 48 hours. Although the use pattern of rescue medication (number of rescue intake and number of tablets) did not differ much among rescue users in the two treatment groups, the treatment difference in the proportion of patients taking rescue was remarkable: 43% to 49% less in the DPSGC group compared to placebo on Day 1 and 2, and 24% to 29% less on Day 3 and 4, which are clinically meaningful. The clinical significance of the findings was further supported by the size of the treatment differences in patient global assessment of study medication that about 45% more in the DPSGC group than in the placebo group rated their response as 'very good' or 'excellent' at the end of 48-hour assessment as well as the end of study assessment.

Single-dose effects of the initial dose were supported by demonstration of statistically significant treatment differences in the time-specific measurements of pain relief from 1-8 hours, time-weighted summation of pain scores SPID and TOTPAR, peak pain relief scores, proportion of patients achieving perceptible and meaningful relief, and median time to the onset of meaningful relief. The median time to remedication for DPSGC treatment was statistically significantly different from placebo, but was only about 2.6 hours. Relatively short single-dose duration had been shown in studies of other NSAIDs using a major inpatient surgical model in comparison to the dental pain model. The clinical meaningfulness of the treatment differences in support of single-dose effects was indicated by the results of responder analysis that 20 to 24% more patients on DPSGC treatment than on placebo were classified as responders by each of the three criteria: achieving at least 30% reduction in pain, having both ≥30% reduction in pain and meaningful onset of pain relief, and experiencing mild to no pain after the initial dose of study medication.

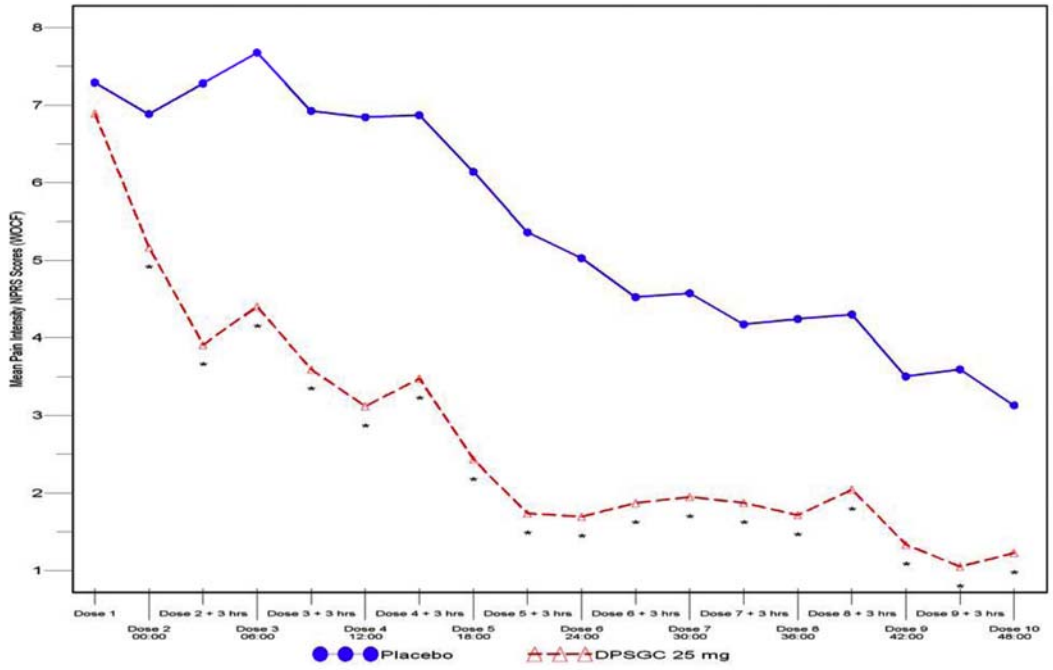
Dosing interval
Because of the left shift of the time-concentration curve relative to the listed drug, one of the major concerns with the new formulation had been whether the duration of analgesic effect would support the proposed dosing interval. The effect sizes of the treatment differences (about 3.5 units on an 11-point scale in the first 24 hours and about 2.5 units in the second 24 hours) from time-specific mid dosing interval and end of dosing interval measurements of the every 6-hour dosing during the 48-hour evaluation period and the demonstration of the daily and overall rescue interval (the interval between the dosing of study medication and administration of rescue) of 5 to 6 hours support the proposed 6-hour dosing interval.

5.3.1.4 Conclusion

Diclofenac Potassium Soft Gelatin Capsules (DPSGC) 25 mg dosed repeatedly every six hours for four days is considered efficacious in treating acute post-operative pain following bunionectomy surgery based on the demonstration of statistically significant and clinically meaningful treatment differences in Study 301.

5.3.1.5 Appendix

Figure 5.3.1A-1: Mean Time-Specific PI (NPRS) during the Inpatient 48-Hour Period



*Statistically significant difference versus placebo using 2-way ANOVA with factors for treatment and site.
Following the second dose of the study, subsequent doses occurred every 6 hours (+/- 1 hour from the 6-hour schedule).
Source: Figure 3 on page 60 of the report for study 301.

Table 5.3.1A-1 Pain Intensity (NPRS) during the Multi-Dose Period

Dose	**1**	**2**		**3**		**4**		**5**	
Time		0 hr	3 hr	0 hr	3 hr	0 hr	3 hr	0 hr	3 hr
		H0	H3	H6	H9	H12	H15	H18	H21
DPSGC 25 mg									
N	102	102	102	102	94	102	65	102	65
Mean	6.89	5.17	3.91	4.40	3.60	3.12	3.48	2.43	1.74
SD	1.746	2.678	3.038	3.103	2.788	2.737	3.073	2.547	2.387
Placebo									
N	99	99	99	99	98	98	79	99	44
Mean	7.29	6.89	7.28	7.68	6.93	6.85	6.87	6.14	5.36
SD	1.859	2.240	2.277	1.999	2.352	2.370	2.244	2.900	3.328
Effect size		-1.72	-3.37	-3.28	-3.33	-3.73	-3.39	-3.71	-3.62
p-value	0.1211	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Dose	**6**		**7**		**8**		**9**		**10**
Time	0 hr	3 hr	0 hr	3 hr	0 hr	3 hr	0 hr	3 hr	
	H24	H27	H30	H33	H36	H39	H42	H45	H48
DPSGC 25 mg									
N	102	102	102	95	102	64	102	60	102
Mean	1.70	1.87	1.95	1.87	1.72	2.05	1.33	1.05	1.23
SD	2.053	2.224	2.266	2.367	2.222	2.522	1.977	2.103	1.970
Placebo									
N	99	99	99	98	99	80	99	42	99
Mean	5.03	4.53	4.58	4.17	4.24	4.30	3.51	3.60	3.13
SD	2.862	2.967	2.854	2.836	2.792	2.940	2.873	3.408	2.794
Effect size	-3.33	-2.66	-2.63	-2.3	-2.52	-2.25	-2.18	-2.55	-1.9
p-value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Note: P-value is from 2-way ANOVA with factors for treatment and site.
The period between Dose 1 and Dose 2 is variable as specified by the study design.
NPRS scores obtained during the variable period between Dose 1 and Dose 2 are not presented.
Source: Table 14.2.1.4 on pages 153 to 157 of the report for Study 301.

Table 5.3.1A-2: SPID Scores Over the 48-Hour Multiple Dose Period

Study 301 SPID Over 48 Hours	Placebo (N=99)	DPSGC 25 mg (N=102)	p-value(a)
Mean (SD)	90.26 (90.846)	210.01 (81.813)	
Median	82.63	209.27	
Min, Max	-123.28, 350.90	-114.43, 369.68	
LS-mean	86.56	206.00	< 0.0001
Difference in LS-means	-119.44		
95% CI for difference in LS-means	-143.23, -95.64		

SD = standard deviation; Min = minimum; Max = maximum; LS-mean = least squares mean
a From 2-way ANOVA with factors for treatment and site.
Reference: Appendix Table 14.2.12.1
Source: Table 8 on page 63 of the report for Study 301.

Table 5.3.1A-3 Peak PID during the 48-Hour Multiple Dose Period

Study 301 Peak PID	Placebo (N=99)	DPSGC 25 mg (N=102)	p-value(a)
Mean	5.47	6.44	
Std Dev	2.651	1.651	
Median	5.00	6.00	
Min, Max	-1.00, 10.00	3.00, 10.00	< 0.0001
Difference in LS-means	-1.33		
95% CI for difference in LS-means	-1.79, -0.87		

a From ANCOVA with factors for treatment and site, and with baseline pain intensity as covariate.
Source: Table 14.2.17.1 on page 287 of the report for Study 301.

Table 5.3.1A-4: Summary of Rescue Medication Use during the 48-Hour Multiple Dose Period

	Placebo (N=99)			DPSGC 25 mg (N=102)		
Study 301	Day 1	Day 2	Day 3 (up to discharge)	Day 1	Day 2	Day 3 (up to discharge)
Rescue Medication Use						
N (%) Used Rescue Medication	87 (87.9%)	64 (64.6%)	29 (29.3%)	40 (39.2%)	22 (21.6%)	5 (4.9%)
p-value vs. placebo (a)				< 0.0001	< 0.0001	< 0.0001
Number of Administrations (among users of rescue medications)						
Mean (SD)	2.37 (1.221)	2.17 (1.121)	1.07 (0.258)	1.93 (1.047)	2.09 (1.269)	1.00 (0.000)
Median	2.00	2.00	1.00	2.00	2.00	1.00
Min-Max	1-5	1-5	1-2	1-4	1-5	1-1
p-value vs. placebo (b)				0.0497	0.7782	0.5591
Amount of Rescue Medication (Tablets) (among users of rescue medications)						
Mean (SD)	3.78 (2.020)	3.28 (1.804)	1.62 (0.677)	3.03 (2.106)	2.95 (1.889)	1.40 (0.548)
Median	4.00	3.00	2.00	2.00	2.50	1.00
Min-Max	1-8	1-10	1-4	1-8	1-8	1-2
p-value vs. placebo [b]				0.0553	0.4710	0.4962

SD = standard deviation; Min = minimum; Max = maximum
a From Cochran Mantel Haenszel test with site as strata.
b From ANOVA with factors for pool site and treatment.
Reference: Appendix Table 14.2.6.1
Source: Table 9 on page 64 of the report for Study 301.

Table 5.3.1A-5 Mean Interval between Dosing and Rescue during the 48-Hour Multiple Dose Period

Study 301	Placebo	DPSGC 25 mg	p-value (a)
Overall Mean Rescue Interval (minutes)			
N	99	102	
Mean	263.88	331.54	<0.0001

Std Dev	72.461	45.181	
Median	271.88	354.19	
Min, Max	11.00, 364.38	152.50, 365.63	
LS-means	258.77	325.77	
Difference in LS-means	-67.00		
95% CI for Difference in LS-means	-82.38, -51.6		
Day 1			
N	99	102	
Mean	201.55	308.95	<0.0001
Std Dev	91.667	75.107	
Median	192.50	360.00	
Min, Max	11.00, 372.50	121.67, 390.00	
LS-means	193.59	300.36	
Difference in LS-means	-106.77		
95% CI for Difference in LS-means	-128.39, -85.1		
Day 2			
N	97	102	
Mean	292.61	340.44	<0.0001
Std Dev	67.571	45.565	
Median	292.80	360.00	
Min, Max	81.25, 378.33	110.00, 380.00	
LS-means	288.74	336.44	
Difference in LS-means	-47.70		
95% CI for Difference in LS-means	-62.93, -32.4		
Day 3 (Up to Discharge)			
N	97	101	
Mean	315.66	350.03	0.0001
Std Dev	83.817	38.453	
Median	360.00	360.00	
Min, Max	60.00, 385.00	59.00, 405.00	
LS-means	312.78	347.27	
Difference in LS-means	-34.49		
95% CI for Difference in LS-means	-52.02, -16.9		

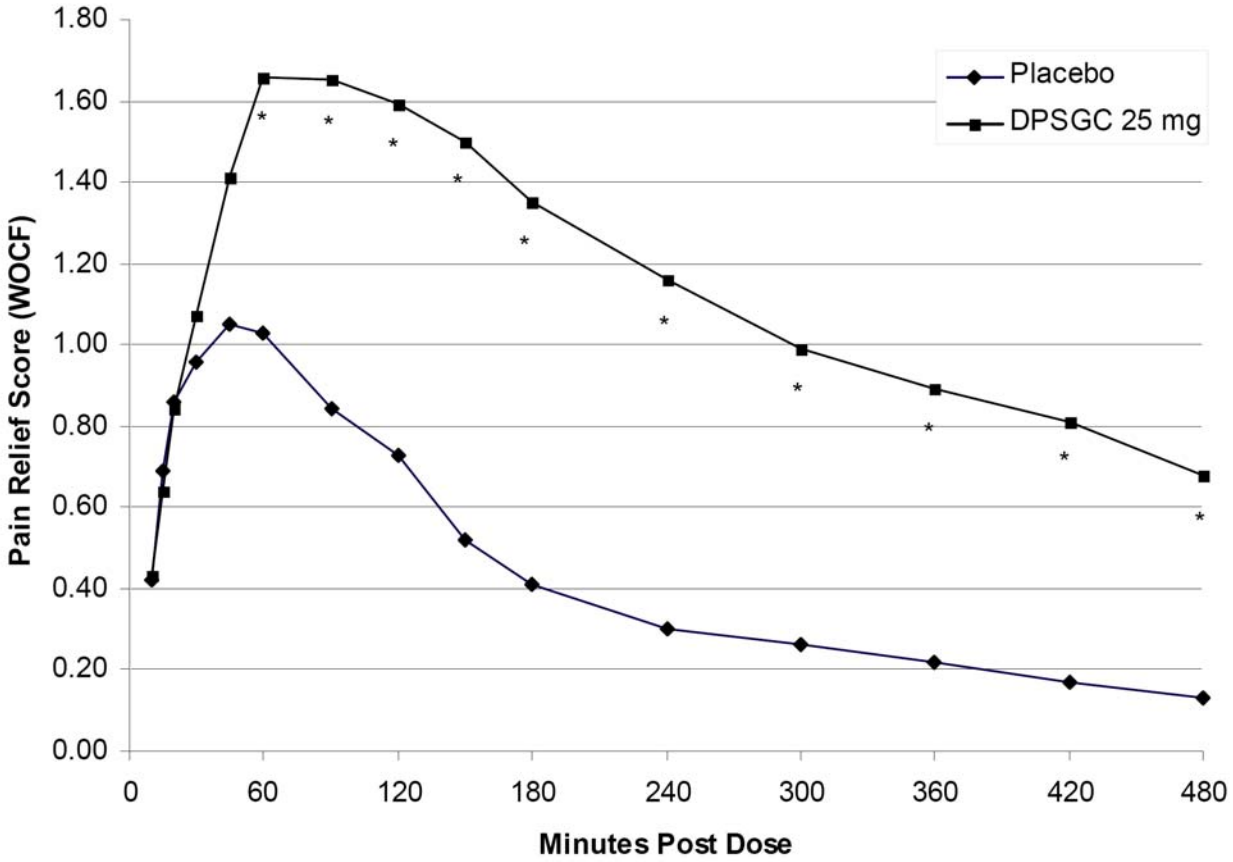
Note: a P-value is from 2-way ANOVA with factors for treatment and site.
Rescue interval is defined as the time between a rescue and the previous dose or the time between the doses when there is no rescue.
Days are based on calendar dates, starting with the date of initial dose as Day 1. Day 3 only includes data up to discharge.
Source: Table 14.2.7.1 on pages 201 to 202 of the report for Study 301.

Table 5.3.1A-6: Patient Global Assessment of Study Drug at Discharge

Study 301 **Patient global at discharge**	**Placebo** **(N=99)**	**DPSGC 25 mg** **(N=102)**	**p-value(a)**
Poor, n (%)	25 (25.3%)	1 (1.0%)	
Fair, n (%)	15 (15.2%)	6 (5.9%)	
Good, n (%)	24 (24.2%)	14 (13.7%)	
Very Good, n (%)	19 (19.2%)	28 (27.5%)	
Excellent, n (%)	15 (15.2%)	52 (51.0%)	
Mean Response	2.84	4.23	< 0.0001

SD = standard deviation; Min = minimum; Max = maximum; CI = confidence interval
a From Cochran-Mantel-Haenszel test with site as stratification factor.
Reference: Appendix Table 14.2.14.1
Source: Table 11 on page 67 of the report for Study 301.

Figure 5.3.1A-2: Day 1 Mean Pain Relief Scores over Time



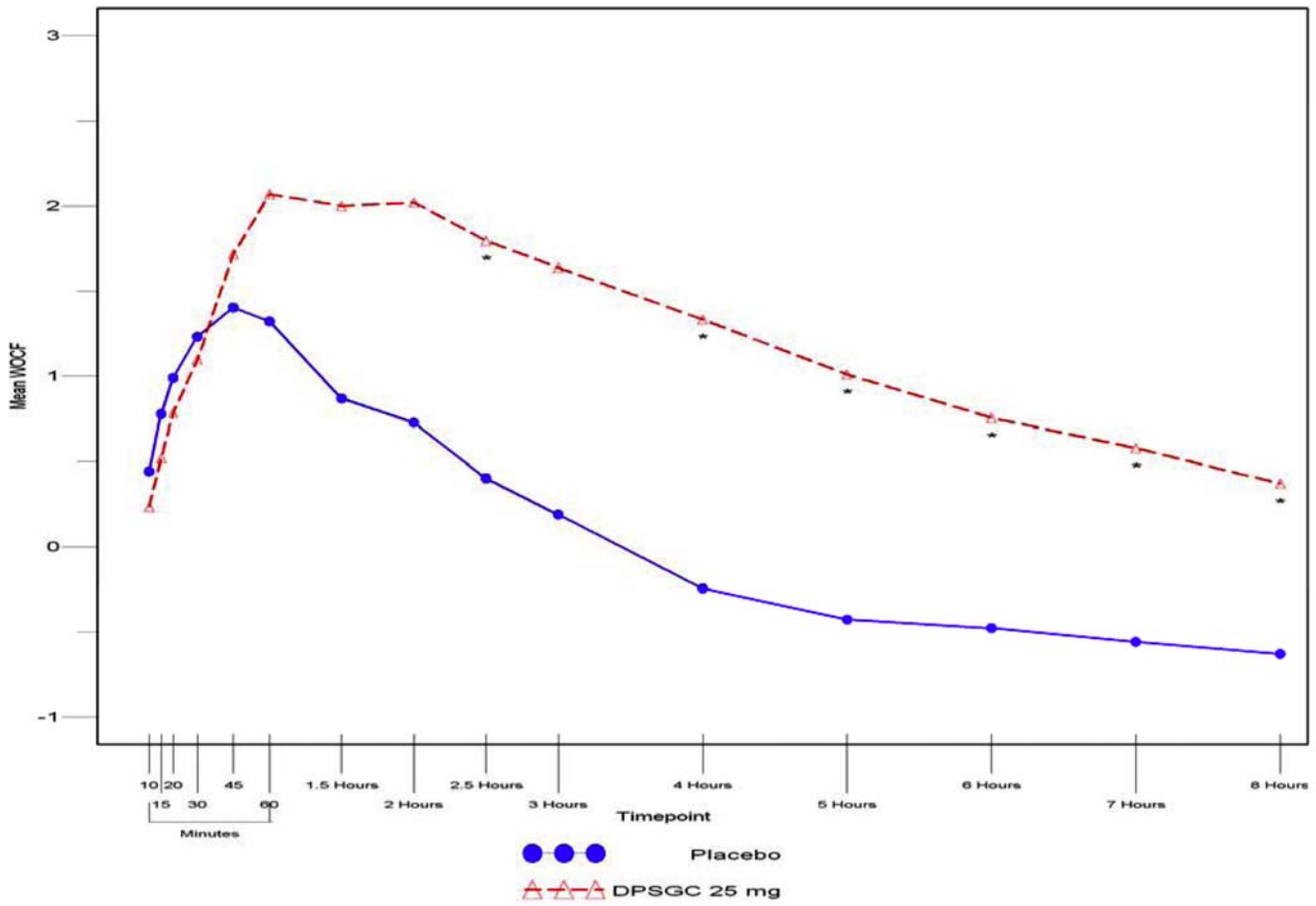
*Statistically significant difference versus placebo using Cochran-Mantel-Haenszel test with site as stratum.
Reference: Appendix Table 14.2.11
Source: Figure 5 on page 71 of the report for study 301.

Table 5.3.1A-7 Day 1 Pain Relief Score over Time Using WOCF or LOCF

Time	10 min	15 min	20 min	30 min	45 min	1 hr	1.5 hr	2 hr	2.5 hr	3 hr	4 hr	5 hr	6 hr	7 hr	8 hr
DPSGC 25 mg															
N	102	102	102	102	102	101	70	61	52	49	42	36	28	26	22
Mean	0.43	0.64	0.84	1.07	1.41	1.66	1.65	1.59	1.50	1.35	1.16	0.99	0.89	0.81	0.68
SD	0.839	0.842	0.972	1.065	1.277	1.301	1.474	1.498	1.540	1.487	1.481	1.397	1.371	1.280	1.145
Placebo															
N	99	99	99	99	99	97	46	36	28	21	13	8	5	2	0
Mean	0.42	0.69	0.86	0.96	1.05	1.03	0.84	0.73	0.52	0.41	0.30	0.26	0.22	0.17	0.13
SD	0.730	0.888	0.979	1.068	1.128	1.199	1.193	1.150	0.973	0.833	0.692	0.694	0.615	0.516	0.420
Effect size						0.63	0.81	0.86	0.98	0.94	0.86	0.73	0.67	0.64	0.55
p-value	0.637	0.483	0.922	0.762	0.226	0.0011	0.0022	0.0002	<0.0001	<0.0001	0.0001	0.0005	0.001	0.0004	0.0008

Note: P-value from Cochran-Mantel-Haenszel test with site as strata.
Source: Tables 14.2.11.1 (WOCF) and 14.2.11.2 (LOCF) on pages 255 to 260 and Table 21 on page 92 of the report for Study 301.

Figure 5.3.1A-3: Day 1 Mean PID Scores over Time (Full Analysis Population)



*Statistically significant difference versus placebo using Cochran-Mantel-Haenszel test with site as stratum.
Reference: Appendix Table 14.2.10
Source: Figure 4 on page 69 of the report for study 301.

Table 5.3.1A-8 Day 1 PID (NPRS) over Time Using WOCF or LOCF

Time	10 min	15 min	20 min	30 min	45 min	1 hr	1.5 hr	2 hr	2.5 hr	3 hr	4 hr	5 hr	6 hr	7 hr	8 hr
DPSGC 25 mg															
N	102	102	102	102	102	101	70	61	52	49	42	36	28	26	22
Mean	0.24	0.52	0.78	1.10	1.72	2.07	2.00	2.02	1.79	1.64	1.33	1.01	0.75	0.58	0.37
SD	1.026	1.175	1.520	1.799	2.195	2.426	2.835	2.887	2.929	2.866	2.730	2.550	2.455	2.249	2.058
Placebo															
N	99	99	99	99	99	97	46	36	28	21	13	8	5	2	0
Mean	0.44	0.78	0.99	1.23	1.40	1.32	0.87	0.73	0.40	0.19	-0.24	-0.42	-0.47	-0.56	-0.63
SD	1.099	1.549	1.781	1.910	2.272	2.535	2.566	2.637	2.555	2.174	1.578	1.485	1.452	1.287	1.093
Effect size									1.39		1.57	1.43	1.22	1.14	1
p-value	0.284	0.160	0.650	0.577	0.114	0.169	0.156	0.162	0.047	0.066	0.0057	0.0062	0.013	0.0087	0.017

Notes: P-value from Cochran-Mantel-Haenszel test with site as strata.
The NPRS pain score at each evaluation was subtracted from the NPRS pain score at Day 1 pre-dose to obtain the pain intensity difference.
Source: Table 14.2.10.1 (WOCF) and 14.2.10.2 (LOCF) on pages 237 to 242 and Table 21 on page 92 of the report for Study 301.

Table 5.3.1A-9: SPID Scores over 8 Hours Post Initial Dose of Study Drug

Study 301 SPID over 8 Hours Post Initial Dose	Placebo (N=99)	DPSGC 25 mg (N=102)	p-value(a)
Mean (SD)	4.06 (7.286)	11.67 (14.302)	< 0.0001
Median	0.86	3.28	
Min-Max	-2.99-38.72	-5.24-50.69	
LS-mean	3.83	11.40	
Difference in LS-means	-7.57		
95% CI for difference in LS-means	-10.75, -4.38		

SD = standard deviation; Min = minimum; Max = maximum; LS-mean = least squares mean
a From 2-way ANOVA with factors for treatment and site.
Reference: Appendix Table 14.2.12.1
Source: Table 12 on page 70 of the report for Study 301.

Table 5.3.1A-10: TOTPAR Scores 8 Hours Post Initial Dose of Study Drug

Study 301 TOTPAR over 8 Hours Post Initial Dose	Placebo (N=99)	DPSGC 25 mg (N=102)	p-value(a)
Mean (SD)	2.63 (3.921)	8.16 (9.330)	< 0.0001
Median	0.79	4.49	
Min-Max	0.00-18.57	0.00-29.97	
LS-mean	2.47	7.98	
Difference in LS-means	-5.51		
95% CI for difference in LS-means	-7.51, -3.50		

SD = standard deviation; Min = minimum; Max = maximum; LS-mean = least squares mean
a From 2-way ANOVA with factors for treatment and site.
Reference: Appendix Table 14.2.13.1
Source: Table 13 on page 72 of the report for Study 301.

Table 5.3.1A-11 Day 1 Peak Pain Relief Scores

Study 301 Peak Pain Relief Score Distribution	Placebo (N=99)	DPSGC 25 mg (N=102)	CMH P-value
0	29 (29.3)	17 (16.7)	
1	25 (25.3)	21 (20.6)	
2	21 (21.2)	13 (12.7)	
3	20 (20.2)	28 (27.5)	
4	4 (4.0)	23 (22.5)	
Summary Statistics N	99	102	0.0006
Mean	1.44	2.19	
Std Dev	1.222	1.426	
Median	1.00	2.50	
Min, Max	0.00, 4.00	0.00, 4.00	

Note: P-value from Cochran-Mantel-Haenszel test with site as strata.
Source: Table 14.2.18.1 on page 293 of the report for Study 301.

Table 5.3.1A-12: Time to Onset of Perceptible and Meaningful Pain Relief

Study 301	Placebo (N=99)	DPSGC 25 mg (N=102)	Log-rank p-value	Wald Chi-square p-value	Cochran Mantel Haenszel p-value
Time to perceptible pain relief					
Patients with relief, n (%)	69 (69.7%)	84 (82.4%)			0.0380
Mean (SD)	20.1 (16.41)	25.2 (19.43)			
Median	14.9	18.8			
Min-Max	2-105	1-91			
Median time (a)	22.18	26.01			
95% CI of time (a)	16.58-35.82	18.58-31.32	0.2348	0.3571	
Time to meaningful pain relief					
Patients with relief, n (%)	35 (35.4%)	58 (56.9%)			0.0025
Mean (SD)	50.7 (28.65)	50.3 (32.14)			

Median	45.5	46.1			
Min-Max	13-114	11-152			
Median time (a)	106.30	70.22			
95% CI of time (a)	84.72-NC	61.18-92.00	0.0080	0.0142	

SD = standard deviation; Min = minimum; Max = maximum; CI = confidence interval; NC = not calculable
a The median, confidence interval and the logrank p-value for time-to-event are estimated using Kaplan-Meier product limit estimates. P-value from Cochran-Mantel-Haenszel (CMH) test with site as stratification factor.
Notes: The Wald Chi-squared p-value is based on the coefficients and corresponding standard errors derived from the Cox Proportional Hazards model with factors for treatment and baseline NPRS score. Subjects who remedicated before onset of relief were censored at the time of remedication. Subjects who discontinued were censored at the time of their last pain assessment.
NC = Not Calculable
Source: Table 14.2.3.1 on pages 169 and 170 of the report for Study 301.

Table 5.3.1A-13: Time to Remedication

Study 301 Remedication data	**Placebo (N=99)**	**DPSGC 25 mg (N=102)**	**Log-rank p-value a**	**Wald Chi-square p-value a**
Patients with remedication, n (%)	99 (100.0%)	102 (100.0%)		
Median time (a)	80.00	156.50		
95% CI of time (a)	70.00-110.00	124.00-245.00	< 0.0001	< 0.0001

SD = standard deviation; Min = minimum; Max = maximum; CI = confidence interval
a Estimated using Kaplan-Meier product limit estimates.
Reference: Appendix Table 14.2.2.1
Source: Table 15 on page 79 of the report for Study 301.

Table 5.3.1A-14 Onset and Duration of Achieving at Least 30% Reduction from Baseline on NPRS (minutes) on Day 1

Study 301 Responder Analysis	**Placebo (N=99)**	**DPSGC 25 mg (N=102)**	**p-value**
Patient with 30% Reduction in NPRS	40 (40.4)	62 (60.8)	0.0043 (1)
Time to 30% Reduction in NPRS			
Median Time	150.00	60.00	0.0376 (2)
95% CI of Time	90.00 - NC	45.00 -90.00	0.0945 (3)
Duration of 30% Reduction in NPRS			
N	40	62	
Mean	134.08	241.44	0.0018 (4)
Std Dev	107.177	175.959	
Median	102.50	222.50	
Min, Max	5.00, 415.00	5.00, 475.00	
LS-means	137.64	220.14	0.0132 (5)
Difference in LS-means	-82.51		
95% CI for Difference in LS-means	-147.37, -17.65		

Notes: The median, confidence interval and logrank p-value for time-to-30% reduction are estimated using Kaplan-Meier product limit estimates. The Wald Chi-squared p-value is based on the coefficients and corresponding standard errors derived from the Cox Proportional Hazards model with factors for treatment and baseline NPRS score.
(1) = P-value from Cochran-Mantel-Haenszel (CMH) test with site as stratification factor.
(2)=Logrank P-value,
(3)=Wald Chi-Square P-value,
(4)=P-value from ANOVA,
(5)=P-value for LS-Mean Difference from ANOVA.
NC=Not Calculable.
Patients who discontinued from the study before onset were censored at the time of the last on-study NPRS evaluation. Patients who received rescue medication or study drug remedication before onset were censored at the time of remedication.
Source: Table 14.2.5.1 on page 185 of the report for Study 301.

Table 5.3.1A-15 Day 1 Responders Analysis during the 8-Hour Period Post Initial

Study 301 Response Definition	**Placebo (N=99)**	**DPSGC 25 mg (N=102)**	**Logrank p-value**	**Chi-Square p-value**	**p-value (a)**
Time to Clinically Significant Relief (Meaningful relief by stopwatch and ≥30% improvement from baseline NPRS (1)					
Patients with Clinically Significant Relief, n (%)	29 (29.3%)	54 (52.9%)			0.0008

Median Time (2)	120.00	90.00	0.0140	0.0339	
95% CI of Time (2)	90.00 - 156.00	66.48 -135.00			
Achieving no or mild pain (NPRS <= 2)	23 (23.2%)	45 (44.1%)			0.0019

Note: a P-value for the proportion of subjects achieving clinically significant relief is from Cochran-Mantel-Haenszel (CMH) test with site as stratification factor.

(1) The events may occur at any time after dosing on Day 1 and the two events may occur at different times on Day 1. Subjects were considered failures for this endpoint if they discontinued the study, received rescue medication, or received study drug remedication before the last event occurred.

(2) The median, confidence interval and the Logrank p-value for time-to-event are estimated using Kaplan-Meier product limit estimates. The Wald Chi-squared p-value is based on the coefficients and corresponding standard errors derived from the Cox Proportional Hazards model with factors for treatment and baseline NPRS score.

Source: Table 14.2.4.1 on page 179 of the report for Study 301.

Table 5.3.1A-16: Summary of Average Pain Intensity Scores by Day during the Outpatient Period

Study 301	**Placebo**			**DPSGC 25 mg**		
Daily average PI	Day 3	Day 4	Day 5	Day 3	Day 4	Day 5
Full Analysis Population	(N = 95)	(N = 94)	(N = 91)	(N = 101)	(N = 100)	(N = 94)
Mean (SD)	3.18 (2.010)	2.51 (1.813)	1.96 (1.775)	1.41 (1.699)	1.23 (1.547)	1.16 (1.499)
Median	2.75	2.14	1.50	1.00	0.86	1.00
Min-Max	0.00-8.60	0.00-7.00	0.00-9.00	0.00-8.00	0.00-8.14	0.00-8.00
p-value vs. placebo (a)				< 0.0001	< 0.0001	0.0011

SD = standard deviation; Min = minimum; Max = maximum

a From 2-way ANOVA with factors for treatment and site.

Reference: Appendix Table 14.2.15.1

Source: Table 18 on page 88 of the report for Study 301.

Table 5.3.1A-17: Summary of Rescue Medication Use during the Outpatient Period

	Placebo			**DPSGC 25 mg**		
Study 301 **Rescue Data: Outpatient**	Day 3 (after discharge)	Day 4	Day 5	Day 3 (after discharge)	Day 4	Day 5
Rescue Medication Use, n (%)	39 (39.4%)	38 (38.4%)	9 (9.1%)	13 (12.7%)	10 (9.8%)	7 (6.9%)
p-value vs. placebo (a)				< 0.0001	< 0.0001	0.5502
Number of Administrations (among users of rescue medications)						
Mean (SD)	1.46 (0.643)	1.92 (1.075)	1.44 (1.014)	1.62 (0.650)	2.30 (1.160)	1.57 (1.134)
Median	1.00	2.00	1.00	2.00	2.00	1.00
Min-Max	1-3	1-4	1-4	1-3	1-4	1-4
p-value vs. placebo (b)				0.4595	0.3340	0.8167
Amount of Rescue Medication (Tablets) (among users of rescue medications)						
Mean (SD)	1.85 (1.182)	2.39 (1.264)	1.67 (1.000)	2.00 (1.000)	2.30 (1.160)	1.57 (1.134)
Median	1.00	2.00	1.00	2.00	2.00	1.00
Min-Max	1-6	1-4	1-4	1-4	1-4	1-4
p-value vs. placebo (b)				0.6755	0.8313	0.8610

SD = standard deviation; Min = minimum; Max = maximum

a From Cochran Mantel Haenszel test with site as strata.

b From ANOVA with factors for pool site and treatment.

Reference: Appendix Table 14.2.16.1

Source: Table 19 on page 89 of the report for Study 301.

Table 5.3.1A-18: Subject Global Assessment of Study Drug at Study Completion

Study 301 **Assessment at Study Completion**	**Placebo (N=99)**	**DPSGC 25 mg (N=102)**	**p-value (a)**
Poor, n (%)	29 (29.3%)	5 (4.9%)	
Fair, n (%)	12 (12.1%)	3 (2.9%)	
Good, n (%)	24 (24.2%)	12 (11.8%)	
Very Good, n (%)	19 (19.2%)	20 (19.6%)	
Excellent, n (%)	14 (14.1%)	61 (59.8%)	
Mean Response	2.77	4.28	< 0.0001

SD = standard deviation; Min = minimum; Max = maximum; CI = confidence interval

a From Cochran-Mantel-Haenszel test with site as stratification factor.

Reference: Appendix Table 14.2.14.1
Source: Table 20 on page 90 of the report for Study 301.

Eligibility criteria

Inclusion Criteria
Patients were going to be required to meet the following criteria for inclusion in the study if they:

1. Were male or female between the ages of 18 and 65 years of age (inclusive) at the time of the screening visit.
2. Had undergone primary unilateral first metatarsal bunionectomy surgery (osteotomy and internal fixation) with no collateral procedures.
3. Had body mass index (BMI) 19-35 (See Appendix 3 for the calculation of BMI).
4. Had received only specified preoperative, intraoperative, and postoperative medication/anesthetics.
5. Were willing and able to comply with the protocol, and able to score their pain intensity throughout the inpatient and outpatient periods.
6. Were in relatively good health with no major organ dysfunction as determined by the Investigator on the basis of medical history, physical examination, and screening laboratory results.
7. Had an initial pain intensity score of at least 4 on a 0-10 NPRS at rest defined as no activity of the affected toe for at least 10 minutes prior to pain assessments.
8. If female, were physically incapable of childbearing potential (postmenopausal for more than one year or surgically sterile) or were practicing an acceptable method of contraception (hormonal, barrier with spermicide, or intrauterine device (IUD), or abstinence) or had received at least one cycle of treatment with birth control pill or patch prior to randomization, and had pregnancy test (for females of childbearing potential) before dosing.
9. Had signed an informed consent form,
10. Had a negative urine test for common drugs of abuse.

Exclusion Criteria
Patients were going to be excluded from this study if they:
1. Were pregnant or lactating.
2. Had experienced an allergic reaction to diclofenac, NSAIDs, aspirin, COX-2 inhibitors, opioids including hydrocodone or codeine, or acetaminophen (e.g., anaphylaxis, urticaria).
3. Had a known history of substance or alcohol abuse within 2 years prior to screening.
4. Had any clinically significant condition, or a significant laboratory abnormality, that would, in the Investigator's or designee's opinion, preclude study participation.
5. Had taken analgesics (Opioids, NSAIDs, or COX-2 inhibitors) other than protocol-specified analgesics following surgery up to the initial dose of study drug.
6. Had gastrointestinal bleeding or a history of gastrointestinal bleeding.
7. Were using opioid analgesics in a chronic or routine manner. All opioid analgesics use on an occasional/ as needed basis is to be discontinued after the screening visit until post surgery.
8. Had taken analgesic medications within 4 hours of receiving the first dose of study drug.
9. Were receiving any medication that, in the opinion of the Investigator or designee, may cause a clinically significant interaction when used concomitantly with hydrocodone or NSAID analgesics.
10. Had used aspirin within 10 days of surgery, except as a thromboembolic prophylaxis.
11. Had participated in a study of an investigational drug or device within 30 days prior to randomization or during this trial.

5.3.2 Bunionectomy Study 302

5.3.2.1 Protocol

Study XP21L-302 was planned as a randomized, double-blind, placebo-controlled, parallel, multiple-dose (4-day) study of Diclofenac Potassium Soft Gelatin Capsules (DPSGC) 25mg in patients with postoperative pain following bunionectomy surgery.

Eligible subjects were to have been adult patients scheduled to undergo primary unilateral first metatarsal bunionectomy surgery with osteotomy and internal fixation and no collateral procedures; with sufficient baseline pain intensity score of ≥4 on an 11-point (0 to 10) numerical scale at rest; without any clinically significant condition or a significant laboratory abnormality (refer to the complete list of the eligibility criteria attached as the last item in the Appendix of study review).

Within 21 days prior to surgery, patients were to have been screened for eligibility and given informed consent. Following the completion of the primary unilateral metatarsal bunionectomy on Day 0, patients were to receive the routine standard of care until discharge to the study unit on the same day.

Upon arrival in the study unit, patients were to have been evaluated for continuing eligibility for the study. Eligible patients were to remain in the study unit and to have limited physical activity. Post operative pain management to be allowed included hydrocodone/APAP (5mg/500mg) to be taken 1-2 tablets every 4 to 6 hours as needed for pain with the total daily dosage not to exceed 8 tablets, up to four hours prior to randomization, and the use of ice packs on Day 0 and Day 1 (up to three hours after the last analgesic dose before randomization).

Patients were to have been instructed to assess their pain intensity (PI) using an 11-point (0-10) numerical scale (NPRS) every 30 minutes upon awakening the next morning on Day 1. Patients with PI at rest that reached ≥4 were to have been randomized to one of the two treatment groups to receive the initial dose of the study medication. The planned pain measurements included baseline PI at rest (no activity of the affected toe for at least 10 minutes prior to pain assessment), PI and pain relief (PR, on a 5-point categorical scale) at rest and at 10, 15, 20, 30, 45, and 60 minutes and 1.5, 2, 2.5, 3, 4, 5, 6, 7, and 8 hours after the initial dose or until the request of remedication. Two stop watches were planned to record the onset of the first perceptible and meaningful pain relief. Rescue medication was not to have been allowed after the initial dose. Patients were to have been encouraged to delay their request for remedication until one hour after the initial dose.

The planned remedication dose (upon request or at six hours after the initial dose) was to have been identified as the start of the 48-hour assessment period and was to have been followed by repeated dosing every six hours thereafter. PI was to have been assessed immediately prior to and three hours after every dose of study medication until midnight on Day 4. Rescue medication, hydrocodone/APAP (5mg/500mg), was to have been allowed during the multiple-dose evaluation period. Patients were to have been encouraged to delay their request for rescue medication until at least one hour after each dose of study medication. Patients taking rescue medication were to record pain assessment at the time of rescue, take the subsequent doses of study medication on schedule, and continue the remaining pain assessments.

The plan for the inpatient 48-hour multiple-dose evaluation included 48-hour pain assessments at mid dosing interval (three hours after dosing) and at the end of the dosing interval (six hours after dosing), report of the time and the amount of rescue intake, and patient global assessment of study medication. Patients were to receive the 10^{th} dose of the study medication before discharge on Day 3.

During the outpatient multiple-dose evaluation period, patients were to have been instructed to take their study medication on a fixed time schedule at 6 am, 12 noon, 6 pm, and 12 midnight (±1 hour), to respond to an interactive voice response system (IVRS) prior to each dose of the study medication and at three hours after the 6 am, 12 noon, and 6 pm doses to provide PI data, and to record the use of rescue medication and PI scores prior to taking rescue.

The planned primary efficacy endpoint was the average pain intensity over the 48-hour inpatient multiple-dose period. The planned secondary efficacy endpoints for the multiple-dose evaluation included total number and percentage of patients requiring rescue medication, total number of rescue doses, and quantity of rescue medication on each postoperative day; mean rescue interval, calculated from the rescue intervals during each 6-hour dosing interval for postoperative Days 1-4 (except the first six hours while rescue was not permitted); number of patients discontinuing due to inadequate pain relief; patient global assessment of study medication at discharge and on Day 5 or early termination. The planned secondary efficacy endpoints for the single-dose evaluation included time to remedication following the initial dose on Day 1; onset of perceptible and meaningful pain relief (double stopwatch) on Day 1; number and percentage of patients achieving clinically significant analgesic efficacy (defined as having both ≥ 30% reduction in baseline pain intensity by NPRS and meaningful relief as indicated by the stopwatch method) after the administration of the first dose of the study medication on Day 1; the onset and duration of obtaining a ≥ 30% reduction in pain intensity after the administration of the first dose of the study medication on Day 1; pain intensity, pain intensity difference, and pain relief measured at 10, 15, 20, 30, 45, and 60 minutes as well as 1.5, 2, 2.5, 3, 4, 5, 6, 7, and 8 hours after the initial dose and the derived total scores, Sum of Pain Intensity Differences (SPID) and Total Pain Relief (TOTPAR); and number of patients obtaining mild to no pain (NPRS ≤ 2) after the administration of the first dose of study medication on Day 1.

Safety monitoring was planned to consist of reports of adverse events (AEs) during the study and serious AEs until 15 days after the last dose of the study medication, vital signs at screening visit, prior to the initial dose, and at completion or early termination visit; physical examination and laboratory tests at screening visit and at completion or early termination visit; a urine pregnancy test for female of child-bearing potential at screening, on the day of surgery or prior to the first dose on Day 1, and on Day 5.

Population for analysis

The planned primary population for efficacy analysis was to be the full analysis population (same as the safety population) consisting of all randomized patients who received study drug regardless if they had post dose NPRS scores or not.

The planned evaluable (per protocol) population was a subset of the full analysis population that had no major protocol violations that could influence the efficacy evaluation.

Efficacy analysis

- The planned primary efficacy parameter, the arithmetic average of pain intensity over 48 hours, was to be analyzed using an Analysis of Covariance (ANCOVA) model with factors for treatment, center, and baseline pain intensity score (based on the Pain Intensity NPRS Score).
- Other planned continuous variables were to be analyzed by an Analysis of Covariance (ANCOVA) model with factors for treatment and center.
- Planned categorical efficacy parameters, such as global assessment of study medication, were to be analyzed using the Cochran-Mantel-Haenszel (CMH) test with the site as a stratification factor.
- Planned time-to-event variables were to be summarized for each treatment group using the Kaplan-Meier survival curves and analyzed by using the Logrank test with additional analysis using a Cox proportional hazard model.

Missing data management

Missing data at a particular time point were to have been imputed by the Worst Observation Carried Forward (WOCF) with the additional analyses by using LOCF and observed cases.

Sample size
The planned sample size was 86 patients per treatment group based on an estimated effect size of 1.5 unit (SD=3) on an 11-point scale in the average PI over 48 hours, using a two-sided, two-sample comparison of means at the 5% level of significance, to provide over 90% power to detect a treatment difference from placebo. A total of 200 patients were to have been enrolled to achieve 172 evaluable patients.

The original protocol was dated May 22, 2006 and amended on July 26, 2006. The amended protocol was reviewed by IRB before the study initiation on September 12, 2006. The major amendments were the change of primary efficacy parameter from 6-hour SPID to the average PI during the 48 hours from the start of remedication, the widening of the observation period following the initial dose from 6 hours to 8 hours, and the replacement of rescue medication by remedication in assessment of single-dose duration. The study described above included the content of the amended protocol.

The major components of the protocol are also summarized in the table below.

Table 5.3.2-1 Protocol

Study #	XP21L-302
Objectives	To study single-dose and multiple-dose efficacy, tolerability, and safety of Diclofenac Potassium Soft Gelatin Capsules (DPSGC) 25mg in patients with postoperative pain following bunionectomy surgery.
Design	Randomized, double-blind, single-dose (up to 8 hours) followed by multiple-dose (every 6 hours until midnight on Day 4), placebo-controlled, parallel study at six U.S. centers
Sample population	Healthy male and non-pregnant female; 18 to 65 years of age; scheduled to undergo primary unilateral first metatarsal bunionectomy surgery (osteotomy and internal fixation) with no collateral procedures; had sufficient baseline pain intensity score of ≥4 on a 0-10 numerical scale at rest (refer to the complete list of the eligibility criteria in Appendix at the end of study review)
Baseline	Moderate to severe pain by a categorical scale and ≥50 mm on a 100-mm VAS within the required time periods
Treatment	A single dose of DPSGC 25 mg or placebo initially followed by repeated dosing every 6 hours starting from the time of request of remedication (up to 8 hours post initial dose) until midnight on Day 4
Rescue and concomitant medication	**Rescue medication**: No rescue was permitted in the time interval after the initial dose of study medication before remedication. Patients were encouraged to delay requesting for remedication until at least 1 hour after the initial dose of study medication. Rescue medication, hydrocodone/APAP (5 mg/500 mg, 1 to 2 tablets every 4 to 6 hours as needed for pain, not to exceed 8 tablets daily) was allowed during the multiple-dose period. Hydrocodone/APAP was also allowed for initial post surgical pain until at least 4 hours before the initial dose of study medication **Anesthetics** allowed: local anesthesia block (e.g., 3% mepivacaine), intravenous sedation a suitable combination of the following agents: propofol, midazolam or diazepam, nitrous oxide, or fentanyl; Not allowed: succinylcholine, corticosteroids, other sedatives or hypnotic agents, and local anesthetics; **Ice packs** not allowed during the treatment with study medication; can be used only for initial post surgical pain for up to 3 hours following the last analgesic dose taken prior to randomization
Raw efficacy data	Initial dose: PI (on a 11-point numerical scale, NPRS) and PR (on a 5-point categorical scale) at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 hours post initial dose or until request of remedication; time to first perceptible PR and time to meaningful PR by using two stopwatches; time to remedication Multiple-dose: PI immediately prior to and 3 hours after every repeated dose of study medication until midnight of each day and at the time of each rescue; time to taking each rescue and amount of rescue; global assessment at the end of 48 hours and last visit.
Efficacy parameter	***Primary:*** average pain intensity over the 48-hour inpatient multiple-dose period ***Secondary:*** • Time to re-medication following initial dose on Day 1; • Onset of perceptible and meaningful pain relief (double stopwatch) on Day 1; • Number and percent of subjects achieving clinically significant analgesic efficacy (defined as both ≥ 30% reduction in baseline pain intensity using NPRS and meaningful relief as indicated by the stopwatch method) after the administration of the first dose of the study medication on Day 1; • Total number and percentage of subjects requiring rescue medication, total number of rescues, and quantity of rescue medication on each postoperative day; • Mean rescue interval, calculated from the rescue intervals during each 6-hour dosing interval for postoperative Days 1-4, during the multiple dose period (Days 1-4). The rescue interval was defined as the difference between the dosing time and either the time that a rescue medication was taken (if any) or the time of the next study medication administration, whichever was less; • The onset and the duration of obtaining a ≥ 30% reduction in pain intensity after the administration of the first dose of the study medication on Day 1; • Number of subjects discontinuing due to inadequate pain relief; • Pain intensity, pain intensity difference, and pain relief measured at 10, 15, 20, 30, 45, and 60 minutes as well as 1.5, 2, 2.5, 3, 4, 5, 6, 7, and 8 hours after the initial dose. Sum of Pain Intensity Differences (SPID) and Total Pain Relief (TOTPAR) were also evaluated; • Patient global assessment of study medication at discharge and on Day 5 or early termination; and • Number of subjects obtaining mild to no pain (NPRS ≤ 2) after the administration of the first dose of study medication on Day 1
Statistical analysis	ITT: randomized patients taking ≥1 dose of study medication and completed ≥1 post dose efficacy evaluation Primary analysis: median time by Kaplan-Meier estimate; pair wise comparison by log-rank test and p-values evaluation by a Step-down procedure
Safety monitoring	Vital signs at screening, baseline, and 0.5, 1, 2, 4, and 6 hours post dose; adverse events (AEs) report

5.3.2.2 Results

Demographic and other baseline characteristics

The study sample population consisted of 200 patients enrolled who received the study medication, with an age range of 18 to 65 years and a mean of 42 years. Of the 200 patients, 62% were Caucasian, 12% were African American, 24% were Hispanic, 2% were Asian, and 86% were female. The treatment groups were approximately balanced with regard to demographic characteristics such as age, gender, race, height, and weight and with regard to the use of ice packs and analgesics (hydrocodone/acetaminophen) before randomization. The level of baseline pain intensity (PI) was balanced across treatment groups with a group mean of approximately 7.5 on an 11-point (0 to 10) numerical scale.

Table 5.3.2-2 Demographics and Baseline Characteristics

Study 302 Characteristics	Placebo (N = 101)	DPSGC 25 mg (N = 99)	Total (N=200)	P-value (a)
Age (years)				
Mean (SD)	39.7 (12.04)	41.2 (12.72)	40.4 (12.37)	0.3805
Median	42.0	42.0	42.0	
Minimum, Maximum	18-63	18-65	18-65	
Gender, n (%)				
Male	15 (14.9%)	13 (13.1%)	28 (14.0%)	0.7259
Female	86 (85.1%)	86 (86.9%)	172 (86.0%)	
Race, n (%)				
Caucasian	57 (56.4%)	66 (66.7%)	123 (61.5%)	0.1371 (b)
Black	15 (14.9%)	8 (8.1%)	23 (11.5%)	
Hispanic	26 (25.7%)	21 (21.2%)	47 (23.5%)	
Asian	2 (2.0%)	2 (2.0%)	4 (2.0%)	
Other	1 (1.0%)	2 (2.0%)	3 (1.5%)	
Height (cm)				
Mean (SD)	166.0 (7.36)	164.9 (9.73)	165.5 (8.61)	0.3844
Median	165.1	165.1	165.1	
Minimum, Maximum	152.4-186.7	147.3-195.6	147.3-195.6	
Weight (kg)				
Mean (SD)	72.6 (12.12)	72.3 (15.21)	72.4 (13.71)	0.8803
Median	71.7	69.4	71.0	
Minimum, Maximum	52.2-103.4	47.2-107.5	47.2-107.5	
Used ice packs before randomization, n (%)	56 (55.4%)	59 (59.6%)	115 (57.5%)	0.5527
Used hydrocodone before randomization, n (%)	101 (100.0%)	98 (99.0%)	199 (99.5%)	0.3113
Baseline pain NPRS score Mean (SD)	7.44 (1.424)	7.52 (1.561)	7.48 (1.49)	0.5680

SD = standard deviation; Min = minimum; Max = maximum
a From 1-way ANOVA for continuous variables and chi-square test for categorical variables.
b Test performed for Caucasian versus non Caucasian.
Reference: Appendix Tables 14.1.4.1 and 14.2.9.1 and Appendix Listing 16.2.3
Source: Table 4 on page 55 of the report for Study 302.

Patient disposition

Of the 200 patients who received study medication, 191 (95%) completed the study and nine discontinued early. Three patients in the DPSGC group dropped out due to adverse event, withdrawal of consent, and family matter, respectively. Six patients dropped out from the placebo group due to lack of efficacy in two, withdrawal of consent in two, adverse event in one, and investigator's discretion in one.

Table 5.3.2-3 Patient Disposition

Study 302 Patient Disposition n (%)	Placebo (N = 101)	DPSGC 25 mg (N = 99)	Total (N=200)
Randomized	101	99	200
All Treated Patients	101	99	200
Completed treatment Period	95	96	191

Discontinued	**6 (5.9)**	**3 (3.0)**	**9 (4.5)**
Lack of Efficacy	2 (2.0)	0	2 (1.0)
Adverse Event	1 (1.0)	1 (1.0)	2 (1.0)
Withdrew Consent	2 (2.0)	1 (1.0)	3 (1.5)
Other	1 (1.0)	1 (1.0)	2 (1.0)

Source: Figure 1 on pages 51 and Table 3 on page 52 of the report for Study 302.

Protocol violations

There was a high rate of report of protocol violations, 98% in the DPSGC group and 93% in the placebo group. More than 70% of patients in either group had stopwatch uncovered, which was the most frequent reason for protocol violation. In response to this reviewer's request for clarification, an additional analysis submitted on March 25, 2008 indicated that time-to-relief data were recorded by all the patients who reported relief; median times to perceptible and meaningful relief were similar when the stopwatch was either covered or uncovered; the response to treatment was not differentially affected by the use of a covered or an uncovered stopwatch in the two treatment groups.

Other than uncovered stopwatch the most frequently reported reasons for protocol violations were missing assessment (mostly missing assessment at time of rescue), medication dosing time off schedule or assessment off schedule (mostly a few minutes off schedule), and Day 5 visit off schedule. Fewer cases of protocol violations were reported in each of the other categories listed in the table below. Most of them were balanced in the two treatment groups.

Table 5.3.2-4 Summary of Protocol Violations

Study 302 **Protocol violations**	**Placebo** **(N = 101)**	**DPSGC 25 mg** **(N = 99)**	**Total** **(N=200)**
Total number of patients with violations	93 (92%)	97 (98%)	190 (95%)
# of patients with stopwatch uncovered	73 (72%)	71 (72%)	144 (72%)
Total number of violations	140	146	286
1. Uncovered stopwatch	73	71	144
2. Others	67	75	142
Missing assessment	22	11	33
Assessment off schedule	7	13	20
Day 5 visit off schedule	9	11	20
Study medication-dosing time	2	13	15
Study medication-extra dose	4	3	7
Study medication-missing dose	2	3	5
Study medication-lost	2	4	6
Missing signature on informed consent	5	5	10
Use of ice packs	3	5	8
Discontinue early	4	2	6
Eligibility criteria	0	3	3
Randomization out of order	0	2	2
Delayed surgery	1	1	2
Rescue medication-extra dose	1	1	2
Rescue medication- dosing time	1	0	1
Use of prohibited medication	2	0	2
Missing lab	1	0	1
Physical activity	1	0	1

Source: Appendix listing 16.2.26 of the report for Study 301.

Exposure

The exposure information is summarized in the table below. More than 90% of patients in both treatment groups had at least 15 doses and ≥85% had at least 16 doses, which is equivalent to four days of continuous exposure, as scheduled. About 10% of patients had ≥20 doses or five days of multiple-dose exposure. Drug exposure was similar in the two treatment groups.

Table 5.3.2-5 Exposure during the Multiple-Dose Period

Study 302 Exposure	Placebo (N = 101)	DPSGC 25 mg (N = 99)	Placebo (N = 101)	DPSGC 25 mg (N = 99)
Number of Doses Taken, n (%)	**Distribution**		**Cumulative**	
Inpatient period				
1	1 (1.0%)	0	101 (100%)	99 (100%)
2	3 (3.0%)	0	100 (99.0%)	99 (100%)
3	0	0	97 (96.0%)	99 (100%)
4	1 (1.0%)	0	97 (96.0%)	99 (100%)
5	0	2 (2.0%)	96 (95.0%)	99 (100%)
6	0	1 (1.0%)	96 (95.0%)	97 (98.0%)
7	1 (1.0%)	0	96 (95.0%)	96 (97.0%)
8	0	0	95 (94.1%)	96 (97.0%)
9	1 (1.0%)	0	95 (94.1%)	96 (97.0%)
10			94 (93.1%)	96 (97.0%)
Outpatient period				
11	0	0	94 (93.1%)	95 (96.0%)
12	0	0	94 (93.1%)	95 (96.0%)
13	0	1 (1.0%)	94 (93.1%)	95 (96.0%)
14	0	2 (2.0%)	94 (93.1%)	94 (94.9%)
15	5 (5.0%)	8 (8.1%)	94 (93.1%)	92 (92.9%)
16	18 (17.8%)	20 (20.2%)	89 (88.1%)	84 (84.8%)
17	43 (42.6%)	41 (41.4%)	71 (70.3%)	64 (64.6%)
18	9 (8.9%)	12 (12.1%)	28 (27.7%)	23 (23.2%)
19	8 (7.9%)	2 (2.0%)	19 (18.8%)	11 (11.1%)
20	2 (2.0%)	2 (2.0%)	11 (10.9%)	9 (9.1%)
>20	9 (8.9%)	7 (7.1%)	9 (8.9%)	7 (7.1%)

Reference: Appendix Tables 14.3.6 and 14.3.7
Source: Table 22 on page 98 of the report for Study 302.

Efficacy results

Primary efficacy endpoint: mean average PI (48-hour inpatient post first remedication dose)

The mean scores for the average of PI measured at mid (three hours post dose) and end of the 6-hour dosing interval during the 48 hours after the first dose of remedication are presented in the table below. The treatment difference in LS-means of the average PI was 2.45 units and was highly statistically significant.

Table 5.3.2-6: Average 48-Hour Pain Intensity NPRS Score during Multiple-Dose Period

Study 302 Average PI	Placebo (N = 101)	DPSGC 25 mg (N = 99)	p-value (a)
Mean (SD)	5.74 (2.127)	3.29 (2.191)	
Median	5.94	3.17	
Min-Max	0.21-10.00	0.00-8.78	
LS-Mean	5.24	2.79	< 0.0001
Difference in LS-Means	2.45		
95% CI for difference in LS-Means	1.91, 2.99		

WOCF = worst observation carried forward; SD = standard deviation; Min = minimum; Max = maximum;
LS-mean = least squares means
a From ANCOVA with factors for treatment and site, and with baseline pain intensity as covariate.
Reference: Appendix Table 14.2.1.1
Source: Table 6 on page 61 of the report for Study 302.

Multiple-dose effects (48-hour inpatient): time-specific pain intensity scores

The results of statistical comparisons of time-specific pain measurements are summarized in the table below. DPSGC 25 mg performed statistically significantly better than placebo during the entire 48-hour inpatient evaluation period. The effect size of the statistically significant treatment difference in PI (measured by the 11-point numerical scale at mid and end of dosing interval) basically ranged from -2.0 to -2.9 units during the 48

hours of measurements, except -1.6 units at Hour 45, most likely as a result of a dramatic decrease in sample size in both treatment groups at that particular time point and contribution from carryforward data. As shown in Table 5.3.2A-1 the actual sample size was only 46 out of 101 for the placebo group, the lowest during the 48-hour period. The sample size at Hour 42 and 48 (the time points before and after Hour 45) was 101 for the placebo group. The same pattern occurred in the DPSGC group (n=64 at Hour 45 and n=99 at Hour 42 and 48). The graphs of the mean PI (NPRS) scores plotted against time during the inpatient 48-hour period (refer to Figure 1 in Appendix) provided a visual impression of the effect size of the treatment difference over 48 hours.

Table 5.3.2-7 Summary of Time-Specific PI - 48 Hours after the First Remedication Dose

Study 301 Efficacy parameter	Time (stat. sign. diff: DPSGC > placebo)	Effect size (units) corresponding to stat. sign. differences		Refer to Appendix
		Hour 0	Hour 3 to 48	
PI	0 to 48 hours	-0.93	Mostly between -1.96 and -2.88 (peak at H12 and H18) except -1.58 at H45	Table 5.3.2A-1 Figure 5.3.2A-1

Multiple-dose effects (48-hour inpatient): SPID and peak PID

The LS-mean scores for SPID and peak PID are summarized in the table below. The effect size of the treatment difference was 117 in SPID (203 for diclofenac versus 86 for placebo) and was 1.6 in peak PID (6.2 for diclofenac versus 4.6 for placebo). These treatment differences were statistically significant at $p< 0.0001$ for each comparison.

Table 5.3.2-8 Summary of SPID and Peak PID during the 48-Hour Multiple Dose Period

Study 302 Summation and Peak PID: 48-Hour Inpatient	Placebo (N = 101)	DPSGC 25 mg (N = 99)	Effect size	p-value	Refer to Appendix
SPID, LS-Mean	86.13	202.96	116.83	< 0.0001	Table 5.3.2A-2
Peak PID, LS-Mean	4.59	6.20	1.61	< 0.0001	Table 5.3.2A-3

Multiple-dose effects (48-hour inpatient): use of rescue medication

The data on the use of rescue medication during the 48-hour multiple-dose period are summarized in the table below. The proportion of patients who used rescue medication was significantly lower in the diclofenac group than the placebo group: 39% less on the first day, 37% less on the second day, and 14% less on the third treatment day prior to discharge. The number of administrations of rescue and the number of tablets taken (both representing use pattern among rescue users) were significantly less in the diclofenac group in comparison to the placebo group and the treatment differences were very similar on the first two treatment days. The effect sizes of treatment differences were much smaller and did not reach statistical significance on the third day of treatment. Rescue interval (defined by the time interval between dosing with study medication and dosing with rescue) ranged from 4.8 to 6.0 hours for patients on diclofenac and was significantly different from placebo on each treatment day.

Table 5.3.2-9: Summary of Rescue Data during the 48-Hour Multiple Dose Period

Study 302 Rescue Data: 48-Hour Inpatient	Placebo (N = 101)	DPSGC 25 mg (N = 99)	Effect size	p-value	Refer to Appendix
Rescue use- proportion of patients (%)					Table 5.3.2A-4
Day 1	92.1%	53.5%	-38.60%	< 0.0001	
Day 2	67.3%	30.3%	-37.00%	< 0.0001	
Day 3 (up to discharge)	18.8%	4.0%	-14.80%	0.0010	
Rescue use- # administration among users, mean (SD)					
Day 1	2.52 (1.069)	1.79 (0.968)	-0.73	< 0.0001	
Day 2	2.49 (1.099)	1.73 (0.980)	-0.76	0.0017	
Day 3 (up to discharge)	1.16 (0.375)	1.00 (0.000)	-0.16	0.4172	
Rescue use- # tablets among users, mean (SD)					
Day 1	3.85 (1.608)	2.55 (1.462)	-1.3	< 0.0001	
Day 2	3.72 (1.969)	2.37 (1.691)	-1.35	0.0015	
Day 3 (up to discharge)	1.79 (0.855)	1.00 (0.000)	-0.79	0.0842	
Rescue interval, LS-mean (min): overall	255.54	324.86	69.32	< 0.0001	Table 5.3.2A-5

Day 1	184.11	287.50	103.39	< 0.0001	
Day 2	277.57	334.83	57.26	< 0.0001	
Day 3 (up to discharge)	331.73	357.42	25.69	0.0003	

Multiple-dose effects (48-hour inpatient): patient global assessment

The patient global assessment of study medication at the end of 48-hour period before discharge is summarized in the table below. The mean response to DPSGC treatment was between good and very good (mean score of 3.6) and that to placebo treatment was between fair and good (mean score of 2.4). The treatment difference was statistically significant. The proportion of patients with 'good' to 'excellent' response was 79% in the DPSGC groups versus 43% in the placebo group. The proportion of patients with 'very good' and 'excellent' responses was 62% in the DPSGC groups versus 22% in the placebo group.

Table 5.3.2-10: Summary of Patient Global Assessment of Study Drug at Discharge

Study 302 **Patient's global assessment at discharge (%)**	**Placebo (N = 101)**	**DPSGC 25 mg (N = 99)**	**Effect size**	**p-value**	**Refer to Appendix**
Poor (score=1)	38.6%	15.2%	-23.40%		Table 5.3.2A-6
Fair (score=2)	14.9%	5.1%	-9.80%		
Good (score=3)	20.8%	17.2%	-3.60%		
Very Good (score=4)	10.9%	28.3%	17.40%		
Excellent (score=5)	10.9%	33.3%	22.40%		
Patient's global at discharge-mean response	2.38	3.60	1.22	< 0.0001	

Initial dose effects (8-hour inpatient): time-specific pain measurements

The results of statistical comparison of time-specific pain measurements are summarized in the table below. DPSGC 25 mg performed statistically significantly better than placebo from 2 to 8 hours in PR and from 2.5 to 6 hours in PID using WOCF analyses. The effect size of the statistically significant treatment difference in PR (measured by a 5-point scale) started as 0.55 units at Hour 2, reached a maximum of 0.81 units at Hour 3, and decreased to 0.30 units at Hour 8. The effect size of the statistically significant treatment difference in PID (PI measured by an 11-point scale) started as 1.24 units at Hour 2.5, reached a maximum of 1.58 units at Hour 3, and decreased to 0.93 units at Hour 6.

Table 5.3.2-11 Summary of Time-Specific Pain Measurements - 8 Hours after the Initial Dose

Study 301 **Efficacy parameter**	**Time (stat. sign. diff: DPSGC > placebo)**	**Effect size (units) corresponding to stat. sign. differences**			**Refer to Appendix**
		Start	**Maximum**	**End**	
PR	2 to 8 hours	0.55	0.81	0.30	Table 5.3.2A-7, Figure 5.3.2A-2
PID	2.5 to 6 hours	1.24	1.58	0.93	Table 5.3.2A-8, Figure 5.3.2A-3

Initial dose effects (8-hour inpatient): summation of pain scores and peak relief

Time-weighted summation of pain scores and peak pain relief over the first eight hours of evaluation of the initial dose are briefly summarized in the table below with details presented in the Appendix. Statistically significant differences from placebo were shown in all three parameters listed.

Table 5.3.2-12 Summary of SPID, TOTPAR, and Peak PR - 8 Hours after the Initial Dose

Study 302 **8-Hour Initial Dose: Pain Parameters**	**Placebo (N = 101)**	**DPSGC 25 mg (N = 99)**	**Effect size**	**p-value**	**Refer to Appendix**
SPID, LS-mean	2.64	9.07	6.43	< 0.0001	Table 5.3.2A-9
TOTPAR, LS-mean	1.97	5.94	3.98	< 0.0001	Table 5.3.2A-10
Peak pain relief, mean	1.15	1.68	0.53	0.0094	Table 5.3.2A-11

Initial dose effects (8-hour inpatient): onset

Median time to the onset of perceptible and meaningful pain relief and proportion of patients achieving the onset are summarized in the table below. There were 10% more patients achieving perceptible relief in the

DPSGC group than in the placebo group and the difference was not statistically significant. The median time to onset of perceptible relief was close to 40 minutes in both groups. There was statistically significantly higher proportion of patients achieving meaningful relief in the DPSGC group than in the placebo group (51% versus 30%) and longer median time to onset of meaningful relief (1.5 hours) in the DPSGC group in comparison to the placebo group for which median was not calculable due to less than 50% achieving onset. Although 72% of patients in both treatment groups had their stopwatch uncovered when the onset was recorded, the treatment effects were not differentially affected by the use of a covered or an uncovered stopwatch in the two treatment groups.

Table 5.3.2-13 Summary of Onset Data - 8 Hours after the Initial Dose

Study 302 8-Hour Initial Dose - Onset	Placebo (N = 101)	DPSGC 25 mg (N = 99)	Effect size	p-value	Refer to Appendix
Proportion of patients achieving perceptible pain relief	62.4%	72.7%	10.3%	0.1480	Table 5.3.2A-12
Median onset to perceptible pain relief (minutes)a	35.99	42.90	6.91	0.6733	
Proportion of patients achieving meaningful pain relief	29.7%	50.5%	20.8%	0.0031	
Median onset to meaningful pain relief (minutes)a	NC	90.63	NC	0.0351	

NC means not calculable

Initial dose effects (8-hour inpatient): duration

The duration was defined as the median time to request of remedication during the first eight hours after the initial dose. As shown in the table below the median time to remedication was about 3.0 hours for DPSGC and 1.6 hours for placebo and the treatment difference was statistically significant.

Table 5.3.2-14 Summary of Duration - 8 Hours after the Initial Dose

Study 302 8-Hour Initial Dose - Duration	Placebo (N = 101)	DPSGC 25 mg (N = 99)	Effect size	p-value	Refer to Appendix
Median time to re-medication (minutes)a	96.00	177.00	81	< 0.0001	Table 5.3.2A-13

Initial dose effects (8-hour inpatient): responder analyses

As summarized in the table below about 20% more patients in the DPSGC group than in the placebo group were classified as responders by each of the three criteria, i.e., those who achieved ≥ 30% reduction in pain, achieved clinically significant analgesic efficacy defined as having both ≥ 30% reduction in baseline pain and meaningful relief by stopwatch, and experienced mild to no pain after the initial dose.

Median time to onset of ≥ 30% reduction was 1.8 hours in patients on DPSGC versus 5.0 hours in patients on placebo. Mean duration of ≥ 30% reduction in pain was 3.8 hours in patients on DPSGC versus 2.0 hours in patients on placebo. The treatment differences in terms of the five parameters used in the responder analyses were all statistically significant.

Table 5.3.2-15 Summary of Responder Analysis - 8 Hours after the Initial Dose

Study 302 8-Hour Initial Dose - Responder Analyses	Placebo (N = 101)	DPSGC 25 mg (N = 99)	Effect size	p-value	Refer to Appendix
Proportion of patients achieving ≥ 30% reduction in pain	30.7%	51.5%	20.8%	0.0034	Table 5.3.2A-14
Median time to onset of ≥ 30% reduction in pain (minutes)	300.00	110.00	-190	0.0259	
Mean (LS) duration of ≥ 30% reduction in pain (minutes)	120.46	227.31	106.85	0.0008	
Proportion achieving clinically sign. efficacy after first dose	25.7%	47.5%	21.80%	0.0014	Table 5.3.2A-15
Proportion experiencing mild to no pain after first dose	12.9%	32.3%	19.40%	0.0010	

Multiple-dose effects (outpatient):

The mean scores for the average PI measured at the mid and end of the 6-hour dosing interval after discharge are summarized by day in the table below. The levels of pain and the effect sizes of treatment differences were much lower than the results obtained from the 48-hour inpatient comparisons. The treatment differences were statistically significant.

Table 5.3.2-16: Summary of Average Pain Intensity by Day during the Outpatient Period

Study 302 Outpatient - Mean average PI	Placebo (N = 101)	DPSGC 25 mg (N = 99)	Effect size	p-value	Refer to Appendix
Day 3	3.66	2.08	-1.58	< 0.0001	Table 5.3.2A-16
Day 4	3.24	1.86	-1.38	< 0.0001	
Day 5	2.69	1.58	-1.11	0.0002	

Multiple-dose effects (outpatient): use of rescue medication

The data on the use of rescue medication during the outpatient period are summarized in the table below. The proportion of patients who used rescue medication was significantly lower in the DPSGC group than in the placebo group on each of the three outpatient treatment day (14% to 38% less). The differences in the use pattern among rescue users (the number of administrations of rescue and the number of tablets taken) were small and were not statistically significant.

Table 5.3.2-17: Summary of Rescue Data during the Outpatient Period

Study 302 Rescue Data: Outpatient	Placebo (N = 101)	DPSGC 25 mg (N = 99)	Effect size	p-value	Refer to Appendix
Rescue use- proportion of patient n (%)					Table 5.3.2A-17
Day 3 (after discharge)	52.5%	14.1%	-38.40%	< 0.0001	
Day 4	46.5%	22.2%	-24.30%	0.0003	
Day 5	14.9%	1.0%	-13.90%	0.0003	
Rescue use- # administration among users					
Day 3 (after discharge)	1.83	1.64	-0.19	0.4220	
Day 4	1.74	1.41	-0.33	0.1753	
Day 5	1.40	1.00	-0.4	0.4577	
Rescue use- # tablets among users					
Day 3 (after discharge)	2.55	1.93	-0.62	0.1250	
Day 4	2.38	1.77	-0.61	0.1274	
Day 5	2.20	1.00	-1.2	0.2373	

Multiple-dose effects (outpatient): patient global assessment

The patient global assessments of study medication at the end of study are summarized in the table below. The mean response to DPSGC treatment was between good and very good (mean score of 3.7) and to placebo treatment was between fair and good (mean score of 2.5). The treatment difference was statistically significant. The proportion of patients with 'good' to 'excellent' response was 80% in the DPSGC groups versus 46% in the placebo group. The proportion of patients with 'very good' and 'excellent' responses was 41% in the DPSGC groups versus 27% in the placebo group.

Table 5.3.2-18: Summary of Patient Global Assessment of Study Drug at the End of Study

Study 302 Patient's global assessment at end of study (%)	Placebo (N = 101)	DPSGC 25 mg (N = 99)	Effect size	p-value	Refer to Appendix
Poor (score=1)	39.6%	16.2%	-23.40%		Table 5.3.2A-18
Fair (score=2)	12.9%	3.0%	-9.90%		
Good (score=3)	18.8%	12.1%	-6.70%		
Very Good (score=4)	12.9%	29.3%	16.40%		
Excellent (score=5)	13.9%	38.4%	24.50%		
Patient's global at discharge-mean response	2.47	3.71	1.24	< 0.0001	

Discontinued due to lack of efficacy

There were only two placebo patients who discontinued due to inadequate pain relief.

Table 5.3.2-19 Number and Percent of Subjects Who Discontinued Due to Inadequate Pain Relief

Study 302	Statistics	Placebo	DPSGC 25 mg	P-value (a)

Response Definition		(N=101)	(N=99)	
Discontinued Due to Inadequate Pain Relief	Yes [N (%)]	2 (2.0)	0	0.1609

a P-value from Cochran-Mantel-Haenszel test with site as stratification factor. NC = Not Calculable
Source: Table 14.2.8.1 on page 220 of the report for Study 302.

5.3.2.3 Summary of Findings and Discussions

The treatment groups in Study 302 were basically balanced with regard to the demographic characteristics and baseline pain intensity. There were relatively small proportions of dropouts, 6% from the placebo group and 3% from the DPSGC group. The main contributor to the high rate of protocol violation was stopwatch uncovered, which occurred in 72% of the study population in both treatment groups and had no differential impact on treatment effects of the study medication. There were twice as many missing assessment cases reported in the placebo group than the DPSGC group (22 versus 11), mostly at the time of rescue. More cases of dosing time off schedule were reported in the DPSGC group than the placebo group (13 versus 2), mostly only a few minutes off the scheduled time. None of the above are considered as having a major impact on treatment differences. Most patients (85% on DPSGC and 88% on placebo) received at least 16 doses of study medication or four days of continuous treatment.

Efficacy
Multiple-dose effects were supported by demonstration of statistically significant treatment differences in the primary efficacy parameter and almost all of the secondary efficacy parameters, especially during the 48 hours of inpatient evaluation. Most of these statistically significant treatment differences are also considered clinically meaningful because of their effect sizes. The effect size of treatment difference between DPSGC and placebo was 2.5 units by an 11-point scale in primary efficacy parameter, the average PI from the mid and end of the 6-hour dosing interval measurements during the 48-hour inpatient period. The magnitude of the effect size of the treatment differences can be illustrated by the distance between the two pain curves of time-specific measurements over the 48 hours. The proportion of patients taking rescue was statistically significantly less in the DPSGC group in comparison to the placebo group, 39% less on Day 1, 37% less on Day 2, 15% less before discharge and 38% less after discharge on Day 3, and 24% less on Day 4, which are considered clinically meaningful findings. The clinical significance of the findings was further supported by the size of the treatment differences in patient global assessment of study medication that about 35% more in the DPSGC group than in the placebo group rated their response as 'good' to 'excellent' at the end of 48-hour assessment as well as the end of study assessment.

Single-dose effects of the initial dose were supported by demonstration of statistically significant treatment differences in the time-specific measurements of pain relief from 1-8 hours, time-weighted summation of pain scores SPID and TOTPAR, peak pain relief scores, proportion of patients achieving perceptible and meaningful relief, and median time to the onset of meaningful relief. The median time to remedication for DPSGC treatment was statistically significantly different from placebo, but was only about 3 hours. Relatively short single-dose duration had been shown in studies of other NSAIDs using a major inpatient surgical model in comparison to the dental pain model. The clinical meaningfulness of the treatment differences in support of single-dose effects was indicated by the results of responder analysis that about 20% more patients on DPSGC treatment than on placebo were classified as responders by each of the three criteria: achieving at least 30% reduction in pain, having both ≥30% reduction in pain and meaningful onset of pain relief, and experiencing mild to no pain after the initial dose of study medication.

Dosing interval
Because of the left shift of the time-concentration curve relative to the listed drug, one of the major concerns with the new formulation had been whether the duration of analgesic effects would support the proposed dosing interval. The effect sizes of the treatment differences (2.2 to 2.9 units on an 11-point scale in the first 24 hours and 2.0 to 2.6 units in the second 24 hours) from time-specific mid-dosing interval and end-of-dosing interval

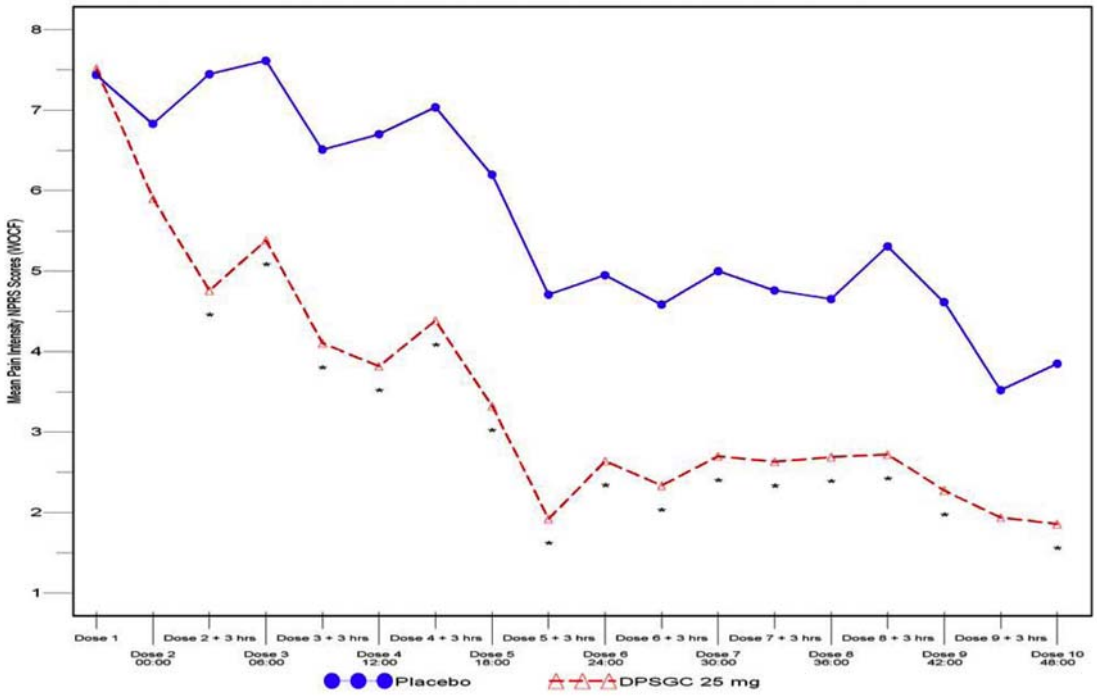
measurements of the every 6-hour dosing during the 48-hour evaluation period and the demonstration of the daily and overall rescue interval (the interval between the dosing of study medication and administration of rescue) of 5 to 6 hours support the proposed 6-hour dosing interval.

5.3.2.4 Conclusion

Diclofenac Potassium Soft Gelatin Capsules (DPSGC) 25 mg dosed repeatedly every six hours for four days was shown to be effective in treating acute post-operative pain following bunionectomy surgery based on the results of Study 302. The positive findings of study 301 were replicated in this study of an identical design.

5.3.2.5 Appendix

Figure 5.3.2A-1: Mean Time-Specific PI (NPRS) during the Inpatient 48-Hour Period



*Statistically significant difference versus placebo using 2-way ANOVA with factors for treatment and site.
Following the second dose of the study, subsequent doses occurred every 6 hours (+/- 1 hour from the 6-hour schedule).
Source: Figure 3 on page 60 of the report for Study 302.

Table 5.3.2A-1 Pain Intensity (NPRS) during the Multi-Dose Period

Dose	**1**	**2**		**3**		**4**		**5**	
Time		0 hr	3 hr	0 hr	3 hr	0 hr	3 hr	0 hr	3 hr
		H0	H3	H6	H9	H12	H15	H18	H21
DPSGC 25 mg									
N	99	99	99	99	89	99	68	99	63
Mean	7.52	5.90	4.76	5.38	4.10	3.82	4.38	3.32	1.92
SD	1.561	2.819	2.886	2.795	2.772	2.764	3.008	2.788	2.260
Placebo									
N	101	101	101	101	100	101	80	101	48
Mean	7.44	6.83	7.45	7.61	6.51	6.70	7.04	6.20	4.71
SD	1.424	2.200	2.243	1.923	2.418	2.339	2.236	2.796	3.003
Effect size		-0.93	-2.69	-2.23	-2.41	-2.88	-2.66	-2.88	-2.79
p-value	0.7368	0.0084	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Dose	**6**		**7**		**8**		**9**		**10**
Time	0 hr	3 hr	0 hr	3 hr	0 hr	3 hr	0 hr	3 hr	
	H24	H27	H30	H33	H36	H39	H42	H45	H48
DPSGC 25 mg									
N	99	99	99	89	99	71	99	64	99
Mean	2.64	2.33	2.70	2.63	2.69	2.72	2.27	1.94	1.86
SD	2.577	2.458	2.742	2.913	2.884	2.758	2.519	2.794	2.445
Placebo									
N	101	101	101	100	101	81	101	46	101
Mean	4.95	4.58	5.00	4.76	4.65	5.31	4.61	3.52	3.85
SD	2.632	2.885	2.728	2.753	2.747	3.007	2.902	3.352	2.947
Effect size	-2.31	-2.25	-2.3	-2.13	-1.96	-2.59	-2.34	-1.58	-1.99
p-value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0067	<0.0001

Note: P-value is from 2-way ANOVA with factors for treatment and site.
The period between Dose 1 and Dose 2 is variable as specified by the study design.
NPRS scores obtained during the variable period between Dose 1 and Dose 2 are not presented.
Source: Table 14.2.1.4 on pages 160 to 164 of the report for Study 302.

Table 5.3.2A-2: SPID Scores Over the 48-Hour Multiple Dose Period

Study 302 **SPID over 48 hours**	**Placebo** **(N = 101)**	**DPSGC 25 mg** **(N = 99)**	**p-value (a)**
Mean (SD)	86.56 (95.163)	203.13 (94.765	< 0.0001
Median	65.64	212.99	
Min, Max	-133.14, 357.43	-32.07, 412.43	
LS-mean	86.13	202.96	
Difference in LS-means	-116.83		
95% CI for difference in LS-means	-143.24, -90.43		

SD = standard deviation; Min = minimum; Max = maximum; LS-mean = least squares mean
a From 2-way ANOVA with factors for treatment and site.
Reference: Appendix Table 14.2.12.1
Source: Table 8 on page 63 of the report for Study 302.

Table 5.3.2A-3 Peak PID during the 48-Hour Multiple Dose Period

Study 302 **Peak PID**	**Placebo** **(N = 101)**	**DPSGC 25 mg** **(N = 99)**	**p-value (a)**
Mean	4.72	6.44	<0.0001
Std Dev	2.534	1.944	
Median	5.00	6.00	
Min, Max	-2.00, 9.00	1.00, 10.00	
LS-means	4.59	6.20	
Difference in LS-means	-1.61		
95% CI for Difference in LS-means	-2.18, -1.04		

a From ANCOVA with factors for treatment and site, and with baseline pain intensity as covariate.
Source: Table 14.2.17.1 on page 296 of the report for Study 302.

Table 5.3.2A-4: Summary of Rescue Medication Use during the 48-Hour Multiple Dose Period

	Placebo (N = 101)			**DPSGC 25 mg (N = 99)**		
Study 302 **Rescue Medication**	Day 1	Day 2	Day 3 (up to discharge)	Day 1	Day 2	Day 3 (up to discharge)
Rescue Medication Use						
N (%) Used Rescue Medication	93 (92.1%)	68 (67.3%)	19 (18.8%)	53 (53.5%)	30 (30.3%)	4 (4.0%)
p-value vs. placebo (a)				< 0.0001	< 0.0001	0.0010
Number of Administrations (among users of rescue medications)						
Mean (SD)	2.52 (1.069)	2.49 (1.099)	1.16 (0.375)	1.79 (0.968)	1.73 (0.980)	1.00 (0.000)
Median	3.00	2.00	1.00	2.00	1.00	1.00
Min-Max	1-7	1-6	1-2	1-5	1-5	1-1
p-value vs. placebo (b)				< 0.0001	0.0017	0.4172
Amount of Rescue Medication (Tablets) (among users of rescue medications)						
Mean (SD)	3.85 (1.608)	3.72 (1.969)	1.79 (0.855)	2.55 (1.462)	2.37 (1.691)	1.00 (0.000)
Median	4.00	3.00	2.00	2.00	2.00	1.00
Min-Max	1-7	1-8	1-4	1-6	1-8	1-1
p-value vs. placebo (b)				< 0.0001	0.0015	0.0842

SD = standard deviation; Min = minimum; Max = maximum
a From Cochran Mantel Haenszel test with site as strata.
b From ANOVA with factors for pool site and treatment.
Reference: Appendix Table 14.2.6.1
Source: Table 9 on page 64 of the report for Study 302.

Table 5.3.2A-5 Mean Interval between Dosing and Rescue during the 48-Hour Multiple Dose Period

Study 302 **Rescue Medication**	**Placebo**	**DPSGC 25 mg**	**p-value (a)**
Overall Mean Rescue Interval (minutes)			

N	101	99	
Mean	255.58	324.52	<0.0001
Std Dev	68.293	43.934	
Median	255.13	338.50	
Min, Max	75.25, 360.13	207.00, 362.13	
LS-means	255.54	324.86	
Difference in LS-means	-69.32		
95% CI for Difference in LS-means	-85.29, -53.3		
Day 1			
N	101	99	
Mean	183.51	286.27	<0.0001
Std Dev	82.875	81.503	
Median	177.50	327.50	
Min, Max	51.67, 365.00	77.33, 364.00	
LS-means	184.11	287.50	
Difference in LS-means	-103.39		
95% CI for Difference in LS-means	-126.12, -80.6		
Day 2			
N	101	99	
Mean	277.67	334.59	<0.0001
Std Dev	78.646	44.700	
Median	277.25	359.75	
Min, Max	79.25, 367.50	177.25, 371.25	
LS-means	277.57	334.83	
Difference in LS-means	-57.26		
95% CI for Difference in LS-means	-75.14, -39.3		
Day 3 (Up to Discharge)			
N	99	97	
Mean	332.53	358.53	0.0003
Std Dev	65.572	21.207	
Median	360.00	360.00	
Min, Max	74.00, 418.00	237.00, 454.50	
LS-means	331.73	357.42	
Difference in LS-means	-25.68		
95% CI for Difference in LS-means	-39.41, -11.9		

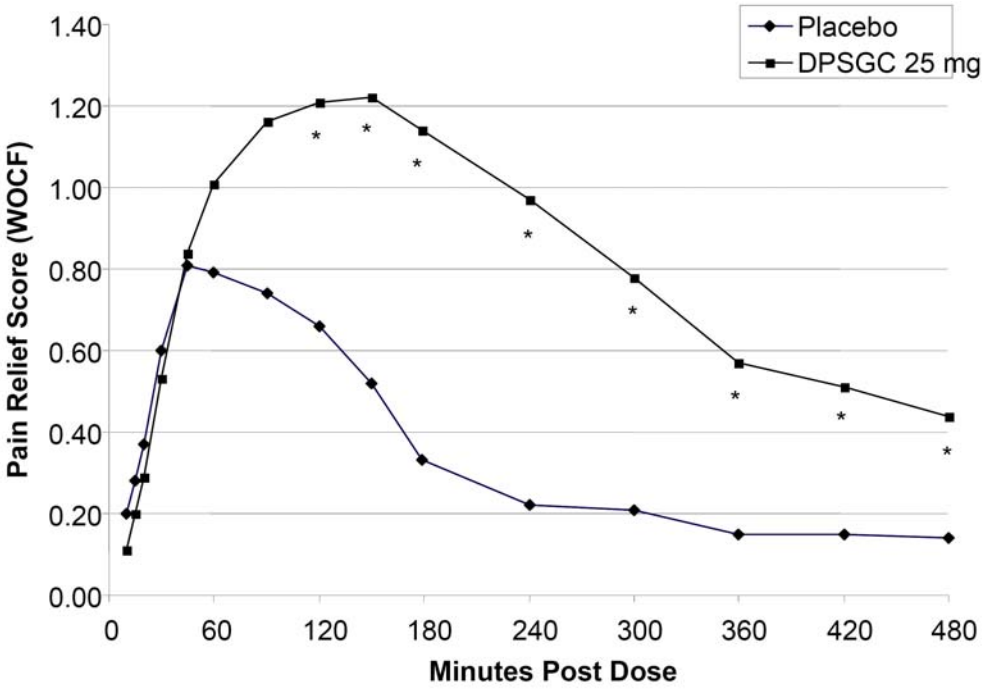
a P-value is from 2-way ANOVA with factors for treatment and site.
Rescue interval is defined as the time between a rescue and the previous dose or the time between the doses when there is no rescue.
Days are based on calendar dates, starting with the date of initial dose as Day 1. Day 3 only includes data up to discharge.
Source: Table 14.2.7.1 on pages 210 to 211 of the report for Study 302.

Table 5.3.2A-6: Patient Global Assessment of Study Drug at Discharge

Study 302 **Patient global at discharge**	**Placebo** **(N = 101)**	**DPSGC 25 mg** **(N = 99)**	**p-value (a)**
Poor, n (%)	39 (38.6%)	15 (15.2%)	
Fair, n (%)	15 (14.9%)	5 (5.1%)	
Good, n (%)	21 (20.8%)	17 (17.2%)	
Very Good, n (%)	11 (10.9%)	28 (28.3%)	
Excellent, n (%)	11 (10.9%)	33 (33.3%)	
Mean Response	2.38	3.60	< 0.0001

SD = standard deviation; Min = minimum; Max = maximum; CI = confidence interval
a From Cochran-Mantel-Haenszel test with site as stratification factor.
Reference: Appendix Table 14.2.14.1
Source: Table 11 on page 67 of the report for Study 302.

Figure 5.3.2A-2: Day 1 Mean Pain Relief Scores over Time



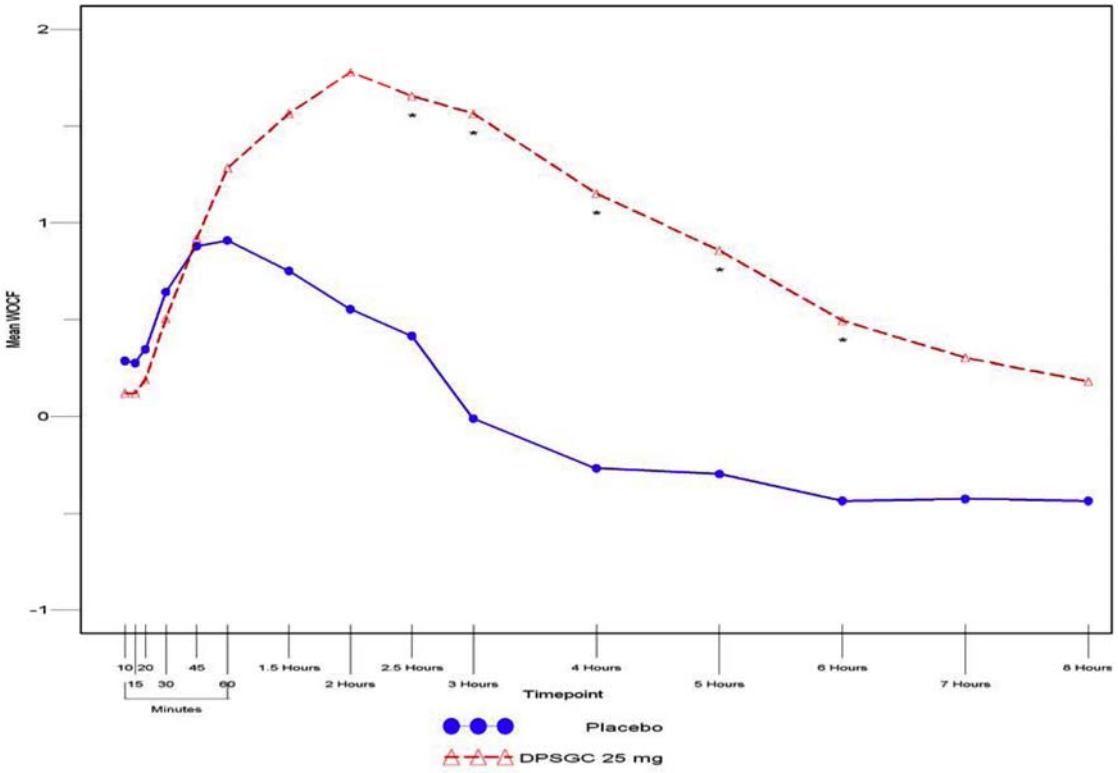
*Statistically significantly greater than placebo using Cochran-Mantel-Haenszel test with site as stratum.
Reference: Appendix Table 14.2.11.1
Source: Figure 5 on page 71 of the report for Study 302.

Table 5.3.2A-7 Day 1 Pain Relief Score over Time Using WOCF

Time	10 min	15 min	20 min	30 min	45 min	1 hr	1.5 hr	2 hr	2.5 hr	3 hr	4 hr	5 hr	6 hr	7 hr	8 hr
DPSGC 25 mg															
N	99	99	99	99	99	98	63	55	52	47	36	28	23	16	14
Mean	0.11	0.20	0.29	0.53	0.84	1.01	1.16	1.21	1.22	1.14	0.97	0.78	0.57	0.51	0.44
SD	0.316	0.451	0.539	0.774	1.007	1.064	1.275	1.380	1.367	1.378	1.388	1.266	1.071	1.073	0.992
Placebo															
N	101	101	101	101	101	99	53	33	26	16	6	5	4	2	1
Mean	0.20	0.28	0.37	0.60	0.81	0.79	0.74	0.66	0.52	0.33	0.22	0.21	0.15	0.15	0.14
SD	0.448	0.634	0.717	0.838	1.027	1.125	1.137	1.107	1.045	0.801	0.642	0.605	0.410	0.410	0.401
Effect size				-0.07				0.55	0.7	0.81	0.75	0.57	0.42	0.36	0.3
p-value	0.229	0.446	0.205	0.0177	0.850	0.128	0.0881	0.0017	<0.0001	<0.0001	0.0001	0.0013	0.0039	0.0124	0.0436

Note: P-value from Cochran-Mantel-Haenszel test with site as strata.
Source: Tables 14.2.11.1 (WOCF) on pages 264 to 266 and Table 21 on page 93 of the report for Study 302.

Figure 5.3.2A-3: Day 1 Mean PID Scores over Time (Full Analysis Population)



*Statistically significant difference versus placebo using Cochran-Mantel-Haenszel test with site as stratum.
Reference: Appendix Table 14.2.10.1
Source: Figure 4 on page 69 of the report for Study 302.

Table 5.3.2A-8 Day 1 PID (NPRS) over Time Using WOCF

Time	10 min	15 min	20 min	30 min	45 min	1 hr	1.5 hr	2 hr	2.5 hr	3 hr	4 hr	5 hr	6 hr	7 hr	8 hr
DPSGC 25 mg															
N	99	99	99	99	99	98	63	55	52	47	36	28	23	16	14
Mean	0.12	0.12	0.19	0.51	0.92	1.28	1.57	1.78	1.66	1.57	1.15	0.86	0.49	.30	0.18
SD	0.594	0.760	1.007	1.335	1.850	2.167	2.532	2.746	2.692	1.565	1.207	1.100	0.805	0.817	0.805
Placebo															
N	101	101	101	101	101	99	53	33	26	16	6	5	4	2	1
Mean	0.29	0.28	0.35	0.64	0.88	0.91	0.75	0.55	0.42	-0.01	-0.27	-0.30	-0.44	-0.43	-0.44
SD	0.876	1.132	1.260	1.622	1.971	2.371	2.334	2.170	2.108	2.815	2.636	2.395	2.047	1.849	1.637
Effect size									1.24	1.58	1.42	1.16	0.93		
p-value	0.323	0.643	0.837	0.460	0.204	0.361	0.188	0.062	0.023	0.0030	0.0022	0.017	0.015	0.077	0.073

Notes: P-value from Cochran-Mantel-Haenszel test with site as strata.
The NPRS pain score at each evaluation was subtracted from the NPRS pain score at Day 1 pre-dose to obtain the pain intensity difference.
Source: Table 14.2.10.1 (WOCF) on pages 246 to 248 and Table 21 on page 93 of the report for Study 302.

Table 5.3.2A-9: SPID Scores at 8 Hours Post Initial Dose of Study Drug

Study 302 SPID over 8 hours after initial dose	**Placebo (N = 101)**	**DPSGC 25 mg (N = 99)**	**p-value (a)**
Mean (SD)	2.61 (5.648)	9.01 (12.430)	< 0.0001
Median	0.37	1.92	
Min-Max	-2.20-31.36	-1.38-58.97	
LS-mean	2.64	9.07	
Difference in LS-means	-6.43		
95% CI for difference in LS-means	-9.12, -3.75		

SD = standard deviation; Min = minimum; Max = maximum; LS-mean = least squares mean
a From 2-way ANOVA with factors for treatment and site.
Reference: Appendix Table 14.2.12.1
Source: Table 12 on page 70 of the report for Study 302.

Table 5.3.2A-10: TOTPAR Scores 8 Hours Post Initial Dose of Study Drug

Study 302 TOTPAR over 8 Hours Post Initial Dose	**Placebo (N = 101)**	**DPSGC 25 mg (N = 99)**	**p-value (a)**
Mean (SD)	1.93 (3.649)	5.89 (7.390)	< 0.0001
Median	0.58	1.46	
Min-Max	0.00-19.46	0.00-25.01	
LS-mean	1.97	5.94	
Difference in LS-means	-3.98		
95% CI for difference in LS-means	-5.60, -2.36		

SD = standard deviation; Min = minimum; Max = maximum; LS-mean = least squares mean
a From 2-way ANOVA with factors for treatment and site.
Reference: Appendix Table 14.2.13.1
Source: Table 13 on page 72 of the report for Study 302.

Table 5.3.2A-11 Day 1 Peak Pain Relief Scores

Study 302 Peak Pain Relief Score Distribution	**Placebo (N=99)**	**DPSGC 25 mg (N=102)**	**CMH p-value**
0	36 (35.6)	30 (30.3)	
1	37 (36.6)	23 (23.2)	
2	11 (10.9)	7 (7.1)	
3	11 (10.9)	27 (27.3)	
4	6 (5.9)	12 (12.1)	
Summary Statistics			0.0094
N	101	99	
Mean	1.15	1.68	
Std Dev	1.195	1.456	
Median	1.00	1.00	
Min, Max	0.00, 4.00	0.00, 4.00	

Note: P-value from Cochran-Mantel-Haenszel test with site as strata.
Source: Table 14.2.18.1 on page 302 of the report for Study 302.

Table 5.3.2A-12: Time to Onset of Perceptible and Meaningful Pain Relief

Study 302	**Placebo**	**DPSGC 25 mg**	**Log-rank p-value (a)**	**Wald Chi-square p-value (a)**
Full Analysis Population				
Time to perceptible pain relief	(N = 101)	(N = 99)		
Subjects with relief, n (%)	63 (62.4%)	72 (72.7%)		
Mean (SD)	25.9 (20.04)	36.0 (31.98)		
Median	21.5	29.8		
Min-Max	0-106	3-242		
Median time (a)	35.99	42.90		
95% CI of time (a)	29.83-60.35	33.63-53.25	0.6733	0.0448
Time to meaningful pain relief	(N = 101)	(N = 99)		
Subjects with relief, n (%)	30 (29.7%)	50 (50.5%)		

Mean (SD)	52.0 (31.68)	72.6 (36.97)		
Median	44.6	67.0		
Min-Max	8-122	15-180		
Median time (a)	NC	90.63		
95% CI of time (a)	118.00-NC	84.98-119.72	0.0351	0.0385

SD = standard deviation; Min = minimum; Max = maximum; CI = confidence interval; NC = not calculable
a Estimated using Kaplan-Meier product limit estimates including all subjects in the given population.
Reference: Appendix Table 14.2.3.1
Source: Table 14 on page 74 of the report for study 302.

Table 5.3.2A-13: Time to Remedication

Study 302 Remedication	**Placebo (N = 101)**	**DPSGC 25 mg (N = 99)**	**Log-rank p-value (a)**	**Wald Chi-square p-value (a)**
Subjects with re-medication, n (%)	100 (99.0%)	99 (100.0%)		
Median time (a)	96.00	177.00		
95% CI of time (a)	87.00-118.00	99.00-225.00	< 0.0001	< 0.0001

SD = standard deviation; Min = minimum; Max = maximum; CI = confidence interval
a Estimated using Kaplan-Meier product limit estimates.
Reference: Appendix Table 14.2.2.1
Source: Table 15 on page 79 of the report for Study 302.

Table 5.3.2A-14 Onset and Duration of Achieving at Least 30% Reduction from Baseline on NPRS (minutes) on Day 1

Study 302 Responder Analysis	**Placebo (N=101)**	**DPSGC 25 mg (N=99)**	**P-value**
≥30% Reduction in NPRS			
Patient with 30% Reduction in NPRS	31 (30.7)	51 (51.5)	0.0034 (1)
Time to 30% Reduction in NPRS			
Median Time	300.00	110.00	0.0259 (2)
95% CI of Time	120.00 - 300.00	90.00 - 147.00	0.0020 (3)
Duration of 30% Reduction in NPRS			
N	31	51	
Mean	116.65	225.00	0.0003 (4)
Std Dev	108.852	140.281	
Median	81.00	211.00	
Min, Max	5.00, 470.00	5.00, 470.00	
LS-means	120.46	227.31	0.0008 (5)
Difference in LS-means	-106.85		
95% CI for Difference in LS-means	-167.86, -45.84		

Notes: The median, confidence interval and logrank p-value for time-to-30% reduction are estimated using Kaplan-Meier product limit estimates. The Wald Chi-squared p-value is based on the coefficients and corresponding standard errors derived from the Cox Proportional Hazards model with factors for treatment and baseline NPRS score.
(1) = P-value from Cochran-Mantel-Haenszel (CMH) test with site as stratification factor.
(2)=Logrank P-value,
(3)=Wald Chi-Square P-value,
(4)=P-value from ANOVA,
(5)=P-value for LS-Mean Difference from ANOVA.
NC=Not Calculable.
Patients who discontinued from the study before onset were censored at the time of the last on-study NPRS evaluation. Patients who received rescue medication or study drug remedication before onset were censored at the time of remedication.
Source: Table 14.2.5.1 on page 194 of the report for Study 302.

Table 5.3.2A-15 Day 1 Responder Analysis during the 8-Hour Period Post Initial

Study 302	**Placebo**	**DPSGC 25 mg**	**Logrank P-value**	**Chi-Square P-value**	**P-value (a)**
Response Definition	(N = 101)	(N = 99)			
Time to Clinically Significant Relief (Meaningful relief by stopwatch and ≥30% improvement from baseline NPRS (1)					
Patients with Clinically Significant Relief, n (%)	26 (25.7)	47 (47.5)			0.0014
Median Time (2)	162.00	120.00	0.0791	0.1525	

95% CI of Time (2)	121.00 - NC	90.00 -148.00			
Achieving no or mild pain (NPRS <= 2)	13 (12.9)	32 (32.3)			0.0010

Note: a P-value for the proportion of subjects achieving clinically significant relief is from Cochran-Mantel-Haenszel (CMH) test with site as stratification factor.

(1) The events may occur at any time after dosing on Day 1 and the two events may occur at different times on Day 1. Subjects were considered failures for this endpoint if they discontinued the study, received rescue medication, or received study drug remedication before the last event occurred.

(2) The median, confidence interval and the Logrank p-value for time-to-event are estimated using Kaplan-Meier product limit estimates. The Wald Chi-squared p-value is based on the coefficients and corresponding standard errors derived from the Cox Proportional Hazards model with factors for treatment and baseline NPRS score.

Source: Table 14.2.4.1 on page 188 of the report for Study 302.

Table 5.3.2A-16: Summary of Average Pain Intensity Scores by Day during the Outpatient Period

Study 302	**Placebo**			**DPSGC 25 mg**		
Average PI-Outpatient	Day 3	Day 4	Day 5	Day 3	Day 4	Day 5
Full Analysis Population	(N = 95)	(N = 94)	(N = 91)	(N = 101)	(N = 100)	(N = 94)
Mean (SD)	3.66 (2.104)	3.24 (2.105)	2.69 (2.077)	2.08 (1.908)	1.86 (1.823)	1.58 (1.834)
Median	3.67	3.00	2.50	1.63	1.29	1.00
Min-Max	0.00-8.80	0.00-8.71	0.00-8.17	0.00-8.43	0.00-8.75	0.00-9.00
p-value vs. placebo (a)				< 0.0001	< 0.0001	0.0002

SD = standard deviation; Min = minimum; Max = maximum

a From 2-way ANOVA with factors for treatment and site.

Reference: Appendix Table 14.2.15.1

Source: Table 18 on page 88 of the report for Study 302.

Table 5.3.2A-17: Summary of Rescue Medication Use during the Outpatient Period

	Placebo			**DPSGC 25 mg**		
Study 302	Day 3			Day 3		
Rescue Medication-Outpatient	(after discharge)	Day 4	Day 5	(after discharge)	Day 4	Day 5
Rescue Medication Use, n (%)	53 (52.5%)	47 (46.5)	15 (14.9%)	14 (14.1%)	22 (22.2%)	1 (1.0%)
p-value vs. placebo (a)				< 0.0001	0.0003	0.0003
Number of Administrations (among users of rescue medications)						
Mean (SD)	1.83 (0.778)	1.74 (1.010)	1.40 (0.507)	1.64 (0.745)	1.41 (0.796)	1.00
Median	2.00	1.00	1.00	1.50	1.00	1.00
Min-Max	1-3	1-5	1-2	1-3	1-4	1-1
p-value vs. placebo (b)				0.4220	0.1753	0.4577
Amount of Rescue Medication (Tablets) (among users of rescue medications)						
Mean (SD)	2.55 (1.422)	2.38 (1.751)	2.20 (0.941)	1.93 (0.829)	1.77 (0.869)	1.00
Median	2.00	2.00	2.00	2.00	2.00	1.00
Min-Max	1-6	1-8	1-4	1-4	1-4	1-1
p-value vs. placebo (b)				0.1250	0.1274	0.2373

SD = standard deviation; Min = minimum; Max = maximum

a From Cochran Mantel Haenszel test with site as strata.

b From ANOVA with factors for pool site and treatment.

Reference: Appendix Table 14.2.16.1

Source: Table 19 on page 90 of the report for Study 302.

Table 5.3.2A-18: Patient Global Assessment of Study Drug at Study Completion

Study 302 **Patient Global Assessment**	**Placebo** **(N = 101)**	**DPSGC 25 mg** **(N = 99)**	**p-value (a)**
Assessment at Study Completion			
Poor, n (%)	40 (39.6%)	16 (16.2%)	
Fair, n (%)	13 (12.9%)	3 (3.0%)	
Good, n (%)	19 (18.8%)	12 (12.1%)	
Very Good, n (%)	13 (12.9%)	29 (29.3%)	
Excellent, n (%)	14 (13.9%)	38 (38.4%)	
Mean Response	2.47	3.71	< 0.0001

SD = standard deviation; Min = minimum; Max = maximum; CI = confidence interval

a From Cochran-Mantel-Haenszel test with site as stratification factor.

Reference: Appendix Table 14.2.14.1
Source: Table 20 on page 91 of the report for Study 302.

Eligibility criteria

Inclusion Criteria
Patients were going to be required to meet the following criteria for inclusion in the study if they:

1. Were male or female between the ages of 18 and 65 years of age (inclusive) at the time of the screening visit.
2. Had undergone primary unilateral first metatarsal bunionectomy surgery (osteotomy and internal fixation) with no collateral procedures.
3. Had body mass index (BMI) 19-35 (See Appendix 3 for the calculation of BMI).
4. Had received only specified preoperative, intraoperative, and postoperative medication/anesthetics.
5. Were willing and able to comply with the protocol, and able to score their pain intensity throughout the inpatient and outpatient periods.
6. Were in relatively good health with no major organ dysfunction as determined by the Investigator on the basis of medical history, physical examination, and screening laboratory results.
7. Had an initial pain intensity score of at least 4 on a 0-10 NPRS at rest defined as no activity of the affected toe for at least 10 minutes prior to pain assessments.
8. If female, were physically incapable of childbearing potential (postmenopausal for more than one year or surgically sterile) or were practicing an acceptable method of contraception (hormonal, barrier with spermicide, or intrauterine device (IUD), or abstinence) or had received at least one cycle of treatment with birth control pill or patch prior to randomization, and had pregnancy test (for females of childbearing potential) before dosing.
9. Had signed an informed consent form,
10. Had a negative urine test for common drugs of abuse.

Exclusion Criteria
Patients were going to be excluded from this study if they:
1. Were pregnant or lactating.
2. Had experienced an allergic reaction to diclofenac, NSAIDs, aspirin, COX-2 inhibitors, opioids including hydrocodone or codeine, or acetaminophen (e.g., anaphylaxis, urticaria).
3. Had a known history of substance or alcohol abuse within 2 years prior to screening.
4. Had any clinically significant condition, or a significant laboratory abnormality, that would, in the Investigator's or designee's opinion, preclude study participation.
5. Had taken analgesics (Opioids, NSAIDs, or COX-2 inhibitors) other than protocol-specified analgesics following surgery up to the initial dose of study drug.
6. Had gastrointestinal bleeding or a history of gastrointestinal bleeding.
7. Were using opioid analgesics in a chronic or routine manner. All opioid analgesics use on an occasional/ as needed basis is to be discontinued after the screening visit until post surgery.
8. Had taken analgesic medications within 4 hours of receiving the first dose of study drug.
9. Were receiving any medication that, in the opinion of the Investigator or designee, may cause a clinically significant interaction when used concomitantly with hydrocodone or NSAID analgesics.
10. Had used aspirin within 10 days of surgery, except as a thromboembolic prophylaxis.
11. Had participated in a study of an investigational drug or device within 30 days prior to randomization or during this trial.

5.3.3 Dental Studies 395 and 400

5.3.3.1 Protocol

Study CL-000395 and Study CL-000400 were conducted using the same protocol. The studies were planned as randomized, double-blind, placebo-controlled, parallel, single-dose, dose ranging studies of Diclofenac Potassium Soft Gelatin Capsules (DPSGC) 25mg, 50 mg, and 100 mg in patients with postoperative pain following dental surgery.

Eligible subjects were to have been adult patients scheduled to undergo surgical extraction of one or more impacted third molars, at least one of which was a bony mandibular impaction, who had sufficient level of pain (≥50 mm on a 100-mm VAS) within four hours post extraction.

The initial screening for eligibility was planned to occur within 30 days prior to dental extraction and final determination of eligibility was to be based on baseline pain intensity as described above. Eligible patients were to have been randomized to one of the four treatment groups to receive a single dose of the study medication.

The planned pain measurements included pain intensity (PI, named as Pain Severity Rating or PSR by the protocol) on a 4-point categorical scale and pain relief (PR, named as Dental Pain Relief Rating or DPRR by the protocol) on a 5-point categorical scale at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, and 6 hours post dose and within one minute after rescue; PR at the time of recording of perceptible relief and meaningful relief; time to first perceptible PR and time to meaningful PR by using two stopwatches; time to rescue medication; global evaluation of study medication as a pain reliever (on a 5-point categorical scale) at the end of 6-hour period or at the time of taking rescue.

The planned primary efficacy endpoint was the Time-Weighted Sum of Pain Intensity Differences (SPID6) over the entire 6-hour period. The planned secondary efficacy endpoints included Time-Weighted Sum of PID over the first 3 hours post dose (SPID3), Time-Weighted DPRR over the first 3 hours post dose (TOTPAR3), TOTPAR6, and time-specific PID, PR and PRID (the sum of PID and PR); PR associated with the onset of perceptible and meaningful pain relief; time to onset of perceptible pain relief; time to onset of meaningful pain relief; time to rescue medication; Overall Global Evaluation score.

Population for analysis
The planned primary population for efficacy analysis was to be the full analysis population consisting of all randomized patients who received study drug and had any post dose PI assessment.

The planned evaluable (per protocol) population was a subset of the full analysis population that met eligibility criteria and had no major protocol violations that could influence the efficacy evaluation.

Efficacy analysis
- The planned efficacy analyses, except those measuring 'time-to-event', were to use an Analysis of Covariance (ANCOVA) model with factors for treatment, center, and baseline pain intensity score. Least-Squares Means (LSMeans) and the Mean Squared Error were estimated by the ANCOVA model and used to compare individual dose levels of DPSGC to placebo using the Dunnett's test.
- Planned time-to-event variables were to be summarized for each treatment group using the Kaplan-Meier survival curves to estimate the median and 95% confidence interval. Each dose level of DPSGC was going to be compared with placebo using a Cox proportional hazard model with effects for treatment and baseline pain intensity scores.

Missing data management
Missing data at a particular time point were to have been imputed by the Worst Observation Carried Forward (WOCF) with the additional analyses by using LOCF and observed cases.

Sample size
The planned sample size was 240 patients, 55 patients per treatment group to achieve 220 evaluable patients. The sample size calculation was based on the primary efficacy variable of SPID at 6 hours, comparing each of the DPSGC treatment groups with placebo using the Dunnett's test. The sample size calculation assumed an estimated error or variance of 16 and a 95% confidence interval no wider than 2.5 units, and was based on data from previous studies.

The original protocol was dated August 30, 2001 and amended on October 26, 2001 and December 26, 2001. The study was initiated on December 11, 2001. The major amendments were prohibition of the use of rescue medication within the first hour post dose, no longer requiring AE reports during surgery, and the change of time period for reporting serious AE from 30 days to 15 days after the single-dose exposure to study medication.

The major components of the protocol are also summarized in the table below.

Table 5.3.3-1 Protocol

Study #	CL-395 and CL-400
Objectives	To study efficacy, dose response, tolerability, and safety of Diclofenac Potassium Soft Gelatin Capsules (DPSGC) 25, 50, and 100 mg in patients with postoperative dental pain.
Design	Randomized, double-blind, placebo-controlled, parallel, single-dose, dose ranging study at 6 U.S. centers
Sample population	Healthy male and non-pregnant female; 18 to 65 years of age; scheduled to undergo surgical extraction of 1 or more impacted third molars, at least 1 of which was a bony mandibular impaction; had sufficient levels of pain (≥50 mm on a 100-mm VAS) within 4 hours post extraction;
Baseline	Moderate to severe pain by a categorical scale and ≥50 mm on a 100-mm VAS within the required time periods
Treatment	A single dose of DPSGC 25 mg, DPSGC 50 mg, and DPSGC 100 mg, or placebo
Rescue and concomitant medication	**Rescue medication**: prohibited within the first hour after dosing; sample rescue medication: acetaminophen and hydrocodone (Lorcet® 10/650 or Lortab®) or acetaminophen and oxycodone (Percocet); **Anesthetics a**llowed: local anesthesia block (e.g., 3% mepivacaine), intravenous sedation a suitable combination of the following agents: propofol, midazolam or diazepam, nitrous oxide, or fentanyl; Not allowed: succinylcholine, corticosteroids, other sedatives or hypnotic agents, and local anesthetics; **Ice pack**s allowed to the affected 2 hours after dosing and had to be removed at least 15 minutes prior to any scheduled pain assessments
Raw efficacy data	PI (on a 100-mm VAS scale) and PR (on a 5-point categorical scale) at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, and 6 hours post dose and within one minute after rescue; time to first perceptible PR and time to meaningful PR by using two stopwatches; time to rescue medication; global evaluation of study medication as a pain reliever (on a 5-point categorical scale) at the end of 6-hour period or at the time of taking rescue
Efficacy parameter	***Primary:*** SPID6 - Time-weighted Sum of Pain Intensity Differences (SPID6) over the entire 6-hour period ***Secondary:*** • SRID3 - Time-weighted sum of PID over the first 3 hours after treatment • TOTPAR3 - Time-weighted DPRR over the first 3 hours after treatment • TOTPAR6 - Time-weighted DPRR over the entire 6-hour period • PID at each evaluation time point • Pain relief at each evaluation time point based on the DPRR • DPRR associated with the onset of perceptible pain relief • DPRR associated with the onset of meaningful pain relief • Overall Global Evaluation score • Time to onset of perceptible pain relief • Time to onset of meaningful pain relief • Time to rescue medication • PRID, the sum of PID and PR, at the corresponding evaluation time point
Statistical analysis	ITT: randomized patients taking ≥1 dose of study medication and completed ≥1 post dose efficacy evaluation Primary analysis: median time by Kaplan-Meier estimate; pair wise comparison by log-rank test and p-values evaluation by a Step-down procedure
Safety monitoring	Adverse events (AEs) throughout the study and serious AEs up to 15 days after treatment.

5.3.3.2 Results

Demographic and other baseline characteristics

The sample population of Study 395 consisted of 265 patients enrolled who received the study medication, with an age range of 18 to 46 years and a mean of 23 years. Of the 265 patients, 75% were Caucasian, 10% were African American, 7% were Hispanic, 5% were Asian, and 58% were female. The treatment groups were approximately balanced with regard to demographic characteristics such as age, gender, race, height, and weight. The level of baseline pain intensity (PI) was balanced across treatment groups with a group mean ranged from 2.1 to 2.4 on a 4-point (0 to 3) categorical scale.

Table 5.3.3-2a Demographics and Baseline Characteristics (Study 395)

Study 395 Characteristics	Placebo (N = 68)	DPSGC 25 mg (N = 63)	DPSGC 50 mg (N = 68)	DPSGC 100 mg (N= 66)	Total (N = 265)	Overall P-value
Age (years)						0.4934
Mean	22.7	23.7	23.7	23.1	23.3	
Std. Dev.	3.55	4.67	4.72	4.34	4.33	
Minimum, Maximum	18.0, 35.7	18.0, 46.2	18.1, 42.2	1 8.0, 44.2	18.0, 46.2	
Gender, n (%)						0.1894
Male	28 (41.2)	28 (44.4)	34 (50.0)	21 (31.8)	111(41.9)	
Female	40 (58.8)	35 (55.6)	34 (50.0)	45 (68.2)	154(58.1)	
Race, n (%)						0.5114
Caucasian	54 (79.4)	51 (81.0)	45 (66.2)	49 (74.2)	199(75.1)	
Black	9 (13.2)	4 (6.3)	8 (11.8)	5 (7.6)	26 (9.8)	
Hispanic	2 (2.9)	6 (9.5)	5 (7.4)	5 (7.6)	18 (6.8)	
Asian	1 (1.5)	1 (1.6)	6 (8.8)	5 (7.6)	13 (4.9)	
Native American	1 (1.5)	0	2 (2.9)	1 (1.5)	4 (1.5)	
Other	1 (1.5)	1 (1.6)	2 (2.9)	1 (1.5)	5 (1.9)	
Height (cm)						0.3256
Mean	170.1	170.8	170.8	167.8	169.9	
Std. Dev.	10.65	11.24	11.43	10.19	10.90	
Minimum, Maximum	152.4, 198.0	147.3, 205.7	129.5, 95.6	150.0, 198.1	129.5, 205.7	
Weight (kg)						0.7349
Mean	72.8	69.7	72.3	71.0	71.5	
Std. Dev.	18.27	13.26	17.88	19.13	17.28	
Minimum, Maximum	(48.6, 126.0)	(46.3, 100.0)	(44.9, 117.6)	(43.7, 135.9)	(43.7, 135.9)	
Baseline PI, Mean (SD)	2.35	2.27	2.12	2.24	2.25	

Reference: Tables 14.1.4, Section 14.
Source: Table 3 on page 46 of the report for Study 395.

The sample population of Study 400 consisted of 249 patients enrolled who received the study medication, with an age range of 18 to 47 years and a mean of 24 years. Of the 249 patients, 71% were Caucasian, 12% were African American, 7% were Hispanic, 9% were Asian, and 54% were female. The treatment groups were approximately balanced with regard to demographic characteristics such as age, gender, race, height, and weight. The level of baseline pain intensity (PI) was balanced across treatment groups with a group mean of about 2.3 on a 4-point (0 to 3) categorical scale.

Table 5.3.3-2b Demographics and Baseline Characteristics (Study 400)

Study 400 Characteristics	Placebo (N = 61)	DPSGC 25 mg (N = 63)	DPSGC 50 mg (N = 62)	DPSGC 100 mg (N= 63)	Total (N = 249)	Overall P-value
Age (years)						0.0930
Mean	24.2	24.0	25.7	23.7	24.4	
Std. Dev.	4.82	4.87	5.33	4.S1	4.92	
Minimum, Maximum	(18.5,39.2)	(18.1, 46.8)	(18.2, 42.9)	(18.0, 41.5)	(1 8.0,46.8)	
Gender, n (%)						0.8577
Male	29 (47.5)	28 (44.4)	31 (50.0)	27 (42.9)	115 (46.2)	

Female	32 (52.5)	35 (55.6)	31(50.0)	36 (57.1)	134 (53.8)	
Race, n (%)						0.2038
Caucasian	43 (70.5)	44 (69.8)	43 (69.4)	46 (73.0)	176 (70.7)	
Black	4 (6.6)	9 (14.3)	11(17.7)	6 (9.5)	30 (12.0)	
Hispanic	8 (13.1)	1 (1.6)	2 (3.2)	7 (Il.)	18 (7.2)	
Asian	6 (9.8)	8 (12.7)	5 (8.1)	4 (6.3)	23 (9.2)	
Native American	0	0	0	0	0	
Other	0	1(1.6)	1 (1.6)	0	2 (0.8)	
Height (cm)						0.5794
Mean	170.0	169.7	171.6	169.2	170.1	
Std. Dev.	9.91	10.59	9.68	10.69	10.21	
Minimum, Maximum	(145.5, 190.5)	(147.0, 194.0)	(153.5, 194.0)	(145.0, 192.0)	(145.0, 194.0)	
Weight (kg)						0.3762
Mean	71.7	74.1	75.8	71.2	73.2	
Std. Dev.	16.07	16.84	19.79	14.00	16.80	
Minimum, Maximum	(44.5, 113.6)	(45.9, 135.1)	(42.1, 149.8)	(44.6, 107.7)	(42.1, 149.8)	
Baseline PI, Mean (SD)	2.31	2.37	2.34	2.30	2.33	

Reference: Tables 14.1.4, Section 14.
Source: Table 3 on page 48 of the report for Study 400.

Patient disposition

There was only one case of dropout reported in each of the two dental studies. A placebo patient dropped out from Study 395 after he left clinic against medical advice. A placebo patient in Study 400 withdrew his consent prior to receiving rescue medication because of his claustrophobia.

Protocol violations

About 30% patients per treatment group had one or more protocol violations in each of the two dental studies. Most of the protocol violation categories listed in the summary tables below would not have an impact on the efficacy evaluation. Assessment off schedule reported in Study 395 included mainly delayed assessment when stopwatch was clicked or assessment prior to, instead of after, rescue medication. Assessment off schedule in Study 400 was reported in four patients on DPSGC 25 mg and six patients on DPSGC 100 mg and occurred mainly at 0.5-hour and 0.75-hour assessment time points.

Table 5.3.3-3a Summary of Protocol Violations (Study 395)

Study 395 Protocol violations	**Placebo (N = 68)**	**DPSGC 25 mg (N = 63)**	**DPSGC 50 mg (N = 68)**	**DPSGC 100 mg (N= 66)**	**Total (N = 265)**
Total number of patients with violations	19 (28%)	16 (25%)	20 (29%)	22 (33%)	77 (29%)
Total number of violations	29	29	27	33	118
Alternative rescue	12	8	10	6	36
Assessment off schedule	3	8	5	12	28
Vital signs missing	4	5	4	6	19
Lab test missing	4	2	5	1	12
Postop assessment missing or timing	3	2	3	2	9
Vital signs off schedule	0	3	0	2	5
Eligibility criteria	0	0	0	2	2
Surgical procedure	1	0	0	1	2
Medication dosing time	0	1	0	0	1
Missing assessment	0	0	0	1	1
Consent signature timing	1	0	0	0	1
Left clinic against advise	1	0	0	0	1

Source: Appendix listing 16.2.13 on pages 1057-1082 of the report for Study 395.

Table 5.3.3-3b Summary of Protocol Violations (Study 400)

Study 400 Protocol violations	**Placebo (N = 61)**	**DPSGC 25 mg (N = 63)**	**DPSGC 50 mg (N = 62)**	**DPSGC 100 mg (N= 63)**	**Total (N = 249)**

Total number of patients with violations	13 (21%)	15 (24%)	20 (32%)	19 (30%)	67 (27%)
Total number of violations	14	24	23	23	84
Alternative rescue	3	6	4	1	14
Vital signs off schedule	3	3	3	3	12
Assessment off schedule	0	4	0	6	10
Lab test missing or lab error	1	3	3	3	10
Eligibility criteria	0	1	4	4	9
Vital signs missing	2	2	1	2	7
Use of ice packs	2	2	1	1	6
Pre-surgical or surgical procedure	2	1	2	0	5
Study medication dosing time	0	1	2	1	4
Missing assessment	0	0	2	0	2
Lab test off schedule	0	1	0	1	2
Medication less dose	0	0	1	0	1
Randomization timing	0	0	0	1	1
Rescue medication dosing time	1	0	0	0	1

Source: Appendix listing 16.2.13 on pages 1060-1083 of the report for Study 400.

Exposure

All the patients enrolled in the study received a single dose of study medication.

Efficacy results

Primary efficacy endpoint: SPID (over 6 hours post dose)

The mean scores of the time-weighted sum of pain intensity differences over entire six hours after dosing are presented in the tables below. The treatment differences in LS-means of the SPID scores for pair wise comparison between each DPSGC treatment and placebo ranged from 4 to 7.5 units and were all highly statistically significant.

Table 5.3.3-4a: Time-Weighted Sum of Pain Intensity Differences over Entire 6 Hours (Study 395)

Study 395 SPID6	**Treatments**				**Treatment Interaction P values**	
	Placebo	**DPSGC 25 mg**	**DPSGC 50 mg**	**DPSGC 100 mg**	**Site**	**Baseline DPIS**
N	68	63	68	66		
Mean	0.67	4.37	5.10	7.73	0.7391	0.6062
Std. Devi	5.12	5.21	4.55	3.97		
(Min, Max)	(-6.0, 14.0)	(-6.0, 15.3)	(-5.8, 12.3)	(-4.5, 16.8)		
LSMean	0.36	4.30	5.37	7.85		
SE (LSMean)	0.55	0.57	0.55	0.56		
Difference in LSMean from placebo		3.94	5.01	7.49		
Dunnett-adjusted P value		<0.0001	<0.0001	<0.0001		

Reference: Table 14.2.1.1, Section 14.
Source: Table 6 on page 49 of the report for Study 395.

Table 5.3.3-4b: Time-Weighted Sum of Pain Intensity Differences over Entire 6 Hours (Study 400)

Study 400 SPID6	**Treatments**				**Treatment Interaction P values**	
	Placebo	**DPSGC 25 mg**	**DPSGC 50 mg**	**DPSGC 100 mg**	**Site**	**Baseline DPIS**
N	61	63	62	63		
Mean	-0.38	4.12	5.96	6.37	0.1944	0.8775
Std. Devi	4.85	4.79	5.13	4.79		
(Min, Max)	(-6.0, 14.5)	(-5.5, 14.5)	(-5.8, 16.5)	(-5.5, 17.0)		
LSMean	-0.28	4.12	5.94	6.29		
SE (LSMean)	0.61	0.60	0.61	0.60		
Difference in LSMean from placebo		4.4	6.22	6.57		
Dunnett-adjusted P value		<0.0001	<0.0001	<0.0001		

Reference: Table 14.2.1, Section 14.

Source: Table 6 on page 51 of the report for Study 400.

Secondary efficacy endpoint:

Time-specific pain measurements

The results of statistical comparison of time-specific pain measurements are summarized in the tables below. DPSGC 25 mg performed statistically significantly better than placebo in PR for up to five hours and in PID for six hours in Study 395 and in both PR and PID during the entire 6-hour period in Study 400. The effect sizes of the statistically significant treatment differences in PR (measured by a 5-point scale) and PID (derived from PI, which was measured by a 4-point scale) were basically above 0.5 units and reaching about 2 units in PR and 1.5 units in PID. DPSGC 50 mg and 100 mg performed statistically significantly better than placebo in both PR and PID during the entire 6-hour period in the two studies. Post hoc dose response analyses conducted by the Applicant upon request by this reviewer showed positive linear regression slopes for the active doses, statistically significant (refer to the tables in Appendix) in both PR and PID from two to six hours in Study 395 and from three to six hours in Study 400. The statistically significant positive slopes and the effect sizes of statistically significant treatment differences in last half of the 6-hour observation period suggested a dose response toward the later part of the evaluation interval.

Table 5.3.3-5a Time-Specific Pain Measurements: PR and PID (Study 395)

Study 395 Efficacy parameter	Time interval for statistically significant treatment differences (diclofenac > placebo) based on pairwise comparison (effect size of such treatment differences at start, maximum, and end)			
	DPSGC 25 mg	DPSGC 50 mg	DPSGC 100 mg	Refer to Appendix
PR-categorical	0.5-6h (0.5—2.1—0.6)	0.5-6h (0.5—2.3—1.0)	0.5-6h (0.7—2.6—1.5)	Table 5.3.3A-1a
PID-categorical	0.75-5h (1.0—1.5—0.4)	0.75-6h (0.6—1.4—0.5)	0.5-6h (0.4—1.8—1.0)	Table 5.3.3A-2a

Note: the time or time intervals included only the significant results from pairwise comparison when the overall treatment effect was significant at the specific time point. P-values not corrected for multiple comparisons

Table 5.3.3-5b Time-Specific Pain Measurements: PR and PID (Study 400)

Study 400 Efficacy parameter	Time interval for statistically significant treatment differences (diclofenac > placebo) based on pairwise comparison (effect size of such treatment differences at start, maximum, and end)			
	DPSGC 25 mg	DPSGC 50 mg	DPSGC 100 mg	Refer to Appendix
PR-categorical	0.5-6h (0.6—1.8—0.8)	0.25-6h (0.3—2.1—1.1)	0.25-6h (0.3—2.2—1.3)	Table 5.3.3A-1b
PID-categorical	0.5-5h (0.3—1.4—0.5)	0.5-6h (0.3—1.5—0.8)	0.5-6h (0.5—1.5—0.9)	Table 5.3.3A-2b

Note: the time or time intervals included only the significant results from pairwise comparison when the overall treatment effect was significant at the specific time point. P-values not corrected for multiple comparisons

Time-Weighted Summation of Pain Scores

Time-weighted summation of pain scores over the first three hours and over the entire 6-hour evaluation period are briefly summarized in the table below with details presented in Appendix. Statistically significant differences from placebo were shown in all three parameters listed.

Table 5.3.3-6a Summary of the Time-Weighted Summation of Pain Scores (Study 395)

Study 395 Summation of Pain Scores	Effect size as difference in LSMean from placebo (p value)			Refer to Appendix
	DPSGC 25 mg	DPSGC 50 mg	DPSGC 100 mg	
$SPID_{0-3}$ (categorical)	2.79 (<0.0001)	2.78 (<0.0001)	3.89 (<0.0001)	Table 5.3.3A-3a
$TOTPAR_{0-3}$ (categorical)	4.42 (<0.0001)	5 (<0.0001)	6 (<0.0001)	
$TOTPAR_{0-6}$ (VAS)	6.69 (<0.0001)	8.87 (<0.0001)	11.17 (<0.0001)	

Table 5.3.3-6b Summary of the Time-Weighted Summation of Pain Scores (Study 400)

Study 400 Summation of Pain Scores	Effect size as difference in LSMean from placebo (p value)			Refer to Appendix
	DPSGC 25 mg	DPSGC 50 mg	DPSGC 100 mg	
$SPID_{0-3}$ (categorical)	2.83 (<0.0001)	3.46 (<0.0001)	3.74 (<0.0001)	Table 5.3.3A-3b
$TOTPAR_{0-3}$ (categorical)	3.99 (<0.0001)	4.86 (<0.0001)	5.17 (<0.0001)	
$TOTPAR_{0-6}$ (VAS)	6.61 (<0.0001)	8.86 (<0.0001)	9.47 (<0.0001)	

Analgesic onset

Median time to the onset of perceptible and meaningful pain relief and proportion of patients achieving the onset are summarized in the tables below. There were much higher proportions of patients achieving perceptible and meaningful pain relief in the DPSGC treatment groups than in the placebo group (≥22% more for perceptible relief and ≥56% more for meaningful relief in Study 395; ≥35% more for perceptible relief and ≥53% more for meaningful relief in Study 400). These treatment differences are considered clinically meaningful. The median time to onset of perceptible relief was within 30 minutes (20 to 25 minutes) for all the treatment groups. The median time to onset of meaningful relief was within one hour for DPSGC treatments in both studies, was four hours for placebo in Study 395, and could not be calculated for placebo in Study 400.

Table 5.3.3-7a Summary of Onset Data (Study 395)

Study 395 Onset	Placebo (N = 68)	DPSGC 25 mg (N = 63)	DPSGC 50 mg (N = 68)	DPSGC 100 mg (N= 66)	Refer to Appendix
Proportion of patients achieving perceptible PR (%)	72.1	93.7	94.1	98.5	Table 5.3.3A-4a
Difference from placebo (%)		21.6	22	26.4	
Median onset to perceptible pain relief (minutes)	24.5	22.0	22.5	19.5	
Wald chi-squared p-value		0.0022	0.0024	<0.0001	
Proportion of patients achieving meaningful PR (%)	26.5	82.5	86.8	93.9	
Difference from placebo (%)		56	60.3	67.4	
Median onset to meaningful pain relief (minutes)	242.0	45.0	53.0	43.0	
Wald chi-squared p-value		<0.0001	<0.0001	<0.0001	

Table 5.3.3-7b Summary of Onset Data (Study 400)

Study 400 Onset	Placebo (N = 61)	DPSGC 25 mg (N = 63)	DPSGC 50 mg (N = 62)	DPSGC 100 mg (N= 63)	Refer to Appendix
Proportion of patients achieving perceptible PR (%)	57.4	96.8	91.9	96.8	Table 5.3.3A-4b
Difference from placebo (%)		39.4	34.5	39.4	
Median onset to perceptible pain relief (minutes)a	30.0	25.0	17.0	21.0	
Wald chi-squared p-value		0.0002	<0.0001	<0.0001	
Proportion of patients achieving meaningful PR (%)	27.9	81.0	83.9	85.7	
Difference from placebo (%)		53.1	56	57.8	
Median onset to meaningful pain relief (minutes)a	NC	52.0	47.5	52.0	
Wald chi-squared p-value		<0.0001	<0.0001	<0.0001	

NC indicates parameter is not calculable

Analgesic duration

The duration was defined as the median time to request for rescue medication after taking study medication. As shown in the tables below there were much lower proportions of patients requesting rescue medication in the DPSGC treatment groups than in the placebo group (27 to 46% less in Study 395 and 18 to 37% less in Study 400). These treatment differences are considered clinically meaningful. The median time to rescue medication for DPSGC 25 mg was about 6 hours in Study 395 and about 5 hours in Study 400 in comparison to <1.7 hours for the placebo group. The median time to rescue medication could not be calculated for the DPSGC 50 mg and 100 mg groups in both studies.

Table 5.3.3-8a Summary of Duration (Study 395)

Study 395 Duration	Placebo (N = 68)	DPSGC 25 mg (N = 63)	DPSGC 50 mg (N = 68)	DPSGC 100 mg (N= 66)	Refer to Appendix
Proportion of patients taking rescue (%)	77.9	50.8	36.8	31.8	Table 5.3.3A-5a
Difference from placebo (%)		-27.1	-41.1	-46.1	
Median time to rescue (minutes)a	100.0	350.0	NC	NC	
Wald chi-squared p-value		<0.0001	<0.0001	<0.0001	

Table 5.3.3-8b Summary of Duration (Study 400)

Study 400 Duration	Placebo (N = 61)	DPSGC 25 mg (N = 63)	DPSGC 50 mg (N = 62)	DPSGC 100 mg (N= 63)	Refer to Appendix
Proportion of patients taking rescue (%)	72.1	54.0	35.5	39.7	Table 5.3.3A-5b

Difference from placebo (%)		-18.1	-36.6	-32.4	
Median time to rescue (minutes)a	95.0	303.0	NC	NC	
Wald chi-squared p-value		<0.0001	<0.0001	<0.0001	

Patient global assessment

The results of patient global assessment of study medication at the end of study are summarized in the tables below. The mean response was between 'good' and 'very good' (mean scores between two and three) for DPSGC treatments and between 'poor' and 'fair' (mean scores between zero and one) for placebo treatment. The treatment differences were statistically significant. More DPSGC patients than placebo patients had 'good' to 'excellent' response in patient global assessment, 47% more at 25 mg, 57 to 63% more at 50 mg, and 65 to 73% more at 100 mg. The effect sizes of these treatment differences which appeared to be dose-related are considered clinically meaningful.

Table 5.3.3-9a: Summary of Patient Global Assessment (Study 395)

Study 395 Patient Global Assessment	**Placebo (N = 68)**	**DPSGC 25 mg (N = 63)**	**DPSGC 50 mg (N = 68)**	**DPSGC 100 mg (N= 66)**	**Refer to Appendix**
LSMean	0.82	2.22	2.65	3.06	Table 5.3.3A-6a
Difference in LSMean from placebo		1.4	1.83	2.24	
Dunnett-adjusted P value		<0.0001	<0.0001	<0.0001	

Table 5.3.3-9b: Summary of Patient Global Assessment (Study 400)

Study 400 Patient Global Assessment	**Placebo (N = 61)**	**DPSGC 25 mg (N = 63)**	**DPSGC 50 mg (N = 62)**	**DPSGC 100 mg (N= 63)**	**Refer to Appendix**
	N = 61	N = 63	N = 62	N= 63	
LSMean	0.65	2.08	2.51	2.84	Table 5.3.3A-6b
Difference in LSMean from placebo		1.43	1.86	2.19	
Dunnett-adjusted P value		<0.0001	<0.0001	<0.0001	

Table 5.3.3-10a: Summary of Patient Global Assessment-Response by Categories (Study 395)

Study 395 Patient Global Assessment, % in each category	**Placebo (N = 68)**	**DPSGC 25 mg (N = 63)**	**DPSGC 50 mg (N = 68)**	**DPSGC 100 mg (N= 66)**
Poor (score=0)	59.7%	11.1%	8.8%	3.0%
Fair (score=1)	19.4%	20.6%	7.4%	3.0%
Good (score=2)	6.0%	14.3%	22.1%	13.6%
Very Good (score=3)	9.0%	42.9%	33.8%	45.5%
Excellent (score=4)	6.0%	11.1%	27.9%	34.9%
% with "good" to 'excellent' response	*21.0%*	*68.3%*	*83.8%*	*94.0%*
Difference from placebo		47.3%	62.8%	73.0%

Table 5.3.3-10b: Summary of Patient Global Assessment-Response by Categories (Study 400)

Study 400 Patient Global Assessment, % in each category	**Placebo (N = 61)**	**DPSGC 25 mg (N = 63)**	**DPSGC 50 mg (N = 62)**	**DPSGC 100 mg (N= 63)**
Poor (score=0)	63.3%	12.7%	8.2 %	6.4%
Fair (score=1)	18.3%	22.2%	16.4%	11.1%
Good (score=2)	11.7%	25.4%	18.0%	9.5%
Very Good (score=3)	3.3%	23.8%	31.2%	38.1%
Excellent (score=4)	3.3%	15.9%	26.2%	34.9%
% with "good" to 'excellent' response	*18.3%*	*65.1%*	*75.4%*	*82.5%*
Difference from placebo		46.8%	57.1%	65.2%

5.3.3.3 Summary of Findings and Discussions

Study conduct

The treatment groups in each of the two dental studies, Study 395 and 400, were basically balanced with regard to the demographic characteristics and baseline pain intensity. There was only one placebo patient who dropped out from each of the study. Although about 30% patients per treatment group had one or more protocol violations in each of the two dental studies, the types of the protocol violation were mostly considered of having no impact on the efficacy evaluation.

Efficacy
In both studies, single-dose effects of DPSGC 25mg, 50 mg, and 100 mg were supported by demonstration of statistically significant treatment differences in the time-specific measurements of pain scores, PID and PR, for up to six hours and time-weighted summation of pain scores, SPID and TOTPAR, at 3 and 6 hours. The clinical meaningfulness of the treatment differences from placebo was suggested by effect sizes of PR and PID differences (0.5 to >2 units) during the 6-hour evaluation period, much higher proportions of patients on DPSGC achieving perceptible (>20%) and meaningful pain relief (>50%), onset of meaningful relief (within one hour for DPSGC treatments versus four hours for placebo), much lower proportions of DPSGC patients requesting rescue medication (18 to 46% less than placebo), time to rescue medication (five to six hours for DPSGC 25 mg versus less than 1.7 hours for placebo), and comparison of patient global assessment (an overall response of 'good' to 'very good' for DPSGC treatments versus 'poor' to 'fair' for placebo and the proportion with 'good' to 'excellent' response: 65% to 94% in the DPSGC groups versus about 20% in the placebo group).

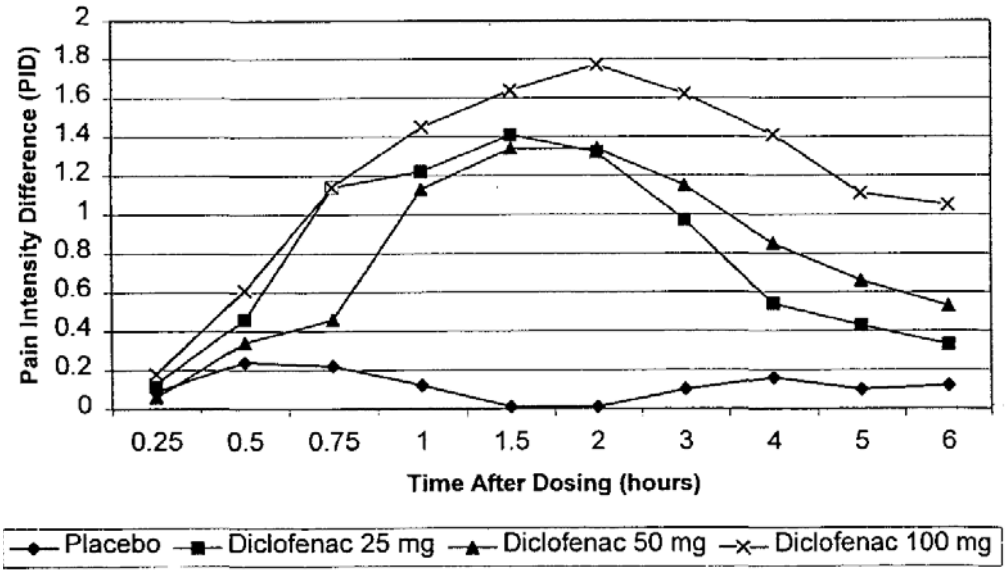
Dosing interval
Because of the left shift of the time-concentration curve relative to the listed drug one of the major concerns with the DPSGC formulation had been whether the duration of analgesic effect would support the proposed dosing interval. The single-dose duration was supported by the demonstration of median time to rescue medication of five to six hours for DPSGC 25 mg in both studies.

5.3.3.4 Conclusion

The positive effects of a single-dose treatment with Diclofenac Potassium Soft Gelatin Capsules (DPSGC) at 25 mg, 50 mg, and 100 mg lasting for five to six hours in duration were replicated in the two dental studies.

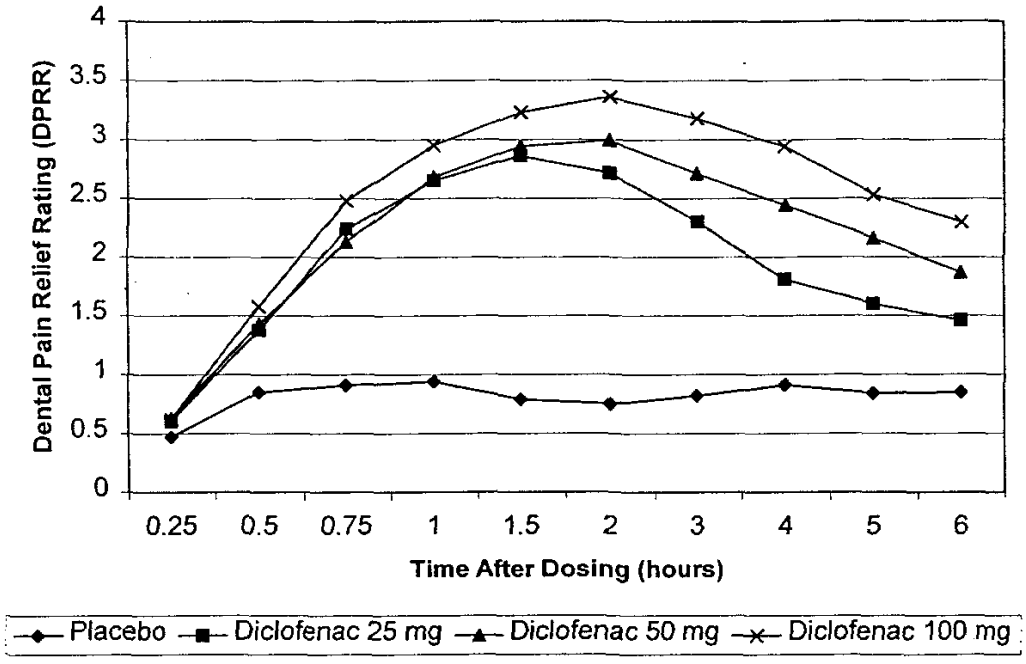
5.3.3.5 Appendix

Figure 5.3.3A-1a: Pain Intensity Difference over Time in Study 395



Reference: Table 14.2.3, Section 14
Source: Figure 1 on page 50 of the report for Study 395.

Figure 5.3.3A-2a: Pain Relief over Time in Study 395



Reference: Table 14.2.5, Section 14
Source: Figure 2 on page 52 of the report for Study 395.

Table 5.3.3A-1a PID by Dose and Time

Study 395			Estimated Response		Paired Differences (P-value [1][3])			
Hour	Dose	N	LS Mean (SE)	P- value	Placebo	25 mg	50 mg	100 mg
0.25 Hrs	Placebo DPSGC	68	0.08 (0.059)	0.1814	NA	0.05 (0.5958)	-0.01 (0.8741)	0.11 (0.2141)
	25 mg DPSGC	63	0.12 (0.061)	0.0428		NA	-0.06 (0.4928)	0.06 (0.4846)
	50 mg DPSGC	68	0.07 (0.059	0.2652			NA	0.12 (0.1595)
	100 mg Slope [2]	66	0.19 (0.060)	0.0023				NA
			0.00 (0.001)	0.3767				
0.5 Hrs	Placebo DPSGC	68	0.21 (0.086)	0.0132	NA	0.24 (0.0512)	0.14 (0.2435)	0.40 (0.0012)
	25 mg DPSGC	63	0.46 (0.089)	<.0001		NA	-0.10 (0.4241)	0.16 (0.2015)
	50 mg DPSGC	68	0.36 (0.086)	<.0001			NA	0.26 (0.0351)
	100 mg Slope [2]	66	0.61 (0.087)	<.0001				NA
			0.00 (0.002)	0.1293				
0.75 Hrs	Placebo DPSGC	68	0.18 (0.089)	0.0444	NA	0.95 (<.0001)	0.62 (<.0001)	0.97 (<.0001)
	25 mg DPSGC	63	1.13 (0.092)	<.0001		NA	-0.33 (0.0098)	0.02 (0.8868)
	50 mg DPSGC	68	0.80 (0.089)	<.0001			NA	0.35 (0.0057)
	100 mg Slope [2]	66	1.15 (0.090)	<.0001				NA
			0.00 (0.002)	0.4519				
1 Hr	Placebo DPSGC	67	0.06 (0.097)	0.5114	NA	1.15 (<.0001)	1.11 (<.0001)	1.41 (<.0001)
	25 mg DPSGC	63	1.21 (0.100)	<.0001		NA	-0.03 (0.8259)	0.27 (0.0599)
	50 mg DPSGC	68	1.18 (0.097)	<.0001			NA	0.30 (0.0324)
	100 mg Slope [2]	66	1.47 (0.098)	<.0001				NA
			0.00 (0.002)	0.0329				
1.5 Hrs	Placebo DPSGC	42	-0.05 (0.104)	0.6413	NA	1.45 (<.0001)	1.44 (<.0001)	1.71 (<.0001)
	25 mg DPSGC	55	1.40 (0.108)	<.0001		NA	-0.00 (0.9737)	0.26 (0.0824)
	50 mg DPSGC	65	1.39 (0.104)	<.0001			NA	0.27 (0.0712)
	100 mg Slope [2]	65	1.66 (0.105)	<.0001				NA
			0.00 (0.002)	0.0587				
2 Hrs	Placebo DPSGC	26	-0.05 (0.106)	0.6657	NA	1.35 (<.0001)	1.44 (<.0001)	1.84 (<.0001)
	25 mg DPSGC	55	1.30 (0.109)	<.0001		NA	0.09 (0.5671)	0.49 (0.0015)
	50 mg DPSGC	63	1.39 (0.106)	<.0001			NA	0.40 (0.0074)
	100 mg Slope [2]	64	1.80 (0.107)	<.0001				NA
			0.01 (0.002)	0.0008				
3 Hrs	Placebo DPSGC	17	0.04 (0.114)	0.7270	NA	0.91 (<.0001)	1.16 (<.0001)	1.60 (<.0001)
	25 mg DPSGC	51	0.95 (0.118)	<.0001		NA	0.25 (0.1314)	0.69 (<.0001)
	50 mg DPSGC	59	1.20 (0.114)	<.0001			NA	0.44 (0.0065)
	100 mg Slope [2]	61	1.64 (0.115)	<.0001				NA
			0.01 (0.002)	<.0001				
4 Hrs	Placebo DPSGC	16	0.11 (0.120)	0.3810	NA	0.42 (0.0154)	0.80 (<.0001)	1.32 (<.0001)
	25 mg DPSGC	43	0.53 (0.124)	<.0001		NA	0.38 (0.0310)	0.90 (<.0001)
	50 mg DPSGC	57	0.90 (0.120)	<.0001			NA	0.53 (0.0021)
	100 mg Slope [2]	59	1.43 (0.121)	<.0001				NA
			0.01 (0.002)	<.0001				
5 Hrs	Placebo DPSGC	15	0.05 (0.117)	0.6531	NA	0.36 (0.0306)	0.65 (0.0001)	1.07 (<.0001)
	25 mg DPSGC	34	0.42 (0.120)	0.0006		NA	0.29 (0.0865)	0.71 (<.0001)
	50 mg DPSGC	49	0.71 (0.116)	<.0001			NA	0.42 (0.0117)
	100 mg Slope [2]	51	1.12 (0.118)	<.0001				NA
			0.01 (0.002)	<.0001				
6 Hr	Placebo DPSGC	14	0.07 (0.117)	0.5484	NA	0.25 (0.1371)	0.50 (0.0030)	0.99 (<.0001)
	25 mg DPSGC	31	0.32 (0.121)	0.0084		NA	0.25 (0.1438)	0.74 (<.0001)
	50 mg DPSGC	43	0.57 (0.117)	<.0001			NA	0.49 (0.0033)
	100 mg Slope [2]	44	1.06 (0.119)	<.0001				NA
			0.01 (0.002)	<.0001				

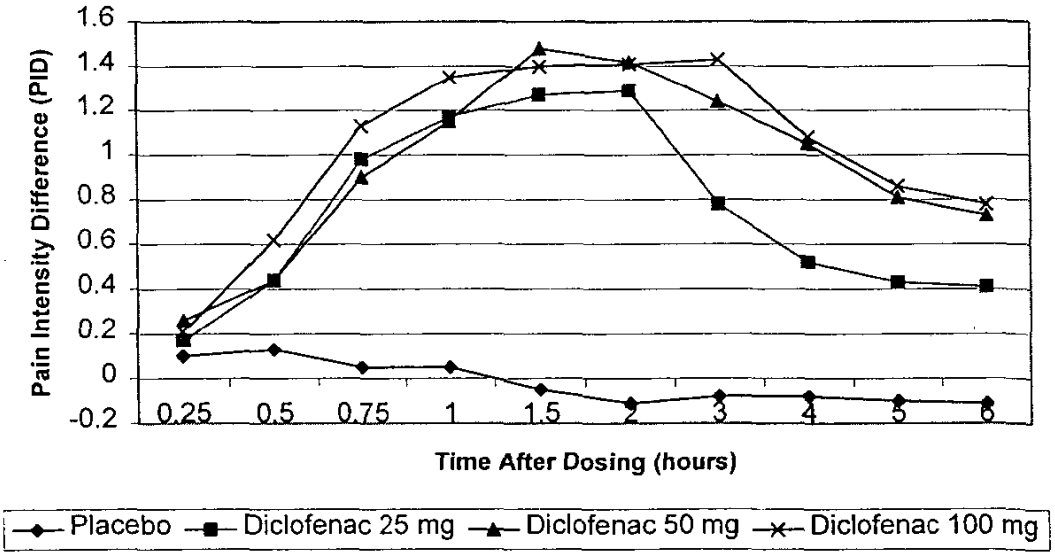
[1] Test of null hypothesis that the estimate is equal if difference is equal to zero. Model includes baseline pain and treatment group.
[2] Estimate of the linear regression slope for the active doses only.
[3] P-values not corrected for multiple comparisons.
Reference: pid_cl000395.tbl generated by pid_cl000395.sas at 13:52 on 22FEB2008
Source: Table 2.3 of the Study 395 report amendment submitted on 3/25/2008

Table 5.3.3A-2a PR by Dose and Time

Study 395			Estimated Response		Paired Differences (P-value [1][3])			
Hour	**Dose**	**N**	**LS Mean (SE)**	**P- value**	**Placebo**	**25 mg**	**50 mg**	**100 mg**
0.25 Hrs	Placebo	68	0.49 (0.089)	<.0001	NA	0.12 (0.3450)	0.13 (0.2939)	0.13 (0.3082)
	DPSGC 25 mg	63	0.61 (0.092)	<.0001		NA	0.01 (0.9246)	0.01 (0.9470)
	DPSGC 50 mg	68	0.62 (0.089)	<.0001			NA	-0.00 (0.9775)
	DPSGC 100 mg	66	0.62 (0.090)	<.0001				NA
	Slope [2]		0.00 (0.002)	0.9755				
0.5 Hrs	Placebo DPSGC	68	0.88 (0.127)	<.0001	NA	0.51 (0.0056)	0.53 (0.0038)	0.69 (0.0002)
	25 mg DPSGC	63	1.39 (0.131)	<.0001		NA	0.02 (0.9249)	0.18 (0.3292)
	50 mg DPSGC	68	1.40 (0.127)	<.0001			NA	0.16 (0.3684)
	100 mg Slope [2]	66	1.57 (0.128)	<.0001				NA
			0.00 (0.002)	0.3113				
0.75 Hrs	Placebo DPSGC	68	0.92 (0.133)	<.0001	NA	1.32 (<.0001)	1.20 (<.0001)	1.56 (<.0001)
	25 mg DPSGC	63	2.24 (0.138)	<.0001		NA	-0.12 (0.5447)	0.24 (0.2126)
	50 mg DPSGC	68	2.12 (0.133)	<.0001			NA	0.36 (0.0599)
	100 mg Slope [2]	66	2.48 (0.135)	<.0001				NA
			0.00 (0.003)	0.1343				
1 Hr	Placebo DPSGC	67	0.94 (0.137)	<.0001	NA	1.71 (<.0001)	1.74 (<.0001)	2.02 (<.0001)
	25 mg DPSGC	63	2.65 (0.141)	<.0001		NA	0.03 (0.8741)	0.31 (0.1223)
	50 mg DPSGC	68	2.68 (0.137)	<.0001			NA	0.28 (0.1569)
	100 mg Slope [2]	66	2.96 (0.138)	<.0001				NA
			0.00 (0.003)	0.0952				
1.5 Hrs	Placebo DPSGC	42	0.78 (0.139)	<.0001	NA	2.07 (<.0001)	2.17 (<.0001)	2.45 (<.0001)
	25 mg DPSGC	55	2.85 (0.144)	<.0001		NA	0.10 (0.6207)	0.38 (0.0612)
	50 mg DPSGC	65	2.95 (0.139)	<.0001			NA	0.28 (0.1585)
	100 mg Slope [2]	65	3.23 (0.141)	<.0001				NA
			0.01 (0.003)	0.0565				
2 Hrs	Placebo	26	0.74 (0.144)	<.0001	NA	1.97 (<.0001)	2.25 (<.0001)	2.63 (<.0001)
	DPSGC 25 mg	55	2.71 (0.149)	<.0001		NA	0.28 (0.1736)	0.66 (0.0018)
	DPSGC 50 mg	63	2.99 (0.144)	<.0001			NA	0.37 (0.0682)
	DPSGC 100 mg	64	3.37 (0.145)	<.0001				NA
	Slope [2]		0.01 (0.003)	0.0020				
3 Hrs	Placebo	17	0.82 (0.158)	<.0001	NA	1.48 (<.0001)	1.89 (<.0001)	2.37 (<.0001)
	DPSGC 25 mg	51	2.30 (0.163)	<.0001		NA	0.41 (0.0718)	0.88 (0.0001)
	DPSGC 50 mg	59	2.71 (0.158)	<.0001			NA	0.47 (0.0359)
	DPSGC 100 mg	61	3.18 (0.160)	<.0001				NA
	Slope [2]		0.01 (0.003)	0.0002				
4 Hrs	Placebo DPSGC	16	0.91 (0.164)	<.0001	NA	0.90 (0.0002)	1.54 (<.0001)	2.04 (<.0001)
	25 mg DPSGC	43	1.81 (0.170)	<.0001		NA	0.64 (0.0073)	1.13 (<.0001)
	50 mg DPSGC	57	2.45 (0.164)	<.0001			NA	0.50 (0.0344)
	100 mg Slope [2]	59	2.94 (0.166)	<.0001				NA
			0.01 (0.003)	<.0001				
5 Hrs	Placebo DPSGC	15	0.84 (0.164)	<.0001	NA	0.77 (0.0013)	1.33 (<.0001)	1.69 (<.0001)
	25 mg DPSGC	34	1.60 (0.170)	<.0001		NA	0.56 (0.0185)	0.93 (0.0001)
	50 mg DPSGC	49	2.16 (0.164)	<.0001			NA	0.37 (0.1157)
	100 mg Slope [2]	51	2.53 (0.166)	<.0001				NA
			0.01 (0.003)	0.0003				
6 Hr	Placebo DPSGC	14	0.85 (0.172)	<.0001	NA	0.61 (0.0146)	1.02 (<.0001)	1.45 (<.0001)
	25 mg DPSGC	31	1.46 (0.178)	<.0001		NA	0.41 (0.1009)	0.84 (0.0008)
	50 mg DPSGC	43	1.87 (0.172)	<.0001			NA	0.44 (0.0758)
	100 mg Slope [2]	44	2.30 (0.174)	<.0001				NA
			0.01 (0.003)	0.0011				

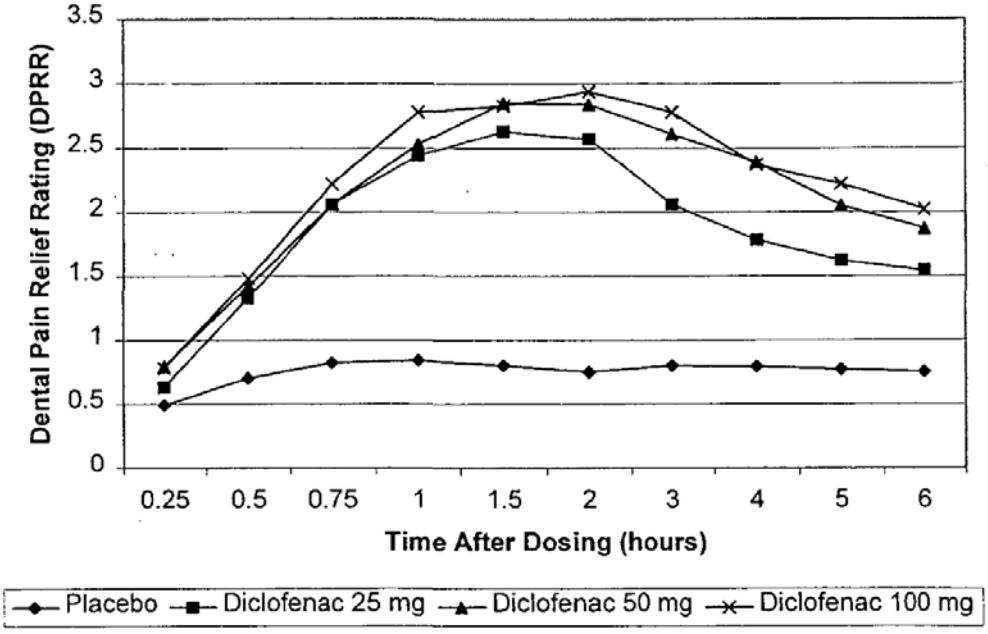
[1] Test of null hypothesis that the estimate is equal if difference is equal to zero. Model includes baseline pain and treatment group.
[2] Estimate of the linear regression slope for the active doses only.
[3] P-values not corrected for multiple comparisons.
Reference: pid_cl000395.tbl generated by pid_cl000395.sas at 13:52 on 22FEB2008
Source: Table 2.4 of the Study 395 report amendment submitted on 3/25/2008

Figure 5.3.3A-1b: Pain Intensity Difference over Time in Study 400



Reference: Table 14.2.3, Section 14
Source: Figure 1 on page 52 of the report for Study 400.

Figure 5.3.3A-2b: Pain Relief over Time in Study 400



Reference: Table 14.2.5, Section 14
Source: Figure 2 on page 54 of the report for Study 400.

Table 5.3.3A-1b PID by Dose and Time

Study 400			Estimated Response		Paired Differences (P-value [1][3])			
Hour	Dose	N	LS Mean (SE)	P- value	Placebo	25 mg	50 mg	100 mg
0.25 Hrs	Placebo DPSGC	61	0.10 (0.072)	0.1635	NA	0.07 (0.4607)	0.16 (0.1208)	0.10 (0.3021)
	25 mg DPSGC	63	0.17 (0.071)	0.0140		NA	0.08 (0.4083)	0.03 (0.7651)
	50 mg DPSGC	62	0.26 (0.071)	0.0004			NA	-0.05 (0.5965)
	100 mg Slope [2]	63	0.20 (0.071)	0.0041				NA
			0.00 (0.001)	0.8899				
0.5 Hrs	Placebo DPSGC	61	0.14 (0.102)	0.1843	NA	0.31 (0.0328)	0.30 (0.0397)	0.48 (0.0010)
	25 mg DPSGC	63	0.44 (0.101)	<.0001		NA	-0.01 (0.9436)	0.17 (0.2349)
	50 mg DPSGC	62	0.43 (0.102)	<.0001			NA	0.18 (0.2099)
	100 mg Slope [2]	63	0.61 (0.101)	<.0001				NA
			0.00 (0.002)	0.2003				
0.75 Hrs	Placebo DPSGC	61	0.06 (0.120)	0.6100	NA	0.92 (<.0001)	0.84 (<.0001)	1.05 (<.0001)
	25 mg DPSGC	63	0.98 (0.118)	<.0001		NA	-0.08 (0.6183)	0.13 (0.4322)
	50 mg DPSGC	62	0.90 (0.119)	<.0001			NA	0.22 (0.2009)
	100 mg Slope [2]	63	1.12 (0.118)	<.0001				NA
			0.00 (0.002)	0.3584				
1 Hr	Placebo DPSGC	61	0.07 (0.121)	0.5890	NA	1.11 (<.0001)	1.08 (<.0001)	1.27 (<.0001)
	25 mg DPSGC	63	1.18 (0.119)	<.0001		NA	-0.03 (0.8447)	0.16 (0.3438)
	50 mg DPSGC	61	1.14 (0.120)	<.0001			NA	0.19 (0.2550)
	100 mg Slope [2]	63	1.34 (0.119)	<.0001				NA
			0.00 (0.002)	0.3008				
1.5 Hrs	Placebo DPSGC	32	-0.04 (0.120)	0.7612	NA	1.31 (<.0001)	1.52 (<.0001)	1.42 (<.0001)
	25 mg DPSGC	59	1.27 (0.118)	<.0001		NA	0.21 (0.2080)	0.11 (0.4910)
	50 mg DPSGC	57	1.48 (0.119)	<.0001			NA	-0.10 (0.5659)
	100 mg Slope [2]	60	1.39 (0.118)	<.0001				NA
			0.00 (0.002)	0.6488				
2 Hrs	Placebo DPSGC	23	-0.10 (0.120)	0.4279	NA	1.38 (<.0001)	1.51 (<.0001)	1.49 (<.0001)
	25 mg DPSGC	56	1.29 (0.118)	<.0001		NA	0.13 (0.4398)	0.11 (0.5155)
	50 mg DPSGC	56	1.42 (0.119)	<.0001			NA	-0.02 (0.9007)
	100 mg Slope [2]	59	1.40 (0.118)	<.0001				NA
			0.00 (0.002)	0.6069				
3 Hrs	Placebo DPSGC	18	-0.06 (0.126)	0.6274	NA	0.84 (<.0001)	1.30 (<.0001)	1.47 (<.0001)
	25 mg DPSGC	48	0.78 (0.123)	<.0001		NA	0.46 (0.0093)	0.63 (0.0004)
	50 mg DPSGC	50	1.24 (0.124)	<.0001			NA	0.17 (0.3287)
	100 mg Slope [2]	56	1.41 (0.124)	<.0001				NA
			0.01 (0.002)	0.0014				
4 Hrs	Placebo DPSGC	16	-0.06 (0.129)	0.6213	NA	0.59 (0.0013)	1.11 (<.0001)	1.13 (<.0001)
	25 mg DPSGC	39	0.52 (0.127)	<.0001		NA	0.52 (0.0043)	0.54 (0.0031)
	50 mg DPSGC	49	1.05 (0.128)	<.0001			NA	0.02 (0.9205)
	100 mg Slope [2]	53	1.06 (0.127)	<.0001				NA
			0.01 (0.002)	0.0115				
5 Hrs	Placebo DPSGC	16	-0.08 (0.126)	0.5102	NA	0.51 (0.0040)	0.89 (<.0001)	0.93 (<.0001)
	25 mg DPSGC	34	0.43 (0.124)	0.0006		NA	0.37 (0.0342)	0.41 (0.0189)
	50 mg DPSGC	46	0.80 (0.125)	<.0001			NA	0.04 (0.8216)
	100 mg Slope [2]	46	0.84 (0.124)	<.0001				NA
			0.00 (0.002)	0.0405				
6 Hr	Placebo DPSGC	16	-0.10 (0.127)	0.4436	NA	0.51 (0.0044)	0.82 (<.0001)	0.86 (<.0001)
	25 mg DPSGC	29	0.41 (0.124)	0.0010		NA	0.31 (0.0815)	0.35 (0.0490)
	50 mg DPSGC	40	0.72 (0.125)	<.0001			NA	0.04 (0.8242)
	100 mg Slope [2]	38	0.76 (0.125)	<.0001				NA
			0.00 (0.002)	0.0874				

[1] Test of null hypothesis that the estimate is equal if difference is equal to zero. Model includes baseline pain and treatment group.
[2] Estimate of the linear regression slope for the active doses only.
[3] P-values not corrected for multiple comparisons.
Reference: pid_cl000400.tbl generated by pid_cl000400.sas at 13:52 on 22FEB2008
Source: Table 2.3 of the Study 400 report amendment submitted on 3/25/2008.

Table 5.3.3A-2b PID by Dose and Time

Study 400			Estimated Response		Paired Differences (P-value [1][3])			
Hour	Dose	N	LS Mean (SE)	P- value	Placebo	25 mg	50 mg	100 mg
0.25 Hrs	Placebo DPSGC	61	0.48 (0.111)	<.0001	NA	0.16 (0.3141)	0.32 (0.0448)	0.32 (0.0451)
	25 mg DPSGC	63	0.63 (0.110)	<.0001		NA	0.16 (0.3080)	0.16 (0.3105)
	50 mg DPSGC	62	0.79 (0.110)	<.0001			NA	-0.00 (0.9928)
	100 mg Slope [2]	63	0.79 (0.110)	<.0001				NA
			0.00 (0.002)	0.3950				
0.5 Hrs	Placebo DPSGC	61	0.69 (0.144)	<.0001	NA	0.64 (0.0016)	0.73 (0.0004)	0.80 (<.0001)
	25 mg DPSGC	63	1.33 (0.142)	<.0001		NA	0.09 (0.6562)	0.16 (0.4309)
	50 mg DPSGC	62	1.42 (0.143)	<.0001			NA	0.07 (0.7339)
	100 mg Slope [2]	63	1.49 (0.142)	<.0001				NA
			0.00 (0.003)	0.4861				
0.75 Hrs	Placebo DPSGC	61	0.81 (0.158)	<.0001	NA	1.26 (<.0001)	1.26 (<.0001)	1.43 (<.0001)
	25 mg DPSGC	63	2.06 (0.156)	<.0001		NA	0.00 (0.9850)	0.17 (0.4353)
	50 mg DPSGC	62	2.07 (0.157)	<.0001			NA	0.17 (0.4483)
	100 mg Slope [2]	63	2.23 (0.156)	<.0001				NA
			0.00 (0.003)	0.4405				
1 Hr	Placebo DPSGC	61	0.82 (0.150)	<.0001	NA	1.62 (<.0001)	1.71 (<.0001)	1.97 (<.0001)
	25 mg DPSGC	63	2.44 (0.147)	<.0001		NA	0.09 (0.6648)	0.35 (0.0985)
	50 mg DPSGC	61	2.53 (0.148)	<.0001			NA	0.25 (0.2242)
	100 mg Slope [2]	63	2.79 (0.147)	<.0001				NA
			0.00 (0.003)	0.1059				
1.5 Hrs	Placebo DPSGC	32	0.79 (0.151)	<.0001	NA	1.84 (<.0001)		
	25 mg DPSGC	59	2.63 (0.148)	<.0001		NA	2.07 (<.0001)	2.05 (<.0001)
	50 mg DPSGC	57	2.86 (0.149)	<.0001			0.22 (0.2900)	0.20 (0.3343)
	100 mg Slope [2]	60	2.84 (0.148)	<.0001			NA	-0.02 (0.9233)
			0.00 (0.003)	0.4271				
2 Hrs	Placebo DPSGC	23	0.75 (0.156)	<.0001	NA	1.82 (<.0001)	2.09 (<.0001)	2.19 (<.0001)
	25 mg DPSGC	56	2.57 (0.153)	<.0001		NA	0.27 (0.2172)	0.37 (0.0877)
	50 mg DPSGC	56	2.84 (0.154)	<.0001			NA	0.10 (0.6377)
	100 mg Slope [2]	59	2.94 (0.153)	<.0001				NA
			0.00 (0.003)	0.1235				
3 Hrs	Placebo DPSGC	18	0.80 (0.166)	<.0001	NA	1.27 (<.0001)	1.82 (<.0001)	1.99 (<.0001)
	25 mg DPSGC	48	2.06 (0.163)	<.0001		NA	0.55 (0.0181)	0.72 (0.0020)
	50 mg DPSGC	50	2.61 (0.164)	<.0001			NA	0.17 (0.4624)
	100 mg Slope [2]	56	2.78 (0.163)	<.0001				NA
			0.01 (0.003)	0.0061				
4 Hrs	Placebo DPSGC	16	0.78 (0.172)	<.0001	NA	1.00 (<.0001)	1.61 (<.0001)	1.60 (<.0001)
	25 mg DPSGC	39	1.78 (0.169)	<.0001		NA	0.61 (0.0115)	0.60 (0.0134)
	50 mg DPSGC	49	2.39 (0.171)	<.0001			NA	-0.02 (0.9501)
	100 mg Slope [2]	53	2.37 (0.169)	<.0001				NA
			0.01 (0.003)	0.0389				
5 Hrs	Placebo DPSGC	16	0.76 (0.167)	<.0001	NA	0.86 (0.0003)	1.29 (<.0001)	1.47 (<.0001)
	25 mg DPSGC	34	1.62 (0.165)	<.0001		NA	0.43 (0.0658)	0.61 (0.0090)
	50 mg DPSGC	46	2.05 (0.166)	<.0001			NA	0.18 (0.4378)
	100 mg Slope [2]	46	2.23 (0.165)	<.0001				NA
			0.01 (0.003)	0.0169				
6 Hr	Placebo DPSGC	16	0.74 (0.174)	<.0001	NA	0.80 (0.0012)	1.13 (<.0001)	1.28 (<.0001)
	25 mg DPSGC	29	1.54 (0.171)	<.0001		NA	0.33 (0.1700)	0.49 (0.0449)
	50 mg DPSGC	40	1.87 (0.172)	<.0001			NA	0.15 (0.5278)
	100 mg Slope [2]	38	2.03 (0.171)	<.0001				NA
			0.01 (0.003)	0.0673				

[1] Test of null hypothesis that the estimate is equal if difference is equal to zero. Model includes baseline pain and treatment group.
[2] Estimate of the linear regression slope for the active doses only.
[3] P-values not corrected for multiple comparisons.
Reference: pid_cl000400.tbl generated by pid_cl000400.sas at 13:52 on 22FEB2008 Source:
Source: Table 2.4 of the study 400 report amendment submitted on 3/25/2008

Table 5.3.3A-3a: Time-Weighted Summation Pain Scores SPID3, TOTPAR3, and TOTPAR6

Study 395	Treatments				Treatment Interaction P values	
	Placebo	DPSGC 25 mg	DPSGC 50 mg	DPSGC 100 mg	Site	Baseline DPIS
N	68	63	68	66		
SPID3						
Mean	0.28	3.07	3.06	4.17	0.9691	0.7824
Std. Devi	2.25	2.60	1.96	1.79		
(Min, Max)	(-3.0,6.3)	(-3.0, 8.3)	(-2.8,6.5)	(-1.5, 8.3)		
LSMean	0.13	3.03	3.19	4.22		
SE (LSMean)	0.25	0.26	0.25	0.25		
Difference in LSMean from placebo		2.79	2.78	3.89		
Dunnett-adjusted P value		<0.0001	<0.0001	<0.0001		
TOTPAR3						
Mean	2.39	6.81	7.39	8.39	0.6365	0.4951
Std. Devi	2.94	3.24	3.00	2.23		
(Min, Max)	(0.0, 11.3)	(0.0, 11.3)	(0.0, 11.8)	(0.0, 11.3)		
LSMean	2.38	6.80	7.39	8.39		
SE (LSMean)	0.35	0.36	0.35	0.35		
Difference in LSMean from placebo		4.42	5	6		
Dunnett-adjusted P value		<0.0001	<0.0001	<0.0001		
TOTPAR6						
Mean	4.99	11.68	13.86	16.16	0.3453	0.4027
Std. Devi	6.69	6.66	6.79	5.17		
(Min, Max)	(0.0,21.5)	(0.0,23.3)	(0.0,23.8)	(0.0,23.0)		
LSMean	4.98	11.67	13.87	16.16		
SE (LSMean)	0.78	0.80	0.78	0.79		
Difference in LSMean from placebo		6.69	8.87	11.17		
Dunnett-adjusted P value		<0.0001	<0.0001	<0.0001		

Reference: Tables 14.2.1.1 and 14.2.4, Section 14.
Source: Table 7 on page 51 and Table 8 on page 53 of the report for Study 395.

Table 5.3.3A-3b: Time-Weighted Summation Pain Scores SPID3, TOTPAR3, and TOTPAR6

Study 400	Treatments				Treatment Interaction P values	
	Placebo	DPSGC 25 mg	DPSGC 50 mg	DPSGC 100 mg	Site	Baseline DPIS
N	61	63	62	63		
SPID3						
Mean	-0.08	2.75	3.38	3.66	0.2872	0.9479
Std. Devi	2.25	2.25	2;59	2.17		
(Min, Max)	(-3.0,5.5)	(-2.5,8.3)	(-2.8,8.5)	(-2.5,8.0)		
LSMean	-0.04	2.75	3.37	3.62		
SE (LSMean)	0.29	0.29	0.29	0.29		
Difference in LSMean from placebo		2.83	3.46	3.74		
Dunnett-adjusted P value		<0.0001	<0.0001	<0.0001		
TOTPAR3						
Mean	2.30	6.29	7.16	7.47	0.0118	0.4646
Std. Devi	2.81	2.84	3.37	2.90		
(Min, Max)	(0.0, 10.3)	(0.0, 11.5)	(0.0, 11.3)	(0.3, 11.5)		
LSMean	2.26	6.28	7.17	7.50		
SE (LSMean)	0.38	0.37	0.38	0.,37		
Difference in LSMean from placebo		3.99	4.86	5.17		
Dunnett-adjusted P value		<0.0001	<0.0001	<0.0001		
TOTPAR6						
Mean	4.61	11.22	13.47	14.08	0.0055	0.3961
Std. Devi	6.11	5.96	6.76	6.58		
(Min, Max)	(0.0,21.3)	(0.0,22.0)	(0.0,23.0)	(0.3,23.5)		

LSMean	4.54	11.22	13.48	14.13		
SE (LSMean)	0.81	0.80	0.80	0.80		
Difference in LSMean from placebo		6.61	8.86	9.47		
Dunnett-adjusted P value		<0.0001	<0.0001	<0.0001		

Reference: Tables 14.2.1.1 and 14.2.4, Section 14.
Source: Table 7 on page 53 and Table 8 on page 55 of the report for Study 400.

Table 5.3.3A-4a: Time to Onset of Perceptible and Meaningful Pain Relief (Study 395)

Study 395 Onset	**Placebo (N = 68)**	**DPSGC 25 mg (N = 63)**	**DPSGC 50 mg (N = 68)**	**DPSGC 100 mg (N= 66)**	**Site**	**Baseline DPIS**
Onset of Perceptible PR					0.9173	0.7560
Patients with relief, n (%)	49 (72.1)	59 (93.7)	64 (94.1)	65 (98.5)		
Median Time	24. 5	22.0	22.5	19.5		
95% CI of Time	17.0 - 46.0	16.0 - 27.0	17.0 - 26.0	16.0 - 22.0		
Wald chi-squared p-value		0.0022	0.0024	<0.0001		
Onset of Meaningful PR					0.8091	0.4411
Patients with relief, n (%)	18 (26.5)	52 (82.5)	59 (86.8)	62 (93.9)		
Median Time	242.0	45.0	53.0	43.0		
95% CI of Time	221.0 - NC	43.0 - 59.0	45.0 - 59.0	39.0 - 50.0		
Wald chi-squared p-value		<0.0001	<0.0001	<0.0001		

Note: The median and confidence interval for time-to-event are estimated using Kaplan-Meier product limit estimates. The Wald chi-squared p-values are based on the coefficients and corresponding standard errors derived from the Cox Proportional Hazards model with factors for treatment and baseline DPIS.
NC indicates parameter is not calculable.
Source: Tables 14.2.9 and 14.2.10 on pages 104 and 105 of the report for Study 395.

Table 5.3.3A-4b: Time to Onset of Perceptible and Meaningful Pain Relief (Study 400)

Study 400 Onset	**Placebo (N = 61)**	**DPSGC 25 mg (N = 63)**	**DPSGC 50 mg (N = 62)**	**DPSGC 100 mg (N= 63)**	**Site**	**Baseline DPIS**
Onset of Perceptible PR					0.0737	0. 0299
Patients with relief, n (%)	35 (57.4)	61 (96.8)	57 (91.9)	6l (96.8)		
Median Time	30.0	25.0	17.0	21.0		
95% CI of Time	25. 0 - NC	20.0 - 30.0	14.0 - 24. 0	17.0 - 27.0		
Wald chi-squared p-value		0.0002	<0.0001	<0.0001		
Onset of Meaningful PR					0.2538	0. 1626
Patients with relief, n (%)	17 (27.9)	51 (81.0)	52 (83.9)	54 (85.7)		
Median Time	NC	52.0	47.5	52.0		
95% CI of Time	42.0 - 77.0	37.0 - 55.0	44.0 - 60.0	39.0 - 50.0		
Wald chi-squared p-value		<0.0001	<0.0001	<0.0001		

Note: The median and confidence interval for time-to-event are estimated using Kaplan-Meier product limit estimates. The Wald chi-squared p-values are based on the coefficients and corresponding standard errors derived from the Cox Proportional Hazards model with factors for treatment and baseline DPIS.
NC indicates parameter is not calculable.
Source: Tables 14.2.9 and 14.2.10 on pages 105 and 106 of the report for Study 400.

Table 5.3.3A-5a: Time to Rescue Medication

Study 395 Duration	**Placebo (N = 68)**	**DPSGC 25 mg (N = 63)**	**DPSGC 50 mg (N = 68)**	**DPSGC 100 mg (N= 66)**	**Site**	**Baseline DPIS**
Rescue Medication					0.5199	0.4526
Patients with rescue, n (%)	53 (77.9)	32 (50.8)	25 (36.8)	21 (31.8)		
Median Time	100.0	350.0	NC	NC		
95% CI of Time	91.0 - 123.0	245.0 - NC	NC	NC		
Wald chi-squared p-value		<0.0001	<0.0001	<0.0001		

Note: The median and confidence interval for time-to-event are estimated using Kaplan-Meier product limit estimates. The Wald chi-squared p-values are based on the coefficients and corresponding standard errors derived from the Cox Proportional Hazards model with factors for treatment and baseline DPIS.
Dunnett-adjusted p-values based on the LSMeans and MSE from the ANCOVA Model with factors for treatment and baseline DPIS.
NC indicates parameter is not calculable.

Source: Table 14.2.11 on pages 106 and 107 of the report for Study 395.

Table 5.3.3A-5b: Time to Rescue Medication

Study 400 Duration	Placebo (N = 61)	DPSGC 25 mg (N = 63)	DPSGC 50 mg (N = 62)	DPSGC 100 mg (N= 63)	Site	Baseline DPIS
Rescue Medication					0.0803	0.0354
Patients with rescue, n (%)	44 (72.1)	34 (54.0)	22 (35.5)	25 (39.7)		
Median Time	95.0	303.0	NC	NC		
95% CI of Time	70.0 - 120.0	225.0 - NC	NC	345.0 - NC		
Wald chi-squared p-value		<0.0001	<0.0001	<0.0001		

Note: The median and confidence interval for time-to-event are estimated using Kaplan-Meier product limit estimates. The Wald chi-squared p-values are based on the coefficients and corresponding standard errors derived from the Cox Proportional Hazards model with factors for treatment and baseline DPIS.
Dunnett-adjusted p-values based on the LSMeans and MSE from the ANCOVA Model with factors for treatment and baseline DPIS.
NC indicates parameter is not calculable.
Source: Table 14.2.11 on pages 107 and 108 of the report for Study 400.

Table 5.3.3A-6a: Patient Global Assessment

Study 395	Placebo	Diclofenac K 25mg	Diclofenac K 50mg	Diclofenac K 100 mg	Site	Baseline DPIS
	N = 68	N = 63	N = 68	N= 66	0.6254	0.5123
Mean	0.82	2.22	2.65	3.06		
Std. Devi	1.24	1.22	1.22	0.94		
Median	0.0	3.0	3.0	3.0		
(Min, Max)	(0.0, 4.0)	(0.0, 4.0)	(0.0, 4.0)	(0.0, 4.0)		
LSMean	0.82	2.22	2.65	3.06		
SE (LSMean)	0.14	0.15	0.14	0.14		
Dunnett-adjusted P value		<0.0001	<0.0001	<0.0001		

Note: The treatment main effect p-values are based on the LSMeans and MSE from the ANCOVA model with factors for treatment and baseline DPIS. The interaction p-values are based on the ANCOVA model with factors for treatment, baseline DPIS, site, treatment-by-site interaction, and treatment-by-baseline-DPIS interaction.
Source: Table 14.2.8 on page 103 of the report for Study 395.

Table 5.3.3A-6b: Patient Global Assessment

Study 400	Placebo	Diclofenac K 25mg	Diclofenac K 50mg	Diclofenac K 100 mg	Site	Baseline DPIS
n	N = 61	N = 63	N = 62	N= 63	0.5611	0.8870
Mean	0.65	2.08	2.51	2.84		
Std. Devi	1.04	1.27	1.27	1.21		
Median	0.0	2.0	3.0	3.0		
(Min, Max)	(0.0, 4.0)	(0.0, 4.0)	(0.0, 4.0)	(0.0, 4.0)		
LSMean	0.65	2.08	2.51	2.84		
SE (LSMean)	0.16	0.15	0.15	0.15		
Dunnett-adjusted P value		<0.0001	<0.0001	<0.0001		

Note: The treatment main effect p-values are based on the LSMeans and MSE from the ANCOVA model with factors for treatment and baseline DPIS. The interaction p-values are based on the ANCOVA model with factors for treatment, baseline DPIS, site, treatment-by-site interaction, and treatment-by-baseline-DPIS interaction.
Source: Table 14.2.8 on pages 104 of the report for Study 400

Eligibility criteria

Inclusion Criteria
Patients were going to be required to meet the following criteria for inclusion in the study if they:

1. Were able to read, comprehend, and sign the consent form, and willing to stay in the study unit for 6 hours post dosing.

2. Were healthy individuals free from significant cardiac, pulmonary, gastrointestinal, hepatic, renal, hematological, infectious, neurological, and psychiatric disease as determined by history, physical examination, and/or clinical laboratory test results.
3. Were men and women 18 to 65 years of age.
4. Were outpatients scheduled to undergo surgical extraction of 1 or more impacted third molars, at least 1 of which was a bony mandibular impaction.
5. Had surgery conducted under local anesthesia block (e.g., 3% mepivacaine). Intravenous sedation was used as required according to usual clinical practice using a suitable combination of the following agents: propofol, midazolam or diazepam, nitrous oxide, or fentanyl.
6. Were reliable, cooperative, and of adequate intelligence to record the requested information on the analgesic questionnaire form.
7. Were women of childbearing potential who were not pregnant, as assessed by a urine pregnancy quick test on the day of the procedure prior to surgery. Women were using a method of birth control deemed acceptable by the Investigator and continued to use this method during the duration of dosing with study medication.
8. Had developed sufficient levels of pain (rated at 50 mm or more out of a possible 100 mm) on the DPIS within 4 hours post extraction.
9. Were not morbidly obese and did not have significant health problems related to obesity.
10. Had agreed not to take analgesics other than protocol-defined rescue analgesics during the postoperative treatment period of 6 hours.
11. Had agreed to refrain from alcohol and sedative consumption during the postoperative period of 6 hours.

Exclusion Criteria

Patients were going to be excluded from this study if they:

1. Had clinically significant laboratory abnormalities, such as a(n):
    - Hemoglobin less than 11 g/dL
    - White blood cell count less than 3,500/mm3
    - Platelet count less than 100,000/mm3
    - Aspartate transaminase (AST) greater than 1.5 times the upper limits of normal
    - Alanine transaminase (ALT) greater than 1.5 times the upper limits of normal
    - Alkaline phosphatase greater than 1.5 times the upper limits of normal
    - Creatinine level greater than 2.0 mg/dL
2. Had taken an analgesic drug (including prescription and over the counter NSAIDs) within 24 hours prior to start of the surgery was prohibited. Use of Tylenol was allowed.
3. Had exposure to aspirin and/or aspirin containing products within 5 days prior to the start of surgery.
4. Had known sensitivity to NSAIDs and/or aspirin, who were prone to peptic ulceration, angioedema, or/and bronchospasm known to be triggered by NSAIDs and/or aspirin.
5. Had used prophylactic antibiotics for reasons other than dentoalveolar infections. (Use of antibiotics for treatment of acne was allowed.)
6. Presence of a bleeding disorder.
7. Were on risk of infective endocarditis.
8. Were on risk of adrenal suppression.
9. Had known alcohol or drug abuse within 1 year prior to enrollment in the study.
10. Had used an investigational drug within the past 30 days.
11. Were a member or relative of the study site staff or Sponsor, and directly involved in the study.
12. Had donation of blood exceeding 450 mL within the previous month.
13. Had used succinylcholine, corticosteroids, all other sedatives or hypnotic agents, and all local anesthetics not listed in Inclusion Criterion Number 5.
14. Were nursing or pregnant women.
15. Had been using phenothiazine antiemetics during surgery or in the postoperative period.

5.3.4 Knee Arthroscopy Studies 396 and 401

5.3.4.1 Protocol

Study CL-000396 and Study CL-000401 were conducted using the same protocol. The studies were planned as randomized, double-blind, placebo-controlled, parallel, multiple-dose (4-day) study of Diclofenac Potassium Soft Gelatin Capsules (DPSGC) 25mg and 50 mg in patients with postoperative pain following arthroscopy knee surgery.

Eligible patients were to have been adult patients scheduled to undergo arthroscopic knee surgery with sufficient baseline pain intensity score of ≥50 mm on an 100 mm Visual Analog Pain Intensity Scale (PIS), measured at least every hour within 6 hours after the end of surgery without any clinically significant condition or a significant laboratory abnormality.

Patients were to have been randomized to receive one of the three treatments, DPSGC 25 mg, 50 mg, and placebo and to have their initial dose evaluated for eight hours on site followed by repeated dosing of the same medication every eight hours for a total of 14 doses (with last 12 doses taking as outpatient).

The planned pain measurements included pain intensity (PI) using a 4-point categorical scale and pain relief (PR) using a 5-point categorical scale at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 hours after the initial dose or until the request of remedication. Two stopwatches were planned to record the onset of the first perceptible and meaningful pain relief. Rescue medication was to have been allowed after the initial dose. The plan for those who took rescue was to discontinue hourly pain assessments, complete patient global evaluation, and wait until the end of 8-hour period to receive the second dose of study medication before discharge. Ice packs to the affected area of the knee were to have been allowed and removed at least 15 minutes prior to any scheduled pain assessment within the first eight hours after the initial dose. Patient global assessments were to have been measured using a 5-point categorical scale eight hours after each dose (prior to each repeated dose and eight hours after the last dose or at the time rescue medication was taken).

The planned primary efficacy endpoint was the Time-Weighted Sum of Pain Intensity Differences (SPID8) over the first 8-hour period after the initial dose. The planned secondary efficacy endpoints included Time-Weighted Sum of PID over the first 4 hours (SPID4), Time-Weighted PR over the first 4 hours (TOTPAR4), TOTPAR8, and time-specific PID, PR and PRID (the sum of PID and PR); PR associated with the onset of perceptible and meaningful pain relief; time to onset of perceptible pain relief; time to onset of meaningful pain relief; time to rescue medication; Overall Global Evaluation score at each evaluation time point.

Safety monitoring was planned to consist of reports of adverse events (AEs) during the study and 7 to 10-day follow up period and serious AEs up to 30 days after the last dose of study medication; vital signs at screening visit, prior to the initial dose, at multiple time points during the first 8 hours, and at completion or early termination visit; laboratory tests at screening visit and at completion or early termination visit; a urine pregnancy test for female of child-bearing potential immediately prior to surgery.

5.3.4.2 Results

The two post operative knee pain studies had similar demographic compositions. The patients enrolled in these studies had an age range of 18 to 79 years and a mean age of 46 years. Of the 190 patients treated in Study 396, 79% were Caucasian, 13% were African American, 7% were Hispanic, and 35% were female. Of the 192 patients treated in Study 401, 79% were Caucasian, 9% were African American, 10% were Hispanic, and 42% were female. The treatment groups were approximately balanced with regard to demographic characteristics

such as age, gender, race, height, and weight. The group mean of baseline pain intensity (PI) ranged from 63 to 64 (on a 100 mm scale) in Study 396 and from 62 to 66 in Study 401.

Only 7 of 190 patients in Study 396 discontinued early: three from the placebo group, three from the DPSGC 25 mg group, and one from the DPSGC 50 mg group. Five patients withdrew consent (due to lack of efficacy in a placebo patient and a patient on DPSGC 50 mg and reasons unspecified in one placebo patient and two patients on DPSGC 25 mg). One patient on DPSGC 25 mg dropped out for family reason. One placebo patient discontinued because of severe pain in need of IV opioid. Only 4 of 192 patients in Study 401 discontinued early: one from the placebo group due to headache and nausea and three from the DPSGC 50 mg group for anxiety, protocol violation, and investigator's discretion, respectively.

About 95% or more patients exposed to 11 to 14 doses, which were equivalent to about four days of continuous exposure as scheduled, in both studies as shown in the tables below.

Table 5.3.4-1 Summary of Exposure (Study 396)

Study 396 Exposure	**DPSGC 25 mg (N=67)**	**DPSGC 50 mg (N=61)**	**Placebo (N=61)**
Number of Doses Taken, n (%)			
1 -5	3 (4.5%)	1 (1.6%)	2 (3.3%)
6-10	1 (1.5%)	1 (1.6%)	0
11-14	63 (94.0%)	59 (96.7%)	59(96.7%)

Source: Table 1.1 on page 2 of the amendment to report for Study 396 submitted March 19, 2008.

Table 5.3.4-2 Summary of Exposure (Study 401)

Study 401 Exposure	**DPSGC 25 mg (N=64)**	**DPSGC 50 mg (N=63)**	**Placebo (N=65)**
Number of Doses Taken, n (%)			
1 -5	1 (1.6%)	3 (4.8%)	0
6-10	1 (1.6%)	0	1 (1.5%)
11-14	62 (96.9%)	60 (95.2%)	64 (98.5%)

Source: Table 1.1 on page 2 of the amendment to report for Study 401 submitted March 19, 2008.

Efficacy

Statistically significant treatment differences were not demonstrated in the primary efficacy endpoint or any of the secondary efficacy parameters in Study 396 and not shown in the primary and basically all the secondary efficacy parameters measuring single-dose effects in Study 401. Statistically significant treatment differences from placebo were demonstrated in proportion of patients taking rescue during Days 2 to 5 (44% and 30% for DPSGC 25 mg and 50 mg groups, respectively, versus 63% in the placebo group) and in patient global assessments during Days 2 to 5 (recorded three times a day in the multiple-dose period as shown in the table below). The effect sizes of treatment differences from placebo were 20 to 30% in terms of the proportion taking rescue and about 0.5 units (on a 5-point scale) for DPSGC 25 mg and one unit for DPSGC 50 mg in terms of global assessment.

Table 5.3.4-3 Patient Global Assessment

Study 401 Patient's Global	**Placebo (N=65)**	**DPSGC 25 mg (N=64)**	**Treatment differences**		**DPSGC 50 mg (N=63)**	**Treatment differences**	
Time point		LSMean	Effect size	p-value	LSMean	Effect size	p-value
8 Hours After 1st Dose	2.08	2.16	0.08	0.9145	2.47	0.39	0.2010
Day 2 Morning	1.61	2.21	0.6	**0.0125**	2.57	0.96	**<0.0001**
Day 2 Afternoon	1.61	2.23	0.62	**0.0095**	2.72	1.11	**<0.0001**
Day 2 Evening	1.69	2.23	0.54	**0.0265**	2.65	0.96	**<0.0001**
Day 3 Morning	1.84	2.28	0.44	0.0830	2.84	1	**<0.0001**
Day 3 Afternoon	1.77	2.31	0.54	**0.0335**	2.81	1.04	**<0.0001**
Day 3 Evening	1.89	2.40	0.51	**0.0416**	2.95	1.06	**<0.0001**

Day 4 Morning	1.92	2.47	0.55	**0.0288**	2.99	1.07	**<0.0001**
Day 4 Afternoon	1.98	2.53	0.55	**0.0335**	2.88	0.9	**0.0003**
Day 4 Evening	1.84	2.40	0.56	**0.0328**	2.85	1.01	**<0.0001**
Day 5 Morning	1.92	2.51	0.59	**0.0140**	2.90	0.98	**<0.0001**
Day 5 Afternoon	1.98	2.48	0.5	**0.0430**	2.98	1	**<0.0001**
Day 5 Evening	2.00	2.52	0.52	**0.0452**	3.01	1.01	**<0.0001**

Source: Table 14.2.8 on pages 118 to 124 of the report for Study 401.

5.3.4.3 Conclusion

The results of the two studies of postoperative pain following arthroscopy knee surgery did not support single-dose efficacy. The data from limited assessments of repeated dosing in Study 401 suggested some multiple-dose effects of the DPSGC treatments.

6. INTEGRATED REVIEW OF EFFICACY

Summary of Efficacy Results and Conclusions

There were six Phase 3 efficacy studies of randomized, double-blind, placebo-controlled design with two studies of identical design in each post operative pain model, bunionectomy (Study 301 and 302), dental procedure (Study 395 and 400), and knee arthroscopy (Study 396 and 401). The studies enrolled representative sample populations with treatment groups approximately balanced in demographic characteristics and baseline pain intensity. Only a very small proportion of patients dropped out from the studies, in a range of 1.5% to 4.5% in the multiple-dose studies and 0.4% in the single-dose studies. Dropout due to lack of efficacy was reported in five placebo patients and one DPSGC patient overall in the six studies.

Positive outcomes were replicated in each of the two different pain models, bunionectomy and dental pain. Statistically significant and clinically meaningful treatment differences in support of single-dose and multiple-dose efficacy were shown in all primary and an overwhelming majority of secondary efficacy parameters in the bunionectomy and dental studies.

The key clinically significant evidence in support of multiple-dose efficacy in bunionectomy studies included an effect size of 2.5 to 2.9-unit treatment difference measured by an 11-point scale in the average of pain intensity (PI) recorded at mid dosing and end of 6-hour dosing interval during 48 hours and an effect size of treatment difference of 2.5 to 3.5 units in time-specific PI at most time points over 48 hours; a rescue interval of 5-6 hours for DPSGC treatment derived from data on time to rescue in each 6-hour dosing interval; less DPSGC patients than placebo patients taking rescue, 39-49% less on the first day, 37-43% less on the second day, 15-24% less before discharge and 27-38% less after discharge on the third day, and 24-29% less on the fourth day of treatment; and response of 'good' to 'excellent' in patient global assessment in 35% more DPSGC patients than placebo patients.

The key clinically significant evidence in support of single-dose efficacy in dental studies included effect size of ≥1 unit treatment differences in time-specific PID (PI measured on a 4-point scale) and ≥0.5 units in time-specific PR (measured on a 5-point scale) at most time points of the 6-hour interval in the two studies; more DPSGC patients than placebo patients reporting onset of pain relief, 22-26% more in terms of onset of perceptible relief and 56-67% more in terms of onset of meaningful relief at three DPSGC doses; median time to onset of meaningful relief of <1 hour for DPSGC treatments versus >4 hours for placebo treatment; less DPSGC patients than placebo patients requesting rescue: 27%, 41%, and 46% less at 25, 50, and 100 mg levels, respectively, in Study 395, and 18%, 37%, and 32% less at 25, 50, and 100 mg levels, respectively, in Study 400; median time to rescue of 5-6 hours with DPSGC 25 mg treatment versus <1.7 hours with placebo treatment in the two studies; and at least 47% more DPSGC treated patients than placebo patients had 'good' to 'excellent' response in patient global assessment. Single-dose efficacy was further supported by clinically meaningful effect sizes of treatment differences in bunionectomy studies, mainly in terms of time-specific pain measurements, proportion reporting onset of meaningful relief, and proportion of responders defined by the proportion achieving ≥30% pain reduction, the proportion achieving clinically significant efficacy (having both ≥ 30% reduction in baseline pain and meaningful relief by stopwatch), and the proportion experiencing mild to no pain after the initial dose.

Dose response in efficacy could not be properly assessed due to lack of inclusion of higher dose levels in bunionectomy studies, lack of adequate measurements in knee arthroscopy studies, and lack of predefined dose response analysis in dental studies. The sample sizes of subpopulations were too small to allow subpopulation analyses with regard to age, gender, or race.

DPSGC 25 mg has been shown to be efficacious in treating acute post operative pain at the proposed dosing interval of six hours based on the replicated positive results of the four efficacy studies.

6.1 Proposed Indication

The proposed indication for Diclofenac Potassium Soft Gelatin Capsule (DPSGC) 25 mg is for the relief of mild to moderate pain.

6.2 Methods/Study Design

The six Phase 3 studies were randomized, double-blind, placebo-controlled efficacy studies of post operative pain associated with bunionectomy (Study 301 and 302), dental procedure (Study 395 and 400), and knee arthroscopy (Study 396 and 401). Their protocol designs are discussed in detail in the individual study reviews in Section 5.3. The focus of the efficacy review is the evaluation of analgesic duration of DPSGC 25 mg because of the concerns about inadequate analgesia during the later part of the dosing interval, in which a single dose of DPSGC 25 mg was associated with lower serum concentration than that of Cataflam® 50 mg as shown in the relative bioavailability study where peak concentrations of the two were equivalent. The key efficacy parameters used to evaluate analgesic duration upon multiple dosing in bunionectomy studies were the average of pain measurements at mid and end of the 6-hour dosing interval, time-specific pain measurements at mid and end of dosing interval, rescue information in terms of daily and overall rescue interval calculated based on time to rescue in each 6-hour dosing interval, daily proportion of patients taking rescue, and the rescue use pattern (number of use per day and number of tablets per use) among users. The key efficacy parameters used to evaluate analgesic duration after a single dose of DPSGC treatment included time-specific measurements of pain during the entire dosing interval in all efficacy studies; time to request for remedication after the initial dose in bunionectomy studies; time to rescue and proportion taking rescue in dental studies. In knee arthroscopy studies single-dose duration was assessed in a similar way as in dental studies and multiple-dose duration was not adequately evaluated that only a few parameters such as the proportion taking rescue during Days 2 to 5, the number of rescue administrations among users, and patient global assessment, were included in the studies.

6.3 Demographics

Demographic and baseline characteristics of the sample population in each study are tabulated and described in detail in the individual study review in Section 5.3. Bunionectomy studies had mainly non-elderly female patients (>85% female with a maximum age of 65 years). Dental studies involved younger patients (with a maximum age of 46 years). Knee arthroscopy studies enrolled patients of both genders in a wide age range. Caucasians accounted for about 60% of the study population in bunionectomy studies, 75% in dental studies, and 80% in knee arthroscopy studies. The treatment groups were approximately balanced with regard to demographic characteristics such as age, gender, race, height, and weight in all the studies. Baseline pain intensity was between 6.9 and 7.5 (on an 11-point numerical scale) among the treatment groups in bunionectomy studies, between 2.1 to 2.4 (on a 4-point categorical scale) in dental studies, and between 62 and 66 (on a 100 mm VAS scale) in knee arthroscopy studies.

6.4 Patient Disposition

Patient disposition in each study is presented and discussed in details in Section 5.3. There were very few dropouts from any of the studies, three out of 201 (1.5%) patients in Study 301, nine of 200 (4.5%) patients in Study 302, one of 265 (0.4%) in Study 395, one of 249 in study 400 (0.4%), seven of 190 in Study 396 (3.7%), and four of 192 (2.1%) in Study 401. Dropouts due to lack of efficacy were reported in six patients, five placebo patients and one DPSGC patient, including a placebo patient in Study 301, two placebo patients in Study 302, two placebo patients and one patient on DPSGC 50 mg in Study 396. Dropouts due to adverse events (AEs) in Phase 3 efficacy studies were reported in four patients, one placebo patient and one patient on

DPSGC 25 mg in Study 302 and one placebo patient and one patient on DPSGC 50 mg in Study 401. The AE-related dropouts will be discussed in detail in Section 7.3.

6.5 Analysis of the Primary Endpoint(s)

The primary efficacy endpoint in the two bunionectomy studies was the mean score of the average of pain intensity (PI) measurements recorded at mid dosing interval (three hours after dosing) and the end of dosing interval (six hours after dosing) during the 48 hours following the first dose of remedication (or the first of the repeated doses). The results of the two studies are summarized in the table below. The effect of DPSGC in terms of LS-means was about twice that of placebo. The treatment difference from placebo was statistically significant in both studies. The size of the treatment difference was 2.9 units (measured on an 11-point numerical scale) in Study 301 and 2.5 units in Study 302. The treatment differences are considered clinically meaningful.

Table 6-1 Results of the Primary Efficacy Measurements in Bunionectomy Pain Study 301 and 302

	Study 301			Study 302		
	Placebo	**DPSGC 25 mg**	**p-value**	**Placebo**	**DPSGC 25 mg**	**p-value**
	N = 99	N = 102		N = 101	N = 99	
LS-Mean	5.60	2.71		5.24	2.79	
Difference in LS-Means	2.89		< 0.0001	2.45		< 0.0001
95% CI for difference in LS-Means	2.43, 3.35			1.91, 2.99		

The primary efficacy endpoint in the two dental studies was the time-weighted sum of pain intensity differences over six hours post dose. The summed total pain score by itself is not considered sufficient in demonstrating single-dose efficacy because of the potential bias against the treatment group with early dropouts due to lack of efficacy and because of its potential representation of accumulation of small and non significant differences over time. It has been accepted as a primary efficacy parameter under the provision that the separation between pain curves (the curve formed by time-specific pain measurements) is also statistically significant and clinically meaningful. Also, the size of the treatment difference in summed pain score is difficult to interpret clinically due to a wide variation in its numerical value in different settings (i.e., the magnitude of summed pain score changes dramatically in studies of different medication using the same pain model or studies of the same medication using different pain models, etc.). The results of analyses of the primary efficacy assessments in the two dental studies are summarized in the same table as shown below. The treatment differences were statistically significant and the findings were further supported by the treatment differences shown in time-specific measurements as discussed in Section 5.3 and 6.6.

Table 6-2 Results of the Primary Efficacy Measurements in Dental Pain Studies 395 and 400

	DPSGC 25 mg	**DPSGC 50 mg**	**DPSGC 100 mg**	**Placebo**
Study 395	N=63	N=68	N=66	N=68
LSMean	4.30	5.37	7.85	0.36
Difference in LSMean from placebo	3.94	5.01	7.49	
Dunnett-adjusted P value	<0.0001	<0.0001	<0.0001	
Study 400	N=63	N=62	N=63	N=61
LSMean	4.12	5.94	6.29	-0.28
Difference in LSMean from placebo	4.4	6.22	6.57	
Dunnett-adjusted P value	<0.0001	<0.0001	<0.0001	

6.6 Secondary Endpoint(s)

The results of analyses of all of the secondary endpoint measurements in the two bunionectomy studies are summarized in terms of effects per treatment, size of the treatment differences, and p-values by three evaluation intervals: 48-hour inpatient period, 8-hour initial dose, and multiple-dose outpatient period in three tables following the discussion below.

In the 48-hour inpatient evaluation statistically significant treatment differences were demonstrated in pain intensity scores (time-specific PI measurements during the course of treatment, summation of PID, and peak PID), in major parameters used to measure dosing interval (daily and overall rescue interval and daily proportion of patients taking rescue), and in patient global evaluation.

The effect size of the statistically significant treatment difference in time-specific PI was around 3.5 units (on an 11-point scale) at most time points during the first 24 hours and 2.5 units during the second half of the 48-hour period in Study 301 and around 2.5 units during the 48-hour period in Study 302 (refer to Section 5.3 for details). The proportion of patients taking rescue was remarkably less in the DPSGC group than the placebo group, 49% less on the first day, 43% less on the second day, and 24% less up to discharge on the third day in Study 301 and 39% less on the first day, 37% less on the second day, and 15% less up to discharge on the third day in Study 302. Rescue interval was shown to be between 5-6 hours for DPSGC treatment, about an hour longer than placebo treatment in terms of overall rescue interval in both studies. The mean response in patient global assessment to the DPSGC treatment was between 'very good' and 'excellent' (a mean score of 4.2 on a scale of 1-5) in Study 301 and between 'good' and 'very good' (a mean score of 3.6) in Study 302. It was between 'fair' and 'good' (mean scores of 2.4 and 2.8) to the placebo treatment in the two studies. About 35% more DPSGC patients than placebo patients had 'good' to 'excellent' response in patient global assessment. The effect sizes of these treatment differences are all considered clinically meaningful.

The number of rescue doses used per day and the number of tablets per use among the rescue users were numerically less in the DPSGC group than the placebo group and the treatment differences in the number of tablets per use reached statistical significance. The difference in use pattern among rescue users in general, was not considered clinically meaningful.

Table 6-3 Secondary Endpoints: 48-Hour Inpatient in Bunionectomy Pain Studies 301 and 302

	Study 301				Study 302			
	Placebo	**DPSGC 25 mg**	**Effect size of txn diff**	**p-value**	**Placebo**	**DPSGC 25 mg**	**Effect size of txn diff**	**p-value**
Time-specific PI		0-48 hrs	1.72-3.73	**< 0.0001**		0-48 hrs	0.93-2.88	**< 0.0001**
SPID: LS-Mean	86.56	206.00	119.44	**< 0.0001**	86.13	202.96	116.83	**< 0.0001**
Peak PID: LS-Mean	5.15	6.47	1.33	**< 0.0001**	4.59	6.20	1.61	**< 0.0001**
Rescue use- proportion of patients (%)								
Day 1	87.9%	39.2%	**-48.7%**	**< 0.0001**	92.1%	53.5%	**-38.60%**	**< 0.0001**
Day 2	64.6%	21.6%	**-43.0%**	**< 0.0001**	67.3%	30.3%	**-37.00%**	**< 0.0001**
Day 3 (up to discharge)	29.3%	4.9%	**-24.4%**	**< 0.0001**	18.8%	4.0%	**-14.80%**	**0.0010**
Rescue use- # dosing among users: mean								
Day 1	2.37	1.93	-0.44	**0.0497**	2.52	1.79	-0.73	**< 0.0001**
Day 2	2.17	2.09	-0.08	0.7782	2.49	1.73	-0.76	**0.0017**
Day 3 (up to discharge)	1.07	1.00	-0.07	0.5591	1.16	1.00	-0.16	0.4172
Rescue use- # tablets among users: mean								
Day 1	3.78	3.03	-0.75	0.0553	3.85	2.55	-1.3	**< 0.0001**
Day 2	3.28	2.95	-0.33	0.4710	3.72	2.37	-1.35	**0.0015**
Day 3 (up to discharge)	1.62	1.40	-0.22	0.4962	1.79	1.00	-0.79	0.0842
Rescue interval, LS-mean (min)								
Overall	258.77	**325.77**	67.00	**< 0.0001**	255.54	**324.86**	69.32	**< 0.0001**
Day 1	193.59	**300.36**	106.77	**< 0.0001**	184.11	**287.50**	103.39	**< 0.0001**
Day 2	288.74	**336.44**	47.70	**< 0.0001**	277.57	**334.83**	57.26	**< 0.0001**
Day 3 (up to discharge)	312.78	**347.27**	34.49	**0.0001**	331.73	**357.42**	25.69	**0.0003**
Patient global at discharge								
-mean response	2.84	4.23	1.39	**< 0.0001**	2.38	3.60	1.22	**< 0.0001**
-% as 'good' to 'excellent'	58.6%	92.2%	33.6%		42.6%	78.8%	36.2%	

In the 8-hour inpatient evaluation of the initial dose, statistically significant treatment differences were demonstrated in pain scores (time-specific pain measurements in PID and PR during the course of treatment, summation of PID and PR, and peak PR), onset of meaningful relief (proportion with meaningful relief and median time to meaningful relief), single-dose duration (median time to remedication), and proportion of responders defined by all three criteria used in the responder analyses including the proportion achieving ≥30% pain reduction, the proportion achieving clinically significant efficacy (defined as having both ≥ 30% reduction of baseline pain and meaningful relief by stopwatch), and the proportion experiencing mild to no pain after the initial dose.

The effect size of the statistically significant treatment difference was ≥1 unit in time-specific PID (PI measured on a 4-point scale) and ≥0.5 units in time-specific PR (measured on a 5-point scale) at most time points of the 8-hour interval in the two studies. There were 13% more patients in the DPSGC group than the placebo group reporting the onset of perceptible pain relief in Study 301 and 10% more in Study 302, though the median time to onset of perceptible relief was within one hour for all the treatment groups in the two studies. At least 20% more patients in the DPSGC group than the placebo group reported the onset of meaningful pain relief in both studies. The median time to onset of meaningful relief was within 1.5 hours for the DPSGC treatment and was 36 minutes shorter than that of placebo treatment in Study 301. Analgesic duration of the initial dose measured by median time to remedication was close to three hours for the DPSGC treatment and about twice of that of placebo treatment. About 20% more patients in the DPSGC group than the placebo group were classified as responders based on each of the three criteria used in the responder analyses (refer to the last paragraph) in both studies. The effect sizes of most of these statistically significant treatment differences are considered clinically meaningful.

Table 6-4 Secondary Endpoints: 8-Hour Initial Dose in Bunionectomy Pain Studies 301 and 302

	Study 301				**Study 302**			
	Placebo	**DPSGC 25 mg**	**Effect size of txn diff**	**p-value**	**Placebo**	**DPSGC 25 mg**	**Effect size of txn diff**	**p-value**
Diff in Time-Specific PID		2.5, 4-8 hrs	1.0-1.6	**< 0.05**		2.5-6 hrs	0.9-1.6	**< 0.05**
Diff in Time-Specific PR		1-8 hrs	0.6-1.0	**< 0.005**		2-8 hrs	0.3-0.8	**< 0.05**
Mean SPID: LS-mean	3.83	11.40	7.57	**< 0.0001**	2.64	9.07	6.43	**< 0.0001**
Mean TOTPAR: LS-mean	2.47	7.98	5.51	**< 0.0001**	1.97	5.94	3.98	**< 0.0001**
Peak pain relief: mean	1.44	2.19	0.75	**0.0006**	1.15	1.68	0.53	**0.0094**
Onset								
-Proportion with perceptible PR (%)	69.7%	82.4%	12.7%	**0.0380**	62.4%	72.7%	10.3%	0.1480
-Median time to perceptible PR (min)	22.18	26.01	3.83	0.2348	35.99	42.90	6.91	0.6733
-Proportion with meaningful PR (%)	35.4%	56.9%	**21.5%**	**0.0025**	29.7%	50.5%	**20.8%**	**0.0031**
-Median time to meaningful PR (min)	106.30	70.22	-36.08	**0.0080**	NC	90.63	NC	**0.0351**
Duration								
Median time to re-medication (min)	80.00	156.50	76.5	**< 0.0001**	96.00	177.00	81	**< 0.0001**
Responder analyses								
1. Achieving ≥30% pain reduction Proportion	40.4%	60.8%	**20.4%**	**0.0043**	30.7%	51.5%	**20.8%**	**0.0034**
Median time to onset of (min)	150	60	-90	**0.0376**	300.00	110.00	-190	**0.0259**
Mean duration of (min): LS-mean	137.64	220.14	82.51	**0.0132**	120.46	227.31	106.85	**0.0008**
2. Proportion achieving clinically significant efficacy after 1st dose (%)	29.3%	52.9%	**23.6%**	**0.0008**	25.7%	47.5%	**21.80%**	**0.0014**
3. Proportion experiencing mild to no pain after 1st dose (%)	23.2%	44.1%	**20.9%**	**0.0019**	12.9%	32.3%	**19.40%**	**0.0010**

The results of the multiple-dose evaluation in the outpatient period showed a similar pattern as that of the inpatient evaluation. The effect sizes of all statistically significant treatment differences were decreasing with the length of treatment. There were still at least a quarter less patients in the DPSGC group than the placebo group taking rescue during the third and fourth day of treatment.

Table 6-5 Secondary Endpoints: Multiple-Dose Outpatient in Bunionectomy Pain Studies 301 and 302

	Study 301				Study 302			
	Placebo	**DPSGC 25 mg**	**Effect size of txn diff**	**p-value**	**Placebo**	**DPSGC 25 mg**	**Effect size of txn diff**	**p-value**
Mean average PI								
Day 3 (after discharge)	3.18	1.41	-1.77	**< 0.0001**	3.66	2.08	-1.58	**< 0.0001**
Day 4	2.51	1.23	-1.28	**< 0.0001**	3.24	1.86	-1.38	**< 0.0001**
Day 5	1.96	1.16	-0.8	**0.0011**	2.69	1.58	-1.11	**0.0002**
Rescue use- proportion of patients (%)								
Day 3 (after discharge)	39.4%	12.7%	**-26.7%**	**< 0.0001**	52.5%	14.1%	**-38.40%**	**< 0.0001**
Day 4	38.4%	9.8%	**-28.6%**	**< 0.0001**	46.5%	22.2%	**-24.30%**	**0.0003**
Day 5	9.1%	6.9%	-2.2%	0.5502	14.9%	1.0%	-13.90%	**0.0003**
Rescue use- # dosing among users: mean								
Day 3 (after discharge)	1.46	1.62	0.16	0.4595	1.83	1.64	-0.19	0.4220
Day 4	1.92	2.30	0.38	0.3340	1.74	1.41	-0.33	0.1753
Day 5	1.44	1.57	0.13	0.8167	1.40	1.00	-0.4	0.4577
Rescue use- # tablets among users: mean								
Day 3 (after discharge)	1.85	2.00	0.15	0.6755	2.55	1.93	-0.62	0.1250
Day 4	2.39	2.30	-0.09	0.8313	2.38	1.77	-0.61	0.1274
Day 5	1.67	1.57	-0.1	0.8610	2.20	1.00	-1.2	0.2373
Patient global at discharge								
-mean response	2.77	4.28	1.51	**< 0.0001**	2.47	3.71	1.24	**< 0.0001**
-% as 'good' to 'excellent'	57.5%	91.2%	33.7%		45.6%	79.8%	34.2%	

The results of analyses of all secondary endpoint measurements in the single-dose studies are summarized in terms of effects per treatment, effect sizes of treatment differences, and p-values for each of the two dental studies as shown in the tables below.

Statistically significant treatment differences were demonstrated in pain scores (time-specific pain measurements of PID and PR during the course of treatment and summation of PID and PR over three and six hours), onset of relief (median time to perceptible and meaningful relief), single-dose duration (median time to rescue medication), and patient global assessment.

The effect size of the statistically significant treatment difference was ≥1 unit in time-specific PID (PI measured on a 4-point scale) and ≥0.5 units in time-specific PR (measured on a 5-point scale) at most time points of the 6-hour interval in the two studies. Greater proportions of patients in the DPSGC groups than the placebo group reported onset of pain relief: at least 22% more in Study 395 and at least 35% more in Study 400 reported perceptible relief; at least 56% more in Study 395 and at least 53% more in Study 400 reported meaningful relief. Median time to onset of perceptible relief was within 30 minutes for all the treatment groups including placebo. Median time to onset of meaningful relief was within one hour for all the DPSGC groups in both studies versus more than four hours for the placebo group in Study 395 (not calculable in Study 400). In comparison to the placebo group, less patients in the DPSGC groups requested rescue medication: 27% less at 25 mg, 41% less at 50 mg, and 46% less at 100 mg in Study 395; 18% less at 25 mg, 37% less at 50 mg, and 32% less at 100 mg in Study 400. The proportion taking rescue appeared to be different between the 25 mg dose and the two higher doses. The duration measured by median time to rescue medication for DPSGC 25 mg treatment was about six hours in Study 395 and about five hours in Study 400 in comparison to less than two hours for the placebo treatment in both studies. The mean response in patient global assessment to the DPSGC treatments was between 'good' and 'very good' (mean scores of 2.1 to 3.1 on a scale of 0-4) and between 'poor' and 'fair' (mean scores of 0.65 and 0.82) to the placebo treatment in the two studies. More DPSGC patients than placebo patients had 'good' to 'excellent' response in patient global assessment, 47% more at 25 mg, about 60% more at 50 mg, and about 70% more at 100 mg, and the response appeared to be dose-related. The effect sizes of most treatment differences are considered clinically meaningful.

Table 6-6a Secondary Endpoints: Single Dose (6-Hour Evaluation) in Dental Pain Study 395

Study 395	Treatment effects				Effect size of Treatment differences (p-value)		
Secondary efficacy parameters	**Placebo**	**25mg**	**50mg**	**100 mg**	**25mg**	**50mg**	**100 mg**
Diff in Time-Specific PID	(Time	0.75-5h	0.75-6h	0.5-6h	0.4-1.5 (**<0.05**)	0.5-1.4 (<0.005)	0.4-1.8 (<0.005)
Diff in Time-Specific PR	points)	0.5-6h	0.5-6h	0.5-6h	0.5-2.1 (**<0.05**)	0.5-2.3 (<0.005)	0.7-2.6 (<0.0005)
$SPID_{0-3}$, LSMean	0.13	3.03	3.19	4.22	2.79 (<**0.0001**)	2.78 (<0.0001)	3.89 (<0.0001)
$TOTPAR_{0-3}$, LSMean	2.38	6.80	7.39	8.39	4.42 (**<0.0001**)	5 (<0.0001)	6 (<0.0001)
$TOTPAR_{0-6}$, LSMean	4.98	11.67	13.87	16.16	6.69 (**<0.0001**)	8.87 (<0.0001)	11.17 (<0.0001)
Onset							
-Proportion with perceptible PR (%)	72.1	93.7	94.1	98.5	**21.6**	**22**	**26.4**
-Median time to perceptible PR (min)	24.5	22.0	22.5	19.5	-2.5 (**0.0022**)	-2 (0.0024)	-5 (<0.0001)
-Proportion with meaningful PR (%)	26.5	82.5	86.8	93.9	**56**	**60.3**	**67.4**
-Median time to meaningful PR (min)	242.0	45.0	53.0	43.0	-197 (<**0.0001**)	-189 (<0.0001)	-199 (<0.0001)
Duration							
-Proportion taking rescue (%)	77.9	50.8	36.8	31.8	**-27.1**	**-41.1**	**-46.1**
-Median time to rescue (min)	100.0	**350**.0	NC	NC	**250**.0 (**<0.0001**)	NC (<0.0001)	NC (<0.0001)
Patient Global Assessment, LSMean	0.82	2.22	2.65	3.06	1.40 (**<0.0001**)	1.83 (<0.0001)	2.24 (<0.0001)
Response as 'good' to 'excellent', %	21.0%	68.3%	83.8%	94.0%	47.3%	62.8%	73.0%

Table 6-6b Secondary Endpoints: Single Dose (6-Hour Evaluation) in Dental Pain Study 400

Study 400	Treatment effects				Effect size of Treatment differences (p-value)		
Secondary efficacy parameters	Placebo	25mg	50mg	100 mg	25mg	50mg	100 mg
Diff in Time-Specific PID	(Time	0.5-5h	0.5-6h	0.5-6h	0.4-1.5 (**<0.05**)	0.5-1.4 (<0.05)	0.4-1.8 (≤0.001)
Diff in Time-Specific PR	points)	0.5-6h	0.25-6h	0.25-6h	0.5-2.1 (**<0.005**)	0.5-2.3 (<0.05)	0.7-2.6 (<0.05)
$SPID_{0-3}$, LSMean	-0.04	2.75	3.37	3.62	2.83 (**<0.0001**)	3.46 (<0.0001)	3.74 (<0.0001)
$TOTPAR_{0-3}$, LSMean	2.26	6.28	7.17	7.50	3.99 (**<0.0001**)	4.86 (<0.0001)	5.17 (<0.0001)
$TOTPAR_{0-6}$, LSMean	4.54	11.22	13.48	14.13	6.61 (**<0.0001**)	8.86 (<0.0001)	9.47 (<0.0001)
Onset							
-Proportion with perceptible PR (%)	57.4	96.8	91.9	96.8	**39.4**	**34.5**	**39.4**
-Median time to perceptible PR (min)	30.0	25.0	17.0	21.0	-5 (**0.0002**)	-13 (<0.0001)	-9 (<0.0001)
-Proportion with meaningful PR (%)	27.9	81.0	83.9	85.7	**53.1**	**56**	**57.8**
-Median time to meaningful PR (min)	NC	52.0	47.5	52.0	NC (**<0.0001**)	NC (<0.0001)	NC (<0.0001)
Duration							
-Proportion taking rescue (%)	72.1	54.0	35.5	39.7	**-18.1**	**-36.6**	**-32.4**
-Median time to rescue (min)	95.0	**303**.0	NC	NC	**208**.0 (**<0.0001**)	NC (<0.0001)	NC (<0.0001)
Patient Global Assessment, LSMean	0.65	2.08	2.51	2.84	1.43 (**<0.0001**)	1.86 (<0.0001)	2.19 (<0.0001)
Response as 'good' to 'excellent', %	18.3%	65.1%	75.4%	82.5%	46.8%	57.1%	65.2%

The results of the arthroscopy studies did not support single-dose efficacy. Statistically significant treatment differences in overall proportions taking rescue and time-specific three times a day patient global assessment during Days 2-5 in study 401 suggested some multiple-dose effects.

6.7 Subpopulations

Subpopulation analyses of efficacy in acute pain studies were limited by the sample size and the demographic composition associated with the pain model used in the study. The two studies of post bunionectomy pain had mainly female patients. There were less than 15 male patients per treatment group in each study, too few to analyze gender difference. The single-dose dental studies had about 30 patients per gender per treatment group on average. The sample size was again too small for subpopulation analyses of gender difference. The maximum age was 65 years in the bunionectomy studies. Dental studies involved patients younger than 47 years of age. There were no patients aged greater than 65 years in any of the four efficacy studies to provide database for subgroup analyses with respect to elderly status.

6.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The proposed dosing interval of six hours was supported mainly by demonstration of analgesic duration of 5-6 hours measured by rescue interval in the 48-hour multiple-dose evaluation and by time to rescue in single-dose

dental studies, and supported further by showing treatment differences in pain measurements targeted at mid and end of dosing effects in bunionectomy studies and in proportions taking rescue in bunionectomy and dental studies.

Different DPSGC dose levels were included in single-dose dental studies (25, 50, and 100 mg) and multiple-dose knee arthroscopy studies (25 and 50 mg) with no predefined analysis of dose response. Nevertheless, dose response was suggested by the trend of increase in treatment effects with increasing dose in a number of efficacy parameters.

6.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The persistence of efficacy and/or tolerance effects could not be adequately assessed in acute analgesic studies because acute pain resolves spontaneously in a relatively short period and leaves only a small window of opportunity for demonstration of treatment effects.

6.10 Additional Efficacy Issues/Analyses

None.

7. INTEGRATED REVIEW OF SAFETY

Summary of Safety Results and Conclusions

The safety database contains safety data from 12 clinical studies including four Phase 1 single-dose PK studies and three single-dose and five multiple-dose Phase 2 and 3 studies.

A total of 1114 subjects were exposed to the Diclofenac Potassium Soft Gel Capsules (DPSGC), including 149 healthy volunteers exposed to DPSGC 25 mg and/or 50 mg in Phase 1 studies and 965 patients exposed to DPSGC 25 mg, 50 mg, or 100 mg in Phase 2/3 studies. The multiple-dose exposure to DPSGC was reported in 483 patients with the longest exposure to 25 mg or 50 mg QID or TID dosing for 4-5 days in 451 patients and TID dosing for 5-8 days in 17 patients.

The study population of the Phase 2/3 studies consisted of 97% non-elderly patients, about 2/3 were female, and about 3/4 were Caucasian.

There were no reports of death. Three patients had serious nonfatal AEs, including one patient treated with DPSGC 50 mg for five days who developed deep venous thrombosis and joint effusion, one placebo patient with arthralgia, and one placebo patient with deep venous thrombosis. None of the serious AEs were considered treatment-related. Early discontinuation due to AEs were reported in five cases: a case of rash with DPSGC 25 mg treatment, a case of nervousness and anxiety with DPSGC 50 mg treatment, and three cases of each of the following: headache, headache/nausea, and muscle spasm, in the placebo group.

The most commonly reported AEs were GI symptoms including abdominal pain, nausea, and vomiting and nervous system symptoms including headache and dizziness. The incidence of AEs was low (<15%) in the single-dose studies and similar across treatment groups (DPSGC 25, 50, and 100mg and placebo) in terms of individual symptoms, organ systems involved, and proportion of patients with any AEs. The multiple-dose exposure was associated with a much higher incidence of AEs than the single-dose exposure in all the treatment groups including placebo, which could be explained by many factors associated with a particular type of surgical procedure used in a study. The proportions reporting AEs in general and reporting individual events in particular were mostly similar between the treatment groups or somewhat higher in the placebo group than the active treatment groups (DPSGC 25 and 50 mg). The noticeably higher rates of AE reports in the DPSGC groups than the placebo group were abdominal pain and elevation of liver enzymes.

The results of liver function tests revealed dose-related increases in ALT (7% on placebo, 10% on DPSGC 25 mg, and 12% on DPSGC 50 mg) and AST (3% on placebo, 8% on DPSGC 25 mg, and 10% on DPSGC 50 mg) from normal baseline to above the Upper Limit of Normal range (ULN) at follow up. Six patients treated with DPSGC 25 mg had liver enzyme elevation of ≥3 x ULN (four had increase in ALT from normal baseline and two had increase in ALT and/or AST from above normal baseline). One patient treated with DPSGC 50 mg had elevations of both ALT and AST to ≥3 x ULN from normal baseline. There were no reports of associated increase in total bilirubin. Spontaneous resolution was reported in those who had follow up laboratory tests. There were no reports of liver enzyme elevation to >8 x ULN.

The analyses of vital signs showed decreases in the group mean systolic and diastolic blood pressure in all treatment groups. Individual cases of BP elevation were reported as AEs for two patients in each of the three DPSGC treatment groups and four placebo patients.

Data from subpopulation analyses did not suggest treatment differences with respect to gender or race. Safety data on elderly were limited since only 39 patients enrolled were in the age range of 65 years or above. Limited

exposure in pediatric patients at ages 8 to 16 years in a small (about 50 per group), single-dose, uncontrolled study of dose response between 25 and 50 mg doses showed higher proportion of any AE, more CNS AEs, and less GI AEs in pediatric patients than adult patients based on cross study comparison of single-dose safety data.

Based on the review of safety data there were no new safety issues or signals identified. The DPSGC treatment-related findings were GI irritation and elevation of liver enzymes, known to be associated diclofenac treatment. The use of DPSGC 25 mg four times a day for 4-5 days is considered relatively safe.

7.1 Method

The safety of Cataflam at a single dose of up to 100 mg and multiple doses of up to 200 mg per day during long-term use has already been studied extensively with an established safety profile described in the product labeling of the approved diclofenac oral formulations. Safety information applicable to some of the subsections of the safety review can be found in the product labeling of the approved diclofenac oral formulations. Although the amount of active ingredient in DPSGC 25 mg is only half of the amount of diclofenac in Cataflam® 50 mg, which is the dosage recommended for a pain indication, the maximum concentration (Cmax) associated with a single dose of DPSGC 25 mg is close to that of Cataflam® 50 mg. The total exposure (AUC) to DPSGC 25 mg is half of the exposure to Cataflam® 50 mg. The safety review is focused on the short-term use for up to 5 days of the DPSGC treatment at 25 mg level as proposed by the Applicant.

7.1.1 Discussion of Clinical Studies Used to Evaluate Safety

There were 12 clinical studies in the NDA submission including six efficacy studies discussed in Sections 5 and 6, two Phase 2 studies, and four Phase 1 PK studies. Safety data from all 12 studies were used to evaluate safety.

7.1.2 Adequacy of Data

The safety exposure included any exposure to DPSGC in 1114 subjects, to the 25 mg dose in 620 subjects, and multiple-dose exposure to 25 and 50 mg doses for four to five days in 451 patients. Therefore, the database is considered adequate for this 505(b)(2) application.

7.1.3 Pooling Data across Studies to Estimate and Compare Incidence

The data were pooled across studies and were organized in terms of single-dose versus multiple-dose drug administration to evaluate AEs associated with the length of exposure. The data were also pooled and organized by dose levels to assess dose response in adverse events (AEs).

7.2 Adequacy of Safety Assessments

Safety assessments in the current submission are considered adequate based on data on relative bioavailability, the number of patients exposed to single and/or multiple dosing, and the type and amount of safety monitoring during the study.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

As summarized in the table below the overall exposure to at least one dose of DPSGC was reported in 1114 subjects, including 620 subjects exposed to DPSGC 25 mg, 419 subjects exposed to DPSGC 50 mg, and 129 subjects exposed to DPSGC 100mg.

Table 7-1 Exposure by Dose Levels

	Number of patients exposed

	Placebo	Diclofenac liquid		DPSGC			Cataflam	Total
		12.5 mg	25 mg	**25 mg**	**50 mg**	**100mg**	50mg	
Phase 2 & Phase 3 studies								
301	99			**102**				201
302	101			**99**				200
396	62			**67**	**61**			190
401	65			**64**	**63**			192
2000		14		**13**	**14**		12	53
395	68			**63**	**68**	**66**		265
400	61			**63**	**62**	**63**		249
424				**47**	**50**			97
Subtotal	456	14		**518**	**318**	**129**	12	1447
Phase 1 PK studies								
142					**24**		24	24
119				**24**	**23**			47
170				**54**	**54**		54	54
171			24	**24**				24
Subtotal			24	**102**	**101**		78	149
Total	*456*	*14*	*24*	***620***	***419***	***129***	*90*	1596

Five of the 12 studies had patients receive repeated exposure to DPSGC including 201 patients exposed to 25 mg every six hours, and 144 patients exposed to 25 mg and 138 patients exposed to 50 mg every eight hours as shown in the table below. At least 90% (451/483) patients had exposure to either QID or TID dosing with DPSGC for at least four to five days (180/201 on QID dosing in Studies 301 and 302 and 271/282 on TID dosing in Studies 396, 401, and 2000).

Table 7-2 Exposure by Duration in the Multiple-Dose Studies

	Number of patients exposed				
	Placebo	Dic liquid	DPSGC		Cataflam
		12.5 mg	**25 mg**	**50 mg**	50mg
QID dosing	N=200		**N=201**		
1-5	7		**2**		
6-10	2		**2**		
11-15	10		**16**		
16-20	163		**164**		
>20	18		**16**		
TID dosing	N=126	N=14	***N=144***	***N=138***	N=12
1-5	2		***4***	***4***	
6-10	1		***2***	***1***	
11-15	123		***125***	***119***	
16-20		2	***1***	***0***	
21-25		12	***12***	***14***	12
Total	326	14	***345***	***138***	

The demographic characteristics of patients in Phase 2 and 3 studies are summarized in the table below. Except for 39 patients who were age 65 years or older, more than 97% (1382/1421) of the study population were non-elderly patients. Female patients accounted for one half to two thirds of the entire Phase 2/3 study population and represented an overwhelming majority in the bunionectomy studies. About three fourths of patients were Caucasian.

Table 7-3 Demographics for DPSGC and Placebo Patients by Dose Level

	DPSGC 25 mg	**DPSGC 50 mg**	**DPSGC 100 mg**	**Placebo**	**Total**
	N=518	**N=318**	**N=129**	**N=456**	**1421**
Age (years)					
mean (SD)	36.2 (15.6)	30.9 (15.8)	22.9 (4.4)	37.9 (14.6)	
Age Group (n/%)					

<18	47 (9.1)	50 (15.7)	0	0	
18-40	261 (50.4)	183 (57.5)	127 (98.4)	250 (54.8)	
41-64	196 (37.8)	73 (23.0)	2 (1.6)	193 (42.3)	
65-75	13 (2.5)	7 (2.2)	0	11 (2.4)	31
>75	1 (0.2)	5 (1.6)	0	2 (0.4)	8
Gender (n/%)					
Male	181 (34.9)	164 (51.6)	48 (37.2)	164 (36.0)	
Female	337 (65.1)	154 (48.4)	81 (62.8)	292 (64.0)	
Race (n/%)					
White	381 (73.6)	244 (76.7)	95 (73.6)	312 (68.4)	
Black	63 (12.2)	34 (10.7)	11 (8.5)	59 (12.9)	
Hispanic	50 (9.7)	23 (7.2)	12 (9.3)	63 (13.8)	
Asian/ Pacific Islander	15 (2.9)	12 (3.8)	9 (7.0)	14 (3.1)	
American Indian/Alaskan Native	0	2 (0.6)	1 (0.8)	2 (0.4)	
Other	9 (1.7)	3 (0.9)	1 (0.8)	6 (1.3)	
Height (cm) Mean (range)	168.0 (122-206)	170.1 (130-198)	168.4 (145-198)	169.0 (144-198)	
Weight (kg) Mean (range)	75.0 (29-146)	76.0 (23-150)	71.1 (44-136)	78.2 (45-170)	

Source: Table 2.7.4-6 on page 9 of the clinical safety summary report

7.2.2 Explorations for Dose Response

The Applicant has no intension to market doses higher than 25 mg in the current submission and did not include higher doses in most of the multiple-dose studies (345 patients had multiple-dose exposure to 25 mg versus 138 to 50mg and none to 100 mg in the studies of repeated dosing). Therefore, dose response in safety could not be well characterized using such a limited database.

7.2.3 Special Animal and/or In Vitro Testing

Toxicology studies to address safety concerns with three impurities exceeding the ICH qualification threshold are still pending (refer to Section 4 of this review).

7.2.4 Routine Clinical Testing

Safety monitoring consisted of mainly AE reporting and laboratory tests and is considered adequate in the studies of DPSGC 25 mg dose of several days in duration.

7.2.5 Metabolic, Clearance, and Interaction Workup

The relative bioavailability data are available for bridging the known safety information on the active ingredient.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The potential AEs associated with the NSAID drug class were measured by monitoring of GI events, measurement of blood pressure and heart rates, and laboratory tests of liver and renal function.

7.3 Major Safety Results and Discussion

7.3.1 Deaths

There were no deaths reported in any of the 12 clinical studies. (b) (4)

7.3.2 Nonfatal Serious Adverse Events

Nonfatal serious adverse events (AEs) were reported in three patients in the overall safety database, one case of deep venous thrombosis and joint effusion in a patient on diclofenac and one case of arthralgia and one case of deep venous thrombosis in patients on placebo. The first case was reported in a 43 years old female who had past injury to her right knee and received five days of treatment with DPSGC 50 mg after knee surgery (medial meniscus repair, debridement of femoral/tibial grade 2 chondromalacia, and plicectomy). She had severe pain and swelling in her right calf on the fourth day of DPSGC treatment and then was diagnosed as having deep venous thrombosis and hospitalized for the treatment of the condition. The event resolved at the follow up visit. She had also moderately severe joint effusion, which had not resolved at the end of the study. Neither event was considered attributable to DPSGC treatment.

7.3.3 Dropouts and/or Discontinuations

Only five patients, three on DPSGC and two on placebo, in three of the 12 clinical studies discontinued early due to adverse events. One patient on DPSGC 25 mg in Study 302 discontinued early due to rash after receiving six doses of study medication. The event resolved spontaneously on the same day. One patient on DPSGC 50 mg in Study 401 stopped taking the study medication on the second day because of moderately severe nervousness and anxiety, which resolved in two days. A 15 years old female in the pediatric study, Study 424, developed moderate headache before the 6-hour assessment after a single dose of DPSGC 50 mg. Her headache responded to acetaminophen. One placebo patient dropped out from Study 401 due to nausea and headache and one dropped out from Study 302 due to muscle spasm.

7.3.4 Significant Adverse Events

No significant AEs have been identified in the safety database.

7.3.5 Submission Specific Primary Safety Concerns (optional)

None.

7.4 Supportive Safety Results and Discussion

7.4.1 Common Adverse Events

Adverse events (AEs) reported in adult studies are summarized by treatment group and presented in two separate tables, one for AEs associated with single-dose exposure and one for AEs associated with multiple-dose exposure. In patients treated with a single dose of study medication only less than 15% reported any AE. The type and rate of AEs were similar in all four treatment groups as shown in the table below. The data did not suggest treatment differences between diclofenac treatments and placebo or a dose response with increasing DPSGC dose levels.

Table 7-4 Treatment Emergent AEs in Single-Dose Dental Studies in Adults

System Organ Class Preferred Term	DPSGC 25 mg	DPSGC 50 mg	DPSGC 100 mg	Placebo
	N=126	N=130	N=129	N=129
Number of patients with any AE (%)	15 (11.9)	13 (10.0)	12 (9.3)	16 (12.4)

Cardiac Disorders	0	0	0	2 (1.6)
Tachycardia NOS	0	0	0	2 (1.6)
Gastrointestinal Disorders	8 (6.3)	8 (6.2)	5 (3.9)	7 (5.4)
Abdominal Pain upper	1 (0.8)	0	0	1 (0.8)
Nausea	6 (4.8)	5 (3.8)	4 (3.1)	4 (3.1)
Nausea postoperative	0	0	0	1 (0.8)
Pharyngolaryngeal pain	0	1 (0.8)	0	0
Vomiting NOS	5 (4.0)	4 (3.1)	4 (3.1)	4 (3.1)
Investigations	2 (1.6)	3 (2.3)	2 (1.6)	2 (1.6)
Blood Pressure Increased	2 (1.6)	2 (1.5)	2 (1.6)	2 (1.6)
Heart rate increased	0	1 (0.8)	0	0
Nervous System Disorders	6 (4.8)	2 (1.5)	5 (3.9)	6 (4.7)
Dizziness (excl vertigo)	1 (0.8)	0	1 (0.8)	2 (1.6)
Headache NOS	5 (4.0)	2 (1.5)	4 (3.1)	4 (3.1)
Skin & Subcutaneous Tissue Disorders	1 (0.8)	0	0	2 (1.6)
Rash NOS	0 (0)	0	0	1 (0.8)
Sweating Increased	1 (0.8)	0	0	1 (0.8)

Source: Table 10 on page 59 of the report for study 395 and Table 10 on page 60 of the report for study 400

In the multiple-dose studies the most commonly reported AEs were GI symptoms such as abdominal pain (7% in the DPSGC 25 mg group and 10% in the DPSGC 50 mg group), nausea (17% in the 25 mg group and 12% in the 50 mg group), and vomiting (6% in the 25 mg group and 3% in the 50 mg group), and symptoms of nervous system such as headache (13% in each of the two DPSGC groups) and dizziness (4% in the 25 mg group and 6% in the 50 mg group). Comparing DPSGC 25 mg to placebo treatment, the reporting rates for any AE, for organ systems, and for individual events were either similar between the two groups or lower in the DPSGC 25 mg group for most of the AEs. The only remarkably higher AEs associated with DPSGC treatments than placebo were abdominal pain and liver enzyme increased as highlighted in the table below. They appeared to be dose-related as well.

Table 7-5 Treatment Emergent AEs in ≥1% of DPSGC Treated Patients in Multiple-Dose Studies

	DPSGC 25 mg	**DPSGC 50 mg**	**Placebo**
	N=345	**N=138**	**N=327**
Patients with any AE, n (%)	144 (41.7)	69 (50.0)	181 (55.4)
Gastrointestinal Disorders	100 (29.0)	40 (29.0)	114 (34.9)
Abdominal Pain	***24 (7.0)***	***14 (10.1)***	***11 (3.4)***
Constipation	11 (3.2)	5 (3.6)	9 (2.8)
Diarrhea	8 (2.3)	6 (4.3)	9 (2.8)
Dry Mouth	3 (0.9)	3 (2.2)	6 (1.8)
Dyspepsia	4 (1.2)	3 (2.2)	8 (2.4)
Flatulence	3 (0.9)	2 (1.4)	2 (0.6)
Loose Stools	0 (0.0)	3 (2.2)	0 (0.0)
Nausea	57 (16.5)	16 (11.6)	66 (20.2)
Vomiting	20 (5.8)	4 (2.9)	26 (8.0)
General & Administrative Site Disorders	9 (2.6)	7 (5.1)	25 (7.6)
Pyrexia	1 (0.3)	3 (2.2)	10 (3.1)
Investigations	8 (2.3)	7 (5.1)	12 (3.7)
Alanine Aminotransferase Increase	***3 (0.9)***	***6 (4.3)***	***2 (0.6)***
Aspartate Aminotransferase Increase	***2 (0.6)***	***3 (2.2)***	***1 (0.3)***
Gamma-glutamyltransferase Increase	0 (0.0)	2 (1.4)	1 (0.3)
Musculoskeletal and Connective Tissue Disorders	9 (2.6)	5 (3.6)	26 (8.0)
Muscle Cramps	1 (0.3)	3 (2.2)	1 (0.3)
Nervous System Disorders	62 (18.0)	25 (18.1)	77 (23.5)
Dizziness	12 (3.5)	8 (5.8)	17 (5.2)
Headache	43 (12.5)	18 (13.0)	56 (17.1)
Somnolence	9 (2.6)	1 (0.7)	6 (1.8)
Psychiatric Disorders	13 (3.8)	5 (3.6)	11 (3.4)
Nervousness	1 (0.3)	2 (1.4)	0 (0.0)

Skin and Subcutaneous Tissue Disorders	14 (4.1)	6 (4.3)	19 (5.8)
Pruritus	5 (1.4)	4 (2.9)	6 (1.8)
Sweating Increase	4 (1.2)	1 (0.7)	2 (0.6)

Note: Data from 13 patients treated with diclofenac 25 mg in Study 2000 were pooled together with the 201 patients from the two larger bunionectomy trials. The other three treatment groups with 12 to 14 patients per treatment group in Study 2000 were not included in the table because of small sample size. The most frequent AEs reported in Study 2000 were nausea, vomiting, headache, and somnolence. There were two cases of bradycardia in patients treated with diclofenac 12.5 mg liquid.
Source: Table 14.3.1 on pages 120-123 of the report for study 396; Table 14.3.1 on pages 136-139 of the report for study 401; Table 14.3.1.1 on pages 318-320 of the report for study 301; Table 14.3.1.1 on pages 327-332 of the report for study 302; Table 8 on page 73 of the report for study 2000; Table 2.7.4-9 on page 13 of the clinical safety summary report.

7.4.2 Laboratory Findings

The increase in liver enzymes from a normal baseline value to a value above the Upper Limit of Normal (ULN) range at follow-up was summarized by treatment groups for the multiple-dose studies. DPSGC 25 mg and 50 mg treatments were associated with a higher incidence of liver enzyme elevation than placebo. The trend suggested a dose response. Four patients treated with DPSGC 25 mg in bunionectomy studies had an elevation of ALT ≥3 x ULN from normal baseline with no associated increase in total bilirubin. Three of the four cases had ALT levels returned back to normal at the additional laboratory follow up and one refused to return to the clinic for a repeated test. In knee arthroscopy studies two patients treated with DPSGC 25 mg had an elevation of ALT and/or AST ≥3 x ULN from already elevated (above normal) baseline values. One patient on DPSGC 50 mg group had an elevation of ALT and AST to ≥3 x ULN from normal baseline. None were associated with an increase in total bilirubin. The follow up laboratory tests were not required by the protocol. There were no reported cases of liver enzyme elevation to >8 x ULN.

Table 7-6 Frequency and Percentage of Patients with Increase in ALT and AST (from a Normal Baseline Value to a Value above ULN at Follow-up) by Dose Level in the Multiple Dose Studies

Liver Function Test	DPSGC 25 mg	DPSGC 50 mg	Placebo
Alanine Aminotransferase increase, n (%)	34/337 (10.1)	15/131 (11.5)	22/317 (6.9)
Aspartate Aminotransferase increase, n (%)	28/339 (8.3)	13/134 (9.7)	11/319 (3.4)

Reference: Table 5.3.5.3.2.29.
Source: Table 2.7.4-12 on page 21 of the clinical safety summary report.

Treatment differences in other laboratory tests in terms of greater percentages of DPSGC treated patients than placebo with an increase from normal baseline to above normal values at follow up were seen in eosinophils, leukocytes, lymphocytes, monocytes, and potassium, reflecting minor variations not of clinical significance.

Table 7-7 Summary of Laboratory Tests Shifts from Normal to Above Normal (DPSGC>Placebo) in Phase II/III Studies

Laboratory Test	DPSGC 25 mg	DPSGC 50 mg	Placebo
Eosinophils, n (%)	9/340 (2.6)	5/135 (3.7)	4/318 (1.3)
Leukocytes, n (%)	14/342 (4.1)	7/136 (5.1)	11/322 (3.4)
Lymphocytes, n (%)	13/340 (3.8)	7/135 (5.2)	2/321 (0.6)
Monocytes, n (%)	8/340 (2.4)	15/135 (11.1)	14/319 (4.4)
Potassium, n (%)	7/315 (2.1)	4/131 (2.9)	2/307 (0.6)

Reference: Table 5.3.5.3.2.29.
Source: Table 2.7.4-13 on page 22 of the clinical safety summary report.

7.4.3 Vital Signs

In Phase 2/3 studies group mean systolic and diastolic blood pressure were decreased in all treatment groups in the pooled database. Individual cases of increased blood pressure reported as AEs include two patients on DPSGC 25 mg, two on DPSGC 50 mg, two on DPSGC 100 mg, and four placebo patients. The increase in group mean pulse rate was reported in all the treatment groups with the greatest increase in the placebo group.

7.5 Other Safety Explorations

Very few AEs were reported in Phase 1 PK studies. There were no AEs in Study 142, two AEs (nasal congestion and light headache) in Study 119, two AEs (lingual paresthesia and acute tonsillitis) in Study 171, and 16 AEs reported in 15 subjects (of the 54 subjects studied) in Study 170, including dizziness in four subjects, headache in eight subjects, phlebitis in two subjects, hematoma in one subject, and rhinitis in one subject. No other safety explorations were available.

7.5.1 Dose Dependency for Adverse Findings

The AE reports and the laboratory test results suggest a dose response in liver enzyme elevations. Refer to Sections 7.4.1 and 7.4.2 for details.

7.5.2 Time Dependency for Adverse Findings

Multiple-dose exposure was associated with higher incidences of AEs than that of single administration of DPSGC. Refer to Sections 7.4.1 for details.

7.5.3 Drug-Demographic Interactions (gender, race)

In general female subjects (about 65% of the sample population) reported more AEs, particularly GI symptoms such as nausea and vomiting than male subjects and male subjects reported more headache than female subjects in both DPSGC 25 mg and placebo groups as shown in the summary table below. The treatment-related differential reports in abdominal pain were shown in both genders. The data did not suggest significant treatment differences with respect to gender.

Table 7-8 Treatment Emergent Adverse Events Occurring in ≥ 1% of Either Male or Female DPSGC 25 mg Treated Subjects

MedDRA System Organ Class and Preferred Term	Male Patients, n (%)		Female Patients, n (%)	
	DPSGC 25 mg	Placebo	DPSGC 25 mg	Placebo
	N=181	N=164	N=337	N=292
Subjects with any AE	56 (30.9)	68 (41.5)	118 (35.0)	138 (47.3)
Gastrointestinal Disorders	36 (19.9)	34 (20.7)	77 (22.8)	88 (30.1)
Abdominal Distension	2 (1.1)	0 (0)	0 (0)	1 (0.3)
Abdominal Pain	12 (6.6)	5 (3.0)	16 (4.7)	7 (2.4)
Constipation	3 (1.7)	2 (1.2)	8 (2.4)	7 (2.4)
Diarrhea	3 (1.7)	2 (1.2)	5 (1.5)	7 (2.4)
Flatulence	2 (1.1)	0 (0)	1 (0.3)	2 (0.7)
Nausea	17 (9.4)	14 (8.5)	47 (13.9)	57 (19.5)
Pharyngolaryngeal pain	3 (1.7)	4 (2.4)	0 (0)	3 (1.0)
Vomiting	3 (1.7)	4 (2.4)	22 (6.5)	26 (8.9)
Musculoskeletal & Connective Tissue Disorders	5 (2.8)	9 (5.5)	4 (1.2)	17 (5.8)
Arthralgia	2 (1.1)	2 (1.2)	0 (0)	1 (0.3)
Nervous System Disorders	29 (16.0)	32 (19.5)	48 (14.2)	52 (17.8)
Dizziness	5 (2.8)	4 (2.4)	10 (3.0)	15 (5.1)
Headache	24 (13.3)	29 (17.7)	30 (8.9)	32 (11.0)
Somnolence	2 (1.1)	0 (0)	9 (2.7)	6 (2.1)
Skin and Subcutaneous Tissue Disorders	5 (2.8)	4 (2.4)	10 (3.0)	17 (5.8)
Pruritus	1 (0.6)	2 (1.2)	4 (1.2)	4 (1.4)
Sweating Increase	2 (1.1)	2 (1.2)	3 (0.9)	1 (0.3)
Vascular Disorders	3 (1.7)	2 (1.2)	1 (0.3)	5 (1.7)
Flushing	2 (1.1)	0 (0)	0 (0)	1 (0.3)

* Occurrence rates for System Organ Class includes all reported events, not just those occurring in ≥ 1% of DPSGC 25 mg male or female subjects. Subjects are counted only once within each unique preferred term and SOC.
Reference: Table 5.3.5.3.2.21

Source: Table 14 on page 32 of ISS.

The greater difference in reports of more abdominal pain in DPSGC-treated patients than placebo patients in the non-White subpopulation was more likely to be due to a smaller sample size since non-White only consisted of 30% of the sample population and of several different racial groups. The data as summarized in the table below did not suggest treatment differences with respect to race.

Table 7-9 Incidences of Treatment Emergent Adverse Events Occurring in ≥ 1% of Either White or Non-White DPSGC 25 mg Treated Subjects

MedDRA System Organ Class and Preferred Term	White Subjects		Non-White Subjects	
	DPSGC 25 mg	Placebo	DPSGC 25 mg	Placebo
	N=381	N=312	N=137	N=144
Subjects with any AE	**134 (35.2)**	**134 (42.9)**	**40 (29.2)**	**72 (50.0)**
Gastrointestinal Disorders	**88 (23.1)**	**85 (27.2)**	**25 (18.2)**	**37 (25.7)**
Abdominal Pain	21 (5.5)	11 (3.5)	7 (5.1)	1 (0.7)
Constipation	8 (2.1)	3 (1.0)	3 (2.2)	6 (4.2)
Diarrhea	8 (2.1)	8 (2.6)	0 (0)	1 (0.7)
Dyspepsia	4 (1.0)	6 (1.9)	0 (0)	2 (1.4)
Nausea	48 (12.6)	50 (16.0)	16 (11.7)	21 (14.6)
Vomiting	18 (4.7)	20 (6.4)	7 (5.1)	10 (6.9)
Investigations	**7 (1.8)**	**12 (3.8)**	**3 (2.2)**	**2 (1.4)**
Alanine Aminotransferase Increased	1 (0.3)	2 (0.6)	2 (1.5)	0 (0)
Nervous System Disorders	**59 (15.5)**	**58 (18.6)**	**18 (13.1)**	**26 (18.1)**
Dizziness	11 (2.9)	12 (3.8)	4 (2.9)	7 (4.9)
Headache	41 (10.8)	45 (14.4)	13 (9.5)	16 (11.1)
Somnolence	8 (2.1)	4 (1.3)	3 (2.2)	2 (1.4)
Psychiatric Disorders	**7 (1.8)**	**6 (1.9)**	**6 (4.4)**	**5 (3.5)**
Insomnia	0 (0)	3 (1.0)	2 (1.5)	0 (0)
Skin and Subcutaneous Tissue Disorders	**12 (3.1)**	**12 (3.8)**	**3 (2.2)**	**9 (6.3)**
Pruritus	5 (1.3)	3 (1.0)	0 (0)	3 (2.1)
Sweating Increase	4 (1.0)	1 (0.3)	1 (0.7)	2 (1.4)

* Occurrence rates for System Organ Class includes all reported events, not just those occurring in ≥ 1% of DPSGC 25 mg White or non-White subjects. Subjects are counted only once with each unique preferred term and SOC
Reference: Table 5.3.5.3.2.23
Source: Table 15 on page 34 of ISS.

7.5.4 Drug Disease Interactions

New drug disease interactions are not expected based on relative bioavailability between DPSGC 25 mg and Cataflam® 50 mg.

7.5.5 Drug-Drug Interactions

New drug-drug interactions are not expected based on relative bioavailability between DPSGC 25 mg and Cataflam® 50 mg.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No new information is required based on relative bioavailability between DPSGC 25 mg and Cataflam® 50 mg.

7.6.2 Human Reproduction and Pregnancy Data

No new information is required based on relative bioavailability between DPSGC 25 mg and Cataflam® 50 mg.

7.6.3 Pediatrics and Assessment and/or Effects on Growth

There was one pediatric study (CL-000424), which was a randomized, double-blind, single-dose, dose response study of diclofenac 25 and 50 mg (with no other control groups) conducted in the U.S. in pediatric patients with orthodontic discomfort. The study was completed in June 2002. And the study protocol did not receive any comment from the original reviewer (Dr. Stauffer). The study enrolled 97 pediatric patients age 8 to 16 years with a mean age of 13.3 years.

In comparison to single-dose safety data obtained from adult dental studies, a higher proportion of pediatric patients than adults reported AEs, especially nervous system AEs such as headache, somnolence, and dizziness. The data did not suggest a dose response between the 25 mg and 50 mg doses in this small sample of pediatric patients.

The Applicant proposed a Phase 4 multiple-dose study of acute pain in 150 patients in the age group of 12 to 17 years to obtain pediatric safety data on short-term use of DPSGC 25 mg (refer to the submission dated April 18, 2008).

Table 7-10 Comparison of AEs Associated with a Single-Dose Exposure between the Pediatric and Adult Populations

	Pediatric		Adult		
	DPSGC 25 mg	**DPSGC 50 mg**	**DPSGC 25 mg**	**DPSGC 50 mg**	**Placebo**
	N=47	N=50	**N=126**	**N=130**	**N=129**
Number of patients with any AE (%)	13 (27.7)	10 (20.0)	15 (11.9)	13 (10.0)	16 (12.4)
Cardiac Disorders			0	0	2
Tachycardia NOS			0	0	2
Gastrointestinal Disorders	4 (8.5)	3 (6.0)	8 (6.3)	8 (6.2)	7 (5.4)
Abdominal Pain upper	3 (6.4)	1 (2.0)	1 (0.8)	0	1 (0.8)
Nausea			6 (4.8)	5 (3.8)	4 (3.1)
Nausea postoperative			0	0	1
Oral pain	0	1 (2.0)			
Pharyngolaryngeal pain	1 (2.1)	0	0	1 (0.8)	0
Toothache	0	1 (2.0)			
Vomiting NOS			5 (4.0)	4 (3.1)	4 (3.1)
General & Administrative Site Disorders	1 (2.1)	0			
Fatigue	1 (2.1)	0			
Investigations			2 (1.6)	3 (2.3)	2 (1.6)
Blood Pressure Increased.			2 (1.6)	2 (1.5)	2 (1.6)
Heart rate increased			0	1 (0.8)	0
Nervous System Disorders	9 (19.1)	7 (14.0)	6 (4.8)	2 (1.5)	6 (4.7)
Dizziness (excl vertigo)	2 (4.3)	1 (2.0)	1 (0.8)	0	2 (1.6)
Headache NOS	6 (12.8)	4 (8.0)	5 (4.0)	2 (1.5)	4 (3.1)
Somnolence	2 (4.3)	2 (4.0)			
Skin & Subcutaneous Tissue Disorders	0	1 (2.0)	1 (0.8)	0	2 (1.6)
Rash NOS			0 (0)	0	1 (0.8)
Sweating Increase			1 (0.8)	0	1 (0.8)
Urticaria NOS	0	1 (2.0)			

Source: Table 5 on page 42 of the report for Study 424.

7.6.4 Overdose, Drug Abuse Potential/ Withdrawal and Rebound

There were no reports of drug overdose in the studies of DPSGC. Diclofenac is not known to have abuse potential and problems with withdrawal and rebound.

7.7 Additional Submission

There were no new clinical safety data available in the 120-day safety update. All clinical studies had been completed and their data submitted in the original NDA.

8. POSTMARKETING EXPERIENCE

DPSGC has not been marketed in any country.

9. APPENDICES

9.1 Literature Review and other Important Relevant Materials/References

The professional labeling of diclofenac oral formulations has just been revised this year with updated safety information based on analyses of post marketing data and literature reports.

9.2 Labeling Recommendations

Labeling will be reviewed separately.

9.3 Advisory Committee Meeting

There is no Advisory Committee Meeting on issues with diclofenac containing products.

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/s/

Christina Fang
6/20/2008 08:06:47 PM
MEDICAL OFFICER

Sharon Hertz
6/23/2008 12:43:06 PM
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I concur.