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RESEARCH**

APPLICATION NUMBER:

022396Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

NDA: 22-396	Submission Date(s): 12/2/2009
Brand Name	Dyloject
Generic Name	Diclofenac Sodium
Clinical Pharmacology Reviewer	Srikanth C. Nallani, Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
OCP Division	Division of Clinical Pharmacology II
OND Division	Anesthesia and Analgesia Products
Sponsor	Javelin Pharmaceuticals/ Hospira Inc.
Relevant IND(s)	65,048
Submission Type; Code	Original NDA; 3P (New Formulation - IV)
Formulation; Strength(s)	IV injection; 37.5 mg/mL
Indication	Treatment of acute moderate to severe pain
Proposed Dosage Regimen	Recommended dose is 37.5 mg every six hours.

(b) (4)



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1 Executive Summary

1.1 Recommendation

The submission is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective provided that a mutually satisfactory agreement can be reached between the sponsor and the Agency regarding the language in the package insert.

1.2 Phase IV Commitments

- None

1.3 Summary of Clinical Pharmacology Findings

Javelin Pharmaceuticals, Inc. (Javelin) submitted an NDA 22-396 via the 505(b)(2) route for Dyloject™ (diclofenac sodium) Injection, a parenteral formulation intended for the management of acute moderate to severe pain in adults. Reference is made to Cataflam (50 mg oral diclofenac potassium tablets) marketed by NOVARTIS, NDA 20-142, approved November 24, 1993 to support safety data of diclofenac. A relative bioavailability study (#006) was conducted to compare systemic exposure of Dyloject (37.5 mg) following IV administration and Cataflam (50 mg) after oral administration.

(b) (4)

reference is also made to NDA 20-966 for Sporanox® (IV itraconazole) owned by Ortho McNeil Janssen, approved on March 30, 1999. Sponsor submitted a letter from Johnson & Johnson (parent company of Ortho McNeil Janssen), permitting Javelin the right of reference to NDA 20-966 and the use of final reports from that NDA as well as permitting the Division to access NDA 20-966 on behalf of Javelin's Dyloject NDA.

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Dyloject (37.5 mg) is to be injected as a 15 second intravenous bolus every six hours. (b) (4)

It is noteworthy that IV and IM use of Dyloject in United Kingdom entails a maximum total daily dose of 150 mg. The IM dose Dyloject may be administered first time as a 75 mg injection followed 30 minutes to 6 hours later by another dose of 75 mg. IV dose of Dyloject should be administered as 75 mg as a bolus followed 4-6 hours later by another dose not to exceed 150 mg within a period of 24 hours.

The clinical pharmacology of Dyloject in healthy subjects, patients and special populations has been characterized in seven studies with respect to active moiety diclofenac sodium and the major excipient hydroxypropyl-β-cyclodextrin (HPβCD).

After IV bolus administration, peak plasma levels are noted obviously at the first time point for blood sample collection (5 mins), followed by a first order rate decrease in plasma levels with a half-life of 1.2 -2.4 hrs.

Without dose normalization (observed values).

- a) As is the case with most IV bolus injections, peak plasma levels of diclofenac with Dyloject 18.75 mg and 37.5 mg were 2.5- and 5-fold higher compared orally administered diclofenac sodium 50 mg tablet Cataflam.
- b) Systemic exposure (AUC_{0-inf}) of diclofenac following IV injection of 18.75 mg dose was lower by ~40 % compared to Cataflam.
- c) Systemic exposure (AUC_{0-inf}) of diclofenac following IV injection of 37.5 mg dose was higher by ~20 - 30% compared to Cataflam.

With dose normalization:

The absolute bioavailability of reference drug oral Cataflam 50 mg was 66% when compared with the recommended IV dose of Dyloject 37.5 mg. The previously reported absolute bioavailability of oral diclofenac in the prescribing information for Cataflam is 55%.

Pharmacokinetics of diclofenac following IV administration of Dyloject appears to be dependent mainly on bodyweight. Patient age, sex, renal impairment and mild hepatic impairment do not significantly affect diclofenac disposition. PK of diclofenac was not evaluated in patients with moderate to severe hepatic impairment. Data suggests that patients with higher bodyweight clear diclofenac faster, thus having lower systemic exposure compared to patients with <95 kg bodyweight.

Figure: Relationship between CL and total body weight after IV administration of single 18.75 or 37.5 mg doses of DIC075V to healthy volunteers.

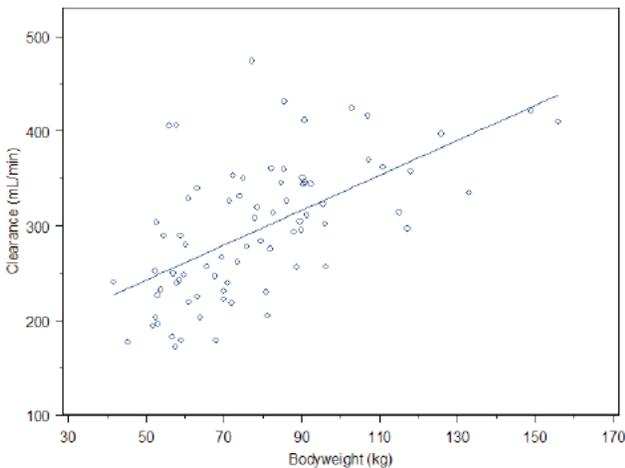
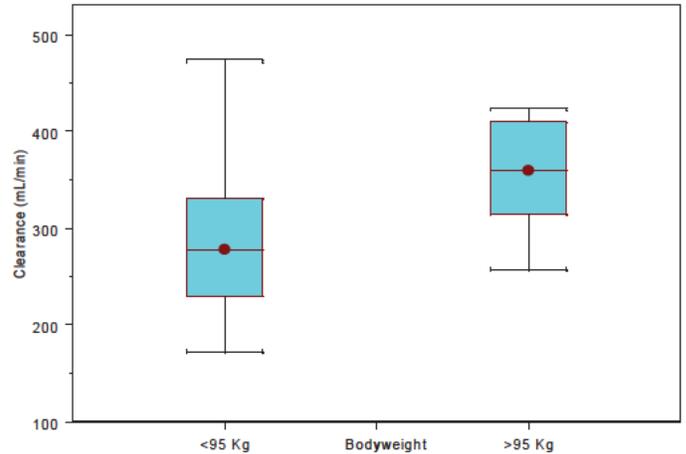


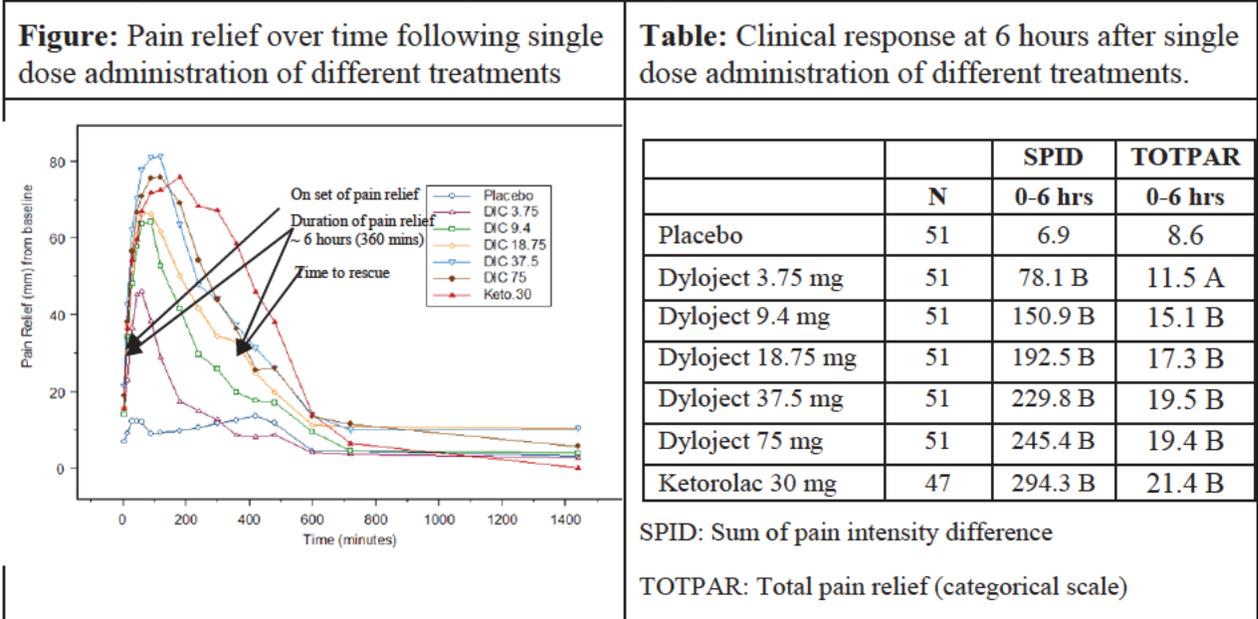
Figure: Box plot of clearance in bodyweight cohorts after IV administration of single 18.75 or 37.5 mg doses of DIC075V to healthy volunteers.



As noted in the figures above, higher clearance is noted in subjects with higher bodyweight/BMI. The sponsor chose to use a cutoff of 95 kg ^{(b) (4)} Clearance of diclofenac in subjects (n=63) below 95 kg is 282±68 mL/min compared to 356±53 mL/min in subjects (n=14) above 95 kg bodyweight (~ 27% higher clearance). Similarly, clearance of diclofenac in subjects with lower (~18%) bodyweight (45 – 60 kg) is lower compared to subjects with higher bodyweight (60 – 100 kg). As an extension to this observation, clearance of diclofenac might be significantly lower in pediatric patients

down to neonates. Further evaluation of a bodyweight effect on pharmacokinetics will be important prior to embarking on pediatric studies.

A single-dose, dose-response study (DFC-002) was conducted in patients with dental-pain after molar tooth extraction. Dose-response study DFC-002, indicates that of the seven dose levels evaluated, single dose of 18.75, 37.5, and 75 mg Dyloject could provide meaningful pain relief starting about 30 minutes after administration. The durations of analgesic effect for the responder population (meaningful pain relief/MPR) as determined by subtracting time to onset from median time to total relief were ~6 hours for Dyloject 18.75, 37.5, and 75 mg, respectively (see figure below). A shallow dose-response (no great incremental benefit with increasing dose) is noted in dental pain model following 6 hours after treatment (See table below).



Following the dose-response evaluation (study DFC-002), the sponsor conducted two adequate well controlled multiple dose efficacy studies using IV ketorolac tromethamine as active control.

Phase III Clinical Trials:

Study DFC-004 was a Phase 3, multicenter multiple-dose, multiple-day, randomized, double-blind, 4-arm, active- and placebo-controlled, parallel-group study designed to assess the analgesic efficacy and safety of fixed-dose, fixed-schedule, IV dosing of Dyloject (18.75 and 37.5 mg) compared with placebo and ketorolac tromethamine 30 mg in male or pelvic surgery.

Study DFC-005 was the second Phase 3, multicenter, randomized, double-blind, 3-arm, active-and placebo-controlled study of fixed-dose, fixed-schedule, repeated intermittent dosing (minimum of 24 hours) of 37.5 mg intravenous (IV) Dyloject every 6 hours, 30 mg IV ketorolac tromethamine every 6 hours, or placebo every 6 hours, in subjects with acute moderate to severe postsurgical pain following elective general orthopedic surgery. Subjects were to receive a reduced dose of 18.75 mg Dyloject or ketorolac tromethamine (15 mg) if they met the following criteria: weight <50 kg; >65 years of age (n=45)

received Dyloject); elevated NSAID-related gastrointestinal risk; moderate hepatic impairment (Child-Pugh score of 6-9, n=3 received Dyloject); or moderate renal impairment (serum creatinine 1.9-3.0 mg/dL). Subjects weighing ≥ 95 kg were to receive DIC075V 50 mg or ketorolac tromethamine 30 mg as appropriate.

Subjects received study treatment every 6 hours for a minimum of 48 hours and up to 5 days. Rescue medication (IV morphine) was available, but subjects were encouraged to wait at least 30 minutes after the initial dose of study medication.

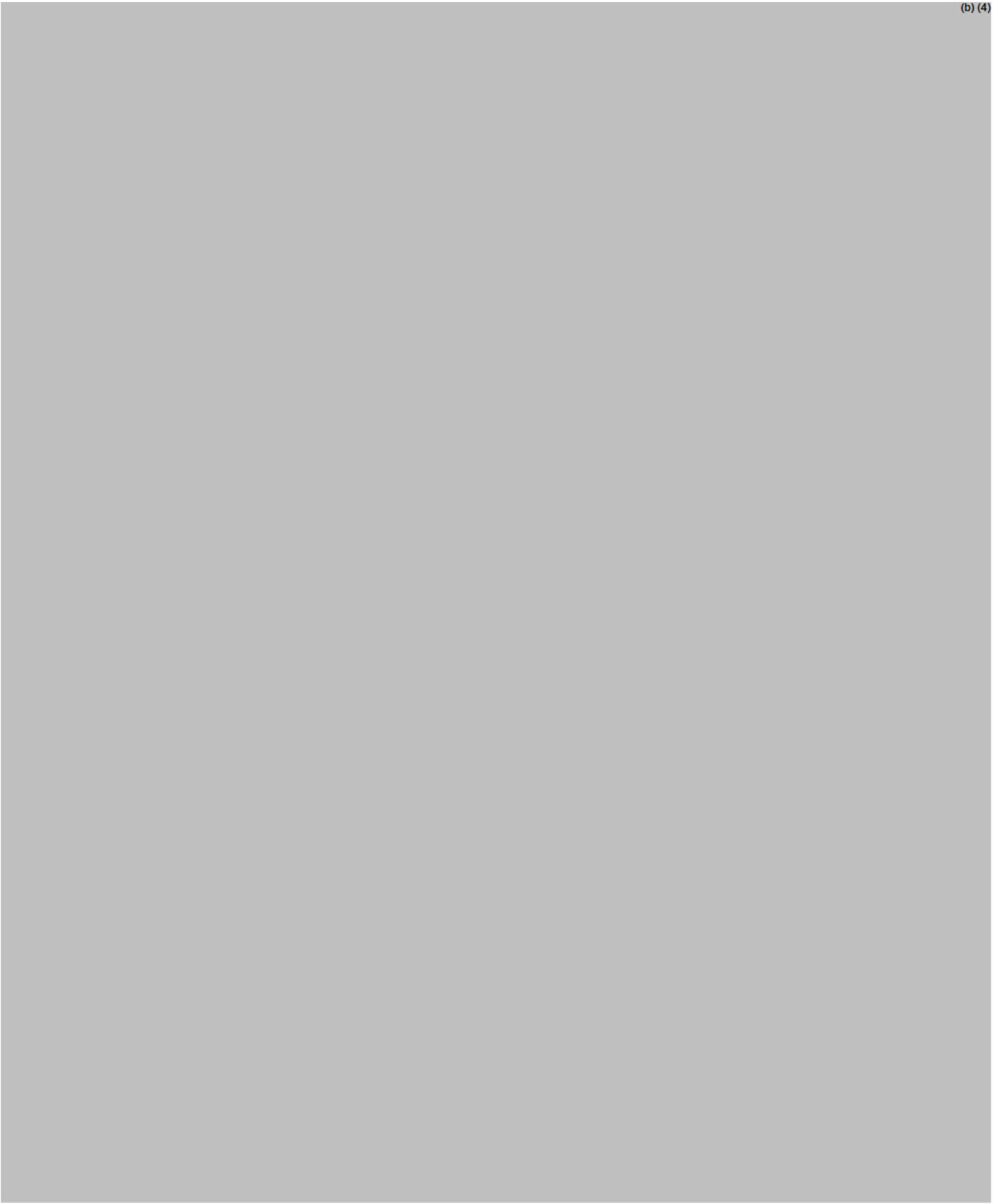
The primary measure of efficacy was SPID over a time interval. In study # DFC-004, SPID results (mean mm.hours \pm SD) over 0-48 hours demonstrated that Dyloject 18.75 mg (1304 \pm 1029; p=0.0316) and 37.5 mg (1574 \pm 1060; p=0.0001), and ketorolac tromethamine 30 mg (1583 \pm 983; p<0.0001) were all statistically superior to placebo (936 \pm 1077).

There was an increase in clinical response (SPID) with increasing doses of Dyloject from 0 mg through 37.5 mg. But the response was not dose-proportional.

Table: Efficacy - Sum of the Pain Intensity Differences Over 0-48 Hours (Study # DFC-004).

	Placebo (N = 76)	DIC075V 18.75 mg (N = 86)	DIC075V 37.5 mg (N = 87)	Ketorolac 30 mg (N = 82)	Treatment- by-Center Interaction
SPID (mm-hours)					
Mean	936.0	1303.6	1573.5	1583.2	
(SD)	(1076.56)	(1029.50)	(1060.34)	(982.74)	
p-value		0.0316 ^a	0.0001 ^a	<0.0001 ^a	0.0786

(b) (4)



(b) (4)

The clinical review by Dr. Rosemarie Neuner addresses the clinical safety and efficacy data with all the different doses of Dyloject investigated in the clinical trials DFC-004 and DFC-005.

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Renal Impairment:

Dose adjustment of Dyloject is not needed in patients with renal impairment. Mild to moderate renal impairment did not alter the pharmacokinetics of diclofenac. Based on previously known information from Cataflam, PK of orally administered diclofenac did not change in patients with mild, moderate or severe renal impairment. On the other hand, HP β CD pharmacokinetics is significantly affected by mild to moderate renal function. However, the dose of HP β CD in Dyloject (333 mg) compared to Sporanox is significantly low (8 gm). Even with severe renal impairment, the systemic exposure to HP β CD following IV injection of Dyloject may be low compared to previously known clinical experience with Sporanox.

Hepatic Impairment:

Diclofenac is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulfate conjugates of the metabolites. Little or no free unchanged diclofenac is excreted in the urine. Approximately 65% of the dose is excreted in the urine, and approximately 35% in the bile as conjugates of unchanged diclofenac plus metabolites. The terminal half-life of unchanged diclofenac is approximately 1 hour. This information is highly indicative of diclofenac being a drug with high hepatic extraction. Such drugs' disposition is potentially affected in situations where decrease in hepatic blood flow is anticipated, as is the case with hepatic impairment.

Lill J.S. et.al (J. Clin. Pharmacol. 2000; 40(3):250-7) investigated the effect of alcoholic cirrhosis on pharmacokinetics of orally administered diclofenac buffered powder (150 mg in 100 mL water). Subjects with alcoholic cirrhosis had a mean \pm SD diclofenac AUC value (19,114 \pm 6806 ng.h/ml) which is ~3-fold higher compared to healthy subjects (7008 \pm 2006 ng.h/ml). Hence, caution should be exercised when using Dyloject in patients with any degree of hepatic impairment. Considerations for Dyloject use in patients with moderate to severe hepatic impairment include:

- Peak plasma diclofenac levels with IV 18.75 mg & 37.5 mg Dyloject are 2.5 & 5-fold higher than oral, respectively.
- Systemic exposure of diclofenac following Dyloject 37.5 mg is ~20 -30% higher than orally administered 50 mg dose of Cataflam.
- Pharmacokinetics of Dyloject are similar in subjects with mild hepatic impairment compared to healthy subjects.
- Subjects with alcoholic cirrhosis had a ~3-fold higher AUC compared to healthy subjects following oral administration of diclofenac sodium.
- Lack of PK and safety data of IV Dyloject in patients with moderate to severe hepatic impairment
- “Hepatic Effects” of diclofenac/NSAID class labeling described in Cataflam label. Although, these observations have not risen to the level of a boxed warning. In addition, the proposed duration of administration is over a few days while recovering from surgery and considerably shorter than the chronic therapies requiring oral diclofenac use for treatment of chronic pain indications.

Clinical reviewer, Dr. Rosemarie Neuner, indicated that there was adequate clinical safety data to support use of 37.5 mg dose in mild hepatic impairment from study # DFC-010. In conclusion, patients with mild hepatic impairment can be given Dyloject 37.5 mg. As recommended in Cataflam label, and to be consistent with the hepatic impairment guidance, patients with moderate and severe hepatic impairment may receive reduced doses of Dyloject over the proposed short term use.

Age:

From a pharmacokinetic perspective, dose adjustment of Dyloject is not needed with regard to age of a patient. Pharmacokinetics of Dyloject was evaluated in young adults in weight-based cohort with 37.5 mg dose compared to elderly patients receiving 18.75 mg dose. However, it should be noted that significant number of elderly (>65 yrs) age were administered 18.75 mg dose in DFC-005. Clinical experience with 18.75 mg dose in elderly should be described in “Section 8.5: Geriatrics”.

Platelet function study:

Sponsor conducted a clinical study (DFC-007) to evaluate the potential for Dyloject to affect platelet function. The study results seem to indicate that Dyloject 37.5 mg and Cataflam (50 mg) have quantitatively less of an effect on platelet function compared to ketorolac (IV 30 mg) and aspirin (325 mg). However, clinical significance of this observation remains unknown. As such, all NSAID’s, including Cataflam, carry a class label “**Precaution**” related to “Hematological effects” reading as follows:

“NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Patients receiving Cataflam who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.”

The study results partially (reversibility of effect is not addressed) confirm the NSAID class labeling language for Dyloject and Cataflam. Hence, a description of the study results in “Clinical Pharmacology, 12.2 Pharmacodynamics” section does not add value to the product label in terms of better informing the practitioner.

Sponsor conducted at TQT study which ruled out the potential for Dyloject to caution QT-prolongation.

Overall, the submission is acceptable from a clinical pharmacology perspective.

2 QBR

2.1 General Attributes

1. What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Javelin Pharmaceuticals, Inc. (Javelin) submitted NDA 22-396 via the 505(b)(2) route for Dyloject™ (diclofenac sodium) Injection, a parenteral formulation intended for the management of acute moderate to severe pain in adults.

Sponsor is relying on the Agency's previous findings of safety and efficacy of Cataflam (50 mg oral diclofenac potassium tablets) currently marketed by NOVARTIS (NDA 20-142, approved on November 24, 1993). A relative bioavailability study (#006) was conducted to compare systemic exposure of Dyloject (37.5 mg) following IV administration and Cataflam (50 mg) after oral administration.

Dyloject was approved by the Medicines and Healthcare Products Regulatory Agency (MHRA) in October 2007 and is currently marketed in the United Kingdom for both IM and IV administration. (b) (4)

2. What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

The sponsor contends that the proposed intravenous formulation of diclofenac was developed (b) (4)

reference is also made to NDA 20-966 for Sporanox® (IV itraconazole) approved on March 30, 1999 and currently marketed by Ortho McNeil Janssen,. Sponsor submitted a letter from Johnson & Johnson

(parent company of Ortho McNeil Janssen), permitting Javelin the right of reference to NDA 20-966 and the use of final reports from that NDA as well as permitting the Division to access NDA 20-966 on behalf of Javelin's Dyloject NDA. Sporanox is being referenced to support the safety of the excipient, hydroxypropyl betadex NF (also referred to as hydroxypropyl- β -cyclodextrin). Since bioavailability is self evident for IV formulations, a relative bioavailability comparison of hydroxypropyl- β -cyclodextrin between Dyloject and Sporanox is not needed.

3. What are the proposed mechanism(s) of action and therapeutic indication(s)?

Diclofenac sodium is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of diclofenac, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition.

4. What are the proposed dosage(s) and route(s) of administration?

Dyloject (37.5 mg) is to be injected as a 15 second intravenous bolus every six hours. (b)
(4)

It is noteworthy that IV and IM use of Dyloject in UK entails a maximum total daily dose of 150 mg. The IM dose of Dyloject may be administered first time as a 75 mg injection followed 30 minutes to 6 hours later by another dose of 75 mg. IV dose of Dyloject should be administered as a 75 mg bolus dose followed 4-6 hours later by another dose not to exceed 150 mg within a period of 24 hours.

2.2 General Clinical Pharmacology

1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The clinical pharmacology of Dyloject in healthy subjects, patients and special populations has been characterized in the following seven studies with respect to active moiety diclofenac sodium and the major excipient hydroxypropyl- β -cyclodextrin (HP β CD).

- Single dose relative bioavailability, multiple dose PK study (DFC-006): An open-label, randomized, single-center study to compare the pharmacokinetics of intravenous diclofenac sodium (Dyloject 18.75 and 37.5 mg) versus oral diclofenac potassium (Cataflam® 50 mg) in healthy adult volunteers following single- and multiple-dose administration study.
- PK study evaluating intrinsic factors affecting Dyloject PK (DFC-008): An open-label, single-dose study to assess the effects of age, weight, and body composition on the pharmacokinetic profile, safety, and tolerability of intravenous Dyloject in healthy adult volunteers.
- PK study evaluating intrinsic factors affecting Dyloject PK (DFC-009): An open-label, single-dose study to evaluate the safety and pharmacokinetics of Dyloject in subjects with mild or moderate chronic renal insufficiency and in patients with mild chronic hepatic impairment compared to healthy adult volunteers and a randomized, open-label, single-dose, 2-way, cross-over study to evaluate the safety and

pharmacokinetics of HP β CD when administered as Dyloject compared to Sporanox[®] in healthy adult volunteers.

- One safety, tolerability and platelet function study (DFC-007): An open-label, randomized, single-dose, 4-treatment cross-over study to evaluate platelet function in healthy adult male volunteers following administration of intravenous diclofenac sodium (Dyloject 37.5 mg), oral diclofenac potassium (Cataflam[®] 50 mg), intravenous ketorolac tromethamine (30 mg) and oral acetylsalicylic acid (325 mg).
- One thorough QT study (DFC-011): A randomized, single-dose, comparative, positive- and placebo-controlled, 4-way, 4-period, cross-over study to evaluate the effect of Dyloject on QTc intervals in healthy subjects.
- One single-dose Janssen HP β CD supportive study in subjects with renal insufficiency (N130310): Previously reviewed under NDA 20-966 for Sporanox.
- One dose-response single dose study (DFC-002): Randomized, parallel group, dose-controlled trial for dose finding in subjects following oral surgery with moderate to severe postsurgical pain.

Following the dose-response evaluation in study DFC-002, the sponsor conducted two adequate well controlled multiple dose efficacy studies using IV ketorolac tromethamine as active control.

- Efficacy Study DFC-004: Randomized, parallel group, dose-controlled trial in subjects with moderate to severe pain following abdominal or pelvic surgery
- Efficacy Study DFC-005: Randomized, trial in subjects with moderate to severe pain following orthopedic surgery

2. What are the clinical response endpoints and what is the basis for selecting the response endpoints, and how are they measured in clinical pharmacology and clinical studies?

The primary efficacy endpoint in analgesic clinical trials (DFC-004 & DFC-005) and clinical pharmacology study (DFC-002) is Sum of Pain Intensity Difference (SPID) over a treatment period. Substantial literature on analgesic methodology supports an approach in which distinct assessments of pain intensity and pain relief are performed, based upon both continuous and categorical measures, followed by construction of cumulative measures (e.g., sum of the pain intensity differences [SPID] and total pain relief score [TOTPAR], respectively) over intervals of interest. Reviews on the assessment of acute postoperative pain and its relief indicate that the 0-100 mm VAS is a valid, sensitive, and reliable instrument for assessment of both postoperative pain intensity and pain relief (Siegel C. et. al., J. Clin. Pharm. 1989, 29:1017-1025; Laska E.M. et. al., Clin. Pharm. Ther. 1991, 49(1): 1-5.).

3. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Systemic exposure of diclofenac and HP β CD were appropriately measured in all PK studies to appropriately assess PK parameters. However, exposure-response relationship could not be assessed as blood samples were not collected in the dose-response clinical pharmacology study (DFC-002) or the two pivotal clinical trials (DFC-004 & DFC-005).

Dose-response characteristics could be assessed in dose-finding study DFC-002 and clinical trial DFC-004.

4. Exposure-response

a) What are the characteristics of dose-response for efficacy? If relevant, indicate the time to the onset and offset of the clinical endpoint.

Dose-response study DFC#002, indicates that single dose of 18.75, 37.5, and 75 mg Dyloject could provide meaningful pain relief starting about 30 minutes after administration. The durations of analgesic effect for the responder population (MPR) as determined by subtracting time to onset (median TMPR) from median TTR were ~6 hours for Dyloject 18.75, 37.5, and 75 mg, respectively. A shallow dose-response (no great incremental benefit with increasing dose) is noted in dental pain model following 6 hours after treatment. Clinical trial in abdominal pain patients suggests a dose-related increase in efficacy at 48 hours following treatment between 18.75 and 37.5 mg doses.

Dose-response noted in study # DFC-002 provides the basis for dose-selection in pivotal clinical trials (DFC#004 and DFC#005). Study # DFC-002 was a phase 2, randomized, double-blind, placebo-controlled, parallel-dose group (7-arms) trial for dose finding in subjects following oral surgery with moderate to severe postsurgical pain.

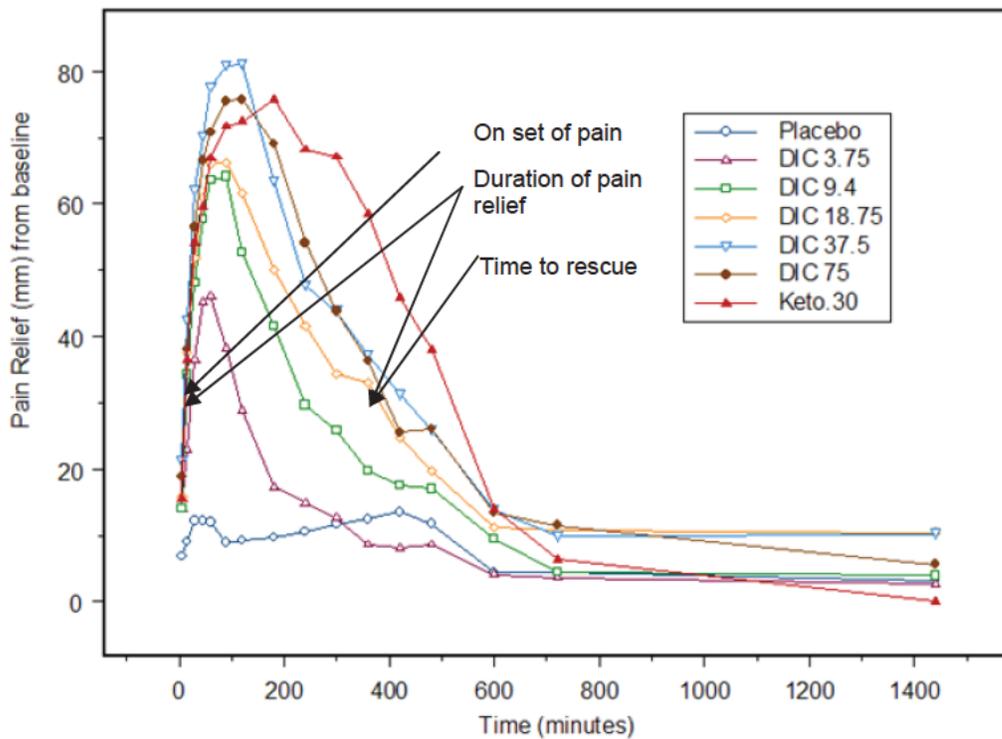
- The primary objective of this study was to assess the dose-response of 5 dose levels of IV diclofenac (3.75, 9.4, 18.75, 37.5 and 75 mg) and IV placebo and IV ketorolac tromethamine as comparators (all treatments were single dose).
- Patients with postsurgical (dental) pain (N=51 per arm) were
 - Male or female between 18 – 65 years of age
 - Undergoing removal of 1 or more third molars
 - Had moderate to severe pain within 6 hours after completion of surgery (Pain VAS \geq 50 mm on 100 mm scale)
 - Generally in good health
- Pain Assessment: Visual Analog Scale (VAS) for pain relief and pain intensity and categorical pain relief by each patient
 - Were assessed at baseline (time 0: only) at 5, 15, 30 and 45 minutes, and 1, 1.5, 2, 3, 4, 5, 6, 7, 8 (In clinic)
 - Were noted in Diary at 10, 12, and 24 hours after administration of study medication and immediately prior to the first dose of rescue medication.

Dose-Response (efficacy/pain relief):

Pain relief scores for ketorolac and all doses of Dyloject increased rapidly within the first hour, and, with the exception of Dyloject 3.75 mg, remained greater than placebo for 8 hours following administration of study drug. Dyloject 37.5 mg had the greatest mean pain relief scores from 30 minutes through 2 hours post dose, and ketorolac 30 mg had the greatest scores from 3 hours through 10 hours post dose; however, pain relief scores for all active treatment groups appeared to be declining monotonically beyond 3 hours. Statistically significant separation from placebo ($p < 0.05$) occurred at 5 minutes following drug administration for patients in the Dyloject 37.5 and 75 mg treatment groups. At 15

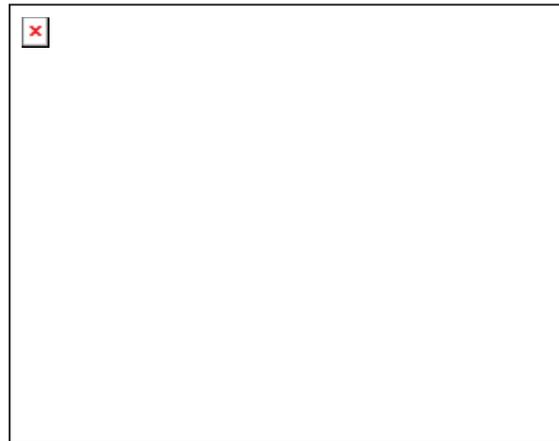
minutes following administration, Dyloject 9.4, 18.75, 37.5, and 75 mg and ketorolac 30 mg were all statistically significantly superior compared with placebo. At 30 minutes, all treatment groups were statistically significant versus placebo. At 3 hours Dyloject 3.75 mg was no longer statistically superior to placebo, and at 5 hours Dyloject 9.4 mg was also no longer statistically superior to placebo. Dyloject 18.75, 37.5 and 75 mg treatment groups remained superior to placebo through 6 hours. This observation in addition to increased need for rescue after 6 hours of initial dose administration supports the administration of Dyloject every six hours. By 7 hours following administration, only ketorolac 30 mg was statistically significant compared with placebo. Beginning with 10 hours post drug administration, no treatment group was significantly different from placebo.

Figure: Mean Pain Relief over Time (Visual Analog Scale)



The mean sum of pain intensity differences (SPID) scores for the ITT population, based on VAS assessments, indicated that Dyloject 18.75, 37.5, and 75 mg and ketorolac 30 mg were statistically superior to placebo ($p < 0.05$) at 0-2, 0-4, 0-6, 0-8, 0-10, 0-12, and 0-24 hours post dose.

Figure: Sum of Pain Intensity Difference (SPID) in terms of duration (2, 4, 6, and 8 hours) following treatment with Dyloject (Dose = 3.75, 9.4, 18.75, 37.5 and 75 mg) or Placebo (dose =0).



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Onset and Duration of Action: Patients were given two stopwatches and were instructed to stop the first stopwatch at Time for Perceptible Pain Relief (TPPR) and the second stopwatch at Time for Meaningful Pain Relief (TMPR). In this single dose study, the median TMPR for all treatments of Dyloject was approximately 30 minutes. The durations of analgesic effect for the responder population (30% reduction in Pain Intensity) as determined by subtracting time to onset (median TMPR) from median TTR were 5 hours 47 minutes, 6 hours 16 minutes and 5 hours 8 minutes for Dyloject 18.75, 37.5, and 75 mg, respectively.

Based on the observed dose-response, sponsor conducted two Phase III clinical trials in patients undergoing abdominal surgery and requiring analgesic medication for more than a single dose (major limitation for the dose-finding study # DFC-002).

Phase III Clinical Trials:

Study DFC-004 was a Phase 3, multicenter multiple-dose, multiple-day, randomized, double-blind, 4-arm, active- and placebo-controlled, parallel-group study designed to assess the analgesic efficacy and safety of fixed-dose, fixed-schedule, IV dosing of Dyloject (18.75 and 37.5 mg) compared with placebo and ketorolac tromethamine 30 mg in male and female subjects, 18-65 years of age and with a body weight of > 50 kg, who had acute moderate to severe pain (>50 mm as measured on a 0-100 mm VAS) within 6 hours following abdominal or pelvic surgery.

Study DFC-005 was the second Phase 3, multicenter, randomized, double-blind, 3-arm, active-and placebo-controlled study of fixed-dose, fixed-schedule, repeated intermittent dosing (minimum of 24 hours) of 37.5 mg intravenous (IV) Dyloject every 6 hours, 30 mg IV ketorolac tromethamine every 6 hours, or placebo every 6 hours, in subjects with acute moderate to severe postsurgical pain following elective general orthopedic surgery. Subjects were to receive a reduced dose of 18.75 mg Dyloject or ketorolac tromethamine (15 mg) if they met the following criteria: weight <50 kg; >65 years of age (n=45 received Dyloject); elevated NSAID-related gastrointestinal risk; moderate hepatic impairment (Child-Pugh score of 6-9, n=3 received Dyloject); or moderate renal

impairment (serum creatinine 1.9-3.0 mg/dL). Subjects weighing ≥ 95 kg were to receive DIC075V 50 mg or ketorolac tromethamine 30 mg as appropriate.

Subjects received study treatment every 6 hours for a minimum of 48 hours and up to 5 days. Rescue medication (IV morphine) was available, but subjects were encouraged to wait at least 30 minutes after the initial dose of study medication.

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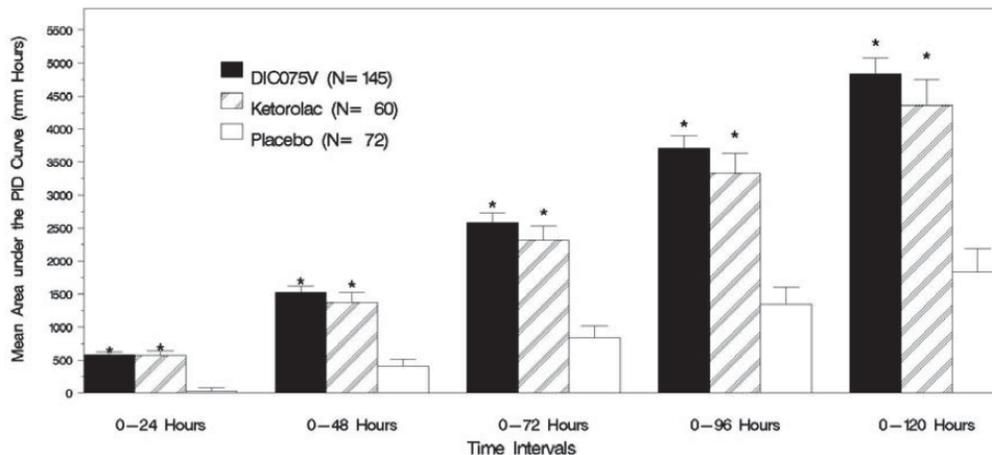
The primary measure of efficacy was SPID over the 0-48 hour time interval. In study # DFC-004, SPID results (mean mm.hours \pm SD) over 0-48 hours demonstrated that Dyloject 18.75 mg (1304 \pm 1029; $p=0.0316$) and 37.5 mg (1574 \pm 1060; $p=0.0001$), and ketorolac tromethamine 30 mg (1583 \pm 983; $p<0.0001$) were all statistically superior to placebo (936 \pm 1077).

There was a dose-related increase in clinical response (SPID) with increasing doses of Dyloject from 0 mg through 37.5 mg. See additional discussion on SPID48 in weight based subgroups in section “2.3 Intrinsic Factors”.

Table: Efficacy and Dose-Response - Sum of the Pain Intensity Differences Over 0-48 Hours.

	Placebo (N = 76)	DIC075V 18.75 mg (N = 86)	DIC075V 37.5 mg (N = 87)	Ketorolac 30 mg (N = 82)	Treatment- by-Center Interaction
SPID (mm-hours)					
Mean	936.0	1303.6	1573.5	1583.2	
(SD)	(1076.56)	(1029.50)	(1060.34)	(982.74)	
p-value		0.0316 ^a	0.0001 ^a	<0.0001 ^a	0.0786

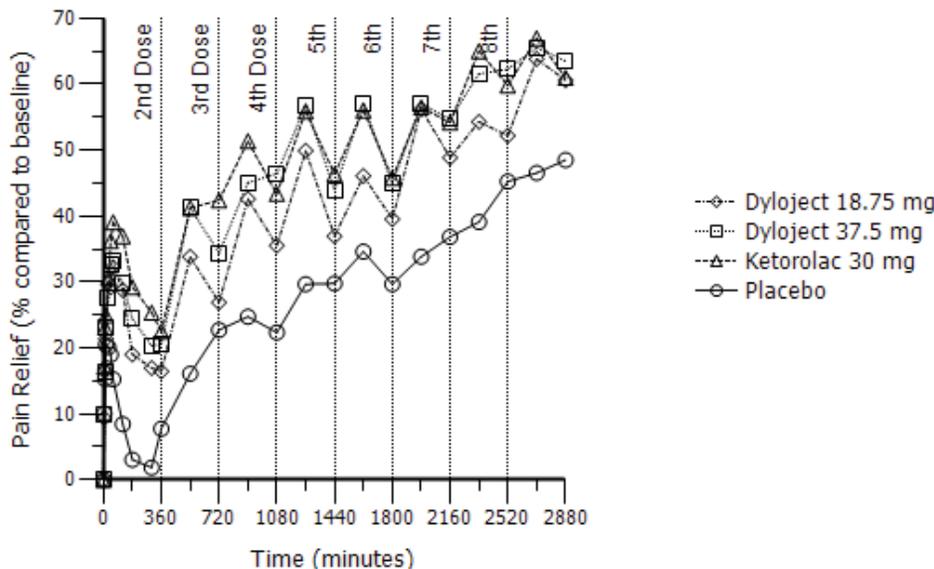
In study # DFC-005, clinical efficacy was measured over a period of up to 120 hours. As shown in the figure below, Dyloject and Ketorolac tromethamine produced significantly higher clinical response (SPID) compared to Placebo. See additional discussion on SPID48 in weight based subgroups in section “2.3 Intrinsic Factors”.



Onset and Duration of Pain Relief: In study # DFC-004, the median TMPR was 43 minutes in the ketorolac tromethamine 30 mg group versus 2 hours 6 minutes in the placebo group; the difference between these groups was statistically significant ($p = 0.0114$). The median TMPR was 61 minutes in the Dyloject 18.75 mg group and 41 minutes in the Dyloject 37.5 mg group; the differences between these groups and placebo were not statistically significant. In study#DFC-005, the TMPR for Dyloject ($p < 0.0001$) and ketorolac tromethamine ($p = 0.0019$) treatment groups as compared with placebo at 41.6 minutes and 42.5 minutes, respectively.

As shown in the figure below, improvement in percent pain change compared to baseline is noted at the assessment time scheduled shortly after administration of Dyloject and ketorolac IV administration. In other words, maximum average pain change occurs a few hours after each dose and clinical response decreases with the drug levels by the end of the six hour interval (not shown in this figure). Improvement in pain change is noted in placebo group by 48 hours potentially due to improvement in patient health post-surgery. Greater average pain relief is noted following drug treatment at the end of 48 hours. There is no apparent difference in pain change at 48 hours between the two Dyloject dose groups. See additional discussion on pain change in weight based subgroups in section “2.3 Intrinsic Factors”.

Figure: Time course profile of pain change expressed as % change in baseline followed treatment with Placebo (Circles), Dyloject 18.75 mg (Diamonds), Dyloject 37.5 mg (Squares) and Ketorolac tromethamine 30 mg IV (Triangles).



b) What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

Over the short duration (2 -5 days) of clinical evaluation, there was no dose-related increase in adverse events.

Safety of Dyloject following single dose of up to 75 mg was evaluated in study DFC#002. The major adverse events, nausea, headache & dry socket, did not increase with increased dose.

Table: Number of Patients with >5% Treatment-emergent Adverse Events by Treatment Group (Safety Population)

	N	Post Procedural	Procedural Site	Nausea	Headache	Dry Socket
		Pain	Reaction			
		n (%)	n (%)	n (%)	n (%)	n (%)
Placebo	51	12 (23.5)	5 (9.8)	3 (5.9)	3 (5.9)	1 (2.0)
DIC075V 3.75 mg	51	9 (17.6)	4 (7.8)	3 (5.9)	5 (9.8)	4 (7.8)
DIC075V 9.4 mg	51	5 (9.8)	5 (9.8)	9 (17.6)	4 (7.8)	3 (5.9)
DIC075V 18.75 mg	51	5 (9.8)	4 (7.8)	3 (5.9)	4 (7.8)	2 (3.9)
DIC075V 37.5 mg	51	7 (13.7)	5 (9.8)	5 (9.8)	3 (5.9)	5 (9.8)
DIC075V 75 mg	51	2 (3.9)	3 (5.9)	3 (5.9)	2 (3.9)	3 (5.9)
Ketorolac 30 mg	47	3 (6.4)	7 (14.9)	3 (6.4)	3 (6.4)	4 (8.5)
Total	353	43 (12.2)	33 (9.3)	29 (8.2)	24 (6.8)	22 (6.2)

Safety of Dyloject 18.75 mg and 37.5 mg was evaluated in study DFC-004. Only two subjects experienced treatment-related severe nausea and vomiting following Dyloject 18.75 mg dose. There was no dose-relationship in the frequency of adverse events. Most frequently (4%) reported treatment emergent adverse events included injection site irritation, and nausea.

c) Does this drug prolong the QT or QTc interval?

No significant QT prolongation effect of Dyloject (37.5 mg and 75 mg) was detected in this TQT study.

Sponsor conducted a TQT study (DFC-011), a randomized, double-blind, placebo-controlled and open label active-controlled, four-period crossover study to thoroughly assess QT prolongation effects of Dyloject. Seventy healthy subjects received Dyloject 37.5 mg, Dyloject 75 mg, moxifloxacin 400 mg (active control), and placebo. The largest upper bounds of the 2-sided 90% CI for the mean difference between Dyloject (37.5 mg and 75 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. For additional details, see review by QT-IRT team dated April 19, 2010.

Table: The point estimates and the 90% CIs corresponding to the largest upper bounds for Dyloject (37.5 mg and 75 mg) and the largest lower bound for moxifloxacin 400 mg (FDA analysis)

Treatment	Time (hour)	$\Delta\Delta QTcF$ (ms)	90% CI (ms)
DIC075V 37.5 mg	1	1.6	(-0.4, 3.7)
DIC075V 75 mg	1	1.4	(-0.7, 3.4)
Moxifloxacin 400 mg*	4	10.7	(8.6*, 12.8)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is 7.8 ms.

5. What are the PK characteristics of the drug and its major metabolite?

a) What are the single dose and multiple dose PK parameters?

After IV bolus administration, peak plasma levels are noted obviously at the first time point (5 mins) for blood sample collection, followed by a first order rate decrease in plasma levels with a half-life of 1.2 -2.4 hrs.

-Without dose normalization (observed values),

a) As is the case with most IV bolus injections, peak plasma levels of diclofenac with Dyloject 18.75 mg and 37.5 mg were 2.5- and 5-fold higher compared orally administered diclofenac sodium 50 mg tablet Cataflam.

b) Systemic exposure (AUC_{0-inf}) of diclofenac following IV injection of 18.75 mg dose was lower by ~40 % compared to Cataflam.

c) Systemic exposure (AUC_{0-inf}) of diclofenac following IV injection of 37.5 mg dose was higher by ~20 - 30% compared to Cataflam.

-With dose normalization:

The absolute bioavailability of reference drug oral Cataflam 50 mg was 66% when compared with the recommended IV dose of Dyloject 37.5 mg. The previously reported absolute bioavailability of oral diclofenac in the prescribing information for Cataflam is 55% (CV 40%).

Table: Diclofenac PK parameters (mean±SD, n=36) following single dose (Study # DFC-006 & DFC-011):

Parameter	Study # DFC-006			Study # DFC-011	
	Cataflam 50 mg	Dyloject 18.75 mg	Dyloject 37.5 mg	Dyloject 37.5 mg	Dyloject 75 mg
C_{max}(ng/mL)	1,246 ± 732 (36)	2,904 ± 661 (36)	6,031 ± 1178 (36)	6,493± 1,363 (70)	12,102 ± 2,146 (70)
T_{max} (h)	1.50 (36) [0.33 – 3.00]	0.083 (36) [0.083 – 0.150]	0.083 (36) [0.083 – 0.150]	0.083 (70)	0.083 (70)
AUC(0-t) (h.ng/mL)	1,473 ± 488 (36)	866 ± 221 (36)	1,843 ± 394 (36)	1,984 ± 399 (70)	3,943 ± 788 (70)
AUC(inf) (h.ng/mL)	1,562 ± 519 (34)	898 ± 231 (33)	1,859 ± 376 (34)	2,017 ± 397 (66)	3,967 ± 789 (70)
λ_z (h⁻¹)	0.5656 ± 0.1223 (34)	0.5221 ± 0.1108 (33)	0.4964 ± 0.0788 (34)	0.4209 ± 0.075 (66)	0.3887 ± 0.067 (70)
t_{1/2}(h)	1.28 ± 0.27 (34)	1.39 ± 0.29 (33)	1.44 ± 0.27 (34)	1.70 ± 0.33 (66)	1.84 ± 0.35(70)
CL(mL/min)	526 ± 179 (34)	344 ± 87.1 (33)	324 ± 63.0 (34)	299± 57.9 (66)	304 ± 62.1 (70)
V_z(L)	57.3 ± 20.4 (34)	40.4 ± 10.1 (33)	40.1 ± 09.8 (34)	43.4 ± 9.32 (66)	48.1 ± 11.2(70)

Diclofenac PK parameters following multiple doses (Study # DFC-006):

Parameter	Study # DFC-006		
	Cataflam 50 mg	Dyloject 18.75 mg	Dyloject 37.5 mg
C _{max} (ng/mL)	851 ± 462 (36)	3,090 ± 1,029 (36)	5,617 ± 1,799 (36)
T _{max} (h)	1.49 (36) [0.00 – 6.00]	0.083 (36) [0.000 – 0.133]	0.083 (36) [0.067 – 0.183]
AUC(0-t) (h ng/mL)	1,350 ± 601 (36)	935 ± 203 (36)	1,839 ± 506 (36)
λ _z (h ⁻¹)	0.2597 ± 0.0531 (36)	0.4059 ± 0.1056 (35)	0.3256 ± 0.0917 (36)
t _{1/2} (h)	2.80 ± 0.66 (36)	1.82 ± 0.48 (35)	2.29 ± 0.63 (36)
CL(mL/min)	894 ± 1,392 (36)	325 ± 71.6 (36)	387 ± 394 (36)
V _z (L)	242 ± 486 (36)	50.4 ± 14.9 (35)	83.4 ± 127 (36)

b) What are the characteristics of drug distribution?

Following IV administration of Dyloject, the apparent volume of distribution of diclofenac during the terminal elimination phase (V_z) is 40.1 ± 9.77 L.

The following information is already known about diclofenac administered via different routes:

Diclofenac is more than 99% bound to human serum proteins, primarily albumin. Serum binding is constant over the concentration range (0.15-105 mcg/mL) achieved with the recommended doses. Diclofenac diffuses into and out of the synovial fluid. Diffusion into the joint occurs when plasma levels are higher than those in the synovial fluid, after which the process reverses and synovial fluid levels are higher than plasma levels. It is not known whether diffusion into the joint plays a role in the effectiveness of diclofenac.

HPβCD has a volume of distribution during the terminal elimination phase (V_z) of 21.8 ± 7.36 L.

c) What are the characteristics of drug excretion?

The following information is known about diclofenac metabolism and excretion through published literature.

Five diclofenac metabolites have been identified in human plasma and urine. The metabolites include 4'-hydroxy-, 5-hydroxy-, 3'-hydroxy-, 4',5-dihydroxy- and 3'-hydroxy-4'-methoxy diclofenac. The major diclofenac metabolite, 4'-hydroxy-diclofenac, has very weak pharmacologic activity. The formation of 4'-hydroxy diclofenac is primarily mediated by CPY2C9. Both diclofenac and its oxidative metabolites undergo glucuronidation or sulfation followed by biliary excretion. Acylglucuronidation mediated by UGT2B7 and oxidation mediated by CPY2C8 may also play a role in diclofenac metabolism. CYP3A4 is responsible for the formation of minor metabolites, 5-hydroxy and 3'-hydroxy- diclofenac. In patients with renal dysfunction, peak concentrations of

metabolites 4'-hydroxy- and 5-hydroxy-diclofenac were approximately 50% and 4% of the parent compound after single oral dosing compared to 27% and 1% in normal healthy subjects.

Diclofenac is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulfate conjugates of the metabolites. Little or no free unchanged diclofenac is excreted in the urine. Approximately 65% of the dose is excreted in the urine, and approximately 35% in the bile as conjugates of unchanged diclofenac plus metabolites. The terminal half-life of unchanged diclofenac is approximately 1 hour.

Metabolism and excretion of HPβCD:

HPβCD is mainly eliminated through the kidney (~80%-90% of the dose), with a total systemic clearance in plasma of 98.0 ± 22.7 mL/min corresponding to glomerular filtration. A small amount of the IV dose might be eliminated by other pathways, most likely metabolism. The terminal half-life of HPβCD in plasma is approximately 2.7 ± 1.4 hours following IV administration of Dyloject 37.5 mg.

d) Based on PK parameters, what is the degree of linearity in the dose-concentration relationship?

A dose proportional increase in systemic exposure of diclofenac is noted following single dose and multiple dose IV administration of Dyloject.

As shown in the table above, following IV administration of IV Dyloject, diclofenac plasma levels were proportional to the dose.

e) How do the PK parameters change with time following chronic dosing?

Plasma levels of diclofenac after fourth dose are similar to that after the first dose. Consistent with the short half-life, diclofenac does not accumulate upon repeated administration every six hours (See multiple dose PK table above from study # DFC-006).

In studies conducted with Sporanox, HPβCD demonstrated no accumulation following successive daily doses and the majority of the 8 g dose of HPβCD was eliminated in the urine (reviewed under Sporanox NDA 20-966).

2.3 Intrinsic Factors

Demographic information of patients recruited in different clinical studies:

Clinical pharmacology studies: Two clinical pharmacology studies were conducted with Dyloject. Study DFC-PK-008 examined the clinical pharmacology and PK of diclofenac in elderly and higher weight subjects above 95 kg, and study DFC-PK-009 examined the clinical pharmacology and PK of diclofenac and HPβCD in subjects with renal and hepatic impairment (See study synopsis in Appendix). Eight subjects with mild renal impairment ($50 \leq$ creatinine clearance [CrCl] ≤ 80 mL/min), 5 subjects with moderate renal impairment ($30 \leq$ CrCl < 50 mL/min), 8 subjects with mild hepatic impairment

(Child-Pugh Classification A, Score of 5-6 and a bilirubin of ≤ 2.5 mg/dl), and 13 matched healthy controls entered into and completed the study. All subjects received a single 37.5 mg dose of DIC075V, containing 333 (b) (4) mg of HP β CD, administered IV over 15 seconds. Study N130310 evaluated HP β CD PK in Healthy Subjects and in Patients. This study was conducted by Janssen Pharmaceutical Research and examined the clinical pharmacology and PK of HP β CD in subjects with renal impairment. Reference is made to the letter of reference from Johnson and Johnson permitting Javelin access to the Sporanox NDA 20-966.

Clinical Study DFC#004: The mean age of subjects was approximately 43 years in each of the 4 treatment groups. The majority of subjects in each treatment group were female (269 of 331 subjects overall, 81%) and Caucasian (255 subjects, 77%). Overall, mean height and weight, respectively, were 167 cm and 84 kg. With regard to patients with bodyweight above 95 kg, there were 19 subjects in placebo group, 21 subjects in 18.75 mg, 16 subjects in 37.5 mg Dyloject groups, and 26 in ketorolac tromethamine group.

Clinical Study DFC#005: Of the 145 subjects who received Dyloject, 65 subjects were under 65 years of age with normal hepatic and renal function and between the weight of 50 to 95 kg, and received a dose of 37.5 mg. Forty-five subjects who were over 65 years of age or had impaired renal (only one received Dyloject) or mildly impaired hepatic function (only 3 subjects received Dyloject) or were below 50 kg (only five subjects received Dyloject) were considered high-risk in this study and received Dyloject 18.75 mg. Thirty-five subjects in the Dyloject group, 95 kg or greater (95 – 143 kg), received a dose of 50 mg. Of the 60 subjects who received ketorolac tromethamine, 42 subjects were under 65 years of age with normal hepatic and renal function and received a dose of 30 mg. According to the dosing recommendations in the approved package insert for ketorolac tromethamine, 18 subjects who were over 65 years of age or who had impaired renal or impaired hepatic function were considered high-risk and received a dose of 15 mg.

For the non-high-risk cohort in the ITT population (125 subjects), the majority of subjects in each treatment group were female, (96 subjects, 76.8%) and Caucasian (114 subjects, 91.2%), with an average age of 47.4 years, ranging from 19 to 65 years old. There were no significant differences across the treatment groups for any demographic characteristics.

Relative to the non-high-risk population, the majority of subjects in the high-risk cohort were elderly and heavier and had a greater proportion of male subjects. For the high-risk cohort in the ITT population (85 subjects), the majority of subjects in each treatment group were female, (50 subjects, 58.8%) and Caucasian (79 subjects, 92.9%), with an average age of 71.3 years, ranging from 29 to 84 years old. For the high-risk population as a whole, there were no significant differences across the treatment groups for any demographic characteristics.

- 1. What intrinsic factors (age, gender, weight, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?**

1a. What are the pharmacokinetic and pharmacodynamic characteristics of Dyloject in patients with different bodyweight?

Bodyweight has significant effect on clearance of diclofenac. (b) (4)

The product label should describe the effect of bodyweight on pharmacokinetics of Dyloject. (b) (4)

(b) (4)

There was no effect of age on PK of diclofenac (see synopsis of study # DFC-008 in Appendix). Since systemic levels of diclofenac were not collected in any of the Phase 2/3 studies, a formal covariate effect on systemic exposure-response could not be done. Nevertheless, a subset analysis with regard to clinical response in patients with different bodyweight was attempted (see overall conclusions at the end of this discussion).

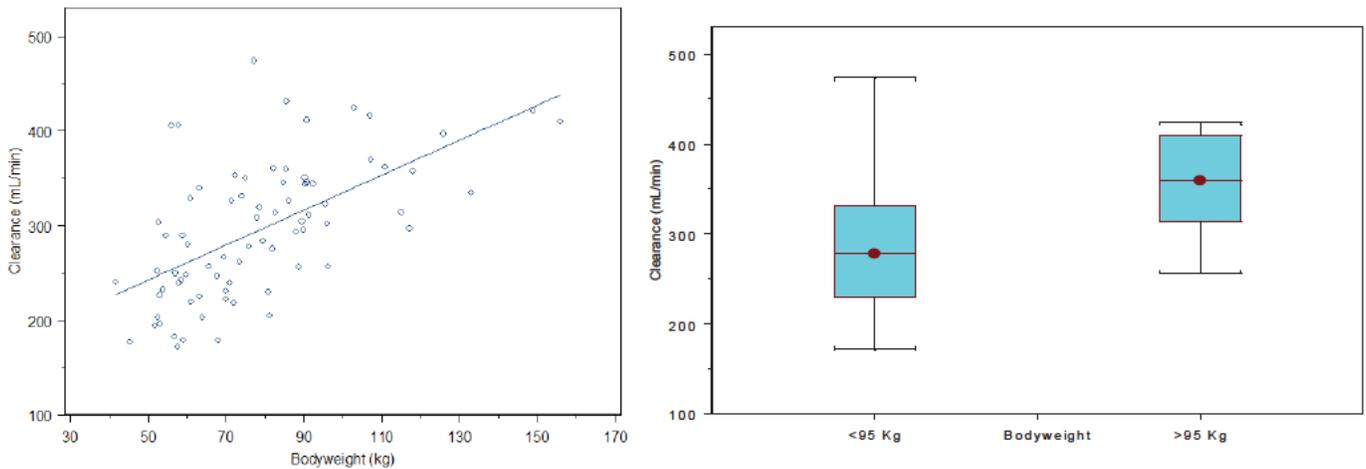
Clinical pharmacology study # DFC-008 assessed the effects of age, weight, and body composition on the pharmacokinetic profile, safety, and tolerability of IV Dyloject in adult volunteers. This study was conducted in 2 cohorts. The first cohort of subjects was selected based on body mass index (BMI) and weight criteria (weight cohort). The second cohort of subjects was selected based on age (age cohort). Each subject in the weight cohort received a single 37.5 mg dose of Dyloject and each subject in the age cohort received a single 18.75 mg dose of Dyloject. Blood samples for the measurement of diclofenac were collected for 18 hours after administration of the dose.

Table: Summary of Pharmacokinetic Parameters (mean±SD) after Single Intravenous Administration of 37.5 mg of Dyloject; Weight-based Cohort.

Parameter	Weight-Based Cohort				
	15≤BMI≤18.9 (N = 5)	19≤BMI≤24.9 45≤Weight<60 kg (N = 11)	19≤BMI<30 60≤Weight≤100 kg (N = 16)	30≤BMI≤40 (N = 13)	BMI>40 (N = 8)
C _{max} (ng/mL)	6,594 ± 2,258 (5)	8,212 ± 1,952 (11)	5,903 ± 1,060 (16)	5,103 ± 0,672 (13)	4,616 ± 1,639 (8)
T _{max} (h)	0.083 (5)	0.083 (11)	0.083 (16)	0.083 (13)	0.083 (8)
AUC _(0-t) (h×ng/mL)	2,190 ± 609 (5)	2,413 ± 616 (11)	1,916 ± 411 (16)	1,740 ± 265 (13)	1,569 ± 316 (8)
AUC _(inf) (h×ng/mL)	2,103 ± 651 (4)	2,429 ± 616 (11)	1,933 ± 412 (16)	1,757 ± 266 (13)	1,640 ± 302 (7)
λ _z (h ⁻¹)	0.3593 ± 0.1011 (4)	0.4321 ± 0.0962 (11)	0.4095 ± 0.0997 (16)	0.4568 ± 0.0847 (13)	0.4205 ± 0.1437 (7)
t _{1/2} (h)	2.03 ± 0.47 (4)	1.67 ± 0.34 (11)	1.79 ± 0.44 (16)	1.56 ± 0.25 (13)	1.81 ± 0.57 (7)
CL (mL/min)	297 ± 92.4 (4)	255 ± 71.4 (11)	314 ± 69.3 (16)	338 ± 53.0 (13)	363 ± 56.0 (7)
V _z (L)	50.4 ± 14.0 (4)	36.1 ± 10.1 (11)	47.9 ± 13.6 (16)	45.5 ± 9.60 (13)	56.4 ± 19.0 (7)

C_{max} - Maximum observed plasma concentration; T_{max} = Time at which C_{max} is observed; AUC_(0-t) = AUC up to the last quantifiable concentration; AUC_(inf) = AUC from time zero to infinite time; λ_z = Terminal elimination rate constant; t_{1/2} = Apparent elimination half-life; V_z = Volume of distribution; CL = Clearance

Figure: Relationship between CL and total body weight (Left figure) and box plot of clearance in bodyweight cohorts (Right figure) after IV administration of single 18.75 or 37.5 mg doses of DIC075V to healthy volunteers.



As noted in the figures above, higher clearance is noted in subjects with higher bodyweight/BMI. The sponsor chose to use a cutoff of 95 kg (b) (4) Clearance of diclofenac in subjects (n=63) below 95 kg is 282 ± 68 mL/min compared to 356 ± 53 mL/min in subjects (n=14) above 95 kg bodyweight (~ 27% higher clearance). Similarly, clearance of diclofenac in subjects with lower (~18%) bodyweight (45 – 60 kg) is lower compared to subjects with higher bodyweight (60 – 100 kg). As an extension to this observation, clearance of diclofenac might be significantly lower in pediatric patients down to neonates. Further evaluation of a bodyweight effect on pharmacokinetics will be important prior to embarking on pediatric studies.

The number of subjects in the higher bodyweight group is approximately 25% of overall subjects recruited in the PK study. In this regard, the number of subjects in the >95 kg bodyweight group in the two clinical trials (DFC-004 & DFC-005) was in the range of 18 – 32 % across different treatment groups.

In clinical trial DFC-005, the dose selected for patients above 95 kg was 50 mg, which is 33% more, compared to 37.5 mg, the regular dose for patients with bodyweight less than 95 kg. Additionally, subjects with bodyweight <50 kg received 18.75 mg Dyloject every six hours.

In clinical trial # DFC-004, clinical response (SPID at 48 hours) was assessed in terms of subgroups with respect to bodyweight (See table below). (b) (4)

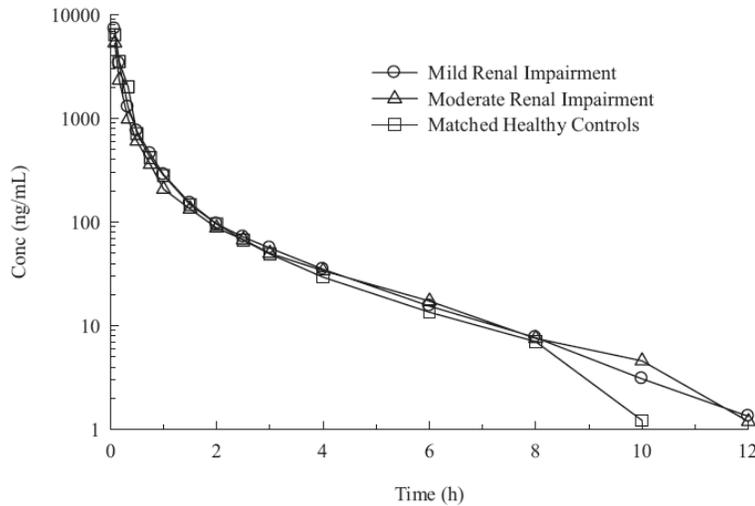
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Ib) What is the effect of renal impairment on diclofenac and HPβCD pharmacokinetics?

Dose adjustment of Dyloject is not needed in patients with renal impairment. Mild to moderate renal impairment did not alter the pharmacokinetics of diclofenac. Based on previously known information from Cataflam, PK of orally administered diclofenac did not change in patients with mild, moderate or severe renal impairment. On the other hand, HPβCD pharmacokinetics is significantly affected by mild to moderate renal function. However, the dose of HPβCD in Dyloject (333 mg) compared to Sporanox is significantly low (8 gm). Even with severe renal impairment, the systemic exposure to HPβCD following IV injection of Dyloject may be low compared to previously know clinical experience with Sporanox with renal impairment.

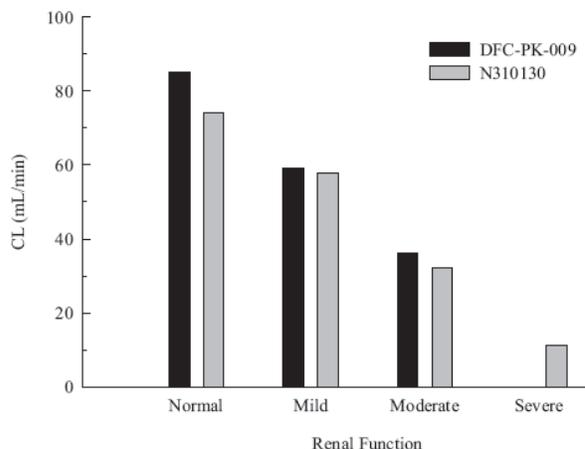
In study # DFC-009, the mean plasma diclofenac concentration-time curves were essentially the same for the subjects with mild and moderate renal impairment and the matched healthy controls.

Figure: PK profile of diclofenac following single dose IV injection of Dyloject 37.5 mg in healthy control subjects (Squares), subjects with mild renal impairment (Circles) and moderate renal impairment (Triangles).



The effect of renal impairment on the PK of HPβCD were examined in 2 studies. In study # DFC-009, conducted by Javelin, subjects with mild or moderate renal impairment and matched healthy controls received a 333 (b) (4) mg dose as a component of Dyloject 37.5 mg. In Study N310130, conducted by Janssen subjects with mild, moderate, and severe renal impairment and healthy controls received an 8000 mg dose as a component of Sporanox. The mean values for CL in healthy volunteers and subjects with mild and moderate renal impairment were in good agreement between the 2 studies (See figure below).

Figure: Clearance of HPβCD in healthy volunteers (Normal), patients with renal impairment (Mild, Moderate, Severe) in two different studies.



Across the two different studies, the systemic exposure of HPβCD following IV administration appears to be dose proportional in subjects with mild and moderate renal impairment and healthy subjects. For example, with a 25-fold increase in dose, AUC of HPβCD is ~20 – 28-fold higher following administration of 8 gram dose IV compared to 0.333 gram dose. Accordingly, assuming dose-proportionality in patients with severe renal impairment and adjusting for a dose of 0.333 gm used in DFC-PK-009, the AUC for HPβCD would be 500 h·μg/mL following administration of Dyloject 37.5 mg in patients with severe renal impairment. Hence, Dyloject may be used without dose adjustment in patients with renal impairment.

Table: PK parameters of HPβCD following IV administration of Dyloject (Study # DFC-009) or SporanoX (study # N310130, NDA 20-966).

Subject type	HPβCD PK Parameters from Study DFC-009 Dyloject (0.333 gm HPβCD given IV over 15 secs)				HPβCD PK Parameters from Study N310130 SporanoX (8gm HPβCD given IV over 60 mins)			
	C _{max} (μg/mL)	AUC (h×μg/mL)	t _{1/2} (h)	CL (mL/min)	C _{max} (μg/mL)	AUC (h×μg/mL)	t _{1/2} (h)	CL (mL/min)
Matched Controls	50.3 ± 7.7	67.3 ± 12.6	3.29 ± 1.66	85.2 ± 16.5	656 ± 100	1,870 ± 450	2.5 ± 0.8	74.2 ± 14.9
Mild Renal Impairment	60.7 ± 16.3	128.3 ± 91.1	2.87 ± 0.69	59.0 ± 31.3	617 ± 129	2,662 ± 1,188	4.1 ± 2.3	57.8 ± 22.7
Moderate Renal Impairment	52.7 ± 18.6	165.7 ± 60.4	6.04 ± 1.94	36.2 ± 10.0	594 ± 147	4,781 ± 2,260	9.2 ± 8.4	32.2 ± 12.1
Severe Renal Impairment	Not Evaluated (NE)	500.4 Estimated Average*	NE	NE	785 ± 96	13,323 ± 5,250	15.6 ± 6.0	11.1 ± 3.32

* Average exposure (AUC) in severe renal impairment estimated using the formula AUC = Dose/Clearance.

1c) What is the effect of hepatic impairment on diclofenac and HPβCD pharmacokinetics?

Hepatic Impairment:

Caution should be exercised when using Dyloject in patients with any degree of hepatic impairment.

Considerations for Dyloject use in patients with hepatic impairment include:

- *Peak plasma diclofenac levels with IV 18.75 mg & 37.5 mg Dyloject are 2.5 & 5-fold higher than oral, respectively.*
- *Systemic exposure of diclofenac following Dyloject 37.5 mg is ~20 -30% higher than orally administered 50 mg dose of Cataflam.*
- *Pharmacokinetics of Dyloject are similar in subjects with mild hepatic impairment compared to healthy subjects.*
- *Subjects with alcoholic cirrhosis had a ~3-fold higher AUC compared to healthy subjects following oral administration of diclofenac sodium.*
- *Lack of PK and safety data of IV Dyloject in patients with moderate to severe hepatic impairment*
- *“Hepatic Effects” of diclofenac/NSAID class labeling described in Cataflam label.*

Clinical reviewer, Dr. Rosemarie Neuner, indicated that there was adequate clinical safety data to support use of 37.5 mg dose in mild hepatic impairment from study # DFC-010. In conclusion, patients with mild hepatic impairment can be given Dyloject 37.5 mg. As recommended in Cataflam label, and to be consistent with the hepatic impairment guidance, patients with moderate and severe hepatic impairment may receive reduced doses of Dyloject over the proposed short term use.

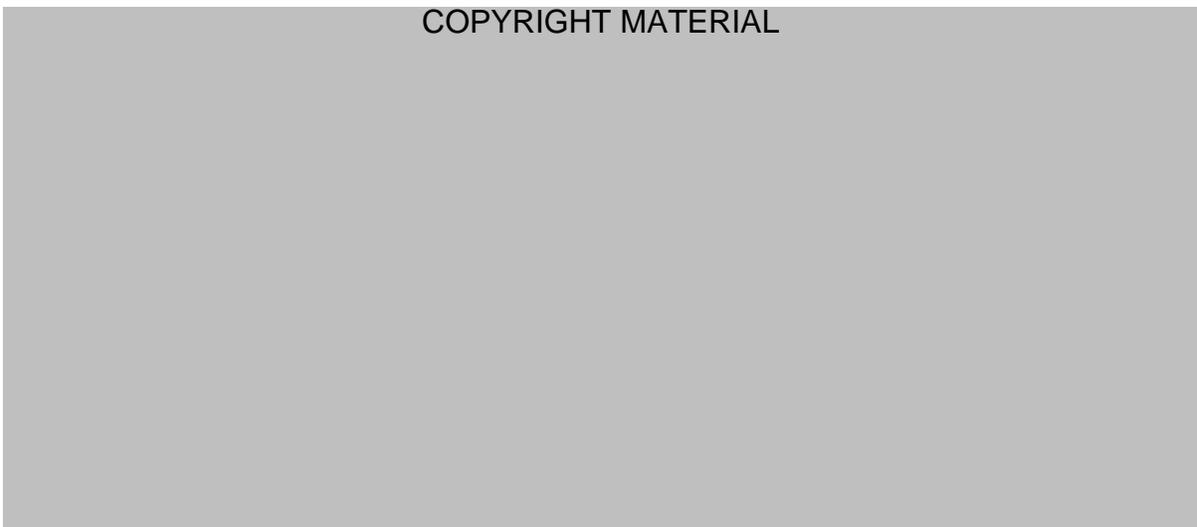
Diclofenac is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulfate conjugates of the metabolites. Little or no free unchanged diclofenac is excreted in the urine. Approximately 65% of the dose is excreted in the urine, and approximately 35% in the bile as conjugates of unchanged diclofenac plus metabolites. The terminal half-life of unchanged diclofenac is approximately 1 hour. This information is highly indicative of diclofenac being a drug with high hepatic extraction. Such drugs' disposition is potentially affected in situations where decrease in hepatic blood flow is anticipated, as is the case with hepatic impairment. That said, PK of diclofenac and HPβCD were not altered following IV administration of Dyloject to subjects with mild hepatic impairment (See tables below). The PK of Dyloject was evaluated in subjects with mild hepatic impairment as defined by Child-Pugh Classification, a score of 5-6 compared with matched healthy subjects DFC-PK-009.

Table: PK of diclofenac following IV administration of 37.5 mg Dyloject in patients with mild hepatic impairment and matched control subjects.

	C_{max} ($\mu\text{g/mL}$)	AUC ($\text{h}\times\mu\text{g/mL}$)	t_{1/2}(h)	CL (mL/min)
Matched Controls	5,884 \pm 897	1,640 \pm 335	1.92 \pm 0.28	367 \pm 74.7
Mild Hepatic Impairment	5,648 \pm 709	1,663 \pm 179	1.97 \pm 0.67	353 \pm 40.7

Lill J.S et.al (J. Clin. Pharmacol. 2000; 40(3):250-7) investigated the effect of alcoholic cirrhosis on pharmacokinetics of orally administered diclofenac buffered powder (150 mg in 100 mL water). Subjects with alcoholic cirrhosis had a mean \pm SD diclofenac AUC value (19,114 \pm 6806 ng.h/ml) which is ~3-fold higher compared to healthy subjects (7008 \pm 2006 ng.h/ml).

Table: Pharmacokinetics of diclofenac and its metabolites following oral administration.



Impact of moderate and severe hepatic impairment on IV diclofenac remains unknown. However, judging by the effect of alcoholic cirrhosis on oral diclofenac PK, higher systemic exposure with IV Dyloject can be a possibility.

Table: PK of HP β CD following IV administration of 37.5 mg Dyloject in patients with mild hepatic impairment and matched control subjects.

	C_{max} ($\mu\text{g/mL}$)	AUC ($\text{h}\times\mu\text{g/mL}$)	t_{1/2}(h)	CL (mL/min)
Matched Controls	40,791 \pm 4,975	53,651 \pm 11,321	2.28 \pm 0.42	107 \pm 21.2
Mild Hepatic Impairment	44,813 \pm 14,985	56,802 \pm 17,412	2.28 \pm 0.60	107 \pm 33.8

Pharmacokinetics of Dyloject has not been evaluated in patients with moderate to severe hepatic impairment patients.

1d) What is the effect of age on diclofenac and HPβCD pharmacokinetics?

Dose adjustment of Dyloject is not needed with regard to age of a patient.

Pharmacokinetics of Dyloject was evaluated in young adults in weight-based cohort with 37.5 mg dose compared to elderly patients receiving 18.75 mg dose. However, it should be noted that significant number of elderly (>65 yrs) age were administered 18.75 mg dose in study DFC-005. Clinical experience with 18.75 mg dose in elderly should be described in “Section 8.5: Geriatrics”.

Pharmacokinetics of Dyloject was evaluated in young adults in weight-based cohort with 37.5 mg dose compared to elderly patients receiving 18.75 mg dose. The table below indicates a dose-proportionally lower systemic exposure in elderly compared to young adults. Hence, pharmacokinetics of diclofenac following IV administration of Dyloject appears to be same in different age subjects.

Table: Summary of diclofenac pharmacokinetic parameters (mean±SD) after single intravenous administration of 18.75 mg of Dyloject in age-based cohort.

	C _{max} (ng/mL)	AUC (h*ng/mL)	t _{1/2} (h)	CL (mL/min)	V _z (L)
Dose of Dyloject: 37.5 mg 60 - 100 kg (18 – 45 years) bodyweight subjects	5,903 ± 1,060	1,933 ± 412	1.79 ± 0.44	314 ± 69.3	47.9 ± 13.6
Dose of Dyloject: 18.75 mg 55 ≤ Age < 65 yrs	3,439 ± 855	1,126 ± 291	1.39 ± 0.43	274 ± 70.6	32.7 ± 13.3
Dose of Dyloject: 18.75 mg 65 ≤ Age < 75 yrs	3,465 ± 738	1,178 ± 263	1.42 ± 0.34	257 ± 52.2	31.5 ± 9.26
Dose of Dyloject: 18.75 mg Age ≥ 75 yrs	3,257 ± 750	1,220 ± 96.8	2.14 ± 0.61	239 ± 19.8	44.3 ± 13.1

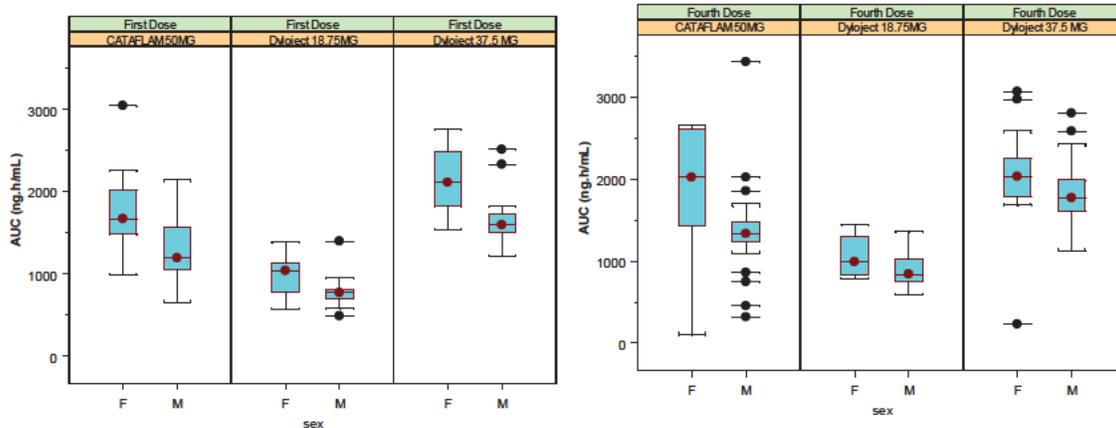
1e) What is the effect of Sex on diclofenac and HPβCD pharmacokinetics?

Plasma diclofenac AUC levels were 30% higher in females compared to males.

However, this is possibly due to the effect of bodyweight on diclofenac pharmacokinetics. In single dose, multiple dose PK studies the bodyweights of females were relatively lower compared to males. Upon bodyweight normalization the difference in clearance and volume of distribution disappear.

In relative bioavailability study # DFC-006 and study #DFC-008, systemic exposure of diclofenac was 30% higher in females compared to males.

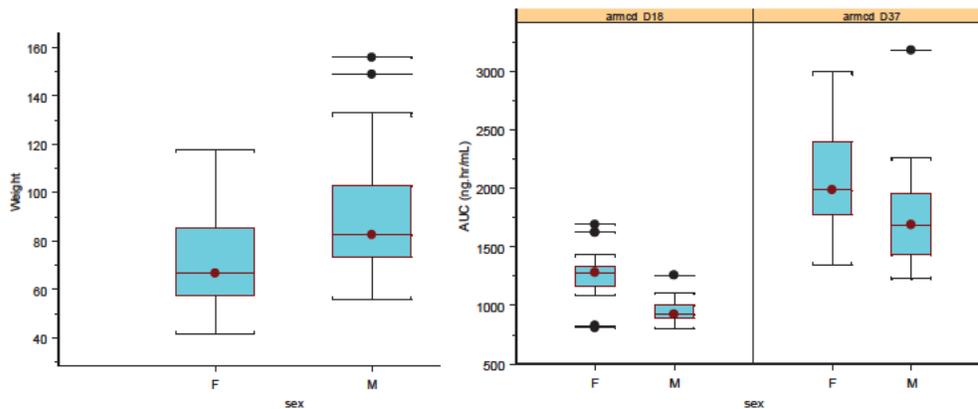
Figure: Box plot of AUC of diclofenac following single dose and multiple dose administration of Cataflam and Dyloject (18.75 or 37.5 mg) in male and female subjects in Study # DFC-006



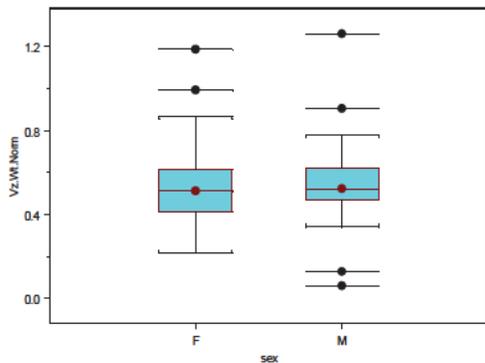
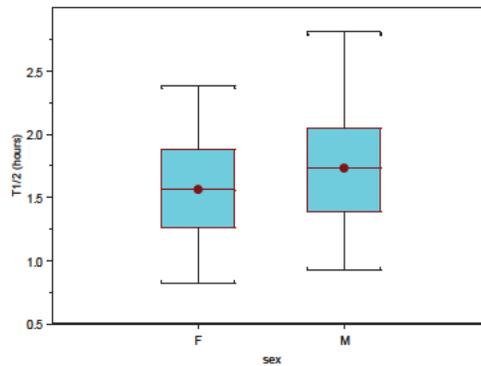
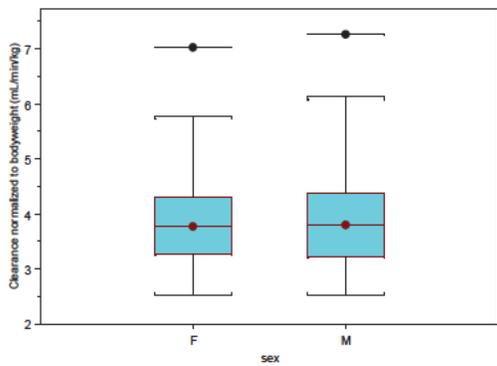
In study # DFC-008, considering all age groups, women (n=45 - 52) generally had lower bodyweight compared to men (n=31 - 33).

Table: First noted plasma concentration and AUC of diclofenac following Dyloject injection in males and females.

	Dyloject 18.75 mg		Dyloject 37.5 mg	
	Female	Male	Female	Male
C_{first} (ng/mL)	Mean: 4186.2 Std Dev. 1707 Total N: 21	Mean: 2843 Std Dev.: 539 Total N: 11	Mean: 6555.806 Std Dev.: 1712 Total N: 31	Mean: 4943.6 Std Dev.1048 Total N:22
AUC (ng hr/mL)	Mean: 1265.9 Std Dev. 243.4 Total N:17	Mean: 962.4 Std Dev. 143.7 Total N: 9	Mean:2088.5 Std Dev.: 470.7 Total N: 28	Mean:1755.33 Std Dev. 417.5 Total N:22



There was a 30% higher AUC in females compared to males as well as the first plasma concentration collected following IV Dyloject injection. Correspondingly clearance in females (269.5 ± 66.2 mL/min) was lower compared to males (317 ± 91.5 mL/min). However, after normalizing diclofenac clearance with bodyweight there was no significant difference with regard to sex. Hence, dose adjustment is not necessary with respect to sex since patients were adequately represented in the clinical trials. This observation is possibly due to the bodyweight effect described above.

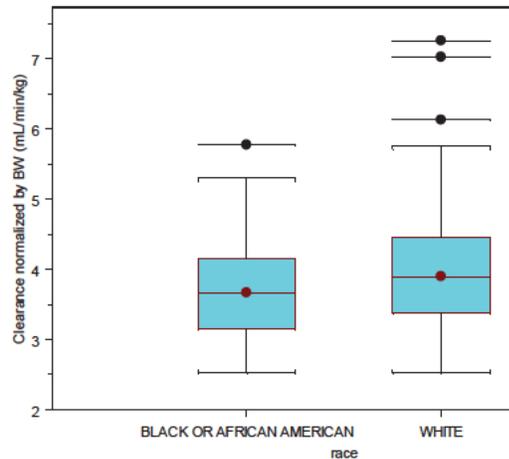
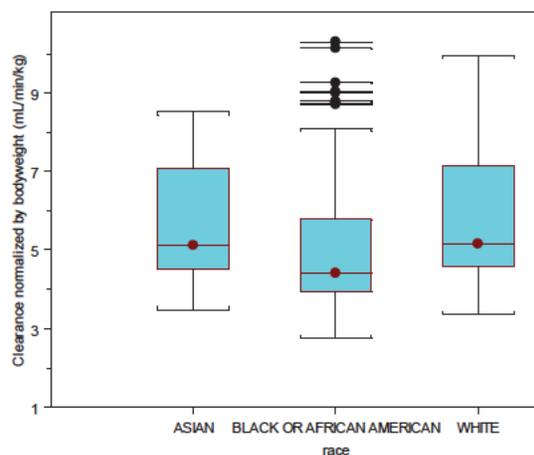


1f) What is the effect of race on diclofenac pharmacokinetics?

Pharmacokinetics of diclofenac following injection of Dyloject was studied in Caucasians, Blacks and Asians. After taking into account their bodyweights there was no difference in PK of diclofenac with respect to race.

In study # DFC-006, PK of Dyloject was investigated in subjects of Caucasian or Black/African origin. In study# DFC-008, Asian, Caucasian or Black/African origin subjects were included. Clearance of diclofenac was similar in subjects of different race after taking bodyweight into account.

Figure: clearance of diclofenac normalized by bodyweight in subjects of different race. Left figure from study # DFC-006, Right figure from study # DFC-008.



2.4 Extrinsic Factors

No new clinical studies have been conducted to evaluate the potential for extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) to influence dose/exposure-response of Dyloject. *In vitro* binding studies were conducted to evaluate potential for HP β CD to sequester concomitantly administered medications. HP β CD is considered for parenteral applications (b) (4)

Hydrophobic drugs may enter the cavity of the cyclodextrin molecule to form an inclusion complex, displacing water molecules and creating a more thermodynamically stable state.

The potential for interference with co-administered drugs from dissociated systemic HP β CD following IV administration of Dyloject was evaluated in *in vitro* study NC-DFC-015. A total of 10 drugs, ranging from low to high protein binding, that might be co-administered with Dyloject in the postsurgical period were examined. Phase-solubility studies were used to determine the stability binding constants ($K_{1:1}$) for drug/HP β CD complexes and the equilibrium dialysis method was used to examine HSA/HP β CD competitive binding. Results from this study demonstrate that protein binding was not affected for drugs that were weakly protein bound across the wide range of concentrations of HP β CD tested (50, 500, and 5,000 mcg/mL).

In study DFC-013 (See synopsis attached), an analysis was conducted using the competitive binding model and the list of actual co-administered drugs used during the postsurgical period for the multiple-dose, multiple-day, pivotal controlled studies DFC-004 and DFC-005 and the open label safety study DFC-010. From the list of 1,711 co-medications from the pivotal studies, vitamins and nutritional supplements were removed and duplicate drug names were eliminated. For the remainder, K_p values based on protein binding were derived for 343 drugs and $K_{1:1}$ values were found for 63 of these drugs from the published literature. These 63 drugs were analyzed using the competitive binding model to predict the impact of HP β CD upon free and protein-bound drug.

A list of 33 drugs that are highly protein bound (for this analysis, any value in excess of 95%) and for which $K_{1:1}$ values were available. The 3 drugs with the highest K_p and $K_{1:1}$ values were telmisartan, testosterone and Anafranil, 331,667 M^{-1} and 40,000 M^{-1} , 81,667 M^{-1} and 12,000 M^{-1} , 53,889 M^{-1} and 9,600 M^{-1} , respectively. The binding coefficient for the drug/protein complexes exceeded those of the drug/HP β CD complexes by 8.3-fold, 6.8-fold and 5.6-fold, respectively. For the co-administered drugs in the pivotal clinical studies, drug/HP β CD complexes have $K_{1:1}$ values in the range of 2.5 to 42,000 M^{-1} . Therefore, for all the 33 drugs listed, regardless of degree of protein binding, $K_{1:1}$ values were well below the threshold of 180,000 M^{-1} at which HP β CD could potentially impact the PK profile of these drugs.

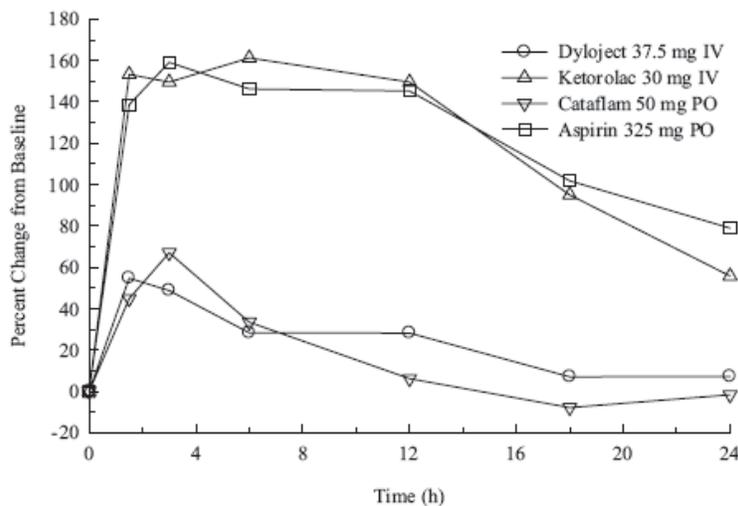
Effect of Dyloject on Platelet function:

In clinical study # DFC-007, sponsor evaluated the effect of Dyloject on platelet function. Study # DFC-007 is an open-label, randomized, single-dose, four-treatment crossover study to evaluate platelet function in healthy adult male volunteers following administration of intravenous diclofenac sodium (Dyloject 37.5 mg), oral diclofenac potassium (Cataflam® 50 mg), intravenous ketorolac tromethamine 30 mg and oral

acetylsalicylic acid (ASA 325 mg). Blood samples for platelet function closure time measured by PFA-100 were obtained at screening; baseline; time 0 (immediately pre-dose); 1.5, 3, 6, 12, 18, and 24 hours post-dose on Days 1, 3, 5, and 7; and at the follow-up visit (7 +/- 3) days after discharge from the unit on Day 8 [or at the discretion of the investigator]. Blood samples for platelet count, PT, and aPTT were collected at screening; baseline; time 0, 3, and 24 hours postdose; and at the follow-up visit.

Employing PFA-100 analyzer, equipment that measures platelet plug formation in a small, whole blood sample and reports a closure time, the time to platelet plug formation was routinely measured during exposure to collagen and epinephrine (CEPI) or, separately, collagen and adenosine diphosphate (CADP). The sponsor determined the area under the curve of platelet closure time difference from baseline over 0-6 hours (AUEC_{0-6h}) (See Figure below). Just as in PK analysis, the trapezoidal rule was used to estimate this AUE. Actual sampling times were used in all pharmacodynamic (PD) analyses.

Figure: Mean Percent Change from Pre-dose in Platelet Closure Time (Collagen and Epinephrine) Following Administration of Intravenous DIC075V 37.5 mg, Intravenous Ketorolac 30 mg, Oral Cataflam® 50 mg, and Oral Aspirin 325 mg to Healthy Adult Male Subjects.



As measured by PFA CEPI, there was a statistically significant ($p < 0.0001$) overall treatment effect for the primary endpoint, the area under the platelet closure time difference curve over 0-6 hours (AUEC_{0-6h}). In addition, there were statistically significant ($p < 0.0001$) treatment effects for PFA CEPI-measured AUEC over 0-12, 0-18, and 0-24 hours. Mean AUEC_{0-6h} for platelet function closure time based on differences from baseline was significantly less following administration of IV DIC075V 37.5 mg than after PO ASA 325 mg ($p < 0.0001$), and IV ketorolac tromethamine 30 mg ($p < 0.0001$), but there was no difference between Dyloject and oral diclofenac (Cataflam). For PO ASA 325 mg and IV ketorolac tromethamine 30 mg, this effect persisted over all subsequent time intervals. Mean PFA CEPI-measured AUEC_{0-12h}, AUEC_{0-18h}, and AUEC_{0-24h} were each significantly ($p < 0.0001$) lower for Dyloject 37.5 mg than for either of the other drugs. However, there were no significant differences between the two diclofenac treatments over the 0-6, 0-12, 0-18, and 0-24 hour intervals.

As measured by PFA CADP, there were statistically significant overall treatment effects for mean AUEC_{0-12h}, AUEC_{0-18h}, and AUEC_{0-24h} platelet function closure times based on differences from baseline. Mean AUEC_{0-6h} following Dyloject 37.5 mg administration was significantly lower than after PO ASA 325 mg (p=0.0026) and IV ketorolac tromethamine 30 mg (p=0.0288), but no difference was noted with diclofenac 50 mg (Cataflam). Secondary analyses revealed that following Dyloject 37.5 mg administration mean PFA CADP-measured AUEC_{0-12h}, AUEC_{0-18h}, and AUEC_{0-24h} were all significantly lower than after PO ASA 325 mg and IV ketorolac tromethamine 30 mg (p<0.0184 or less at all times for both comparator drugs), with no differences observed from PO Cataflam 50 mg.

In conclusion, the study results seem to indicate that Dyloject 37.5 mg and Cataflam have quantitatively less of an effect on platelet function compared to ketorolac and aspirin. However, clinical significance of this observation remains unknown. As such all NSAID's, including Cataflam, carry a class label related "**Precaution**" pertaining to "Hematological effects" reading as follows:

"NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Patients receiving Cataflam who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored."

In this regard, the study results partially (reversibility of effect not addressed) confirm the NSAID class labeling language for Dyloject and Cataflam. Hence, a description of the study results in "Clinical Pharmacology, 12.2 Pharmacodynamics" section does not add value to the product label in terms of better informing the practitioner.

2.5 General Biopharmaceutics

(b) (4)

Earlier studies were conducted with exploratory formulations DIC075U and DIC075T (b) (4)

Subsequently, all clinical studies were conducted with formulation DIC075V which is the "to be marketed" formulation and contains a higher concentration of diclofenac sodium (37.5 mg/mL).

Table: Comparison of the compositions of the exploratory and "to-be-marketed" formulations of Dyloject (diclofenac sodium) Injection

Component	DIC075T (b) (4)	DIC075U (b) (4)	DIC075V ¹ (b) (4)
Diclofenac sodium	(b) (4)	(b) (4)	37.5 mg/mL
HPβCD	(b) (4)	(b) (4)	333 (b) (4) mg/mL
Monothioglycerol	(b) (4)	(b) (4)	5 mg/mL
Sodium hydroxide	(b) (4)	(b) (4)	Adjust pH
Hydrochloric acid	(b) (4)	(b) (4)	Adjust pH
Water	(b) (4)	(b) (4)	(b) (4)

¹DIC075V is the intended "to be marketed" formulation. (b) (4)

2.6 Analytical

Plasma concentrations of diclofenac were measured using validated high pressure liquid chromatography with ultraviolet detection (HPLC/UV) (b)(4) and liquid chromatography with tandem mass spectrometry (LC-MS/MS) (b)(4) methods. Urine concentrations of diclofenac were measured using a validated HPLC/UV method. Plasma concentrations of HPβCD were measured using validated HPLC/UV (b)(4) and LC-MS/MS (b)(4) assays. Plasma concentrations of ketorolac were determined using a validated HPLC/UV method and concentrations of acetylsalicylic acid and salicylic acid were measured using a validated LC-MS/MS assay; these methods were conducted (b)(4)

Table: Summary of bioanalytical laboratories, methods and applicable studies for diclofenac in plasma

Laboratory (b)(4)	Method	Studies (b)(4)
(b)(4)	HPLC/UV	19/94, 26/97, 27/97
	LC-MS/MS	DFC-PL1, DFC-003
	LC-MS/MS	DFC-PK-006, DFC-PK-008, DFC-PK-009, DFC-011
	LC-MS/MS	DFC-007 (b)(4)

Table: Summary of validation results for the assay of diclofenac in human plasma – (b)(4)

Range (ng/mL) ¹	Quality Control Samples (ng/mL)	Precision (%) With-In Day
30-3,000	36.3; 72.2; 108.6; 1,086	1.78-13.2
1,000-20,000	2,174; 4,362; 12,230; 20,387	1.04-2.89

Table: Summary of validation results for the assay of diclofenac in human plasma – (b)(4)

Quality Control Samples ¹ (ng/mL)	Precision (%) Within-Day	Precision (%) Between-Day
QC1: 25.60	2.9	-
QC2: 75.48 ²	-	8.0
QC3: 1821.33 ²	1.5	4.7
QC4: 4036.45 ²	3.6	5.7
QC5: 7974.45	1.9	4.4
QC6: 24612.50 ¹	-	1.2
QC7: 246.13 ¹	-	13.2
QC8: 39380.00 ¹	-	8.6

Table: Summary of validation results for the assay of diclofenac in human plasma – (b)(4)

Quality Control Samples (ng/mL)	Precision (%) Within-Day	Precision (%) Between-Day
5 (LLOQ)	2.5	6.3
15 (low)	2.0	3.2
400 (medium)	1.0	1.9
1,600 (high)	0.5	3.4
10,000 (very high, dilution)	--	1.9

Table: Summary of validation results for the assay of diclofenac in human plasma –
(b) (4)

Quality Control Samples (ng/mL)	Precision (%) Within-Day	Precision (%) Between-Day
10	3.81	4.22
20	2.67	2.69
50	2.65	5.50
150	3.74	2.23
400	2.08	3.16
1,500	2.85	2.53

Plasma and urine concentrations of HP β CD have been measured using HPLC/UV and LCMS/

MS. The pharmacokinetic studies, bioanalytical methods, and bioanalytical laboratories are summarized in Table below.

Laboratory	Method	Studies
(b) (4)	HPLC/UV	N99397, N79079, N130310
	LC-MS/MS	DFC-PK-009, DFC-011

Table: Summary of validation results for the assay of HP β CD in human plasma –
(b) (4)

Quality Control Samples (ng/mL)	Precision (%) Within-Day	Precision (%) Between-Day
300	2.3-8.0	4.8
1,500	3.7-10.9	3.6
7,500	3.5-7.0	7.6

3 Labeling

Sponsor proposed changes to the product label are indicated in regular font. Revisions are indicated as strikethrough text for deletion, highlighted text for addition.

(b) (4)



4.2 Individual Study Reviews

4.2.1 Study # DFC-006 Synopsis:

Name of finished product: DIC075V (diclofenac sodium) Injection 37.5 mg/mL

Name of active ingredient: Diclofenac sodium

Title of study: An Open-Label, Randomized, Single-center Study to Compare the Pharmacokinetics of Intravenous Diclofenac Sodium (DIC075V 18.75 and 37.5 mg) versus Oral Diclofenac Potassium (Cataflam® 50 mg) in Healthy Adult Volunteers Following Single- and Multiple-dose Administration

Investigators: Terri H. Lunsford, MD

Study center: Single-center study

PAREXEL Clinical Pharmacology Research Unit
Baltimore, Maryland, 21225 USA

Publication: None

Study period: First subject enrolled: 20 March 2007; Last subject completed: 01 May 2007

Development phase: Phase 1

Objectives: To assess the pharmacokinetic parameters of intravenous diclofenac sodium (DIC075V) 18.75 mg and 37.5 mg following single- and multiple-dose administration, as compared to oral diclofenac potassium (Cataflam® 50 mg), the approved reference product.

Methodology: Open-label, 3-treatment, 6-sequence, 3-period, single-center crossover study to evaluate the pharmacokinetics of IV diclofenac sodium (DIC075V 18.75 and 37.5 mg) versus oral diclofenac potassium (Cataflam 50 mg) following single- and multiple-dose administration. Study drug was administered every 6 hours for a total of 4 doses during each 1-day treatment period. The treatment sequences are summarized below:

1. DIC075V 18.75 mg as a 0.5 mL IV bolus on Day 1, DIC075V 37.5 mg as a 1.0 mL IV bolus on Day 4, and Cataflam 50 mg orally with 240 mL water on Day 7
2. DIC075V 18.75 mg as a 0.5 mL IV bolus on Day 1, Cataflam 50 mg orally with 240 mL water on Day 4, and DIC075V 37.5 mg as a 1.0 mL IV bolus on Day 7
3. DIC075V 37.5 mg as a 1.0 mL IV bolus on Day 1, DIC075V 18.75 mg as a 0.5 mL IV bolus on Day 4, and Cataflam 50 mg orally with 240 mL water on Day 7
4. DIC075V 37.5 mg as a 1.0 mL IV bolus on Day 1, Cataflam 50 mg orally with 240 mL water on Day 4, and DIC075V 18.75 mg as a 0.5 mL IV bolus on Day 7
5. Cataflam 50 mg orally with 240 mL water on Day 1, DIC075V 18.75 mg as a 0.5 mL IV bolus on Day 4, and DIC075V 37.5 mg as a 1.0 mL IV bolus on Day 7
6. Cataflam 50 mg orally with 240 mL water on Day 1, DIC075V 37.5 mg as a 1.0 mL IV bolus on Day 4, and DIC075V 18.75 mg as a 0.5 mL IV bolus on Day 7

The study was completed as planned.

Number of subjects: It was planned to include 36 subjects in the study. A total of 71 subjects underwent screening visits and 36 subjects (21 male/15 female, 20-52 years old) were dosed in the study. All 36 of these subjects were included in both the pharmacokinetic and safety analyses. Thirty-five subjects completed the study in full compliance with the protocol. One subject failed to return for the follow-up visit and was recorded as lost-to-follow-up.

Indication and main criteria for inclusion: Healthy, adult volunteers between the ages of 18 and 55 years weighing ≥ 50 kg and with a BMI between 18 and 30 kg/m² were to be enrolled.

Investigational drug: DIC075V (diclofenac sodium), 18.75 mg and 37.50 mg administered as an IV bolus. Batch number: IDDS062804.

Reference therapy: Cataflam[®] (oral diclofenac potassium), 50 mg administered via oral tablet with 240 mL of room-temperature bottled water. Batch number: C5J00751.

Duration of treatment: Three 1-day treatment periods separated by a 2-day washout period. Total treatment duration was approximately 8 days, with a 7-day follow-up period.

Criteria for evaluation:

Efficacy: No assessments of efficacy were performed.

Safety: Safety was assessed throughout the study using the following measures: Adverse event monitoring, laboratory tests, ECGs, physical examinations, vital signs, and concomitant medications evaluations.

Pharmacokinetics: Blood samples were obtained on Day 1, Day 4, and Day 7 at the following times: before the first dose, 5, 10, 20, 30, and 45 minutes and 1, 1.5, 2, 2.5, 3, 4, and 6 hours after the first dose; before the third dose; before the fourth dose and 5, 10, 20, 30, and 45 minutes and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 hours after the fourth dose. The following PK parameters were evaluated for each treatment using a noncompartmental analysis: C_{max} , T_{max} , $AUC_{(0-t)}$, AUC_{∞} , λ_{z} , and $t_{1/2}$ (first dose); C_{max} , T_{max} , $AUC_{(0-6)}$, λ_{z} , and $t_{1/2}$ (fourth dose); CL and Vz (IV treatments); CL/F and Vz/F (oral treatment).

Statistical methods: PK parameters – C_{max} and AUC_{∞} for the first dose and C_{max} and $AUC_{(0-6)}$ for the fourth dose – were compared among treatments using an ANOVA model with subject and dose number as the classification variables, using the natural logarithms of the data. Confidence intervals (90%) were constructed for the geometric mean ratios (fourth dose to first dose) of both parameters using the log-transformed data and the two one-sided t tests procedure. CL, Vz, and $t_{1/2}$ were compared between the 18.75 and 37.5 mg IV doses using an ANOVA model with subject and dose as the classification variables.

Results:

Efficacy: Not applicable.

Safety: Adverse events were reported for 8% to 14% of subjects during any given treatment period. All of the events were of mild intensity and resolved spontaneously without treatment. The highest incidence of AEs was observed during the IV DIC075V 18.75 mg treatment period (14% of subjects). The most commonly reported treatment emergent AEs are summarized in the table below.

MedDRA Preferred term	DIC075V 18.75 mg	DIC075V 37.5 mg	Cataflam 50 mg
	(N = 36) n (%)	(N = 36) n (%)	(N = 36) n (%)
Number of subjects with at least 1 AE	5 (13.9)	3 (8.3)	3 (8.3)
Headache	1 (2.8)	1 (2.8)	1 (2.8)
Abdominal Pain	1 (2.8)	0	1 (2.8)
Dental Discomfort	0	1 (2.8)	0
Dyspepsia	1 (2.8)	0	0
Flatulence	1 (2.8)	0	0
Injection Site Irritation	1 (2.8)	0	0
Injection Site Pain	1 (2.8)	0	0
Dizziness	0	0	1 (2.8)

No subjects were discontinued from the study due to AEs and there were no serious AEs and no deaths. No clinically significant chemistry or hematology changes were observed. There were no observed differences between treatments for vital signs or ECG findings.

Pharmacokinetics: Plasma concentrations and PK parameters of diclofenac are presented in the table below.

Variable ^a	DIC075V 18.75 mg IV	DIC075V 37.5 mg IV	Cataflam 50 mg Oral
<i>First dose</i>			
C _{max} (ng/mL)	2904 (661)	6031 (1178)	1246 (732)
T _{max} (h)	0.083 (0.083 – 0.150)	0.083 (0.083 – 0.150)	1.50 (0.33 – 3.00)
t _{1/2} (h)	1.39 (0.29)	1.44 (0.27)	1.28 (0.27)
AUC ₀₋₄ (h·ng/mL)	866 (221)	1843 (394)	1473 (488)
AUC _∞ (h·ng/mL)	898 (231)	1859 (376)	1562 (519)
<i>Fourth dose</i>			
C _{max} (ng/mL)	3090 (1029)	5617 (1799)	851 (462)
T _{max} (h)	0.083 (0.000 – 0.133)	0.083 (0.067 – 0.183)	1.49 (0.000 – 6.000)
t _{1/2} (h)	1.82 (0.48)	2.29 (0.63)	2.80 (0.66)
AUC ₀₋₆ (h·ng/mL)	935 (203)	1839 (506)	1350 (601)

^aArithmetic mean (SD) except for T_{max} for which the median (range) is reported.

Conclusions: The C_{max} of IV DIC075V 37.5 mg exceeds that of oral Cataflam by approximately 5 fold (6031 vs 1246 ng/mL). Mean plasma concentrations and dose-related PK parameters increased in a dose-proportional manner after IV administration of 18.75 and 37.5 mg of DIC075V. The bioavailability of oral diclofenac after dosing with Cataflam 50 mg was approximately 66% of that after IV DIC075V. Absolute exposure (AUC uncorrected for dose) to diclofenac after IV administration of 18.75 mg and 37.5 mg of DIC075V bracketed that after oral administration of 50 mg of Cataflam.

Both dose levels of DIC075V were safe and well tolerated in this study. Reported AEs were comparable to those observed after oral administration of 50 mg Cataflam.

4.2.2 Study # DFC-008 synopsis:

Name of finished product: DIC075V (diclofenac sodium) Injection 37.5 mg/mL

Name of active ingredient: Diclofenac sodium

Title of study: An Open-label, Single-dose Study to Assess the Effects of Age, Weight, and Body Composition on the Pharmacokinetic Profile, Safety, and Tolerability of Intravenous Diclofenac Sodium (DIC075V) in Adult Volunteers

Investigators: Terri Lunsford, MD; William A. Gerson, DC (b) (4)

Study centers: Multi-center study.

PAREXEL Clinical Pharmacology Research Unit (CPRU)
3001 S. Hanover St.
Baltimore, Maryland 21225, USA

Comprehensive Phase One
3400 Enterprise Way
Miramar, Florida 33025, USA

Publications: None

Study period: First subject enrolled: 24 August 2007; Last subject completed: 11 March 2008

Development phase: Phase 1

Objectives: To assess the effects of age, weight, and body composition on the PK profile, safety, and tolerability of IV DIC075V in adult volunteers.

Methodology: This was an open-label, single-dose study to assess the effects of age, weight, and body composition on the PK profile, safety, and tolerability of IV diclofenac sodium (18.75 mg or 37.5 mg DIC075V) in adults. This study was conducted in two cohorts. The first cohort of subjects (Weight-based Cohort) was selected based on body mass index (BMI) and weight criteria. These subjects received a single dose of 37.5 mg DIC075V administered as a bolus IV injection. The second cohort of subjects (Age-based Cohort) was selected based on age. These subjects received a single dose of 18.75 mg DIC075V administered as a bolus IV injection. The study was completed as planned. The two study cohorts are outlined in the tables below.

Treatment Group / Description	Subjects Planned (N)	Weight-based Cohort			
		Subjects Enrolled (N)	Weight (kg)	BMI (kg/m ²)	DIC075V (mg)
A: Underweight	9	5	Not defined	≥ 15 and ≤ 18.9	37.5
B: Small	9	11	≥ 45 and < 60	≥ 19 and ≤ 24.9	37.5
C: Large	9	16	≥ 60 and ≤ 100	≥ 19 and < 30	37.5
D: Obese	9	13	Not defined	≥ 30 and ≤ 40	37.5
E: Extremely Obese	9	9	Not defined	>40	37.5
Total	45	54			

Treatment Group / Description	Age-based Cohort		DIC075V (mg)
	Subjects Planned (N)	Subjects Enrolled (N)	
A: Age \geq 55 and < 65 yrs	12	15	18.75
B: Age \geq 65 and < 75 yrs	12	14	18.75
C: Age \geq 75 yrs	12	5	18.75
Total	36	34	

Number of subjects: A total of 88 subjects were enrolled in the study. For the Weight-based Cohort, 45 subjects were planned and 54 (23 male/31 female, 18-54 years old) subjects were enrolled. For the Age-based Cohort, 36 subjects were planned and 34 (13 male/21 female, 55-82 years old) subjects were enrolled. All subjects completed the study and all were included in the safety analysis. One subject in the Weight-based Cohort and 6 subjects in the Age-based Cohort had plasma concentrations of diclofenac that were considered aberrant; these subjects were not included in the primary PK analysis.

Indication and main criteria for inclusion: Adult male and female subjects were enrolled in this study. For the Weight-based Cohort, subjects were \geq 18 and <55 years of age, with a BMI \geq 15 kg/m² and body weight in the range of 40 – 159 kg. For the Age-based Cohorts, subjects were \geq 55 years of age, with a BMI \geq 19 and \leq 30 kg/m², and body weight \geq 45 kg and \leq 95 kg.

Investigational drug: DIC075V (diclofenac sodium) Injection 18.75 mg and 37.5 mg, administered as a bolus IV injection. Lot number PPS04010.

Reference therapy: None

Duration of treatment: Subjects received a single dose of study drug and were discharged from the clinic approximately 24 hours later. A safety follow-up visit was performed approximately 7 days after study drug dosing.

Criteria for evaluation:

Efficacy: No assessments of efficacy were performed.

Safety: Safety was assessed during the study by monitoring AEs, concomitant medications, vital signs, laboratory results, ECGs and by physical examinations.

Pharmacokinetics: Blood samples for PK analysis were obtained at the following time points: Time 0 (pre-dose), 5, 10, 20, 30, and 45 minutes and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, and 18 hours post-dose. The following PK parameters were calculated using non-compartmental analysis: Maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), area under the time-concentration curve to the last sample with a measurable concentration (AUC_{0-t}) and to infinity (AUC_{∞}), elimination rate constant (λ_z), elimination half-life ($t_{1/2}$), clearance (CL), and volume of distribution (V_z).

Statistical methods: Plasma concentrations and PK parameters were summarized by cohort and dose using descriptive statistics. Potential relationships between the independent PK parameters CL and V_z and the dependent parameter $t_{1/2}$ and the demographic variables age, total body weight, and BMI were examined using linear regressions of each PK parameter against each demographic variable. Since age, body weight, and BMI are continuous variables, data from the Weight-based and Age-based Cohorts were combined for these analyses.

Adverse event, clinical laboratory, vital signs, physical examination, and ECG data were tabulated using descriptive statistics.

Safety: There were no deaths, no SAEs, no AEs of severe or moderate severity, and no AEs that led to discontinuation from the study in either the Weight-based or the Age-based Cohort during this study.

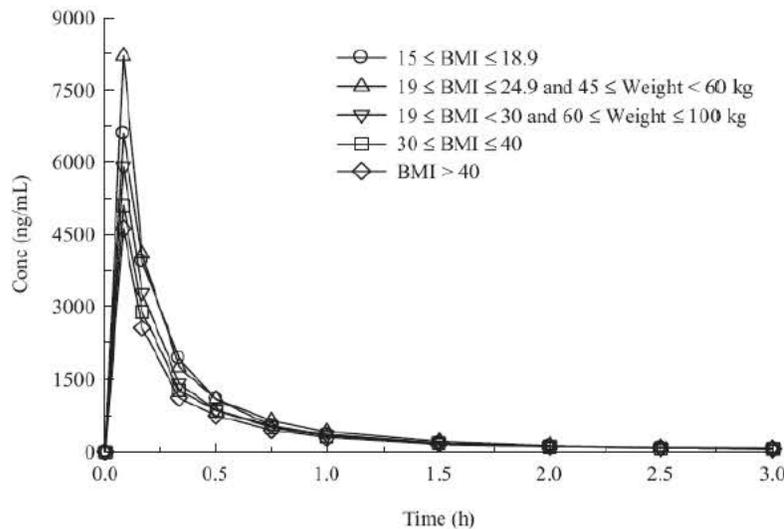
Nine of 54 subjects (16.7%) in the Weight-based Cohort experienced treatment-emergent AEs following single doses of 37.5 mg DIC075V. Treatment Group B (Small) had the highest percentage of subjects with treatment-emergent AEs (36.4%), followed by Treatment Groups D (Obese; 23.5%), and C (Large; 12.5%). No treatment-emergent AEs were reported in Treatment Groups A (Underweight) or E (Extremely Obese). There were no clinically significant findings in vital signs, clinical laboratory results, ECGs, or physical examinations and there were no apparent trends in safety signals relative to weight.

In the Age-based Cohort, 3 of 34 subjects (8.8%) experienced treatment-emergent AEs following single doses of 18.75 mg DIC075V. One clinically significant vital sign abnormality was reported as a mild, unrelated AE (elevated systolic blood pressure) in Treatment Group C (78 years of age). There were no clinically significant findings in ECGs or physical examinations and there were no apparent trends in safety signals relative to age.

Pharmacokinetics: One subject in the Weight-based Cohort and 6 subjects in the Age-based Cohort had plasma concentrations of diclofenac that were considered aberrant; analyses with these subjects excluded are presented below.

Weight-based Cohort:

The mean plasma concentrations and PK parameters of diclofenac in the Weight-based Cohort are presented in the figure and table below. The mean plasma diclofenac concentration-time curves were essentially the same for the 5 treatment groups in the Weight-based Cohort as were mean values for all parameters.



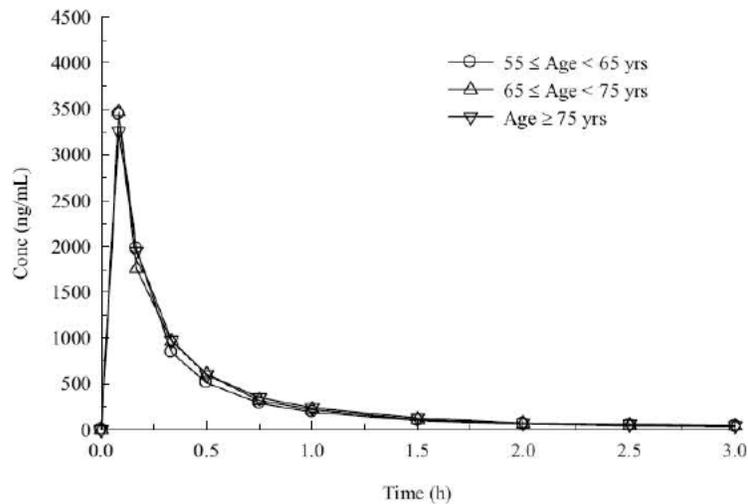
Parameter ²	Weight-Based Cohort ¹				
	15 ≤ BMI ≤ 18.9 (N = 5)	19 ≤ BMI ≤ 24.9 45 ≤ Weight ≤ 60 kg (N = 11)	19 ≤ BMI < 30 60 ≤ Weight ≤ 100 kg (N = 16)	30 ≤ BMI ≤ 40 (N = 13)	BMI > 40 (N = 8)
C _{max} (ng/mL)	6,594 ± 2,258 (5)	8,212 ± 1,952 (11)	5,903 ± 1,060 (16)	5,103 ± 0,672 (13)	4,616 ± 1,639 (8)
T _{max} (h)	0.083 (5)	0.083 (11)	0.083 (16)	0.083 (13)	0.083 (8)
AUC(0-t) (h×ng/mL)	2,190 ± 609 (5)	2,413 ± 616 (11)	1,916 ± 411 (16)	1,740 ± 265 (13)	1,569 ± 316 (8)
AUC(inf) (h×ng/mL)	2,103 ± 651 (4)	2,429 ± 616 (11)	1,933 ± 412 (16)	1,757 ± 266 (13)	1,640 ± 302 (7)
λ _z (h ⁻¹)	0.3593 ± 0.1011 (4)	0.4321 ± 0.0962 (11)	0.4095 ± 0.0997 (16)	0.4568 ± 0.0847 (13)	0.4205 ± 0.1437 (7)
t _{1/2} (h)	2.03 ± 0.47 (4)	1.67 ± 0.34 (11)	1.79 ± 0.44 (16)	1.56 ± 0.25 (13)	1.81 ± 0.57 (7)
CL (mL/min)	297 ± 92.4 (4)	255 ± 71.4 (11)	314 ± 69.3 (16)	338 ± 53.0 (13)	363 ± 56.0 (7)
V _z (L)	50.4 ± 14.0 (4)	36.1 ± 10.1 (11)	47.9 ± 13.6 (16)	45.5 ± 9.60 (13)	56.4 ± 19.0 (7)

1 Number in parenthesis is the number of subjects dosed that did not have aberrant plasma concentrations.

2 Arithmetic mean ± standard deviation (N) except for T_{max} for which the median (N) is reported.

Age-based Cohort:

The mean plasma concentrations and PK parameters of diclofenac in the Age-based Cohort are presented in the figure and table below. Overall, the mean plasma diclofenac concentration-time curves were comparable among the 3 treatment groups in the Age-based Cohort, as were the mean values for the PK parameters.



Parameter ²	Age-Based Cohort ¹		
	55 ≤ Age < 65 yrs (N = 12)	65 ≤ Age < 75 yrs (N = 13)	Age ≥ 75 yrs (N = 3)
C _{max} (ng/mL)	3,439 ± 855 (12)	3,465 ± 738 (13)	3,257 ± 750 (3)
T _{max} (h)	0.083 (12)	0.083 (13)	0.083 (3)
AUC(0-t) (h×ng/mL)	1,087 ± 288 (12)	1,143 ± 261 (13)	1,200 ± 95.9 (3)
AUC(inf) (h×ng/mL)	1,126 ± 291 (11)	1,178 ± 263 (12)	1,220 ± 96.8 (3)
λ _z (h ⁻¹)	0.5437 ± 0.1728 (11)	0.5165 ± 0.1351 (12)	0.3438 ± 0.1035 (3)
t _{1/2} (h)	1.39 ± 0.43 (11)	1.42 ± 0.34 (12)	2.14 ± 0.61 (3)
CL (mL/min)	274 ± 70.6 (11)	257 ± 52.2 (12)	239 ± 19.8 (3)
V _z (L)	32.7 ± 13.3 (11)	31.5 ± 9.26 (12)	44.3 ± 13.1 (3)

1 Number in parenthesis is the number of subjects dosed that did not have aberrant plasma concentrations.

2 Arithmetic mean ± standard deviation (N) except for T_{max} for which the median (N) is reported.

Effects of Age, Weight, and BMI on CL, V_z, and t_{1/2}:

Since age, weight, and BMI are continuous variables, data from the Age- and Weight-based Cohorts were combined for regression analyses of these parameters. Examination of the relationships between CL, V_z, and t_{1/2} and age, total body weight and BMI indicated significant relationships between CL and weight (p < 0.0001), V_z and age (p = 0.0183), V_z and weight (p < 0.0001), and t_{1/2} and age (p = 0.0480). Relationships with BMI were consistent with those for weight, a major component of BMI.

The clearance of diclofenac did not appear to be affected by age. However, there was a significant increase in CL with increased body weight, suggesting that maintaining a “standard” exposure (AUC) by varying dose in higher-weight subjects should be considered.

There was also a significant decrease in V_z, which resulted in a decrease in t_{1/2} with increased age.

Conclusions: There were no deaths, no SAEs, no AEs of severe or moderate severity, and no AEs that led to discontinuation from the study. Therefore recommendations for dosing are based upon analyses of the effect of subject age and weight upon PK parameters.

Regression analysis of all subjects demonstrated no effect of age upon CL. There was, however, a significant decrease in V_z with increased age which resulted in a decrease in t_{1/2} with increased age. This suggests that there would be a decreased risk of accumulation of DIC075V in elderly subjects. Therefore, modification of the dosing regimen of DIC075V should not be necessary for elderly subjects.

Regression analysis of all subjects demonstrated that CL increased significantly with increasing body weight. This finding suggests that an increased DIC075V dose may be indicated in order to achieve an effective drug exposure (AUC) in individuals whose body weight exceeds 95 kg.

Additional Comments:

Apparent Aberrant Diclofenac Plasma Concentrations

One subject in the Weight-based Cohort and 6 subjects in the Age-based Cohort had plasma concentrations of diclofenac that were considered aberrant ([Table below](#)). Subjects 9116 and 9117 had concentrations 0.083 hour (5 minutes) after drug injection that were 27,600 ng/ml and 102,000 ng/ml, respectively, 8- and 30-fold higher than the mean concentration at that time excluding those subjects. In addition, the concentration in the next sample, 14,500 ng/ml, for Subject 9117 was 7.4-fold higher than the mean for the remainder of the Age-based Cohort. A plausible explanation for these samples is that they were drawn from the same cannula used to inject drug. The aberrant concentrations in the remainder of the subjects occurred essentially during the elimination phase. Concentrations increased 10.5-fold between the preceding and succeeding samples for Subject 9002, 65.8-fold for Subject 9106, 268-fold for Subject 9107, and 934-fold for

Subject 9118. Sponsor indicates that although all concentrations were verified analytically, none are realistic from a physiologic perspective and it is unlikely that the source of these discrepancies can be determined. But it is likely that these samples may have been drawn from the same cannula used to inject drug.

Table: Subjects with Apparent Aberrant Diclofenac Plasma Concentrations

Cohort	Subject	Group	Time (h)	Conc (ng/mL)	Fold Increase ¹
Weight	9002	E	4.0	296	10.5
Age	9106	A	4.0	2,820	65.8
	9107	A	2.5	4,570	268.2
	9113	B	10.0	432	— ²
			12.0	465	— ²
			18.0	16	— ²
	9116	A	0.083	27,600	8.0
	9117	C	0.083	102,000	31.3
			0.167	14,500	7.4
9118	C	6.0	11,100	934.3	

Conc. = Concentration

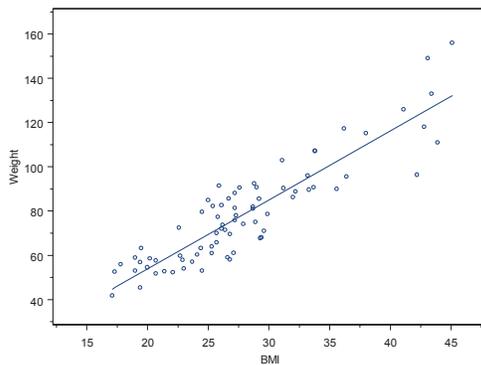
Age-based Cohort: A: 55 ≤ Age < 65 yr ; B: 65 ≤ Age < 75 yr; C: 75 yr ≤ Age

Weight-based Cohort E: 40 < BMI kg/m²

¹Fold increase over the mean concentration at that time, excluding the apparent aberrant subjects.

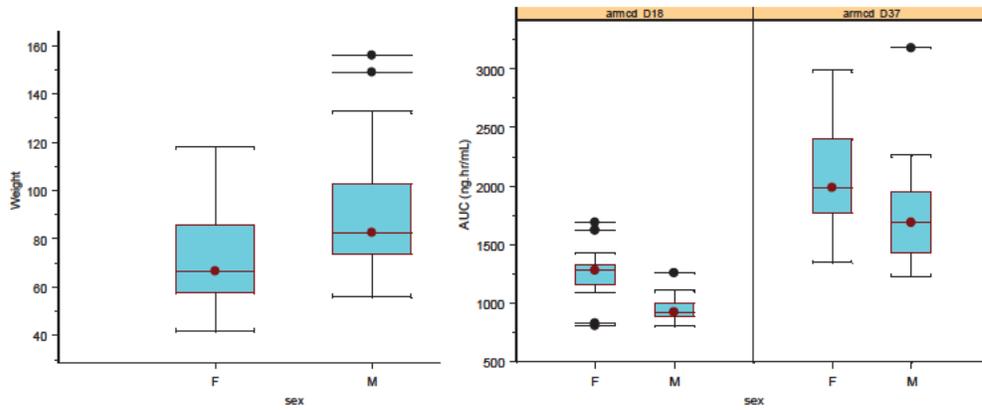
²All other concentrations were 0, i.e., < lower limit of quantitation and no fold increase could be calculated.

In this study, data indicates that BW and BMI are very well correlated.

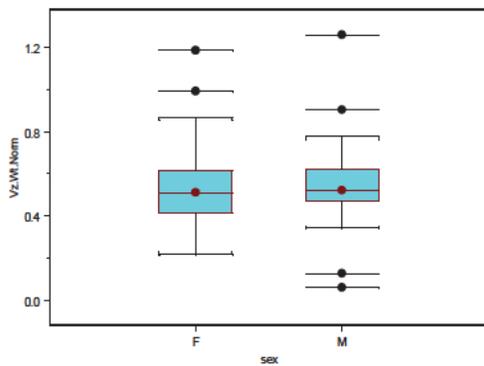
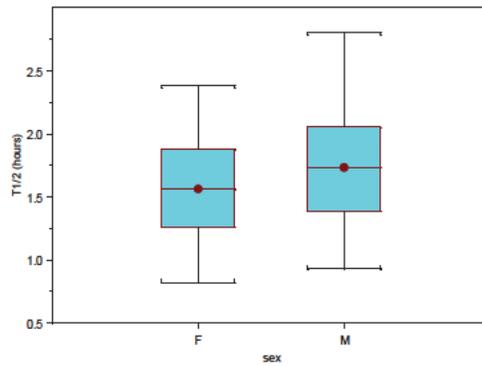
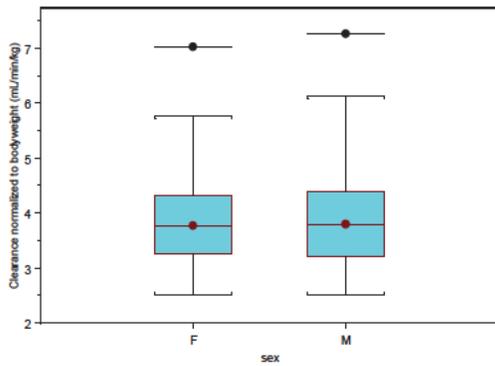


Considering all age groups, women (n=45 - 52) generally had lower bodyweight in this study compared to men (n=31 - 33).

	Dyloject 18.75 mg		Dyloject 37.5 mg	
	Female	Male	Female	Male
Cmax (ng/mL)	Mean: 4186.2 Std Dev. 1707 Total N: 21	Mean: 2843 Std Dev.: 539 Total N: 11	Mean: 6555.806 Std Dev.: 1712 Total N: 31	Mean: 4943.6 Std Dev.1048 Total N:22
AUC (ng hr/mL)	Mean: 1265.9 Std Dev. 243.4 Total N:17	Mean: 962.4 Std Dev. 143.7 Total N: 9	Mean:2088.5 Std Dev.: 470.7 Total N: 28	Mean:1755.33 Std Dev. 417.5 Total N:22



There was a 30% higher AUC in females compared to males as well as the first plasma concentration collected following IV Dyloject injection. Correspondingly clearance in females (269.5 ± 66.2 mL/min) was lower compared to males (317 ± 91.5 mL/min). After normalizing diclofenac clearance with bodyweight there was no significant difference with regard to sex. Hence, this observation can be indicated in the label. However, dose adjustment is not necessary with respect to sex since patients were adequately represented in the clinical trials. This observation is possibly due to the bodyweight effect described above.



4.2.3 Study # DFC-009 Synopsis:

Name of finished product: DIC075V (diclofenac sodium) Injection) 37.5 mg/mL

Name of active ingredient: Diclofenac sodium

Title of study: An Open-label, Single-dose Study to Evaluate the Safety and Pharmacokinetics of DIC075V in Subjects with Mild or Moderate Chronic Renal Insufficiency and in Patients with Mild Chronic Hepatic Impairment Compared to Healthy Adult Volunteers and a Randomized, Open-label, Single-dose, Two-way, Crossover Study to Evaluate the Safety and Pharmacokinetics of HPβCD when Administered in DIC075V Compared to Sporanox[®] in Healthy Adult Volunteers

Investigators: Salvatore Febbraro, MD; Suzanne Swan, MD; William Smith, MD; Thomas Marbury, MD

Study centers: Multi-center study

Davita Clinical Research
825 South 8th Street, Suite 300
Minneapolis, Minnesota 55404, USA

New Orleans Clinical Center for Research
1928 Alcoa Highway, Suite G50
Knoxville, Tennessee 37920, USA

Orlando Clinical Research Center
5055 South Orange Avenue
Orlando, Florida 32809, USA

Simbec Research Limited
Merthyr Tydfil Industrial Park
Mid Glamorgan CF48 4DR, UK

Publications: None

Study period: First subject enrolled: 8 December 2008; Last subject completed: 23 March 2009

Development phase: Phase I

Objectives: 1) To evaluate the safety and pharmacokinetics of diclofenac and HPβCD following a single-dose of DIC075V in subjects with mild or moderate chronic renal insufficiency and in subjects with mild hepatic impairment compared to healthy adult volunteers. 2) To evaluate the safety and pharmacokinetics of HPβCD following a single-dose of DIC075V and Sporanox in healthy adult volunteers.

Methodology: This was an open-label, single-dose study to evaluate the safety and pharmacokinetics of DIC075V 37.5 mg given as an IV bolus over 15 seconds in subjects with mild or moderate chronic renal insufficiency and in subjects with mild chronic hepatic impairment compared to matched healthy adult volunteers. Additionally, the healthy adult volunteers participated in a randomized, open-label, crossover study in which they received a single dose of Sporanox[®] 200 mg given as an IV infusion over 60 minutes to compare the safety and pharmacokinetics of HPβCD when administered in DIC075V compared to Sporanox. The study was completed as planned.

Number of subjects: A total of 40 subjects were enrolled: 13 subjects with renal insufficiency, 8 subjects with mild hepatic impairment, and 19 healthy subjects. All subjects with renal insufficiency and hepatic impairment were included in the safety and PK analyses. Of the 19 healthy subjects, all were included in the safety analysis and 13 were included in the final PK analysis.

Indication and main criteria for inclusion: Adult male and female subjects were enrolled in the study, including subjects 18 – 75 years of age with mild or moderate chronic renal insufficiency (creatinine clearance [CrCl] 50 to 80 or 30 to < 50 mL/min), mild chronic hepatic impairment (Child-Pugh Classification A, Score of 5-6 and a bilirubin of ≤ 2.5 mg/dL), and healthy subjects 18 – 65 years of age with normal renal function (CrCl > 80 mL/min) and normal hepatic function. The healthy subjects were matched by age (± 10 years), gender, and body weight (± 10 kg) to the subjects with mild chronic renal insufficiency and to the subjects with mild chronic hepatic impairment.

Investigational drug: DIC075V 37.5 mg administered to all subjects as an IV bolus over 15 seconds. DIC075V contains diclofenac sodium (37.5 mg/mL) as the active ingredient and hydroxypropyl-β-cyclodextrin (HPβCD, 333.5 mg/mL) as a solubilizing agent. Lot number P028060Z.

Reference therapy: Sporanox 200 mg administered as an IV infusion over 60 minutes to healthy subjects only. Sporanox (itraconazole injection for intravenous infusion) contains itraconazole (10 mg/mL) as the active ingredient and HPβCD (400 mg/mL) as a solubilizing agent. Lot number 6JBK000.

Duration of treatment: All subjects received a single dose of DIC075V. Healthy volunteers also received a single dose of Sporanox. Subjects were discharged from the clinic approximately 24 hours after study drug administration was completed. A safety follow-up visit was performed approximately 7 days after study drug dosing.

Criteria for evaluation:

Efficacy: No assessments of efficacy were performed.

Safety: Safety was assessed during the study by monitoring AEs, concomitant medications, vital signs, laboratory results, ECGs and by physical examinations.

Pharmacokinetics: Blood samples for PK analysis were obtained at the following time points: Time 0 (pre-dose), 5, 10, 20, 30, and 45 minutes and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, and 24 hours post-dose. The following PK parameters for diclofenac and HPβCD were calculated using non-compartmental analysis: C_{max} , T_{max} , AUC_{0-t} , AUC_{∞} , λ_z , $t_{1/2}$, CL, and V_z .

Statistical methods: Pharmacokinetic parameters C_{max} , AUC_{0-t} , and AUC_{∞} for diclofenac and HPβCD were compared among healthy adult volunteers and subjects with mild chronic renal insufficiency using graphical displays and an ANOVA model with renal function as the classification variable using the natural logarithms of the data. Pharmacokinetic parameters C_{max} , AUC_{0-t} , and AUC_{∞} for HPβCD were compared for the healthy volunteers after receiving DIC075V and Sporanox using graphical displays and an ANOVA model using the natural logarithms of the data.

Results:

Efficacy: Not applicable.

Safety: There were no deaths, withdrawals due to AEs, or serious adverse events (SAEs) in this study. All reported events were mild or moderate in intensity. The overall incidence and severity of treatment-emergent AEs was similarly low in all cohorts. Following DIC075V administration, 2 subjects (15.4%) with renal insufficiency, and 1 subject (12.5%) with mild hepatic impairment were recorded as having drug-related AEs and no drug-related AEs were reported by healthy subjects. There were no reports of adverse hepatic or renal AEs in the patients with renal or hepatic impairment. No clinically significant study drug effects were observed for clinical chemistry or hematology parameters or for renal function or liver function tests. No clinically significant out-of-range vital signs or ECG results were observed during the study.

Pharmacokinetics:

Renal Impairment

The elimination rate of diclofenac was not dependent upon the degree of renal impairment. The degree of renal impairment did affect the elimination rate of HPβCD. There was a decrease in the CL of HPβCD, with corresponding increases in $AUC_{(inf)}$ and $t_{1/2}$ with decreased renal function and a 2.4-fold decrease in CL and a 1.8-fold increase in $t_{1/2}$ were observed in subjects with moderate renal impairment when compared to healthy subjects. Exposure to HPβCD was markedly reduced following administration of DIC075V compared to Sporanox. Using moderate renal impairment as the “worst case,” the exposure to HPβCD after a 37.5 mg dose of DIC075V is 7.9-fold lower based on AUC, and 3.9-fold lower based on C_{av} , than in healthy subjects administered Sporanox, indicating that exposure to HPβCD in DIC075V poses no risk to patients with mild or moderate renal impairment. A summary of PK parameters for diclofenac and HPβCD after administration of DIC075V 37.5 mg to subjects with mild or moderate renal impairment and to healthy subjects is presented below.

Parameter ^a	Diclofenac			HPβCD		
	Renal Impairment		Healthy Matches n = 7	Renal Impairment		Healthy Matches n = 7
	Mild n = 8	Moderate n = 5		Mild n = 8	Moderate n = 5	
C_{max} (ng/ml)	7286 ± 1430	5332 ± 1629	7163 ± 950	60750 ± 16275	52700 ± 18565	50329 ± 7731
T_{max} (h)	0.083	0.083	0.083	0.083	0.083	0.083
$AUC_{(inf)}$ (h·ng/ml)	1943 ± 409	1550 ± 422	1968 ± 315	128349±91132	165728±60386	67316±12615
$\lambda_{(inf)}$ (h ⁻¹)	0.3856 ± 0.088	0.3427±0.080	0.3725 ± 0.055	0.2549 ± 0.068	0.1226 ± 0.033	0.2510 ± 0.095
$t_{1/2}$ (h)	1.89 ± 0.46	2.10 ± 0.44	1.90 ± 0.30	2.87 ± 0.69	6.04 ± 1.94	3.29 ± 1.66
CL (ml/min)	312 ± 73.0	401 ± 126	303 ± 55.6	59.0 ± 31.3	36.2 ± 10.0	85.2 ± 16.5
V_z (l)	49.8 ± 12.1	69.7 ± 9.22	50.2 ± 14.1	13.6 ± 5.38	17.7 ± 1.88	23.3 ± 9.84

^aArithmetic mean ± standard deviation except for T_{max} , for which the median is reported

Hepatic Impairment

There were no differences in the PK of diclofenac or HPβCD in subjects with mild hepatic impairment compared to matched healthy controls. A summary of PK parameters for diclofenac and HPβCD after administration of DIC075V 37.5 mg to subjects with mild hepatic impairment is presented below.

Parameter ^a	Diclofenac		HPβCD	
	Mild Impairment (n = 8)	Healthy Matches (n = 7)	Mild Impairment (n = 8)	Healthy Matches (n = 7)
C_{max} (ng/ml)	5648 ± 709	5884 ± 897	44813 ± 14985	40917 ± 4975
T_{max} (h)	0.083	0.083	0.083	0.083
$AUC_{(inf)}$ (h·ng/ml)	1663 ± 179	1640 ± 335	56802 ± 17412	53651 ± 11,321
$\lambda_{(inf)}$ (h ⁻¹)	0.3793 ± 0.098	0.3678 ± 0.050	0.3226 ± 0.084	0.3127 ± 0.052
$t_{1/2}$ (h)	1.97 ± 0.67	1.92 ± 0.28	2.28 ± 0.60	2.28 ± 0.42
CL (ml/min)	353 ± 40.7	367 ± 74.7	107 ± 33.8	107 ± 21.2
V_z (l)	60.1 ± 21.5	59.9 ± 9.4	20.0 ± 4.19	20.6 ± 2.45

^aArithmetic mean ± standard deviation except for T_{max} , for which the median is reported

Conclusions: No adjustment in DIC075V dose is recommended for patients with mild or moderate renal insufficiency or mild hepatic impairment. The elimination rate of diclofenac was not dependent on the degree of renal insufficiency following administration of DIC075V 37.5 mg. The rate of elimination of HPβCD was dependent on the degree of renal insufficiency although exposure levels were significantly lower compared to Sporanox. The elimination rate of diclofenac and HPβCD was not dependent on the degree of hepatic impairment following administration of DIC075V 37.5 mg.

4.2.4 Study # DFC-007 Synopsis

Name of finished product: DIC075V (diclofenac sodium) Injection 37.5 mg/mL

Name of active ingredient: Diclofenac sodium

Title of study: An Open-Label, Randomized, Single-Dose, Four-Treatment Crossover Study to Evaluate Platelet Function in Healthy Adult Male Volunteers Following Administration of Intravenous Diclofenac Sodium (DIC075V 37.5 mg), Oral Diclofenac Potassium (Cataflam® 50 mg), Intravenous Ketorolac Tromethamine 30 mg and Oral Acetylsalicylic Acid (ASA 325 mg)

Investigator: William A. Gerson, DO

Study center: Comprehensive Phase One
3400 Enterprise Way
Miramar, FL 33025 USA

Publications: None

Study period: First subject enrolled: 01 October 2007; Last subject completed: 13 November 2007

Development phase: Phase 1

Objectives: The objective of this study was to assess platelet function and safety in healthy male subjects following single-dose administration of IV diclofenac sodium (DIC075V 37.5 mg) versus oral diclofenac potassium (Cataflam 50 mg), IV ketorolac tromethamine 30 mg, and oral acetylsalicylic acid (ASA 325 mg).

Methodology: This was an open-label, randomized, single-dose, 4-treatment, 4-phase, 6-sequence crossover study conducted in healthy adult male subjects. Study drug administration occurred on Days 1 (Period 1), 3 (Period 2), 5 (Period 3), and 7 (Period 4). Subjects received a single dose of each study drug treatment, with ASA as the last treatment for all sequence groups in this crossover design. DIC075V and ketorolac were administered as a 1 mL bolus IV injection. Cataflam and ASA were administered orally with 240 mL of water. The six sequences were as follows:

1. DIC075V 37.5 mg on Day 1, ketorolac 30 mg on Day 3, Cataflam 50 mg on Day 5, and ASA 325 mg on Day 7
2. DIC075V 37.5 mg on Day 1, Cataflam 50 mg on Day 3, ketorolac 30 mg on Day 5, and ASA 325 mg on Day 7
3. Ketorolac 30 mg on Day 1, DIC075V 37.5 mg on Day 3, Cataflam 50 mg on Day 5, and ASA 325 mg on Day 7
4. Ketorolac 30 mg on Day 1, Cataflam 50 mg on Day 3, DIC075V 37.5 mg on Day 5, and ASA 325 mg on Day 7
5. Cataflam 50 mg on Day 1, ketorolac 30 mg on Day 3, DIC075V 37.5 mg on Day 5, and ASA 325 mg on Day 7
6. Cataflam 50 mg on Day 1, DIC075V 37.5 mg on Day 3, ketorolac 30 mg on Day 5, and ASA 325 mg on Day 7

Number of subjects: Approximately 80 subjects were to be screened and approximately 30 subjects were to be randomized to obtain 24 completed subjects (4 in each of the 6 treatment sequences). Thirty subjects (30 male, 21-54 years old) were randomized and 29 subjects completed the study. The 29 subjects who completed all 4 treatments were included in the PK Population. All 30 randomized subjects who received at least 1 dose of study drug were included in the Safety and Platelet Function Populations.

Indication and main criteria for inclusion: Healthy, non-smoking male volunteers between 18 and 55 years of age.

Investigational drug: DIC075V (diclofenac sodium) 37.5 mg administered as a 1 mL bolus IV injection. Lot No. PPS04010.

Reference therapy:

- Cataflam (diclofenac potassium) 50 mg administered orally. Lot No. C5J00751.
 - Ketorolac tromethamine 30 mg administered as a 1 mL bolus IV injection. Lot No. 51-174-DK.
 - Oral acetylsalicylic acid (ASA) 325 mg administered orally. Lot No. 3015.
-

Duration of treatment: Four 1-day treatment periods separated by a 2-day washout period. Total treatment duration was approximately 8 days.

Criteria for evaluation:

Efficacy: No efficacy variables were evaluated.

Safety: Adverse event monitoring, physical examination assessments, vital sign measurements, 12-lead ECGs, and standard laboratory tests (hematology, blood chemistry, and urinalysis).

Pharmacokinetics: Plasma concentration levels of diclofenac (following IV and oral administration), ketorolac, and ASA and salicylic acid were determined. Blood samples were obtained at time 0 (pre-dose); 1.5, 3, 6, 12, 18, and 24 hours post-dose on Days 1, 3, 5, and 7; and at the follow-up visit (7 days after discharge from the unit on Day 8). Blood samples for drug concentration measurements were obtained immediately after each platelet function sample was drawn. The following PK parameters for each treatment were generated from plasma concentration-time data using standard non-compartmental methods: maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), and area under the plasma concentration-time curve from zero to the final sample with a concentration at or above the limit of quantitation (LOQ) (AUC_{0-t}).

Pharmacodynamics (platelet function): Blood samples for platelet function closure time measured by PFA-100 were obtained at screening; baseline; time 0 (pre-dose); 1.5, 3, 6, 12, 18, and 24 hours post-dose on Days 1, 3, 5, and 7; and at the follow-up visit (7 days after discharge from the unit on Day 8). Blood samples for platelet count, PT, and aPTT were collected at screening; baseline; time 0 (pre-dose), 3, and 24 hours post-dose; and at the follow-up visit.

Statistical methods: Descriptive statistics were calculated to summarize the PK parameters (C_{max} , T_{max} , and AUC_{0-t}). The primary platelet function endpoint was area under the curve of the platelet closure time difference from baseline over 0-6 hours (AUC_{0-6h}), as measured by the PFA-100. The secondary endpoints included areas under the curve of the platelet closure time difference from baseline over 0-12 (AUC_{0-12h}), 0-18 (AUC_{0-18h}), and 0-24 (AUC_{0-24h}) hours; the maximum change from baseline in closure time as measured by the PFA-100; observed values and changes from baseline for closure time as measured by PFA-100; platelet count, PT, and aPTT at each time point, and shifts from baseline for the platelet count, PT, and aPTT tests at each time point.

Relationships between platelet function and the exposure to each drug were explored graphically by plotting the absolute and percentage change from baseline versus plasma concentration and plotting the area under the percentage change from baseline versus the area under the plasma concentration-time curve.

Efficacy: Not applicable.

Safety: All reported AEs were mild in intensity. There were no deaths, SAEs, or withdrawals due to AEs. Study medications were well tolerated and AEs for each of the study drugs were similar in incidence, severity, and attribution. All 4 single-dose treatments (IV DIC075V 37.5 mg, IV ketorolac 30mg, PO Cataflam 50 mg, and PO ASA 325 mg) were well tolerated. Five subjects experienced at least 1 treatment-emergent AE: 1 (3.3%) subject experienced flatulence following administration of IV DIC075V; 2 (6.9%) subjects experienced flatulence following administration of IV ketorolac; 1 (3.4%) subject experienced flatulence and 1 (3.4%) subject experienced headache following administration of oral Cataflam, and no AEs were reported following the administration of oral ASA. The only event assessed by the investigator as related to study drug was headache following administration of Cataflam.

MedDRA Preferred Term	DIC075V 37.5 mg	Ketorolac 30 mg	Cataflam 50 mg	ASA 325 mg
	(N = 30) n (%)	(N = 29) n (%)	(N = 29) n (%)	(N = 29) n (%)
At least 1 AE	1 (3.3) ^a	2 (6.9)	2 (6.9)	0
Flatulence	1 (3.3) ^a	2 (6.9)	1 (3.4)	0
Headache	0	0	1 (3.4)	0

^aNumber of subjects with an event (percentage of the total)

No meaningful study drug effects were observed for clinical chemistry or hematology parameters or for QT interval at discharge. Mean changes in vital signs were small following all 4 treatments, and shifts in blood pressure from pre-dose to post-dose occurred infrequently.

Pharmacokinetics: Mean plasma concentration levels of diclofenac at 1.5, 3, and 6 hours following IV DIC075V 37.5 mg and oral Cataflam 50 mg in this study were compared with those from Study DFC-PK-006. Mean plasma concentration levels following IV administration of diclofenac were essentially the same between the 2 studies, while those following oral diclofenac were lower in the current study. However, taking into account the higher variability of diclofenac plasma concentration levels, the data were consistent between the 2 studies. The C_{max} of ketorolac, acetylsalicylic acid, and salicylic acid were consistent with published PK data available in the literature for these drugs.

Parameter ^{a, b}	Treatment Group				
	DIC075V 37.5 mg (N = 30)	Ketorolac 30 mg (N = 29)	Cataflam 50 mg (N = 29)	ASA 325 mg (N = 29)	
				ASA	SA
C _{max}	191 ± 49.5 ng/mL	1.61 ± 0.25 µg/mL	447 ± 211 ng/mL	0.97 ± 0.46 µg/mL	17.4 ± 2.71 µg/mL
T _{max}	1.5 h	1.5 h	1.5 h	1.5 h	1.5 h
AUC _(0-t)	414 ± 132 h·ng/mL	8.47 ± 1.85 h·µg/mL	1029 ± 423 h·x ng/mL	1.59 ± 0.80 h·µg/mL	90.3 ± 21.5 h·µg/mL

^aMean ± standard deviation except for T_{max}, for which the median is reported

^bThese values relate to the observed concentration-time profile of this particular study and are not indicative of the actual drug PK.

Pharmacodynamics: As measured by PFA CEPI, the mean AUEC_{0-6h} for platelet function closure time (co-primary endpoint) was significantly longer following administration of oral ASA 325 mg (p<0.0001) and IV ketorolac 30 mg (p<0.0001) compared to IV DIC075V 37.5 mg. For oral ASA 325 mg and IV ketorolac tromethamine 30 mg, this effect persisted over all subsequent time intervals, as mean PFA CEPI-measured AUEC_{0-12h}, AUEC_{0-18h}, and AUEC_{0-24h} platelet function closure times were each statistically significantly (p<0.0001) longer compared to IV DIC075V 37.5 mg. There were no significant differences between the 2 diclofenac treatments over the 0-12, 0-18, and 0-24 hour intervals.

Mean AUEC_{0-6h} for platelet function closure time (co-primary endpoint) measured by PFA CADP following IV DIC075V 37.5 mg administration was significantly longer than after oral ASA 325 mg (p=0.0026) and IV ketorolac 30 mg (p=0.0288). Secondary analyses revealed that following IV DIC075V

37.5 mg administration mean PFA CADP-measured AUEC_{0-12h}, AUEC_{0-18h}, and AUEC_{0-24h} platelet function closure times were all statistically significantly longer for oral ASA 325 mg and IV ketorolac tromethamine 30 mg ($p \leq 0.0184$ or less at all times for both comparator drugs) compared to DIC075V 37.5 mg. There were no significant differences observed from oral Cataflam 50 mg in comparison to DIC075V 37.5 mg. The smallest mean maximum change from baseline in PFA closure time throughout the 24-hour post-dose period was observed following IV DIC075V administration. The differences were significant ($p < 0.0050$ or less) for comparisons between IV DIC075V and IV ketorolac and oral ASA for all time points assessed using both the CADP and CEPI tests. The mean (SD) area under platelet function analyzer closure time difference curve is summarized in the table below.

	Treatment Group			
	DIC075V 37.5 mg (n=30)	Ketorolac 30 mg (n=29)	Cataflam® 50 mg (n=29)	ASA 325 mg (n=29)
Collagen and epinephrine (CEPI) cartridge test results				
0-6 hours	n=30 249.3 ± 215.68 ^{a,b}	n=28 949.6 ± 287.19	n=27 285.7 ± 264.61 ^a	n=29 853.3 ± 243.27
0-12 hours	n=29 373.8 ± 359.16 ^{a,b}	n=29 1965.9 ± 400.96	n=28 430.6 ± 424.84 ^a	n=29 1770.0 ± 590.59
0-18 hours	n=29 472.9 ± 532.22 ^{a,b}	n=29 2776.4 ± 603.53	n=27 368.3 ± 560.60 ^a	n=29 2549.3 ± 960.70
0-24 hours	n=28 436.1 ± 635.08 ^{a,b}	n=28 3282.3 ± 881.69	n=27 377.6 ± 694.44 ^a	n=29 3148.8 ± 1230.58
Collagen and adenosine diphosphate (CADP) cartridge test results				
0-6 hours	n=30 29.1 ± 77.18 ^{d,e}	n=28 83.5 ± 125.91	n=29 48.2 ± 86.41 ^d	n=29 143.0 ± 225.01
0-12 hours	n=30 69.3 ± 154.90 ^{d,e}	n=29 251.7 ± 410.56	n=29 107.1 ± 136.43	n=29 263.9 ± 396.24
0-18 hours	n=29 69.7 ± 221.13 ^{d,e}	n=29 311.7 ± 515.51	n=28 120.3 ± 181.50 ^d	n=29 332.1 ± 453.62
0-24 hours	n=29 55.3 ± 284.02 ^{d,e}	n=29 322.6 ± 544.82	n=29 120.8 ± 245.16 ^d	n=29 375.9 ± 518.96

Source: Section 14.4, Table 14.4.1.1A

^a $p < 0.0001$ compared with oral ASA 325 mg

^b $p < 0.0001$ compared with intravenous ketorolac 30 mg

^d $p < 0.05$ compared with oral ASA 325 mg

^e $p < 0.05$ compared with intravenous ketorolac 30 mg

ASA = acetylsalicylic acid

The mean change from baseline in platelet count, PT, and aPTT were small following all 4 single-dose treatments.

4.2.5 Study # DFC-002 Synopsis:

Name of finished product: DIC075V (diclofenac sodium) Injection 37.5 mg/mL

Name of active ingredient: Diclofenac sodium

Title of study: A Randomized, Double-blind, Placebo- and Comparator-controlled, Single-dose, Parallel-group Comparison of the Analgesic Efficacy and Safety of Intravenous DIC075V (diclofenac sodium injection), Ketorolac Tromethamine, and Placebo Following Surgery

Investigators: Donald Bandy, DDS, et al. (3 investigators)

Study centers: Multicenter study. Three centers in the USA.

Publication: None

Study period: First patient enrolled: 25 July 2005; Last patient completed: 26 October 2005

Development phase: Phase 2

Objectives: The primary objective of this study was to assess the dose-response of 5 dose levels of DIC075V in patients with postsurgical pain using ketorolac tromethamine and placebo as comparators.

The secondary objectives of this study were to establish the dose tolerance of DIC075V in the postsurgical patient population, demonstrate the efficacy and safety of DIC075V, and demonstrate the superiority of DIC075V to placebo.

Methodology: This was a 7 treatment arm, randomized, double-blind, single-dose, placebo- and active comparator-controlled, parallel-group study to compare the dose response of 5 DIC075V doses to IV ketorolac tromethamine and placebo for the management of moderate to severe postsurgical pain. Patients were randomly assigned to receive a single dose of one of the following treatments:

1. Single dose of DIC075V 3.75 mg administered as a bolus IV injection
2. Single dose of DIC075V 9.4 mg administered as a bolus IV injection
3. Single dose of DIC075V 18.75 mg administered as a bolus IV injection
4. Single dose of DIC075V 37.5 mg administered as a bolus IV injection
5. Single dose of DIC075V 75 mg administered as a bolus IV injection
6. Single dose of ketorolac tromethamine 30 mg administered as a bolus IV injection
7. Placebo

The study was completed as planned.

Number of patients: Approximately 350 (336 evaluable) patients were planned for the study. A total of 353 patients were enrolled and included in the ITT analysis (the per protocol population consisted of 346 evaluable patients).

Indication and main criteria for inclusion: Healthy male and female dental patients 18-65 years of age undergoing the removal of one or more third molars (one of which had to have been a fully or partially impacted mandibular third molar requiring bone removal). Patients were to have had moderate or severe pain within 6 hours after completion of surgery, as measured by a categorical pain intensity scale (moderate or severe descriptor) and a pain intensity of ≥ 50 mm on a 100 mm VAS at baseline.

Investigational drug: DIC075V (diclofenac sodium) 75 mg, 37.5 mg, 18.75 mg, 9.4 mg or 3.75 mg administered as a single dose bolus IV injection. Batch number: 063004 (PPS04010)

Reference therapy: Ketorolac tromethamine 30 mg, administered as a single-dose bolus IV injection. Batch number: 21-430-DK.

Duration of treatment: Single dose of study medication followed by 8 hours of follow-up in clinic. Patients were asked to record their pain assessments in a diary up to 24 hours post dosing.

Criteria for evaluation:

Efficacy: The primary measure of efficacy was total pain relief (TOTPAR) over 6 hours (TOTPAR6) as measured by the VAS scale. The secondary measures of efficacy were: TOTPAR over 2, 4, 6 (categorical scale), 8, 10, 12, and 24 hours measured on both VAS and categorical scales; sum of pain intensity differences (SPID) over 2, 4, 6, 8, 10, 12, and 24 hours measured on both VAS and categorical scales; time specific pain intensity difference (PID); time specific pain relief (PR) scores; peak pain intensity difference (PPID); peak pain relief (PPR); sum of pain relief intensity difference (SPRID) scores over 2, 4, 6, 8, 10, 12, and 24 hours; time to rescue medication (TTR) (Overall and Responder Populations); proportion of patients requiring rescue medication; time to meaningful pain relief (TMPR); time to perceptible pain relief (TPPR); and patient global evaluation (PGE).

Safety: Safety was assessed by routine laboratory analyses, vital signs, ECG, AEs, pregnancy testing, and physical examination.

Pharmacokinetics: No PK assessments were performed.

Statistical methods: Demographic and baseline variables were summarized by treatment group and overall. Efficacy analyses were performed on the Intent-to-Treat (ITT) and Per Protocol populations. TOTPAR, PR, PPR, SPID, PID, PPID, SPRID, and PGE were analyzed using analysis of covariance (ANCOVA) models with treatment, center, and baseline categorical pain intensity as factors. Comparisons of the DIC075V groups with placebo were performed with Dunnett’s test. The presence of a linear dose response for the ordered DIC075V dose levels was tested with orthogonal contrasts for TOTPAR, SPID, and SPRID. Determinations of the Minimum Effective Dose were conducted with the Tukey, Ciminera, and Heyse (Tukey et al, 1985) step-down testing procedure, using linear orthogonal contrasts. Time to onset of perceptible relief, time to onset of meaningful relief, and time from administration of study medication to first rescue medication was analyzed with survival analysis techniques. The proportion of patients rescuing was analyzed with the Cochran-Mantel-Haenszel test with center as a stratification variable. Safety assessments were based on tabulations of clinical laboratory results, physical examinations, vital signs, ECG, thrombophlebitis evaluation and AE data.

Results:

Efficacy: The primary efficacy endpoint of this study was met: mean TOTPAR scores over 0-6 hours for the 4 highest DIC075V dose groups (9.4, 18.75, 37.5, and 75 mg) and ketorolac tromethamine 30 mg were statistically superior to placebo (p<0.05).

The minimum effective doses of DIC075V 3.75 mg for the ITT population and DIC075V 9.4 mg for the Per Protocol population were defined.

There were no statistically significant differences between DIC075V 37.5 mg or DIC075V 75 mg and ketorolac tromethamine 30 mg for TOTPAR over 0-6 hours.

TOTPAR 0-6 hours	DIC075V						Ketorolac 30 mg (N = 47)
	Placebo (N = 51)	3.75 mg (N = 51)	9.4 mg (N = 51)	18.75 mg (N = 51)	37.5 mg (N = 51)	75 mg (N = 51)	
Mean (SD) ^a	62.8 (134.52)	134.1 (136.19) A	237.7 (170.21) B	284.4 (201.11) B	348.2 (164.25) B	347.3 (167.45) B	393.5 (173.24) B
P-value for determination of minimum effective dose ^b	--	0.0341	<0.0001	<0.0001	<0.0001	<0.0001	--

a Results of Dunnett’s test: A = not significantly different from placebo; B = significantly different from placebo (p<0.05).

b p-value based on results of Tukey-Ciminera-Heyse step-down testing procedure.

Characterization of the dose-response relationship of the 5 doses and 20-fold concentration range of DIC075V demonstrated a statistically significant relationship between increasing dose and reduction in pain intensity. A dose-response analysis based on mean SPID from 0-6 hours for 6 dose levels including placebo (0, 3.75, 9.8, 18.75, 37.5 and 75 mg) demonstrated there were highly significant ($p < 0.0001$) linear, quadratic and ($p < 0.0053$) cubic dose effect. These results indicate there was a clear, statistically significant relationship between increasing doses and greater reductions in pain intensity. The plateau dose of effectiveness of DIC075V was defined as 75 mg. A dosing interval of approximately 6 hours was defined for DIC075V 18.75, 37.5, 75 mg as the duration from the onset of meaningful pain relief (MPR) until the time to administration of rescue medication (TTR). The onset of action was more rapid for DIC075V 37.5 and 75 mg (5 minutes) as compared to ketorolac tromethamine 30 mg (15 minutes) and placebo.

Safety: DIC075V was safe and well tolerated. No deaths or discontinuations occurred in this study and a single SAE (appendicitis, placebo group) was reported. AE reports were similar across all treatment groups with respect to overall incidence, severity, and attribution. The majority of AEs were mild to moderate in severity. There was no evidence of a dose-response relationship for systemic or local AEs. No patients had elevated alanine transaminase (ALT) levels and 1 patient in the lowest DIC075V treatment group had an increase in aspartate transaminase (AST) greater than 3 times the upper limit of normal. There were no reports of acute renal or hepatic impairment. There was no indication of an increased risk of cardiovascular thrombotic AEs.

AEs occurring in at least 5% of patients in any treatment group are summarized below.

MedDRA Preferred Term	Placebo (N = 51) n (%)	DIC075V					Ketorolac 30 mg (N = 47) n (%)
		3.75 mg (N = 51) n (%)	9.4 mg (N = 51) n (%)	18.75 mg (N = 51) n (%)	37.5 mg (N = 51) n (%)	75 mg (N = 51) n (%)	
Nausea	3 (5.9)	3 (5.9)	9 (17.6)	3 (5.9)	5 (9.8)	3 (5.9)	3 (6.4)
Vomiting	4 (7.8)	2 (3.9)	4 (7.8)	1 (2)	2 (3.9)	3 (5.9)	1 (2.1)
Dry Socket	1 (2)	4 (7.8)	3 (5.9)	2 (3.9)	5 (9.8)	3 (5.9)	4 (8.5)
Post Procedural Pain	12 (23.5)	9 (17.6)	5 (9.8)	5 (9.8)	7 (13.7)	2 (3.9)	3 (6.4)
Procedural Site Reaction	5 (9.8)	4 (7.8)	5 (9.8)	4 (7.8)	5 (9.8)	3 (5.9)	7 (14.9)
Headache	3 (5.9)	5 (9.8)	4 (7.8)	4 (7.8)	3 (5.9)	2 (3.9)	3 (6.4)
Nasal Congestion	1 (2)	0	1 (2)	0	0	0	3 (6.4)

Pharmacokinetics: Not applicable.

Conclusions: This randomized, double-blind, placebo- and comparator-controlled study assessed the safety and efficacy of DIC075V in a specific, well-recognized model of acute moderate to severe pain. The results in this model demonstrate that DIC075V provides analgesic efficacy, safety, and tolerability similar to ketorolac tromethamine 30 mg and statistically superior to placebo. Moreover, DIC075V 37.5 and 75 mg provide a magnitude of pain relief similar to ketorolac tromethamine 30 mg with an apparently faster onset of action. The dose-response relationship for pain relief, onset of analgesic action, and adverse effects of DIC075V were well characterized in this study, allowing identification of the minimally effective dose, several doses that provide maximum effectiveness, and a plateau dose above which incremental analgesic effects diminish. The dosing interval was characterized for several doses in the population that responded to study medication by calculating the duration from the onset of meaningful pain relief until the TTR. Bearing in mind that the results in the present model may not fully generalize to other painful conditions, such as postsurgical models having a greater intensity and/or duration of pain, these data provisionally support investigation of DIC075V at doses of 18.75 and 37.5 mg administered every 6 hours in multiple-dose, multiple-day postsurgical pain studies. Accordingly, exploration of DIC075V doses of 18.75 and 37.5 mg would appear appropriate for subsequent investigations in which acute pain is the primary focus.

4.2.6 Study # DFC-004 Synopsis:

Name of finished product: DIC075V (diclofenac sodium) Injection 37.5 mg/mL

Name of active ingredient: Diclofenac sodium

Title of study: A Randomized, Double-blind, Active- and Placebo-controlled Study of the Analgesic Efficacy and Safety of Repeated Dosing of Two Dose Levels of DIC075V Relative to Parenteral Ketorolac and Placebo in Patients with Acute Post-operative Pain after Abdominal or Pelvic Surgery

Investigators: Gilbert Podolsky, et al. (16 investigators).

Study centers: Multicenter study (16 sites in the USA).

Publication: None

Study period: First patient enrolled: 30 May 2006; Last patient completed: 21 June 2007

Development phase: Phase 3

Objectives: The primary objective was to evaluate the efficacy and safety of 2 dose levels of DIC075V (diclofenac sodium injection) relative to placebo in a multiple-dose, postoperative pain study using ketorolac tromethamine as an active comparator.

Methodology: Multicenter, multiple-dose, multiple-day, randomized, double-blind, 4-arm, active- and placebo-controlled, parallel-group study designed to compare the analgesic efficacy and safety of fixed-dose, fixed-schedule, IV dosing every 6 hours of 2 dose levels of DIC075V (18.75 and 37.5 mg) with placebo and ketorolac tromethamine 30 mg for the management of moderate to severe postsurgical pain from abdominal or pelvic surgery. The study was completed as planned. The treatment groups are summarized below:

1. DIC075V 18.75 mg as a 1 mL (0.5 mL DIC075V, 0.5 mL normal saline) bolus IV injection every 6 hours for up to 5 days
2. DIC075V 37.5 mg as a 1 mL bolus IV injection every 6 hours for up to 5 days
3. Ketorolac tromethamine 30 mg as a 1 mL bolus IV injection every 6 hours for up to 5 days
4. Placebo as a 1 mL bolus IV injection of normal saline every 6 hours for up to 5 days

Number of patients: Approximately 320 patients were planned to be randomized into the study (80 per group). A total of 348 patients were randomized and enrolled in the study. A total of 331 patients (62 male/269 female, 18-65 years old) received study treatment and 266 completed the study. All 331 patients who received study treatment were included in the ITT and safety population analyses and 265 were included in the per protocol population analysis.

Indication and main criteria for inclusion: Male or female patients between 18-65 years of age and with a body weight of > 50 kg who were in good health and were scheduled within 2 weeks of the screening visit to undergo abdominal or pelvic surgery (abdominal and vaginal hysterectomy, abdominal and pelvic laparoscopic surgery [including laparoscopic cholecystectomy], gastric surgery [excluding obesity procedures], salpingo-oophorectomy, uncomplicated open appendectomy, partial colectomy, myomectomy, or open ventral or inguinal hernia repair). Patients were to have moderate to severe pain (≥ 50 mm as measured on a 0-100 mm VAS) within 6 hours following surgery.

Investigational drug: DIC075V (diclofenac sodium), 37.5 mg and 18.75 mg, administered as a bolus IV injection every 6 hours. Batch number: IDDS062804.

Reference therapy: Ketorolac tromethamine, 30 mg, administered as a bolus IV injection every 6 hours. Batch numbers: 32-427-DK; 36-187-DK; 43-380-DK; and 37-135-DK.

Placebo (normal saline), administered as a bolus IV injection every 6 hours.

Duration of treatment: Minimum 48 hours and up to 5 days.

Criteria for evaluation:

Efficacy: The primary measure of efficacy was the sum of the pain intensity differences (SPID) over the 0-48 hour time interval. Pain intensity was measured on a 0-100 mm VAS.

Secondary measures of efficacy included: SPID over the 0-24 hour interval (and the 0-72, 0-96, and 0-120, intervals if data permitted), pain intensity difference at each scheduled assessment, proportion of patients attaining at least 30% reduction in pain intensity at each scheduled assessment, area under the pain relief curve over the 0-24 and 0-48 hour intervals (and the 0-72, 0-96, and 0-120 hour intervals if data permitted), pain relief at each scheduled assessment, time to perceptible pain relief, time to meaningful pain relief, time from administration of study drug to administration of rescue medication, frequency and amount of rescue medication, and patient global evaluation.

Safety: Safety was evaluated by analysis of AEs, laboratory assessments, ECGs, vital signs, thrombophlebitis assessments, and physical examination.

Pharmacokinetics: No PK assessments were performed.

Statistical methods: Descriptive statistics are presented by treatment group for each of the efficacy measures at each of the assessments. Area under the pain intensity difference curve (SPID), area under the pain relief curve, pain intensity difference, pain relief, amount of rescue medication, and patient global evaluation were analyzed with analysis of covariance (ANCOVA) models with treatment and center as factors and baseline pain intensity as a covariate. Differences between active treatment and placebo were tested with linear contrasts. The comparison of active treatment and placebo with respect to 48-hour SPID was analyzed with the following closed testing procedure: DIC075V 37.5 mg versus placebo at the 0.05 level of significance; if the result of this test was significant, DIC075V 18.75 mg was tested versus placebo at the 0.05 level of significance. The number of patients who underwent pain intensity and pain relief assessments subsequent to 48 hours was insufficient for significance testing purposes; therefore, descriptive statistics are presented for pain intensity, pain relief, and the measures derived from them.

Time to onset of perceptible pain relief, time to onset of meaningful pain relief, and time from administration of study drug to rescue medication were analyzed with Kaplan-Meier survival analysis techniques. These variables were also summarized with number of observations, mean, standard deviation, median, and range. Log-rank tests were used to compare treatments with respect to survival distributions. The median time to event for each treatment group was estimated with the Kaplan-Meier product limit estimator. A 95% confidence interval (CI) for each estimated median time to event was calculated.

The proportion of patients who reported at least 30% reduction from baseline in pain intensity was analyzed with the Cochran-Mantel-Haenszel test with center as a stratification variable.

Descriptive statistics are presented for AEs, laboratory test results, vital signs, thrombophlebitis, and ECGs. In addition, shift analyses from baseline to each on study assessment are presented for laboratory test results. Logistic regression was used to estimate the relative risk of cardiovascular events.

Results: A total of 348 patients were randomized and enrolled in the study and 331 patients received study treatment: 86 received DIC075V 18.75 mg, 87 received DIC075V 37.5 mg, 82 received ketorolac tromethamine 30 mg, and 76 received placebo. The majority (80%) of treated patients completed the study. The aggregate mean baseline pain intensity was 68.4 mm, falling within the moderate to severe range. Baseline pain intensity was moderate ($50 \leq \text{VAS} < 70$) for 197 (60.2%) subjects and severe ($\text{VAS} \geq 70$) for 130 (39.8%) subjects. There were no statistically significant differences across the treatment groups for any demographic or other baseline characteristics such as type of procedure, surgical factors and intensity

of baseline pain. The mean age was approximately 43 years in each of the 4 treatment groups. The majority of patients in each treatment group were female (81%) and Caucasian (77%).

Efficacy: The primary efficacy endpoint for this study, SPID over 0-48 hours, was met. DIC075V was statistically significantly superior to placebo in decreasing pain intensity over the 0-48 hour treatment period. A numeric dose-response was evident with mean SPID 0-48 values higher for DIC075V 37.5 mg than DIC075V 18.75 mg. SPID 0-48 values were similar between DIC075V 37.5 mg and ketorolac tromethamine 30 mg treatment groups. Mean SPID scores over 0-48 hours are summarized for the ITT population in the table below.

SPID 0-48 (mm-hours)	Placebo (N = 76)	DIC075V 18.75 mg (N = 86)	DIC075V 37.5 mg (N = 87)	Ketorolac 30 mg (N = 82)
Mean (SD)	936.0 (1076.56)	1303.6 (1029.50)	1573.5 (1060.34)	1583.2 (982.74)
P-value ^a		0.0316 ^b	0.0001 ^b	<0.0001 ^b
95% CI			-30.3, 562.4 ^c	-7.6, 590.4 ^d -274.1, 324.8 ^e

a P < 0.0001 for overall treatment effect

b P-value from linear contrast comparing each active treatment versus placebo.

c 95% confidence interval for difference between DIC075V 18.75 mg and DIC075V 37.5 mg.

d 95% confidence interval for difference between DIC075V 18.75 mg and ketorolac tromethamine 30 mg.

e 95% confidence interval for difference between DIC075V 37.5 mg and ketorolac tromethamine 30 mg.

The orthogonal polynomial dose-response test indicated a statistically significant (p=0.0001) linear dose response across 3 dose levels, DIC075V 0 mg (placebo), 18.75 mg, and 37.5 mg, in this randomized, active-and placebo- controlled, 4-arm, parallel-group study. Mean SPID scores were statistically significantly superior to the placebo group in each of the 3 active treatment groups over 0-24 and 0-72 hours; and DIC075V 37.5 mg and ketorolac tromethamine 30 mg were also significantly better than placebo over 0-96 and 0-120 hours, for the ITT population. Mean total pain relief (TOTPAR) scores were statistically significantly better in each of the 3 active treatment groups compared with the placebo group over 0-24, 0-48, and 0-72 hours; and DIC075V 37.5 mg and ketorolac tromethamine 30 mg were also statistically significantly better than placebo over 0-96 and 0-120 hours, for the ITT population.

Onset of analgesic action was assessed in terms of the proportion of subjects achieving a clinically meaningful 30% reduction in pain intensity compared with baseline pain levels as measured using a 0-100 mm VAS for pain intensity. A statistically significant treatment effect was observed for the proportion of subjects who attained at least 30% reduction in pain intensity starting 45 minutes after the first dose of study drug and then at all assessments through 39 hours, with the exception of each pre-dose time point at 6, 12, 24, and 30, and 36 hours. The proportion of subjects who attained at least 30% reduction in pain intensity was numerically similar in the DIC075V 37.5 mg and ketorolac tromethamine 30 mg treatment groups through 48 hours, with the exception of the first dosing interval (0-6) hours. At 45 minutes post-dose, 34% of subjects in the placebo group compared with 42% of subjects in the DIC075V 18.75 mg group, 46% of subjects in the DIC075V 37.5 mg group, and 57% of subjects in the ketorolac tromethamine 30 mg group had attained a $\geq 30\%$ reduction in pain intensity (p = 0.0229 for all 3 active groups versus placebo).

The median TTR, based on Kaplan-Meier estimates, was statistically significantly longer in each of the active treatment groups than in the placebo group. There was a statistically significant difference among the treatment groups in the frequency of rescue medication administration for subjects in the placebo group requiring more frequent administration compared with subjects in the active treatment groups (except at 0-24 hours). There also was a statistically significant difference among the treatment groups in the amount of rescue medication used. Subjects in the placebo group required twice the total amount of morphine rescue medication compared with subjects in the active treatment groups. Subjects given DIC075V 37.5 mg had a slightly higher frequency of rescue after the 0-48 hour interval compared to subjects in the ketorolac tromethamine 30 mg group (70% compared to 65%) which was offset by a lower total amount of rescue

medication taken (7.3 mg compared to 8.5 mg). Subjects in the placebo group required 16.0 mg IV morphine on average.

The median time to onset of meaningful pain relief was 43 minutes in the ketorolac tromethamine 30 mg group versus 2 hours 6 minutes in the placebo group; the difference between these groups was statistically significant ($p = 0.0114$). The median TMPR was 61 minutes in the DIC075V 18.75 mg group and 41 minutes in the DIC075V 37.5 mg group; the differences between these groups and placebo were not statistically significant.

The analysis of PGE yielded results similar and consistent with the other secondary endpoints. PGE ratings showed a statistically significant superiority of both DIC075V dose groups and the ketorolac tromethamine 30 mg group over placebo for both the 0-24 hour and 0-48 hour periods. Regarding satisfaction with their study drugs, 83% to 87% of subjects in the active treatment groups assessed their study drug as “good,” “very good,” or “excellent.”

Safety: The incidence and severity of AE reports was similar among DIC075V and ketorolac tromethamine treatment groups. Overall, 85% of subjects reported at least 1 AE, including 82% of patients in the placebo group, 85% of patients in the DIC075V 18.75 mg group, 84% of patients in the DIC075V 37.5 mg group, and 88% of patients in the ketorolac tromethamine 30 mg group. The most frequently reported AEs in both the DIC075V 18.75 mg and 37.5 mg groups were nausea (30.2%, 25.3%), flatulence (25.6%, 13.8%), and constipation (19.8%, 18.4%). In both the ketorolac tromethamine 30 mg and placebo groups, the most frequently reported AEs were nausea (26.8%, 38.2%), flatulence (26.8%, 25.0%), and headache (17.1%, 19.7%). Adverse events occurring in at least 5% of patients in any treatment group are summarized below.

MedDRA Preferred term	Placebo	DIC075V 18.75	DIC075V 37.5 mg	Ketorolac 30 mg
	(N=76) n (%)	mg (N=86) n (%)	(N=87) n (%)	(N=82) n (%)
Nausea	29 (38.2)	26 (30.2)	22 (25.3)	22 (26.8)
Flatulence	19 (25.0)	22 (25.6)	12 (13.8)	22 (26.8)
Constipation	11 (14.5)	17 (19.8)	16 (18.4)	8 (9.8)
Headache	15 (19.7)	9 (10.5)	7 (8.0)	14 (17.1)
Insomnia	9 (11.8)	9 (10.5)	7 (8.0)	7 (8.5)
Vomiting	11 (14.5)	7 (8.1)	5 (5.7)	7 (8.5)
Blood CPK increased	3 (3.9)	7 (8.1)	6 (6.9)	12 (14.6)
Thrombophlebitis	9 (11.8)	6 (7.0)	3 (3.4)	6 (7.3)
Pyrexia	8 (10.5)	2 (2.3)	6 (6.9)	9 (11.0)
Infusion site pain	4 (5.3)	9 (10.5)	2 (2.3)	2 (2.4)
Pruritus	5 (6.6)	4 (4.7)	6 (6.9)	3 (3.7)
Injection site pain	1 (1.3)	6 (7.0)	2 (2.3)	7 (8.5)
Tachycardia	5 (6.6)	2 (2.3)	2 (2.3)	4 (4.9)
Injection site irritation	0	4 (4.7)	4 (4.6)	5 (6.1)
Diarrhoea	3 (3.9)	2 (2.3)	0	6 (7.3)
Injection site reaction	0	0	6 (6.9)	3 (3.7)

The incidence of treatment-related AEs was highest in the ketorolac tromethamine 30 mg (23%) treatment group with similar rates among DIC075V and placebo treatment groups (18% to 20%).

No deaths were reported during the study. Eleven subjects discontinued study medication because of treatment-emergent AEs, and 9 subjects withdrew from the study because of AEs. Serious AEs were

reported for 3 patients each in the DIC075V 18.75 mg, ketorolac tromethamine 30 mg, and placebo groups, and 4 patients in the DIC075V 37.5 mg group. No treatment-related SAEs were reported in either DIC075V dose group; in comparison 1 (abdominal hematoma) was reported in the ketorolac tromethamine 30 mg group.

There was no indication of an increased risk of cardiovascular thrombotic events for DIC075V. The overall incidence of cardiovascular AEs was highest in the placebo group. An analysis of ECG data indicated no clinically meaningful findings in any treatment group.

There were no reports of acute hepatic impairment or acute renal impairment in this study. Notable elevations ($> 3 \times$ ULN) of ALT and AST levels were higher in the placebo group (1.3% and 2.6%) than in either DIC075V group. There were no reports of acute renal impairment or renal-related AEs in this study; mild fluid retention was reported by 1% of subjects in the DIC075V 37.5 mg group. Mean creatinine, BUN, and albumin levels were comparable among all groups pre- and post-treatment.

DIC075V did not appear to increase the risk of postsurgical bleeding in the overall safety population or in the subset of patients who received concomitant anticoagulant medications. The risk of postsurgical bleeding, as measured by bleeding related AEs (excluding anemia) and a shift to low hemoglobin, appeared to be greater for the ketorolac tromethamine 30 mg treatment group as compared to the DIC075V treatment groups.

There was no apparent impairment of wound healing and no reports of hemorrhagic complications or anaphylactoid reactions during the study.

Local AEs and the site of injection were infrequent, with injection site and infusion related AEs similar in frequency and severity across the active treatment groups. Treatment-related injection site AEs and thrombophlebitis assessments indicated a higher rate of injection-related AEs associated with ketorolac tromethamine 30 mg than with DIC075V.

There were no clinically meaningful differences between the active treatment groups and the placebo group for changes from baseline in hematology or clinical chemistry parameters and a majority of patients had vital signs measurements within normal limits at all assessment times.

Pharmacokinetics: Not applicable.

Conclusions: The results of this multicenter, multiple-dose, multiple-day, randomized, double-blind, 4-arm, active- and placebo-controlled, parallel-group study confirm the analgesic efficacy of DIC075V for the treatment of acute moderate to severe postsurgical visceral pain. The dose-response relationship for DIC075V was characterized over a 2-fold dose range across 3 dose levels, DIC075V 0 mg (placebo), 18.75 mg, and 37.5 mg. The orthogonal polynomial dose-response test indicated a statistically significant ($p=0.0001$) linear dose response across the 3 dose levels of DIC075V. The analysis of the primary and several secondary endpoints demonstrated a numeric dose-response relationship between the 2 dose levels of DIC075V tested, with DIC075V 37.5 mg showing numeric superiority to DIC075V 18.75 mg as measured by SPID, TOTPAR, proportion of subjects achieving 30% reduction in pain intensity, proportion of subjects not requiring rescue medication, and average amount of rescue medication used. These results support the recommended dosage of DIC075V 37.5 mg every 6 hours for the relief of acute moderate to severe pain.

4.2.7 Study # DFC-005 Synopsis:

Name of finished product: DIC075V (diclofenac sodium) Injection, 37.5 mg/mL

Name of active ingredient: Diclofenac sodium

Title of study: A Randomized, Double-blind, Active- and Placebo-controlled Study of the Analgesic Efficacy and Safety of Repeated Dosing of DIC075V Relative to Parenteral Ketorolac tromethamine and Placebo in Patients with Acute Post-operative Pain after Elective Orthopedic Surgery

Investigators: Stephen Daniels, DO; Joseph Gimbel, MD; R. Kevin Jones, MD; Timothy Melson, MD; Bradley Barter, DO; Hayes Williams, MD; David Williams, MD; John Zimmerman, DMP; Max McLaughlin, MD; Maurice Jove, MD; Henry Frazer, PharmD; and Ira Gottlieb, DPM

Study centers: Multi-center study: 12 centers in the USA.

Publications: None

Study period:

First patient enrolled: 25 July 2007

Last patient completed: 14 October 2008

Development phase: Phase 3

Objectives: The primary objective of this study was to evaluate the analgesic efficacy and safety of DIC075V relative to placebo in a repeat-dose, post-operative pain study using ketorolac tromethamine as an active comparator in a patient population representative of the elective orthopedic surgical population.

Methodology: This was a multi-center, randomized, double-blind, 3-arm, active-and placebo-controlled parallel group study of fixed-dose, fixed-schedule, repeated intermittent dosing in subjects with acute moderate to severe post-surgical pain following mixed elective general orthopedic surgery.

Stratification determined the selection of dose for each of the two active treatments. Subjects stratified to the high-risk cohort (weight <50 kg, age ≥ 65 , elevated NSAID-related GI risk factors, or with hepatic or renal impairment) received 18.75 mg doses of DIC075V and 15 mg doses of ketorolac tromethamine. Subjects without any risk factor and weighing ≥ 95 kg received 50 mg doses of DIC075V and 30 mg doses of ketorolac tromethamine. Subjects weighing ≥ 95 kg with any risk factor received 18.75 mg doses DIC075V and 15 mg doses of ketorolac tromethamine. All other subjects received 37.5 mg doses of DIC075V and 30 mg doses of ketorolac tromethamine. After evaluating all the pre-defined entry criteria during the screening period and baseline visit, eligible subjects were randomly assigned (2:1:1 ratio) to one of the following treatments:

- DIC075V IV bolus every 6 hours for up to 5 days;
- Ketorolac tromethamine IV bolus every 6 hours for up to 5 days;
- Placebo (normal saline) IV bolus every 6 hours for up to 5 days.

Hepatic impairment was defined as subjects having Child-Pugh score of 6-9 at baseline. Renal impairment was defined serum creatinine between 1.9-3.0 mg/dL at baseline. Patients weighing > 136 kg were excluded.

The study was completed as planned.

Number of patients: Approximately 240 per protocol subjects (120 patients randomized to receive DIC075V and 60 subjects each randomized to receive either ketorolac or placebo) were planned.

A total of 277 subjects were randomized and 239 completed the study: 277 subjects were included in the ITT analyses and 277 were included in the safety population, 145 patients (52.3%) in the DIC075V arm, 60 subjects (21.7%) in the ketorolac tromethamine arm, and 72 subjects (26%) in the placebo arm.

Indication and main criteria for inclusion: Male and female subjects, 18 – 85 years of age, undergoing mixed elective general orthopedic surgery who were representative of the elective orthopedic surgical population (such as upper extremity or lower extremity surgery, knee or hip replacement, fracture repair (>72 hours post-injury), discectomy, or laminectomy). The subject population selected was to be representative of the indication with approximately 1/2 short stay (120 surgical patients requiring ≤24 hour inpatient stay) and 1/2 long stay (120 surgical patients requiring >24 hours inpatient stay) patients. All patients were expected to have moderate to severe pain requiring continuous IV analgesia for at least 24 hours and once randomized, all patients were required to have an inpatient stay for a minimum of 24 hours regardless of the normal discharge practice.

Investigational drug: DIC075V (diclofenac sodium) Injection, 37.5 mg IV bolus every 6 hours for approximately 24 hours (short-stay patients) or 24-120 hours (long-stay patients). The dose of DIC075V was reduced to 18.75 mg for patients weighing < 50 kg, ≥ 65 years of age, or with elevated NSAID-related GI risk factors or who had moderate hepatic (Child-Pugh score of 6-9) or renal (serum creatinine between 1.9-3.0 mg/dL) impairment. The dose of DIC075V was increased to 50 mg for patients weighing ≥ 95 kg. Lot numbers: C077072, PPS04008, and PPS04009.

Reference therapy:

- Placebo (normal saline) IV bolus every 6 hours for approximately 24 hours (short-stay patients) or 24-120 hours (long-stay patients),
 - Ketorolac tromethamine 30 mg IV bolus every 6 hours for approximately 24 hours (short-stay patients) or 24-120 hours (long-stay patients). The dose of ketorolac tromethamine was reduced to 15 mg for patients weighing < 50 kg, ≥ 65 years of age, or with elevated NSAID-related GI risk factors or who had moderate hepatic (Child-Pugh score of 6-9) or renal (serum creatinine between 1.9-3.0 mg/dL) impairment and the dose was increased to 30 mg for patients weighing ≥ 95 kg. Lot number 48-232DK.
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Duration of treatment: Study drug was administered for approximately 24 hours for short-stay patients and between approximately 24 and 120 hours for long-stay patients. Patients had a follow-up visit 5 – 9 days after last dose and a telephone follow-up 30 – 37 days after last dose.

Criteria for evaluation:

Efficacy: The primary measure of efficacy was the sum of the pain intensity differences (SPID) over the following 5 intervals: 0-24, 0-48, 0-72, 0-96, and 0-120 hours. Pain intensity was measured on a 0-100 mm VAS.

Secondary measures of efficacy included: pain intensity difference at each scheduled assessment, proportion of patients attaining at least 30% reduction in pain intensity at each scheduled assessment, area under the pain relief curve over the 0-24, 0-48, 0-72, 0-96, and 0-120 hour intervals, pain relief at each scheduled assessment, time to perceptible pain relief, time to meaningful pain relief, time from administration of study drug to administration of rescue medication, frequency and amount of rescue medication, and patient global evaluation.

Safety: Safety was evaluated by analysis of AEs, laboratory assessments, ECGs, vital signs, thrombophlebitis assessments, wound assessment, and physical examination.

Pharmacokinetics: No PK assessments were performed.

Statistical methods: Descriptive statistics are presented by treatment for each efficacy measure at each assessment. The analyses of SPID, pain intensity difference, total pain relief, pain relief, patient global evaluation, and amount of rescue medication were based on ANCOVA models with treatment and center as

factors and baseline pain as a covariate. The presence of a treatment-by-center interaction was also tested with an ANCOVA model. Point estimates and confidence intervals were calculated for all treatment differences. These confidence intervals were based on the pooled standard deviation obtained from an ANCOVA model. Treatment differences were tested with linear contrasts. The time to perceptible relief, time to meaningful relief, and time from administration of study drug to administration of rescue medication were analyzed with Kaplan-Meier survival analysis techniques. The proportion of patients attaining at least 30% reduction in pain intensity and the frequency of rescue medication use were analyzed with Cochran-Mantel-Haenszel test with center as a stratification variable.

Descriptive statistics were tabulated by treatment for each of the safety measures. These tabulations were performed both overall and by risk category.

Results:

Efficacy: The primary efficacy endpoint for this study, SPID over 0-24, 0-48, 0-72, 0-96, and 0-120 hours, was met. DIC075V was statistically significantly superior to placebo in decreasing pain intensity over each of these time periods ($p < 0.0001$). There were no statistically significant differences between DIC075V and ketorolac tromethamine groups in mean SPID score over any of these periods. SPID results for the 0-24, 0-48, and 0-72 hour periods are summarized below.

SPID (mm-hours)/ Time Interval	DIC075V (N=145)	Ketorolac (N=60)	Placebo (N=72)
0-24 hours			
Mean (SD)	577.0 (570.90)	563.2 (586.21)	28.0 (428.43)
P-value ^a	<0.0001	<0.0001	
0-48 hours			
Mean (SD)	1527.5 (1139.30)	1371.8 (1152.19)	400.4 (949.54)
P-value ^a	<0.0001	<0.0001	
0-72 hours			
Mean (SD)	2592.1 (1730.92)	2312.1 (1743.73)	836.8 (1564.24)
P-value ^a	<0.0001	<0.0001	

SD = standard deviation

a P-value from linear contrast comparing each active treatment versus placebo.

All secondary efficacy endpoints also were met. Statistical separation of active treatment groups from placebo for PID first occurred in the DIC075V group at 10 minutes following administration of study drug ($p=0.0297$) and was maintained through to 120 hours. Statistical separation from placebo for PID first occurred in the ketorolac tromethamine group 30 minutes from administration of study drug ($p=0.0055$) and was maintained through to 120 hours.

Mean total pain relief (TOTPAR) scores were statistically significantly better in the DIC075V group, and the ketorolac tromethamine group, compared with the placebo group over 0-24, 0-48, 0-72, 0-96, and 0-120 hours ($p<0.0001$). The difference in mean TOTPAR was not statistically different between the DIC075V and ketorolac tromethamine groups for any of these time periods.

Onset of action was assessed using several secondary endpoints. Statistically significant differences ($p<0.05$) for PID, PR, and 30% reduction PID compared to placebo occurred earlier for subjects who received DIC075V (10, 5, and 15 minutes, respectively) than for those who received ketorolac tromethamine (30, 30 and 45 minutes, respectively). There was a statistically significant shorter TTPR in the DIC075V group compared to the placebo group based on the Kaplan-Meier analysis ($p=0.0009$), but there was no significant difference between the ketorolac tromethamine and placebo groups or the DIC075V and ketorolac tromethamine groups. There was also a statistically significant shorter TMPR in the DIC075V group, as well as in the ketorolac tromethamine group, compared to the placebo group ($p<0.0001$). The difference between the DIC075V and ketorolac tromethamine groups in TMPR was not statistically significant.

The median TTR, based on Kaplan-Meier estimates, was statistically significantly longer in the DIC075V and ketorolac tromethamine treatment groups than in the placebo group ($p < 0.0001$); the difference between the DIC075V and ketorolac tromethamine was not statistically significant. Overall, 4 (5.6%) subjects in the placebo group, 38 (26.2%) subjects in the DIC075V group, and 16 (26.7%) subjects in the ketorolac tromethamine group did not require any rescue medication during the treatment phase of the study. For the ITT population, DIC075V treated subjects required 42.4% less morphine over the first 5 days post surgery compared with placebo. Subjects in the placebo group required a mean of 20.5 mg of morphine rescue compared with 11.8 mg in the DIC075V group, which was statistically significant ($p < 0.0001$). Statistically significant differences for the DIC075V treatment group compared with placebo were observed over each of the 0-24, 0-48, 0-72, 0-96 and 0-120 hour time periods ($p < 0.0001$). Subjects in the DIC075V treatment group also used significantly less morphine over the 5-day treatment period than subjects who received ketorolac tromethamine (11.8 mg versus 18.1 mg, $p = 0.0084$). Moreover, significant differences in morphine use for the DIC075V treatment group compared with ketorolac tromethamine were observed over 0-48 hours ($p = 0.0302$), 0-72 hours ($p = 0.0081$), 0-96 hour time periods ($p = 0.0090$), and 0-120 hour time periods ($p = 0.0084$).

A post hoc analysis was conducted to compare mean SPID scores between the non-high-risk and higher-weight cohorts in the revised ITT population. This analysis showed very close agreement across 0-6, 0-24, 0-48, 0-72, 0-96, and 0-120 time intervals, confirming the appropriateness of a 50 mg dose as a basis to assure equivalent efficacy in the latter cohort to the 37.5 mg dose in the non-high-risk cohort. In contrast, subjects who were considered high-risk that received DIC075V 18.75 mg had poorer outcomes (64.1 and 526.2 mm-hours, respectively) for the first postsurgical day as measured by SPID 0-6 and 0-24 hours with lower pain scores than for subjects that received the regular dose of 37.5 mg (96.0 and 651.3 mm-hours, respectively). By the second and third postsurgical day, high-risk subjects had similar pain scores (1190.8 and 1704.4 mm-hours, respectively) to those that received the usual dose (1111.9 and 1601.2 mm-hours, respectively). The majority of patients in the high-risk cohort were only treated for 0-72 hours and the data beyond 72 hours is largely based on imputed pain scores.

Thus in summary, subjects who were considered high-risk received DIC075V 18.75 mg and demonstrated lower analgesic efficacy during the first postsurgical day as measured by SPID 0-6 and 0-24 hours with lower pain scores than subjects who received the regular dose of 37.5 mg. By the second and third postsurgical day, pain scores were similar in high-risk subjects and those who received the usual dose.

For the elderly subset of the high-risk group, subjects in the placebo group required an average of 17.2 mg of morphine rescue medication over 0-120 hours, those in the ketorolac tromethamine group required an average of 14.9 mg, and those in the DIC075V group required an average of 9.6 mg. Significant differences in morphine use for the DIC075V treatment group compared with ketorolac tromethamine were observed over the 0-24 ($p = 0.0383$), 0-48 ($p = 0.0405$), 0-72 ($p = 0.0454$), and 0-120-hour time periods ($p = 0.0500$). Significant differences in morphine use for the DIC075V 18.75 mg treatment group compared with placebo were observed at all time points. Subjects in the high-risk cohort who received DIC075V had superior SPID scores in comparison to ketorolac tromethamine over the 0-24 ($p = 0.0217$) and 0-48 ($p = 0.0188$) hour time intervals and in comparison to placebo over the 0-6 ($p = 0.0041$), 0-24 ($p = 0.0005$), 0-48 ($p = 0.0004$), 0-72 ($p = 0.0015$), 0-96 ($p = 0.0022$) and 0-120 ($p = 0.0020$) hour time intervals.

Patient global evaluation ratings showed a statistically significant superiority of DIC075V and ketorolac tromethamine over placebo for the 0-24 and 0-120 hour periods, and also of DIC075V over placebo for the 0-48 hour period. Mean PGE scores were 2.6 and 2.9 (good to very good) in the DIC075V group for 0-24 and 0-48 hours, compared with 2.4 and 2.6 (good to very good) in the ketorolac tromethamine group and 1.1 and 1.9 (fair to good) in the placebo group during these periods.

Safety: DIC075V was safe and well tolerated when administered by IV injection every 6 hours in this orthopedic postsurgical population. No deaths were reported in this study; there were 2 subjects who withdrew from the study due to AEs and there were 14 SAEs. The incidence of SAEs in the DIC075V group was similar to placebo at 4.8% and 4.2%, respectively; 1 treatment-related SAE was attributed to DIC075V (renal failure acute).

Overall 77.6% of subjects reported at least 1 AE, which were reported with similar frequency across the active treatment groups, including 83.3% of subjects in the placebo group, 75.2% in the DIC075V group, and 76.7% in the ketorolac tromethamine group. Postoperative nausea was the most commonly reported AE overall and in each of the risk and weight cohorts. Nausea, vomiting, and constipation were the most frequently reported AEs in the placebo group. Subjects who received DIC075V reported nausea, CPK increased, and constipation more frequently. Nausea, CPK increased, and anaemia were more frequently reported by subjects who received ketorolac tromethamine. Commonly reported AEs were similar across the treatment groups for the overall population and the risk and weight cohorts, with the exception of anemia in the high-risk cohort. There was a higher incidence of anemia reported overall in the high-risk cohort (18.8%) compared to the non-high-risk and higher-weight cohorts at 4.0% and 4.5%, respectively. The number of subjects experiencing common AEs, as defined by >5% incidence in any treatment group, are summarized below.

MedDRA Preferred Term	Placebo (N=72) n (%)	DIC075V (N=145) n (%)	Ketorolac (N=60) n (%)
Nausea	26 (36.1)	36 (24.8)	18 (30.0)
Blood creatine phosphokinase increased	9 (12.5)	21 (14.5)	8 (13.3)
Constipation	11 (15.3)	19 (13.1)	6 (10.0)
Dizziness	5 (6.9)	16 (11.0)	5 (8.3)
Headache	5 (6.9)	12 (8.3)	5 (8.3)
Infusion site pain	5 (6.9)	11 (7.6)	5 (8.3)
Vomiting	14 (19.4)	11 (7.6)	6 (10.0)
Anaemia	8 (11.1)	9 (6.2)	7 (11.7)
Oedema peripheral	2 (2.8)	8 (5.5)	3 (5.0)
Postoperative wound infection	2 (2.8)	8 (5.5)	1 (1.7)
Procedural site reaction	0 (0)	8 (5.5)	3 (5.0)
Pruritus	5 (6.9)	5 (3.4)	5 (8.3)
Pyrexia	9 (12.5)	4 (2.8)	3 (5)
Rash	0 (0)	4 (2.8)	6 (10)
Body temperature increased	5 (6.9)	2 (1.4)	2 (3.3)
Hypokalemia	4 (5.6)	1 (0.7)	1 (1.7)

The incidence, severity and attribution of AEs was similar across the treatment groups. Incidence, severity and attribution of AEs in the non-high risk cohort was similar to or lower than placebo for subjects who received DIC075V. Subjects in the high-risk cohort had greater incidence of SAEs and severe AEs overall; however, the incidence and attribution of AEs in the high-risk cohort was similar to or lower than placebo for subjects who received DIC075V and the incidence of severe AEs was highest in the ketorolac tromethamine group (16.7%) compared to DIC075V (6.7%) and placebo (0%). Higher-weight subjects reported a lower incidence, similar attribution and higher severity of AEs compared to the overall population. The incidence, severity and attribution of AEs in the high-weight cohort was lower for subjects who received DIC075V than for subjects who received placebo. Higher weight subjects experience more serious pulmonary and vascular AEs.

The incidence of cardiovascular events was low and reported more frequently in the high-risk and higher-weight cohorts, with reports of deep vein thrombosis more common (3 subjects) in the DIC075V group and congestive heart failure (1 subject) in the ketorolac tromethamine group. The risk of a cardiovascular event did not differ statistically between the active treatment groups and the placebo group. There were no subjects with Antiplatelet Trialists' Collaboration (APTC) composite events. Blinded third party analysis of ECGs revealed no obvious significant QT prolongation or moderate to severe clinical post dose morphological findings.

There were no reports of worsening of hepatic impairment or hepatic related AEs in this study. The majority of the LFT elevations were among subjects in the high-risk cohort. Notable elevations of ALT and AST levels (3 to < 8 x ULN) of subjects in the DIC075V group were comparable to placebo and

reported by 2.1% and 2.8% of subjects, respectively. AE reports of abnormal ALT, AST, and bilirubin levels were highest in the placebo group.

There were 2 reports of acute renal failure in this study, including 1 report of a mild treatment-related SAE in the DIC075V group resulting in withdrawal from the study and 1 report of a moderate treatment-emergent AE in the placebo group. Notable elevations of creatinine and BUN levels (1.5 to < 3 x ULN) were reported by 0.7% of subjects in the DIC075V group and the placebo group. There were no AE reports of abnormal creatinine or BUN laboratory levels.

The overall incidence of AEs decreased with increasing exposure. Rates of acute onset AEs were not higher in the first 45 minutes post-dose compared to 45 minutes to 6 hours post-dose.

Wound healing was assessed prospectively using a questionnaire and retrospectively by a post hoc analysis of related AEs. The prospective questionnaire assessment did not disclose any adverse effect of either active treatment compared with placebo. The retrospective analysis of related AEs demonstrated a low overall incidence of AEs with a higher incidence in the active treatment groups (10.0% and 13.8% for ketorolac tromethamine and DIC075V, respectively) compared to placebo (2.8%).

A higher risk of postoperative bleeding for DIC075V compared to placebo was not apparent. Bleeding-related AEs were reported with a slightly lower incidence in subjects given placebo than either active treatment. The observed shifts from screening in hematology parameters demonstrated no clinically meaningful differences between the active treatment groups and the placebo group.

Local site reactions were rare and reported with a similar incidence between both active groups and placebo as evidenced by local site reaction AE reporting and prospective thrombophlebitis assessment.

Pharmacokinetics: Not applicable.

Office of Clinical Pharmacology				
New Drug Application Filing and Review Form				
General Information About the Submission				
	Information		Information	
NDA/BLA Number	22-396	Brand Name	Dyloject	
OCP Division (I, II, III, IV, V)	DCP2	Generic Name	Diclofenac Sodium	
Medical Division	DAARP	Drug Class	NSAID	
OCP Reviewer	Srikanth C. Nallani, Ph.D.	Indication(s)	Acute pain	
OCP Team Leader	Suresh Doddapaneni, Ph.D.	Dosage Form	Injection	
Pharmacometrics Reviewer	NA	Dosing Regimen	37.5 mg qid	
Date of Submission	12/2/2009	Route of Administration	(b) (4) IV bolus	
Estimated Due Date of OCP Review	8/9/2010	Sponsor	Javelin Pharmaceuticals Inc.	
Medical Division Due Date	8/9/2010	Priority Classification	Standard	
PDUFA Due Date	10/1/2010			
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	2	2	
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-	X			
single dose:	X	1	1	
multiple dose:	X	1	1	
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:	X	1	1	
pediatrics:				
geriatrics:	X	1	1	
renal impairment:	X	1	1	
hepatic impairment:	X	1	1	
PD -				
Phase 2:	X	1	1	
Phase 3:	X	1	1	
PK/PD -				

Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability	X	1	1	
Relative bioavailability -	X	1	1	
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		10	10	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			NA	
Studies and Analyses					

11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			NA	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			NA	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			NA	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		X		

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Dyloject was approved by the Medicines and Healthcare products Regulatory Agency (MHRA) in October 2007 and is currently marketed in the United Kingdom for both IM and IV administration. Sponsor indicated their intent to propose use of Dyloject by (b) (4) IV route in US. (b) (4)

(b) (4)

(b) (4)

Srikanth C. Nallani, Ph.D.

Reviewing Clinical Pharmacologist

Date

Suresh Doddapaneni, Ph.D.

Team Leader/Supervisor

Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22396	ORIG-1	HOSPIRA INC	diclofenac sodium injection

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SRIKANTH C NALLANI
08/17/2010

SURESH DODDAPANENI
08/17/2010