CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022396Orig1s000

MEDICAL REVIEW(S)

Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesia, Analgesia, and Addiction Products
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Summary Review for Regulatory Action

Date	December 23, 2013
From	Rigoberto Roca, M.D.
Subject	Deputy Division Director Summary Review
NDA/Supplement No.	022396/000
Applicant Name	Hospira, Inc.
Date of Original Submission	December 2, 2009 Complete Response letter issued October 1, 2010
Date of Complete Response Submission	June 28, 2013
PDUFA Goal Date	December 28, 2013
Proprietary Name / Established (USAN) Name	Dyloject / diclofenac sodium
Dosage Forms / Strength	Solution for intravenous injection / 37.5 mg/mL
Proposed Indications	1. Management of acute mild to moderate to pain 2. Management of acute moderate to severe pain alone or in combination with opioid analgesics
Action	Complete response

Material Reviewed/Consulted OND Action Package, including:	
CDTL Review	Josh Lloyd, MD
Statistical Review	Janice Derr, PhD
Pharmacology Toxicology Review	Armaghan Emani, PhD / Adam Wasserman, PhD
ONDQA Review	Julia Pinto, PhD / Prasad Peri, PhD
Clinical Pharmacology Review	Srikanth Nallani, PhD / Yun Xu, PhD
Project Management Staff	Swati Patrwardhan
OMP/OPDP	L. Shenee Toombs
OMPQ/DGMPA/NDMAB	Juandria Williams, PhD
OSE/DMEPA	Rachna Kapoor, PharmD / Morgan Walker, PharmD, MBA

CDTL = Cross-Discipline Team Leader
DGCPC = Division of Good Clinical Practice Compliance
DGMPA = Division of GMP Assessment
DMEPA = Division of Medication Error Prevention and Analysis
NDMAB = New Drug Manufacturing Assessment Branch
OMP = Office of Medical Policy
OMPQ = Office of Manufacturing and Product Quality
OND = Office of New Drugs
ONDQA = Office of New Drug Quality Assessment
OPDP = Office of Professional Drug Promotion
OSE = Office of Surveillance and Epidemiology

1. Introduction

Dyloject, is an injectable formulation of diclofenac sodium, a nonsteroidal anti-inflammatory drug (NSAID) that is an inhibitor of both isoforms of cyclooxygenase (COX-1 and COX-2). It exhibits analgesic, anti-inflammatory and antipyretic effects. Diclofenac is approved and marketed in the United States in immediate-release and modified-release oral formulations, as well as a topical formulation. There are no approved intravenous formulations in the United States.

This formulation was originally developed by Javelin Pharmaceuticals, Inc., under IND 65,048. The company was acquired by Hospira, Inc. (the Applicant), and a new drug application (NDA) was submitted on December 2, 2009, under section 505(b)(2) of the federal Food, Drug, and Cosmetic Act. The referenced drug was Cataflam (NDA 020142). The final assessment at the end of that review cycle resulted in a complete response letter, issued on October 1, 2010. This submission consists of the Applicant's response to that complete response letter.

This review will provide an overview of the regulatory and scientific facts of this application and issues that were identified during the course of the review of the submission. Aspects that will be touched upon include the regulatory history, the adequacy of the data to support the application, and the labeling requested by the Applicant.

2. Background

As noted in Dr. Lloyd's review, the supporting data for the original NDA included 16 clinical studies, two of which were Phase 3 efficacy trials (DF-004 and DFC-005), and one Phase 3 open-label safety study (DFC-010). The review team's conclusion at the end of the first review cycle was that adequate information had been submitted to evaluate the drug product's efficacy and safety. No concerns were identified related to the efficacy of the product. There was concern that the safety profile of one of the doses proposed by the Applicant did not result in a favorable risk:benefit assessment; however, the team concluded that the data supported the risk:benefit assessment of a lower dose regimen.

From a drug quality perspective, the review team concluded that there was a lack of assurance of an acceptable manufacturing process.

Both of these issues resulted in the NDA not being approved during the first review cycle. The Complete Response letter issued on October 1, 2010, identified two deficiencies as the reasons for the action:

CLINICAL

1. Data submitted do not support the proposed (b) (4)

(b) (4)

CHEMISTRY, MANUFACTURING AND CONTROLS

2. (b) (4)

(b) (4)

Based on the currently available data provided in the amendment dated September 23, 2010, we are recommending a "For Cause Inspection" of the drug product manufacturer's facility (b) (4) An inspection must be performed and a satisfactory recommendation issued for all manufacturing sites by the Office of Compliance prior to marketing of this product.

In the current submission, the Applicant addressed the clinical deficiency (b) (4) The Applicant addressed the (b) (4) concern (b) (4)

3. Chemistry, Manufacturing, and Controls (CMC)

General Product Considerations

The drug product is an aqueous solution, presented in a 1-mL fill volume in a 2- mL USP Type I flint glass vial. The stopper is a 13-mm (b) (4) rubber stopper, and there is an aluminum overseal.

Specific Issues Identified in the Course of the Review

No new data related to the drug substance or drug product were submitted in this application. The primary issue that needed to be evaluated during this review cycle (b) (4) was sufficient to address the concerns (b) (4)

Outstanding or Unresolved Issues

I concur with the conclusions reached by Dr. Peri that the application's approvability is dependent on the inspection of the drug product manufacturing facility, and final assessment and recommendation of the Office of Compliance.

4. Nonclinical Pharmacology/Toxicology

There were no new nonclinical data submitted during this review cycle.

Outstanding or Unresolved Issues

There were no outstanding or unresolved pharmacology/toxicology issues that precluded approval during the first review cycle, and there are none during this review cycle.

5. Clinical Pharmacology/Biopharmaceutics

There were no new clinical pharmacology data submitted during this review cycle.

Outstanding or Unresolved Issues

There were no outstanding or unresolved clinical pharmacology issues that precluded approval during the first review cycle, and there are none during this review cycle.

6. Clinical Microbiology

Dyloject is not a therapeutic antimicrobial; therefore, clinical microbiology data were not required or submitted for this application.

7. Clinical/Statistical – Efficacy

There were no new clinical data submitted during this review cycle. As noted above, the review team concluded that the Applicant had submitted adequate data to support efficacy of the product during the review cycle.

Outstanding or Unresolved Issues

Although the conclusion of the review team during the first review cycle was that efficacy had been demonstrated, there was the concern (b) (4)

(b) (4)

Therefore, I concur with the overall conclusion reached by the review team that the data submitted are adequate to demonstrate the efficacy of the product and that, from an efficacy standpoint, there are no outstanding issues or concerns that would preclude approval.

8. Safety

There were no new clinical data submitted during this review cycle. As noted above, the conclusion of the review team during the first review cycle was that the Applicant had successfully demonstrated that the drug product had a favorable risk:benefit profile for the lower dose (37.5 mg) (b) (4) The Applicant was advised in the Complete Response letter of October 1, 201 (b) (4)

(b) (4)

It was noted in Dr. Lloyd's review that the review team had identified other safety issues during the first review cycle, which were felt to not impede the approvability of the application, but could potentially be addressed with labeling.

These issues are summarized in Dr. Lloyd's review and consist of the following: bleeding events, thromboembolic events, wound healing, safety profile in patients with renal impairment. I concur with his assessment and recommendations regarding how these issues should be addressed in the package insert.

Outstanding or Unresolved Issues

(b) (4) the Applicant addressed the clinical deficiency identified in the Complete Response letter of October 1, 2010. Therefore, I concur with the review team that there are no outstanding safety issues that would preclude approval.

9. Advisory Committee Meeting

An advisory committee meeting was not convened for this supplemental application, as there were no issues in this supplemental application that required presentation or discussion at an advisory committee meeting.

10. Pediatrics

The Applicant has not conducted any clinical trials in pediatric patients. At present, the Applicant's proposed pediatric plan is to request a waiver from studying pediatric patients between the ages of birth and 12 months of age, and a deferral for studying pediatric patients

between the ages of 1 year and 17 years of age. The Applicant's plan includes the following studies:

Study 1:
An open-label pharmacokinetic and safety study or studies of an age appropriate formulation of Dyloject in pediatric patients 2 to <17 years of age with acute pain.

Study 2:
A pharmacokinetic, safety, and efficacy study or studies of an age-appropriate formulation of Dyloject in pediatric patients 1 to <2 years of age with acute pain.

The pediatric study plan was presented at the Pediatric Research Committee (PeRC) meeting of November 6, 2013. The following text, reproduced from Dr. Lloyd's review, summarizes the committee's recommendations:

> PeRC noted that the variability in development of metabolic pathways for this product have not been clearly established and would not preclude studies in pediatric patients birth to <12 months of age. Therefore, PeRC did not agree with the Applicant's partial waiver request in that age group. However, due to the theoretical concerns associated with immature metabolic pathways, PeRC recommended that even though the Applicant will be required to conduct studies in all pediatric age ranges, that studies should be conducted sequentially in older age groups first. If studies in older age groups reveal safety concerns, studies in younger age groups could be waived at that time. Additionally, if more commonly used NSAIDs (e.g., ibuprofen) receive approval down to birth, a waiver in patients less than one year of age could be considered at that time. PeRC recommended that the postmarketing requirements (PMRs) under the Pediatric Research Equity Act (PREA) be issued such that each pediatric age group has sequential, non-overlapping protocol submission and study completion dates.

I concur with Dr. Lloyd's recommendation that studies should be conducted in all the pediatric age groups, that these studies may be deferred on the basis that studies in adults have been completed and that the drug development program has progressed to the point that the drug is ready for approval, and that efficacy may be extrapolated from adults to pediatric patients two years of age and older. The studies to be requested as post-marketing requirements, as noted in Dr. Lloyd's review, are as follows:

(b) (4)

(b) (4)

11. Other Relevant Regulatory Issues

The Office of Compliance conducted an inspection of the manufacturing facility (b) (4)
(b) (4)

The final recommendation from the Office of Compliance was to withhold approval of the application due to the following observed deficiency (as noted in the memo dated December 17, 2013):

(b) (4)

Outstanding or Unresolved Issues

In view of the results of the inspection of the manufacturing facilities, and the final recommendation from the Office of Compliance, there is still a concern (b) (4) and, therefore, this application cannot be approved at this time.

12. Labeling

The Pediatric and Maternal Health Staff (PMHS) recently provided recommended language for the nursing mothers section of the package inserts of another diclofenac-containing product. The recommended language was based on published literature, and the ability to incorporate that language into this product's package insert, based on potential 505(b)(2) regulatory implications, is currently being evaluated.

In addition, the Division of Medication Error Prevention and Analysis (DMEPA) provided recommendations for modifications to the package insert, container labels, and carton labeling. The Office of Prescription Drug Products (OPDP) also provided comments on the package insert.

13. Decision/Action/Risk Benefit Assessment

Regulatory Action

Complete Response.

Risk:Benefit Assessment

The Applicant has submitted adequate information and data to demonstrate the safety and effectiveness of the product. However, the inspection of the manufacturing facilities identified significant issues that preclude approval of this application at this time.

The package insert, container labels, and carton labeling have been reviewed extensively during this cycle. Recommendations regarding the carton and container labels have been conveyed to the Applicant during the course of this review cycle; the modifications to the package insert will be conveyed to the Applicant with the action letter and discussed during the next review cycle.

Recommendation for Postmarketing Risk Management Activities

The review team's assessment of the Applicant's proposed pediatric plan will be conveyed with the action letter.

Recommendation for other Postmarketing Study Commitments

None.

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/s/

RIGOBERTO A ROCA
12/23/2013

Cross-Discipline Team Leader Review

Date	December 11, 2013
From	Joshua M. Lloyd, MD
Subject	Cross-Discipline Team Leader Review
NDA#	22-396
Applicant	Hospira
Date of Submission	June 28, 2013
PDUFA Goal Date	December 28, 2013
Proprietary Name / Established (USAN) names	Dyloject/ diclofenac sodium
Dosage forms / Strength	Solution for IV injection, 37.5 mg/ml
Proposed Indications	1. Management of acute mild to moderate pain 2. Management of acute moderate to severe pain alone or in combination with opioid analgesics
Recommended Action:	Approval pending a final acceptable recommendation from the Office of Compliance for all manufacturing and testing facilities

1. Introduction

Javelin Pharmaceuticals, Inc., (subsequently purchased by Hospira; also referred to as "the Applicant") developed Dyloject, an injectable drug product containing diclofenac sodium, under IND 65,048 for the short-term management of acute moderate to severe pain. The Applicant submitted a New Drug Application (NDA) under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, on December 2, 2009 (received December 3, 2009), referencing the Agency's prior findings of efficacy and safety for diclofenac potassium (Cataflam; NDA 20142).

The Applicant has submitted this NDA for Dyloject (administered as a 37.5 mg intravenous bolus injection) as a response to the Complete Response (CR) action issued by the Division on October 1, 2010. The deficiencies cited in the CR letter were related to both the clinical and the chemistry, manufacturing, and controls (CMC) disciplines, as well as labeling. The clinical and CMC deficiencies are reproduced below:

CLINICAL

1. Data submitted do not support the proposed (b) (4)

(b) (4)

CHEMISTRY, MANUFACTURING AND CONTROLS

2. (b) (4)

(b) (4)

Based on the currently available data provided in the amendment dated September 23, 2010, we are recommending a "For Cause Inspection" of the drug product manufacturer's facility (b) (4)

An inspection must be performed and a satisfactory recommendation issued for all manufacturing sites by the Office of Compliance prior to marketing of this product.

The Applicant responded with a CR submission to address the deficiencies outlined in the CR letter and, specifically, has responded to the clinical deficiency (b) (4) (b) (4) Therefore, they are pursuing the 37.5 mg dose, and this is acceptable given the findings for the 37.5 mg dose documented in Dr. Larissa Lapteva's combined cross-discipline team leader review (CDTL)-Division Deputy Director memo dated October 1, 2010. The Applicant's

responses to the deficiencies are discussed further in this review, as are relevant data and conclusions regarding the proposed labeling.

I have concluded that this application should receive an Approval action pending a final acceptable recommendation from the Office of Compliance for all manufacturing and testing facilities as discussed in Section 13 below.

2. Background

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities and is a potent inhibitor of both COX-1 and COX-2. Diclofenac is approved and marketed in the United States as various salt forms in oral (immediate-release and modified-release) and topical formulations for multiple painful conditions. There are no approved intravenous (IV) formulations of diclofenac in the United States.

The original NDA for Dyloject was submitted on December 2, 2009. The basis for the NDA was 16 clinical studies including two Phase 3 efficacy trials (DFC-004 and DFC-005) and one Phase 3 open-label safety study (DFC-010). Details regarding the safety and efficacy reviews are available in Dr. Larissa Lapteva's combined CDTL-Division Deputy Director memo dated October 1, 2010. Also refer to Dr. Lapteva's review for a discussion of the relevant pre-submission regulatory history.

3. CMC/Device

Dr. Peri noted in his review that:

> Javelin Pharmaceuticals Inc. originally submitted an NDA on 3-Dec-2009 for their drug product diclofenac sodium injection. [redacted (b) (4)] Office of Compliance recommended a withhold recommendation for the manufacturing facility and hence a Complete Response action was taken for the NDA.

The drug product manufacturing facility has undergone inspection and a final recommendation from the Office of Compliance is pending. The CMC team recommends approval of the NDA pending a final acceptable recommendation from the Office of Compliance for all manufacturing and testing facilities.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology/toxicology data were submitted with this CR submission.

5. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology/biopharmaceutics data were submitted with this CR submission.

6. Clinical Microbiology

N/A

7. Clinical/Statistical- Efficacy

No new efficacy data were submitted with this CR submission.

The Applicant's proposed indications in this submission are slightly different than what was recommended by the Division in the first review cycle. The Applicant's proposed indication appears below with their changes from the Division's recommendations indicated in red font (additions) and red strikethrough font (deletions).

> Dyloject is an NSAID indicated in adults for the (b) (4) management of (b) (4) mild to moderate pain and (b) (4) management of (b) (4) moderate to severe pain alone or in combination with (b) (4) opioid analgesics.

I recommend that the indication be further modified to:

> Dyloject is an NSAID indicated in adults for the management of mild to moderate pain and management of moderate to severe pain alone or in combination with opioid analgesics.

This indication is consistent with recently approved injectable non-opioid analgesics and the results of the pivotal Phase 3 clinical trials. Additional information about the pivotal clinical trials will be included in the clinical trials section of the labeling (Section 14) to communicate basic study population characteristics and to further guide prescribers on proper patient selection for therapy with Dyloject.

8. Safety

No new safety data were submitted with this CR submission.

Dr. Lapteva noted several safety concerns with Dyloject in her combined CDTL-Division Deputy Director Memo, including bleeding-related events, thromboembolic events, and anticoagulation therapy; wound healing; and safety in patients with renal impairment. Please refer to her review dated October 1, 2010, for additional information. Although these safety concerns were not approvability issues during the first cycle, they were handled in the context of labeling. These issues continue to not be approvability issues; however, I will explore them further as they relate to the current proposed labeling.

Bleeding Events

Dr. Lapteva raised the concern of bleeding events with Dyloject, particularly in patients on concomitant anticoagulation therapy. The labeling sent to the Applicant at the end of the first review cycle included cautionary language in the highlights section (b) (4) (b) (4) Applicant proposes removing the language from the highlights section.

Dr. Lapteva notes that fewer patients were receiving concurrent anticoagulation therapy in the controlled trials compared to the open-label safety study. Two patients on concurrent anticoagulation therapy in the controlled Phase 3 clinical trials developed bleeding events (i.e., epistaxis and rectal bleeding). However, 5.5% of patients treated with Dyloject and concomitant anticoagulation therapy in the open-label safety study developed bleeding-related events. Dr. Neuner, the primary clinical reviewer during the first cycle, notes in her review dated September 3, 2010, that the observed rates of bleeding events in the open-label study are comparable with the incidence of bleeding events described with anticoagulating agents reported in the literature. Additionally, the Applicant noted in the CR submission that of the seven subjects who reported incision site hemorrhage, six received anticoagulants at some point during the study. Only two of those subjects received Dyloject and anticoagulants concurrently. The remaining 4 subjects received anticoagulants 10 to 15 hours after the last dose of Dyloject, including 2 that had resolution of the adverse event prior to administration of anticoagulants and 3 who received anticoagulants greater than 5 half-lives after Dyloject.

The small numbers of patients who developed incisional site hemorrhage with concurrent Dyloject and anticoagulation therapy limit the ability to conclude that there is increased risk with Dyloject beyond what is already described for NSAIDs in general. Dyloject labeling, consistent with NSAID class labeling, already contains adequate information about NSAIDs and the increased risk of bleeding with concomitant anticoagulation therapy. Therefore, I concur that the language (b) (4) (b) (4) be removed from the highlights section of Dyloject labeling.

Thromboembolic Events

Dr. Lapteva expressed concern that the use of Dyloject influenced clinicians' choice of deep venous thrombosis (DVT) and pulmonary embolism (PE) prophylaxis in clinical trials due to the known and labeled interaction between NSAIDs and anticoagulant therapies. I reviewed the amendments to this application dated September 30, 2010, that were sent in response to the review team's inquiries during the first review cycle.

Fourteen patients developed serious adverse events of DVT or PE in Phase 3 trials with ten of those receiving anticoagulant therapy at various doses and durations for DVT/PE prophylaxis. The remaining four patients who did not receive DVT/PE prophylaxis with anticoagulant therapy underwent laparoscopic cholecystectomy, open reduction of the fifth metatarsal, ankle surgery, or rotator cuff repair. In patients not considered to be at higher risk for DVT/PE, the routine use of pharmacologic DVT/PE prophylaxis is not considered standard of care for these procedures. Two of the four patients who developed DVT/PE and did not receive anticoagulation therapy for prophylaxis as part of their treatment plan were assigned to the placebo or active control treatment arms and not the Dyloject treatment arm.

Given the limited numbers and lack of a clear, definitive clinical indication for pharmacologic DVT/PE prophylaxis in patients who developed DVT/PE and were not treated with such prophylactic therapy, I cannot conclude with certainty that the use of an injectable NSAID in postoperative pain management influenced the decision to treat or not treat patients with pharmacologic DVT/PE prophylaxis in the Phase 3 clinical study population. Therefore, I have no further recommendations beyond what has already been included in labeling for this product during the first review cycle.

Wound Healing

Dr. Lapteva noted in her review that the observed occurrence of adverse events related to wound healing was higher in the NSAID-treated patients and that although interpretation of these data was limited, knowledge of these data will be important to communicate to prescribers. Given the concern for wound healing impairment with NSAID therapy, the review team made recommendations to include this information in labeling during the first review cycle. (b) (4)

The retrospective wound healing analysis was based on a review of adverse events related to wound healing and was conducted using data from the controlled and open-label Phase 3 studies. In contrast, the prospective wound healing analysis consisted of a six-item questionnaire related to wound healing that included an assessment of the extent of healing and extent and degree of inflammation in relation to the clinician's expectations and assessments of incisional separation, infection at the surgical site, and use of postoperative systemic antibiotics. The prospective assessment was carried out in one of the pivotal Phase 3 clinical trials and in the open-label safety study following a request by the Division during drug development to collect information on any possible negative effects on wound healing.

Adverse events related to wound healing were overall more frequent in the Dyloject-treated groups compared to placebo. Although the results from the prospective wound healing analysis appear to contradict those of the retrospective analysis, the clinical significance of the wound healing questionnaire is uncertain as it relates to the observations seen in the retrospective analysis and it may be potentially impacted by clinician's perceptions of their own practice. Therefore, information regarding adverse reactions related to wound healing remains important information that should be communicated to prescribers in labeling as recommended during the first review cycle.

Safety in Patients with Renal Impairment

The Applicant proposes (b) (4)

Cases of acute renal failure in the Phase 3 trial population are summarized in the table below.

Table 1. Acute renal failure in patients treated in trials DFC-004, DFC-005, and DFC-010.

MedDRA System Organ Class/ Preferred Term	Placebo		DIC075V			
	Total Impaired (N=8)	Total Not Impaired (N= 139)	18.75 mg Impaired (N=8)	Combined 37. 5 mg and 50 mg Impaired (N=60)	Total Impaired (N=68)	Total Not Impaired (N=1216)
Acute Renal Failure	0	1 (0.7%)	1 (12.5%)	2 (3.3%)	3 (4.4%)	8 (0.66%)

Source: Table 15 from Dr. Lapteva's review.

Among patients with pre-existing renal impairment (including 60 patients with mild renal impairment and 8 patients with moderate renal impairment) who were treated with Dyloject, 4.4% developed acute renal failure as compared to 0.66% of patients without pre-existing renal impairment. The frequency of acute renal failure in patients without pre-existing renal impairment was similar between Dyloject groups and placebo. According to Dr. Lapteva's review, the vast majority of patients with acute renal failure were volume-depleted when they developed the event.

These results demonstrate a risk for developing acute renal failure in patients with pre-existing renal impairment who are treated with Dyloject. Therefore, I recommend that Dyloject be contraindicated in patients with moderate to severe renal insufficiency. As an injectable NSAID will likely be used in hospitalized and perioperative patients who are at risk for the development of acute renal failure and the majority of patients who developed acute renal failure in the clinical development program were volume-depleted, I recommend that, to further inform prescribers on the appropriate patient population for whom the risk-benefit profile would be favorable, the contraindication be further qualified to patients with moderate and severe renal insufficiency in the perioperative period and who are at risk for volume depletion.

Additional Safety Concerns

The Pediatric and Maternal Health Staff (PMHS) were recently consulted on another diclofenac-containing product, and they provided recommended language for the nursing mothers section of the labeling to be applied to all diclofenac-containing products. Their recommended language was based upon the published literature, however, the Division is currently exploring the 505(b)(2) implications with respect to the inclusion of this language. The recommended information from PMHS represents important safety information and

should be included in labeling to inform prescribers, pending resolution of any potential 505(b)(2) issues.

9. Advisory Committee Meeting

An Advisory Committee meeting was not convened for this application.

10. Pediatrics

No studies have been carried out in pediatric patients. The Applicant submitted a pediatric study plan that includes the following studies:

- *Study 1*: An open-label pharmacokinetic and safety study or studies of an age-appropriate formulation of Dyloject in pediatric patients 2 to <17 years of age with acute pain
- *Study 2*: A pharmacokinetic, safety, and efficacy study or studies of an age-appropriate formulation of Dyloject in pediatric patients 1 to <2 years of age with acute pain

The Applicant requested a deferral for pediatric patients ages 1 to <17 years. The Applicant also requested a partial waiver for pediatric patients birth to <12 months of age because the product would be ineffective and/or unsafe in this age group due to immaturity of the enzymes required for metabolism.

The Applicant's pediatric study plan was discussed at a meeting of the Pediatric Research Committee (PeRc) on November 6, 2013, and the PeRC had the following recommendations: PeRC noted that the variability in development of metabolic pathways for this product have not been clearly established and would not preclude studies in pediatric patients birth to <12 months of age. Therefore, PeRC did not agree with the Applicant's partial waiver request in that age group. However, due to the theoretical concerns associated with immature metabolic pathways, PeRC recommended that even though the Applicant will be required to conduct studies in all pediatric age ranges, that studies should be conducted sequentially in older age groups first. If studies in older age groups reveal safety concerns, studies in younger age groups could be waived at that time. Additionally, if more commonly used NSAIDs (e.g., ibuprofen) receive approval down to birth, a waiver in patients less than one year of age could be considered at that time. PeRC recommended that the postmarketing requirements (PMRs) under the Pediatric Research Equity Act (PREA) be issued such that each pediatric age group has sequential, non-overlapping protocol submission and study completion dates.

I recommend issuing PMRs for the pediatric studies outlined in Section 13 below and granting a deferral for studies in pediatric patients (b) (4) to <17 years of age on the basis that adult studies are completed and ready for approval. Efficacy may be extrapolated from adults to pediatric patients two years of age and older for NSAIDs, consistent with the Division's current policy.

11. Other Relevant Regulatory Issues

This application was presented at a 505(b)(2) clearance meeting on November 25, 2013, and it was cleared for action from their perspective.

12. Labeling

The proprietary name, Dyloject, was found acceptable from both a promotional and safety perspective following review by the Division of Medication Error Prevention and Analysis (DMEPA). DMEPA also concluded that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product. DMEPA made recommendations for improving the package insert, container labels, and carton labeling and requested that these recommendations be implemented prior to approval of this NDA.

Labeling is ongoing at the time of this writing, and specific recommendations have been made in the relevant sections of this review.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

  Approval pending a final acceptable recommendation from the Office of Compliance for all manufacturing and testing facilities

- Risk Benefit Assessment

  The Applicant submitted this NDA on June 28, 2013, in response to a CR action taken by the Division on October 1, 2010. The main deficiencies during the first review cycle were related to the clinical and CMC disciplines. The Applicant has adequately responded to the clinical deficiency outlined in the CR letter. The CMC deficiency involved (b) (4) At the time of this writing, the drug product manufacturing facility has undergone inspection and a final recommendation from the Office of Compliance is pending. As the Applicant has adequately addressed the clinical deficiencies from the first review cycle, I recommend approval of this product pending a final acceptable recommendation from the Office of Compliance for all manufacturing and testing facilities with the recommended labeling changes documented throughout this review.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

  None

- Recommendation for other Postmarketing Requirements and Commitments

  The following pediatric studies are required:

(b) (4)

- Recommended Comments to Applicant

  None

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/s/

JOSHUA M LLOYD
12/11/2013

Summary Review for Regulatory Action

Date	October 1, 2010
From	Larissa Lapteva, M.D., M.H.S.
Subject	Division Deputy Director Summary Review
NDA #	22-396
Applicant Name	Hospira
Date of Submission	December 2, 2009
PDUFA Goal Date	October 3, 2010
Proprietary Name / Established (USAN) Name	Dyloject/ diclofenac sodium
Dosage Forms / Strength	Solution for IV injection, 37.5mg/mL
Proposed Indication(s)	Management of acute moderate to severe pain
Action	Complete Response

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	**Rosemarie Neuner, M.D., M.P.H.**
Statistical Review	**Jonathan Norton, Ph.D., Dionne Price, Ph.D.**
Pharmacology Toxicology Review	**Armaghan Emami Ph.D., Adam Wasserman, Ph.D**
CMC Review	**Martin Haber, Ph.D., Danae Christodoulou, Ph.D. Prasad Peri, Ph.D.**
Product Quality Microbiology Review	**John Metcalfe, Ph.D.**
Clinical Pharmacology Review	**Srikanth Nallani, Ph.D., Suresh Doddapaneni, Ph.D.**
DDMAC Review	**Mathilda Fienkeng**
DSI Memorandum	**Robert Young, Tejashri Purohit-Sheth, M.D.**
OSE/DMEPA Review	**Walter Fava, R.Ph.,Carlos Mena-Grillasca, R.Ph., Denise Toyer, Pharm.D., Carol Holquist, R.Ph.**
Interdisciplinary Review Team for QT studies Review	**Moh Jee NG, M.D., Joanne Zhang M.D., Jiang Liu M.D., Hao Zhu M.D., Monica L Fiszman M.D., Norman Stockbridge, M.D.**
Environmental Assessment/OPS/OI/SRS Review	**Emily McVey, Ph.D.** **Nakissa Sadrieh, Ph.D.**

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication ErrorsPrevention
DSI=Division of Scientific Investigations
CDTL=Cross Discipline Team Leader

1. Introduction

This NDA was submitted as a 505(b)(2) application for an intravenous formulation containing 37.5mg/mL of diclofenac sodium with the proposed proprietary name, Dyloject. The product has been developed by Javelin Pharmaceuticals under IND 65,048 for the short term management of acute moderate to severe pain.

This review will outline the main findings of safety and efficacy of IV diclofenac (also referred to in this review as DIC075V) as well as recommendations provided by different scientific disciplines. Several specific issues raised during the review cycle for this NDA will be discussed in detail, including the proposed routes of administration, the proposed dosing regimens, the recent recall of Dyloject™ from the United Kingdom (UK) market and product manufacturing issues, change in product expiry during the review cycle, conduct of the controlled trials in the studied population, and the Environmental Assessment submitted by the Applicant in response to the Agency's requirement based on the finding of the extraordinary circumstances of the ecotoxic effects of diclofenac (CFR 21 CFR 25.21).

2. Background

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) with several decade history of use worldwide. Diclofenac is a benzeneacetic acid derivative and its mechanism of action is associated with inhibition of prostaglandin synthesis via non-selective inhibition of both isoforms of cyclooxygenase, COX-1 and COX-2. As other NSAIDs, diclofenac exerts anti-inflammatory, analgesic, and antipyretic activities.

Oral diclofenac is marketed in the United States as delayed release tablet (sodium salt, Voltaren), extended release tablet (sodium salt, Voltaren-XR), immediate release tablet (potassium salt, Cataflam), oral solution (potassium salt, Cambia), delayed release combination tablet (sodium salt in combination with misoprostol, Arthrotec), and oral capsule (potassium salt, Zipsor). Diclofenac is also approved and marketed in the United States as the active ingredient in topical gels (Flector, Solaraze, and Voltaren), topical solution (Pennsaid), and ophthalmic solution products.

There are no approved intravenous (IV) formulations of diclofenac for management of pain in the United States.

Two parenteral formulations of NSAIDs are approved in the US: ketorolac tromethamine (Toradol) approved for intravenous and intramuscular administration for analgesic indication and intravenous ibuprofen (Caldolor) approved for intravenous administration for analgesic and antipyretic indications. Of note, a formulation identical to the article under review, Dyloject™ , distributed by Therabel Pharma UK Limited, was approved by the Medicines and Healthcare Products Regulatory Agency (MHRA) in the United Kingdom in October 2007 as a solution for injection at 75mg/2mL twice a day (not to exceed 150 mg/day), for both

intravenous and intramuscular administration for treatment of acute forms of pain, including renal colic, osteoarthritis, rheumatoid arthritis, acute back pain, acute gout, acute trauma and fractures, and post-operative pain.

This NDA was submitted as a 505(b)(2) application for intravenous formulation of diclofenac solution containing 37.5mg/mL of diclofenac sodium and hydroxypropyl-β-cyclodextran (HPβCD) (b) (4) along with other excipients (refer to CMC section of this review). In this application, reference is made to the Agency's prior findings of efficacy and safety of diclofenac potassium in the approved drug Cataflam (NDA 20-142). In addition, Sporanox (itraconazole) injection (NDA 20-966) was referenced for the Agency's previous findings of safety of HPβCD.

During the End of Phase 2 (EOP2) meeting held on April 21, 2006, the Agency agreed to the Sponsor's proposal to reference Cataflam for the 505(b)(2), because Cataflam was the only immediate-release systemic formulation of diclofenac approved in the US at the time. Given that the C_{max} for DIC075V when administered intravenously at the dose 37.5 mg is five folds higher than the C_{max} for Cataflam administered orally at the dose 50 mg, the Agency informed the Applicant that a safety database of adequate size (about 1000 patients exposed to multiple doses over multiple days of treatment with the to-be-marketed formulation) would be needed to assess the safety profile of DIC075V. The Agency informed the applicant that they would need to collect data on safety of DIC075V in postoperative patient population and include individuals with renal and hepatic impairment and elderly patients (>65 years of age). In addition, the Applicant was advised to collect data on any possible negative effects of IV diclofenac on wound healing. Also, at the EOP2 meeting, the Agency indicated that the sponsor's proposed primary endpoint for efficacy assessment Summary of Pain Intensity Differences (SPID) at 48 hours post dose was acceptable.

During the pre-NDA meeting held on March 10 2008, the sponsor stated that they planned to contraindicate their product in patients with moderate and severe renal impairment and in moderate and severe liver disease. The Agency indicated that even though the sponsor plans to contraindicate DIC075V in patients with moderate to severe renal impairment, the pharmacokinetic (PK) characteristics of HPβCD in patients with mild renal impairment must be assessed with PK studies to understand the potential for renal toxicity associated with both DIC075V and HPβCD (refer to pre-NDA meeting minutes dated March 10, 2008 for details).

Upon submission of this NDA, the application has been granted a Standard Review.

For this NDA, the Applicant initially proposed (b) (4) intravenous (IV) (b) (4) 37.5mg/mL (b) (4) While the clinical trials to support this NDA were conducted with DIC075V administered intravenously, the Applicant did not submit sufficient data (b) (4)

Further, the Applicant's proposed dosing for management of acute pain was 37.5 mg IV every 6 hours to the maximum of 150 mg daily (b) (4)

This NDA was initially granted a categorical exclusion for Environmental Assessment (EA) for diclofenac contained in DIC075V. During the 6th month of the review cycle, the new information about environmental impact of diclofenac became available. In particular, ONDQA review team, environmental group (Dr. Emily McVey) in their review cited several recent publications indicating that diclofenac has a potential to harm the environment at environmentally-relevant concentrations. Diclofenac has been found to be highly toxic to certain bird and fish species including rainbow trouts and brown trouts species as well as some avian species. It was also found that diclofenac is extremely toxic to the Oriental white-backed vultures, which are now a critically endangered species as a result of inappropriate veterinary use of diclofenac in cattle in India. The influx of the new data prompted the Agency to reconsider the current approach to diclofenac-containing products and require the Applicant to submit an Environmental Assessment (EA) to evaluate the impact of diclofenac from DIC075V to the overall environmental burden of diclofenac. The Applicant submitted the EA during the ninth month of the review cycle on August 22, 2010, and the results of the review of this submission are described further in the CMC section.

(b) (4)

[redacted] Refer to further discussion on the manufacturing and facility issues to the CMC section of this review.

While the review of this application was ongoing, the original Applicant's company Javelin Pharmaceuticals was purchased by Hospira, thus the ownership of this application was transferred to Hospira.

This clinical development program contained 16 trials; ten Phase 1 trials, three Phase 2 trials, and three Phase 3 trials (DFC-004, 005, and 010) as well as 3 HPβCD PK studies conducted by Janssen. The relevant pivotal studies conducted with the to-be-marketed formulation DIC075V administered intravenously (IV) will be discussed in this review.

3. CMC/Device

The primary CMC review was done by Dr. Martin Haber and the secondary review by Dr. Prasad Peri. The original CMC review by Dr. Haber was finalized on September 3, 2010. [redacted] Dr. Haber wrote a memorandum to incorporate the new information, which changed the recommendation on approvability. A separate review of the Environmental Assessment submitted by the Applicant was conducted by Dr. Emily McVey with concurrence from Dr. Nakissa Sadrieh and is discussed later in this section. The following contains some excerpts from Dr. Haber's review.

Drug Product

The drug product is an aqueous solution presented in a 1 mL fill volume in a 2 mL USP Type I flint glass vial with a 13 mm [redacted] rubber stopper and aluminum overseal. The active concentration is 3.75%, resulting in strength of 37.5 mg of diclofenac sodium in 1 mL.

The drug product vial also contains the following excipients: 33 [redacted] mg hydroxypropyl-betadex (β-cyclodextran), 5.0 mg monothioglycerol, and traces of hydrochloric acid and sodium hydroxide added to adjust the pH [redacted]

Both CMC and the Pharmacology Toxicology reviewers were concerned about a likely impurity [redacted] present in the drug product at the concentrations exceeding the ICH recommended threshold. The respective Information Request was sent to the Applicant. In the subsequent amendments submitted by the Applicant on 7/12/10 and 7/19/10, the specification limits for osmolality, pH, hydroxypropyl betadextran [redacted] were tightened to [redacted]% as per ICH Q3B.

In addition, because the submitted [redacted] studies [redacted] remained within the proposed acceptance

limits [redacted] the Applicant reduced the originally proposed expiry [redacted] to 18 months in the amendment dated 7/19/10. This was found acceptable by both CMC and Pharmacology Toxicology reviewers (refer to Section 4 for additional information).

Drug Substance

The drug substance, diclofenac sodium, was first approved in the 1970's and is the subject of a USP monograph. The bulk drug substance is manufactured [redacted]

There are two Type II DMF's for drug substance diclofenac sodium: DMF [redacted] and DMF [redacted] the DMF holder is the same firm, [redacted] for both.

DMF [redacted] provided information [redacted] which was reviewed by Dr Haber on 8/11/10 and found adequate.

In his original CMC review dated Sept 3, 2010, Dr. Haber reviewed the drug substance specifications and found them to be in compliance with the USP monograph and acceptable. Testing of the drug substance by the drug product manufacturer was also found acceptable.

Description of Intended Use of the Drug Product

DIC075V Injection vials are for single use only [redacted] The intended usage is for the management of acute pain in adults. The dosage is 37.5 mg/mL administered by intravenous bolus injection every 6 hours, not to exceed 150 mg/day.

The proposed storage condition for the commercial product is controlled room temperature, "Store at Controlled Room Temperature 20-25°C (68-77°F) [see USP]", with a proposed expiration period of 18 months.

Environmental Assessment

Dr. McVey reviewed the EA submitted by the Applicant on August 22, 2010. (Refer to the EA review for further details.) As agreed with the Agency, the Sponsor provided Estimated Introductory Concentrations (EIC) at the peak year of the next five years and compared the EIC with the lowest toxic effect levels found in the environment based on a literature search that included multiple environmental species. The literature search provided in this EA was determined to be acceptable to the Agency. Dr. McVey with concurrence of Dr. Sardrieh recommended a Finding of No Significant Impact (FONSI) for this application.

In her review Dr. McVey noted:

[redacted]

[redacted] The report was reviewed by the CMC reviewers and the evaluation conducted by the Applicant was found inadequate. Further evaluation was recommended by the Office of New Drug Quality Assessment, the Office of Compliance, Division of Manufacturing and Product Quality and the District Office for the site. An on-site inspection to verify that the investigation was adequate and that appropriate changes have been correctly implemented was also recommended. The CMC review team concluded [redacted] Of note, the [redacted] site was not inspected for this NDA by the district office and the facility was found acceptable based on profile as of 3/16/2010.

Based on the evaluation of the data submitted by the Applicant, CMC reviewers have recommended a "For Cause" inspection of the Applicant's contract manufacturing facility [redacted] to comply with current Good Manufacturing Practices prior to the approval of this NDA. (Refer to CMC review addendum for further details.)

Overall conclusions from CMC discipline:

Because the quality of the product to be marketed in the US cannot be assured at this time, it was recommended that the application be not approved from the CMC perspective.

I concur with the conclusions reached by the chemistry reviewers regarding the lack of assurance of an acceptable manufacturing process in this NDA. A "For Cause" inspection of the Applicant's contract manufacturing facility [redacted] and further evaluation [redacted] at the drug product manufacturing and testing facilities remain outstanding issues for this NDA.

4. Nonclinical Pharmacology/Toxicology

The primary Pharmacology Toxicology review was performed by Dr. Armaghan Emami and the secondary review by Dr. Adam Wasserman. As noted previously, the nonclinical development program for this 505(b)(2) NDA application relied on the Agency's previous findings of safety for the two approved drug products Cataflam® (diclofenac potassium) Tablets 50 mg (NDA 20-142) and Sporanox® (itraconazole, NDA 20-966) as well as literature references. Because the route of administration and systemic exposure of DIC075V differed from the listed drugs Cataflam and Sporanox, the applicant submitted several bridging single and repeat dose toxicity studies, genotoxicity studies, and local tolerance studies in support of this application. Of note, some of the non-clinical studies were conducted with earlier formulation of DIC075U, which both Dr. Emami and Dr Wasserman found acceptable. The following contains excerpts from Dr. Wasserman's review verbatim.

> " …the Applicant has provided sufficient information to support the proposed formulation of Dyloject. There are no novel excipients, all being represented in the FDA Inactive Ingredients Database. Additionally, the levels of HPβCD are within that of the approved Sporanox on a daily intake basis (1,332 mg/day vs.16,000 mg/day) though the administered concentration in Dyloject (333 mg/mL) is (b) (4) formulation of Sporanox (b) (4) and the administration rate for the current product may be much greater (bolus) versus Sporanox (slow infusion over 60 minutes). Support for the levels of HPβCD was derived from data from the NDA as allowed by the Letter of Authorization the Applicant obtained from Johnson & Johnson Pharmaceutical Research & Development on behalf of Ortho McNeil Janssen Pharmaceuticals, Inc. Finally, nonclinical toxicology studies evaluated the local and systemic safety of HPβCD as part of a separate vehicle arm in a 28-day monkey IV (bolus) monkey toxicology study which provided a significant (~13X) safety margin based on the area under the plasma concentration-time curve (AUC) of the study No Observed Adverse Effect Level (NOAEL).
>
> The acceptability of using a different formulation (DIC075U, containing lower concentrations of diclofenac and HPβCD) in the majority of the nonclinical toxicology program to support the to-be-marketed Dyloject formulation (DIC075V) was considered by Dr. Emami. I [Dr. Wasserman] agree with Dr. Emami that the critical support needed is local tolerance data and is provided by the use of the DIC075V formulation in dedicated local tolerance studies conducted in rat and rabbit. Though mild local toxicity was observed characterized as reversible perivascular inflammation, this does not preclude nonclinical recommendation for approval though it did predict data from clinical studies which notes some adverse findings.
>
> The applicant previously sought acceptance of specifications for a drug product degradant, (b) (4) that exceeded ICHQ3B specifications but provided an incomplete supporting safety qualification package. When informed of this inadequacy, the Applicant agreed to (b) (4) to comply with ICHQ3B limits (b) (4) which I [Dr. Wasserman] find acceptable.
>
> During CMC review, the compound (b) (4) was determined to be a leachable. (b) (4) (b) (4) (b) (4) The compound was reported to be negative in two published genetic toxicity studies (Ames assay and Mouse Lymphoma assay) and has a high oral LD50 in rat of 8000 mg/kg which suggests low (oral) toxicity. I (Dr. Wasserman) note that the Agency currently has no official guidance on acceptable levels of leachables in drug products; however, a position paper jointly created by Industry, Academia and FDA representatives under the auspices of the Product Quality Research Institute (PQRI) on this subject recommended a qualification threshold (b) (4) I [Dr. Wasserman] believe the publically

> available genetic toxicology information and acute oral toxicity study of this leachable compound, combined with the acute use of the product and very low levels of leachable is sufficient to consider the compound toxicologically qualified as it relates to its presence in the drug product at the end of shelf life."

Both Dr Wasserman and Dr. Emami indicated in their reviews that the observations in the non-clinical studies with rats and monkeys represented the expected and known effects of diclofenac and cyclodextrans. The genetic toxicology studies demonstrated that neither HPβCD nor diclofenac was genotoxic. Because diclofenac was previously sufficiently evaluated in carcinogenicity studies, the applicant relied on carcinogenicity data described in the Cataflam label. Both Dr. Emami and Dr. Wasserman found this acceptable.
Dr. Wasserman concluded:

> "The Applicant has provided nonclinical toxicology evaluation of the drug product in 28-day intravenous rat and monkey toxicology studies using an earlier developmental formulation which adequately support the safety of diclofenac systemic exposures associated with the maximum recommended human dose. Target organ toxicities were expected and are common to NSAID drug products being principally associated with GI lesions and secondary regenerative anemia as well as evidence of impaired wound healing from skin lesions. Histologic evidence of kidney effects at high dose levels is considered non-adverse and related to the vehicle containing hydroxy-propyl β-cyclodextrin. Levels of these excipients and others in formulation are also supported based on prior use in approved drug products. Local tolerance of the to-be-marketed drug product formulation was supported by a single- and repeat-dose IV study in the rat. While mild to moderate irritation was observed in this local tolerance study, this appears reversible and local safety is further supported by clinical safety data. Other aspects of the formulation, including impurity/degradant specifications and a leachable compound observed in stability are acceptable based on ICH guidelines or are considered toxicologically qualified based on publicly available data.
>
> On this basis, I [Dr. Wasserman] concur with Dr. Emami that NDA 22-396 for Dyloject may be approved based on the nonclinical data provided."

I concur with the conclusions reached by the pharmacology/toxicology reviewers that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology/Biopharmaceutics review was completed by Srikanth Nallani, Ph.D. with concurrence from Suresh Doddapaneni, Ph.D. The following paragraphs summarize Dr. Nallani's review.

Pharmacokinetic data were obtained from one single-dose relative bioavailability study (DFC-006), two pharmacokinetic (PK) studies evaluating influence of the intrinsic factors such as age, weight, and renal and hepatic insufficiency on the PK of DIC075V (DFC-008 and DFC-009), one platelet function study (DFC-007), one thorough QT study (DFC-011), one dose response single dose study (DFC-002), as well as a single dose supportive study (N-130310) previously reviewed under NDA 20-966 for Sporanox.

In Study DFC-006, the systemic exposures after IV bolus administration of single and multiple doses of DIC075V (18.75 mg and 37.5 mg) were compared to 50 mg of LD Cataflam administered orally. The peak plasma levels of diclofenac following administration of

DIC075V at 18.75 mg and 37.5 mg were 2.5- and 5-fold higher compared to orally administered 50 mg tablet Cataflam (Tables 1). The systemic exposure (AUC0-inf) of diclofenac following IV injection at 37.5 mg dose was ~30% higher compared to Cataflam. The PK parameters of the 75 mg dose of DIC075V exceeded C_{max} of oral Cataflam ~ 11 times and systemic exposure (AUC) ~3 times. Dr. Nallani noted that a dose proportional increase in systemic exposure of diclofenac was noted following single dose and multiple dose IV administration of DIC075V at 37.5 mg.

The absolute bioavailability of the LD oral Cataflam 50 mg was 66% compared with the IV DIC075V at the dose 37.5mg.

Table 1. Diclofenac PK parameters (mean±SD, n=36) following single dose (Study # DFC-006 & DFC-011)

	Study # DFC-006			Study # DFC-011	
Parameter	**Cataflam 50 mg**	**Dyloject 18.75 mg**	**Dyloject 37.5 mg**	**Dyloject 37.5 mg**	**Dyloject 75 mg**
Cmax(ng/mL)	1,246 ± 732 (36)	2,904 ± 661 (36)	6,031 ± 1178 (36)	6,493± 1,363 (70)	12,102 ± 2,146 (70)
Tmax (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)
λz (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)
t½(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)
Vz(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)

Source: Dr. Nallani's review, p.8

Diclofenac PK parameters following multiple doses of IV or oral diclofenac administration were consistent with the PK parameters following single dose administration (Table 2).

Table 2. Diclofenac PK parameters following multiple doses.

	Study # DFC-006		
Parameter	**Cataflam 50 mg**	**Dyloject 18.75 mg**	**Dyloject 37.5 mg**
Cmax(ng/mL)	851 ± 462 (36)	3,090 ± 1,029 (36)	5,617 ± 1,799 (36)
Tmax (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)
λz (h^{-1})	0.2597 ± 0.0531 (36)	0.4059 ± 0.1056 (35)	0.3256 ± 0.0917 (36)
t½(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)
Vz(L)	242 ± 486 (36)	50.4 ± 14.9 (35)	83.4 ± 127 (36)

Source: Dr. Nallani's review, p.9

Although the UK approved Dyloject ™ was approved at the dose 75 mg/2mL twice a day, the results of the below described dose-response study DFC-002 influenced the Applicant's decision to pursue testing of the lower doses of DIC075V in this development program.

Dose-response was evaluated in study DFC-002, where 336 patients with moderate to severe pain (VAS ≥50 mm on 100mm scale) post-dental surgery were treated with escalating doses of DIC075V (3.75, 9.4, 18.75, 37.5 and 75 mg), IV placebo, or IV ketorolac tromethamine (n=51 in each group, 5-8 subjects weighing >95 kg included in each group).

The results of the primary efficacy endpoint (total pain relief over 6 hours- TOTPAR6) after adjustment for multiple comparisons revealed that dose escalation above 37.5 mg did not result in providing additional pain relief (Table 3).

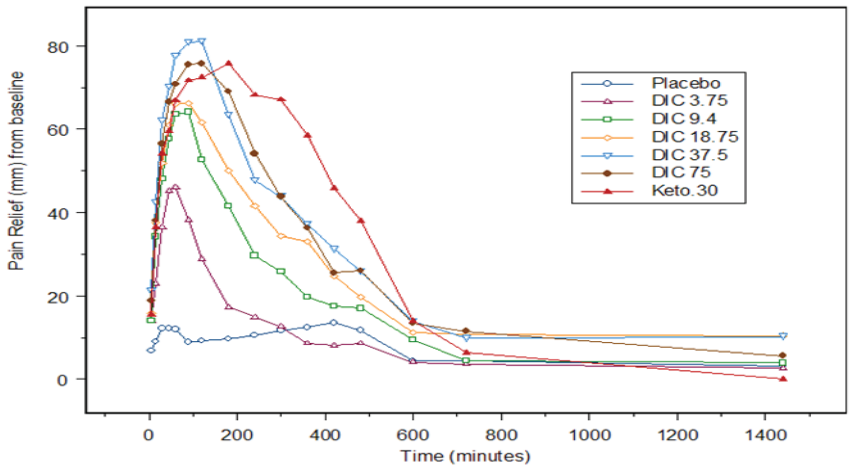
Table 3. Mean Total Pain Relief for first 6 hours (TOTPAR-6), study DFC-002

TOTPAR 0-6 hours	N	Mean[a]	Standard Deviation
Placebo	51	62.8	134.52
DIC075V 3.75 mg	51	134.1 A	136.19
DIC075V 9.4 mg	51	237.7 B	170.21
DIC075V 18.75 mg	51	284.4 B	201.11
DIC075V 37.5 mg	51	348.2 B	164.25
DIC075V 75 mg	51	347.3 B	167.45
Ketorolac 30 mg	47	393.5 B	173.24
			p-value <0.0001[b]
Step-down Dose Response Tests			**p-value[c]**
DIC075V 75 mg			<0.0001
DIC075V 37.5 mg			<0.0001
DIC075V 18.75 mg			<0.0001
DIC075V 9.4 mg			<0.0001
DIC075V 3.75 mg			0.0341

Table 11-5 from Applicant's submission DFC-002 study report, p 48.

For the onset of action, statistically significant separation from placebo occurred at 5 min following administration of 37.5 mg and 75 mg of DIC075V (refer to Dr. Nallani's review). Of note, the slopes showing efficacy of the 37.5 mg dose and 75 mg dose appeared to follow a similar pattern, further supporting that dose increase beyond 37.5 mg may not be beneficial (Figure 1).

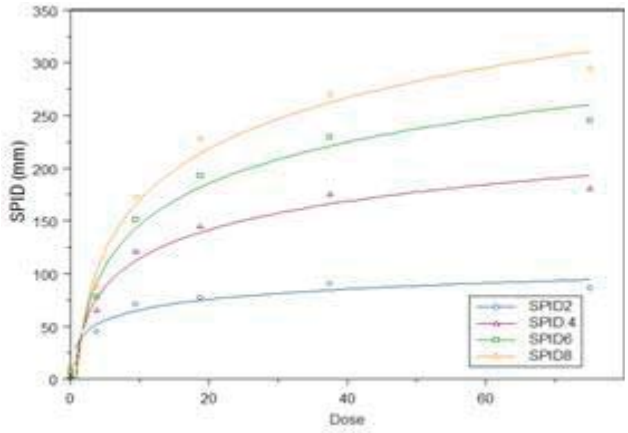
Figure 1: Mean Pain Relief over Time (Visual Analog Scale)



Source: Dr. Nallani's review, p.14

As further indicated in Dr. Nallani's review, pain relief measured by the Sum of Pain Intensity Differences in this study (Figure 2) demonstrated "a shallow dose-response" or no great incremental benefit with increasing dose beyond 37.5 mg following 6 hours after treatment.

Figure 2: Sum of Pain Intensity Difference (SPID) in terms of duration (2, 4, 6, and 8 hours) following treatment with DIC075V (Dose = 3.75, 9.4, 18.75, 37.5 and 75 mg) or Placebo (dose =0).



Source: Dr. Nallani's review, p.15.

Note: The individual points along the graphs indicate dosages (3.75, 9.4, 18.75, 37.5 and 75 mg)

I agree with Dr. Nallani that the incremental benefit measured by SPID and TOTPAR in study DFC-002 is not dose proportional to the dose increase in the 18.75-75 mg dose range and

conclude that dose increase beyond 37.5 mg does not provide a significant clinical benefit beyond that achieved with the 37.5 mg dose of DIC075V.

Dr Nallani's review of study DFC-007 investigating the effects on platelets did not reveal any new effects of DIC075V that would not be previously known for the class of NSAIDs.

From his review of studies DFC-008, DFC-009, and N-130310, Dr Nallani concluded that pharmacokinetics of DIC075V is not changed in elderly patients or patients with mild renal or mild hepatic impairment.

Refer to Section 7 of this review for additional discussion of safety of DIC075V in patients with renal and hepatic impairment.

Effect of body weight on DIC075V exposure

In his review, Dr. Nallani also discussed the effect of body weight on pharmacokinetics of DIC075V. In study DFC-008, the Applicant found a modest (~27-30%), but statistically significant increase in clearance of DIC075V upon increase in body weight and BMI (Table 4).

Table 4: Summary of Pharmacokinetic Parameters (mean±SD) after Single Intravenous Administration of 37.5 mg of Dyloject; Weight-based Cohort.

	Weight-Based Cohort				
Parameter	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)
Cmax (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)
Tmax (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)
λz (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)
t½ (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)
Vz (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)

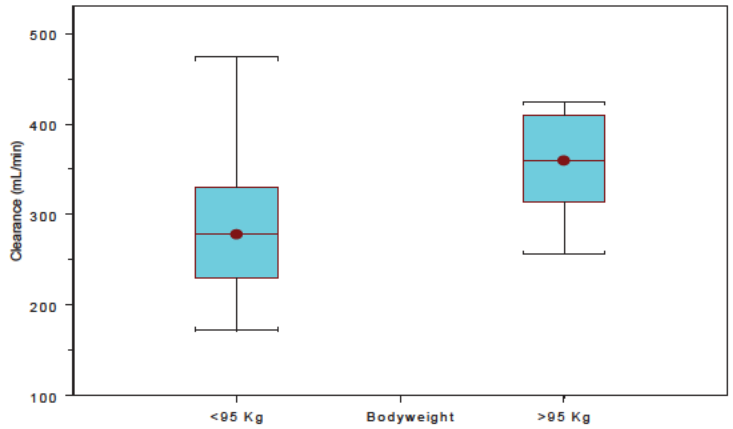
C_{max} = Maximum observed plasma concentration; T_{max} = Time at which C_{max} is observed; $AUC_{(0-t)}$ = AUC up to the last quantifiable concentration; $AUC_{(inf)}$ = AUC from time zero to infinite time; λ_z = Terminal elimination rate constant; $t_{1/2}$ = Apparent elimination half-life; Vz = Volume of distribution; CL = Clearance
Source: Dr. Nallani's review, p.23.

Of interest from Table 4 is that even when the clearance is highest with the lowest corresponding AUC in subjects with BMI > 40, the average C max of DIC075V administered at the dose 37.5 mg remains ~ 3 times higher than, and the systemic exposure parameters (AUC(0-t) and AUC(inf)) remain equivalent to, the respective PK paramaters observed after administration of Cataflam at the dose 50 mg (Refer to Table 1 above, Cataflam: Cmax: 1,246 ± 732, AUC(0-t): 1,473 ± 488, AUC(inf): 1,562 ± 519.) Thus, these data show that despite the modest increase in clearance seen in patients with higher weight, the systemic exposure to DIC075V after administration of 37.5 mg dose to the higher weight patients remains adequate and comparable to that of the referenced drug Cataflam.

It is also notable from Table 4 that there is a great individual variability in clearance of DIC075V in patients with body weight below and above 95 kg. Dr. Nallani graphed the box and whiskers plots on clearance in different body weight cohorts (Figure 3) and noted:

> "…higher clearance is noted in subjects with higher bodyweight/BMI. The sponsor chose to use a cutoff of 95 kg for proposing a dose adjustment in higher bodyweight patients. 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."

Figure 3: Relationship between CL and total body weight in the bodyweight cohort from study DFC-008 after IV administration of single 37.5 mg doses of DIC075V to healthy volunteers.



Source: Dr. Nallani's review, p.24

As could be seen from Figure 3, some patients weighing <95 kg had higher clearance rates compared to the patients weighing ≥ 95 kg, despite the overall higher mean clearance for the group of the individuals with higher weight. This variability in clearance of DIC075V somewhat undermines the conclusion of clear influence of body weight on the DIC075V clearance.

From the above data I am in general agreement with Dr. Nallani's conclusion that clearance of DIC075V modestly increases with increase in body weight. As stated earlier, the data also show that DIC075V, when administered at the dose 37.5 mg to individuals with a wide range of body weights, provides an adequate systemic exposure to diclofenac equivalent to the exposure of the referenced Cataflam, which is known to correspond to an effective pain relief. I agree with Dr. Nallani that the body weight effect should be included in considerations for the pediatric studies. Approval of the DIC075V was recommended by the clinical pharmacology reviewers with a note in the PI about the increase in clearance of DIC075V with increase in body weight.

QT study

The Interdisciplinary Review Team for QT studies concluded that no significant QT prolongation effect of DIC075V was detected in the tQT study DFC-011. (Refer to QT IRT review.)

I overall concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewers that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

The product microbiology review was done by Dr. John Metcalfe. Dr. Metcalfe found no issues with the application and recommended approval on the basis of product quality microbiology. Because the formulation of DIC075V 37.5mg/mL is a single use vial (b) (4) Dr Metcalfe recommended including precautionary language in the package insert. (Refer to Dr. Metcalfe's review.)

I concur with the conclusions reached by the clinical microbiology reviewer that there are no outstanding clinical microbiology or sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

The primary clinical review was performed by Rosemarie Neuner, M.D, and the statistical review was completed by Jonathan Norton, Ph.D. in concurrence with statistical team leader, Dr. Dionne Price. The discussion below includes aspects of these reviews where noted.
The indication sought by the applicant for DIC075V is short term treatment of moderate to severe pain. In support of efficacy, the results of two Phase 3 efficacy trials (DFC-004 and DFC-005) were submitted.

Both trials evaluated analgesic properties and safety profile of IV diclofenac in postoperative patients following abdominal, pelvic, or orthopedic surgical procedures. The efficacy results of both of these trials would be applicable to management of acute moderate to severe pain.

Both Dr. Neuner and Dr. Norton found that the studies DFC-004 and DFC-005 were overall adequate to draw conclusions regarding findings of efficacy.

Study DFC-004 was a multi-center, randomized, double-blind, placebo- and active comparator- controlled, parallel, fixed dose, fixed schedule, multiple-dose trial of IV diclofenac injection (DIC075V) given every 6 hours at doses 18.75 mg or 37.5 mg to hospitalized patients with postoperative pain following abdominal or pelvic surgery.

The study population consisted of 331 patients who received the study medication, with an age range of 18 to 65 years and a mean of 43 years with the average baseline moderate-to-severe pain of 68 mm as assessed on 100 mm pain intensity Visual Analogue Scale (VAS). Of the

331 patients, 77% were Caucasian, 12% were Hispanic, 9% were African American, and 81% were female. The treatment groups were approximately balanced with regard to demographic and clinical characteristics such as age, gender, race, height, weight, and baseline pain intensity.

Subjects were randomized into 4 groups: DIC075V 18.75 mg, DIC075V 37.5 mg, ketorolac tromethamine 30 mg, or placebo in approximately equal numbers. The initial dose of study medication was administered within 6 hours of completing surgery as a bolus IV injection over 15 seconds and every six hours thereafter for up to 5 days. While the rescue medication (morphine) was available to patients at any time after administration of the study drug, patients were encouraged to delay using it for at least 1 hour following the initiation of study treatment. Use of other narcotics or NSAIDS was prohibited during the study.

Close to 80% of the 331 patients completed the study. There were 66 (20%) dropouts balanced across the groups. The main reasons for dropouts were lack of efficacy (8%), subject request (4%), and adverse events (3%). Dr. Norton noted that seventeen randomized subjects did not receive study medication, the majority of these patients were from the placebo group. Dr. Norton performed a sensitivity analysis which excluded the possibility that the disposition of these subjects changed the outcome of the trial.

Major protocol deviations were reported in 20% of patients, most commonly reported as received less than 3 doses of study drug (12%), received prohibited medication (10%), and did not have at least 1 post-baseline pain assessment (0.2%). Dr. Norton noticed that a large number of minor protocol deviations were reported in this trial, although concluded that the deviations were fairly well balanced and mainly related to not awakening patients for study assessments as was mandated by the protocol (refer to Dr. Norton's review). These deviations were unlikely to change the results of the trial.

The pre-specified primary efficacy endpoint was the Sum of the Pain Intensity Differences (SPID) over the 48 hour interval relative to dosing. The following table from Dr. Norton's review adapted from the DFC-004 study report illustrates that the higher mean SPID-48 scores were achieved by patients in both the DIC075V 18.75 mg and 37.5 mg treatment groups when compared to patients in the placebo group. According to the Applicant's analysis, statistical significance was demonstrated for both 18.75 mg dose and 37.5 mg dose when compared to placebo.

Table 5 – Sum of the Pain Intensity Differences (SPID) Over 0-48 Hours for Study DFC-004 (ITT Population)

SPID (mm.hours)	Placebo (N = 76)	DIC075V 18.75 mg (N = 86)	DIC075V 37.5 mg (N = 87)	Ketorolac 30 mg (N=82)
Mean	936	1304	1574	1583
Standard Deviation	1077	1030	1060	983
P-value		p = 0.0316[a]	p = 0.0001[a]	p <0.0001[a]

[a]P-value from linear contrast comparing each active treatment versus placebo
Modified Sponsor's Table 14.2.1.1a; p 182."

Both Dr. Neuner and Dr. Norton in their reviews raised a concern about the lack of adjustment for multiple comparisons (two doses tested) for the primary endpoint in this trial. Dr. Norton conducted two additional analyses adjusting for multiple comparisons: Bonferonni correction and sequential testing of the higher to the lower dose of DIC075V versus placebo. The excerpt from Dr. Norton's review describing the results of these analyses is below:

> "A common approach to multiple doses is to test them sequentially from highest to lowest. Using this method, both doses are significantly better than placebo. Alternatively, one can use a Bonferroni adjustment, i.e., multiply each p-value by number of doses. With this method, the effect of the 18.75 dose is no longer significant at the .05 level using the planned analysis. Based on these results there is still strong evidence for the efficacy of the 37.5 mg dose, but the nominally significant p-value for the 18.75 dose is statistically questionable."

Dr. Neuner agreed with the analyses and conclusions made by Dr. Norton.

I agree with Drs. Neuner and Norton that in the trial DFC-004, the applicant was able to demonstrate effectiveness of 37.5 mg dose as compared to placebo. The 18.75 mg dose appeared less efficacious and raised statistical questions based on the analysis of the primary efficacy endpoint described above. The analyses of the secondary endpoints are discussed further in this review.

Study DFC-005 was a multi-center, randomized, double-blind, placebo- and active comparator- controlled, 3-arm, multiple-dose trial of DIC075V in hospitalized patients with postoperative pain following elective orthopedic surgery.

The study population consisted of 277 patients who received study medication, with an age range of 19 to 84 years and a mean of 55 years. Of the 277 patients, 92% were Caucasian, 6% were African American, and 64% were male. The mean moderate-to-severe baseline pain intensity was 69 mm as assessed on 100 mm VAS. Overall, the treatment groups were approximately balanced with regard to demographic characteristics and the baseline pain intensity. (Refer to Dr. Neuner's review for further details on characteristics of study population.)

Subjects were randomized into 3 groups: DIC075V multi-dose group (n=145), ketorolac trometamine group (n=60), or placebo group (n=72). All subjects were then stratified into the following 3 subgroups that differed in dosing regimens:

1) High risk subgroup included patients weighing <50 kg, or older 65 years of age, or with non-steroidal anti-inflammatory drug [NSAID] -related GI risk factors, or having moderate hepatic (Child-Pugh 6-9) or moderate renal (serum Cr ≥ 1.9- <3 mg/dL) impairment. Patients who weighed ≥95 kg and had any of the above listed risk factors were also included in this subgroup.
2) Non-high risk subgroup included patients weighing < 95 kg without known risk factors for NSAID toxicity and included patients with mild hepatic (Child Pugh <6) or mild renal (serum Cr up to 1.9 mg/dL) impairment.
3) Higher weight subgroup included patients weighing ≥95 kg without any known risk factors for NSAID toxicity.

Table 6 adapted from the applicant's DFC-005 study report shows the dosing regimen received by patients in these three subgroups:

Table 6. Dose Adjusted Treatment Regimens for Study DFC-005

Treatment	Patient Type	Dose	Administered as IV Bolus over 15 sec
DIC075V (n=145)	Non- High Risk (n=65)	37.5 mg	1 ml DIC075V
	High Risk* (n=45)	18.75 mg	0.5 mL DIC075V
	Higher Weight** (n=35)	50 mg	1.3 mL DIC075V
Ketorolac tromethamine (n=60)	Non- High Risk (n=27)	30 mg	1 mL Ketorolac
	High Risk* (n=18)	15 mg	0.5 mL Ketorolac
	Higher Weight** (n=15)	30 mg	1 mL Ketorolac and 0.3 mL normal saline
Placebo (n=72)	Non- High Risk(n=33)		1 mL Placebo (normal saline)
	High Risk* (n=22)		0.5 mL Placebo (normal saline)
	Higher Weight** (n=17)		1.3 mL Placebo (normal saline)

*High risk patients were defined by the protocol as individuals who met any of the following criteria: weight < 50 kg, age ≥ 65 years, elevated NSAID-related GI risk, moderate renal impairment (serum creatinine > 1.9 mg/dL) or moderate hepatic impairment (Child-Pugh score of 6-9).
**Higher Weight Threshold ≥ 95 kg (210 lbs)

All subjects were receiving study medication administered as a bolus IV injection every six hours for up to 5 days.

Similar to trial DFC-004, concomitant morphine use (rescue medication) was available to patients any time after the initial dose of study drug, patients were encouraged to delay using it for at least 1 hour following the initiation of study dosing. Refer to section 7 of this review for further discussion of study conduct as related to the use of concomitant anticoagulating agents.

Approximately 86% of the 277 patients completed the study. There were 38 dropouts, mainly from the placebo group (n=21), followed by the diclofenac group (n=13), and ketorolac group (n=4). The main reasons for dropouts were lack of efficacy (11%), AEs (1%) and subject withdrew consent (1%).

Major protocol deviations were reported in 19% of patients, mainly as received <3 doses of study drug (9%), taking prohibited medication (5%), violation of exclusion criteria for

prohibited medication (2%). The specific types of protocol deviations were balanced between the treatment groups and would not be expected to have differential impact on study outcomes.

Because patients enrolled in the study were undergoing a wide variety of orthopedic surgical procedures from bunionectomy to a total knee replacement, the duration of their inpatient stay varied. According to the applicant's definition, patients who stayed in the hospital for less than 24 hours were considered "short stay", and patients who stayed in the hospital for longer than 24 hours were considered "long stay". However, as Dr. Norton notes in his review, in the study settings, the long stay patients either withdrew before 24 hours or stayed for at least 48 hours.

The pre-specified primary efficacy endpoint was the Sum of the Pain Intensity Differences (SPID) over the 5 intervals: 0-24, 0-48, 0-72, 0-96, and 0-120 hours. To control for multiplicity the applicant conducted a sequential closed testing procedure starting with the 0-24h time point. As shown in Table 7, after controlling for multiplicity, the mean SPID scores for the DIC075V group were significantly higher as compared to the placebo group.

Table 7. Tabular Summary of Pain Intensity Differences (SPID) [mm·hours] over 0-24, 0-48, 0-72, 0-96, and 0-120 Hours for Subjects in Study DFC-005 (ITT Population)

SPID (mm·hrs) Time Interval	Placebo (N =72)	DIC075V* (N = 145)	Ketorolac (N = 60)
0-24 hrs:			
Mean (SD)	28.0 (428)	577 (571)	563 (586)
P-value[a]		<0.0001[b]	<0.0001[b]
95% CI		(374, 664)[c]	(281, 635)[d]
0-48 hrs:			
Mean (SD)	400 (950)	1528 (1139)	1372 (1152)
P-value[a]		<0.0001[b]	<0.0001[b]
95% CI		(776, 1357)[c]	(454, 1163)[d]
0-72 hrs:			
Mean (SD)	837 (1564)	2592 (17310	2312 (1744)
P-value[a]		<0.0001[b]	<0.0001[b]
95% CI		(1213, 2111)[c]	(674, 1770)[d]
0-96 hrs:			
Mean (SD)	1338 (2262)	3711 (2347)	3332 (2356)
P-value[a]		<0.0001[b]	<0.0001[b]
95% CI		(1623, 2865)[c]	(888, 2405)[d]
0-120 hrs:			
Mean (SD)	1841(2988)	4836 (2989)	4359 (3001)
P-value[a]		<0.0001[b]	<0.0001[b]
95% CI		(2028, 3632)[c]	(1099, 3057)[d]

SD=standard deviation; CI = confidence interval
[a]P=0.001 for overall treatment effect
[b]P-value from linear contrast comparing each active treatment versus placebo
[c]95% confidence interval for difference between DIC075 IV and placebo
[d]95% confidence interval for difference between Ketorolac and placebo
Source: DFC-005 study report; Modified Sponsor's Table 11-5
* includes all three doses of DIC075V

Dr. Norton notes in his review:

> "I find the Applicant's use of the words "primary efficacy endpoint" to be nonstandard terminology, as their "endpoint" encompasses five distinct variables with an explicit hierarchy reflected in the sequence of testing. The SPID24 is their ***primary efficacy endpoint*** as the term is conventionally used, because they test it first in the sequence. For regulatory purposes, I consider the primary endpoint to be the SPID48. This endpoint was recommended by the Division at the End of Phase 2 meeting and was used in the other [DFC-004] study. Furthermore, I consider the primary analysis set to be the 155 patients in the "long stay" stratum. I do not include the "short stay" patients because it was known ***before randomization*** that they would not be able to provide complete data for what I take to be the primary endpoint. This decision did not lead me to differ with the Applicant on whether the trial showed efficacy."

Dr. Norton's re-analysis of the primary outcome for time point 0-48 hours is further described below:

> "Table 19 shows the results for what I deem to be the primary efficacy analysis, with the outcome being the SPID 48. For reasons explained earlier, my analysis is restricted to the 155 "long stay" patients. BOCF imputation was used for patients who withdrew before 48 hours. The significant treatment effect for diclofenac was verified using an exact Wilcoxon test ($p < .0001$).

Table 8: Primary Analysis (SPID48) based on "long stay" data.

	Placebo (n=40)	**Diclo. (n=83)**	**Keto. (n=32)**
Mean (SD)	209 (589)	1280 (1211)	1032 (1247)
P-value	--	< .0001	.008
Difference in L.S. means (95% C.I.)	--	984 (608, 1359)	631 (167, 1095)

Source: Dr. Norton's review, Table 19, p 24.

To eliminate the effect of the natural pain reduction upon post-operative recovery from the results of the SPID analyses in study DFC-005, Dr. Norton performed an additional analysis yielding "normalized" SPID scores, which further supported the results of the primary efficacy analysis and demonstrated that over the first 48 hours patients in the DIC075V group averaged about 24 mm less pain than patients in the placebo group. (Refer to Dr. Norton's review for further details.)

Dr. Neuner agreed with Dr. Norton that in trial DFC-005 the Applicant was able to demonstrate efficacy of the 37.5 mg dose.

Analyses of the secondary efficacy endpoints in trials DFC-004 and DFC-005

Both studies DFC-004 and DFC-005 included pre-specified multiple (n=10) secondary efficacy endpoints evaluating pain outcomes. For detailed discussion and description of the analyses of these secondary endpoints refer to Dr. Neuner's review. Since no multiplicity corrections were planned or implemented by the Applicant in the analyses of the multiple secondary endpoints in either study, both Dr. Norton and Dr. Neuner indicated that declaring statistical significance of these secondary endpoints using unadjusted p-values would be

inappropriate, except where clinically relevant. Additionally, based on Dr. Norton's concerns about possible bias introduced in the primary analysis for study DFC-005 by the imputation of patients who stayed in the hospital short term, the same bias argument would apply to the Applicant's analysis of the secondary endpoints.

Overall descriptively, the results of the secondary efficacy endpoints were supportive to the primary efficacy analyses and consistently demonstrated superiority of IV diclofenac over placebo. Analyses of the secondary endpoints in study DFC-004 revealed that 18.75 mg dose was performing consistently worse than the 37.5 mg dose of DIC075V.

Opioid-sparing effect

Dr. Neuner recommended that opioid-sparing effect of DIC075 be mentioned in the label to inform the healthcare providers:

> " Since no correction for multiplicity was applied during the analyses of the secondary endpoints for both pivotal trials, these results should not be included other than to communicate information that may be clinically useful to health care providers such as opiate sparing effects."

Dr. Norton noted in his review that, if the information on the opioid-sparing effect is included in the label, only the data for the long stay cohort (DFC-005) should be shown in the label given the statistical concerns described above. The corrected analysis of the rescue medication is shown below (Table 8a).

Table 8a: Rescue Medication Use, Long Stay

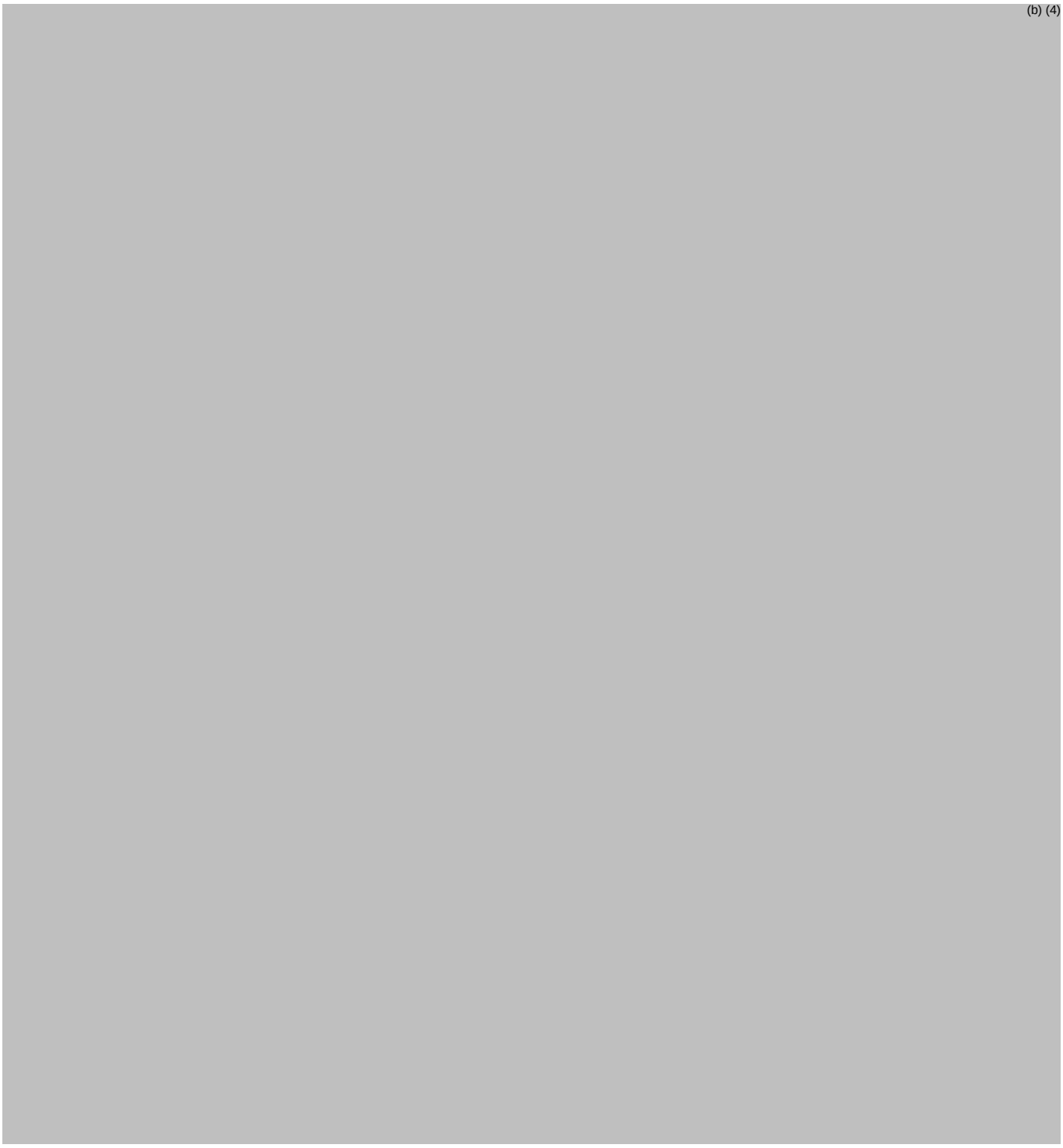
Time Interval	Treatment	Mean Rescue in mg (SD)	p-value vs. Placebo
0-24	Placebo	15.9 (11.1)	--
	Diclofenac	7.2 (6.6)	< .0001
	Ketorolac	10.3 (9.0)	. 01
0-48	Placebo	21.0 (15.9)	--
	Diclofenac	9.6 (9.6)	< .0001
	Ketorolac	16.2 (16.3)	.19
0-72	Placebo	23.5 (18.9)	--
	Diclofenac	10.3 (10.3)	<.0001
	Ketorolac	19.7 (23.4)	.46

Source: Table 21, Dr. Norton's review

I concur with Dr. Neuner's and Dr. Norton's assessments and analysis. Although the corrected analysis does demonstrate the statistically significant opioid dose reduction, the observed ~ 8-13 mg reduction can be translated into meaningful clinical benefit only when reduction in clinically observed opioid toxicity is also demonstrated. In this NDA, such reduction in opioid-related adverse events was not investigated or demonstrated by the Applicant. As such, the submitted data do not contain all relevant information to adequately inform healthcare providers about the opioid-sparing effects of DIC075V. (b) (4)

(b) (4)

(b) (4)



(b) (4)

Efficacy conclusions

Based on the results of the two adequate and well controlled trials DFC-004 and DFC-005, the Applicant was able to demonstrate that IV diclofenac DIC075V at the dose 37.5 mg IV every 6 hours was effective when compared to placebo in treatment of moderate to severe pain measured by SPID-48 as an adjunct to opioid therapy. Although the statistically significant reduction in opioid dose was observed, no reduction in opioid toxicity was demonstrated in the controlled trials.

Although there does appear to be some clinical benefit to the use of 18.75 mg of IV diclofenac in patients with acute pain, given the statistical concerns and the apparent small treatment effect, I conclude that trial DFC-004 did not demonstrate efficacy of 18.75 mg dose for the treatment of acute moderate to severe pain in this setting.

8. Safety

The safety assessment was conducted by Dr. Neuner. The safety database submitted by the Applicant included safety results from 16 trials and other supportive safety data for the drug identified during a search of the worldwide literature, an analysis of postmarketing adverse event reports associated with the use of systemic formulations of diclofenac collected by the FDA and the World Health Organization (WHO), as well as postmarketing reports and periodic safety updates (PSURs) for DIC075V from the Medicines and Healthcare Products Regulatory Agency (MHRA) in the United Kingdom where this drug is currently registered for marketing.

For the purposes of assessing safety of DIC075V in the multi-dose trials, Dr. Neuner evaluated the pooled data from the two placebo controlled trials DFC-004, DFC-005 and the open-label safety study DFC-010; overall, the pooled database included 1289 patients exposed to DIC075V.

The open-label study DFC-010 enrolled 971 patients with acute moderate to severe pain treated with 37.5 mg or 50 mg DIC075V every 6 hours up to five days following a variety of surgical procedures (mainly abdominal and orthopedic). Demographic characteristics of patients enrolled in DFC-010 were similar to the demographic characteristics of patients

enrolled in the two controlled trials. (Refer to Dr. Neuner review of further details.) There were 31 patients with mild hepatic impairment and 57 patients with mild renal impairment treated in this study.

Safety monitoring consisted of AE reporting, vital signs, and routine laboratory tests, and is considered adequate in studying short term use of IV diclofenac in hospitalized populations.

There were total of two reports of deaths in the safety database. Both deaths occurred in the open-label study 010 in older patients with multiple comorbid conditions; both were likely due to complications of underlying disease and were not considered study drug-related.

As per Dr. Neuner's review, there were 80 reports of non-fatal SAEs, all were consistent with events occurring in post-operative populations after major surgeries. Notably, no serious adverse events unexpected for the NSAID class of drugs or for the concomitant opioid treatment were observed. The vast majority of the events were complications of surgeries and not study drug related based on the nature of the events, the time of occurrence with respect to the study drug administration, and Dr. Neuner's review of individual case reports. (Refer to Dr. Neuner's review for further details.)

The most commonly reported non-serious AEs occurring in (≥ 2%) subjects are shown in Table 11 below.

Table 11. The most common AEs in DFC-004, DFC-005, and DFC-010 occurring in ≥2% (4 or more subjects).

MEDDRA preferred term		DIC075V		
	Placebo* (N=126)	DFC-004/005* (N=187)	DFC-010 (N=969)	Total (N=1156)
Nausea	50(40%)	45(24%)	360 (37%)	405(35%)
Constipation	14(11%)	25(13%)	180(19%)	205(18%)
Blood CPK increased	9(7%)	20(11%)	63(6.5%)	83(7%)
Headache	20(16%)	19(10%)	55(6%)	74(6%)
Infusion site pain	10(8%)	19(10%)	50(5%)	69(6%)
Dizziness	2(1.6%)	15(8%)	49(5%)	64(5.5%)
Flatulence	20(16%)	15(8%)	38(4%)	53(5%)
Vomiting	23(18%)	12(6%)	83(9%)	95(8%)
Insomnia	12(9.5%)	11(6%)	130(13%)	141(12%)
Pruritis	10(8%)	9(5%)	125(13%)	134(12%)
Hypotension	6(5%)	9(5%)	59(6%)	68(6%)
Pyrexia	13(10%)	8(4%)	58(6%)	66(6%)
Infusion site extravasation	1(<1%)	6(3%)	14(1%)	20(2%)
Anemia	7(6%)	6(3%)	14 (1%)	20 (1%)
Postoperative wound infections	4(3%)	5(3%)	6(<1%)	11(1%)
Back pain	3(2%)	5(3%)	7(<1%)	12(1%)
Edema peripheral	1(<1%)	4(2%)	37(4%)	41(3.5%)

Modified from Sponsor's Table 4-20: ISS; p 83
*patients treated with 18.75mg dose are excluded

As noted from Table 11, the most commonly observed AEs were nausea, constipation, headache, infusion site pain, and dizziness. Higher rates among patients treated with placebo are not unexpected because of the concomitant morphine treatment. Accordingly, these

adverse events were included in the product's label along with a notation of the use of morphine in all treatment groups. Increased blood CPK is a common and expected observation in post-operative population.

Dr. Neuner also evaluated AEs of special interest (related to NSAID class toxicity and parenteral route of administration of DIC075V) which included cardiovascular, renal, hepatoiblliary, gastrointestinal, bleeding related events, injection site reactions and local thrombotic events, and events related to delayed wound healing. As extensively discussed in Dr. Neuner's review, per her analysis of these data and evaluation of the case report forms, the vast majority of these events were explained by pre-existing comorbidities or patients' post-operative status. Upon review of these data no new safety signal unexpected for an NSAID product was identified by Dr. Neuner.

The most commonly occurring events were GI-related (56% in placebo group, 38% in the two controlled trials with DIC075V and 53% in the open label study DFC-010). Injection site reactions were expected with the parenteral route of administration and occurred in comparable rates in placebo and DIC075V treated patients (15.9% and 17.6% respectively) in the controlled trials and did not increase in the open label trial DFC-010 (12.6%).

Bleeding related events, thromboembolic events and anticoagulation therapy in the placebo-controlled trials DFC-004, DFC-005 and the open-label study DFC-010

As discussed in Dr. Neuner's review, the analysis of the data from the controlled trials (DFC-004 and DFC-005) revealed that the incidences of bleeding related events were small and comparable between the placebo-treated patients 3/126 (2.4%) and DIC075V- treated patients 4/187(2%).

Compared to the controlled trials, more subjects (57/969 (5.9%)) developed bleeding events in the open-label study DFC-010 where the combined rate of incision site hemorrhages and postprocedural hemorrhages was 11/969 (1.1%). Seven bleeding related serious AEs were reported in DFC-010, including upper GI bleeding, rectal hemorrhage (resulted in study treatment discontinuation), post-procedural hemorrhage, incision site hematoma, anastomotic hemorrhage, hematoma, and hematochezia. As per Dr. Neuner's review of the case report forms, three of these events (incision site hematoma, post-procedural hemorrhage, and upper GI bleeding) occurred in patients who were also receiving anticoagulation therapy.

The Applicant also provided an analysis of incidences of bleeding events occurring in patients who were receiving an anticoagulating agent concurrently with the study medication in the post-operative period. Notably, much fewer patients were receiving concurrent anticoagulation therapy in the controlled trials compared to the open-label study DFC-010 (Table 11a). According to the Applicant, no patients in the placebo group (0/17) developed any bleeding events, while 2/24 (8%) patients of those receiving DIC075V concurrently with an anticoagulating agent in the controlled trials developed epistaxis and rectal bleeding. Of those treated in the open-label DFC-010, 33/601(5.5%) patients developed bleeding related events (Table 11a).

Table 11a. Overall Incidence of Bleeding-Related Events in Subjects Receiving Concomitant Anticoagulant Therapy in the Multiple Dose Pain Studies.

MedDRA System Organ Class/ Preferred Term	Placebo[b] (N=17) n (%)	DIC075V 37.5 mg and 50 mg[a] DFC-004/ DFC-005 (N=24) n (%)	DFC-010 (N=601) n (%)	Total (N=625) n (%)
Subjects with Any Bleeding-Related Events	0	2 (8.3)	33 (5.5)	35 (5.6)
Prothrombin time prolonged	0	0	10 (1.7)	10 (1.6)
Incision site haemorrhage	0	0	6 (1.0)	6 (1.0)
Activated partial thromboplastin time prolonged	0	0	6 (1.0)	6 (1.0)
Epistaxis	0	1 (4.2)	2 (0.3)	3 (0.5)
Wound haemorrhage	0	0	3 (0.5)	3 (0.5)
International normalised ratio increased	0	0	2 (0.3)	2 (0.3)
Haematuria	0	0	2 (0.3)	2 (0.3)
Rectal haemorrhage	0	1 (4.2)	0	1 (0.2)
Haematemesis	0	0	1 (0.2)	1 (0.2)
Haematochezia	0	0	1 (0.2)	1 (0.2)
Upper gastrointestinal haemorrhage	0	0	1 (0.2)	1 (0.2)
Infusion site haematoma	0	0	1 (0.2)	1 (0.2)
Infusion site haemorrhage	0	0	1 (0.2)	1 (0.2)
Injection site haemorrhage	0	0	1 (0.2)	1 (0.2)
Post procedural haemorrhage	0	0	1 (0.2)	1 (0.2)
Blood urine present	0	0	1 (0.2)	1 (0.2)
Fibrin D dimer increased	0	0	1 (0.2)	1 (0.2)
Vaginal haemorrhage	0	0	1 (0.2)	1 (0.2)
Ecchymosis	0	0	1 (0.2)	1 (0.2)

Source: Appendix 13.5, Table 3.12.1.2.2.

a The DIC075V 37.5 mg and 50 mg dose groups are included in this analysis (b) (4) (b) (4)

b Includes subjects in the placebo group that match subjects in the DIC075V group who received the proposed dose.

Adapted Sponsor's table ISS 4-50; p. 162.

Dr. Neuner notes in her review that the observed rates of bleeding events in the open label study appeared comparable with the literature reported incidence rates of bleeding events described with anticoagulating agents (refer to Dr. Neuner's review for further details). Upon examining the bleeding-related events for dose dependency, Dr. Neuner notes that the rate of GI bleedings was higher in the 50 mg group (1.1%, including the upper GI bleeding) compared to 37.5 mg group (0.5%).

While occurrence of bleeding events in this safety database is notable, it is not unexpected with a parenteral NSAID use given the known effect of NSAIDs to inhibit the platelet cyclooxygenase. It is also not unexpected for the risk of bleeding to increase when DIC075V is used concurrently with anticoagulation therapy as observed from the uncontrolled DFC-010 open-label data. While Dr. Neuner's review and analysis did not reveal any unexpected signals and reported on the small number of events, these observations have to be interpreted with understanding of the conduct of the controlled trials as discussed below.

The majority of the patient population of the two controlled trials (n=608 in all dosing groups) were patients after major abdominal, pelvic, spinal, and orthopedic surgeries (refer to Tables 8

and 19 in Dr. Neuner's review). Such patients frequently require post-operative anticoagulation treatment for prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE). Notably, the UK label of Dyloject ™ contraindicates concomitant use of Dyloject and anticoagulating agents (including low molecular weight heparin) due to the known increased risk of bleeding. The NSAID class labeling in the US warns about the drug-drug interactions between the NSAIDs and anticoagulating agents because of the risk of bleeding complications. While the exclusion criteria for the controlled trials DFC-004 and DFC-005 did not specify exclusion of patients treated with anticoagulating agents and the Investigator's Brochures cautioned about the known increased risk of bleeding with concurrent anticoagulation, the resulting number of patients who ended up receiving concurrent anticoagulation in the controlled trials was small (Table 11a). In the uncontrolled study DFC-010, 601 of 969 patients received anticoagulating agents concurrently with the study medication.

Dr. Neuner has also examined cases of SAEs of deep vein thromboses and pulmonary embolism (Refer to Table 65, Dr. Neuner's review). There were 2 cases of pulmonary embolism and 3 cases of deep vein thrombosis in the controlled trials and 6 cases of pulmonary embolism and 3 cases of deep vein thrombosis in the open label study. According to Dr. Neuner's review of the respective case report forms, only 4 of these 14 case reports had clear documentation of anticoagulating treatment in postoperative period. Two IRs were sent to the Applicant with the request to provide an explanation on the approach to thromboembolism prophylaxis in the clinical development program and specifically in patients who later developed DVT and PE events. The Applicant's response to first IR was received on September 17 and to the second IR on September 29, 2010 (a few days before the PDUFA date). The preliminary overview of the Applicant's response is summarized below.

The Applicant indicated that 10 out of 14 patients who developed DVTs or PEs received anticoagulating agents at various doses and durations for DVT/PE prophylaxis. Nine of these ten patients have had knee replacement surgeries and one patient has had an abdominal surgery. The remaining four patients who did not receive DVT and PE prophylaxis underwent the following procedures: cholecystectomy, open reduction of the fifth metatarsal, ankle surgery, and rotator cuff repair. Although the majority of the patients experiencing the above decribed thrombolembolic events were either receiving prophylaxis with anticoagulants or had additional risk factors and could have alternative explanations for the observed outcomes, it remains uncertain from the preliminary review of the provided documentation whether the choice of DVT and PE prophylaxis could have influenced the observed outcomes. In response to the question about the methods utilized for DVT/PE prophylaxis in the controlled trials and uncontrolled open-label study, the Applicant provided the following explanation:

> In designing the study protocols, we relied upon current, evidence-based clinical practice guidelines for thromboprophylaxis in hospital patients. Recent knowledge in this area available at the time of the drafting of the three clinical Dyloject protocols was incorporated into recommendations from the American College of Chest Physicians in 2004 (Geerts et al, Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126: 338S-400S). The latest update of that evidence is summarized in the eighth edition from the same source (Geerts WH, et al. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008; 133: 381S-453S.

> Geerts et al summarize risk factors for venous thromboembolism and point out that "there is little formal understanding of how the various risk factors interact in a quantitative manner to determine the position of each patient along a continuous spectrum of thromboembolic risk". Therefore in a footnote to their summary table that triages patients into low, moderate and high categories of risk, they state "the descriptive terms are purposely left undefined to allow individual clinician interpretation." For patients who are mobile after minor surgery, they consider them low risk and recommend "no specific thromboprophylaxis" and "early and 'aggressive' ambulation". As described in our prior response, such patients formed a larger proportion of the controlled trials DFC-004 and DFC-005 than in the single-arm safety study DFC-010. Patients following hip or knee arthroplasty are considered to be high risk by Geerts et al and are recommended to receive low molecular weight heparin, fondaparinux, an oral vitamin K antagonist or nonmedical therapy and/or mechanical prophylaxis (graduated compression stockings, venous foot pump, or intermittent pneumatic compression). For patients at "high bleeding risk" (again undefined) a separate table footnote indicates that one should "consider switch from [mechanical prophylaxis] to anticoagulant thromboprophylaxis when high bleeding risk decreases". From these considerations one may conclude that anticoagulant thromboprophylaxis, while generally recommended as a guideline, is not a uniform standard of care and the individual clinical context carries great importance. For this reason we did not require thromboprophylaxis in our trials and instead relied upon each investigator's judgment."

This aspect of trial conduct may reflect on the applicability of the trial results to clinical practice. If the trial investigators were choosing to avoid use of the study medication (IV NSAID) concurrently with anticoagulating agents due to the risk of bleeding in the post-operative patient population enrolled in this development program, then IV diclofenac may not find its use in patients for whom anticoagulation may be clinically indicated. It is possible that in practice clinicians will likely choose to anticoagulate rather than to add an IV NSAID to the analgesic regimen in post-operative patients who meet the recommended criteria for anticoagulation in the post-operative period.

While the current US approved NSAID class labeling warns about the drug-drug interactions with anticoagulating agents, use of an NSAID in the postoperative population requiring anticoagulation must be carefully considered and DIC075V treatment initiated only when the risk-benefit appears favorable in the context of other concomitantly administered treatments. Labeling of DIC075V will be amended to further warn about the drug-drug interactions in postoperative patients.

An in depth review of the amendment to this application received on September 29, 2010 will be conducted during the next review cycle and remains an outstanding issue at the time of this action.

Effect DIC075V on wound healing

Because of the possibility that NSAID-induced inhibition of cyclooxygenase may interfere with the mechanisms of wound healing, the Applicant examined the events reported in association with wound healing in this safety database. Overall, ~ 95% of wounds and surgical sites were healing as expected or better than expected, although a higher proportion of subjects exposed to DIC075V experienced at least one wound healing event compared to placebo. Procedural site reactions and postoperative wound infections were most commonly reported in the enrolled post-operative population. Table 12 below summarizes occurrences of events

related to wound healing in the controlled trials and shows that more events occurred in the DIC075V treated patients (7.5%) and ketorolac treated patients (6%) compared to placebo treated patients (4%).

Table 12. Adverse events related to wound healing from controlled trials DFC-004 and DFC-005 (all doses).

Patients with at least 1 event related to wound healing	Placebo	DIC075V	Ketorolac
DFC-004	4/76 (5.3%)	4/173 (2.3%)	3/82 (3.7%)
DFC-005	2/72 (2.8%)	20/145 (13.8%)	6/60 (10%)
DFC-004 and 005 combined	6/148 (4%)	24/318 (7.5%)	9/142 (6%)

Modified from Sponsor's Tables 12-6 (DFC-005 Study report) and Table 12-6 (DFC-004 Study report).

When the data on the wound healing events were pooled from the three studies (DFC-004, DFC-005, and DFC-010), wound dehiscence occurred in 9/1289 (0.7%) patients treated with DIC075V compared to 0/148 patients treated with placebo and 2/142 (1.4%) patients treated with ketorolac; incision site complications were reported in 15/1289 (1.2%) patients treated with DIC075V compared to 0/148 patients treated with placebo and 2/142 (1.4%) patients treated with ketorolac.

Upon examining dose-dependency for SAEs related to wound healing from the pooled data from both controlled and uncontrolled trials, Dr. Neuner noticed higher proportions of infections around the postoperative wounds and incision sites occurring with dose escalation (DICO75V: 18.75 mg: 0.8%, 37.5 mg: 1.8%; and 50 mg: 3.0%) as compared to 0.7% for the placebo group and 2.4% for the ketorolac 30 mg group).

Thus, the observed occurrence of adverse events related to wound healing was higher in the NSAID-treated patients, although the data interpretation is limited by the small number of patients in the placebo group and the confounding effects of other factors in post-operative hospitalized populations. Nevertheless, knowledge of these data will be important to practitioners selecting to administer IV DIC075V to post-operative patients.

Amended labeling noting these observations was recommended by Dr. Neuner and I concur.

Dose-related NSAID toxicity of DIC075V

Dr. Neuner describes in her review that the dose dependent NSAID-related toxicity was observed for renal, hepatic, hematological (hemoglobin and platelets), gastrointestinal, and blood pressure effects upon exposure to DIC075V. Additionally, as described earlier in this review, more wound infections were observed with higher doses of DIC075V.

Table 13 below adapted from Dr. Neuner's review exemplifies dose-dependent increases in serum creatinine and BUN observed in the data pooled across the placebo-controlled and open label studies. Of other laboratory parameters, dose dependency was also observed with

increases in total bilirubin (2% in placebo; 2.25%, 1.7% and 4% in the 18.75 mg, 37.5 mg, and 50 mg dose groups, respectively) and decreases in hemoglobin and platelets (data not shown).

Table 13. Tabular Summary of Treatment-Emergent Elevations in Renal Function for Subjects Participating in the Multidose, Phase 3 Pain Trials.

		DIC075V				Ketorolac	
Elevation Test	Placebo (N=148) n (%)	18.75 mg (N=133) n (%)	37.5 mg (N=786) n (%)	50 mg (N=370) n (%)	Total (N=1289) n (%)	15 mg (N=18) n (%)	30 mg (N=124) n (%)
Creatinine (μmol/L)							
> 1 to < 1.5 times ULN	0	1 (0.8)	10 (1.3)	11 (3.0)	22 (1.7)	2 (11.1)	0
1.5 to < 3 times ULN	1 (0.7)	1 (0.8)	12 (1.5)	5 (1.4)	18 (1.4)	0	0
≥ 3 times ULN	0	0	0	1 (0.3)	1 (0.1)	0	0
BUN (mmol/L)							
> 1 to < 1.5 times ULN	2 (1.4)	1 (0.8)	16 (2.0)	21 (5.7)	38 (2.9)	1 (5.6)	2 (1.6)
1.5 to < 3 times ULN	0	1 (0.8)	6 (0.8)	6 (1.6)	13 (1.0)	0	0
≥ 3 times ULN	0	0	0	0	0	0	0

Source: Appendix 13.5, Table 3.18.1.1
Modified Sponsor's table 3.18.1.1; p. 2904
Modified Table 79 from Dr. Neuner's review

Table 14 below exemplifies increases in treatment-emergent AEs observed in patients treated with 50 mg dose in study DFC-005.

Table 14. Treatment Emergent AEs for non-high risk and high weight subjects in Study DFC-005.

MedDRA SOC and selected TEAEs	DIC075V	
	37.5 mg (N=65)	50 mg (N=35)
Number (%) of Subjects with Any AEs:	49 (75.4%)	24 (68.9%)
Gastrointestinal Disorders:	17 (26.%)	14 (40%)
Constipation	5 (7.7%)	4 (11.4%)
Diarrhea	3 (4.6%)	0
Nausea	11 (16.9%)	12 (34.3%)
Vomiting	4 (6.2%)	3 (8.6%)
Rectal hemorrhage	0	1 (2.9%)
Injury, Poisoning and Procedural Complications:	7 (10.8%)	7 (20.0%)
Anemia Postoperative	0	2 (5.7%)
Investigations:	9 (13.8%)	7 (20.0%)
Blood Creatinine Increased	7 (10.8%)	7 (20.0%)
Nervous System Disorders:	17 (26.2%)	13 (37.1%)
Dizziness	7 (10.8%)	4 (11.4%)
Headache	7 (10.8%)	5 (14.3%)
Vascular Disorders:	4 (6.2%)	5 (14.3%)
Hypotension	2 (3.1%)	3 (8.6%)

Modified Sponsor's Table A14.3.5.1; p.
Source: Table 81 Dr. Neuner's review

I conclude that the dose-dependent toxicity was observed with dose escalation of DIC075V; this finding is consistent with previous knowledge of NSAID class effects.

Safety in patients with renal impairment

Renal toxicity associated with NSAIDs is well known and includes effects on renal tubules, papillary necrosis, and effects associated with direct action on cyclooxygenase. Inhibition of cyclooxygenase (COX) leading to decreased synthesis of prostanglandins resulting in interference with normal mechanisms of renal compensation is one commonly observed and reversible renal insult associated with NSAIDs. Consequently, use of NSAIDs in the conditions of pre-existing renal disease or prerenal azotemia and volume depletion can lead to an overt renal decompensation. High incidence of acute renal failure has been reported in hospitalized and critically ill patients with the rates ranging from 5% to 60% with the highest incidence reported in elderly, individuals with pre-existing renal disease, cardiovascular comorbid conditions, and recent hospitalization for diseases other than renal [3, 4, 5, 6]. Some studies have reported that the risk of hospitalizations for ARF among current and recent users of oral formulations of NSAIDs was 2-4 fold higher compared to NSAID non-users; the risk is dose-dependent and is higher during the first month of therapy [1,7]. One meta-analysis on the topic of occurrence of acute renal failure in hospitalized post-surgical patients without pre-existing renal disease did not reveal an increase in the risk of acute renal failure with use of oral NSAIDs perioperatively (OR-0.95 ; 95% CI 0.37-2.46) [2].

A total of 68 patients with renal impairment were treated in this development program. As noted previously, because of the specific design of studies DFC-004, DFC-005, and DFC-010, patients with mild renal insufficiency (Cr < 1.9 mg/dl) were treated with either 37.5 mg dose or 50 mg dose, whereas patients with moderate renal insufficiency (Cr >1.9 - <3 mg/dl) were treated with 18.75 mg dose. Based on the observed data, only 8 patients with moderate renal insufficiency were treated in the clinical development program, yet still one event of acute renal decompensation was observed in this group despite the treatment with the reduced dose of DIC075V. One event of acute renal decompensation occurred in the placebo group making the rates of acute renal failure similar between the placebo treated patients (0.7%) and DIC075V treated patients (0.66%) among those without preexisting renal disease (Table 15). Not unexpectedly, in patients exposed to DIC075V, the observed incidence of acute renal decompensation in patients with pre-existing renal impairment was higher than in patients without pre-existing renal impairment.

According to Dr. Neuner's examination of the case report forms, none of the patients with the acute renal events observed in this clinical development program required renal replacement therapy; the vast majority of patients were volume depleted when developed an event and all events resolved over time with fluid and blood volume repletion and diuretic therapy.

Notably, the rates of acute renal events in this clinical development program were considerably lower than the rates in the hospitalized populations reported in the literature. From the clinical descriptions of the renal events, it appears unlikely that the presence of cyclodextran in DIC075V formulation contributed to the renal outcomes in this program, although the available data do not permit making this assessment with certainty.

1 Am J Epidemiol. 2006 Nov 1;164(9):881-9. Epub 2006 Sep 27. Association of selective and conventional nonsteroidal antiinflammatory drugs with acute renal failure: A population-based, nested case-control analysis. Schneider V, Lévesque LE, Zhang B, Hutchinson T, Brophy JM.

2 Can J Anaesth. 2006 Jan;53(1):46-59. NSAID-analgesia, pain control and morbidity in cardiothoracic surgery. Bainbridge D, Cheng DC, Martin JE, Novick R; Evidence-Based Perioperative Clinical Outcomes Research (EPiCOR) Group.

Table 15. Acute renal failure in patients treated in trials DFC-004, DFC-005, and DFC-010.

MedDRA System Organ Class/ Preferred Term	Placebo		DIC075V			
	Total Impaired (N=8)	Total Not Impaired (N= 139)	18.75 mg Impaired (N=8)	Combined 37. 5 mg and 50 mg Impaired (N=60)	Total Impaired (N=68)	Total Not Impaired (N=1216)
Acute Renal Failure	0	1 (0.7%)	1 (12.5%)	2 (3.3%)	3 (4.4%)	8 (0.66%)

Source: modified Table 86 from Dr. Neuner's review

Given that IV diclofenac will likely be used in hospitalized patients who are at increased risk for development of acute renal failure, it would be important to advise prescribers on appropriate selection of patients for whom risk-benefit profile of DIV075V would be favorable. While the renal warning already exists in the NSAID class labeling, strengthening of the warning for DIC075V is warranted to contraindicate use of this drug in patients with pre-existing renal impairment and to recommend on the use of the drug only after assurance of adequate volume repletion.

Safety in patients with hepatic impairment

A total of 34 patients with hepatic impairment were treated in this development program. More nausea and vomiting and elevations in liver transaminases reported as AEs were observed in patients with pre-existing hepatic impairment compared to those without impairment upon exposure to DIC075V, although the small number of patients with hepatic impairment as well as confounding effects of opioid treatment limited interpretation of the data (refer to Dr. Neuner's review for further details). Overall, the observations in this development program are consistent with the previous knowledge of the effects associated with diclofenac products. However, the potential for use of DIC075V in hospitalized patients who may be more vulnerable to liver injury due to other comorbid conditions and the fact that the Cmax with 37.5 mg dosing of DIC075V is 5 times higher than the C max of Cataflam 50 mg support further strengthening of the hepatic warning for IV diclofenac.

Accordingly, the labeling will be amended to recommend against use of DIC075V in patients with moderate and severe liver disease.

3 Crit Care Med. 2010 Jun;38(6 Suppl):S169-74. Drug-induced acute kidney injury in the critically ill adult: recognition and prevention strategies. Bentley ML, Corwin HL, Dasta J.
4 Nephrol Dial Transplant. 2000 Feb;15(2):212-7. Treatment-related acute renal failure in the elderly: a hospital-based prospective study. Kohli HS, Bhaskaran MC, Muthukumar T, Thennarasu K, Sud K, Jha V, Gupta KL, Sakhuja V. Nephrol Dial
5 Am J Kidney Dis. 2002 May;39(5):930-6. Hospital-acquired renal insufficiency. Nash K, Hafeez A, Hou S.
6 Ren Fail. 2008;30(9):848-55. Predicting hospital-acquired acute kidney injury--a case-controlled study. Drawz PE, Miller RT, Sehgal AR
7 Am J Med. 2001 Feb 19;110 Suppl 3A:20S-7S. Epidemiologic assessment of the safety of conventional nonsteroidal anti-inflammatory drugs. Hernández-Díaz S, García-Rodríguez LA.

Safety conclusions:

Overall, I am in agreement with Dr. Neuner's conclusions that based on the review of safety data there are no new safety signals or major issues identified and that the dose-dependent toxicity was observed with administration of DIC075V.

Although no unexpected safety signals were found, some of the concerning but known effects of NSAIDs appeared more prominent in the population of post-surgical patients (e.g. wound healing related events, acute renal decompensation) and in patients with renal and hepatic impairment. Further, the Applicant selected to enroll post-operative patients following major abdominal and orthopedic surgeries, yet the knowledge of the increased risk of bleeding may have influenced the diminished use of anticoagulating agents, that are typically used in these patients for DVT and PE prophylaxis, likely reflecting the potential for limited use of DIC075V in this patient population.

9. Advisory Committee Meeting

No advisory committee meeting was held for this application. The drug substance is not an NME and the indication is not novel.

10. Pediatrics

To fulfill the PREA requirements for this NDA, the Applicant submitted a Pediatric Plan proposing to conduct a clinical efficacy, safety, and pharmacokinetics study of DIC075V in pediatric patients. The Pediatric Plan contained a request to defer pediatric studies in children (b) (4) because adult studies have been completed and are ready for approval. The Pediatric Plan also contained a request to waive pediatric studies in children 0 (b) (4) years of age for which the Applicant did not provide adequate rationale. In addition, the Applicant's proposed dose for pediatric use was (b) (4)

Given the high likelihood for dosing errors with the proposed use within the pediatric program, the Division requested that the Applicant develop a new age-appropriate formulation for this product. Also, the Division agreed to waive the pediatric studies for children under 1 year of age because the pharmacokinetic pathways for the drug metabolism are not fully developed at this age and the COX2 enzymes are not matured by the age of 1 year. Given the lack of understanding of efficacy, safety, and pharmacokinetics of diclofenac in the age group of 1-2 years, the pediatric studies for this group were not waived.

In December 2009, the Division conducted a workshop with academic experts in the pediatric pain field and determined that, for analgesics where the mechanisms of action are understood (NSAIDs included), findings of efficacy in the adult population and older children may be extrapolated to the pediatric population down to the age of 2 years. Therefore, efficacy assessments for IV diclofenac (DIC075V) were waived in children 2-17 years of age.

The Division's recommendations to revise the Pediatric Plan were presented to (and accepted by) the Pediatric Research Committee on September 1, 2010. The respective comments were sent to the Applicant. The Applicant submitted the revised proposed Pediatric Plan on September 27, 2010.

11. Other Relevant Regulatory Issues

DSI inspections

The Division of Scientific Investigation (DSI) performed inspections of three study sites. There were no outstanding issues based on the inspection of these sites that would preclude approval.

Financial disclosures

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

505(b)(2) Issues

There are no outstanding 505(b)(2) issues related to this application.

12. Labeling

The Applicant's proposed proprietary name for IV diclofenac is Dyloject, which the Division of Medication Error Prevention and Analysis (DMEPA) and DDMAC found acceptable. DMEPA's recommendations for revisions of the carton and container labeling and the PI were sent to the Applicant. Draft labeling was submitted in PLR (Physician's Labeling Rule) format. In addition to product specific information, the contents of this label will follow the NSAID template that was instituted in 2005, and required the inclusion of warnings (including a Box Warning) regarding serious cardiovascular and gastrointestinal adverse events associated with NSAID use. Since this product is intended for use in hospitals, a Medication Guide is considered unnecessary.

The label will not contain dosing recommendations for pediatric patients. Studies in this population must be completed prior to the inclusion of the pediatric indication in the product label. Unlike RLD Cataflam label, this label will contain a contraindication for use in patients with moderate and severe renal impairment and a statement that use of IV diclofenac is not

recommended in patients with moderate and severe hepatic impairment. The label will also inform on occurrence of wound healing events in postoperative patients.

DDMAC has reviewed the proposed product labeling including the PI and carton/container labels. The reviewer had no comments on the carton and container label; the comments about the PI consisted mainly of the recommendations to remove the promotional language and keep the consistency throughout the label. (Refer to Ms. Fienkeng review for details.)

Appropriate comments were sent to the Applicant. The labeling was amended as noted in the relevant sections above.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Complete Response

- Risk Benefit Assessment

There is an adequate demonstration of efficacy of DIC075V at the dose 37.5 mg for the treatment of pain based on the clinical studies submitted in support of this application and the Agency's prior findings of efficacy of systemically administered diclofenac and safety of systemically administered cyclodextran (HPβCD). The safety assessment did not reveal any signals unexpected for the NSAID class of products or for the proposed route of administration. (b) (4)

While the Applicant's requested indication for the treatment of acute pain is broad, the safety of the drug in this clinical development program was studied in post-operative patients after major surgeries.

The risk-benefit assessment of an IV NSAID in post-operative population following major surgery deserves further discussion. In the recent years, the concept of multimodal analgesia (concomitant use of an opioid and a non-opioid analgesic) has been discussed in the literature by the pain treatment experts, mainly for the promising potential for opioid-sparing and patient-centered analgesia. While combining analgesics from different classes is viewed as beneficial for reduction of cumulative toxicities of opioids, when a drug with the lower [than an opioid] efficacy, for example an NSAID, is added to the analgesic regimen, some additional degree of pain relief and reduction in opioid dose is achieved, however, at the expense of the toxicities associated with the NSAID's dosing. To this end, a clinically meaningful reduction in opioid toxicity becomes an essential component of the risk-benefit assessment for the combined use of analgesics.

The clinical development program for DIC075V contained a robust safety database which allowed capturing the undesirable but expected effects of DIC075V in the post-operative setting including acute renal decompensation, bleeding events, and wound healing impairment. These adverse effects were not unexpected as the increased risk for NSAID toxicity in post-operative and hospitalized patients has been described in the medical literature and the NSAID class labeling contains warnings for renal, hepatic, and GI toxicity as well as for the drug-drug interaction with anticoagulating agents. The observation that the majority of patients in the controlled trials in this development program were not receiving concomitant anticoagulating therapy due to the expected risk of bleeding reveals the difficulty of using an IV NSAID in post-operative patients after major surgeries.

Thus, the favorable risk-benefit for DIC075V use will be in patients with a relatively low background risk for NSAID-related toxicities and in the absence of concomitant treatments potentiating these toxicities.

Consequently, labeling for DIC075V will be amended to guide the clinicians in their decisions for use of IV diclofenac in individual patients for treatment of acute pain.

- Comments to the Applicant

CMC:

1) (b) (4)

(b) (4)

Based on the currently available data provided in the amendment dated Sept 23, 2010, the review division is recommending a "For Cause Inspection" of the drug product manufacturer's facility (b) (4)

Until an inspection is performed and a satisfactory recommendation issued for all manufacturing sites by the Office of Complaince, this NDA can not be recommended for approval.

2) In your proposed Environmental Assessment, the Estimated Introductory Concentration (EIC) for diclofenac was calculated with the assumption that no diclofenac solution will be wasted because of the discrepancy between the proposed dosing and the proposed formulation. A Finding of No Significant Impact (FONSI) was granted based on your calculated EIC and the above described assumption. At this time, the proposed formulation for your product is a 37.5 mg/mL solution in a 2mL vial. If you pursue another dosing regimen that results in excessive overage, a new environmental assessment would be required.

Clinical:

1) Data submitted in this NDA do not support the proposed [redacted] (b) (4)

2) We acknowledge receipt of your amendment dated September 29, 2010, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in the CR letter.

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

/s/

LARISSA LAPTEVA
10/01/2010

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: September 9, 2010

TO: Kathleen Davies, Regulatory Project Manager
Rosemarie Neuner, Medical Officer
Division of Anesthesia, Analgesia, and Rheumatology Drug Products

FROM: Robert Young
Good Clinical Practice Branch 2
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch 2
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22 396

APPLICANT: Javelin Pharmaceuticals, Inc.

DRUG: Dyloject (diclofenac)

NME: No

THERAPEUTIC CLASSIFICATION: Standard

INDICATIONS: Management of acute moderate to severe pain in adults

CONSULTATION REQUEST DATE: April 30, 2010

DIVISION ACTION GOAL DATE: October 1, 2010

PDUFA DATE: October 3, 2010

I. BACKGROUND: Diclofenac is the subject of an approved NDA (1988). It is currently marketed in several formulations including tablets for oral administration, solution for ophthalmic use, and gel for topical use. This NDA proposes a parental formulation for i.v.

(b) (4) administration for pain management. The drug is a nonsteroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and antipyretic activity. It is 100% absorbed after oral administration. Associated adverse effects include: cardiovascular, GI, renal and skin side effects. Two clinical studies were submitted in support of the application:

> DFC-004: 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 Postoperative Pain after Abdominal or Pelvic Surgery.
>
> DFC-005: A Randomized, Double-blind, Active- and Placebo-Controlled Study of the Analgesic Efficacy and Safety of Repeated Dosing of DIC075V Relative to Parenteral Ketorolac and Placebo in patients with Acute Post-Operative Pain after Elective Orthopedic Surgery

Three clinical investigator sites were selected for inspection due to relatively high enrollment.

II. RESULTS (by Site):

Name of CI, IRB, or Sponsor & Location	Protocol # / # of Subjects	Inspection Date	Final Classification
Gilbert Podolsky Jean Brown Research 1045 East 3900 South Salt Lake City, UT 84124	DFC-004/35	August 10-17, 2010	Preliminary classification: VAI
Bradley Barter 101 Regent Court State College, PA 16801	DFC-005/39	June 2-4, 2010	NAI
Timothy Melson Helen Keller Hospital 1300 S. Montgomery Ave. Sheffield, AL 35660	DFC-004/87 DFC-005/74	June 28, 2010 – July 10, 2010	Preliminary classification: VAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. **Gilbert Podolsky**

   Note: Observations are based on the issued Form FDA 483 and communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

   a. **What was inspected**: The records of 18 subjects were reviewed for among other things protocol compliance, pain scores, data capture and adverse events.

No limitations to the inspection were encountered.

b. **General observations/commentary**: The records were well organized. A few lapses were noted on the issued Form FDA 483 including the isolated failure

- to test for barbiturates in two subjects
- to do a clinical test panel 24 hours after dosing in one subject
- to follow up on an elevated Lipase in one subject
- non concordance between source documents and case report forms regarding the date of a previous surgical procedure in one subject
- to document whether a single subject with myopia wore glasses
- to document the time of blood sampling and urine collection disparity of five minutes in one subject

c. **Assessment of data integrity**: Although regulatory violations were noted, these are unlikely to importantly impact data reliability as they are isolated occurrences. The data from this site is acceptable in support of the pending application.

2. **Bradley Barter**

a. **What was inspected**: A 100% review of the 15 subjects' consent forms was conducted. An in depth audit was conducted on 15 of the subjects who were enrolled into the study. Specific records reviewed included, but were not limited to, inclusion/exclusion criteria, drug accountably (receipt, storage, dispensing, and quantity returned), randomization, screen failures, withdraws, serious/adverse events, early discontinuation, monitoring, IRB approval, comparison of site CRF with data listings provided with the assignment, primary and efficacy endpoint and overall protocol compliance. No limitations to the inspection were encountered.

b. **General observations/commentary**: The study appeared to have been conducted adequately and No Form FDA 483 was issued.

c. Assessment of data integrity: The data generated by this site is acceptable in support of the respective application.

3. **Timothy Melson**

Note: Observations are based on the issued Form FDA 483 and communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

a. **What was inspected**: The records of 26 Study DFC-004 subjects and 25 DFC-005 subjects were reviewed for among other parameters adverse events, end points, data listings and source documentation. No limitations to the inspection were encountered.

b. **General observations/commentary**: A Form FDA 483 was issued and included the following observations: the use of superseded consent forms due to delays in delivering newly approved consent forms by the IRB; the use by two subjects of a consent form which was missing page 7; and in ten subject records there were isolated instances of non-matching source and data listing points related to a variety of collected information such as reserve medications, EKGs, concomitant medications, rescue medications, points in the medical history and study drug administration. Otherwise the data was complete and well organized.

c. **Assessment of data integrity**: Although regulatory violations were noted, these are considered isolated in nature and unlikely to impact data reliability. The data generated by this site is acceptable in support of the respective application.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three clinical investigators were inspected in support of this application. Although regulatory violations were noted for two clinical investigator sites (Podolsky and Melson), the findings are considered isolated in nature, and unlikely to importantly impact data reliability. Data from these three sites may be used as the basis for approval of the respective application.

Note: For the two inspections for which the final classifications are pending (Drs. Podolsky and Melson), an addendum to this clinical inspection summary will be forwarded to the Review Division should there be a change in the final classification or if additional observations of clinical and regulatory significance are discovered after reviewing the EIRs.

{See appended electronic signature page}

Robert Young
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/

ROBERT S K YOUNG
09/09/2010

TEJASHRI S PUROHIT-SHETH
09/13/2010

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22-396
Priority or Standard	Standard
Submit Date	December 2, 2009
Received Date	December 3, 2009
PDUFA Goal Date	October 3, 2010
Division / Office	Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)/ODEII
Reviewer Name(s)	Rosemarie Neuner, MD, MPH
Review Completion Date	September 3, 2010
Established Name	Diclofenac sodium
(Proposed) Trade Name	Dyloject™ Injection
Therapeutic Class	Nonsteroidal anti-inflammatory drug
Applicant	Hospira, Inc.
Formulation	37.5 mg/mL
Dosing Regimen	37.5 mg via intravenous (IV) bolus every 6 hours (b) (4) Maximum dose not to exceed 150 mg in 24 hours.
Indication	Management of acute moderate to severe pain
Intended Population	Adults

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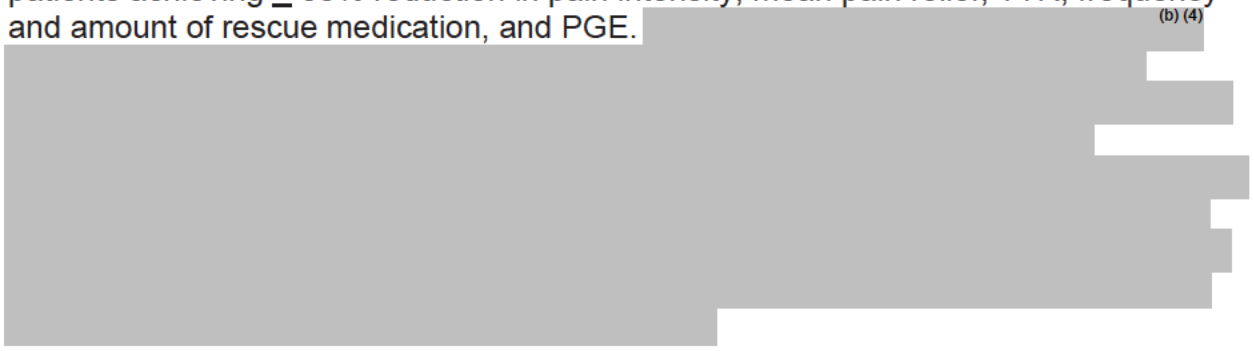
1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This clinical reviewer recommends approval for this 505(b)(2) drug application for injectable diclofenac sodium (DIC075V) for the treatment of acute moderate to severe pain in adults. The data contained in this application is sufficient to support a finding of efficacy and safety for DIC075V when administered via intravenous bolus injection at a dose of 37.5 mg every 6 hours (b) (4) for the indication of the management of acute moderate to severe pain in adults.

1.2 Risk Benefit Assessment

The efficacy of DIC075V for the management of acute moderate to severe pain was demonstrated by two adequate and well-controlled comparative trials, DFC-004 and -005.These were multicenter, randomized, double-blind, placebo- and active-controlled, parallel group dose comparison trials in 625 patients following abdominal, pelvic or orthopedic surgeries. In both of these trials, a greater proportion of patients treated with DIC075V achieved higher mean SPID interval scores at 0-48 hours as compared to placebo. These results were supported by similarly significant outcomes observed in the analyses of a majority of the secondary endpoints evaluated at the 48 hour time interval for both trials such as the mean PID score, the mean TOTPAR score, the proportion of patients achieving ≥ 30% reduction in pain intensity, mean pain relief, TTR, frequency and amount of rescue medication, and PGE. (b) (4)



1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Diclofenac has been available in this country for over 20 years as a symptomatic treatment for pain associated with arthritis conditions and other conditions. In view of the extensive experience associated with the use of this drug, its well documented

safety profile, and the lack of new safety signals identified during the course of this review of data generated from clinical and pharmacokinetic studies, postmarketing adverse events, and the worldwide literature, no postmarketing risk management activity should be required as this drug will be systemically administered via a new route of administration (e.g., intravenous bolus) that limits its use to a hospital setting by trained medical personnel.

1.4 Recommendations for Postmarket Requirements and Commitments

As per provisions of the Pediatric Research Equity Act (PREA), the Applicant has submitted a request for a partial waiver not to conducted a trial in neonates and infants (b) (4) as well as a request for a deferral to conduct a study in children ages ≥ 2 through ≤ 17 years old. Pursuant to the latter request, this submission contained a proposed pediatric development plan to evaluate (b) (4) DIC075V (b) (4) in the pediatric population via a (b) (4) efficacy and safety study (b) (4) The Applicant's request for a waiver to study neonates and infants (b) (4) is unreasonable (b) (4) However, the requirement for conducting a pediatric study in neonates and infants for ages birth to 1 year should be waived due to concerns of safety in this pediatric age group. Therefore, the Applicant will need to conduct a trial in children ages ≥ 13 months to less than 2 years of age evaluating the efficacy, safety as well as the pharmacokinetic profile of DIC075V since this drug could potentially be administered to children in this age group. Another trial in children ages ≥ 2 through ≤ 17 years old will also need to be done. The Applicant's proposed pediatric plan to evaluate DIC075V in children ≥ 2 through ≤ 17 years old needs to be amended to collect only safety and pharmacokinetic data since efficacy can be extrapolated from the adult population for this pediatric age group as the underlying pathology for pain is the same in adults and children over the age of 2 years. An age appropriate formulation will also need to be developed for this pediatric program due to the potential for dosing errors to occur associated with the use of small fractions of DIC075V from the 37.5 mg/1 ml vial.

Since this formulation is also known to be marketed for administration via intramuscular injection in the United Kingdom, the Applicant should be encouraged to submit the necessary PK and safety study to support administration of DIC075V via this route in view of the potential for off-label use and the associated risk for serious injection site reactions and infections noted on review of foreign postmarketing data submitted in support of its safety. The Applicant should be encouraged to study this drug as a treatment for other painful conditions such as gout and acute low back pain.

2 Introduction and Regulatory Background

2.1 Product Information

DIC075V (proposed trade name: Dyloject) is a new parenteral form of the nonsteroidal anti-inflammatory drug (NSAID) diclofenac sodium that contains hydroxypropyl-β-cyclodextrin (HPβCD) (b) (4) which permits this product to be administered by intravenous (IV) bolus (b) (4) Javelin Pharmaceuticals, who originally developed this formulation, purports that DIC075V has the potential to act as an alternative to orally administered NSAIDs for the treatment of acute moderate to severe pain, as well as the ability to act as a morphine sparing agent in patients with acute postsurgical pain prior to transitioning to oral analgesics. They are seeking marketing approval for this 37.5 mg/mL ready-to-use injectable formulation for the management of acute moderate to severe pain in adults with a proposed dosing regimen of 37.5 mg every six hours not to exceed 150 mg/day (b) (4)

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1 lists currently available injectable NSAIDs:

Table 1 – Currently Available Injectable NSAIDs

Product	Year of Approval	Indication
Ketorolac tromethamine	1989	Short-term (up to 5 days) management of moderately severe, acute pain that requires analgesia at the opioid level.
Ibuprofen	2009	Management of mild to moderate pain, and moderate to severe pain as an adjunct to opioid analgesics, and for the reduction of fever

2.3 Availability of Proposed Active Ingredient in the United States

Multiple formulations of diclofenac sodium are available in this country for oral and topical administration as follows:

- Voltaren® (sodium salt) delayed-release tablets marketed in the United States (U.S.) since 1988 (100-200 mg/day)
    - Symptomatic treatment of rheumatoid arthritis (RA), osteoarthritis (OA) and ankylosing spondylitis (AS)

- Cataflam® (potassium salt) immediate-release tablets marketed in U.S. since 1994 (100-150 mg/day)
    - Treatment of primary dysmenorrhea
    - Relief of mild to moderate pain
    - Symptomatic treatment of RA and OA
- Voltaren ® SR (sustained-release) tablets (100 mg/day) marketed in U.S. since 1996
    - Symptomatic treatment of RA and OA
- Arthrotec (diclofenac sodium and misoprostol) marketed in U.S. since 1997
    - Treatment of OA and RA in patients at high risk of developing NSAID-induced gastric and duodenal ulcers and their complications
- Cambia® (diclofenac potassium for oral solution) marketed in U.S. since 2009
    - Acute treatment of migraine attacks with or without aura
- Voltaren® Gel (diclofenac sodium topical gel) 1%
    - Pain of OA joints amenable to topical treatment
- Flector® Patch (diclofenac epolamine) marketed in U.S. since 2007
    - Treatment of acute pain due to minor strains, sprains and contusions
- Pennsaid® (diclofenac sodium) 1.5% topical solution marketed in U.S. since 2009
    - Treatment of the signs and symptoms of OA of knee
- Solaraze® (diclofenac sodium) 3% Gel marketed in U.S. since 2000
    - Topical treatment of actinic keratoses
- Voltaren ® Ophthalmic (diclofenac sodium) 0.1% solution
    - Treatment of postoperative inflammation
    - Temporary relief of pain and photophobia

If approved, DIC075V will be the first diclofenac sodium formulation for parenteral administration.

2.4 Important Safety Issues With Consideration to Related Drugs

No issues with pharmacologically related products have been identified that would be expected to have an impact on either the safety or efficacy of DIC075V.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The following are highlights of the regulatory activity that occurred during the development program for DIC075V.

IND 65,048 was opened on June 14, 2002 with a submission by Javelin Pharmaceutics.

An End-of-Phase 2 meeting was held on April 21, 2006. The key clinical and regulatory issues that were discussed at that time are itemized below.

- Applicant was informed that they could use Cataflam (diclofenac potassium) as reference drug (RD) for a 505(b)(2) application due to the lack of approved immediate release diclofenac sodium formulations
- Applicant needed replicated multiple-dose studies in order to support efficacy (ex. hip and knee replacement studies)
- Primary end point in pivotal trial could be assessed at 48 hours. However, safety data was to be collected as long as patients used drug (out to 5 days of prolonged exposure if possible)
- Sum of the pain intensity difference (SPID) was acceptable as primary endpoint in the pivotal trials provided the Applicant included an evaluation through Day 3
    - Missing data could not be imputed using "good scores" or using a 6-hour time window with worst observation carried forward (WOCF)
    - Baseline observation carried forward (BOCF) could not be used for patients who withdrew due to adverse events or inadequate pain relief but could use the 6-hour time window
- Applicant needed to assess both time to onset of analgesia and to re-medication in order to support both indication and dosing regimen in clinically relevant patient population
- Applicant needed to have 1000 patients exposed to drug followed for 4 weeks post exposure in support of safety since Cmax of RL would be exceeded
    - Participation of patients < 80 years old, and with renal and/or liver impairment was acceptable
- Wound healing would have to be reported as an adverse event
- Applicant needed to capture post-discharge use of analgesics in view of risk for cumulative toxicity with an oral NSAID or possible APAP associated hepatic toxicity
- Pediatric studies would not be required for NDA filing

A pre-NDA meeting was held on March 10, 2008. The following items summarize the understandings reached between the Applicant and the Division at that time.

- Applicant needed to identify all RDs for which published literature will be used in support of the sponsor's 505(b)(2) application (e.g., HPβCD used in Sporanox)
- Applicant must have comparative bioavailability "bridging" study data for each RD
- Published literature in support of the safety of IV administered diclofenac should be analyzed separately from other routes of administration
- Applicant needed to submit a pediatric drug development plan with NDA for deferred pediatric studies including milestone dates and age range to be deferred
- Applicant would have to submit CRFs for all dropouts
- Applicant needed to conduct either a 2-arm or 3-arm PK study in patients with renal impairment (normal, mild and moderate renal impairment) to support proposed drug's safety
- Applicant needed to conduct a PK study in patients with mild liver disease

An advice letter was issued on May 19, 2009 in response to questions regarding safety data sources and clinical development plan. The following are key points made by the Division at that time.

- No more than 200 patients with pain associated with dental surgery or bunionectomy would be permitted to satisfy the regulatory requirement of 1,000 "target" population patients treated for safety
- Safety data from an open-label study conducted in the United Kingdom utilizing a different dosing regimen (i.e., 75 mg every 12 hours) would be considered as supportive safety information but would count toward the total safety database requirement
- The Division would not accept [redacted] (b) (4) The Applicant's proposed [redacted] (b) (4) would need to have the necessary data in support of the drug's safe use
- Literature review should focus on the safety evaluation of parenteral administration of diclofenac and not just short-term use of diclofenac for acute pain in general

2.6 Other Relevant Background Information

According to information supplied by the Applicant, DIC075V has been marketed in the United Kingdom since 2007 as Dyloject® 75 mg/2 mL Solution for Injection. It is approved for IM use for the treatment of acute forms of pain including renal colic, exacerbations of OA and RA, acute back pain, acute gout, acute trauma and fractures, and postoperative pain. It is also approved for IV use for the treatment and prevention of postoperative pain in supervised healthcare settings. The IV dosing and administration recommendation is 75 mg, repeated if necessary after 4-6 hours not to exceed 150 mg within any period of 24 hours. As of May 21, 2010, this product was subject to an ongoing Class 2 medicines recall due to the presence of a white particulate matter in some vials of Dyloject.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Javelin Pharmaceuticals' submission was appropriately organized to allow information to be reviewed in an acceptable manner. The Applicant's responses to all of the FDA's requests were timely and well organized.

3.2 Compliance with Good Clinical Practices

According to the statements included in the reports for Studies DFC-004, 005 and 010, the Applicant certified that these trials were conducted in compliance with the following: good clinical practice standards as outlined in the Declaration of Helsinki or the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, with the institutional review board regulations as per 21 CFR (56), and the informed consent regulation as per 21 CFR (50).

3.3 Financial Disclosures

The financial disclosure form signed by the Applicant certified that no financial arrangements had been made with any of the principal investigators or subinvestigators involved with the clinical studies where outcomes affected compensation as defined in 21 CFR 54.2(a). Additionally, none of the principal investigators or subinvestigators reportedly had a proprietary interest as described in 21 CFR 54.2(b) in this drug or a significant equity in Javelin Pharmaceuticals, who is commercially developing this drug for marketing in the United States.

At the time this review was written, a final inspection report for the 3 study sites audited by the FDA's Division of Scientific Investigations (DSI) was pending.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Dr. Martin Haber is the Chemistry, Manufacturing and Controls (CMC) reviewer of this application. At the time this review was written, the CMC review was pending the completion of the EER for the drug substance manufacturing sites (b) (4) and the resolution or receipt of the following from the Applicant:

- Responses to three outstanding information requests regarding two deficiencies on drug substance specifications (i.e., particle size distribution measurement and limits (b) (4)) and one method validation question (quantitative sodium content measurement and limit)
- Submission of a revised (b) (4) leachables study report. (If the revised report is inadequate, additional studies on (b) (4) leachables may be required.)
- Due to the negative impact diclofenac has on fish and bird species an environmental assessment (EA) is to be submitted by 8/20/10. (FONSI is anticipated by the EA team)

4.2 Clinical Microbiology

The clinical microbiology data included in this application was reviewed by Dr. John Metcalfe who did not find any microbiology deficiencies and recommends approval of this application on the basis of product quality microbiology. Since the drug product is a single use product [redacted], Dr. Metcalfe recommends that the labeling information contain a statement instructing users to discard any unused portion of the drug product immediately following administration.

4.3 Preclinical Pharmacology/Toxicology

The clinical pharmacology/toxicology data included in this application was reviewed by Dr. Armaghan Emami who recommends approval of this application based on the following:

- Principal toxicity studies conducted were conducted with DIC075U which is a different formulation than the to be marketed DIC075V. DIC075U contains [redacted] diclofenac ([redacted] mg/mL versus 37.5 mg/mL) and the excipient HPβCD ([redacted] mg/mL versus 333 mg/mL)
- Rat and monkey toxicology IV studies were conducted with DIC075U to support the dose and duration of the proposed treatment with the systemic exposure coverage
- All general toxicity reflects known diclofenac/NSAID-related toxicity
- Local tolerance study was conducted with the to be marketed DIC075V to support the immediate local concentration of clinical use
- Excipients are within the approved levels in IIG guidance
- The release and stability specifications for [redacted] (impurity/degradant) is NMT [redacted]% to comply with ICH Q3B limits
- The pharmacology/toxicology sections of the label appears acceptable

4.4 Clinical Pharmacology

Dr. Srikanth Nallani reviewed the clinical pharmacology data contained in this application. Dr. Nallani recommends approval of this application with the following caveats:

- Dose adjustment in mild hepatic impairment is not needed from a PK perspective however, the clinical experience of DIC075V in mild hepatic impairment should be described in the drug's label
- The oral PK of diclofenac in alcoholic cirrhosis should be described in the label in order to indicate the lack of clinical safety and PK of the drug in moderate to severe hepatic impairment
- Caution should be exercised when using this drug in patients with moderate to severe hepatic impairment

- PK in elderly and young adults is similar. The clinical experience with 18.75 mg dose in the elderly should be described in Section 8.5
- No differences in the PK profile of DIC075V observed in the following subpopulation analyses: age, gender, race, or mild to moderate renal impairment

4.4.1 Mechanism of Action

Diclofenac is a bezeneacetic acid derivative of the NSAID class of drugs. It is a non-selective cyclooxygenase inhibitor that decreases prostaglandin synthesis resulting in anti-inflammatory, analgesic and antipyretic effects.

4.4.2 Pharmacodynamics

Since pharmacodynamic studies are not required under 505(b)(2) the Appliacant referenced the current product labeling for the reference drug (RD) Cataflam (NDA 20-142) and Sporonox Injection (NDA 20-966) for background information on the biopharmaceutics of diclofenac potassium and the pharmacokinetics (PK) of the (b) (4) HPβCD, respectively.

4.4.3 Pharmacokinetics

The results from the two pharmacokinetic studies (DFC-PK-006 and DFC-PK-009) conducted by the Applicant are presented and discussed in section 7.2.5 of this review.

5 Sources of Clinical Data

The clinical data used in this review were derived from trials conducted by the Applicant. Literature pertaining to the safety of intravenously administered diclofenac sodium as well as postmarketing adverse event reports associated with the use of any systemic formulation of this drug marketed in the United States that had been collected by the Adverse Event Report System (AERS) for the time period between 2004 through 2009, and postmarketing Adverse Drug Reactions (ADRs) associated with the administration of Dyloject™ in the United Kingdom contained in the first four annual Periodic Safety Update Reports (PSURs) for the time period from 2007 to 2010 were also reviewed in support of this application.

5.1 Tables of Studies/Clinical Trials

The following

Table 2 lists all of the clinical trials conducted by the Applicant and summarized information on the study design, objectives, entry criteria, doses and number of subjects studied. (Note: For purposes of this review, Dyloject™ will also be referred to as DIC075V).

Table 2 -Tabular Summary of Clinical and Pharmacokinetic Trials for Dyloject™

Study/Objectives	Study Design; Duration; Number of Study Sites	Dosage Regimen; Route of Adm.	Number of Subjects	Diagnosis and Entry Criteria	Primary Endpoint (EP)
Phase 3 studies					
DFC-004 Objective: Assess the efficacy and safety of 2 dose levels of DIC075V versus placebo in patients with acute moderate to severe post-op pain	Multicenter, randomized, double-blind, active and placebo-controlled, parallel group, multiple dose study Study utilized 1:1:1:1 randomization ratio 16 sites in U.S.	DIC075V 18.75 mg every 6 hours via IV bolus for up to 5 days DIC075V 37.5 mg every 6 hours via IV bolus for up to 5 days Ketorolac 30 mg every 6 hours via IV bolus for up to 5 days Placebo every 6 hours via IV bolus for up to 5 days	N=331 DIC075V 18.75 mg: DIC075V 35.7 mg : Ketorolac 30 mg: Placebo:	Age ≥ 18 years with acute moderate to severe post-op pain as assessed by ≥ 50 mm VAS 6 hours after abdominal or pelvic surgery	The sum of the pain intensity differences (SPID) over 0-48 hours
DFC-005 Objective: Assess the efficacy and safety of multiple doses of DIC075V versus placebo in patients with acute moderate to severe post-op pain	Multicenter, randomized, double-blind, active and placebo-controlled, 3-arm, parallel group, multiple dose study Study utilized 1:1:1 randomization ratio 12 sites in U.S.	DIC075V 37.5 mg every 6 hours via IV bolus for up to 5 days (18.75 mg for high risk subjects; 50 mg for subjects ≥ 95 kg) Ketorolac 30 mg every 6 hours via IV bolus for up to 5 days (15 mg for high risk subjects; 30 mg for subjects ≥ 95 kg) Placebo every 6 hours via IV bolus for up to 5 days	N=277 DIC075V 35.7 mg : Ketorolac 30 mg: Placebo:	Age ≥ 18 years with acute moderate to severe post-op pain as assessed by ≥ 50 mm VAS 6 hours after elective orthopedic surgery	The sum of the pain intensity differences (SPID) over 0-24, 0-48, 0-72, 0-96, and 0-120 hours
DFC-010 Objective: Assess the safety of multiple doses of DIC075V in patients with acute moderate to severe post-op pain	Multicenter, open-label, multiple dose, single arm safety study sites in US	DIC075V 37.5 mg every 6 hours via IV bolus for up to 5 days (50 mg for subjects ≥ 95 kg)	N= 971	Age ≥ 18 years with acute moderate to severe post-op pain as assessed by ≥ 50 mm VAS 6 hours after orthopedic, pelvic or abdominal surgery	Safety assessment Patient global evaluation at 24 and 48 hours

Table 2. Tabular Summary of Clinical and Pharmacokinetic Trials for Dyloject™ (Cont.)

Study/Objectives	Study Design; Duration; Number of Study Sites	Dosage Regimen; Route of Adm.	Number of Subjects	Diagnosis and Entry Criteria	Primary Endpoint (EP)
Phase 2					
DFC-002 Objectives: 1.Characterize the dose response for placebo and the 5 doses of DIC075V; 2. To determine the minimum effective dose of DIC075V	Multicenter, randomized, double-blind, active and placebo controlled, 3-arm, parallel group single dose, dose-response study Study utilized 1:1:1:1:1:1:1 randomization ratio 3 Sites in US	DIC075V: 3.75, 9.4, 18.75, 37.5 or 75 mg via IV bolus x 1 dose Ketorolac 30 mg via IV bolus x 1 dose Placebo via IV bolus x 1 dose	N=353 DIC075V: 3.75 mg: 51 subjects 9.4 mg: 51 subjects 18.75 mg: 51 subjects 37.5 mg: 51 subjects 75 mg: 51 subjects Ketorolac: 47 subjects Placebo: 51 subjects	Age ≥ 18 years with acute moderate to severe pain as assessed by ≥ 50 mm VAS 6 hours following third molar extraction	TOTPAR over 0-6 hours
DFC-001 Objectives: 1. Assess the safety, tolerability and superiority of DIC075V to placebo; 2. Show DIC075V and Votarol are equivalent in efficacy compared to placebo	Single center, randomized, double-blind, active and placebo controlled, 3-arm, parallel group single dose study Study utilized 1:1:1 randomization ratio 1 site in UK	DIC075V: 75 mg via IV bolus x 1 dose Voltarol 75 mg via IV bolus x 1 dose Placebo via IV bolus x 1 dose	N=155 DIC075V 75 mg: 53 subjects Voltarol 75 mg: 50 subjects Placebo: 52 subjects	Age ≥ 18 years with acute moderate to severe pain as assessed by ≥ 50 mm VAS 6 hours following third molar extraction	TOTPAR over 0-4 hours
Phase 1 PK and Drug-Drug Interaction Studies					
DFC-006 Objective: Assess the PK parameters of DIC075V 18.75 mg and 37.5 mg IV following single and multiple dose administration compared to oral diclofenac potassium	Open-label, 3-treatment, 3-period, crossover study 1 site US	DIC075V: 18.75 mg and 37.5 mg via IV bolus every 6 hours x 4 doses Cataflam (diclofenac potassium) 50 mg orally every 6 hours x 4 doses	N=36	Healthy male and female volunteers ages 18-55 years old with body weight ≥ 50 kg and BMI between 18-30 kg/m^2	Pharmacokinetic parameters and safety
DFC-008 Objective: Assess the effects of age, weight, and body composition on the PK profile, safety and tolerability of IV DIC075V	Open-label, single dose, 2 cohort study 1 site US	Age-based cohort: DIC075V 18.75 mg via IV bolus x 1 dose; Weight based cohort: DIC075V 37.5 mg x 1 dose	N=88 Age-based cohort: 34 subjects Weight-based cohort: 54 subjects	Age-based cohort: age ≥ 55 yrs and BMI ≥ 19 and ≤ 30 kg/m^2 Weight-based cohort: ages between 18-55 yrs old and BMI ≥ 15 kg/m^2	Pharmacokinetic parameters and safety

Table 2. Tabular Summary of Clinical and Pharmacokinetic Trials for Dyloject™ (Cont.)

Study/Objectives	Study Design; Duration; Number of Study Sites	Dosage Regimen; Route of Adm.	Number of Subjects	Diagnosis and Entry Criteria	Primary Endpoint (EP)
Phase 1 PK and Drug-Drug Interaction Studies (cont.)					
DFC-009 Objectives: 1. Assess the safety and PK of diclofenac and HPβCD following a single dose of DIC075V in subjects with mild-moderate chronic renal insufficiency and in subjects with mild hepatic impairment compared to healthy volunteers; 2. Evaluate the safety and PK of HPβCD following a single-dose of DIC075V and Sporonox in healthy volunteers	Open-label, single dose study in patients with mild or moderate renal impairment or mild hepatic impairment vs healthy volunteers Randomized, open label, single dose, 2-way, crossover evaluation of HPβCD when administered in DIC075V compared to Sporonox in healthy volunteers 1 site US	DIC075V 37.5 mg via IV bolus x 1 dose Sporonox 200 mg IV x 1 dose	N=40 DIC075V: 21 subjects (Renal impairment: 13 subjects Hepatic impairment: 8) Healthy volunteers: 19 subjects	Healthy volunteers and subjects with mild or moderate renal impairment or mild hepatic impairment	Pharmacokinetic parameters and safety

5.2 Review Strategy

The applicant conducted two adequate and well-controlled trials, Studies DFC-004 and 005, in support of this application which were reviewed for efficacy. The other trials (DFC-001, 002, 006, 008, 009 and 010) were not reviewed in support of Dyloject's efficacy as a treatment for acute moderate to severe post-operative pain for the following reasons: some of them were uncontrolled open-label trials, some did not contain secondary efficacy endpoints necessary to support efficacy, some of the studies evaluated doses or regimens different than the dose and regimen being developed for marketing, and one study used an active comparator not approved for marketing in this country.

The safety database included all subjects who participated in the pivotal Phase 3 trials, the open label trial as well as the safety data collected from the Phase 1 and 2 trials. These data will be discussed in Section 7.

5.3 Discussion of Individual Studies/Clinical Trials

Dyloject's efficacy as an analgesic was evaluated by the Applicant in two Phase 3 clinical efficacy trials, DFC-004 and 005. Additional safety information was generated

from the open label trial DFC-010. The design of each of these protocols will be presented first followed by a discussion of the individual study reports for these trials.

Study Number and Title: DFC-004 - A Randomized, Double-Blind, Active- and Placebo-Controlled Study of the Analgesic Efficacy and Safety of Repeated Dosing of Two Dose Levels of DIC075 Relative to Parenteral Ketorolac and Placebo in Patients with Acute Post-Operative Pain After Abdominal Surgery.

Dates Conducted: This trial was started on May 30, 2006 and completed on June 21, 2007.

Objectives:
Primary Objective:

- To assess the efficacy and safety of two DIC075 doses versus placebo and the active comparator ketorolac tromethamine in a repeat dose, post-operative pain setting

Study Design:
Study DFC-004 was to have been a 48-hour, multicenter, randomized, double-blind, placebo- and active-controlled, 4 arm, parallel group, Phase 3 trial to evaluate the efficacy and safety of 18.75 and 37.5 mg DIC075V administered every 6 hours intravenously (IV) versus placebo IV every 6 hours or 30 mg ketorolac tromethamine every 6 hours IV in patients with moderate to severe acute postoperative pain following abdominal or pelvic surgery. A total enrollment of 260 subjects was planned. The overall duration of the trial was to have been 5 months from the time of the last patient's enrollment. The duration of participation for each subject from the time of initial screening to the completion of the study was to have been approximately 25 days.

Patients who had successfully completed the screening process and whose eligibility had been confirmed within 6 hours of surgery by the presence of pain as assessed by ≥ 50 mm on a 100 mm visual analogue scale (VAS) were to have been randomized via a 1:1:1:1 ratio to one of four treatment groups:

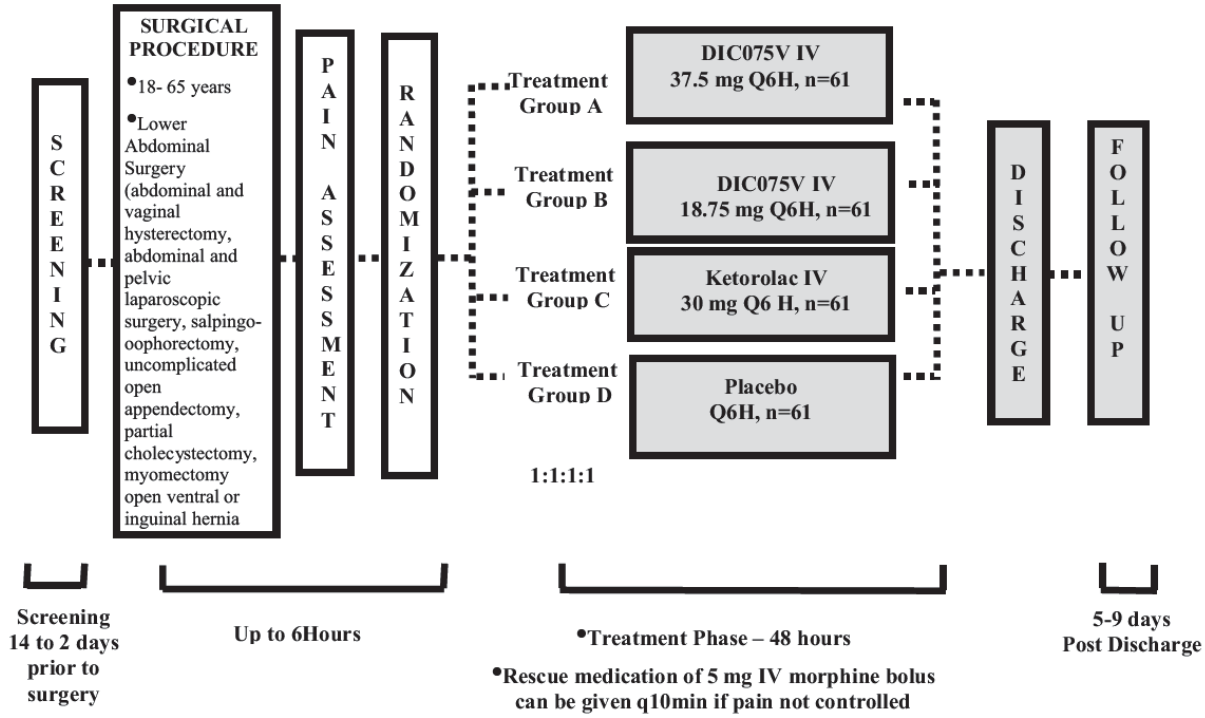
- IV DIC075V 37.5 mg every 6 hours
- IV DIC075V 18.75 mg every 6 hours
- IV ketorolac tromethamine 30 mg every 6 hours
- IV Placebo every 6 hours

All subjects were to have been observed for up to 48 hours. Although rescue medication was to have been available to patients any time after the initial dose of study drug, subjects were to have been encouraged to delay using it for at least 1 hour following the initiation of study dosing. Patients were to have completed their pain intensity and pain relief assessments prior to receiving their rescue medication. The protocol also mandated that subjects were not to have been awaken if they had been asleep during a

scheduled assessment time. Patients who withdrew from the trial were to have their pain managed as per the investigator's usual practice. All subjects were to have returned to the study clinic for a follow-up safety visit within 5-9 days post discharge.

Figure 1 below is a schema of the protocol for DFC-004.

Figure 1 - Schema for Study DFC-004



Major Inclusion Criteria:

Subjects were to have been men and women ≥ 18 years < 65 years of age who met all of the following criteria:

1. Must have been scheduled within 2 weeks of screening visit to undergo lower abdominal surgery (abdominal and vaginal hysterectomy, abdominal and pelvic laparoscopic surgery, salpingo-oophorectomy, uncomplicated open appendectomy, partial cholecystectomy, myomectomy, open ventral or inguinal hernia repair)
2. Females of childbearing potential must have been practicing abstinence or a medically acceptable form of contraception plus a spermicidal agent
3. Must have been in good health as determined by the Investigator on the basis of medical history and physical examination

4. Must have experienced moderate to severe pain within 6 hours following completion of the required surgery, that was to have been assessed on VAS measurement for pain intensity of ≥ 50 mm at baseline

Exclusion Criteria:
Potential trial candidates were to have been prohibited from participating in this trial if any of the following criteria applied:

1. Had a surgical procedure that involved a subcostal incision or midline excision extending above the umbilicus
2. History of uncontrolled chronic disease such as gastric erosion/ulceration or bleeding, renal impairment or cardiac failure that would have contraindicated study participation or require hospitalization within a month after participation in the trial, or in the opinion of the investigator would have render participation in the trial inadvisable
3. Recent history (≤ 6 months) of cardiovascular events (e.g., MI, stroke)
4. A clinically significant abnormal ECG at screening/baseline visit
5. Had taken aspirin, opioids, other nonsteroidal anti-inflammatory drugs, or other common centrally or peripherally acting analgesic drugs, major and minor tranquilizers, muscle relaxants or antihistamines within 24 hours prior to study drug administration. Nitrous oxide, very short-acting barbiturates, benzodiazepines, and general anesthetics were to have been exempted provided that there had been at least 1.5 hour washout period from the time of last administration. Long acting NSAIDs or COX-2 inhibitors (e.g., naproxen, rofecoxib or sustained release analgesics) were to have been discontinued 3 days prior to surgery
6. Female subjects who had a positive urine pregnancy test within 24 hours of surgery or who had been lactating at screening
7. Had taken monoamine oxidase inhibitors, tryptophan, carbamazapine or valproate within 2 weeks prior to have taken the study drug
8. Known allergy or hypersensitivity to diclofenac, NSAIDs, local anesthetics or to any of the expedients of the study preparation
9. Received any investigational medication within 3 months prior to administration of study drug, had been scheduled to receive an investigational drug during the course of the trial or had been previously admitted to this trial
10. Any clinical significant lab abnormality which would have contraindicated study participation including AST or ALT ≥ 1.5 and/or total bilirubin > 1.0 times the upper limit of the reference range or creatinine > 1.5 mg/dL at the screening visit
11. A confirmed positive result of UDS (Urine Drug Screen) or Alcohol Breath Test that suggested active alcohol and/or drug dependency
12. History of previous and/or present peptic ulceration, GI bleeding or any bleeding diathesis
13. History of severe asthma (controlled or uncontrolled)

Treatment:
Patients were to have started study treatment within 6 hours of completing surgery with DIC075V 37.5 mg every 6 hours, DIC75V 18.5 mg every 6 hours, ketorolac tromethamine 30 mg every 6 hours or placebo (normal saline) administered via bolus intravenous injection over 15 seconds.

Removal of Patients from Treatment or Assessment:
Patients were to have been discontinued from this trial if they withdrew consent, experienced an adverse event, were noncompliant, incurred a protocol violation, due to an administrative reason, or in the subject's best interest as per the investigator. The protocol stipulated that subjects were free to discontinue study participation for any reason at any time over the course of the trial.

Rescue Medication:
The rescue medication for this trial was to have been morphine 5 mg administered via bolus intravenous injection every 3 hours. Although rescue medication was to have been available to patients any time after the initial dose of study drug, patients were to have been encouraged to delay using it for at least 1 hour following the initiation of study dosing.

Concomitant Medications:
Use of the following medications within 24 hours prior to study drug administration by subjects was to have been prohibited unless administrated by the investigator during the surgical procedure: aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), opiods or other analgesic drugs (either centrally or peripherally acting), major and minor tranquilizers, muscle relaxants and antihistamines. Prophylactic administration of antibiotics for bacterial endocarditis or for the treatment of local infections was to have been permitted by the protocol.

Efficacy and Safety Assessments:
Following the completion of the informed consent, subject eligibility was to have been confirmed during the 14-day screening period during which a complete medical history, physical exam including vital signs and weight, ECG, clinical laboratory tests (serum biochemistry, complete blood count, urinalysis, urine pregnancy test [all females]), urine toxicology screening for drugs of abuse and alcohol breath test were to have been obtained (screening visit). At the baseline/post-surgery visit, patients were to have been instructed by study staff on how to record their pain assessments in their pain assessment diary. Subject eligibility for participation in the trial was to have confirmed at the baseline visit by the presence of moderate to severe pain as assessed by a 100 mm VAS (e.g., pain intensity $\geq$ 50 mm) within 6 hours post-surgery in addition to a review of the following: ECG, urine drug and alcohol breath tests, urine pregnancy test for female participants, current medications, adverse events, and trial entry criteria. Efficacy evaluations comprised of pain relief and pain intensity as assessed by 100 mm VAS were to have been performed at the following time points: 5, 10, 30, 45 minutes, and 1,

2, 3, 5, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45 and 48 hours post initial dose. A patient global evaluation (PGE) of the study drug via a 5-point rating system (1 = excellent to 5 = poor) was to have been also completed at 24 and 48 hours post dose. Safety was to have been assessed by monitoring for adverse events, vital sign measurements (immediately prior and 1 hour post-dose), review of concomitant medications, thrombophlebitis evaluation, physical exams, standard clinical laboratory evaluations at 0 and 5 minutes, and then every 6 hours during the 48-hour treatment period as well during the follow-up safety visit on Day 5-9 post dose. Serial ECG were to be done at screening, baseline and during the follow-up safety visit on Day 5-9 post dose.

Study Visit Schedule:
The following Table 3 is a tabular flow chart of the scheduled study observations and procedures:

Table 3 – Schedule of Procedures and Evaluations for Study DCF-004

Event	Screening Day -14 to -2	Baseline Post-Surgery	Treatment Period						Follow-Up Visit Day 5-9
			0 min	5 min – 5 hr [a]	6-23 hr [a]	24 hr [a]	25-47 hr [a]	48 hr [a] Discharge / Early Discontinuation	
Informed Consent	X								
Demographics	X								
Medical History	X								
Current Medications	X	X							
Concomitant Medications				X	X	X	X	X	X
Physical Examination	X								X
Vital Signs[b]	X		X[c]	X[c]	X[c]	X[c]	X[c]	X	X
12-lead ECG	X	X				X			X
Laboratory Tests	X					X		X[h]	X
Urine Drug & Alcohol Breath Test	X	X							
Urine Pregnancy Test	X	X							
Eligibility Criteria	X	X							
Pain Assessment		X[e]		X[d]	X[d]	X[d]	X[d]	X	
Study drug			X		X[f]	X[f]	X[f]		
Patient Global Evaluation						X		X	
Thrombophlebitis Assessment			X[g]	X[g]	X[g]	X[g]	X[g]		
Adverse Events		X	X	X	X	X	X	X	X

[a] All assessments times are relative to the start time of study drug administration
[b] Vital Signs (blood pressure, heart rate, respiratory rate and temperature), patients must be in a seated position for 5 minutes prior to having vital signs obtained
[c] Vital signs will be obtained immediately prior to dosing and 30 minutes after the dosing, at discharge and the follow-up visit
[d] Pain assessments will be obtained prior to any other assessment at that time; collected baseline and then 5, 10, 15, 30, 45 minutes, and 1, 2, 3, 5, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45 and 48 hours post initial dose.
[e] Pain intensity only
[f] Study drug will be administered q6h: 0 and 6, 12, 18, 24, 30, 36 and 42 hours post start time of initial dosing.
[g] Assessments will be performed immediately prior to dosing and 1 hour post-dose
h Select lab tests will be performed

Sponsor's Fig 5.1. ; p 15.

Outcome Measures:
All assessments of efficacy used in this trial were to have been derived from data recorded in the patients' pain assessment diaries and are standard assessments used in clinical analgesic studies.

Primary efficacy endpoint:

The primary efficacy variable for this trial was the sum of the pain intensity differences (SPID) over the 0-48 hour time interval. Patients' pain intensity was to have been measured via a 100 mm VAS. SPID was to have been calculated as the area under the curve of the pain intensity difference scores using the trapezoidal rule to approximate area.

Secondary efficacy endpoints:

This study had a number of secondary efficacy endpoints as follows:

- Sum of the pain intensity differences (SPID) over the 0-48 hour time interval – This is a continuous variable that was to have been calculated as the area under the curve of the pain intensity difference scores using the trapezoidal rule to approximate area.
- Pain intensity difference (PID) – This is a continuous variable that was to have been calculated via subtracting the baseline PID score from the PID score at each scheduled timepoint assessment.
- Total pain relief (TOTPAR) over the 0-24 and 0-48 hour intervals – This is a continuous variable that was to have been calculated based on the area under the relevant segments (e.g., 0-24 hours and 0-48 hours) of the pain relief curve.
- Pain relief score – This is a continuous variable that was to have been measured on a 100 mm VAS scale at each scheduled timepoint assessment.
- Pain relief intensity difference (PID) - This is a continuous variable that was to have been calculated by adding the PID score with the pain relief score from each scheduled timepoint assessment.
- Median time to administration of rescue medication – This endpoint is based on the length of time interval between the administration of study drug and first rescue adjusted for censoring and was to have been calculated via a survival analysis.
- Frequency and amount of rescue medication – The frequency of rescue medication is a categorical variable that was to have been calculated based on the number of times rescue medication was taken by patients over the 48 hours of observation. The amount of rescue medication taken is a continuous variable that was to have been calculated based on the total amount in milligrams (mg) of rescue medication taken over the course of the 48 hours of observation.
- Patient global evaluation – This is a categorical variable that was to have been calculated based on a 5-point system (1 = excellent to 5 = poor) that was to have been completed at 24 and 48 hours post dose.
- Proportion of patients attaining $\geq$ 30% reduction in pain intensity – This is a categorical variable.

Statistical Design, Definitions of Analyzed Populations and Analyses Plan:

The sample size calculation for this study was based on efficacy data generated from the Phase 2 study DFC-002 in dental pain. With a sample size of 62 subjects in each treatment group, the trial was to have 90% power to show a difference of 360 mm·hours

(i.e., an average reduction in pain intensity of 15 mm over the course of 24 hours) between placebo versus each of the DIC075V treatment groups.

Three populations were to have been used for analysis. They were defined as follows:

- Intent-to-Treat (ITT) Population: was to have consisted of all randomized subjects and who received study medication.
- Per-Protocol (PP) Population: was to have consisted of a subset of the ITT population who did not have any major protocol violations.
- Safety Population: was to have consisted of all subjects who received study drug and had recorded safety information.

The statistical analysis plan specified that all comparisons between treatment groups for continuous variables (e.g., SPID, TOTPAR, pain intensity, PRID, patient global evaluation and amount of rescue medication) was to have been conducted via analysis of variance (ANOVA) with treatment and center as factors and baseline pain as a covariate. Comparisons between treatment groups for categorical variables (e.g., frequency of rescue medication use and the proportion of patients attaining $\geq$ 30% reduction in pain intensity) were to have been conducted using the Cochran-Mantel-Haenszel test with center as a stratification variable. Kaplan-Meier survival analysis techniques were to have used to calculate the time from administration of study drug to administration of rescue medication.

Missing pain assessment data (e.g., pain intensity and pain relief) were to have been imputed as follows:

1. Linear interpolation was to have been used for missing assessments and assessments not performed within a time window of $\pm$ 5 minutes of the scheduled time for the 5, 10, 15, 30, 45 minute and 1 hour assessments
2. Worst observation carried forward from the preceding 6 hours was to have been used for subjects who used rescue medication during any 3 hour assessment interval or for patients who discontinued treatment due to adverse events or inadequate pain relief
3. Last observation carried forward was to have been used for subjects with missing assessments for all other situations

In terms of the safety analyses, the protocol specified that descriptive statistics based on tabulated summaries by treatment were to have been used for each of the following: adverse events, lab tests, ECGs, vital signs, physical exams and thrombophlebitis data.

Study Conduct:

Protocol Amendments –

Listed below are the 5 protocol amendments made to Study DFC-004.

1. Amendment 1 (implemented on March 15, 2006)

The following modifications were made to the study conduct:

- Subject population was to have included patients undergoing partial colectomy instead of partial cholecystectomy
- Baseline pain assessment was to have included an evaluation of pain intensity instead of pain relief
- Guideline for the administration of rescue medication for uncontrolled pain was to have been changed from 5 mg IV morphine bolus every 10 minutes to 5 mg IV morphine bolus every 3 hours
- Requirement for baseline urine drug and alcohol testing was to have been removed. Additionally, the screening test for alcohol was to have been changed from an alcohol breath test to an alcohol test.
- Patient global evaluation was to have been added to the 24-29 hours post-dose assessments
- Clarifications to Sections 5.3.1. Study Qualifications and 5.7.9 Concomitant Medications regarding the processing of potential study subjects during the post-operative period in order to confirm eligibility prior to randomization as well as instructions regarding the use of low doses of short acting parenteral opioids (morphine) during the immediate post-op period

2. Amendment 2 (implemented on March 30, 2006)
The following clarifications and modifications were made to the trial protocol:

- Use of muscle relaxants and general anesthetics prior to study entry was to have been removed while a history of allergy or hypersensitivity to morphine was to have been added to the exclusion criteria
- Concomitant use of muscle relaxants was to have been removed from the list of prohibited concomitant medications
- Requirements for a third party to prepare study medication was to have been added while a third party doser to administer study medication was to have been removed

3. Amendment 3 (implemented on May 25, 2006)
The following clarifications and modifications were made to the trial protocol:

- Duration of study treatment was to have been changed from up to 48 hours to a minimum of 48 hours and up to 5 days
- Schedule of evaluations was to have been updated to reflect the revised study treatment period as well as an addition of a telephone contact 30 days post-discharge
- Times to perceptible and meaningful pain relief were to have been included as secondary endpoints
- An ECG was to have been performed at 24-29 hours post-dose
- A global evaluation was to have been conducted every 24 hours until discharge/early discontinuation

- A description of clinically significant treatment emergent LFT elevations requiring follow-up was to have been added
- Analysis of the SPID and TOTPAR over the 0-24 and 0-48 hour intervals was to have been expanded to include the following intervals: 0-72, 0-96 and 0-120 hours. In the event of insufficient data required to statistically test each efficacy parameter at each assessment post 48 hours, this data was to have been presented via descriptive analysis for each treatment.

4. Amendment 4 (implemented on June 26, 2006)
The following clarifications and modifications were made to the trial protocol:

- Subjects undergoing pelvic surgery were to have been permitted to participate in the trial
- Number of study sites was to have been increased from 8 to 10-20 sites
- Criteria for substance abuse were to have been added to the protocol appendix while editorial changes were to have been made to exclusion criterion #11 for substance abuse so that it included a time interval of 12 months
- The NCI CTCAE was to have been used to grade signs and symptoms observed during the study
- Use of rescue medication was to have been clarified to up to 5 mg of morphine administered as an immediate IV bolus not more than every 3 hours except in cases where a patient did not achieve sufficient pain relief following a dose of IV morphine rescue. An additional ½ dose of rescue was to have been permitted at 30 minutes post-rescue in the event that this occurred.
- Advanced preparation of study drug was to have been permitted in the event that pharmacy services were unavailable provided that the drug was to be used within 18 hours of preparation

5. Amendment 5 (implemented on November 27, 2006)
In addition to administrative changes, the following clarifications and modifications were made to the trial protocol:

- 30% of the total number of surgical procedures were to have been laproscopic procedures
- Inclusion criteria were to have been modified to require a body weight of greater than 50 kg and to have required female subjects of child bearing potential to continue using a medically acceptable form of contraception or abstinence for the duration of the study
- Exclusion criteria were to have been modified to permit patients to continue taking 325 mg of aspirin a day for cardiac prophylaxis while prohibiting the use of PCA immediately postoperatively or during study participation
- Screening period was to have been extended from Day -14 through Day -2 to Day -14 through Day -1

- Local labs were to have been permitted to process screening assessments provided that samples drawn at the same time were also submitted to the central lab for testing
- Within 2 hours of administration of the initial dose of study medication, a window of +/- 15 minutes was to have been added for the administration of study drug doses, measurement of vital signs and completion of pain assessments
- A one time dose not to exceed 12.5 mg of meperidine to control shivering was to have been permitted
- The use of rescue medication was to have been changed to permit an additional 2.5 mg of morphine if needed 30 minutes after the initial 5 mg dose. If a patient had not achieved adequate analgesia following the administration of a total of 7.5 mg of IV morphine rescue, that subject was to have been withdrawn from the trial and given pain medication as per standard hospital practice.
- For clarification, a statement was to have been added to the protocol that subjects were to have been encouraged to wait 1 hour after administration of the initial dose of study medication before receiving rescue medication.
- Pain assessments were to have been conducted prior the administration of all rescue medication doses

As discussed with Dr. Jonathan Norton, staff statistician in OTS/Division of Biostatistics II, none of the above changes to the clinical or statistical methodology of the protocol were thought to have impacted on the trial's final outcome results.

RESULTS:

Disposition of Subjects:
A total of 348 subjects from 16 clinical sites in the United States were randomized to the four treatment groups as follows: 85 patients to the placebo group; 89 patients to the DIC075V 18.75 mg group; 88 patients to the DIC075V 37.5 mg group and 86 patients to the ketorolac 30 mg group. Table 4 below, summarizes the disposition of the randomized patients in this trial. Overall, 80% of subjects completed the trial. The highest rate of study completion was in the DIC075V 18.75 mg group, followed by the ketorolac group (82%), the DIC075V 37.5 mg group (78%) and the placebo group (75%). More patients withdrew prematurely due to the lack of efficacy (8%) as compared to subject request (4%), adverse event (3%), lost to follow-up (3%), noncompliance (1%), or other reason (1%). [Note: Review of the data from the 4 patients who discontinued from the trial due to other reasons revealed the following: 1 patient (Subject 11-001 DIC075V 18.75 mg group) was involved in a study medication dispensing error made by the study pharmacist, 1 patient (Subject 07-012 DIC75V 37.5 mg group) was discharged early from the hospital, 1 patient (Subject 02-013 ketorolac group) had an inadequate venous access necessary for the administration of study medication, and 1 patient (Subject 08-022 ketorolac group) was unable to return to the study site for the follow up visit 4-9 days post initial dose.] Rate of withdrawal due to

lack of efficacy was comparable across the 4 treatment groups (range: 7-9%) but more patients were withdrawn from the study at their request in the placebo group (11%) as compared to the 3 other treatment groups (DIC075V 18.75 mg: 1%; DIC075V 37.5 mg: 1%; and Ketorolac 30 mg: 2%).

Table 4 - Subject Disposition for Study DFC-004

Subjects	Placebo N (%)	DIC075V		Ketorolac 30 mg N (%)	Total N (%)
		18.75 mg N (%)	37.5 mg N (%)		
Number of Subjects Randomized	85	89	88	86	348 (100%)
Number of Intent-to-Treat Subjects	76	86	87	82	331 (95%)
Number of Subjects Who Completed	57 (75%)	73 (85%)	68 (78%)	67 (82%)	265 (80%)
Number of Subjects Who Withdrew:	19 (25%)	13 (15%)	19 (22%)	15 (18%)	66 (20%)
Adverse Event	0 (0%)	3 (4%)	4 (5%)	2 (2%)	9 (3%)
Noncompliance	1 (1%)	0 (0%)	2 (2%)	0 (0%)	3 (1%)
Subject Request	8 (11%)	1 (1%)	1 (1%)	2 (2%)	12 (4%)
Investigator Decision	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Lost to Follow-up	2 (3%)	2 (2%)	3 (3%)	3 (4%)	10 (3%)
Lack of Efficacy	7 (9%)	6 (7%)	8 (9%)	6 (7%)	27 (8%)
Other	0 (0%)	1 (1%)	1 (1%)	2 (2%)	4 (1%)

Adapted Sponsor's Table 10-1; p. 58.

Protocol Deviations/Violations:

A total of 66 patients incurred one or more major protocol deviations/violations over the course of this trial. The following table (Table 5) shows the highest rate of protocol major deviations/violations occurred in the DIC075V 18.75 mg group (23%) as compared to the placebo group (21%), DIC075V 37.5 mg group (20%) and the ketorolac group (16%). The most common major protocol deviation/violation was received less than 3 doses of study drug (12%), followed by received prohibited medication (10%) and did not have at least 1 post-baseline pain assessment (0.2%).

Table 5 - Summary of Protocol Violations for Study DFC-004

Protocol Violations	Placebo (N=76)	DIC075V		Ketorolac 30 mg (N=82)	Total (N=331)
		18.75 mg (N=86)	37.5 mg (N=87)		
Number of Subjects with Protocol Violations*:	16 (21%)	20 (23%)	17 (20%)	13 (16%)	66 (20%)
Prohibited Medication	8 (11%)	10 (12%)	9 (10%)	6 (7%)	33 (10%)
Received <3 Doses of Study Drug	12 (16%)	9 (10%)	10 (11%)	8 (10%)	39 (12%)
Did Not Have Baseline and ≥ 1 Post-Baseline Pain Assessment	0	3 (3%)	2 (2%)	1 (1%)	6 (0.2%)

More than 1 reason can be recorded for a given patient
Adapted Sponsor's Table 10-2; p. 60.

Further examination of these protocol deviations revealed that they were balanced across treatment groups and should not have impacted on the trial's outcome.

Treatment Compliance and Drug Exposure:
Since this was an inpatient trial, site personnel were responsible for both the administration and monitoring of subject compliance with study medication. Table 6 summarizes the drug exposure in Study DFC-004. The mean number of doses study medication administered over the course of this trial was 7.1 (range: 1 to 13 doses). Sixty-six percent (66%) of subjects in the placebo group received 8 doses of study medication followed by 70% of the DIC075V 37.5 mg group, 81% of the DIC075V 18.75 mg group and 81% of the ketorolac 30 mg group.

Table 6 - Summary of Study Drug Exposure for Study DFC-004 (ITT and Safety Populations)

Drug Exposure	Placebo (N=76)	DIC075V		Ketorolac 30 mg (N=82)	Total (N=331)
		18.75 mg (N=86)	37.5 mg (N=87)		
Summary of Doses Administered:					
Mean (SD)	6.8 (2.9)	7.2 (2.3)	7.0 (2.5)	7.4 (2.5)	7.1 (2.5)
Median	8.0	8.0	8.0	8.0	8.0
Range	(1, 13)	(1, 10)	(1, 13)	(1, 13)	(1, 13)
Total Number of Doses Administered:					
1	11 (15%)	9 (11%)	10(12%)	7 (9%)	37(11%)
2	1 (1%)	0	0	1 (1%)	2 (1%)
3	1 (1%)	1 (1%)	2 (2%)	1 (1%)	5 (2%)
4	2 (3%)	0	1 (1%)	2 (2%)	5 (2%)
5	4 (5%)	2 (2%)	3 (3%)	0	9 (3%)
6	1 (1%)	0	1 (1%)	0	1 (1%)
7	2 (3%)	2 (2%)	5 (6%)	0	9 (3%)
8	50 (66%)	70 (81%)	61(70%)	66 (81%)	247(75%)
9	0	1 (1%)	2 (2%)	1 (1%)	4 (1%)
10	0	1 (1%)	0	1 (1%)	1 (1%)
11	0	0	0	0	0
12	2 (3%)	0	1 (1%)	3 (4%)	6 (2%)
13	2 (3%)	0	1 (1%)	0	3 (1%)

Adapted Sponsor's Table 14.3.1.1; p. 506.

Demographics:

The demographic characteristics of the ITT population who participated in this trial are shown in Table 7. The subjects who participated in this trial were overwhelmingly female (82%) and Caucasian (73%) and had a mean age of 43 years. Overall mean weight was 84 kg and mean height was 167 inches. The baseline demographics were generally well balanced between the four study arms.

Table 7 - Demographic Characteristics of Subjects in Study DFC-004 (ITT and Safety Populations)

Demographic Characteristic	Placebo (N = 76)	DIC075V		Ketorolac 30 mg (N=82)	Total (N = 331)
		18.75 mg (N = 86)	37.5 mg (N = 87)		
Age (yrs.):					
Mean (SD)	43 (9.7)	43 (11)	43 (11)	43 (11)	43 (11)
Range	(23, 65)	(18, 63)	(20, 64)	(18, 65)	(18, 65)
Race:					
Caucasian	62 (82%)	68 (79%)	65 (75%)	60 (73%)	255 (77%)
Asian	0 (0%)	0 (0%)	2 (2%)	2 (2%)	4 (1%)
Hispanic	8 (11%)	10 (12%)	10 (12%)	10 (12%)	38 (12%)
Black	6 (8%)	6 (7%)	9 (10%)	10 (12%)	31 (9%)
Other	0 (0%)	2 (2%)	1 (1%)	0 (0%)	3 (1%)
Gender:					
Male	15 (20%)	13 (15%)	19 (22%)	15 (18%)	62 (19%)
Female	61 (80%)	73 (85%)	68 (78%)	67 (82%)	269 (81%)
Height (cm):					
Mean (SD)	167 (8.1)	166 (10)	167 (9.6)	168 (9.8)	167 (9.5)
Range	(155, 192)	(137, 191)	(152, 198)	(150, 190)	(137, 198)
Weight (kg)					
Mean (SD)	83 (19)	83 (18)	84 (19)	84 (24)	331 (20)
Range	(46, 142)	(47, 150)	(53, 155)	(41, 157)	(41, 157)

SD = standard deviation
Adapted Sponsor's Tables 11-2 and 14.1.4.1; p. 63 and 157.

Since this was a post-surgical analgesia trial, a variety of surgical factors that could have potentially impacted the study's results were also examined. Table 8 is a tabular summary of subjects' baseline surgical procedure information. The most commonly performed surgical procedures in this trial were abdominal hysterectomy (28%), vaginal hysterectomy (15%), abdominal surgery (15%), and inguinal hernia repair (13%). Further examination of these data showed that the incidences of the different types of abdominal and pelvic surgery varied across the 4 treatment groups, but overall was representative of the types of surgical procedures that would be a source of a patient population that could potentially benefit from administration of DIC075V. The mean duration of procedure was similar for all 4 treatment groups (range: 76 to 83 minutes) as was the length of incision (range: 39 to 43 cm). The mean time from end of surgery to first dose of study medication was lower for the ketorolac group (123 minutes) as compared to the DIC075V 18.75 mg group (128 minutes), placebo group (133 minutes) and DIC075V 37.5mg group (136 minutes). Based on these data, the study population that participated in this trial was reasonably balanced across study arms in terms of baseline surgical procedure.

Table 8 – Summary of Baseline Surgical Procedure Information for Subjects in Study DFC-004 (ITT and Safety Populations)

Procedure Information	Placebo (N = 76)	DIC075V 18.75 mg (N = 86)	DIC075V 37.5 mg (N = 87)	Ketorolac 30 mg (N=82)	Total (N = 331)
Surgical Procedure[1]:					
Abdominal Hysterectomy	25 (33%)	29 (34%)	18 (21%)	20 (24%)	92 (28%)
Vaginal Hysterectomy	9 (12%)	13 (15%)	20 (23%)	15 (18%)	57 (17%)
Abdominal Surgery	14 (18%)	12 (14%)	12 (14%)	12 (15%)	50 (15%)
Inguinal Hernia Repair	9 (12%)	10 (12%)	11 (13%)	14 (17%)	44 (13%)
Myomectomy	3 (4%)	3 (4%)	6 (7%)	5 (6%)	17 (5%)
Partial Colectomy	3 (4%)	1 (1%)	2 (2%)	3 (4%)	9 (3%)
Pelvic Surgery	4 (5%)	6 (7%)	6 (7%)	5 (6%)	21 (6%)
Salpingo-Oophorectomy	2 (3%)	5 (6%)	2 (2%)	3 (4%)	12 (4%)
Ventral Hernia Repair	1 (1%)	3 (4%)	3 (3%)	1 (1%)	8 (2%)
Other	6 (8%)	4 (5%)	7 (8%)	4 (5%)	21 (6%)
Duration of Procedure (min):					
Mean (SD)	81 (49)	83 (51)	76 (40)	77 (43)	79 (46)
Range	(20, 285)	(17, 245)	(15, 299)	(13, 262)	(13, 299)
Length of Incision (cm):					
Mean (SD)	39 (7)	43 (11)	40 (12)	43 (12)	41 (8)
Range	(1.6, 28)	(4.0, 74)	(4.0, 30)	(2.5, 47)	(1.6, 74)
Time from End of Surgery to First Dose of Study Medication (min):					
Mean (SD)	133 (102)	128 (94)	136 (110)	123 (96)	130 (100)
Range	(5, 417)	(5, 376)	(12, 371)	(7, 373)	(5, 417)

[1]Includes open and laporoscopic procedures
Adapted Sponsor's Table 14.1.7.1; p. 159.

Background data regarding the use of intraoperative anesthetics and analgesics prior to study entry were also reviewed (Table 9 below). General anesthetics (98%) followed by opioid anesthetics (94%), quaternary ammonium compounds (88%), benzodiazepine derivatives (84%), and amides (82%) were the most commonly used intraoperative anesthetics and analgesics administered to subjects who participated in this trial. Review of these data revealed that their usage was similar across the 4 treatment groups and should not have affected the study's outcome.

Table 9 – Tabular Summary of Intraoperative Anesthetics and Analgesics Administered to Subjects Who Participated in Study DCF-004 (ITT and Safety Populations)

Intraoperative Anesthetics and Analgesics	Placebo (N = 76)	DIC075V		Ketorolac 30 mg (N=82)	Total (N = 331)
		18.75 mg (N = 86)	37.5 mg (N = 87)		
Amides	65 (86%)	69 (80%)	74 (85%)	64 (78%)	272 (82%)
Benzodiazepine Derivatives	65 (86%)	68 (79%)	71 (82%)	73 (89%)	277 (84%)
General Anesthetics	76 (100%)	84 (98%)	83 (95%)	81 (99%)	324 (98%)
Halogenated Hydrocarbons	19 (25%)	23 (27%)	17 (20%)	16 (20%)	75 (23%)
Opioid Anesthetics	69 (91%)	80 (93%)	84 (97%)	78 (95%)	311 (94%)
Quaternary Ammonium Compounds	70 (92%)	74 (86%)	76 (87%)	72 (88%)	292 (88%)

Adapted Sponsor's Table 14.3.7.1; p. 841.

In this trial, subjects' pain was assessed via a 100 mm visual analogue scale (VAS). Three hundred twenty seven (327) of the 331 randomized patients who comprised the ITT population completed a baseline pain assessment, out of which 60% reported having baseline pain of moderate intensity (defined as pain $\geq$ 50 mm < 70 mm), while the remaining 40% reported having severe baseline pain (defined as $\geq$ 70 mm) . As shown in Table 10, the mean baseline pain intensity for the intent-to-treat population in this study was 68 mm (range: 50-100 mm) and was comparable across the 4 treatment groups. Thus, the patients in this trial had moderate to severe pain and could potentially show a response to study therapy.

Table 10 – Baseline Pain Intensity as Measured by 100 mm Visual Analogue Scale (VAS) for Subjects in Study DFC-004 (ITT Population)

Parameter	Placebo (N = 76)	DIC075V		Ketorolac 30 mg (N=82)	Total (N = 331)[1]
		18.75 mg (N = 86)	37.5 mg (N = 87)		
Baseline Pain Intensity (100 mm):					
Mean (SD)	68 (14)	67 (13)	71 (16)	68 (14)	68 (14)
Range	(50, 98)	(50, 100)	(50, 100)	(50, 99)	(50, 100)

SD = standard deviation
[1]Subjects 02-013, 07-003, 07-005, and 16-003 did not complete a baseline pain assessment.
Modified Sponsor's Tables 11-4 and 14.1.6.1; p. 65 and 158.

Efficacy

Primary Efficacy Results

The primary efficacy endpoint was the sum of the pain intensity differences (SPID) over 0-48 hours. Higher SPID scores signify greater improvement in pain intensity. The results generated from the primary analysis for Study DFC-004 are shown in Table 11.

The mean SPID 0-48 scores for both the DIC075V 18.75 mg (1304 mm·hours) and 37.5 mg (1576 mm·hours) treatment groups as well as for the ketorolac 30 mg active comparator group (1583 mm·hours) were significantly higher as compared to the placebo group (936 mm·hours) [DIC075V 18.75 mg vs placebo: p=0.0316; DIC075V 37.5 mg vs placebo: p = 0.0001; and ketorolac 30 mg vs placebo: p<0.0001].

Table 11 – Sum of the Pain Intensity Differences Over 0-48 Hours for Study DFC-004 (ITT Population)

SPID (mm·hours)	Placebo (N = 76)	DIC075V		Ketorolac 30 mg (N=82)
		18.75 mg (N = 86)	37.5 mg (N = 87)	
Mean	936	1304	1574	1583
Standard Deviation	1077	1030	1060	983
P-value[a]		p = 0.0316[b]	p = 0.0001[b]	p <0.0001[b]
95% Confidence Interval			-30, 562[c]	-7.6, 590[d] -274, 325[e]

Adapted Sponsor's Table 11-5; p. 67.
[a]P=0.0002 for overall treatment effect
[b]P-value from linear contrast comparing each active treatment versus placebo
[c]95% confidence interval (CI) for difference between DIC075V 18.75 and DIC075V 37.5 mg
[d]95% CI for difference between DIC075V 18.75 mg and ketorolac tromethamine 30 mg
[e]95% CI for difference between DIC075V 37.5 mg and ketorolac tromethamine 30 mg

Although a numeric dose-response for the DIC075V 18.75 mg and 37.5 mg treatment groups' SPID 0-48 scores is observed on further examination of the data in the above Table 11, the 95% confidence intervals generated from the between group comparative analyses of the three active treatment groups overlap indicating that their SPID 0-48 scores are not significantly different.

Secondary Efficacy Endpoints

There were multiple secondary endpoints evaluated in DFC-004. They are listed with their results as described by the Applicant in Table 12:

Table 12 – Tabular Summary of Secondary Endpoint Analyses for Study DFC-004

Secondary Efficacy Variable	Comment	P-value
Pain Intensity Difference (PID) at each scheduled assessment	Mean PID scores were higher in the 3 active treatment groups compared to the placebo group over the 0 to 48 hours post-first dose period	Graph (Refer to Figure 4)
Proportion of Subjects Achieving ≥ 30% Reduction in Pain Intensity	Significantly higher proportions of patients achieved a ≥ 30% reduction in baseline pain intensity in the ketorolac 30 mg active comparator group (57%), DIC075V 37.5 mg treatment group (46%), DIC075V 18.75 mg treatment group (42%) as compared to the placebo group (34%) that were observed to have started at 45 minutes post-administration of the first dose for all three study treatments. Rate of response was maintained through 39 hours with the exception of 6, 12, 24, 30 and 36 hour time points in all 3 active treatment groups.	p = 0.0229 for all 3 active treatment groups vs Placebo starting at 45 minutes post administration of study treatments
Total Pain Relief (TOTPAR) 0-24 hours	Mean TOTPAR scores over 0-24 hours were significantly higher for the DIC075V 18.75 mg group (998 mm·hrs), the DIC075V 37.5 mg group (1018 mm·hrs), and the ketorolac 30 mg active comparator group (1186 mm·hrs) as compared to the placebo group (776 mm·hrs)	DIC075V 18.75 mg vs Placebo p = 0.0371 DIC075V 37.5 mg vs Placebo p = 0.0018 Ketorolac 30 mg vs Placebo p <0.0001
TOTPAR 0-48 hours	Mean TOTPAR scores over 0-48 hours were significantly higher for the DIC075V 18.75 mg group (2367 mm·hrs), the DIC075V 37.5 mg group (2438 mm·hrs), and the ketorolac 30 mg active comparator group (2714 mm·hrs) as compared to the placebo group (1876 mm·hrs)	DIC075V 18.75 mg vs Placebo p = 0.0383 DIC075V 37.5 mg vs Placebo p = 0.0018 Ketorolac 30 mg vs Placebo p = 0.0001
Pain Relief (PR) at each scheduled assessment	Mean PR scores were higher in the 3 active treatment groups than in the placebo group through the 48 hours assessment	Graph (Refer to Figure 6)

Table 12- Tabular Summary of Secondary Endpoint Analyses for Study DFC-004 (cont.)

Secondary Efficacy Variable	Comment	P-value
Time to Perceptible Pain Relief (TPPR)	The median TPPR ranged from 8 minutes in the DIC075V 18.75 mg and ketorolac groups, 9 minutes in the DIC075V 37.5 mg group, to 10 minutes in the placebo group and was statistically significant on comparison for the 3 active groups versus placebo	DIC075V 18.75 mg vs Placebo p = 0.8722 DIC075V 37.5 mg vs Placebo p = 0.5390 Ketorolac 30 mg vs Placebo p = 0.2582
Time to Meaningful Pain Relief (TMPR)	The median TMPR ranged from 41 minutes in the DIC075V 37.5mg group, 43 minutes in the ketorolac group, 61 minutes in the DIC075V 18.75 mg group and 126 minutes for the placebo group and was not statistically significant on comparison of either DIC075V group versus placebo	DIC075V 18.75 mg vs Placebo p = 0.2085 DIC075V 37.5 mg vs Placebo p = 0.1400 Ketorolac 30 mg vs Placebo p = 0.0114
Time to First Rescue Medication (TTR)	The median TTR ranged from 2hours 7 minutes in the placebo group, 2 hours 24 minutes DIC075V 37.5 mg group, 3 hours 14 minutes in the DIC075V 18.75 mg group to 4 hours and 15 minutes in the ketorolac group and was statistically significant on comparison of DIC017.75 mg and ketorolac versus placebo; trended on comparison of DIC075V 37.5 mg versus placebo	DIC075V 18.75 mg vs Placebo p = 0.0141 DIC075V 37.5 mg vs Placebo p = 0.0574 Ketorolac 30 mg vs Placebo p = 0.0007
Amount of Rescue Medication: **0-24 hours** **0-48 hours**	Amount of rescue medication used during the 0-24 hrs interval ranged from 6.8 mg morphine for the DIC075V 18.75 group, 6.3 mg morphine for the DIC075V 37.5 mg group, 6.7 mg morphine for the ketorolac group and 11.2 mg morphine for the placebo group, Amount of rescue medication used during the 0-48 hrs interval ranged from 8.4 mg morphine for the DIC075V 18.75 group, 7.3 mg morphine for the DIC075V 37.5 mg group, 8.5 mg morphine for the ketorolac group and 15.2 mg morphine for the placebo group	p <0.0001 for all 3 active treatment groups vs Placebo

Table 12 –Tabular Summary of Secondary Endpoint Analyses for Study DFC-004 (cont.)

Secondary Efficacy Variable	Comment	P-value
Frequency of Rescue Medication	Proportion of patients who used rescue medication within the 48 hours of the treatment phase was lowest for patients in the ketorolac 30 mg active comparator group (63%), followed by the DIC075V 37.5 mg group (63%), and the DIC075V 18.75 mg group (73%) as compared to patients in the placebo group (92%)	Not applicable
Patient Global Evaluation (PGE) 0-24 hours	"Good" or better ratings on PGE were indicated by 84% of subjects in the DIC075V 18.75 mg group, 91% of subjects in the DIC075V 37.5 mg group and 85% of subjects in the Ketorolac group as compared to 70% of placebo subjects	DIC075V 18.75 mg vs Placebo p = 0.0075 DIC075V 37.5 mg vs Placebo p <0.0001 Ketorolac 30 mg vs Placebo p = 0.0006
Patient Global Evaluation (PGE) 0-48 hours	"Good" or better ratings on PGE were indicated by 87% of subjects in the DIC075V 18.75 mg group, 84% of subjects in the DIC075V 37.5 mg group and 83% of subjects in the Ketorolac group compared to 59% of placebo subjects	DIC075V 18.75 mg vs Placebo p <0.0001 DIC075V 37.5 mg vs Placebo p = 0.0003 Ketorolac 30 mg vs Placebo p = 0.0003

Efficacy Conclusion:
Both the 18.75 mg and 37.5 mg doses of DIC075V as well as the 30 mg dose of ketorolac were shown to decrease pain intensity as evidenced by significantly higher mean SPID 0-48 hour interval scores for each of these treatment groups as compared to placebo. The significance of these results for the 18.75 mg dose of DIC075V are statistically questionable since no correction for multiple comparisons across doses was applied during their analyses. These results were supported by similarly significant outcomes observed in the analyses of a majority of the secondary endpoints evaluated at the 48 hour time interval such as the mean PID score, the mean TOTPAR score, the proportion of patients achieving $\geq$ 30% reduction in pain intensity, mean pain relief, TTR, frequency and amount of rescue medication, and PGE. In this trial the median TPPRs were shown to be similar for all 4 treatment groups with the median TMPRs for the 37.5 mg DIC075V group and the ketorolac 30 mg group occurring earlier at 41 and 43 minutes, respectively, as compared to the median TMPRs for the 18.75 mg DIC075V group (61 minutes) and the placebo group (126 minutes). However, 18.75 mg of

DIC075V performed consistently worse than 37.5 mg of DIC075V or ketorolac on the majority of these secondary endpoints (except for the TTR and PGE 0-48 hours). Declaring statistical significance of the secondary endpoints evaluated in this trial using unadjusted p-values would be inappropriate since no multiplicity correction was planned in the protocol or implemented during the analyses of the secondary endpoints.

Study Number and Title: DFC-005 - A Randomized, Double-Blind, Active- and Placebo-Controlled Study of the Analgesic Efficacy and Safety of Repeated Dosing of DIC075 Relative to Parenteral Ketorolac and Placebo in Patients with Acute Post-Operative Pain After Elective Orthopedic Surgery.

Dates Conducted: This trial was started on July 25, 2007 and completed on October 9, 2009.

Objectives:
Primary Objective:

- To assess the efficacy and safety of DIC075 versus placebo and the active comparator ketorolac tromethamine in a repeat dose, post-operative pain setting

Study Design:
Study DFC-005 was to have been a 24- to 120-hour, multicenter, randomized, double-blind, placebo- and active-controlled, 3 arm, parallel group, Phase 3 trial to evaluate the efficacy and safety of DIC075V administered every 6 hours intravenously (IV) versus placebo IV every 6 hours or ketorolac tromethamine every 6 hours IV in patients with moderate to severe acute postoperative pain following elective orthopedic surgery. A total enrollment of 240 subjects was planned. The overall duration of the trial was to have been 10 months from the time of the last patient's enrollment. The duration of participation for each subject from the time of initial screening to the completion of the study was to have been approximately 50 days.

Patients who had successfully completed the screening process and whose eligibility had been confirmed within 6 hours of surgery by the presence of pain as assessed by $\geq$ 50 mm on a 100 mm visual analogue scale (VAS) were to have been randomized via a 2:1:1 ratio stratified by length of hospital stay (e.g., short stay: $\leq$ 24 hours versus long stay: > 24 hours) to one of three treatment groups as shown Table 13. (Note: The protocol mandated an adjustment in the default study dosing regimens based on each subject's weight (e.g., <95 kg versus $\geq$ 95 kg) and risk classification (e.g., non-high risk versus high risk).

Table 13 – Dose Adjusted Treatment Regimens for Study DFC-005

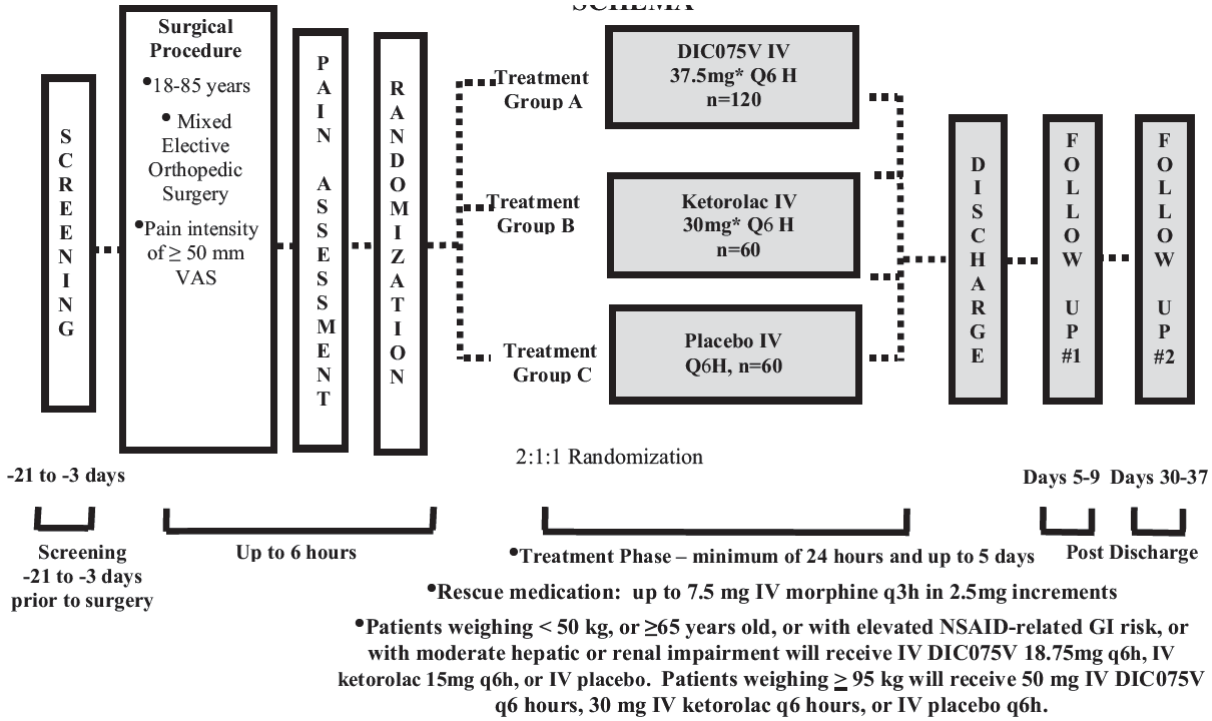
Treatment	Patient Type	Dose	Administered as a 15 Second Bolus
DIC075V	Non- High Risk	37.5 mg	1 ml DIC075V
	High Risk*	18.75 mg	0.5 mL DIC075V
	Higher Weight**	50 mg	1.3 mL DIC075V
Ketorolac tromethamine	Non- High Risk	30 mg	1 mL ketorolac
	High Risk*	15 mg	0.5 mL ketorolac
	Higher Weight**	30 mg	1 mL ketorolac and 0.3 mL normal saline
Placebo	Non- High Risk		1 mL Placebo (normal saline)
	High Risk*		0.5 mL Placebo (normal saline)
	Higher Weight**		1.3 mL Placebo (normal saline)

*High risk patients were defined by the protocol as individuals who met any of the following criteria: weight < 50 kg, age ≥ 65 years, elevated NSAID-related GI risk, moderate renal impairment (serum creatinine > 1.9 mg/dL) or moderate hepatic impairment (Child-Pugh score of 6-9).
**Higher Weight Threshold ≥ 95 kg (210 lbs)

Although rescue medication was to have been available to patients any time after the initial dose of study drug, subjects were to have been encouraged to delay using it for at least 30 minutes following the initiation of study dosing. Patients were to have completed their pain intensity and pain relief assessments prior to receiving their rescue medication. The protocol also mandated subjects were not to have been awaken if they had been asleep during a scheduled assessment time unless the pain assessment was to have been due prior to a dose of study medication. Patients who withdrew from the trial were to have their pain managed as per the investigator's usual practice. All subjects were to have returned to the study clinic for 2 follow-up safety visits scheduled for 5-9 days and 30-37 days post discharge.

Figure 2 below is a schema of the protocol for DFC-005.

Figure 2 –Schema of Study DCF-005



Adapted Sponsor's Fig. 1; p. 5.

Major Inclusion Criteria:

Subjects were to have been men and women between the ages of 18-85 years who met all of the following criteria:

1. Must have been scheduled within 2 weeks of screening visit to undergo mixed elective lower abdominal surgery
2. Females of childbearing potential must have been practicing abstinence or a medically acceptable form of contraception plus a spermicidal agent
3. Must have been in good health as determined by the Investigator on the basis of medical history and physical examination
4. Must have been experiencing moderate to severe pain within 6 hours following completion of the required surgery, that was to have been assessed on VAS measurement for pain intensity of ≥ 50 mm at baseline
5. Must have been weighing between 36-136 kg (300 lbs)

Exclusion Criteria:

Potential trial candidates were to have been prohibited from participating in this trial if any of the following criteria applied:

1. Would have needed their post-operative pain managed by an intra-operative or post-operative regional or multi-nodal anesthesia (central or peripheral), including neural blockade with a long acting local anesthetic

2. Anticipated post-operative pain that would have require higher than anticipated analgesic demand
3. A current diagnosis of cancer or would have required radiation, chemotherapy or immunotherapy during the study period
4. Chronic pain conditions that would have interfered with their ability to assess post-operative pain and/or require chronic analgesic medication
5. Age ≥ 65 years old and had clinical signs or symptoms consistent with dehydration
6. History of uncontrolled chronic disease such as gastric erosion/ulceration or bleeding, renal impairment or cardiac failure that would have contraindicated study participation or require hospitalization within a month after participation in the trial, or in the opinion of the investigator would have render participation in the trial inadvisable
7. Recent history (≤ 6 months) of cardiovascular events (e.g., MI, stroke)
8. Serum creatinine > 3.0 mg/dL
9. Clinically significant abnormal ECG at screening/baseline visit
10. A score > 9 (severe hepatic impairment) on the Pugh's Modification of Child's Classification of Severity of Liver Disease
11. Had taken aspirin, opioids, other nonsteroidal anti-inflammatory drugs, or other common centrally or peripherally acting analgesic drugs, major and minor tranquilizers, muscle relaxants or antihistamines within 24 hours prior to study drug administration. Nitrous oxide, very short-acting barbiturates, benzodiazepines, and general anesthetics were to have been exempted. All opioids and long acting NSAIDs or COX-2 inhibitors (e.g., naproxen, rofecoxib or sustained release analgesics) were to have been discontinued 3 days prior to surgery.
12. Lactating female subjects
13. Had taken monoamine oxidase inhibitors, tryptophan, carbamazapine or valproate within 2 weeks prior to have taken the study drug
14. Known allergy or hypersensitivity to diclofenac, other NSAIDs, morphine, anesthetics or to any of the expedients of the study preparation
15. Had received any investigational medication within 30 days or 5 half-lives prior to administration of study drug or had been previously admitted to this trial
16. History of (within the last 12 months) or had been currently abusing alcohol or drugs
17. Recent history of active peptic ulceration, GI bleeding or any significant bleeding diathesis
18. History of aspirin sensitivity, severe asthma (uncontrolled), or used systemic steroids within the last 6 months

Removal of Patients from Treatment or Assessment:
Patients were to have been discontinued from this trial if they withdrew consent, experienced an adverse event, intercurrent illness, were noncompliant, incurred a

protocol violation, due to an administrative reason, or in the subject's best interest as per the investigator. The protocol stipulated that subjects were free to discontinue study participation for any reason at any time over the course of the trial.

Rescue Medication:
The rescue medication for this trial was to have been a maximum dose of 7.5 mg of morphine administered via bolus intravenous injection every 3 hours in 2.5 mg increments. The protocol mandated that patients who had failed to achieve adequate pain relief following the administration of the first 5 mg cumulative dose of IV morphine rescue were permitted to have received an additional 2.5 mg dose of rescue medication 30 minutes later. Subjects who had failed to achieve adequate analgesic relief after receiving a total of 7.5 mg of IV morphine rescue medication were to have been withdrawn from the trial and administered non-study pain medication. Although rescue medication was to have been available to patients any time after the initial dose of study drug, patients were to have been encouraged to delay using it for at least 1 hour following the initiation of study dosing.

Concomitant Medications:
Use of the following medications within 24 hours prior to study drug administration by subjects was to have been prohibited unless administrated by the investigator during the surgical procedure: aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids or other analgesic drugs (either centrally or peripherally acting), major and minor tranquilizers, muscle relaxants and antihistamines. Nitrous oxide, very short-acting barbiturates, benzodiazepines, and general anesthetics were to have had a 1.5 hour washout period from the time of last administration. Prophylactic administration of antibiotics for bacterial endocarditis or for the treatment of local infections was to have been permitted by the protocol however, the use of patient controlled analgesia (PCA) or corticosteroids over the course of the study was to have been prohibited unless the latter were to have been used to treat nausea or vomiting. Although the protocol prohibited the use of ice over the surgical site for the duration of the study, subjects were to have been permitted to undergo physical therapy.

Efficacy and Safety Assessments:
Following the completion of the informed consent, subject eligibility was to have been confirmed during the 21-day screening period during which a complete medical history, physical exam including vital signs and weight, ECG, clinical laboratory tests (serum biochemistry, complete blood count, urinalysis, urine pregnancy test [all females]), urine toxicology screening for drugs and alcohol were to have been obtained (screening visit). At the baseline/post-surgery visit, patients were to have been instructed by study staff on how to record their pain assessments in their pain assessment diary. Subject eligibility for participation in the trial was to have confirmed at the baseline visit by the presence of moderate to severe pain as assessed by a 100 mm VAS (e.g., pain intensity $\geq$ 50 mm) within 6 hours post-surgery in addition to a review of the following: ECG, urine drug and alcohol tests, urine pregnancy test for female participants, current

medications, adverse events, and trial entry criteria. Efficacy evaluations comprised of pain relief and pain intensity as assessed by 100 mm VAS were to have been performed at the following time points: 5, 10, 15, 30, 45 minutes, and 1, 2, 3, 5, 6, 9, 12, 15, 18, 21, and 24 hours post initial dose and immediately prior to any use of rescue medication. Subjects who remained at the site for more than 24 hours (e.g., long stay patients) were to have pain assessments performed every 3 hours starting at 27 hours post-initial dose. A patient global evaluation (PGE) of the study drug via a 5-point rating system (4 = excellent to 0 = poor) was to have been also completed every 24 hours post initial dose and at discharge/early discontinuation. Safety was to have been assessed by monitoring for adverse events, vital sign measurements (immediately prior to and then every 8 hours post-initial dose and at discharge), review of concomitant medications, thrombophlebitis evaluation to be conducted every 8 hours post initial dose and at discharge, physical exams, standard clinical laboratory evaluations as well as total bilirubin, ALT, AST, and CPK at 24 hours post first dose and discharge, and ECG at baseline and 24-hours post-dose. A wound assessment questionnaire was also to have been completed at discharge and at each follow-up visit.

Study Visit Schedule:
The following Table 14 is a tabular flow chart of the scheduled study observations and procedures:

Table 14 – Schedule of Procedures and Evaluations for Study DFC-005

	Screening Day -21 to -3	Baseline Pre-Surgery	Treatment Period							Early Termination after 24 hr or Study Completion of Long Term Stay [a]	Follow-up Visit Day 5-9 after Last Dose	Follow-up Telephone Call Day 30-37 after Last Dose
			0 min	5 min – 5hr [a]	6-17 hr [a]	18-23 hr [a]	24 hr Early Termination before 24 hr or Study Completion of Short Term Stay [a]	25 -120 hr [a]	Rescue Medication [e,k]			
Informed Consent	X											
Eligibility Criteria	X	X										
Demographics	X											
Physical Examination	X										X	
Medical History	X											
Vital Signs [b]	X		X [c]		X [c]		X [c]	X [c]		X	X	
12-lead ECG	X	X										
Urine Pregnancy Test	X	X										
Urine Drug Screen	X	X										
Clinical Laboratory Tests	X						X			X [h]		
Concomitant Therapies	X	X	X	X	X	X	X	X	X	X	X	X
Pain Assessments			X [d]	X [e]	X [e]	X[e]	X[e]	X[e]	X	X		
Stopwatches [i]			X [i]	X [i]	X [i]							
Study Drug			X [f]		X [f]	X [f]	X [f, i]	X [f]				
Patient Global Evaluation [j]							X [j]	X [j]		X [j]		
Thrombophlebitis Assessment			X [g]		X [g]		X [g]	X [g]		X		
Wound Assessment							X [m]			X	X	X [n]
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X

a All assessments times are relative to the start time of the first dose of study drug administration.
b Vital Signs [blood pressure, heart rate, respiratory rate and temperature (screening only)] at screening, immediately prior to dosing, every 8 hours post first dose, discharge/early discontinuation, and the 5-9 day follow-up visit. Subjects must be resting for at least 5 minutes before having vital signs obtained.
c Vital signs will be obtained immediately prior to the first dose of study drug and every 8 hours thereafter.
d Baseline pain assessment is pain intensity only.
e Pain assessments (pain intensity and pain relief) will be obtained prior to any other assessment at that time; collected at 5, 10, 15, 30, 45 minutes, and 1, 2, 3, 5, 6, 9, 12, 15, 18, 21, 24 hours post first dose. If the subject remains at the study site beyond 24 hours, pain assessments will be made every 3 hours starting at 27 hours post first dose and obtained prior to all rescue medication doses.
f Study drug will be administered q6h: 0 and 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, 96, 102, 108, and 114 hours post start time of initial dosing, while the subject remains at the site.
g Thrombophlebitis assessments will be performed immediately prior to the first dose of study drug and every 8 hours thereafter.
h At Early Termination, select lab tests may be performed (total bilirubin, ALT, AST, and CPK).
i For the first dose of study drug, stopwatches will be used to measure time to perceptible and meaningful pain relief. Stopwatches will be discontinued 6 hours post first dose.
j Patient global evaluations will be done every 24 hours post start time of initial dosing and at completion/early termination.

Sponsor's Table 5.1; p. 19.

Outcome Measures:
All assessments of efficacy used in this trial were to have been derived from data recorded in the patients' pain assessment diaries and are standard assessments used in clinical analgesic studies.

Primary efficacy endpoint:
The primary efficacy variable for this trial was the sum of pain intensity difference (PID) which was the area under the pain intensity difference curve over the following five time intervals: 0-24, 0-48, 072, 0-96 and 0120 hours. Patients' pain intensity was to have been measured via a 100 mm VAS. Sum of the PID was to have been calculated as the area under the curve of the pain intensity difference scores using the trapezoidal rule to approximate area.

Secondary efficacy endpoints:
This study had a number of secondary efficacy endpoints as follows:

- Pain intensity difference (PID) at each scheduled assessment – This is a continuous variable that was to have been calculated via subtracting the baseline PID score from the PID score at each scheduled time point assessment

- Proportion of patients who had attained at least 30% reduction in pain intensity - This is a categorical variable to be calculated at each scheduled time point assessment
- Area under the pain relief curve over the following five intervals: 0-24, 0-48, 0-72, 0-96, and 0-120 hours – This is a continuous variable that was to have involved a trapezoidal approximation of area under the pain relief curve
- Pain relief score – This is a continuous variable that was to have been measured on a 100 mm VAS scale at each scheduled time point assessment
- Median time to administration of rescue medication - This endpoint is based on the length of time interval between the administration of study drug and first rescue adjusted for censoring and was to have been calculated via a survival analysis
- Frequency and cumulative amount of rescue medication – The frequency of rescue medication is a categorical variable that was to have been calculated based on the number of times rescue medication was taken by patients. The amount of rescue medication taken is a continuous variable that was to have been calculated based on the total amount in milligrams (mg) of rescue medication taken over the course of the study
- Patient global evaluation – This is a categorical variable that was to have been calculated based on a 5-point system (4 = excellent to 0 = poor) that was to have been completed every 24 hours post initial dose and at discharge/early discontinuation
- Time to perceptible pain relief – This is a stopwatch assessment that was to have been measured via stopping the first stopwatch when the subject had first felt improvement in pain and was to have been calculated via a survival analysis
- Time to meaningful pain relief – This is a stopwatch value that was to have been measured via stopping a second stopwatch when meaningful pain relief has been achieved and was to have been calculated via a survival analysis

(Note: The dual stopwatch methodology was to have been discontinued at 6 hours post-initiation of study medication if perceptible and/or meaningful relief had not been achieved. Discontinuation of stopwatches was to have also occurred if a subject had received a dose of rescue medication within 6 hours post-first dose of study drug.)

Statistical Design, Definitions of Analyzed Populations and Analyses Plan:
The sample size calculation for this study was based on data generated from Study MOR-003 in orthopedic surgery. With a sample size of 129 subjects in the DIC075V group and 60 patients in placebo group, the trial was to have 95% power to show a difference of 360 mm·hours, 540 mm·hours, 810 mm·hours, 1080 mm·hours, and 1350 mm·hours in area under the pain intensity difference curve are expected over the intervals 0-24 hours, 0-48 hours, 0-72 hours, 0-96 hours and 0-120 hours, respectively, between the DIC075V and placebo treatment groups.

Three populations were to have been used for analysis. They were defined as follows:

- Intent-to-Treat (ITT) Population: was to have consisted of all randomized subjects and received study medication
- Per-Protocol (PP) Population: was to have consisted of a subset of the ITT population who did not have any major protocol violations or did not have a pain intensity score ≥ 50 mm at randomization
- Safety Population: was to have consisted of all subjects who received study drug and had recorded safety information

The statistical analysis plan specified that all comparisons between treatment groups for continuous variables (e.g., area under the pain intensity difference curve, pain intensity difference, area under the pain relief curve, pain relief, patient global evaluation and amount of rescue medication) was to have been conducted via analysis of variance (ANOVA) with treatment and center as factors and baseline pain as a covariate.

To control for multiplicity, a sequential, closed testing procedure was to have been used for the comparative analyses involving the primary endpoint, the area under the pain intensity difference curve, in the following order: 0-24 hours, 0-48 hours, 0-72 hours, 0-98 hours and 0-120 hours. The analysis of the area under the pain curve was to have been conducted in the same manner.

Comparisons between treatment groups for categorical variables (e.g., frequency of rescue medication use and the proportion of patients attaining ≥ 30% reduction in pain intensity) were to have been conducted using the Cochran-Mantel-Haenszel test with center as a stratification variable. Kaplan-Meier survival analysis techniques were to have used to calculate the time to perceptible relief, time to meaningful relief and time from administration of study drug to administration of rescue medication.

Missing pain assessment data (e.g., pain intensity and pain relief) were to have been imputed as follows:

1. Linear interpolation was to have been used for missing assessments and assessments not performed within a time window of ± 5 minutes of the scheduled time
2. Worst observation carried forward from the preceding 6 hours was to have been used for subjects who used rescue medication during any 3 hour assessment interval or for patients who discontinued treatment due to adverse events or inadequate pain relief
3. Baseline observation carried forward (BOCF) was to have been used for subjects who discontinue treatment due to adverse events or inadequate pain relief
4. Last observation carried forward (LOCF) was to have been used for subjects with missing assessments for all other situations

In terms of the safety analyses, the protocol specified that descriptive statistics based on tabulated summaries by treatment were to have been used for each of the following:

adverse events, lab tests, ECGs, vital signs, physical exams, thrombophlebitis and wound healing data.

Study Conduct:
Protocol Amendments –
Listed below are the 4 protocol amendments made to Study DFC-005.
1. Amendment 1 (implemented on May 10, 2007) specified the following clarifications and modifications were to be made to the conduct of the study:

- Study sites were to have been permitted to administer rescue medication as per standard hospital practice
- Clarifications were to have been included regarding the use of intra-operative medications
- Prothrombin time was to have been collected at screening
- Vital signs were to have been measured at rest rather than in a seated position

2. Amendment 2 (implemented on July 6, 2007) stipulated the following clarifications and modifications were to be made to the conduct of the study:

- Number of qualified study personnel permitted to conduct wound assessments was to have been increased
- Alcohol screening was to have been removed from the protocol
- Clarified that only IV morphine was to have been used in the post operative care unit during stabilization
- Clarified the use of ice therapy and physical therapy were to be permitted around pain assessments
- Clarified the dosing regimen to have been used in the higher weight treatment group

3. Amendment 3 (implemented on October 17, 2007) specified the following clarifications and modifications were to be made to the conduct of the study:

- Clarified that a telephone follow-up for safety was to have been conducted 30-days post dose
- Clarified the exclusion duration for the administration of local versus systemic steroids
- Clarified that the efficacy analysis was to have been performed solely on the ITT population and not on the per protocol population

4. Amendment 4 (implemented on June 9, 2008) stipulated the following clarifications and modifications were to be made to the conduct of the study:

- Exclusion criteria #19 was to have been updated to permit subjects who had an intra-articular steroid injection within 1 month prior to study entry to participate in the trial provided that the injected joint was to have undergone orthropedic replacement surgery

As discussed with Dr. Jonathan Norton, staff statistician in OTS/Division of Biostatistics II, none of the above changes to the clinical or statistical methodology of the protocol were thought to have impacted on the trial's final outcome results.

RESULTS:

Disposition of Subjects:
A total of 277 subjects from 12 clinical sites in the United States were randomized to the three treatment groups as follows: 72 patients to the placebo group; 145 patients to the DIC075V group and 60 patients to the ketorolac group. Table 15 below, summarizes the disposition of the randomized patients in this trial. Overall, 86% of subjects completed the trial. The highest rate of study completion was in the ketorolac group (93%), followed by the DIC075V group (91%) and the placebo group (71%). More patients withdrew prematurely due to the lack of efficacy (11%) as compared to subject request (4%), adverse event (3%), lost to follow-up (3%), noncompliance (1%), or other reason (1%). The placebo group had the highest rate of withdrawal (29%) due to lack of efficacy as compared to the DIC075V group (4%) and the ketorolac group (7%).

Table 15 – Subject Disposition for Study DFC-005

	Placebo N (%)	DIC075V N (%)	Ketorolac N (%)	Total N (%)
Number of Subjects Randomized:	72 (26%)	145 (52%)	60 (22%)	277 (100%)
Non-High Risk	33	65	27	125
High Risk	22	45	18	85
Higher Weight	17	35	15	67
Number of Intent-to-Treat Subjects:	72 (26%)	145 (52%)	60 (22%)	277 (100%)
Non-High Risk	33	65	27	125
High Risk	22	45	18	85
Higher Weight	17	35	15	67
Number of Subjects Who Completed:	51 (71%)	132 (91%)	56 (93%)	239 (86%)
Non-High Risk	28	60	25	113
High Risk	13	39	16	68
Higher Weight	10	33	15	58
Total Number of Subjects Who Withdrew:	21 (29%)	13 (9%)	4 (7%)	38 (14%)
Short Stay	2 (3%)	1 (1%)	0	3 (1%)
Long Stay	19 (26%)	13 (9%)	4 (7%)	35 (13%)
Reason for Withdrawal:				
Lack of Efficacy	21 (29%)	6 (4%)	4 (7%)	31 (11%)
Adverse Event	0	2 (1%)	0	2 (1%)
Subject Withdrew Consent	0	2 (1%)	0	2 (1%)
Protocol Violation	0	1 (1%)	0	1 (1%)
Investigator Decision	0	1 (1%)	0	1 (1%)
Other	0	1 (1%)	0	1 (1%)

[1]All subjects who received study medication and had safety data recorded
[2]All subjects who were randomized into the study and who received at least 1 dose of study medication
Modified Sponsor's Table 10-1; p. 54.

Protocol Deviations/Violations:

A total of 41 patients incurred one or more protocol deviations/violations over the course of this trial. The following table (Table 16) shows the highest rate of protocol deviations/violations that lead to exclusion from the per protocol population occurred in placebo group (26%) as compared to the DIC075V 37.5 mg group (12%) and the ketorolac group (7%). The most common protocol deviation/violation was received less than 3 doses of study drug (9%), followed by received prohibited medication (5%), violation of exclusion criteria (2%), weight over 136 kg (1%) and other (0.4%).

Table 16 - Summary of Major Protocol Violations Leading to Exclusion from the Per Protocol Analysis for Study DFC-005

Protocol Violations	Placebo (N =72)	DIC075V (N = 145)	Ketorolac (N = 60)	Total (N = 277)
Number of Subjects with Protocol Violations*:	19 (26%)	18 (12%)	4 (7%)	41 (19%)
Prohibited Medication	6 (8%)	7 (5%)	0	13 (5%)
Received <3 Doses of Study Drug	14 (19%)	7 (5%)	4 (7%)	25 (9%)
Violation of Exclusion Criteria (#11) for Prohibited Medication	2 (3%)	4 (3%)	0	6 (2%)
Weight over 136 kg	1 (1%)	3 (2%)	0	4 (1%)
Other**	0	1 (0.7%)	0	1 (0.4%)

*More than 1 reason can be recorded for a given patient
**Subject 03-008 weighed > 95 kg and did not belong in the high risk cohort but was assigned to the high risk cohort and received the low dose of DICo75V 18.75 mg in error. Although there were 10 other cases of incorrect assignment to a risk cohort, this is the only case where the error resulted in the patient receiving a lower dose.
Adapted Sponsor's Table 10-2; p. 56.

One patient (Subject 05-0130) who was randomized to the DIC075V group, was discontinued from the study due to a protocol violation (randomized after receiving an excluded medication and did not complete baseline assessments in prespecified order) attributed to other reason. Further examination of these protocol violations revealed that the majority should not have impacted on the trial's outcome.

Treatment Compliance:
Since this was an inpatient trial, site personnel were responsible for both the administration and monitoring of subject compliance with study medication. Table 17 summarizes the study drug exposure for Study DFC-005. The majority of subjects (55%) who participated in this trial received 4 doses of the study medication (44% in the placebo group, 43% in the DIC075V group and 47% in the ketorolac group). The majority of patients (120 out of 122 subjects) in the short term stay cohort received 4 doses of study medication with 97% of subjects in the placebo group, 98% of subjects in the DIC075V 37.5 mg group, and 100% of subjects in the ketorolac group receiving 4 doses of study medication. The overall percentages of patients in the non-high risk, high risk and higher weight short stay subcohorts who received 4 doses of study medications were also similar to that of the short stay cohort and were also similar across all 3 treatment groups. In terms of the long term stay cohort, the majority of patients (48%) received 12 doses of study medication as follows: 35% of subjects in the placebo group, 48% of subjects in the DIC075V 37.5 mg group, and 63% of subjects in the ketorolac group.

Table 17 - Summary of Study Drug Exposure for Study DFC-005 (ITT and Safety Populations)

Drug Exposure	Placebo (N =72)	DIC075V (N = 145)	Ketorolac (N = 60)	Total (N = 277)
Total Number of Doses Administered to Entire Safety Population:				
1	14 (19%)	6 (4%)	3 (5%)	23 (8%)
2	0	1 (1%)	1 (2%)	2 (1%)
3	5 (7%)	1 (1%)	0	6 (2%)
4	32 (44%)	62 (43%)	28 (47%)	122 (44%)
5	0	1 (1%)	0	1 (0%)
6	0	1 (1%)	0	1 (0%)
7	1 (1%)	3 (2%)	0	4 (1%)
8	0	9 (6%)	1 (2%)	10 (4%)
9	0	2 (1%)	0	2 (1%)
10	0	2 (1%)	0	2 (1%)
11	2 (3%)	2 (1%)	1(2%)	5 (2%)
12	14 (19%)	40 (28%)	20 (33%)	74 (27%)
Subjects Receiving ≥ 13 Doses	4 (6%)	15 (10%)	6 (10%)	25 (9%)

Adapted Sponsor's Table 12.1 and 14.3.1; p. 92 and 1356-68.

Further examination of these data by subcohort revealed that 60% of the non-high risk long term stay patients had received 12 doses of study medication (47% subjects in the placebo group, 63% of subjects in the DIC075V 37.5 mg group, and 70% of subjects in the ketorolac group) however, the overall percentages of patients who received a total of 12 doses of study medication were lower in both the high risk (37%) and higher weight (50%) subcohorts of the long term stay group (high risk: 28% subjects in the placebo group, 34% of subjects in the DIC075V group receiving 18.75 mg, and 53% of subjects in the ketorolac group; higher weight: 29% subjects in the placebo group, 50% of subjects in the DIC075V 50 mg group, and 71% of subjects in the ketorolac group).

Demographics:

Table 18 summarizes the demographic characteristics of the ITT population who participated in this trial. The subjects who participated in this trial were overwhelmingly male (64%) and Caucasian (92%) and had a mean age of 55 years. Overall mean weight was 88 kg and mean height was 169 inches. The baseline demographics were generally well balanced between the four study arms.

Table 18 – Tabular Summary of Demographic and Baseline Characteristics of Subjects in Study DFC-005 (ITT Population)

Demographic and Baseline Characteristic	Placebo (N=72) n (%)	DIC075V (N=145) n (%)	Ketorolac (N=60) n (%)	Total (N=277) n (%)
Age (yrs.):				
Mean (SD)	55 yrs. (16)	56 yrs. (14)	55 yrs. (16)	55 yrs. (15)
Range	(19, 84)	(19, 81)	(21, 80)	(19,84)
Race:				
Caucasian	68 (94%)	134 (92%)	53 (88%)	255 (92%)
Black	4 (6%)	9 (6%)	3 (5%)	16 (6%)
Asian	0	0	1 (2%)	1 (0%)
Other	0	2 (1%)	3 (5%)	5 (2%)
Gender:				
Male	46 (645)	92 (63%)	40 (67%)	178 (64%)
Female	26 (36%)	53 (37%)	20 (33%)	99 (36%)
Height (cm):				
Mean (SD)	168 (10)	169 (10)	170 (11)	169 (11)
Range	(150, 195)	(147, 193)	(154, 210)	(147, 210)
Weight (kg):				
Mean (SD)	87 (23)	89 (22)	87 (19)	88 (21)
Range	(48, 138)	(45, 143)	(53, 136)	(45, 143)
Risk Cohort:				
Non-High Risk	32 (44%)	63 (43%)	28 (47%)	123 (44%)
High risk	24 (33%)	46 (32%)	18 (30%)	88 (32%)
Higher Weight	16 (22%)	36 (25%)	14 (23%)	66 (24%)
Risk Category:				
Age Risk	23 (32%)	42 (29%)	17 (28%)	82 (30%)
<50 kg	1 (1%)	5 (3%)	0	6 (2%)
Renal Impairment	0	1 (1%)	0	1 (0%)
NSAID Risk	0	0	1 (2%)	1 (0%)
Hepatic Impairment	1 (1%)	3 (2%)	0	4 (1%)
Pugh's Modification of Child's Classification A:				
Mean (SD)	5.0 (0.17)	5.0 (0.25)	5.0 (0.0)	5.0 (0.2)
Range	(5, 6)	(5, 7)	(5, 5)	(5, 7)
Length of Stay:				
Short Term (≤ 24 hrs)	32 (44%)	62 (43%)	28 (47%)	122 (44%)
Long Term (>24 hrs)	40 (56%)	83 (57%)	32 (53%)	155 (56%)

SD = Standard Deviation; NSAID = Nonsteroidal anti-inflammatory drug
Modified Sponsor's Table 114.1.2.1; p. 145-47.

Since this was a post-surgical analgesia trial, a variety of surgical factors that could have potentially impacted the study's results were also examined. Table 19 is a tabular summary of subjects' baseline surgical procedure information. Examination of these data showed the incidences of the different types of orthopedic surgery was comparable across the 3 treatment groups. The mean duration of procedure was similar for all 3

treatment groups (59 minutes; range: 10-172 minutes) as was the duration of anesthesia (91 minutes; range: 13 to 221 minutes). The types of anesthesia technique used prior to study entry were similar across all 3 treatment groups. The mean time from end of surgery to first dose of study medication was lower for the ketorolac group (142 minutes) as compared to the DIC075V 37.5 mg group (150 minutes), placebo group (154 minutes). Based on these data, the study population that participated in this trial was reasonably balanced across study arms in terms of baseline surgical procedure and other surgical factors.

Table 19 – Baseline Surgical Procedure for Subjects in Study DFC-005 (ITT Population)

	Placebo N (%)	DIC075V N (%)	Ketorolac N (%)	Total N (%)
Surgical Procedure:				
Bunionectomy/Foot Bone	23 (32%)	46 (32%)	20 (33%)	89 (32%)
Knee Replacement	22 (31%)	38 (26%)	16 (27%)	76 (27%)
Knee Surgery Other	6 (8%)	23 (16%)	5 (8%)	34 (12%)
Hip Replacement	7 (10%)	19 (13%)	6 (10%)	32 (12%)
Spine Surgery	5 (7%)	4 (3%)	2 (3%)	11 (4%)
Lower Extremity Soft Tissue Excision/Repair	3 (4%)	6 (4%)	2 (3%)	11 (4%)
Shoulder Surgery Other	2 (3%)	3 (2%)	5 (8%)	10 (4%)
Ankle Surgery	2 (3%)	3 (2%)	2 (3%)	7 (3%)
Duration of Surgery (min)[1]:				
Mean (SD)	60 (31)	59 (33)	56 (29)	59 (32)
Range	(13, 172)	(10, 164)	(14, 147)	(10,172)
Duration of Anesthesia (min):				
Mean (SD)	93 (48)	91 (48)	89 (44)	91 (47)
Range	(13, 221)	(14, 218)	(24, 196)	(13, 221)
Anesthesia Technique Used[2]:				
General	46 (64%)	98 (68%)	44 (73%)	188 (68%)
Neuraxial	24 (33%)	48 (33%)	19 (32%)	91 (33%)
Regional	15 (21%)	29 (20%)	12 (20%)	56 (20%)
Time from End of Surgery to First Study Medication (min):				
Mean (SD)	154 (80)	150 (80)	142 (86)	149 (81)
Range	(17, 376)	(14, 396)	(22, 305)	(14, 396)

SD = standard deviation
[1]Duration of surgery is the time from first surgical incision to end of skin closure
[2]Subjects may have more than one anesthesia technique or class of anesthetic agent

In this trial, subjects' pain was assessed via a 100 mm visual analogue scale (VAS). Of the 277 randomized patients who comprised the ITT population, 57% reported having baseline pain of moderate intensity (defined as pain $\geq$ 50 mm < 70 mm), while the remaining 43% reported having severe baseline pain (defined as $\geq$ 70 mm) . As shown in Table 20, the mean baseline pain intensity for the intent-to-treat population in this study was 69 mm (range: 50-100 mm) and was similar across the 3 treatment groups. Mean baseline pain was also comparable for the non-high risk (71 mm), high risk (68

mm) and higher-weight (68 mm) cohorts. Thus, the patients in this trial had moderate to severe pain and could potentially show a response to study therapy.

Table 20 – Summary Table of Baseline Pain Intensity by Treatment Group for Subjects in Study DFC-005 (ITT Population)

Parameter	Placebo (N =72)	DIC075V (N = 145)	Ketorolac (N = 60)	Total (N = 277)
Baseline Pain Intensity (100 mm):				
Mean (SD)	67 (13)	70 (14)	72 (15)	69 (14)
Range	(50, 100)	(50, 100)	(50, 100)	(50, 100)

SD= standard deviation
Modified Sponsor' Table 11-4; p. 62.

Efficacy

Primary Efficacy Results

In DFC-005, the prespecified primary efficacy endpoint was the sum of the pain intensity difference (SPID) over 0-24, 0-48, 0-72, 0-96 and 0-120 hours. In order to control for multiplicity, a sequential, closed testing procedure was to have been used in conducting this analysis as follows: 0-24 hours, 0-48 hours, 0-72 hours, 0-98 hours, and 0-120 hours. Table 21 shows that the mean SPID scores for both the DIC075V 37.5 mg and ketorolac active comparator groups were significantly higher as compared to placebo group at each of these time intervals ($p<0.0001$).

Table 21 – Tabular Summary of Pain Intensity Differences (SPID) [mm·hours] over 0-24, 0-48, 0-72, 0-96, and 0-120 Hours for Subjects in Study DFC-005 (ITT Population)

SPID (mm·hrs) Time Interval	Placebo (N =72)	DIC075V (N = 145)	Ketorolac (N = 60)
0-24 hrs:			
Mean (SD)	28.0 (428)	577 (571)	563 (586)
P-value[a]		<0.0001[b]	<0.0001[b]
95% CI		(374, 664)[c]	(281, 635)[d]
0-48 hrs:			
Mean (SD)	400 (950)	1528 (1139)	1372 (1152)
P-value[a]		<0.0001[b]	<0.0001[b]
95% CI		(776, 1357)[c]	(454, 1163)[d]
0-72 hrs:			
Mean (SD)	837 (1564)	2592 (17310	2312 (1744)
P-value[a]		<0.0001[b]	<0.0001[b]
95% CI		(1213, 2111)[c]	(674, 1770)[d]
0-96 hrs:			
Mean (SD)	1338 (2262)	3711 (2347)	3332 (2356)
P-value[a]		<0.0001[b]	<0.0001[b]
95% CI		(1623, 2865)[c]	(888, 2405)[d]
0-120 hrs:			
Mean (SD)	1841(2988)	4836 (2989)	4359 (3001)
P-value[a]		<0.0001[b]	<0.0001[b]
95% CI		(2028, 3632)[c]	(1099, 3057)[d]

SD=standard deviation; CI = confidence interval
[a]P=0.001 for overall treatment effect
[b]P-value from linear contrast comparing each active treatment versus placebo
[c]95% confidence interval for difference between DIC075 IV and placebo
[d]95% confidence interval for difference between etorolac and placebo
Modified Sponsor's Table 11-5; p. 64.

Secondary Efficacy Endpoints

There were multiple secondary endpoints evaluated in DFC-005. They are listed with their results as described by the Applicant in Table 22 below:

Table 22 - Tabular Summary of Secondary Endpoint Analyses for Study DFC-005

Secondary Efficacy Variable	Comment	P-value
Pain Intensity Difference (PID) at each scheduled assessment	Statistically significant separation of DIC075V from placebo occurred at 10 minutes post administration of study drug and was maintained through 120 hours Statistically significant separation of ketorolac from placebo occurred at 30 minutes post administration of study drug and was maintained through 120 hours	DIC075V vs Placebo p = 0.0297 Ketorolac vs Placebo p = 0.0055
Proportion of Subjects Achieving ≥ 30% Reduction in Pain Intensity	81% of subjects achieved ≥ 30% reduction in pain intensity started at 15 minutes post administration of first dose DIC075V and maintained this level through 120 hours 75% of subjects achieved ≥ 30% reduction in pain intensity started at 45 minutes post administration of first dose ketorolac and maintained this level through 120 hours	DIC075V vs Placebo p = 0.0090 Ketorolac vs Placebo p = 0.0035
Total Pain Relief (TOTPAR) 0-24, 0-48, 0-72, 0-96, and 0-120 hours	Mean TOTPAR scores for the 0-24, 0-48, 0-72, 0-96, and 0-120 time intervals in this trial were significantly higher for both the DIC075V group and the ketorolac group as compared to the placebo group	DIC075V vs Placebo p <0.0001 at all time intervals Ketorolac vs Placebo p <0.0001 at all time intervals
Pain Relief (PR) at each scheduled assessment	Statistically significant separation of DIC075V from placebo occurred at 5 minutes post administration of study drug and was maintained through 120 hr. Statistically significant separation of ketorolac from placebo occurred at 30 minutes post administration of study drug and was maintained through 120 hr.	DIC075V vs Placebo p=0.0294 Ketorolac vs Placebo p=0.0055
Time to Perceptible Pain Relief (TPPR)	The median TPPR ranged from11.2 minutes in the DIC075V group, 15 minutes in the ketorolac group to 15.3 minutes in the placebo group.	DIC075V vs Placebo p = 0.0009 Ketorolac vs Placebo p = 0.0640
Time to Meaningful Pain Relief (TMPR)	The median TMPR ranged from 41.6 minutes in the DIC075V group, 42.5 minutes in the ketorolac group and was not estimatable in the placebo group.	DIC075V vs Placebo p <0.0001 Ketorolac vs Placebo p = 0.0019

Table 22 – Tabular Summary of Secondary Endpoint Analyses for Study DFC-005 (cont.)

Secondary Efficacy Variable	Comment	P-value
Time to First Rescue Medication (TTR)	The median TTR ranged from 3 hours 40 minutes in the DIC075V group, 2 hours and 17 minutes in the ketorolac group to 51 minutes in the placebo group	DIC075V vs Placebo p <0.0001 Ketorolac vs Placebo p <0.0001
Amount of Rescue Medication: 0-24 hours	Significantly lower amounts of rescue medication were used by patients in both the DIC075V and ketorolac groups as compared to the placebo group for all time points evaluated	DIC075V vs Placebo p <0.0001 Ketorolac vs Placebo p <0.0001
Frequency of Rescue Medication	Similar proportion of patients used rescue medication within the 48 hours of the treatment phase in both the ketorolac group (73%) and the DIC075V group (74%) which were both lower as compared to 92% patients in the placebo group.	DIC075V vs Placebo p <0.0001 Ketorolac vs Placebo p <0.0001
Patient Global Evaluation (PGE) 0-24 hours	80% of subjects in the DIC075V group and 80% of subjects in the ketorolac group indicated “good” or better on their PGE compared to 37% of placebo subjects	DIC075V vs Placebo p <0.0001 Ketorolac vs Placebo p = 0.0006
Patient Global Evaluation (PGE) 0-48 hours	88% of subjects in the DIC075V group and 96% of subjects in the ketorolac group indicated “good” or better on their PGE compared to 50% of placebo subjects	DIC075V vs Placebo p = 0.0011 Ketorolac vs Placebo p = 0.0641

Efficacy Conclusion:
Both DIC075V as well as ketorolac were shown to decrease pain intensity as evidenced by significantly higher mean SPID interval scores at 0-24, 0-48, 0-72, 0-96 and 0-120 hours for each of these treatment groups as compared to placebo. These results were supported by similarly significant outcomes observed in the analyses of a majority of the secondary endpoints such as the mean PID score, the mean TOTPAR score, the proportion of patients achieving $\geq$ 30% reduction in pain intensity, mean pain relief, TTR, frequency and amount of rescue medication, and PGE. In this trial the median TPPR for the ketorolac active comparator group and the placebo were similar at 15.0 and 15.3 minutes, respectively however, the estimated median TPPR for the DIC075V group occurred earlier at 11.2 minutes. Additionally, the estimated median TMPRs were similar for DIC075V (41.6 minutes) and ketorolac treatment groups (42.5 minutes) but could not be estimated for the placebo group since the majority of subjects in this group had failed to achieve meaningful pain relief by 6 hours. However, declaring statistical significance of the secondary endpoints evaluated in this trial using unadjusted p-values would be inappropriate since no multiplicity correction was planned in the protocol or implemented during the analyses of the secondary endpoints.

Study Number and Title: DCF-010 - An Open-Label, Multiple-Dose, Multiple-Day, Non-Randomized, Single-Arm Safety Study of Repeat-Doses of DIC075V in Patients with Acute Post-Operative Pain.

Dates Conducted: This trial was started on September 15, 2008 and completed on May 8, 2009.

Objectives:
Primary Objective:

- To assess the safety of DIC075 following IV administration of multiple doses over multiple days in patients with acute post-operative pain.

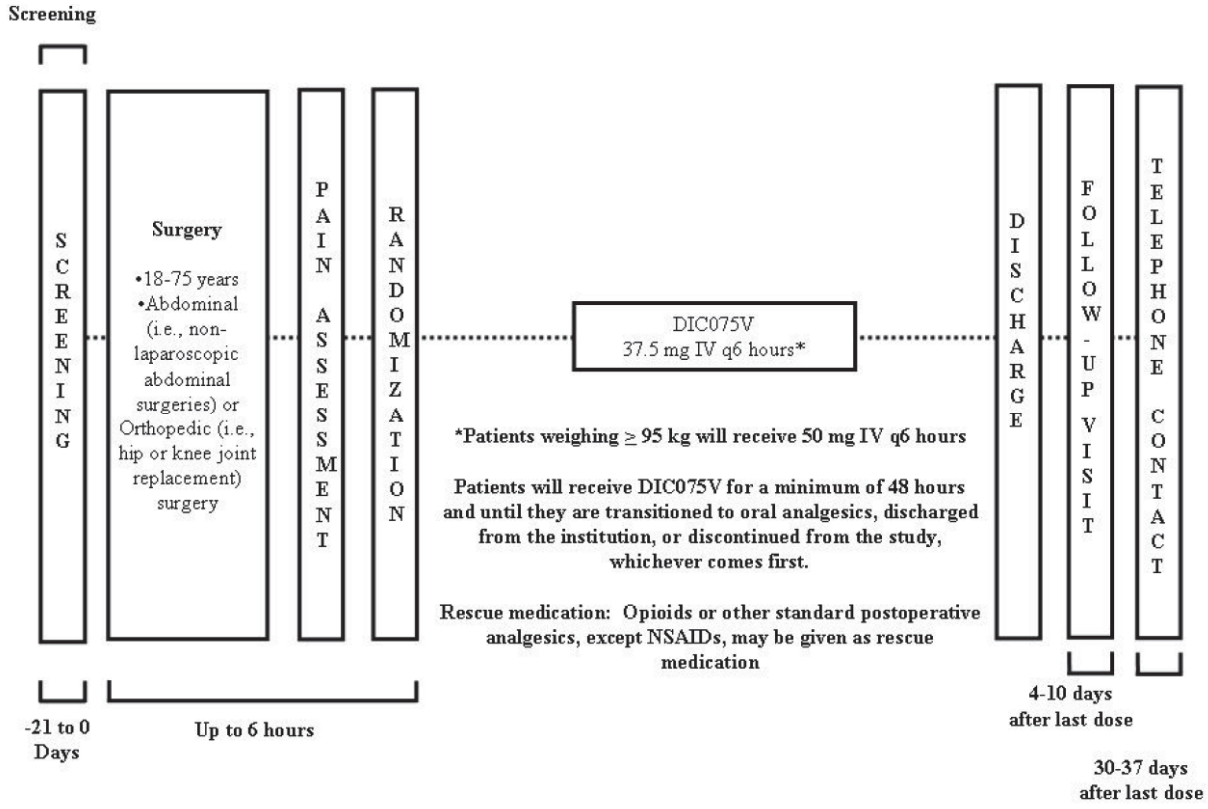
Study Design:
Study DFC-010 was to have been a 48-hour, multicenter, open-label, single-arm, Phase 3 trial to evaluate the safety of 37.5 mg DIC075V administered every 6 hours intravenously in patients with moderate to severe acute postoperative pain following abdominal or orthopedic surgery. A total enrollment of 700 subjects was planned. The overall duration of the trial was to have been 12 months from the time of the last patient's enrollment. The duration of participation for each subject from the time of initial screening to the completion of the study was to have been approximately 60 days.

Patients who had successfully completed the screening process and whose eligibility had been confirmed during the post-operative period were to have received DIC075V 37.5 mg IV every 6 hours while subjects who weighed $\geq$ 95 kg were to have received DIC075V 50 mg IV every 6 hours.

Baseline safety assessments were to have been completed immediately prior to the initial administration of DIC075. The protocol mandated that opioids or other standard postoperative analgesics with the exception of NSAIDs could have been given as rescue medication. Subjects were to have received DIC075V for a minimum of 48 hours and were to have continued taking it until they had been switched to oral analgesics, discharged from the hospital, or withdrew from the study. All patients were to have returned to the study clinic for 2 follow-up safety visits scheduled for 4-10 days and 30-37 days post discharge.

Figure 3 below is a schema of the protocol for DFC-010.

Figure 3 – Schema for Study DCF-010



Adapted Sponsor's Fig. 1; p. 5.

Major Inclusion Criteria:
Subjects were to have been men and women 18 years of age and older who met all of the following criteria:

1. Must have been scheduled within 3 weeks of screening visit to undergo abdominal (non-laparoscopic abdominal surgeries) or orthopedic (i.e., hip or knee joint replacement) surgery
2. Females of childbearing potential must have had a negative urine pregnancy test at screening and pre-surgery
3. Must have been in good health as determined by the Investigator on the basis of medical history and physical examination
4. Must not have had a history or evidence of significant cardiovascular, respiratory, gastrointestinal disease, or psychiatric disorders which significantly increased the risk of study participation

Exclusion Criteria:
Potential trial candidates were to have been prohibited from participating in this trial if any of the following criteria applied:

1. Hepatic insufficiency [Note: In order to permit entry of subjects with mild hepatic impairment defined as bilirubin value above normal range for the lab up to 2.5

mg/dL and the prothrombin time (PT) of no more 20% above the upper limit of normal for the lab was added via Protocol Amendment 1 dated July 15, 2008.]

2. Moderate or severe renal insufficiency (creatinine clearance <50 mg/ml) or end stage renal failure. (Note: Changed to 2.0 mg/dL via Protocol Amendment 1 dated July 15, 2008 and lowered to 1.9 mg/dL via Protocol Amendment 4 dated December 10, 2008.)
3. Females who were lactating
4. Known allergy or hypersensitivity to diclofenac, other NSAIDs or to any of the excipients of the study preparation
5. Known or suspected to have been abusing alcohol or drugs or had a history (within previous 12 months) of active alcohol or drug abuse
6. Required post-operative pain management by intra-operative or post-operative regional or multi-modal anesthesia (central or peripheral), including neural blockade with a long-acting local anesthetic
7. Had chronic pain conditions that would have interfered with their ability to have assessed post-operative pain and/or require chronic analgesic medication
8. Age > 75 years old
9. Exhibited signs or symptoms of clinically significant dehydration or hypovolemia
10. Had a history of uncontrolled active chronic disease; such as gastric erosion/ulceration or bleeding, moderate or severe renal impairment or cardiac failure
11. Recent history (≤ 6 months) of cardiovascular events (e.g., MI or stroke)
12. Had received any investigational medication or participated in a clinical trial within 30 days prior to administration of study drug or had been previously admitted to this trial
13. Had aspirin sensitivity, severe asthma (uncontrolled), or who required systemic steroids within the last 6 months

Treatment:
Patients were to have started receiving DIC075V 37.5 mg IV bolus every 6 hours or 50 mg via IV bolus every 6 hours if they weighed over 95 kg as soon as they were deemed clinically stable during the immediate post-operative period as their primary, around-the-clock, post-operative analgesic.

Removal of Patients from Treatment or Assessment:
Patients were to have been discontinued from this trial if they withdrew consent, experienced an adverse event, were noncompliant, incurred a protocol violation, due to an administrative reason, or in the subject's best interest as per the investigator. The protocol stipulated that subjects were free to discontinue study participation for any reason at any time over the course of the trial.

Rescue Medication:
Although the protocol prohibited the use of NSAIDs as rescue medication, opioids or other standard postoperative analgesics were to have been permitted as rescue

medication. These medications were to have been dosed and administered as per the study site's standard of care.

Concomitant Therapies:
Subjects were to have received standard post-operative care as per the participating clinical site. With the exception of NSAIDs, the protocol permitted the unrestricted use of concomitant medications. Information regarding analgesic use during the 30-37 day safety follow up period following the completion of treatment with DIC075V was to have captured and recorded in patients' CRFs.

Efficacy and Safety Assessments:
Although efficacy assessments for pain intensity and pain relief were not conducted in this trial, patients were to have completed a 5-point global evaluation at study discharge. Safety was to have been assessed by monitoring for adverse events, lab tests, ECG, thrombophlebitis assessment, wound assessment, physical examination, vital signs and concomitant therapies.

Study Visit Schedule:
The following Table 23 is a tabular flow chart of the scheduled study observations and procedures:

Table 23 - Schedule of Procedures and Evaluations for Study DCF-010

	Study Visit or Follow-up						
Assessment or Procedure	Screening Evaluation (Day-21 to 0)	Admission (Pre-surgery)	Baseline[1]	DIC075V Treatment[2]	Study Discharge/ Early Termination	Safety Follow-up Visit (Day 4–10 Post Last Dose)	Safety Follow-up Telephone Call (Day 30-37 Post Last Dose)
Informed Consent	X						
Eligibility Criteria	X	X					
Demographics	X						
Physical Examination	X					X	
Medical History	X						
Vital Signs	X		X		X	X	
12-Lead Electrocardiogram	X		X		X		
Urine Pregnancy Test	X	X					
Urine Alcohol and Drug Screen	X						
Clinical Laboratory Tests[3]	X		X		X		
Concomitant Therapies	X	X	X	X	X	X	X
Study Drug				X			
Patient Global Evaluation					X		
Wound Assessment					X	X	
Thrombophlebitis Assessment			X		X		
Adverse Events		X	X	X	X	X	X

[1] Baseline – immediately prior to starting DIC075V

[2] DIC075V treatments began immediately following completion of Baseline procedures and continued every 6 hours until the subject was transitioned to oral analgesics, discharged from the institution, received a maximum of 5 days of treatment with DIC075V, or discontinued from the study, whichever occurred first.

[3]

Adapted Sponsor's Table 5.1; p. 15.

Statistical Design, Definitions of Analyzed Populations and Analyses Plan:
Since this trial was an open label study, no sample size calculations were performed.

The safety population for this trial was defined as all patients who had received DIC075V and had completed at least one safety assessment. In terms of the safety analyses, the protocol specified that descriptive statistics based on tabulated summaries were to have been used for each of the following: adverse events, lab tests, ECGs, vital signs, physical exams, thrombophlebitis, wound healing data and concomitant therapies. Patient global evaluation scores were to have been also statistically summarized and presented in tabular format.

Study Conduct:
Protocol Amendments –
Listed below are the 4 protocol amendments made to Study DFC-010.
1. Amendment 1 (implemented on July 15, 2008)
The following modifications and clarifications were made to the study conduct:

- Subject population was to have been expanded to include the following:
  - Individuals ages 18 to 85 years old
  - Individuals with mild hepatic impairment (defined as subjects with bilirubin value above normal range for the lab test up to 2.5 mg/dL and prothrombin time (PT) of no more than 20% above the upper limit of normal for the lab test
- Instead of using the creatinine clearance calculated via the Cockcroft-Gault equation, the definition of mild renal impairment was changed as follows: subjects with serum creatinine values above the normal range for the lab test up to 2.0 mg/dL
- Maximum duration of treatment with DIC075V was to have been limited to 5 days
- Dosing and administration of DIC075V was changed as follows:
  - Subjects were to have received 37.5 mg IV bolus every 6 hours however
  - Subjects who weighed $\geq$ 95 kg were to have received 50 mg IV bolus every 6 hours
  - Subjects with impaired renal or hepatic function were to have received 18.75 mg IV bolus every 6 hours

2. Amendment 2 (implemented on July 28, 2008)
Editorial and minor clarifications to study entry criteria and administrative procedures were made to the protocol.

3. Amendment 3 (implemented on September 16, 2008)
In addition to editorial changes, the following clarifications and major modifications were made to the study conduct:

- Subject population was to have been expanded to include the following:
  - Individuals with laparoscopic-assisted abdominal surgery or any other surgical procedures where there was anticipated acute post-surgical pain requiring the administration of multiple doses (minimum 8 consecutive doses) of IV NSAIDs for multiple days (minimum of 48 hours)

- Dosing and administration of DIC075V was changed as follows:
    - Subjects with more than one risk factor (e.g., weighing
- Deletion of following exclusion criteria:
    - Subjects requiring postoperative pain management by intra-operative or post-operative regional or multi modal anesthesia (central or peripheral) including neural blockade with a long acting local anesthetic
- Addition of the following exclusion criteria:
    - Subjects undergoing coronary artery bypass graft (CABG) surgery
    - Subjects who received an IV NSAID intra-operatively
- Clinically significant abnormal EKGs were to be read by a centrally located cardiologist

4. Amendment 4 (implemented on December 10, 2008)
In addition to editorial changes, the following clarifications and major modifications were made to the study conduct:

- Number of subjects to be enrolled was to have been increased to 1000 patients in order to ensure approximately 850 subjects completed a minimum of 8 consecutive doses over 42 hours for evaluation
- Required minimum duration of treatment of 48 hours was to have been replaced with a minimum of 8 consecutive doses over multiple days
- Exclusion criteria were revised as follows:
    - Subjects who underwent CABG with full heparization were not permitted to enter the study
    - Definition of renal impairment was updated to serum creatinine values greater than the normal range for the lab up to 1.9 mg/dL at screening
    - Subjects who received warfarin within one week of surgery or who were expected to receive warfarin before all study medication dosing had been completed were not eligible to enter the study
- Concomitant medications section was updated as follows:
    - Treatment with low molecular weight heparin (LMWH) during the study is permitted. Treatment with warfarin one week prior to surgery and during the study medication dosing period is prohibited. An INR or PT is required within 48 hours of surgery for any subject who has been on warfarin therapy within 2 weeks of surgery.

RESULTS:

Disposition of Subjects:
A total of 971 subjects from 52 clinical sites in the United States were enrolled into the two treatment groups as follows: 634 patients in the DIC075V 37.5 mg group and 335 patients in the DIC075V 50 mg group (based on weight >95 kg). Table 24 below,

summarizes the disposition of the patients who participated in this trial. Overall, 97% of subjects completed the study with comparable rates of completion in the two treatment groups. More patients withdrew prematurely due to lost to follow up (1)%), followed by withdrawing consent (0.5%), noncompliance with study procedures (0.5%), other (0.5%) and adverse event (0.3%).

Table 24 – Disposition of Subjects Who Participated in Study DFC-010 (Safety Population)

Disposition	DIC075V 37.5 mg N (%)	DIC075V 50 mg N (%)	Total DIC075V N (%)
Enrolled:	634 (100%)	335 (100%)	971 (100%)
Completed the Study:	618 (98%)	323 (96%)	943 (97%)
Withdrew From the Study:	16 (3%)	12 (4%)	28 (3%)
Reason for Withdrawal:			
Subject Withdrew Consent	4 (0.6%)	1 (0.3%)	5 (0.5%)
Adverse event	1 (0.2%)	2 (0.6%)	3 (0.3%)
Lost to Follow-Up	7 (1.1%)	3 (0.9%)	10 (1%)
Noncompliance with Study Procedures	2 (0.3%)	3 (0.9%)	5 (0.5%)
Other	2 (0.3%)	3 (0.9%)	5 (0.5%)

Adapted Sponsor's Table 14.1.1.1; p.

Treatment Compliance and Drug Exposure:

Since this was an inpatient trial, site personnel were responsible for both the administration and monitoring of subject compliance with study medication. Table 25 summarizes the drug exposure in Study DFC-010. The mean number of doses study medication administered over the course of this trial was 9 (range: 1 to 21 doses). The majority of the patients (59%) received 8 doses of study medication. A higher percentage of patients (61%) assigned to the 37.5 mg dose as compared to 54% of the higher weight patients assigned to the 50 mg dose received 8 doses of study medication.

Table 25 – Summary of Study Drug Exposure for Study DFC-010 (Safety Population)

Drug Exposure	DIC075V 18.75 mg (N=2)	DIC075V 37.5 mg (N=634)	DIC075V 50 mg (N=335)	Total DIC075V (N=971)
Summary of Doses Administered:				
Mean (SD)	9 (1)	9 (3)	9 (3)	9 (3)
Median	9	8	8	8
Range	(8, 9)	(1, 21)	(1, 20)	(1, 21)
Total Number of Doses Administered:				
1	0	5 (1%)	3 (1%)	8 (1%)
2	0	2 (0%)	3 (1%)	5 (1%)
3	0	5 (1%)	4 (1%)	9 (1%)
4	0	11 (2%)	8 (2%)	19 (2%)
5	0	10 (2%)	4 (1%)	14 (1%)
6	0	7 (1%)	2 (1%)	9 (1%)
7	0	10 (2%)	4 (1%)	14 (1%)
8	1 (50%)	387 (61%)	182 (54%)	570 (59%)
9	1 (50%)	47 (7%)	25 (8%)	73 (8%)
10	0	5 (1%)	8 (2%)	13 (1%)
11	0	25 (4%)	16 (5%)	41 (4%)
12	0	45 (7%)	48 (14%)	93 (10%)
13	0	16 (3%)	8 (2%)	24 (3%)
14	0	8 (1%)	1 (0%)	9 (1%)
15	0	14 (2%)	1 (0%)	15 (2%)
16	0	14 (2%)	9 (3%)	23 (2%)
17	0	8 (1%)	3 (1%)	11 (1%)
18	0	1 (0%)	0	1 (0% .)
19	0	3 1%)	3 (1%)	6 (1%)
20	0	10 (2%)	3 (1%)	13 (1%)
21	0	1 (0%)	0	1 (0%)

Adapted Sponsor's Table 14.1.4; p.887-888.

Demographics:

Table 26 summarizes the demographic characteristics of the population who participated in this trial. Overall, the subjects who participated in this study were predominantly female (64%) and Caucasian (87%), with a mean age of 59 years and had undergone orthopedic surgery (70%). Overall mean weight was 89 kg and mean height was 168 cm. Thirty-six percent (36%) weighed more than 95 kgs. A total of 57 (6%) patients with renal impairment and 31 (3%) patients with hepatic impairment also participated in this trial.

Table 26 – Demographic and Baseline Characteristics of Study DFC-010 (Safety Population)

Baseline and Demographic Characteristics	DIC075V 37.5 mg (N=634)	DIC075V 50 mg (N=335)	Total DIC075V (N=971)
Age (yrs.):			
Mean (SD)	60 (14)	57 (12)	59 (13)
Range	(18, 87)	(23, 83)	(18, 87)
Age Group:			
< 65 years	366 (58%)	236 (70%)	604 (62%)
≥ 65 years	268 (42%)	99 (30%)	367 (39%)
Race:			
Caucasian	554 (87%)	285 (85%)	840 (87%)
Black	60 (10%)	42 (13%)	102 (11%)
Asian	9 (1%)	1 (0.3%)	10 (1%)
Other	11 (2%)	7 (2%)	19 (2%)
Gender:			
Male	175 (28%)	179 (53%)	354 (37%)
Female	459 (72%)	156 (47%)	617 (64%)
Height (cm):			
Mean (SD)	166 (9)	173 (10)	168 (11)
Range	(107, 191	(142, 196)	(107,196)
Weight (kg):			
Mean (SD)	77 (12)	112 (14)	89 (21)
Range	(44, 134)	(95, 196)	(44,196)
Weight Group:			
< 95 kg	620 (99%)	1 (0%)	623 (64%)
≥ 95 kg	14 (2%)	334 (100%)	348 (36%)
Body Mass Index (kg/m^2):			
Mean (SD)	28 (5)	38 (6)	31 (7)
Range	(18, 67)	(27, 66)	(18, 67)
Renal Impairment:			
Yes	34 (5%)	23 (7%)	57 (6%)
No	599 (95%)	311 (93%)	912 (94%)
Missing	1 (0%)	1 (0%)	2 (0%)
Hepatic Impairment:			
Yes	22 (4%)	8 (2%)	31 (3%)
No	611 (96%)	326 (97%)	938 (97%)
Missing	1 (0%)	1 (0%)	2 (0%)
Type of Surgery:			
Orthopedic	409 (65%)	266 (79%)	676 (70%)
Abdominal	224 (35%)	68 (20%)	293 (30%)
Other	1 (0%)	1 (0%)	2 (0%)

Adapted Sponsor's table 14.1.3; p.

Efficacy assessments for pain intensity and pain relief were not conducted in this trial however, patients were to have completed a 5-point global evaluation at study discharge. Although Study DFC-010 was an uncontrolled, open-label study, the results

of this analysis are presented in Table 27 for completeness. A total of 958 out of the 971 (99%) subjects completed this evaluation, out of which 932 (97%) patients rated their experience with DIC075V as good (10%), very good (29%), or excellent (57%).

Table 27 – Summary of Patient Global Evaluations for Study DFC-010 (Safety Population)

Rating	DIC075V (N=971)
Total Responses:	**958 (99%)**
Excellent	556 (57%)
Very Good	283 (29%)
Good	93 (10%)
Fair	16 (2%)
Poor	10 (1%)

Modified Sponsor's Table 11-3, P. 64.

The results from the safety analyses for this trial will be discussed in Section 7.

6 Review of Efficacy

Efficacy Summary

The clinical data submitted in support of DIC075V for the management of acute moderate to severe pain was generated from two Phase 3 trials, DFC-004 and 005. These were multicenter, randomized, double-blind, placebo-and active-controlled (ketorolac tromethamine), parallel group dose comparison trials in 625 patients with acute moderate to severe postoperative pain following abdominal, pelvic or orthopedic surgeries. DFC-004 evaluated the efficacy of 18.75 mg and 37.5 mg of DIC075V administered as IV bolus injections every 6 hours over 48 hours while DFC-005 evaluated the efficacy of DIC075V over 24-120 hours but included dose adjustments in subgroup populations based on weight (> 95 kg) and risk for NSAID toxicity. The primary objective of these trials was to determine the efficacy of DIC075V versus placebo and the active comparator in decreasing pain intensity in a multidose setting as assessed by the primary efficacy endpoint the sum of the pain intensity difference (SPID) over 0-48 hours. In both of these trials, a greater proportion of patients treated with DIC075V and ketorolac achieved higher mean SPID interval scores at 0-48 hours as compared to placebo (DFC-004: DIC075V 18.75 mg: 1304 mm·hours; DIC075V 37.5 mg: 1574 mm·hours; versus ketorolac 30 mg: 1583 mm·hours and placebo: 936 mm·hours) (DFC-005: DIC075V: 1528 mm·hours, ketorolac: 1372 mm·hours and placebo: 400 mm·hours). The difference between the DIC075V groups and the ketorolac groups on comparison with the placebo groups were statistically significant for both trials (DFC-004: DIC075V 18.75 mg versus placebo: p=0.0316; DIC075V 37.5 mg

versus placebo: p=0.0001; ketorolac versus placebo: p<0.0001) (DFC-005: DIC075V versus placebo: p<0.0001; ketorolac versus placebo: p<0.0001). The significance of the results for the 18.75 mg DIC075V treatment group in DFC-004 were statistically questionable since no correction for multiple comparisons across doses was applied during their analyses. Additional post hoc analyses of the primary endpoint performed by the statistical reviewer that corrected for multiplicity resulted in a loss of significance for the outcome of the DIC075V 18.75 mg dose group again raising statistical questions regarding its effectiveness. However, the 37.5 mg dose of DIC075V continued to demonstrate statistical significance and was found to be clinically more efficacious than the 18.75 mg dose of the drug. Due to concerns regarding the potential introduction of bias during the imputation of missing data for the short term stay population during the analysis of the primary efficacy endpoint in DFC-005, the statistical reviewer reanalyzed the primary endpoint using data from the long term stay population in order to minimize this risk. The results of these post hoc analyses were qualitatively similar to that of the original analyses.

The results of the primary efficacy endpoints for DFC-004 and -005 were supported by similarly significant outcomes observed in the analyses of a majority of the secondary endpoints evaluated at the 48 hour time interval for both trials such as the mean PID score, the mean TOTPAR score, the proportion of patients achieving $\geq$ 30% reduction in pain intensity, mean pain relief, TTR, frequency and amount of rescue medication, and PGE. In DFC-004 the median TPPRs were shown to be similar for all 4 treatment groups with the median TMPRs for the 37.5 mg DIC075V group and the ketorolac 30 mg group occurring earlier at 41 and 43 minutes, respectively, as compared to the median TMPRs for the 18.75 mg DIC075V group (61 minutes) and the placebo group (126 minutes). However, the 18.75 mg dose group of DIC075V performed consistently worse than the 37.5 mg dose group of DIC075V or ketorolac on the majority of these secondary endpoints (except for the TTR and PGE 0-48 hours). In DFC-005 the median TPPR for the ketorolac active comparator group and the placebo were similar at 15.0 and 15.3 minutes, respectively however, the estimated median TPPR for the DIC075V group occurred earlier at 11.2 minutes. Additionally, the estimated median TMPRs were similar for DIC075V (41.6 minutes) and ketorolac treatment groups (42.5 minutes) but could not be estimated for the placebo group since the majority of subjects in this group had failed to achieve meaningful pain relief by 6 hours. However, declaring statistical significance of the secondary endpoints evaluated in these trials using unadjusted p-values would be inappropriate since no multiplicity correction was planned in the protocols or implemented during the analyses of the secondary endpoints.

(b) (4)

6.1 Indication

Management of acute moderate to severe postoperative pain

6.1.1 Methods

Data from two studies, DFC-004 and 005, were the basis for assessing the efficacy of DIC075V. These were multicenter, randomized, double-blind, placebo- and active controlled, parallel group, comparative trials in patients with moderate to severe acute postoperative pain. DFC-004 assessed the efficacy of two doses (i.e., 18.75 mg and 37.5 mg) of DIC075V over 48 hours in 348 patients who had undergone either abdominal or pelvic surgery. DCF-005 assessed the efficacy of 37.5 mg of DIC075V over 24-120 hours in 277 patients who had undergone a variety of orthopedic surgical procedures and included dose adjustment in subgroup populations based on weight and operative risk.

Analyses of pertinent subgroups were also conducted. All primary and secondary analyses were confirmed by the FDA's statistical reviewer. The designs of these studies were discussed in Section 5.3.

6.1.2 Demographics

The baseline demographic characteristics and surgical procedure information for the patient population enrolled in DFC-004 were comparable for all 4 treatment groups with respect to age, race, gender, height, weight, duration of surgical procedure, incision length, and types of intra-operative anesthetics and analgesics administered prior to trial entry. Imbalances observed in the 4 treatment groups regarding the types of surgical procedures patients underwent prior to study entry should not have impacted on the trial's results. The baseline demographic characteristics and surgical procedure information for subjects who enrolled in DFC-005 were similarly well balanced between the four treatment groups. These data are discussed in detail in Section 5.3.

6.1.3 Subject Disposition

As discussed in Section 5.3, a total of 265 (80%) of patients were able to complete study DFC-004 as follows: 85% in the DIC075V 18.75 mg group, 82% in the ketorolac 30 mg group, 78% in the DIC075V 37.5 mg group, and 75% in the placebo group. The majority of subjects who prematurely withdrew from this trial did so due to lack of efficacy (8%), followed by subject request (4%), lost to follow-up (3%), adverse event

(3%), noncompliance (1%), or other reason (1%). Rate of withdrawal due to lack of efficacy was comparable across the 4 treatment groups in DFC-004, but more patients were withdrawn from this study at their request in the placebo group (11%) as compared to the 3 other treatment groups (DIC075V 18.75 mg: 1%; DIC075V 37.5 mg: 1%; and ketorolac 30 mg: 2%).

Overall, 86% of patients were able to complete study DFC-005. The highest rate of study completion was in the ketorolac group (93%) followed by the DIC075V treatment group (91%) and the placebo group (71%). More patients withdrew prematurely due to the lack of efficacy (11%) as compared to subject request (4%), adverse event (3%), lost to follow-up (3%), noncompliance (1%), or other reason (1%). The placebo group had the highest rate of withdrawal (29%) due to lack of efficacy as compared to the ketorolac active comparator group (7%) and the DIC075V group (4%).

6.1.4 Analysis of Primary Endpoint

DFC-004 and -005 were adequate and well-controlled trials by virtue of their double-blind, randomized, controlled design. They were intended to evaluate the efficacy and safety of DIC075V in the management of moderate to severe acute post-operative pain in patients who had undergone a variety of abdominal, pelvic and orthopedic surgical procedures. Thus, the results from these trials would be generally applicable to the management of acute pain in the immediate post-operative setting. The use of placebo controlled-studies was appropriate for assessing this drug's efficacy since the study endpoints are subjective in nature (i.e., pain relief). It was appropriate to include the use of rescue medication for intolerable pain since these were placebo-controlled trials and both studies evaluated a lower dose of DIC075V (i.e., 18.75 mg) than traditionally used for systemic analgesic relief when diclofenac sodium is administered as an oral formulation. The short duration of therapy (i.e., 24-120 hours) was also appropriate in view of the drug's intended use as a paranterally administered, non-opiate analgesic during the immediate post-operative period prior to transitioning to oral analgesics.

The primary efficacy endpoint for these trials was the time-interval weighted sum of pain intensity difference (SPID) for 0-48 hours in DFC-004 and for 0-24, 0-48, 0-72, 0-96, and 0-120 hours in DFC-005. The SPID was calculated from pain intensity data collected over the course of study treatment assessed via a 100 mm visual analogue scale (VAS). Both the SPID and VAS have been validated for use as an efficacy endpoint and pain assessment tool, respectively, in analgesic trials. They also have been accepted by the agency for the evaluation of outcomes in pain studies. Higher SPID scores signify greater improvement in pain intensity.

In DFC-004, the mean baseline pain scores were similar for all four treatment groups (range: 67 to 71 mm). As shown in Table 28, higher mean SPID scores were achieved by patients in both the DIC075V 18.75 mg (1304 mm·hours) and 37.5 mg (1576

mm·hours) treatment groups as well as patients in the ketorolac 30 mg active comparator group (1583 mm·hours) as compared to patients in the placebo group (936 mm·hours). The differences between each of the three treatment groups and the placebo group were statistically significant (DIC075V 18.75 mg vs placebo: p=0.0316; DIC075V 37.5 mg vs placebo: p = 0.0001; and ketorolac 30 mg vs placebo: p<0.0001).

Table 28 – Sum of the Pain Intensity Differences (SPID) Over 0-48 Hours for Study DFC-004 (ITT Population)

SPID (mm.hours)	Placebo (N = 76)	DIC075V		Ketorolac 30 mg (N=82)
		18.75 mg (N = 86)	37.5 mg (N = 87)	
Mean	936	1304	1574	1583
Standard Deviation	1077	1030	1060	983
P-value		p = 0.0316[a]	p = 0.0001[a]	p <0.0001[a]

[a]P-value from linear contrast comparing each active treatment versus placebo
Modified Sponsor's Table 14.2.1.1a; p 182.

Since the statistical analysis plan (SAP) for this trial did not prespecify an adjustment for multiple comparisons across doses for the primary endpoint, concerns regarding multiplicity issues were raised. In view of these multiplicity concerns, the agency's statistical reviewer reanalyzed the primary endpoint using two common approaches to multiplicity: a Bonferroni correction and sequentially testing the high then the low dose of DIC075V versus placebo. The results from these post hoc analyses supported the findings of the original analysis for the DIC075V 37.5 mg treatment group. However, the 18.5 mg dose of DIC075V trended but was not significant after Bonferroni adjustment (p=0.063). (Refer to Dr. Norton's statistical review of this application for additional information regarding this analysis.)

In DFC-005, the primary efficacy endpoint was the SPID over 0-24, 0-48, 0-72, 0-96 and 0-120 hours for the entire ITT population. The trial's SAP mandated that all subjects who participated in this trial were to have been analyzed as a single group according to drug assignment. Randomization was to have been stratified by risk and weight to the various doses of diclofenac or ketorolac evaluated in order to minimize selection bias. However, bias may have been potentially introduced when missing data for the short term cohort who were discharged at 24 hours prior to completing the 48 hours of study treatment were imputed during the analyses of the study's results. To control for multiplicity, a sequential, closed testing procedure was to have been used in conducting this analysis as prespecified by the SAP as follows: 0-24 hours, 0-48 hours, 0-72 hours, 0-98 hours, and 0-120 hours. Table 29 shows that the mean SPID scores for both the DIC075V and ketorolac treatment groups were significantly higher as compared to the placebo group at each of these time intervals (p<0.0001).

Table 29 – Tabular Summary of the Sum of Pain Intensity Differences (SPID) [mm hours] over 0-24, 0-48, 0-72, 0-96, and 0-120 Hours for Subjects in Study DFC-005 (ITT Population)

SPID (mm hrs) Time Interval	Placebo (N =72)	DIC075V (N = 145)	Ketorolac tromethamine (N = 60)
0-24 hrs:			
Mean (SD)	28.0 (428)	577 (571)	563 (586)
P-value[a]		<0.0001[b]	<0.0001[b]
95% CI		(374, 664)[c]	(281, 635)[d]
0-48 hrs:	400 (950)		
Mean (SD)		1528 (1139)	1372 (1152)
P-value[a]		<0.0001[b]	<0.0001[b]
95% CI		(776, 1357)[c]	(454, 1163)[d]
0-72 hrs:	837 (1564)		
Mean (SD)		2592 (17310	2312 (1744)
P-value[a]		<0.0001[b]	<0.0001[b]
95% CI		(1213, 2111)[c]	(674, 1770)[d]
0-96 hrs:			
Mean (SD)	1338 (2262)	3711 (2347)	3332 ((2356)
P-value[a]		<0.0001[b]	<0.0001[b]
95% CI		(1623, 2865)[c]	(888, 2405)[d]
0-120 hrs:			
Mean (SD)	1841(2988)	4836 (2989)	4359 (3001)
P-value[a]		<0.0001[b]	<0.0001[b]
95% CI		(2028, 3632)[c]	(1099, 3057)[d]

SD=standard deviation; CI = confidence interval
[a]P=0.001 for overall treatment effect
[b]P-value from linear contrast comparing each active treatment versus placebo
[c]95% confidence interval for difference between DIC075 IV and placebo
[d]95% confidence interval for difference between ketorolac tromethamine and placebo
Modified Sponsor's Table 11-5; p. 64.

To be consistent with DFC-004 which utilized the SPID 0-48 hours as its primary endpoint, the agency's statistician Dr. Norton, reanalyzed the primary endpoint for DFC-005 using data from the long term stay population in order to minimize bias that may have been introduced during imputation of missing data from the short stay population. The results of these post hoc analyses were qualitatively similar to that of the original analysis shown in Table 29 above. (Note: Reader is referred to the statistical review of this application for additional information.)

(b) (4)

Since the original analysis plans did not call for comparative analyses to be conducted on subjects administered either 18.75 mg or 50 mg doses of DIC075V evaluated in DFC-005, Dr.

Norton conducted post hoc analyses of the SPID over 0-48 hours by dose for the long stay cohort patients. As shown in Table 30, the results of these post hoc analyses for subjects treated with any of the three doses of DIC075V were qualitatively similar to that of the original analysis (refer to Table 29).

Table 30 Tabular Summary of the Post Hoc Analyses of the Sum of Pain Intensity Differences (SPID) [mm hours] over 0-48 hours by Dose for the Long Stay Cohort of Study DFC-005 (ITT)

SPID (mm·hrs)	Placebo Long Stay Cohort (N =40)	DIC075V Long Stay Cohort (N = 83)			Ketorolac Tromethamine Long Stay Cohort (N = 32)	
		18.75 mg (n=35)	37.5 mg (n=30)	50 mg (n=18)	15 mg (n=15)	30 mg (n=17)
0-48 hrs: Mean (SD)	206 (691)	1355 (1301)[a]	1534 (1205)[a]	1424 (1067)[a]	729 (1178)	1311 (1267)

SD=standard deviation
[a]p <0.001 vs. Placebo
Analyses courtesy of Dr. Jonathan Norton, FDA Statistician

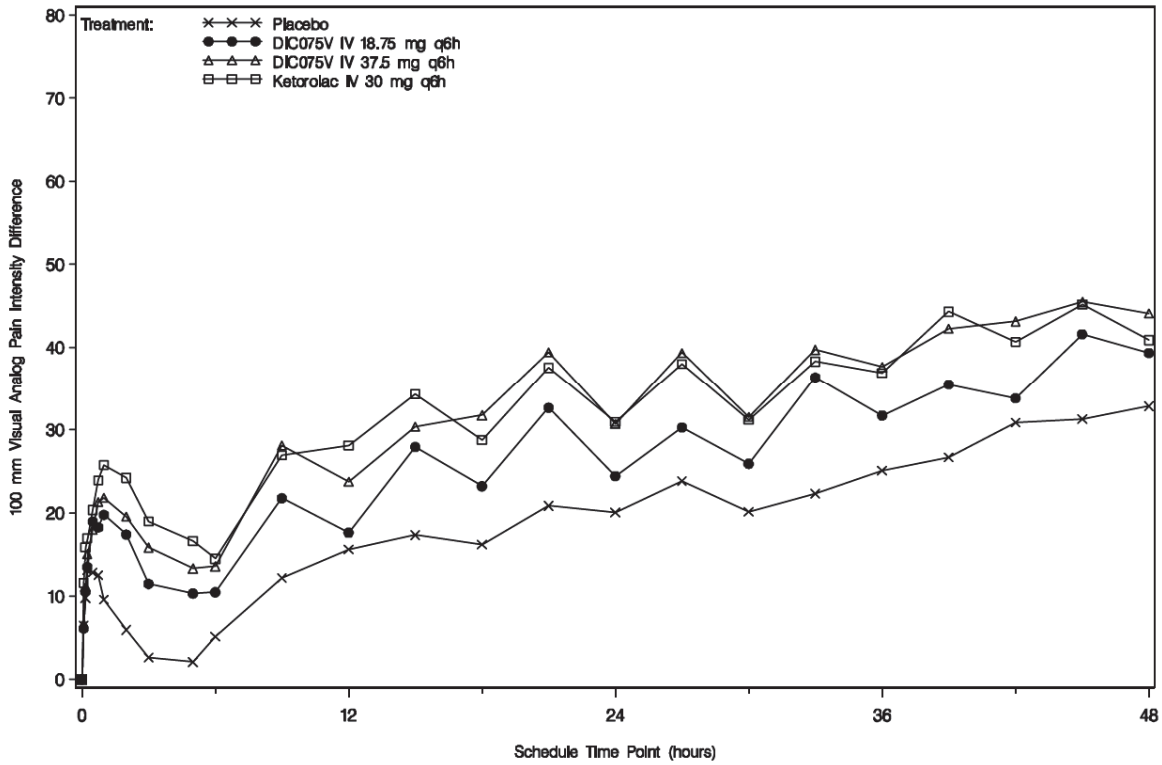
6.1.5 Analysis of Secondary Endpoints

A number of secondary endpoints were evaluated in both DFC-004 and 005. As prespecified in the protocol for DFC-005, the results from the following analyses of the secondary endpoints for this trial were based on the entire ITT population which included both short stay (≤ 24 hours) and long term stay (>24 hours) populations raising concerns again regarding the possible introduction of bias into these analyses due to imputation of missing data for the short stay cohort. No multiplicity correction was planned for in the study protocols or implemented here for the secondary endpoints. Due to multiplicity concerns for both studies, declaring statistical significance of these secondary endpoints using unadjusted p-values may be inappropriate.

Pain Intensity Difference:

Figure 4 graphically depicts the time course of the pain intensity difference (PID) over the 48 hours of pain assessment as measured via a 100 mm VAS for each of the four treatment groups in study DFC-004. Following the administration of the first dose of study medication, mean PID scores were higher for each of the 3 active treatment groups as compared to the placebo group over 0 to 48 hours. Separation of the mean PID curves for the DIC075V 18.75 mg and the 37.5 mg dose groups is suggestive of a dose response within the recommended dose range.

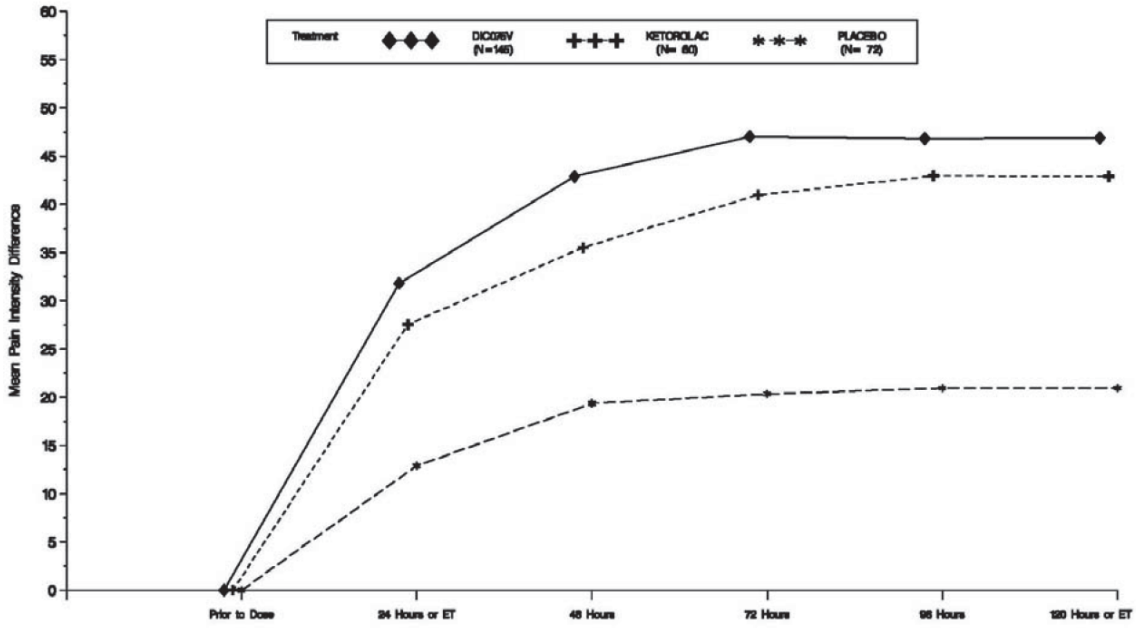
Figure 4 – Mean Pain Intensity Differences Over Time in Study DFC-004 (ITT Population)



Sponsor's Fig. 11-1; p. 68.

A similar pattern of improvement in pain intensity was also observed in patients participating in DFC-005. Figure 5 shows early separation of both the DIC075V and the ketorolac treatment groups from the placebo group as a result of higher mean PID scores in the active treatment groups that were maintained over the 120 hours of study assessment.

Figure 5 - Mean Pain Intensity Differences Over Time in Study DFC-005 (ITT Population)



Sponsor's Fig. 11-2; p. 71.

Proportion of Subjects Achieving > 30% Reduction in Pain Intensity:

Since the primary efficacy endpoint in the two pivotal studies was based on a reduction in pain intensity and a 30% reduction from baseline pain score is considered to be clinically meaningful in analgesic studies, analyses for the proportion of subjects who achieved ≥ 30% reduction in pain intensity were also conducted by the sponsor. In DFC-004, significantly higher proportions of patients achieved a ≥ 30% reduction in baseline pain intensity in the ketorolac 30 mg active comparator group (57%), DIC075V 37.5 mg treatment group (46%), DIC075V 18.75 mg treatment group (42%) as compared to the placebo group (34%) that were observed to have started at 45 minutes post-administration of the first dose for all three study treatments (p=0.0229 for all three treatment groups versus placebo). This rate of response was maintained through 39 hours of study assessment with the exception of the 6, 12, 24, 30 and 36 hour time points. Since the pain assessments for these time points coincided with the study's dosing schedule, they may have been impacted by a decrease in serum concentrations of DIC075V and Ketorolac as well as by missed pain assessments by sleeping patients who were not to have been woken up as mandated by the protocol. At the remaining later time points, all four of the treatment groups had similar proportions of patients with ≥ 30% reduction in baseline pain intensity that may be due to a decrease in post-operative pain observed over time.

Greater proportions of patients achieved a ≥ 30% reduction in baseline pain intensity in the DIC075V treatment group (81%) and ketorolac active comparator group (75%) as compared to the placebo group (43%) in DFC-005. The differences between the DIC075V treatment group and the ketorolac treatment group as compared to the placebo group were statistically significant starting at 15 minutes (p=0.0090) and 45 minutes (p=0.0035) respectively, post-administration of the first dose of study medication and were maintained through the 120 hours of study assessment.

Total Pain Relief (TOTPAR):

The area under the pain relief curve over 0-24 and 0-48 hours or the total pain relief (TOTPAR) score was also calculated for the ITT populations of both DFC-004 and 005. As shown in Table 31, the mean TOTPAR scores over 0-24 hours were significantly higher for the DIC075V 18.75 mg group (998 mm·hrs), the DIC075V 37.5 mg group (1018 mm·hrs), and the ketorolac 30 mg active comparator group (1186 mm·hrs) as compared to the placebo group (776 mm·hrs) [DIC075V 18.75 mg vs placebo: p=0.0371; DIC075V 37.5 mg vs placebo: p = 0.0018; and ketorolac 30 mg vs placebo: p<0.0001). Similar results were observed on the comparative analyses for each active treatment group versus placebo for the TOTPAR 0-48 scores (Table 31). Further examination of these data reveals that the 95% confidence intervals overlap for the between group comparative analyses of the three active treatment groups which indicates that their mean TOTPAR 0-24 and 0-48 scores were not significantly different.

Table 31 – Tabular Summary of Total Pain Relief (TOTPAR) Over 0-24 Hours and 0-48 Hours for Subjects in Study DFC-004 (ITT Population)

TOTPAR (mm.hrs) Time Interval	Placebo (N = 76)	DIC075V		Ketorolac 30 mg (N=82)
		18.75 mg (N = 86)	37.5 mg (N = 87)	
0-24 hours:				
Mean	776	998	1018	1186
Standard Deviation	(571)	(668)	(656)	(652)
p-value[a]		p = 0.0371[b]	p = 0.0018[b]	p <0.0001[b]
95% CI			(-79, 270)[d]	(31, 382)[e] (-65, 287)[f]
0-48 hours:				
Mean	1876	2367	2438	2714
Standard Deviation	(1300)	(1456)	(1428)	(1351)
p-value[c]		p = 0.0383[b]	p = 0.0018[b]	p = 0.0001[b]
95% CI			(-172, 601)[d]	(-6, 774)[e] (-221, 561)[f]

[a]p=0.0002 for overall treatment effect
[b]p-value from linear contrast comparing each active treatment versus placebo
[c]p=0.0008 for overall treatment effect
[d]95% CI for difference between DIC075V 18.75 mg and DIC075V 37.5 mg
[e]95% CI for difference between DIC075V 18.75 mg and ketorolac
[f]95% CI for difference between DIC075V 37.5 mg and ketorolac
Modified Sponsor's Tables 11-8 and 14.2.2.1a; p. 72 and 235.

Table 32 lists the results for the TOTPAR comparative analyses for DFC-005. The mean TOTPAR scores for the 0-24, 0-48, 0-72, 0-96, and 0-120 time intervals in this trial were significantly higher for both the DIC075V treatment group and the ketorolac active comparator group as compared to the placebo group (p<0.0001). However, due to the overlap observed in the 95% confidence intervals for the DIC075V and ketorolac treatment groups, the mean TOTPAR scores for these groups were not significantly different.

Table 32– Tabular Summary of Total Pain Relief (TOTPAR) Over 0-24, 0-48, 0-72, 0-96, and 0-120 Hours for Subjects in Study DFC-005 (ITT Population)

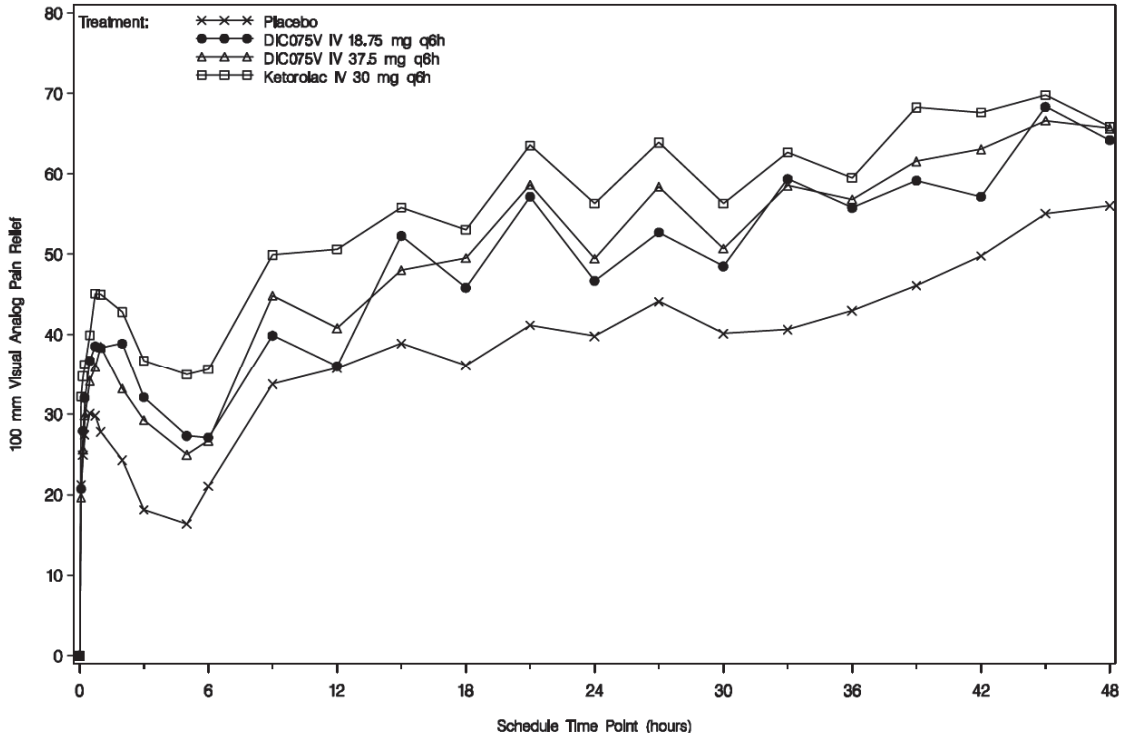
TOTPAR (mm hrs) Time Interval	Placebo (N =72)	DIC075V (N = 145)	Ketorolac tromethamine (N = 60)
0-24 hrs:			
Mean (SD)	485 (503)	1178 (611)	1065 (616)
P-value[a]		<0.0001	<0.0001
95% CI		(555, 878)[b]	(408, 803)
		(-62, 283)[c]	
0-48 hrs:			
Mean (SD)	1328 (1259)	2768 (1239)	2454 (1323)
P-value[a]		<0.0001	<0.0001
95% CI		(1145, 1834)[b]	(747, 1588)
		(-45, 690)[c]	
0-72 hrs:			
Mean (SD)	2215 (2103)	4471 (1899)	3984 (2057)
P-value[a]		<0.0001	<0.0001
95% CI		(1787, 2874)[b]	(1161, 2488)
		(-74, 1086)[c]	
0-96 hrs:			
Mean (SD)	3159 (3003)	6252 (2577)	5576 (2828)
P-value[a]		<0.0001	<0.0001
95% CI		(2435, 3943)[b]	(1560, 3401)
		(-96, 1514)[c]	
0-120 hrs:			
Mean (SD)	4105 (3922)	8043 (3282)	7178 (3628)
P-value[a]		<0.0001	<0.0001
95% CI		(3086, 5029)[b]	(1960, 4334)
		(-127, 1948)[c]	

SD=standard deviation; CI = confidence interval
[a]p=0.0001 for overall treatment effect
[b]95% CI for difference between DIC075V 37.5 mg and Placebo
[c]95% CI for difference between DIC075V 37.5 mg and ketorolac
Modified Sponsor's Tables 11-8 and 14.2.4; p. 72 and 231.

Pain Relief (PR):

Figure 6 graphically depicts mean pain relief (PR) over time as measured via a 100 mm VAS for each of the four treatment groups in study DFC-004. Following the administration of the first dose of study medication, mean PR scores were higher for each of the 3 active treatment groups as compared to the placebo group over 0 to 48 hours. However, no separation of the mean PR curves for the DIC075V 18.75 mg and 37.5 mg treatment groups is observed suggesting a lack of dose response which is consistent with the results observed for the TOTPAR 0-24 and 0-48 analyses for this trial.

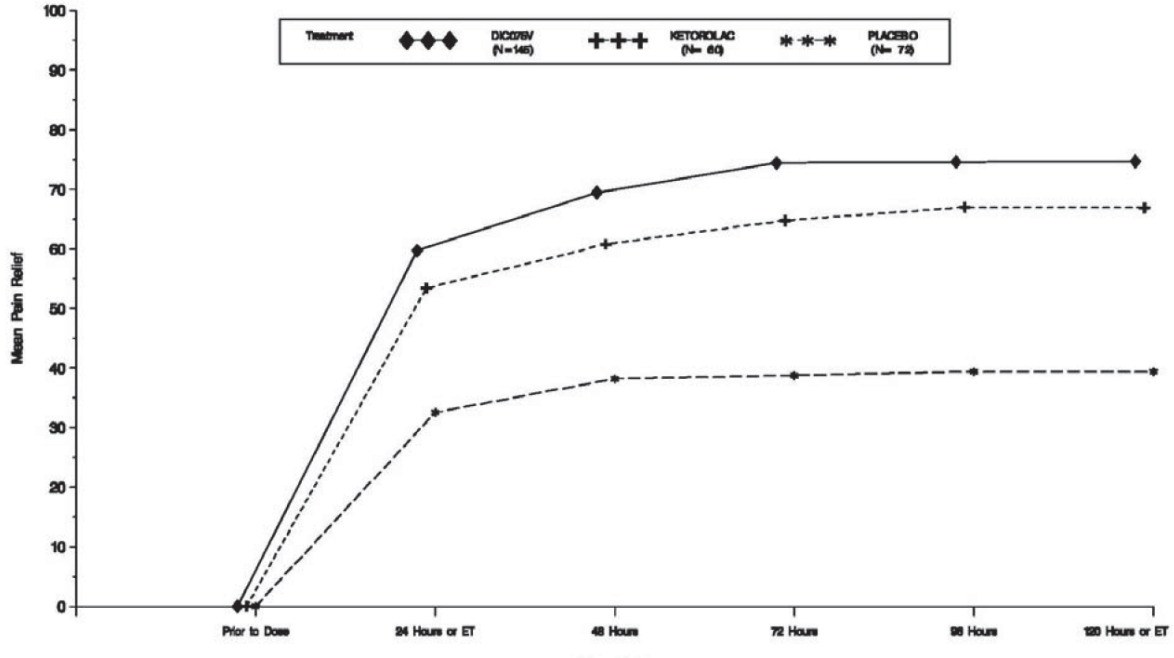
Figure 6 - Mean Pain Relief Over Time by Treatment for Study DFC-004 (ITT Population)



Sponsor's Fig. 11-2; p. 73.

Mean PR over time as measured via a 100 mm VAS from 5 minutes through 120 hours for all three treatment groups in DFC-005 is shown in Figure 7. Both the DIC075V and the ketorolac groups separate early from the placebo group as a result of higher PR scores in these two treatment groups that were maintained over the 120 hours of study assessment.

Figure 7 - Mean Pain Relief Over Time by Treatment for Study DFC-005 (ITT Population)



Sponsor's Fig. 11-4; p. 74.

Time to Perceptible Pain Relief (TPPR) and Meaningful Pain Relief (TMPR):
Time to perceptible pain relief (TPPR) and meaningful pain relief (TMPR) were assessed in both pivotal trials via two-stop watch methodology. Table 33 lists the results for both the estimated median TPPR and TMPR based on Kaplan-Meier analyses for all four treatment groups in DFC-004. The estimated median TPPRs were similar for the four treatment groups in this trial, ranging from 8 minutes for both the DIC075V 18.75 mg and ketorolac 30 mg active comparator groups, to 9 minutes for the DIC075V 37.5 mg group and 10 minutes for the placebo group. The estimated median TMPRs for both the 37.5 mg DIC075V group and the ketorolac 30 mg group were similar and occurred earlier at 41 and 43 minutes, respectively, as compared to 61 minutes for the 18.75 mg DIC075V group and 126 minutes for the placebo group.

Table 33 – Time to Onset of Perceptible Pain Relief (TPPR) and Meaningful Pain Relief (TMPR) in Subjects from Study DFC-004 (ITT Population)

	Placebo (N = 76)	DIC075V		Ketorolac 30 mg (N=82)
		18.75 mg (N = 86)	37.5 mg (N = 87)	
TPPR[1]				
Number of Subjects by 6 hrs Post-First Dose	60 (79%)	68 (79%)	69 (79%)	67 (82%)
Median[2] (hours:minutes) **95% Confidence Interval[2]** **p-value[3]**	0:10 (0:07, 0:13)	0:08 (0:06, 0:10) p=0.8722	0:09 (0:07, 0:13) p=0.5390	0:08 (0:06, 0:12) p=0.2582
TMPR[1]				
Number of Subjects by 6 hrs Post-First Dose	31 (41%)	46 (54%)	46 (53%)	52 (63%)
Median[2] (hours:minutes) **95% Confidence Interval[2]** **p-value[3]**	2:06 (0:34, NE)	1:01 (0:27, 2:14) p=0.2085	0:41 (0:29, 1:32) p=0.1400	0:43 (0:23, 0:55) p = 0.0114

[1]Event times for subjects not reporting perceptible or meaningful relief within 6 hours of first dose of study medication were censored at 6 hours; event times for subjects who withdrew/took rescue medication within 6 hours of first dose were censored at time of withdrawal or rescue medication.
[2]Kaplan-Meier estimate of the median. Greenwood's formula was used in the calculation of the confidence interval.
[3]P-value from log rank test of pairwise comparisons with placebo.
Adapted Sponsor's Tables 11-10 and 11-11; p. 75 and 76.

The results for the Kaplan-Meier analyses for the estimated median TPPR and TMPR for DFC-005 are shown in Table 34. The estimated median TPPR for the ketorolac active comparator group and the placebo were similar at 15.0 and 15.3 minutes, respectively however, the estimated median TPPR for the DIC075V group occurred earlier at 11.2 minutes in this trial. The estimated median TMPRs were similar for the DIC075V group (41.6 minutes) and the ketorolac active comparator group (42.5 minutes) but could not be estimated for the placebo group since the majority of subjects in this group had failed to achieved meaningful pain relief by 6 hours.

Table 34 – Time to Onset of Perceptible Pain Relief (TPPR) and Meaningful Pain Relief (TMPR) for Subjects in Study DFC-005 (ITT Population)

Parameter	Placebo (N =72)	DIC075V (N = 145)	Ketorolac tromethamine (N = 60)
TPPR (min)[a]			
Median[a,b]	15.3	11.2	15.0
95% CI[b]	10.3, NE	8.0, 14.1	10.4, 21.0
P-value[c]		0.0009	0.0640
TMPR (min)[a]			
Median[a,b]	NE	41.6	42.5
95% CI[b]	NE, NE	31, 59	30, 52
P-value[c]		<0.0001	0.0019

CI = confidence interval; NE = not estimate
[a]Event times of subjects not reporting perceptible relief within 6 hours of first dose of study medication were censored at 6 hours; event times, of subjects who withdrew/took rescue medication within 6 hours of first dose were censored at time of withdrawal or rescue medication
[b]Kaplan-Meier estimate of the median. Greenwood's formula was used in the calculation of the confidence limits.
[c]P-value from log rank test of pairwise comparisons with placebo.
Adapted Sponsor's Tables 11-9 and 11-10; p. 77 and 78.

Time to First Rescue Medication (TTR):

As per the trial protocols discussed in Section 5.4, patients who participated in DFC-004 and 005 were to have been encouraged to wait at least 1 hour after administration of the initial dose of study medication dose before receiving a dose of rescue medication. In view of this, the use of rescue medication was also examined as a secondary endpoint. Time to first rescue medication (TTR) is another parameter that can be used to assess the duration of an analgesic's efficacy. Table 35 lists the results for the estimated median TTR based on Kaplan-Meier analyses for all four treatment groups in DFC-004. Patients in the placebo group used rescue medications earlier (i.e., estimated median TTR of 2 hours and 7 minutes) followed by patients in the DIC075V 37.5 mg group (2 hours and 24 minutes), the DIC075V 18.75 mg treatment group (3 hours and 14 minutes) and the ketorolac 30 mg active comparator group (4 hours and 15 minutes).

Table 35 – Time from Administration of Study Drug to Administration of Rescue Medication for Subjects in Study DFC-004 (ITT Population)

Time to Rescue Medication[1]	Placebo (N = 76)	DIC075V		Ketorolac 30 mg (N=82)
		18.75 mg (N = 86)	37.5 mg (N = 87)	
Number of Subjects	61 (80%)	54 (63%)	57 (66%)	45 (55%)
Median[2] (hours:minutes) **95% Confidence Interval[2]** **p-value[3]**	2:07 (1:15, 2:40)	3:14 (2:10, 5:05) p=0.0141	2:24 (1:50, 4:23) p=0.0574	4:15 (3:05, NE) p = 0.0007

NE = Not Estimable
[1]Time from administration of study drug to administration of rescue medication were censored at 6-hour assessment time for subjects not given rescue medication. Event times for subjects who withdrew within 6 hours were censored at time of withdrawal.
[2]Kaplan-Meier estimate of the median. Greenwood's formula was used in the calculation of the confidence interval.
[3]P-value from pairwise comparisons with placebo.
Modified Sponsor's Table 11-12; p. 78.

The results for the Kaplan-Meier analyses for the estimated median TTR for DFC-005 are shown in Table 36. Placebo patients similarly used rescue medications earlier (i.e., estimated median TTR of 51 minutes) as compared to patients in the ketorolac active comparator group (estimated median TTR of 137 minutes) or in the DIC075V group (estimated TTR of 220 minutes).

Table 36 – Time from Administration of Study Drug to Administration of Rescue Medication (TTR) for Subjects in Study DFC-005 (ITT Population)

TTR (min)[a]	Placebo (N =72)	DIC075V (N = 145)	Ketorolac tromethamine (N = 60)
Median[a,b]	51	220	137
95% CI[b]	35, 71	125, 272	63, 302
P-value[c]		<0.0001	<0.0001

CI = confidence interval; NE = not estimate
[a]Time from administration of study drug to administration of rescue medication was censored at time of last pain assessment for subjects who did not receive rescue medication
[b]P-values are from a log-rank test comparing active treatment with placebo.
Modified Sponsor's Table 11-11; p. 80.

Frequency of Rescue Medication

The use of rescue medication was also examined in both trials. The majority of patients (75%) in DFC-004 used rescue medication while participating in this trial. Table 37 shows that the proportion of patients who used rescue medication within the 48 hours of the treatment phase for DFC-004 was lowest for patients in the ketorolac 30 mg active comparator group (63%), followed by the DIC075V 37.5 mg group (63%), and the DIC075V 18.75 mg group (73%) as compared to patients in the placebo group (92%). Additionally, a higher proportion of placebo treated patients (71%) used > 2 doses of

rescue medication, followed by the 42% in the DIC075V 18.75 mg group, 40% in the ketorolac 30 mg group, and 32% in the DIC075V 37.5 mg group.

Table 37- Tabular Summary of the Number (%) of Patients Using Rescue Medication Over the 48 Hours of Treatment in Study DFC-004 (ITT Population)

0-48 Hours Time Interval	Placebo (N = 76)	DIC075V		Ketorolac 30 mg (N=82)
		18.75 mg (N = 86)	37.5 mg (N = 87)	
Number (%) of Patients who Used Rescue Medication:	70 (92%)	64 (73%)	61 (70%)	53 (64%)
Number (%) of Patients who Used > 2 Doses of Rescue Medication	54 (71%)	36 (42%)	28 (32%)	33 (40%)

Adapted Sponsor's Table 14.2.5.3a.; p. 298

The majority of subjects (79%) in DFC-005 also used rescue medication. Table 38 shows that a similar proportion of patients used rescue medication within the 48 hours of the treatment phase for DFC-005 in both the ketorolac active comparator group (73%) and the DIC075V group (74%) which were both lower as compared to 92% patients in the placebo group. Additionally, a higher proportion of placebo treated patients (85%) used > 2 doses of rescue medication, followed by the 65% in the ketorolac group and 58% in the DIC075V group.

Table 38 - Tabular Summary of the Number (%) of Patients Using Rescue Medication Over the 48 Hours of Treatment in Study DFC-005 (ITT Population)

0-48 Hours Time Interval	Placebo (N =72)	DIC075V (N = 145)	Ketorolac tromethamine (N = 60)
Number (%) of Patients who Used Rescue Medication:	**68 (94%)**	**107 (74%)**	**44 (73%)**
Number (%) of Patients who Used > 2 Doses of Rescue Medication	**61 (85%)**	**84 (58%)**	**39 (65%)**

Adapted Sponsor's Table 14.2.10.; p. 254

Amount of Rescue Medication

Morphine IV was used as rescue medication in both pivotal studies. Table 40 shows that over the 0-48 hours time interval in DFC-004 patients in the DIC075V 37.5 mg group used the least amount of rescue medication (7.3 mg), followed by the DIC075V 18.75 mg group (8.4 mg) and the ketorolac active comparator group (8.5 mg) as compared to placebo (15.6 mg). Although the cumulative amount of rescue medication used by 3 all three active groups was significantly less than the amount used by the

placebo group (p<0.0001), the difference in the amount of morphine used by the 3 active comparators may not be a clinically meaningful finding.

Table 39 – Tabular Summary of Cumulative Amount of Rescue Medication Used Over the 48 Hours of Treatment in Study DFC-004 (ITT Population)

0-48 Hours Time Interval	Placebo (N = 76)	DIC075V		Ketorolac 30 mg (N=82)
		18.75 mg (N = 86)	37.5 mg (N = 87)	
Mean Rescue Medication Used (SD): P-value[a]	15.6 mg (13)	8.4 mg (10) <0.0001	7.3 mg (9.3) <0.0001	8.5 mg (10) <0.0001

[a]P-values are from a log-rank test comparing active treatment with placebo.
Adapted Sponsor's Table 14.2.5.2a-1; p. 291.

In response to an information request by the agency's statistician reviewing this application, the sponsor submitted a corrected analysis of the cumulative amount of rescue medication used in DFC-005 on June 16, 2010. The results of this corrected analysis for the ITT population in this trial are displayed in Table 40 and show that significantly lower amounts of rescue medication were used by patients in both the DIC075V and ketorolac active comparator groups as compared to the placebo group for all time points evaluated (DIC075V vs placebo: p<0.0001; ketorolac vs placebo: p≤ 0.01).

Table 40 - Tabular Summary of Cumulative Amount of Rescue Medication Used Over the 48 Hours of Treatment in Study DFC-005 (ITT Population)

Time Interval	Placebo (N =72)	DIC075V (N = 145)	Ketorolac tromethamine (N = 60)
0-24 hrs:			
Mean (SD)	15.1 (10.95)	6.9 (7.43)	8.2 (8.39)
P-value[a]		<0.0001	<0.0001
95% CI		(-10.8, -5.9)	(-10.2, -4.2)
0-48 hrs:			
Mean (SD)	18.0 (14.19)	8.3 (9.20)	11.4 (13.79)
P-value[a]		<0.0001	0.0008
95% CI		(-13.2, -6.6)	(-11.0, -2.9)
0-72 hrs:			
Mean (SD)	19.4 (16.42)	8.7	13.2 (18.96)
P-value[a]		<0.0001	0.0092
95% CI		(-14.8, -7.0)	(-11.2, -1.6)
0-96 hrs:			
Mean (SD)	19.4 (16.41)	8.8 (9.85)	13.3 (18.99)
P-value[a]		<0.0001	0.0099
95% CI		(-14.8, -6.9)	(-11.2, -1.5)
0-120 hrs:			
Mean (SD)	19.4 (16.41)	8.8 (9.85)	13.3 (19.03)
P-value[a]		<0.0001	0.0104
95% CI		(-14.8, -6.9)	(-11.1, -1.5)

[a]P-values are from linear contrasts comparing each active treatment to placebo based on an ANCOVA model with treatment and center as factors and baseline pain as a covariate.
Adapted Sponsor's Table 14.2.9R from June 16, 2010 submission.

Since the sponsor (b) (4) included in the June 16, 2010 response to the agency's information request a corrected analysis of the cumulative amount of rescue medication used by patients in the long stay cohort of DFC-005. The results of this updated subgroup analysis for the 0-24, 0-48 and 0-72 hour time intervals are presented in Table 41. Patients in the long stay cohort who received DIC075V used significantly less rescue medication over the 0-24, 0-48 and 0-72 hour time intervals as compared to the placebo group (P<0.001) which is consistent with the results for the ITT population for this trial (refer to Table 40) and is representative of a clinically meaningful decrease in the amount of opiates used as rescue. However, long stay cohort patients treated with ketorolac were found to have used significantly less rescue medication only over the 0-24 hours time interval as compared to the placebo group (p=0.01) and not at the 0-48 or 0-72 hour interval time points in this trial (p=0.1457 and p=0.3841, respectively).

Table 41 - Tabular Summary of Cumulative Amount of Rescue Medication Used Over the 48 Hours of Treatment by Patients in the Long Stay Cohort in Study DFC-005 (ITT Population)

Time Interval	Placebo (N =40)	DIC075V (N = 83)	Ketorolac tromethamine (N = 32)
0-24 hrs:			
Mean (SD)	15.9 (11.15)	7.3 (6.62)	10.6 (8.77)
P-value[a]		<0.0001	0.0100
95% CI		(-11.7, -5.2)	
0-48 hrs:			
Mean (SD)	21.0 (15.88)	9.7 (9.56)	16.5 (16.12)
P-value[a]		<0.0001	0.1457
95% CI		(-16.0,-6.3)	(-10.4, 1.6)
0-72 hrs:			
Mean (SD)	23.5 (18.92)	10.4 (10.27)	20 (23.21)
P-value[a]		<0.0001	0.3841
95% CI		(-18.9, -6.8)	(-10.8, 4.2)

[a]P-values are from linear contrasts comparing each active treatment to placebo based on an ANCOVA model with treatment and center as factors and baseline pain as a covariate.
Adapted Sponsor's Table 14.2.9RLS from June 16, 2010 submission.

The agency's statistician Dr. Norton, reanalyzed the cumulative amount of rescue medication data from the long term stay population in which he included 2 subjects the sponsor had excluded from their analyses of this endpoint. The results of his post hoc analyses were similar to that of the Applicant's analyses shown in Table 41 above. (Note: Reader is referred to the statistical review of this application for additional information.)

Patient Global Evaluation:

A patient global evaluation of study medication was also assessed via a 5-point categorical scale over the 0-24 and 0-48 hour intervals in both pivotal trials. Table 42 shows the results from these analyses for subjects in DCF-004. The percentage of patients who rated the study medication as "good" or better over the 0-24 hour interval was highest in the DIC075V 37.5 mg group with 91%, followed by a comparable percentage of patients in the ketorolac 30 mg and the DIC075V 18.75 mg groups with 85% and 84%, respectively, which were all higher than observed in the placebo group (70%). The mean PGA values for each of the three active treatment groups evaluated were significantly higher as compared to placebo (DIC075 18.75 mg vs placebo: p= 0.0075; DIC075V 37.5 mg vs placebo: p<0.0001; ketorolac vs placebo: p=0.0006). Over the 0-48 hour interval the percentages of patients who rated the study medication as "good" or better continued to remain higher in the three active treatment groups (DIC075V 18.75 mg: 87%; DIC075V 37.5 mg: 84%; and ketorolac 30 mg: 85%) as compared to 59% of subjects in the placebo group. The mean PGE values for the three active treatment groups were significantly higher as compared to placebo (DIC075

18.75 mg vs placebo: p<0.0001; DIC075V 37.5 mg vs placebo: p=0.0003; ketorolac vs placebo: p=0.0003).

Table 42- Patient Global Evaluation (PGE) Over 0-24 and 0-48 Hours for Subjects in Study DFC-004 (ITT Population)

Patient Global Evaluation (Time Interval)	Placebo (N = 76)	DIC075V		Ketorolac 30 mg (N=82)
		18.75 mg (N = 86)	37.5 mg (N = 87)	
0-24 hours:				
Excellent (4)	7 (12%)	13 (17%)	20 (27%)	18 (25%)
Very Good (3)	16 (26%)	32 (43%)	26 (35%)	26 (36%)
Good (2)	20 (33%)	18 (24%)	22 (29%)	17 (24%)
Fair (1)	7 (12%)	5 (7%)	4 (5%)	9 (13%)
Poor (0)	11 (18%)	7 (9%)	3 (4%)	2 (3%)
Total Number of Subjects:	61	75	75	72
Mean (SD)	2.0 (1.3)	2.5 (1.1)	2.7 (1.0)	2.7 (1.1)
p-value[a]		p=0.0075[b]	p<0.0001[b]	p=0.0006[b]
95% Confidence Interval			(-0.1, 0.6)[d]	(-0.2, 0.5)[e] (-0.5, 0.2)[f]
0-48 hours:				
Excellent (4)	9 (14%)	23 (31%)	19 (25%)	25 (32%)
Very Good (3)	16 (24%)	29 (39%)	28 (37%)	23 (30%)
Good (2)	14 (21%)	13 (17%)	17 (22%)	17 (22%)
Fair (1)	12 (18%)	2 (3%)	3 (4%)	7 (9%)
Poor (0)	15 (23%)	8 (11%)	9 (12%)	6 (8%)
Total Number of Subjects:	66	75	76	78
Mean (SD)	1.9 (1.4)	2.8 (1.2)	2.6 (1.3)	2.7 (1.2)
p-value[f]		p<0.0001[a]	p=0.0003[b]	p=0.0003[b]
95% Confidence Interval			(-0.5, 0.3)[d]	(-0.5, 0.3)[c] (-0.4,0.4)[ef]

SD = Standard Deviation
[a]P=0.0003 for overall treatment effect for 0-24 hours
[b]p-value from linear contrast comparing each active treatment versus placebo
[c]95% confidence interval for difference between DIC075V IV 18.75 mg and DIC075V IV 37.5 mg
[d]95% confidence interval for difference between DIC075V IV 18.75 mg and ketorolac 30 mg
[e]95% confidence interval for difference between DIC075V IV 37.5 mg and ketorolace 30 mg
[f]P=0.0002 for overall treatment effect for 0-48 hours
Adapted Sponsor's Table 11-14; p. 82.

Similar results for these analyses were observed in DFC-005 (Table 43). Over the 0-24 hour interval, 80% of patients in both the DIC075V and ketorolac treatment groups rated the study medication as "good" or better on their global evaluations as compared to the 37% of patients in the placebo group (mean PGA values for both active treatment groups versus placebo: p<0.0001). The percentages of patients at the 0-48 hour interval who rated the study medication as "good" or better continued to remain higher in both

the DIC075V (88%) and ketorolac (96%) groups as compared to 50% of subjects in the placebo group, however, comparison of the mean PGA values was only significantly higher for the DIC075V group versus placebo at this time point (DIC075V vs placebo: p=0.0011; ketorolac versus placebo: p=0.0641). At the last assessment, higher percentages of patients continued to rate the study medication as “good” or better that were similar for both the DIC075V and ketorolac groups (85% and 83%, respectively) as compared to 41% of patients in the placebo group. The mean PGE values for the two active treatment groups at the last assessment were also significantly higher as compared to placebo ($p<0.0001$).

Table 43 – Patient Global Evaluation over 0-24, 0-48, and Last Assessment for Subjects in Study DCF-005 (ITT Population)

Evaluation Time Point	Placebo (N =72)	DIC075V (N = 145)	Ketorolac tromethamine (N = 60)
0-24 hours Rating:			
Excellent (4)	3 (4%)	43 (31%)	12 (20%)
Very Good (3)	9 (13%)	45 (32%)	17 (29%)
Good (2)	14 (20%)	25 (18%)	18 (31%)
Fair (1)	12 (17%)	15 (11%)	8 (14%)
Poor (0)	32 (46%)	13 (9%)	4 (7%)
Missing	2	4	1
Total Number of Subjects:	70	141	59
Mean (SD)	1.1 (1.3)	2.6 (1.3)	2.4 (1.2)
p-value[a]		<0.0001	<0.0001
95% Confidence Interval		(1.2, 1.9)	(0.9, 1.8)
0-48 hours Rating:			
Excellent (4)	5 (25%)	23 (38%)	3 (12%)
Very Good (3)	0	18 (30%)	11 (42%)
Good (2)	5 (25%)	12 (20%)	11 (42%)
Fair (1)	7 (355)	4 (7%)	0
Poor (0)	3 (15%)	3 (5%)	1 (4%)
Missing	0	0	0
Total Number of Subjects:	20	60	26
Mean (SD)	1.9 (1.4)	2.9 (1.2)	2.6 (0.86)
p-value[f]		0.0011	0.0641
95% Confidence Interval		(0.4, 1.5)	(-0.0, 1.3)
Last Assessment Rating:			
Excellent (4)	7 (10%)	62 (44%)	16 (27%)
Very Good (3)	9 (13%)	37 (26%)	18 (31%)
Good (2)	13 (19%)	21 (15%)	15 (25%)
Fair (1)	13 (19%)	10 (7%)	7 (12%)
Poor (0)	28 (40%)	11 (8%)	3 (5%)
Missing	2	4	1
Total Number of Subjects:	70	141	59
Mean (SD)	1.3 (1.4)	2.9 (1.3)	2.6 (1.2)
p-value[a]		<0.0001	<0.0001
95% Confidence Interval		(1.3, 2.0)	(0.9, 1.8)

CI= confidence interval; SD =standard deviation
[a]P-value and root MSE are based on an analysis of variance model, with treatment and center as factors and baseline pain as covariate.
Modified Sponsor's Table 11-14; p. 86.

6.1.6 Other Endpoints

No other exploratory endpoints were evaluated in the Phase 3 pivotal trials.

6.1.7 Subpopulations

No subjects over 65 years of age were enrolled in DFC-004. The protocol for DFC-005 mandated that patients over 65 years receive a reduced dose of 18.75 mg of DIV075V because of the possibility of increase risk for NSAID-induced toxicities. Due to the lack of patients over 65 years of age treated with the 37.5 mg dose of DIC075V in the controlled trials, the Applicant did not conduct pooled analyses of the primary endpoint (SPID over 0-48 hours) based on age. However, the agency's statistical reviewer Dr. Norton, conducted post hoc analyses for age effects on treatment response for each of the pivotal studies which are shown in the following Table 44 and Table 45. Although the mean SPID 0-48 values are qualitatively similar and are not suggestive of age-related effects, the results of these post hoc analyses should be interpreted cautiously given the small number of subjects involved.

Table 44- Analysis of Sum of the Pain Intensity Differences (SPID) Over 0-48 Hours by Age and by Treatment Group for Study DFC-004 (ITT Population)

Age Subgroup	Placebo (N=76)		DIC075V 18.75 mg (n=86)		DIC075V 37.5 mg (n=87)		Ketorolac 30 mg (N=82)	
	Number	Mean SPID (SD)	Number	Mean SPID (SD)	Number	Mean SPID (SD)	Number	Mean SPID (SD)
< 45 yrs	43	809 (1163)	47	1342 (1004)	46	1541 (1099)	49	1622 (930)
≥ 45 yrs	33	1102 (944)	39	1257 (1070)	41	1610 (1027)	33	1525 (1068)

Analyses courtesy of Dr. Jonathan Norton, FDA Statistician

Table 45 - Analysis of Sum of the Pain Intensity Differences (SPID) Over 0-48 Hours by Age and by Treatment Group for the Long Stay Cohort for Study DFC-005 (ITT Population)

Age Subgroup	Placebo (n=40)		DIC075V (N=83)		Ketorolac tromethamine (n=32)	
	Number	Mean SPID (SD)	Number	Mean SPID (SD)	Number	Mean SPID (SD)
< 65 yrs	22	138 (708)	50	1433 (1159)	18	1254 (1253)
≥ 65 yrs	18	289 (681)	33	1437 (1295)	14	762 (1216)

Analyses courtesy of Dr. Jonathan Norton, FDA Statistician

The sponsor also conducted pooled analyses of the SPID 0-48 hours for DFC-004 and 005 based on ethnicity (Table 46) and gender (Table 47). These pooled analyses excluded the high risk subjects who participated in DFC-005, but included subjects from both the long and short stay populations of this trial raising concerns again regarding the possible introduction of bias into these analyses. Thus, the results from the ethnicity and gender analyses are also difficult to interpret given the small number of subjects involved, as well as the inclusion of subjects from both the long and short stay cohorts from DFC-005. Overall, the results from the both the ethnicity and gender subgroup analyses are consistent with the results from the primary endpoint analyses for both pivotal studies presented earlier in this review (refer to Table 28 and Table 29).

Table 46 - Pooled Analysis of Sum of the Pain Intensity Differences (SPID) Over 0-48 Hours by Race for Studies DFC-004 and 005 (Full Analysis Set)[a]

SPID 0-48 hrs (mm·hrs)	Placebo (n=110)				DIC075V (n=152)			
	White	Black	Asian	Other	White	Black	Asian	Other
No. of Subjects: Mean (SD)	94 796 (969)	8 997 (1107)	0	8 541 (791)	127 1331(999)	10 2078 (910)	2 1486 (548)	13 1852 (1301)

[a]Excludes subjects assigned to high risk (≥ 65 years old, hepatic and/or renal impairment)
Adapted Sponsor's Tables 8.1.1.2; p 269.

Table 47 - Pooled Analysis of Sum of the Pain Intensity Differences (SPID) Over 0-48 Hours by Gender for Studies DFC-004 and 005 (Full Analysis Set)[a]

SPID 0-48 hrs (mm·hrs)	Placebo (n=110)		DIC075V (n=152)	
	Male	Female	Male	Female
Number of Subjects: Mean (SD)	21 774 (953)	89 796 (971)	36 1386 (985)	116 1439 (1054)

[a]Excludes subjects assigned to high risk (≥ 65 years old, hepatic and/or renal impairment)
Adapted Sponsor's Tables 8.1.2.2; p 279.

(b) (4)

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(b) (4)

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Diclofenac is a member of the nonsteroidal class of drugs which are known to produce toxicity in many different organ systems including the gastrointestinal, renal, hepatic and cardiovascular systems. Since most of the toxicity associated with the administration of NSAIDs is related to inhibition of prostaglandins which is also the pathway by which they exert their mechanism of action, this class of drugs is said to have a narrow therapeutic window. Review of the safety database submitted in support of this application revealed a dose-dependent increase in the rate of serious adverse events and other adverse events of interest (e.g., hematologic, gastrointestinal, renal and hepatic) experienced by patients administered DIC075V that is consistent with the safety profiles of other diclofenac formulations. In view of this safety finding, the risk benefit ratio is in favor of the 37.5 mg dose of DIC075V.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Persistency of efficacy and tolerance effects are not relevant to this application because these have not been an issue with the analgesic efficacy of the NSAID class of drugs.

6.1.10 Additional Efficacy Issues/Analyses

No correction for multiplicity issues was prespecified by the statistical analysis plan (SAP) for DFC-004 for use in conducting the analyses of the trial's primary and secondary endpoints or by the SAP for DFC-005 in conducting the analyses of that trial's secondary endpoints. Therefore, declaring statistical significance of the primary endpoint in DFC-004 and the secondary endpoints for both of these trials using unadjusted p-values may be inappropriate. Additional analyses of the primary endpoint for DFC-004 correcting for multiplicity resulted in a loss of significance for the outcome of the DIC075V 18.5 mg dose group raising statistical questions regarding its effectiveness. However, the 37.5 mg dose of DIC075V continued to demonstrate statistical significance and was clinically more efficacious than the 18.75 mg dose of the drug. Additionally, there are concerns that the results from the secondary endpoint analyses for DFC-005 may have been potentially biased due to the inclusion of both the short stay (≤ 24 hours) and long term stay (>24 hours) populations as well as subjects treated with a variety of doses of DIC075V and ketorolac (i.e., the active comparator) in these calculations. Thus, the results for the primary endpoint analysis of the long term stay population of DFC-005 should be used in the drug label, while the secondary endpoint analyses for both trials should not be included other than to communicate information that may be clinically useful to health care prescribers (b) (4)

(b) (4)

7 Review of Safety

Safety Summary

The overall safety profile of DIC075V generated from the adequate and well controlled Phase 3 trials DCF-004 and 005 and the open label safety trial DFC-010 which evaluated 18.75 mg, 37.5 mg and 50 mg doses of DIC075V administered via IV bolus every 6 hours in patients with acute postsurgical pain. The overall incidence of serious AEs associated with DIC075V and the active comparator ketorolac were surprising low despite the inclusion of patients at high risk for NSAID toxicity including individuals who had undergone coronary bypass surgery within 6 hours of enrolling in the open-label study DFC-010 and patients with renal (serum creatinine < 3.0 mg/dL) and hepatic impairment (Child Pugh score 6-9) in the pivotal Phase 3 trial DFC-005. The majority of the SAEs contained in the safety database submitted in support of DIC075V's safety profile were the type of events expected to occur in a population following orthopedic and/or general surgery (i.e., pulmonary embolism and deep vein thrombosis). Not surprisingly these rates were higher in the open label study DFC-010 as compared to the randomized controlled trials DFC-004 and 005 and included cases of gastrointestinal bleeding, renal (e.g., acute renal failure) and hepatic (e.g., elevated liver function tests) toxicity consistent with what has been observed in patients treated with oral diclofenac.

Review of adverse events of special interest (e.g., cardiovascular events, arrhythmic events, local thrombotic events, and infusion-site related events) did not identify any potential safety issues related to the IV route of administration of DIC075V, however, none of the trials that evaluated this drug were powered to specifically determine safety risk. Higher rates of wound healing events were observed in both the 37.5 mg and 50 mg treatment groups of DIC075V as compared to placebo that were associated with a dose dependent trend in the rates of serious wound infections. Although more bleeding related events were observed in patients treated with DIC075V this was most likely due to the concomitant administration of prophylactic anticoagulant therapy postsurgery. However, the rates of bleeding events observed in the open-label study in patients treated with DIC075V were comparable to that reported observed in preventative thromboembolism trials in the published literature and associated with LMWH therapy.

Due to the unique mitigation of risk for NSAID toxicity mandated by the protocols for DFC-005 and 010, subjects at high risk for these events received lower doses of both the active comparator ketorolac and DIC075V yet it resulted in higher rates of selected AEs to be observed in the 18.75 mg DIC075V treatment group and the ketorolac 15 mg group as compared to the 37.5 mg and 50 mg doses of DIC075V and ketorolac 30 mg that were evaluated in these trials. Separating the high risk group may have also contributed to the inability to clearly observe dose-related AEs that is commonly observed with the oral administration of NSAIDs. However, dose-dependent increases

in serum creatinine, total bilirubin and systolic blood pressure, as well as decreases in hematocrit were observed on shift table analyses of pooled data that were supported by similar findings on individual examination of lab data generated from DFC-005 and -010. The Applicant stated in the submission that the decrease in hematocrit is an expected postsurgical finding. However, the presence of anemia increases the risk for the occurrence of serious AEs such as acute renal failure, stroke, myocardial infarction, or multiorgan failure particularly following an acute hemorrhage in patients at high risk for NSAID toxicity.

The safety database contained a robust number of subjects with mild renal or mild hepatic impairment treated with 37.5 mg or 50 mg of DIC075V. Overall, the drug's safety profile was similar in these subpopulations to what was observed in nonimpaired patients, however, dose-dependent gastrointestinal toxicity (e.g., nausea and vomiting) was observed on review of safety data collected from patients with mild to moderate renal and hepatic impairment.

The lack of a more pronounced cumulative dose-related occurrence of AEs may have been influenced by the short duration of exposure to DIC075V. Although the majority of subjects (e.g., 682 patients) contained in the safety database submitted in support of the drug's safety profile received 2 days of study treatment or a total of 8 doses of either 37.5 mg or 50 mg of DIC075V, the cumulative number of patients (e.g., 365 patients) with $\geq$ 3-5 days of exposure to either 37.5mg or 50 mg of the drug is too small to support a recommendation of a longer duration of therapy for DIC075V.

Review of the postmarketing data and worldwide literature also failed to identify any new potential safety signals associated with the intravenous administration of DIC075V.

In view of the dose-dependent increases in serum creatinine and systolic blood pressure as well as decreases in hematocrit that could increase the risk for a serious AE to occur and the lack of any additional benefit to be gained in efficacy associated with the administration of 50 mg in subjects weighing more than 95 kg, the data favor the 37.5 mg dose administered via IV bolus every 6 hours for the maximum duration of 2 days treatment for the management of acute pain.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

In support of this NDA, the Applicant submitted safety data from a total of 16 studies: ten Phase 1 trials (FARMOVS 19/94, FARMOVS 27/97, FARMOVS 26/97; DFC-PL1, DFC-003, DFC-PK-006, DFC-007, DFC-PK-008, DFC-PK-009 and DFC-011) , three Phase 2 trials (DFC-001, 002, and SAD21085) and three Phase 3 trials (DFC-004, 005, and 010). A listing of these trials is presented in Table 51. (Note: Studies DFC-003,

FARMOVS 19/94 and 26/97 evaluated DIC075V administered via intramuscular injection. (b) (4) Studies SAD21085, FARMOVS 26/97 and 27/97 also evaluated an earlier formulation (DIC075U) than the to-be-marketed dose while Study DFC-001 evaluated a higher dose than the to-be-marketed dose.)

Table 51 – Tabular Listing of All Clinical Studies of DIC0-75V Included in the Integrated Safety Summary

Study No.	Population Studied/Design	Formulation/ Route	No. Subjects Exposed by Dose
SAD21085	Postoperative subjects (dental surgery) / single dose	DIC075U / IV	25 mg: 63 50 mg: 73 75 mg: 68
DFC-001	Postoperative subjects (dental surgery) / single dose	DIC075V / IV	75 mg: 53
DFC-002	Postoperative subjects (dental surgery) / single dose	DIC075V / IV	3.75 mg: 51 9.4 mg: 51 18.75 mg: 51 37.5 mg: 51 75 mg: 51
DFC-004	Postoperative subjects (abdominal or pelvic surgery) / multiple-dose	DIC075V / IV	18.75 mg: 86 37.5 mg: 87
DFC-005	Postoperative subjects (elective orthopedic surgery) / multiple-dose	DIC075V / IV	18.75 mg: 45 37.5 mg: 65 50 mg: 35
DFC-010	Postoperative subjects (orthopedic, pelvic, abdominal surgery) / multiple-dose	DIC075V / IV	18.75 mg: 2 37.5 mg: 634 50 mg: 335
FARMOVS 19/94	Healthy volunteers / crossover	DIC075T / IM and IV	75 mg: 6
FARMOVS 27/97	Healthy volunteers / crossover	DIC075U / IV	75 mg: 27
DFC-PL1	Healthy volunteers / crossover	DIC075V / IV	75 mg: 8
DFC-003	Healthy volunteers / crossover	DIC075V / IM and IV	75 mg: 23
DFC-PK-006	Healthy volunteers / crossover	DIC075V / IV	18.75 and 37.5 mg: 36
FARMOVS 26/97	Healthy volunteers / single-dose crossover	DIC075U / IM	75 mg: 26
DFC-PK-008	Healthy volunteers / single dose	DIC075V / IV	37.5 mg: 54 18.75 mg: 34
DFC-PK-009	Chronic renal insufficiency, hepatic impairment, healthy volunteers / single-dose crossover	DIC075V / IV	37.5 mg: 19
DFC-007	Healthy volunteers / single-dose crossover	DIC075V / IV	37.5 mg: 30
DFC-011	Healthy volunteers / single-dose crossover	DIC075V / IV	37.5 mg: 70 75 mg: 70

Adapted Sponsor's Table 1-3; p. 28 ISS.

In addition to the safety databases generated from these 16 studies, the submission contained the safety results from three HPβCD PK studies conducted by Janssen, and other supportive safety data for the drug identified during a search of the worldwide literature (117 studies), an analysis of postmarketing adverse event reports associated with the use of any systemic formulation and/or dose of diclofenac collected by the FDA

(82,759 reports) and the World Health Organization (WHO) (4691 reports), as well as postmarketing reports and periodic safety updates (PSURs) for DIC075V from the Medicines and Healthcare Products Regulatory Agency (MHRA) in the United Kingdom where this drug is currently registered for marketing. These data were updated with new safety information contained in the 120-day safety update. Since no studies were ongoing when this application was originally submitted or were initiated following its submission, the updated safety database contains citations from a recent search of the worldwide literature as well as a summary of postmarketing reports from the MHRA's December 12, 2009 PSUR for DIC075V.

Safety data from the 16 studies were summarized in the individual trial reports, the Integrated Summary of Safety and the electronic datasets for adverse events, lab data and vital signs. All safety analyses that were performed of the double –blind safety population and the single and multiple-dose open label safety and PK studies, as well as the reviews from the published citations in the literature, and the tabular summaries of postmarketing adverse events including the data contained in the 120-day safety update were examined by this medical officer.

7.1.2 Categorization of Adverse Events

Verbatim terms of AEs recorded in the case report forms (CRF) from safety information captured in patients' diaries and by investigators was coded by the applicant using MedDRA dictionary Lower level Term, Preferred Term and System Organ Class (SOC). (version 12.0). A listing of all AEs coded in this manner including the corresponding verbatim terms was included in the CRF for review. The MedDRA coding of the information generated from clinical trials conducted by the applicant was generally acceptable. Additionally the clinical lab and vital sign ranges for clinically significant abnormal results were reviewed and appear to be appropriate.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The DIC075V safety population, which was defined as all patients who received at least 1 dose of study medication, was summarized by the Applicant in four pooled population groups as follows:

- Population 1: multi-dose, double-blind, placebo-controlled and uncontrolled Phase 3 studies of DIC075V (DFC-004, 005 and 010) in patients with acute moderate to severe pain following orthopedic, abdominal or pelvic surgery
- Population 2: single-dose, double-blind, placebo-controlled and uncontrolled Phase 2 and 3 studies of DIC075V (DFC-001 and 002) in patients following oral surgery (third molar extraction)

- Population 3: single-dose, Phase 1 special population PK studies (FARMOVS 19/04, FARMOVS 26/97, FARMOVS 27/97, DFC-PL1, DFC-003, DFC-007, DFC-PK-008, and DFC-PK-009).
- Population 4: All randomized, placebo-controlled, postoperative studies inpatients with acute moderate to severe pain regardless of the number of doses received (DFC-001, 002, 004, and 005 and SAD21058).

Populations 3 and 4 contained inappropriately pooled data generated from both uncontrolled and controlled, single- and multiple-dose, parallel group and crossover studies that evaluated a variety of formulations, doses and routes of administration (e.g., intramuscular injection) not under consideration for marketing or evaluated varying durations of exposure (e.g., 1 dose to 1-5 days of cumulative exposure) which could result in a potential underestimation of the safety risk associated with DIC075V. Population 2 contains pooled safety data from single-dose, uncontrolled and controlled Phase 2 and 3 oral surgery studies that evaluated a variety of dose strengths not under consideration for marketing and did not include subjects from the drug's target population (e.g., general and orthopedic postsurgery patients with acute moderate to severe pain).

Population 1 was identified as containing the most appropriately pooled source of safety data for purposes of this review since it contained data generated from adequate and well-controlled trials (DFC-004 and 005) suitable for use in determining the drug's safety profile based on the reported AE, clinical lab results, vital signs and ECG as well as AE data generated from subjects who received multiple doses of DIC075V in the open-label post-operative pain study DFC-005 necessary for the determination of safety risks associated with prolonged drug exposure (e.g. 5 days). However, the pooled safety datasets in Population 1 were analyzed by the Applicant as follows: pooled by study design and treatment or by treatment and dose regardless of study design. The pooled subset of Population 1 that was analyzed by study design and treatment only included subjects who had received 37.5 mg or 50 mg of DIC075V during DFC-004, 005, or 010 as well as subjects in the placebo group that matched subjects in the DIC075V group who had received the proposed dose under consideration for marketing. Although this subset analyses excludes those subjects who had received either the 18.75 mg dose of DIC075V or matching placebo in order to not underestimate the safety risk of DIC075V given the small numbers of AEs reported during these trials, it does not permit examination of the safety data for dose-related AEs necessary to determine the risk-benefit profile of the proposed 37.5 mg standard dose (b) (4) (b) (4) In view of this, this medical reviewer examined the Population 1 pooled datasets first by study design and treatment in order to determine DIC075V's overall safety profile followed by an examination of pooled safety data by treatment and dose regardless of design to identify dose-related toxicities associated with DIC075V.

7.2 Adequacy of Safety Assessments

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

Cumulative exposure data by DIC075V dose for the combined controlled and uncontrolled multiple-dose Phase 3 trials is presented in Table 52. A total of 1,289 post-surgical patients were treated in these trials with the to-be-marketed formulation of DIC075V as follows: 133 patients with 18.75 mg, 786 patients with 37.5 mg and 370 patients with 50 mg. Median duration of DIC075V exposure for the total population was 8 doses (range: 1-21 doses) or 2 days (range: 1-5 days). Of the 1,156 subjects who received DIC075V at the recommended dose of 37.5 mg or 50 mg for weight greater than 95 kg, 71 subjects received 4 doses, 633 subjects received 8 doses, 123 subjects received 12 doses, and 111 subjects received > 12 doses. The number of patients with exposure to 2 or more days of DIC075V (b) (4) 37.5 mg and 50 mg meets the minimum number of subjects required to support the drug's safety as discussed at the EOP2 meeting with the Applicant.

Table 52 – Tabular Summary of Exposure to DIC075V During the Combined Controlled and Uncontrolled Multiple-Dose Phase 3 Trials (Safety Population)

		DIC075V				Ketorolac	
Parameter	Placebo (N=148)	18.75 mg (N=133)	37.5 mg (N=786)	50 mg (N=370)	Total (N=1289)	15 mg (N=18)	30 mg (N=124)
Number of Doses Received - n (%)							
1	25 (16.9)	12 (9.0)	18 (2.3)	3 (0.8)	33 (2.6)	1 (5.6)	9 (7.3)
2	1 (0.7)	0	3 (0.4)	3 (0.8)	6 (0.5)	1 (5.6)	1 (0.8)
3	6 (4.1)	2 (1.5)	7 (0.9)	4 (1.1)	13 (1.0)	0	1 (0.8)
4	34 (23.0)	11 (8.3)	46 (5.9)	25 (6.8)	82 (6.4)	3 (16.7)	27 (21.8)
5	4 (2.7)	2 (1.5)	13 (1.7)	5 (1.4)	20 (1.6)	0	0
6	1 (0.7)	0	8 (1.0)	3 (0.8)	11 (0.9)	0	0
7	3 (2.0)	4 (3.0)	16 (2.0)	4 (1.1)	24 (1.9)	0	0
8	50 (33.8)	77 (57.9)	450 (57.3)	183 (49.5)	710 (55.1)	1 (5.6)	66 (53.2)
9	0	3 (2.3)	49 (6.2)	26 (7.0)	78 (6.1)	0	1 (0.8)
10	0	2 (1.5)	5 (0.6)	9 (2.4)	16 (1.2)	0	1 (0.8)
11	2 (1.4)	1 (0.8)	25 (3.2)	17 (4.6)	43 (3.3)	0	1 (0.8)
12	16 (10.8)	11 (8.3)	66 (8.4)	57 (15.4)	134 (10.4)	8 (44.4)	15 (12.1)
> 12	6 (4.1)	8 (6.0)	80 (10.2)	31 (8.4)	119 (9.2)	4 (22.2)	2 (1.6)
N	148	133	786	370	1289	18	124
Mean (SD)	6.2 (3.7)	7.7 (3.2)	8.7 (3.2)	9.0 (3.1)	8.7 (3.2)	10.2 (5.3)	7.1 (3.1)
Median	7.5	8.0	8.0	8.0	8.0	12.0	8.0
Min-Max	1-16	1-16	1-21	1-20	1-21	1-20	1-13
Number of Exposure Days[a] - n (%)							
1 (≤4 doses)	66 (44.6)	25 (18.8)	74 (9.4)	35 (9.5)	134 (10.4)	5 (27.8)	38 (30.6)
2 (5 - 8 doses)	58 (39.2)	83 (62.4)	487 (62.0)	195 (52.7)	765 (59.3)	1 (5.6)	66 (53.2)
3 (9 - 12 doses)	18 (12.2)	17 (12.8)	145 (18.4)	109 (29.5)	271 (21.0)	8 (44.4)	18 (14.5)
4 (13 - 16 doses)	6 (4.1)	8 (6.0)	56 (7.1)	22 (5.9)	86 (6.7)	3 (16.7)	2 (1.6)
5 (17 - 21 doses)	0	0	24 (3.1)	9 (2.4)	33 (2.6)	1 (5.6)	0
Number of Exposure Days[a]							
N	148	133	786	370	1289	18	124
Mean (SD)	1.8 (0.8)	2.1 (0.7)	2.3 (0.9)	2.4 (0.8)	2.3 (0.8)	2.7 (1.2)	1.9 (0.7)
Median	2.0	2.0	2.0	2.0	2.0	3.0	2.0
Min-Max	1-4	1-4	1-5	1-5	1-5	1-5	1-4

Source: Appendix 13.5, Table 2.1.
a Number of exposure days was determined based on doses received

Modified Sponsor's Table 4-14; p. 73-74.

A summary of the baseline demographics of patients who participated in the pooled multidose Phase 3 trials is shown in

Table 53. Subjects treated with DIC075V were demographically similar to those who received placebo during the controlled trials. The patients who participated in these studies were overwhelmingly Caucasian and female with a mean age 56 years in the total DIC075V group, as compared to 49 years in the placebo group. Baseline characteristics were also similar on cross comparison of the 18.75 mg, 37.5 mg and 50 mg DIC075V treatment groups with the exception of weight. The 50 mg treatment group of DIC075V was mainly comprised of patients who weighed more than in the other treatment groups since the protocols for studies DFC-005 and 010 mandated that subjects weighing $\geq$ 95 kg were to receive 50 mg of DIC075V. The proportions of patients with either mild renal (total of 64 subjects) or mild hepatic (total of 34 subjects) impairment was comparable on cross comparison of treatment groups. All 4 patients with moderate renal insufficiency who participated in these studies were treated with either 37.5 mg (2 subjects) or 50 mg (2 subjects) of DIC075V. Based on the these data, the overall population that participated in these Phase 3 multidose studies was generally representative of post-surgical patients who could potentially benefit from analgesic treatment with DIC075V.

Table 53 – Summary of Demographic and Baseline Characteristics by Treatment Group for Subjects Pooled by Treatment from the Multidose Phase 3 Trials (Safety Population)

Demographic Characteristic	Placebo (N=148)	DIC075V			
		18.75 mg (N=133)	37.5 mg (N=786)	50 mg (N=370)	Total (N=1289)
Age (yrs.):					
Mean (SD)	49 (14)	52 (17)	57 (15)	57 (12)	56 (14)
Range	(19-84)	(18-81)	(18-87)	(23-83)	(18-87)
Group:					
<65 years	124 (84%)	92 (69%)	516 (66%)	270 (73%)	878 (68%)
≥65 years	24 (16%)	41 (31%)	270 (34%)	100 (27%)	411 (32%)
Race:					
Caucasian	130 (88%)	110 (83%)	681 (87%)	316 (85%)	1107 (86%)
Black	10 (7%)	10 (8%)	70 (9%)	46 (12%)	126 (10%)
Asian	0	0	11 (1%)	1 (0%)	12 (1%)
Other	8 (5%)	13 (10%)	24 (3%)	7 (2%)	44 (3%)
Gender:					
Male	41 (28%)	32 (24%)	211 (27%)	196 (53%)	439 (34%)
Female	107 (72%)	101 (76%)	575 (73%)	174 (47%)	850 (66%)
Height (cm):					
Mean (SD)	167 (9.3)	166 (10)	166 (9.4)	174 (10)	168 (10)
Range	(150-195)	(137-191)	(107-198)	(142-197)	(107-198)
Weight (kg):					
Mean (SD)	85 (21)	85 (20)	78 (13)	112 (14)	88 (21)
Range	(46-142)	(45-150)	(44-155)	(93-196)	(44-196)
Group:					
<95 kg	103 (70%)	91 (68%)	755 (96%)	2 (0.5%)	848 (66%)
≥95 kg	44 (30%)	42 (32%)	31 (4%)	368(99.5%)	441 (34%)
BMI (kg/m^2):					
Mean (SD)	30 (7)	31 (7)	28 (5)	37 (6)	31 (7)
Range	(19-53)	(18-71)	(17-67)	(27-66)	(17-71)
Renal Impaired[a]:					
Mild	8 (5%)	8 (6%)	34 (4%)	22 (6%)	64 (5%)
Moderate	0	0	2 (0.3%)	2 (0.5%)	4 (0.3%)
Not Impaired	139 (94%)	125 (94%)	746 (95%)	345 (93%)	1216 (94%)
Hepatic Impaired[b]:					
Mild	2 (1%)	2 (1.5%)	24 (3%)	8 (2%)	34 (3%)
Moderate	0	0	0	0	0
Not Impaired	145 (98%)	131(98.5%)	758(96%)	361 (98%)	1250 (97%)
Type of Surgery:					
Orthopedic	72 (49%)	46 (35%)	474 (60.3%)	301 (81.4%)	821 (63.7%)
Abd./Pelvic	76 (51%)	87 (65%)	311 (39.6%)	68 (18.4%)	466 (36.2%)
Other	0	0	1 (0.1%)	1 (0.3%)	2 (0.2%)

Modified Sponsor's Table 4-8; p. 58.

[a]Mild renal impairment is defined as screening creatinine > ULN to 1.5 x ULN. Moderate renal impairment is defined as screening creatinine > 1.5 x ULN

[b]Mild hepatic impairment is defined as screening bilirubin > ULN to 2.0 x ULN. Moderate hepatic impairment is defined as screening bilirubin > 2.0 x ULN.

7.2.2 Explorations for Dose Response

As part of their product development program for DIC075V, the Applicant conducted two Phase 2 single-dose, placebo-controlled, parallel group, dose-finding studies (SAD21085 and DFC-002) in order to identify an efficacious and safe dose of DIC075V for evaluation in the pivotal Phase 3 studies. Since SAD21085 evaluated 25, 50 and 75 mg doses of an earlier formulation of the drug (DIC075U) utilizing a TOTPAR 0-4 hours as its primary endpoint, its results were considered to be supportive for evaluating a dose range of 3.75, 9.5, 18.75, 37.5, and 75 mg of the to-be-marketed formulation (DIC075V) in the pivotal dose response study, DFC-002. Dose selection in DFC-002 was based primarily on the analysis of the TOTPAR 0-6 hours, onset of analgesic action and duration of analgesic effect. Analyses of the data from this study at 0-6 hours post dose reportedly demonstrated a dose-dependent increase in total pain relief with a corresponding decrease in pain intensity associated with doses in the range of 3.75 to 37.5 mg. Additionally, the dose response of the 75 mg dose of DIC075V did not appear to be better than the 37.5 mg dose. These data supported evaluating doses of 18.75 and 37.5 mg of DIC075V administered every 6 hours in the pivotal Phase 3 studies.

Supportive evidence for using a higher dose of 50 mg of DIC075 was generated from a regression analysis conducted on PK data from DFC-PK-008. The results from this analysis reportedly showed a modest but statistically significant increase in the clearance (CL) of DIC075V at the dose 37.5 mg with increasing body weight suggesting that subjects weighing more than 95 kg may need a higher dose in order to achieve an AUC consistent with the exposure similar to that at 37.5 mg.

7.2.3 Special Animal and/or In Vitro Testing

The Applicant was not required to conduct any special animal or in vitro testing in support of the safety of DIC075V since this submission is a 505(b)(2).

7.2.4 Routine Clinical Testing

The following clinical lab testing were conducted in all the studies submitted in support of DIC075V's safety profile:

- Complete cell count with differential and platelet count, hemoglobulin and hematocrit
- Serum chemistries: ALT, SGPT, AST, SGOT, CPK, alkaline phosphatase, GGT, total bilirubin, BUN, creatinine, albumin, phosphate, bicarbonate, potassium, calcium, sodium, chloride, total protein, glucose, uric acid, and LDH
- Vital signs: systolic and diastolic blood pressure, respiratory rate, and temperature
- Serial 12-lead ECGs

Additional physical evaluations included wound healing (DFC-004 and 005) and a thrombophlebitis assessment (DFC-001, 002, 004, 005, and 010).

Overall, the types of clinical lab testing and physical assessments as well as the timing of these assessments were appropriate for the populations studied in these trials.

7.2.5 Metabolic, Clearance, and Interaction Workup

Since this is a 505(b)(2) application, the Applicant referenced the current product labeling for both the RD Cataflam (diclofenac potassium) (NDA 20-142) and for Sporonax (itraconazole) Injection (NDA 20-966) for background information on the biopharmaceutics of diclofenac potassium and the PK of (b) (4) HPβCD, respectively. However, the Applicant also conducted DFC-PK-006 which was a single and multiple dose cross-over PK study that compared DIC075V administered via intravenous (IV) and intramuscular (IM) routes to 50 mg of Cataflam administered orally. Table 54 summarizes the single dose PK parameters of DIC075V as compared to orally administered Cataflam generated from this study. Peak plasma levels were 5-fold higher and systemic exposure (AUC_{inf}) was approximately 20-30% higher with 37.5 mg of DIC075V when administered IV as compared to 50 mg of Cataflam orally. According to the Applicant, mean values for CL, V_z, and t1/2 for DIC075V were comparable for different doses of the formulation and route of administration. No accumulation of DIC075V was observed following 4 IV doses of the drug.

Table 54 – Tabular Summary of Pharamacokinetic Parameters of DIC075V

Parameter[1,2]	DIC075V 75 mg IV[4]	DIC075V 75 mg IM[4]	DIC075V 37.5 mg IV	Cataflam 50 mg PO
C_{max} (ng/mL)	21,524 ± 30,705[3]	2,569 ± 1,092	6,031 ± 1,178	1,246 ± 732
T_{max} (h)	0.05	0.64	0.083	1.5
$AUC_{(inf)}$ (h×ng/mL)	4,420 ± 1,636	4,304 ± 908	1,859 ± 376	1,562 ± 519
$t_{½}$(h)	1.17 ± 0.32	1.17 ± 0.31	1.44 ± 0.27	1.28 ± 0.27
CL (mL/min)	-	-	324 ± 63.0	526 ± 179

[1]Arithmetic mean ± standard deviation, except for T_{max} for which the median is reported
[2]CL is CL/F for Cataflam
[3]Value is high because 1 subject had a plasma concentration at the 3-minute blood draw time point that was 10-fold higher than expected. The clinical site deems it possible that the same cannula was used for drug administration and for the 3-minute blood draw for that subject.
[4]The 75 mg IV or IM dose is the dose approved and marketed in the United Kingdom. See Dyloject SPC (CTD 1.14.5).
Adapted Sponsor's Table 1; p. 12.

Based on the results from special population studies, no effect on the PK profile of DIC075V after correction for bodyweight was observed with regards to age (DFC-PK-008), sex, race, renal impairment (mild and moderate only) (DFC-PK-009), or mild hepatic impairment (DFC-PK-009).

Approximately 80-90% of HPβCD, the excipient, is eliminated via the kidney with a total systemic clearance in plasma of 22.7 mL/min which corresponds to glomerular filtration. Following IV administration of 37.5 mg of DIC075V, the terminal half-life of HPβCD in plasma is approximately 2.7 ± 1.4 hours. According to the Applicant, overall systemic exposure to HPβCD in patients with moderate renal insufficiency following a single dose of 37.5 mg of DIC075V was 7.9 –fold lower compared with the exposure to HPβCD in healthy subjects receiving a single 200 mg dose of Sporonox. In patients with severe renal impairment, accumulation of HPβCD is predicted to be less than half that of systemic exposure to HPβCD from a single dose of Sporonox to healthy subjects and theoretically should not constitute a safety issue.

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

DIC075V belongs to the nonsteroidal anti-inflammatory class of drugs. The safety profile for NSAIDs has been well document and includes toxicities involving the gastrointestinal, hepatic, renal and hematological systems, as well as an increase in risk for cardiovascular events. Cataflam is a systemic, oral formulation of diclofenac potassium currently approved for marketing in this country. Although it differs from DIC075V in the concentration of diclofenac and other components (e.g.,hydroxyporpyl-β-cycloderin) the adverse event profiles of these two formulations are expected to be similar. In view of this and other drug class related toxicities, the clinical studies conducted in support of DIC075V included hepatic, renal, hematological, and cardiovascular monitoring. Additionally, patients with underlying hepatic and renal disease, or those at high risk for the development of NSAID toxicity (age ≥ 65 years) were either prohibited from participating in one of the pivotal trials for DIC075V (DFC-004) or were administered a lower dose of 18.75 mg of the drug (DFC-005). (Note: Entry criteria for DFC-005 employed the following definitions: mild renal impairment was defined as serum creatinine > ULN value and <1.9 mg/dL while moderate renal impairment was defined as serum creatinine >1.9 mg/dL; mild hepatic impairment was defined as Child-Pugh score <6 while moderate hepatic impairment was defined as Child-Pugh score of 6-9.) However, based on the safety data from the pivotal trials and the PK data generated from special population studies, hepatically and renally impaired patients were treated with either 37.5 mg or 50 mg if their weight was greater than 95 kg in the open-label safety trial DFC-010. Since safety concerns have been raised regarding delayed wound healing and thrombotic events associated with NSAIDs, the Applicant also conducted assessments of wound healing in the pivotal trial DFC- 005 and the large, multidose open-label study DFC-010. In view of the safety data and corresponding analyses contained in this submission, the Applicant has made a diligent effort to monitor and identify adverse events associated with DIC075V similar to those seen with Cataflam. The results of these efforts are discussed in the following sections of this review.

7.3 Major Safety Results

All safety analyses were performed on the population of subjects who had received any study drug and had at least one post-dose safety assessment. Analyses of adverse events (AEs) were performed only for those events considered to be treatment emergent. (Note: The Applicant defined treatment-emergent AEs as events that occurred during the administration of, or after the first dose of, study drug or that were pre-existing but had increased in severity after the first dose of study drug through 30 days after the last dose of study drug.) A tabular summary of AEs that were reported in the DIC075V safety database presented by controlled trials (DFC-004 and 005) and the open label trial (DFC-010) is presented in Table 55 The majority of subjects (over 80% in each of the treatment arms) in these trials experienced at least 1 AE during their participation. In the controlled trials, the rate of serious adverse events (SAEs) was higher in the placebo group (4.0%) as compared to the combined 37.5 mg and 50 mg DIC075V group (3.7%). The rate of SAEs increased to 7.5% in the open label trial DFC-010 that may be the result of patients with increased background risk for NSAID toxicity being treated with higher doses of DIC075V (e.g., 37.5 mg and 50 mg). The rate of severe AEs was also higher in the placebo group (6.3%) as compared to both the combined DIC075V group from the controlled trials (5.3%) and the open label trial (4.3%). There were a total of 2 deaths in the safety database submitted in support of DIC075V which occurred in the open-label study. During the controlled trials, no patients withdrew from the placebo group due to an AE as compared to 3.7% and 3.4% rates of withdrawal due to an AE in the combined DIC075V group and the open-label trial, respectively.

Table 55 – Tabular Summary of Adverse Events for Subjects Who Participated in the Multiple Dose Pain Studies (Safety Population)

	Placebo[b] (N = 126)	DIC075V 37.5 mg and 50 mg[a]		
		DFC-004 and DFC-005 (N =187)	DFC-010 (N=969)	Total (N=1156)
Number of Subjects with Any Treatment Emergent Adverse Events	104 (82.5%)	146 (78.1%)	819 (84.5%)	965 (83.5%)
Number of Subjects with Any Treatment-Related Adverse Events	26 (20.6%)	37 (19.8%)	86 (8.9%)	123 (10.6%)
Number of Subjects with Any Treatment-Emergent Serious Adverse Event	5 (4.0%)	7 (3.7%)	73 (7.5%)	80 (6.9%)
Number of Subjects with Any Treatment-Related Serious Adverse Event	0	0	8 (0.8%)	8 (0.7%)
Number of Subjects with Any Treatment-Emergent Severe Adverse Event	8 (6.3%)	10 (5.3%)	42 (4.3%)	52 (4.5%)
Number of Subjects with Any Treatment-Related Severe Adverse Event	1 (0.8%)	1 (0.5%)	6 (0.6%)	7 (0.6%)
Number of Deaths	0	0	2 (0.2%)	2 (0.2%)
Number of Subjects with Any Treatment-Emergent AE Resulting in Withdrawal	0	7 (3.7%)	33 (3.4%)	40 (3.5%)
Number of Subjects with Any Treatment-Related AE Resulting in Withdrawal	0	1 (0.5%)	14 (1.4%)	15 (1.3%)

[a]The DIC075V 37.5 mg and 50 mg dose groups are included in this analysis (b) (4)
(b) (4)

[b] Includes subjects in the placebo group that match subjects in the DIC075V group who received the proposed dose
Adapted Sponsor's Table 99; submitted 8/6/10

For completeness, Table 56 summarizes the AEs that were reported in the DIC075V safety database presented as pooled safety data from the two controlled trials (DFC-004 and -005) and the open-label, multi-dose trial (DFC-010) by dose treatment group which includes patients treated with 18.75 mg of DIC075V and the placebo matched subjects as per the protocols for the two pivotal trials (DFC-004 and 005) as well as the 2 patients treated with 18.75 mg of DIC075V in error in the open label trial (DFC-010) and patients treated with the active comparator ketorolac in DFC-004 and 005.

Table 56 – Tabular Summary of Adverse Events by Treatment Group for Subjects in Multiple Dose Pain Studies (Safety Population)

		DIC075V				Ketorolac	
Subjects with at least 1:	Placebo (N=148) n (%)	18.75 mg (N=133) n (%)	37.5 mg (N=786) n (%)	50 mg (N=370) n (%)	Total (N=1289) n (%)	15 mg (N=18) n (%)	30 mg (N=124) n (%)
AE	122 (82.4)	110 (82.7)	664 (84.5)	301 (81.4)	1075 (83.4)	15 (83.3)	102 (82.3)
Treatment-related AE	28 (18.9)	22 (16.5)	88 (11.2)	35 (9.5)	145 (11.2)	0	28 (22.6)
SAEs	6 (4.1)	7 (5.3)	50 (6.4)	30 (8.1)	87 (6.7)	3 (16.7)	4 (3.2)
Treatment-related SAE	0	1 (0.8)	8 (1.0)	1 (0.3)	10 (0.8)	0	1 (0.8)
AE leading to discontinuation	0	3 (2.3)	28 (3.6)	12 (3.2)	43 (3.3)	0	2 (1.6)
Treatment-related AE leading to discontinuation	0	2 (1.5)	10 (1.3)	5 (1.4)	17 (1.3)	0	0

Source: Appendix 13.5, Table 3.1.1.1.1, Table 3.3.1.1, Table 3.13.1.1.1, Table 3.14.1, Table 3.15.1.1, and Table 3.15.1.2.

Adapted Sponsor's Table 4-16; p. 77.

The proportion of patients who developed serious adverse events (SAE) was highest in the total DIC075V group (6.7%), followed by the total ketorolac group (4.9%) and the placebo group (4.1%). Additionally, a dose dependent increase in SAE was observed in subjects treated with 18.75 mg (5.3%), 37.5 mg (6.4%) and 50 mg (8.1%) of DIC075V while a higher incidence of SAEs was seen in patients in the 15 mg ketorolac group (16.7%) as compared to the ketorolac 30 mg group (3.2%) that is most likely due to the small number of patients (n=18) in that treatment grouping in addition to an increase in background risk factors. No patients in the placebo group withdrew from treatment due to experiencing an AE, as compared to 1.4% of subjects in the total ketorolac group and 3.3% in the total DIC075V group. Further examination of these data showed that the rate of study withdrawal due to an AE was similar for subjects in the three DIC075V dose groups.

7.3.1 Deaths

There were a total of 2 deaths reported in the DIC0V75 development program which occurred in the open-label, multidose trial, DFC-010. Table 57 lists the two patients who died. Subject 13-072 was a 71 year-old male with a history of deep venous thrombosis (DVT) status post left total knee replacement who died of a pulmonary embolism 3 days post-revision of his total knee replacement despite being on low molecular weight heparin and using athrombic pumps, TED hose and ambulating post surgery. This patient's risk was increased for having a thromboembolic event by his history of DVT and the type of surgical procedure he underwent. The other patient who died due to sepsis and possible congestive heart failure was a 65 year-old male with a history of insulin-dependent diabetes mellitus (IDDM), osteoarthritis, prostate cancer and gout with a preoperative ECG showing normal sinus rhythm and right bundle branch block. This patient was discharged home 3 days after he underwent right hip replacement.

Three days post discharge, his home health nurse sent the patient to the local hospital for evaluation of dyspnea with cough and ashen pallor. Based on his initial evaluation in the emergency room, it was thought that he had a non-Q wave myocardial infarction with congestive heart failure. However, cardiac catherization showed a cardiac output of 3.3. L/min with calcified coronary arteries but no significant disease in this left main artery. Chest CT showed diffuse lung densities consistent with infection. Broncho-alveolar lavage yielded "thick purulent chunks of mucus." Despite aggressive medical care and antibiotics, this patient developed multi-organ failure and died. His death was attributed to sepsis with ongoing congestive heart failure. No autopsy was performed. This patient also increased risk for developing a serious infection due to his history of diabetes.

Table 57 – Tabular Summary of Subjects Who Died While Participating In DIC075V Studies

Subject Number	Age/Sex	Cause of Death	Study	Died >30 Days After Last Dose	Pertinent History
13-072	71yo/M	Pulmonary Embolism	DFC-010	No	Pt. developed diaphoresis and shortness of breath with pain referred to left shoulder. He became hypotensive and hypoxic with O_2 saturation of <85% despite nasal O_2 supplement. Developed pulseless SVT and died despite cardiopulmonary resuscitation. H/O DVT and S/P previous left TKR. Concomitant meds and treatments: Lovenox, lorazepam, Ancef, morphine, Lortab, Ambien, athrombic pumps with TED hose
31-034	65yo/M	Sepsis; Possible CHF	DFC-010	No	Pt. was readmitted 3 days post-discharge with dyspnea with cough with an original diagnosis of non-Q wave MI with CHF which was R/O'd on cardiac cath. However, CX CT showed diffuse lung densities c/w infection. Bronchoscopy revealed "thick purulent chunks of mucus." Pt. developed multi-organ failure due to sepsis and died. No autopsy was performed. H/O IDDM, OA, prostate cancer and S/P right knee arthroplasty and laminectomy. Concomitant meds: Metformin, insulin, Coumadin, suldinac, Singular, Claritin. Pepsid, fentanyl.

7.3.2 Nonfatal Serious Adverse Events

Table 58 is a tabular summary of all of the treatment-emergent SAEs for DIC075V reported in the safety database for both the controlled trials and open-label safety study. Overall, the numbers of SAEs observed in these three trials were low. During the two controlled trials, the proportion of patients who experienced treatment emergent serious adverse events (SAEs) in the combined DIC075V 37.5 mg and 50 mg dose treatment groups was 3.7% which was similar to the 4% observed in the placebo group. Review of the SAEs by system organ class (SOC) for the combined DIC075V 37.5 and 50 mg dose treatment groups as compared to the combined placebo group did not reveal any potential safety signals due to the small numbers of SAEs observed during the controlled trials. The majority of the SAEs reported in both the DIC075V and placebo groups of the controlled trials were adverse events expected to occur in a population following orthopedic and/or general surgery. These included pulmonary embolism (1 case in the placebo group), deep vein thrombosis (2 cases in the combined DIC075V group), ileus (2 cases in the combined DIC075V), and small intestinal obstruction (1 case in the combined DIC075V).

Further review of the data listed in Table 58 showed that the rate of SAEs increased to 7.5% in the open-label safety trial, DFC-010. Five system organ classes contributed to the higher overall rate of SAEs in this trial: infections and infestations (2.5%); injury, poisoning and procedural complications (1.8%); respiratory, thoracic and mediastinal disorders (1.1%); investigations (0.7%); and renal and urinary disorders (0.3%). The higher rate of SAEs in the infections and infestations SOC for the open label study is attributable to 24 cases of a variety of postoperative infections that mainly involved the surgical incision or wound site (17 cases). These wound infections do not appear related to DIC075V since NSAIDs are not known to be immunosuppressive agents, and sepsis and wound infections are expected adverse events following surgical procedures. Five of the 17 SAEs reported under the injury, poisoning and procedural SOC were due to femoral fractures which were all reported to have occurred in patients who had undergone total hip replacements: 2 subjects (13-034 and 14071) developed fractures post falling after discharge; 1 subject (58-001) developed a fracture after twisting her operative leg, and 2 subjects (53-001 and 54-055) developed femoral fractures associated with prosthetic failure. Of the remaining 12 SAEs listed under this SOC, 9 involved the surgical incision site which is unexpected and will be discussed further with other safety areas of interest (wound healing). The higher rate of SAEs in the respiratory SOC for the open label study is due to 6 cases (0.6%) of pulmonary embolism which is an expected postoperative complication as are some of the other SAEs listed under this SOC that maybe associated with general anesthesia such as hypoxia (2 cases), acute respiratory distress syndrome (1 case), aspiration (1 case), atelectasis (1 case), pulmonary edema (1 case) and respiratory arrest (1 case).

There were 3 cases of increased serum creatinine, 2 cases of increased CPK and 1 case of liver function abnormality listed under the investigations SOC for DFC-010.

Elevations in CPK are expected following muscle tissue disruption during surgery. Increases in liver function tests and serum creatinine are expected AEs associated with the NSAID class of drugs which are hepatotoxic and nephrotoxic agents. Additional examination of the renal and urinary disorder SOC for this trial show that there were 3 cases of renal failure and 1 case of renal tubular necrosis associated with the use of DIC075V which has been reported to occur with other NSAIDs including Cataflam and will be discussed further with other safety areas of interest (renal events). There was one SAE of angioedema that occurred in a patient (Subject 31-031) while participating in DFC-010. According to the CFR for this subject, he developed angioedema following the administration of lisinopril/HCTZ two days after he had completed study dosing with 37.5 mg of DIC075V. This SAE should not be attributed to DIC075V in view of the exposure time line.

Table 58 – Tabular Summary of Serious Treatment Emergent Adverse Events in the Pooled Double Blind and Open Label Multiple Dose Pain Studies (Safety Population)

Adverse Event by MedDRA System Organ Class/ Preferred Term	Placebo[b] (N = 126)	DIC075V 37.5 mg and 50 mg[a]		
		DFC-004 and DFC-005 (N =187)	DFC-010 (N=969)	Total (N=1156)
Number (%) of Subjects with Any Serious AEs:	**5 (4.0%)**	**7 (3.7%)**	**73 (7.5%)**	**80 (6.9%)**
Cardiac Disorders:	**0**	**0**	**4 (0.4%)**	**4 (0.3%)**
Atrial Fibrillation	0	0	2 (0.2%)	2 (0.2%)
Bradicardia	0	0	1 (0.1%)	1 (0.1%)
Cardio-Respiratory Arrest	0	0	1 (0.1%)	1 (0.1%)
Gastrointestinal Disorders:	**1 (1.6%)**	**2 (1.1%)**	**14 (1.4%)**	**16 (1.4%)**
Small Intestinal obstruction	0	1 (0.5%)	3 (0.3%)	4 (0.3%)
Nausea	0	0	2 (0.2%)	2 (0.2%)
Vomiting	0	0	2 (0.2%)	2 (0.2%0
Ileus	0	1 (0.5%)	0	1 (0.1%)
Inguinal Hernia	0	1 (0.5%)	0	1 (0.1%)
Abdominal Pain	0	0	1 (0.1%)	1 (0.1%)
Anal Hemorrhage	0	0	1 (0.1%)	1 (0.1%)
Constipation	0	0	1 (0.1%)	1 (0.1%)
Enterocutanous Fistula	0	0	1 (0.1%)	1 (0.1%)
Hematochezia	0	0	1 (0.1%)	1 (0.1%)
Intestinal Perforation	0	0	1 (0.1%)	1 (0.1%)
Pancreatitis	0	0	1 (0.1%)	1 (0.1%)
Peritonitis	0	0	1 (0.1%)	1 (0.1%)
Upper GI Hemorrhage	0	0	1 (0.1%)	1 (0.1%)
Colonic Stenosis	1 (0.8%)	0	0	0
Ileus Paralytic	1 (0.8%)	0	0	0
Gen. Disorders and Administration Site Conditions:	**0**	**2 (1.1%)**	**4 (0.4%)**	**4 (0.3%)**
Pyrexia	0	1 (0.5%)	2 (0.2%)	2 (0.2%)
Non-Cardiac Chest Pain	0	1 (0.55)	1 (0.1%)	1 (0.1%)
Edema Peripheral	0	0	1 (0.1%)	1 (0.1%)

Table 58 (cont.) - Tabular Summary of Serious Treatment Emergent Adverse Events by Dose Group in the Pooled Multidose Phase 3 Trials (Safety Population)

Adverse Event by MedDRA System Organ Class/ Preferred Term	Placebo[b] (N = 126)	DIC075V 37.5 mg and 50 mg[a]		
		DFC-004 and DFC-005 (N =187)	DFC-010 (N=969)	Total (N=1156)
Infections and Infestations:	**1 (0.8%)**	**1 (0.5%)**	**24 (2.5%)**	**25 (2.2%)**
Wound Infection	0	1 (0.5%)	4 (0.3%)	4 (0.3%)
Incision Site cellulitis	0	0	3 (0.3%)	3 (0.3%)
Cellulitis	1 (0.8%)	0	2 (0.2%)	2 (0.2%)
Sepsis	0	0	2 (0.2%)	2 (0.2%)
Abdominal Wall Abscess	0	0	2 (0.2%)	2 (0.2%)
Bacteremia	0	0	1 (0.1%)	1 (0.1%)
Bronchitis	0	0	1 (0.1%)	1 (0.1%)
Catheter Sepsis	0	0	1 (0.1%)	1 (0.1%)
Hematoma Infection	0	0	1 (0.1%)	1 (0.1%)
Incision Site Abscess	0	0	1 (0.1%)	1 (0.1%)
Incision Site Infection	0	0	1 (0.1%)	1 (0.1%)
Lobar Pneumonia	0	0	1 (0.1%)	1 (0.1%)
Pelvic Abscess	0	0	1 (0.1%)	1 (0.1%)
Post Procedural Cellulitis	0	0	1 (0.1%)	1 (0.1%)
Vaginal Cellulitis	0	0	1 (0.1%)	1 (0.1%)
Wound Abscess	0	0	1 (0.1%)	1 (0.1%)
Wound Infection Staphylococcal	0	0	1 (0.1%)	1 (0.1%)
Injury, Poisoning and Procedural Complications:	**1 (0.8%)**	**2 (1.1%)**	**17 (1.8%)**	**19 (1.6%)**
Femur Fracture	0	0	5 (0.5%)	5 (0.4%)
Postoperative Ileus	0	1 (0.5%)	1 (0.1%)	2 (0.2%)
Wound Dehiscence	0	0	2 (0.2%)	2 (0.2%)
Seroma	0	1 (0.5%)	0	1 (0.1%)
Anastomotic Leak	1 (0.8%)	0	1 (0.1%)	1 (0.1%)
Anastomatic Hemorrhage	0	0	1 (0.1%)	1 (0.1%)
Contusion	0	0	1 (0.1%)	1 (0.1%)
Incision Site Hematoma	0	0	1 (0.1%)	1 (0.1%)
Incision Site Pain	0	0	1 (0.1%)	1 (0.1%)
Post Procedural Hemorrhage	0	0	1 (0.1%)	1 (0.1%)
Post Operative Wound Complicat.	0	0	1 (0.1%)	1 (0.1%)
Tendon Rupture	0	0	1 (0.1%)	1 (0.1%)
Investigations:	**0**	**0**	**7 (0.7%)**	**7 (0.6%)**
Blood Creatinine Increased	0	0	3 (0.3%)	3 (0.3%)
Blood CPK Increased	0	0	2 (0.2%)	2 (0.2%)
Blood Culture Positive	0	0	1 (0.1%)	1 (0.1%)
ECG QT Prolongation	0	0	1 (0.1%)	1 (0.1%)
Liver Function Test Abn.	0	0	1 (0.1%)	1 (0.1%)
Metabolism and Nutrition Disorders:	**0**	**0**	**1 (0.1%)**	**1 (0.1%)**
Dehydration	0	0	1 (0.1%)	1 (0.1%)

administration recommendations for DIC075V
[b]Includes subjects in the placebo group that match subjects in the DIC075V group who received the proposed dose
Adapted Sponsor's Table 3.13.2; p. 2196.

Table 58 (cont.) - Tabular Summary of Serious Treatment Emergent Adverse Events by Dose Group in the Pooled Multidose Phase 3 Trials (Safety Population)

Adverse Event by MedDRA System Organ Class/ Preferred Term	Placebo[b] (N = 126)	DIC075V 37.5 mg and 50 mg[a]		
		DFC-004 and DFC-005 (N =187)	DFC-010 (N=969)	Total (N=1156)
Musculoskel. And Connective Tissue Disorders:	**0**	**0**	**2 (0.2%)**	**2 (0.2%)**
Musculoskeletal Pain	0	0	1 (0.1%)	1 (0.1%)
Pain in Extremity	0	0	1 (0.1%)	1 (0.1%)
Rhabdomyolysis	0	0	1 (0.1%)	1 (0.1%)
Neoplasms Benign, Malignant and Unspecified:	**0**	**0**	**1 (0.1%)**	**1 (0.1%)**
Benign Small Intestinal Neoplasm	0	0	1 (0.1%)	1 (0.1%)
Nervous System Disorders:	**0**	**0**	**2 (0.2%)**	**2 (0.2%)**
Sedation	0	0	2 (0.2%)	2 (0.2%)
Psychiatric Disorders:	**0**	**0**	**1 (0.1%)**	**1 (0.1%)**
Mental Status Changes	0	0	1 (0.1%)	1 (0.1%)
Renal and Urinary Disorders:	**0**	**0**	**3 (0.3%)**	**3 (0.3%)**
Renal Failure Acute	0	0	2 (0.2%)	2 (0.2%)
Renal Failure	0	0	1 (0.1%)	1 (0.1%)
Renal Tubular Necrosis	0	0	1 (0.1%)	1 (0.1%)
Respiratory, Thoracic and Mediastinal Disorders:	**1 (0.8%)**	**0**	**11 (1.1%)**	**11 (1.0%)**
Pulmonary Embolism	1 (0.8%)	0	6 (0.6%)	6 (0.5%)
Hypoxia	0	0	2 (0.2%)	2 (0.2%)
Acute Respiratory Distress Synd.	0	0	1 (0.1%)	1 (0.1%)
Aspiration	0	0	1 (0.1%)	1 (0.1%)
Atelectasis	0	0	1 (0.1%)	1 (0.1%)
Dsypnea	0	0	1 (0.1%)	1 (0.1%)
Pleural Effusion	0	0	1 (0.1%)	1 (0.1%)
Pulmonary Edema	0	0	1 (0.1%)	1 (0.1%)
Respiratory Arrest	0	0	1 (0.1%)	1 (0.1%)
Skin and Subcutaneous Tissue Disorders:	**0**	**0**	**1 (0.1%)**	**1 (0.1%)**
Angioedema	0	0	1 (0.1%)	1 (0.1%)
Vascular Disorders:	**1 (0.8%)**	**2 (1.1%)**	**1 (0.1%)**	**3 (0.3%)**
Deep Vein Thrombosis	0	2 (1.1%)	0	2 (0.2%)
Hypotension	1 (0.8%)	0	1 (0.1%)	1 (0.1%)

[a]The DIC075V 37.5 mg and 50 mg dose groups are included in this analysis (b) (4)

[b] Includes subjects in the placebo group that match subjects in the DIC075V group who received the proposed dose
Adapted Sponsor's Table 3.13.2; p. 2196.

The most frequently reported SAEs for the 1156 subjects exposed to either 37.5 mg or 50 mg of DIC075V during the controlled and open label trials were as follows: pulmonary embolism (6 cases), femur fracture (5 cases), wound infection (4 cases), and small intestinal obstruction (4 cases). To determine if a relationship existed between SAEs and dose, these data were examined by dose treatment dose group as shown in Table 59. As noted previously, a dose dependent increase in SAE is seen in subjects

treated with 18.75 mg (5.3%), 37.5 mg (6.4%) and 50 mg (8.1%) of DIC075V. Review of these data reveals a dose dependent increase in SAE for the infections and infestations SOC representing mainly wound infections (DICO75V: 18.75 mg: 0.8%, 37.5 mg: 1.8%; and 50 mg: 3.0%) as compared to 0.7% for the placebo group and 2.4% for the ketorolac 30 mg group and represents the expected effect of increasing NSAID dose on wound healing. A higher proportion of patients treated with the 18.75 mg dose of DIC075V developed acute renal failure (0.8%) and deep vein thrombosis (0.8%) as compared to the 37.5 mg dose group (0.4% and 0%, respectively) and the 50 mg dose group (0% and 0.5%, respectively) that most likely occurred due to background risk factors and occurrence of events despite the use of a lower dose of DIC075V.

Table 59 - Tabular Summary of Serious Treatment Emergent Adverse Events by Dose Group in the Pooled Multidose Phase 3 Trials (Safety Population)

		DIC075V				Ketorolac	
	Placebo (N=148)	18.75 mg (N=133)	37.5 mg (N=786)	50 mg (N=370)	Total (N=1289)	15 mg (N=18)	30 mg (N=124)
Number (%) of Subjects with Any Serious AEs:	**6 (4.1%)**	**7 (5.3%)**	**50 (6.4%)**	**30 (8.1%)**	**87 (6.7%)**	**3 (16.7%)**	**4 (3.2%)**
Gastrointestinal Disorders:	**2 (1.4%)**	**1 (0.8%)**	**11 (1.4%)**	**5 (1.4%)**	**17 (1.3%)**	**0**	**0**
Small Intestinal obstruction	0	0	3 (0.4%)	1 (0.3%)	4 (0.3%)	0	0
Infections and Infestations:	**1 (0.7%)**	**1 (0.8%)**	**14 (1.8%)**	**11 (3.0%)**	**26 (2.0%)**	**1 (5.6%)**	**3 (2.4%)**
Wound Infection	0	0	2 (0.3%)	2 (0.5%)	4 (0.3%)	0	0
Incision Site Cellulitis	0	0	2 (0.3%)	1 (0.3%)	3 (0.2%)	0	0
Postoperat. Wound Infect.	1 (0.7%)	0	1 (0.1%)	1 (0.3%)	2 (0.2%)	0	0
Cellulitis	0	0	1 (0.1%)	1 (0.3%)	2 (0.2%)	0	0
Sepsis	0	0	0	2 (0.55)	2 (0.2%)	0	0
Injury, Poisoning and Procedural Complications:	**1 (0.7%)**	**1 (0.8%)**	**16 (2.0%)**	**3 (0.8%)**	**20 (1.6%)**	**1 (5.6%)**	**2 (1.6%)**
Femur Fracture	0	0	4 (0.5%)	1 (0.3%)	5 (0.4%)	1 (5.6%)	0
Postoperative Ileus	0	0	2 (0.3%)	0	2 (0.2%)	0	0
Wound Dehiscence	0	0	2 (0.3%)	0	2 (0.2%)	0	0
Investigations:	**0**	**0**	**5 (0.6%)**	**2 (0.5%)**	**7 (0.5%)**	**0**	**0**
Blood Creatinine Increased	0	0	3 (0.4%)	0	3 (0.2%)	0	0
Blood CPK Increased	0	0	2 (0.3%)	0	2 (0.2%)	0	0
Renal and Urinary Disorders:	**0**	**1 (0.8%)**	**3 (0.4%)**	**0**	**4 (0.3%)**	**0**	**0**
Renal Failure Acute	0	1 (0.8%)	2 (0.3%)	0	3 (0.2%)	0	0
Renal Failure	0	0	1 (0.1%)	0	1 (0.1%)	0	0
Renal Tubular Necrosis	0	0	1 (0.1%)	0	1 (0.1%)	0	0
Respiratory, Thoracic and Mediastinal Disorders:	**1 (0.7%)**	**0**	**6 (0.8%)**	**5 (1.4%)**	**11 (0.9%)**	**0**	**1 (0.8%)**
Pulmonary Embolism	1 (0.7%)	0	2 (0.3%)	4 (1.1%)	6 (0.5%)	0	1 (0.8%)
Vascular Disorders:	**1 (0.7%)**	**1 (0.8%)**	**1 (0.1%)**	**2 (0.5%)**	**4 (0.3%)**	**0**	**0**
Deep Vein Thrombosis	0	1 (0.8%)	0	2 (0.5%)	3 (0.2%)	0	0

7.3.3 Dropouts and/or Discontinuations

Since AEs can directly influence the disposition of patients in clinical trials, the safety database for DIC075V was examined to determine if there were any safety signals generated by subjects who prematurely withdrew from the trials conducted by the Applicant due to DIC075V-related AEs. Table 60 below is a tabular summary of the AEs experienced by the subjects who discontinued study treatment during the combined controlled trials DFC-004 and 005, and the open label trial DFC-010. The overall proportion of patients who discontinued due to treatment emergent adverse events associated with 37.5 mg or 50 mg of DIC075V in the combined controlled studies (DFC-004 and 005) was 3.7% as compared to no dropouts (0%) in the placebo group. Review of these data failed to identify any potential safety signal since all of the subjects who withdrew prematurely from the combined DIC075V treatment group did so for individual AEs. The rate of early subject withdrawal from the open label trial DFC-010 (3.4%) was similar to that of the combined controlled studies (3.7%).

Table 60 – Tabular Summary of Subjects Who Withdrew Due to Treatment Emergent Adverse Events in the Multiple Dose Pain Studies (Safety Population)

Adverse Event by MedDRA System Organ Class/ Preferred Term	Placebo (N = 126)	DIC075V 37.5 mg and 50 mg		
		DFC-004 and DFC-005 (N =187)	DFC-010 (N=969)	Total (N=1156)
Number (%) of Subjects with AEs Leading to Withdrawal:	**0**	**7 (3.7%)**	**33 (3.4%)**	**40 (3.5%)**
Blood and Lymphatic Syst. Disorders:	**0**	**1 (0.5%)**	**0**	**1 (0.1%)**
Anemia	0	1 (0.5%)	0	1 (0.1%)
Cardiac Disorders:	**0**	**0**	**3 (0.3%)**	**3 (0.3%)**
Atrial Fibrillation	0	0	1 (0.1%)	1 (0.1%)
Bradicardia	0	0	1 (0.1%)	1 (0.1%)
Cardio-Respiratory Arrest	0	0	1 (0.1%)	1 (0.1%)
Gastrointestinal Disorders:	**0**	**0**	**2 (0.2%)**	**2 (0.2%)**
Anal Hemorrhage	0	0	1 (0.1%)	1 (0.1%)
Dyspepsia	0	0	1 (0.1%)	1 (0.1%)
Gen. Disorders and Administration Site Conditions:	**0**	**2 (1.1%)**	**5 (0.5%)**	**7 (0.6%)**
Catheter Site Inflammation	0	1 (0.5%)	0	1 (0.1%)
Infusion Site Pain	0	1 (0.5%)	0	1 (0.1%)
Chest Discomfort	0	0	1 (0.1%)	1 (0.1%)
Chills	0	0	1 (0.1%)	1 (0.1%)
Infusion Site Extravasation	0	0	1 (0.1%)	1 (0.1%)
Infusion Site Irritation	0	0	1 (0.1%)	1 (0.1%)
Pyrexia	0	0	1 (0.1%)	1 (0.1%)

[a]The DIC075V 37.5 mg and 50 mg dose groups are included in this analysis (b) (4)

Includes subjects in the placebo group that match subjects in the DIC075V group who received the proposed dose
Adapted Sponsor's Table 3.14.2; p. 2204

Table 60 (cont.) – Tabular Summary of Subjects Who Withdrew Due to Treatment Emergent Adverse Events in the Multiple Dose Phase 3 Pain Studies (Safety Population)

Adverse Event by MedDRA System Organ Class/ Preferred Term	Placebo (N = 126)	DIC075V 37.5 mg and 50 mg		
		DFC-004 and DFC-005 (N =187)	DFC-010 (N=969)	Total (N=1156)
Infections and Infestations:	0	0	1 (0.1%)	1 (0.1%)
Pelvic Abscess	0	0	1 (0.1%)	1 (0.1%)
Injury, Poisoning and Procedural Complications:	**0**	**0**	**4 (0.4%)**	**4 (0.3%)**
Anemia Postoperative	0	0	3 (0.3%)	3 (0.3%)
Anastomotic Hemorrhage	0	0	1 (0.1%)	1 (0.1%)
Investigations:	**0**	**0**	**10 (1.0)%**	**10 (0.9)%**
Blood Creatinine Increased	0	0	8 (0.8%)	8 (0.7%)
Blood Urea Increased	0	0	1 (0.1%)	1 (0.1%)
Creatinine Renal Clearance Decr.	0	0	1 (0.1%)	1 (0.1%)
Liver Function Test Abn.	0	0	1 (0.1%)	1 (0.1%)
Urine Output Decreased	0	0	1 (0.1%)	1 (0.1%)
Musculoskel. And Connective Tissue Disorders:	**0**	**0**	**3 (0.3%)**	**3 (0.3%)**
Musculoskeletal Pain	0	0	1 (0.1%)	1 (0.1%)
Pain in Extremity	0	0	1 (0.1%)	1 (0.1%)
Rhabdomyolysis	0	0	1 (0.1%)	1 (0.1%)
Renal and Urinary Disorders:	**0**	**1 (0.5%)**	**5 (0.5%)**	**6 (0.5%)**
Renal Failure Acute	0	0	3 (0.3%)	3 (0.3%)
Oliguria	0	1 (0.5%)	0	1 (0.1%)
Azotemia	0	0	1 (0.1%)	1 (0.1%)
Renal Failure	0	0	1 (0.1%)	1 (0.1%)
Renal Tubular Necrosis	0	0	1 (0.1%)	1 (0.1%)
Reproductive System and Breast Disorders:	**0**	**1 (0.5%)**	**0**	**1 (0.1%)**
Priaprism	0	1 (0.5%)	0	1 (0.1%)
Respiratory, Thoracic and Mediastinal Disorders:	**0**	**0**	**3 (0.3%)**	**3 (0.3%)**
Dyspnea	0	0	2 (0.2%)	2 (0.2%)
Aspiration	0	0	1 (0.1%)	1 (0.1%)
Respiratory Arrest	0	0	1 (0.1%)	1 (0.1%)
Skin and Subcutaneous Tissue Dis;	**0**	**2 (1.1%)**	**5 (0.5%)**	**7 (0.6%)**
Pruritus	0	1 (0.5%)	2 (0.2%)	3 (0.3%)
Pruritus Allergic	0	1 (0.5%)	0	0
Erythema	0	0	1 (0.1%)	1 (0.1%)
Hyperhidrosis	0	0	1 (0.1%)	1 (0.1%)
Rash pruritic	0	0	1 (0.1%)	1 (0.1%)
Vascular Disorders:	**0**	**0**	**1 (0.1%)**	**1 (0.1%)**
Hypotension	0	0	1 (0.1%)	1 (0.1%)

[a]The DIC075V 37.5 mg and 50 mg dose groups are included in this analysis (b) (4)

Includes subjects in the placebo group that match subjects in the DIC075V group who received the proposed dose
Adapted Sponsor's Table 3.14.2; p. 2204

Review of AEs experienced by patients who withdrew from the trials by pooled dose treatment group revealed more patients prematurely withdrew from the 37.5 mg dose group of DIC075V due to increased serum creatinine (0.9%) as compared to 50 mg dose group (0.3%) and the 18.75 mg group (0%). No patients withdrew prematurely due to an increase in serum creatinine from either the placebo group or both ketorolac dose groups (data not shown.)

7.3.4 Significant Adverse Events

Table 61 is a tabular listing of AEs observed during the controlled trials DFC-004 and 005 and the open label trial DFC-010 that were rated as severe in nature by the study investigators. A higher proportion of subjects in the placebo group (6.3%) experienced AEs that were severe in nature as compared to subjects in the combined 37.5 mg and 50 mg DIC075V treatment group (5.3%) during the controlled trials. The proportion of subjects (4.3%) in the open label study who experience AEs classified as severe in nature was similar to that observed in the controlled trials for patients treated with 37.5 mg and 50 mg of DIC075V. The higher rate of severe AEs observed in the placebo group was due to the higher rate of severe AEs listed under the gastrointestinal disorder SOC (4.8%) as compared to 1.6% for the combined 37.5 mg and 50 mg DIC075V treated patients from the controlled studies and 1.2% in the open label study. No potential safety signals for DIC075V were observed on examination of the severity data by study or by pooled dose treatment group (data not shown).

Table 61 - Tabular Summary By Severity of Treatment Emergent Adverse Events in the Multiple Dose Pain Studies (Safety Population)

Adverse Event by MedDRA System Organ Class/ Preferred Term	Placebo[b] (N = 126)	DIC075V 37.5 mg and 50 mg[a]		
		DFC-004 and DFC-005 (N =187)	DFC-010 (N=969)	Total (N=1156)
Number (%) of Subjects with TEAEs:				
Unknown	1 (0.8%)	0	0	0
Mild	40 (3.2%)	53 (28.3%)	336 (34.7%)	389 (33.7%)
Moderate	56 (44.4%)	83 (44.4%)	431 (44.5%)	514 (44.5%)
Severe	8 (6.3%)	10 (5.3%)	42 (4.3%)	52 (4.5%)

[a]The DIC075V 37.5 mg and 50 mg dose groups are included in this analysis (b) (4)

[b] Includes subjects in the placebo group that match subjects in the DIC075V group who received the proposed dose
Adapted Sponsor's Table 3.4.2.1; p. 778-922.

7.3.5 Submission Specific Primary Safety Concerns

Since DIC075V is a NSAID, the Applicant also conducted a number of analyses for AEs of special interest for this drug class which are summarized in the following Table 62.

Overall, the rates of patients with at least one AE within each category of special interest were higher for placebo treated patients as compared to patients in the DIC075V treatment group during the controlled trials with the exception of infusion related events which were similar for both treatment groups (placebo 15.9% versus 17.1% for DIC075V). The rates of patients treated with the same dose range of DIC075V in the open label trial DFC-010 were generally higher than that observed in the controlled studies with the exception of infusion related events which was higher the controlled population exposed to DIC075V (17.1% controlled versus 11.7% uncontrolled). However, the rates of treatment emergent AEs of special interest in the open label study were similar to that observed in the placebo controlled group for cardiovascular, arrhythmic, hepatobiliary events and gastrointestinal events but the rates were higher in this trial for bleeding-related and renal events than in the placebo controlled group. However, the rate of local thrombotic events (e.g., peripheral vascular events such as thrombophlebitis and infusion site thrombosis) was higher in the placebo controlled group (7.9%) as compared to that in the open label DIC075V treatment group (0.6%) that may be related to mechanical problems associated with IV placement.

Table 62 – Tabular Summary of Treatment Emergent Events of Special Interest in the Multiple Dose Pain Studies (Safety Population)

		DIC075V 37.5 mg and 50 mg[a]		
Subjects with Any:	**Placebo[b] (N=126) n (%)**	**DFC-004/DFC-005 (N=187) n (%)**	**DFC-010 (N=969) n (%)**	**Total (N=1156) n (%)**
Cardiovascular events	1 (0.8)	0	9 (0.9)	9 (0.8)
Arrhythmic events	8 (6.3)	4 (2.1)	66 (6.8)	70 (6.1)
Local thrombotic events	10 (7.9)	3 (1.6)	6 (0.6)	9 (0.8)
Bleeding-related events	3 (2.4)	5 (2.7)	56 (5.8)	61 (5.3)
Renal events	1 (0.8)	1 (0.5)	27 (2.8)	28 (2.4)
Hepatobiliary events	6 (4.8)	5 (2.7)	38 (3.9)	43 (3.7)
Infusion-site related events	20 (15.9)	32 (17.1)	113 (11.7)	145 (12.5)
Gastrointestinal events	71 (56.3)	71 (38.0)	513 (52.9)	584 (50.5)

Source: Appendix 13.5, Table 3.11.1.4, Table 3.11.2.4, Table 3.11.3.4, Table 3.11.4.4, Table 3.11.5.4, Table 3.11.6.4, Table 3.11.7.4 and Table 3.11.8.4

a The DIC075V 37.5 mg and 50 mg dose groups are included in this analysis [redacted (b) (4)] [redacted (b) (4)]

b Includes subjects in the placebo group that match subjects in the DIC075V group who received the proposed dose.

Adapted Sponsor's Table 4-46; p.155.

These treatment emergent events of special interest were also examined for the possibility of dose-dependent relationships. Table 63 lists these AEs of special interest by pooled dose treatment group. Examination of these data did not reveal a possible dose-dependent relationship associated with DIC075V for these special events of interest.

Table 63 – Tabular Summary of Treatment Emergent Events of Special Interest by Pooled Dose Treatment Group for the Multiple Dose Pain Studies (Safety Population)

		DIC075V				Ketorolac	
Subjects with Any:	Placebo (N=148) n (%)	18.75 mg (N=133) n (%)	37.5 mg (N=786) n (%)	50 mg (N=370) n (%)	Total (N=1289) n (%)	15 mg (N=18) n (%)	30 mg (N=124) n (%)
Cardiovascular events	1 (0.7)	0	6 (0.8)	3 (0.8)	9 (0.7)	2 (11.1)	0
Arrhythmic events	9 (6.1)	5 (3.8)	47 (6.0)	23 (6.2)	75 (5.8)	2 (11.1)	5 (4.0)
Local thrombotic events	10 (6.8)	7 (5.3)	8 (1.0)	1 (0.3)	16 (1.2)	0	7 (5.6)
Bleeding-related events	4 (2.7)	4 (3.0)	41 (5.2)	20 (5.4)	65 (5.0)	0	8 (6.5)
Renal events	1 (0.7)	1 (0.8)	22 (2.8)	6 (1.6)	29 (2.2)	0	2 (1.6)
Hepatobiliary events	7 (4.7)	3 (2.3)	32 (4.1)	11 (3.0)	46 (3.6)	0	4 (3.2)
Infusion-site related events	22 (14.9)	30 (22.6)	96 (12.2)	49 (13.2)	175 (13.6)	4 (22.2)	32 (25.8)
Gastrointestinal events	84 (56.8)	72 (54.1)	408 (51.9)	176 (47.6)	656 (50.9)	11 (61.1)	58 (46.8)

Source: Appendix 13.5, Table 3.11.1.1.1, Table 3.11.2.1.1, Table 3.11.3.1.1, Table 3.11.4.1.1, Table 3.11.5.1.1, Table 3.11.6.1.1, Table 3.11.7.1.1, and Table 3.11.8.1.1, respectively.

Adapted Sponsor's Table 4-45; p.153.

a. Cardiovascular Events:

In 2006, a boxed warning was added to the labels of non-selective NSAIDs regarding an increase in risk for serious cardiovascular thrombotic events, myocardial infaction and stroke associated with the use of these drugs. In view of this, the Applicant conducted an analyses of major adverse cardiac events (MACEs) contained in the safety database for DIC075V. Table 64 shows that there was only MACE case (i.e., congestive heart failure) that occurred in a placebo treated patient during the controlled trials DFC-004 and 005. However, a total of nine subjects treated with DIC075V experienced ten major adverse cardiac events while participating in the open label trial DFC-010 which permitted the enrollment of subjects within 6 hours of undergoing coronary bypass surgery (CABG). Five of these subjects had been treated with 37.5 mg of DIC075V while the remaining 4 subjects had received 50 mg of the study drug. Further review of the case reports for these major adverse cardiovascular events revealed that two of these nine patients (24-020 and 74-002) who had been treated with 37. 5 mg of DIC075V reportedly had myocardial infarctions as interpreted by automated readings of their ECGs which were later determined to be erroneous on clinical review. (Note: The serial ECGs for Subjects 24-020 and 74-002 were examined by an agency cardiologist who concurred that there was no evidence of acute myocardial infarctions on review of these tracings.) There were 2 subjects who developed congestive heart failure (Subjects 31-034 and 47-050) one of whom also developed secondary pulmonary edema (Subject 47-050). Subject 31-034 died as a result of sepsis associated with congestive heart failure and multiorgan failure (refer to section 7.3.1). Subject 47-050 was a 73 year old male with multiple risk factors for congestive heart failure and pulmonary edema including cardiomegaly, hypertension, atrial fibrillation and thyroid disease status post myocardial infarction on Coumadin, dilitazem and Digitek.

The second case of pulmonary edema (Subject 53-001) occurred in a 72 year-old female with history of paroxysmal atrial fibrillation and hypertension who developed pulmonary edema secondary to volume overload after undergoing a second surgery to pin her fractured hip following total hip replacement. These 4 cases of congestive heart failure and pulmonary edema do not appear to be related to DIC075V. The remaining 4 cases with cardiovascular events (Subject 47-014: coronary atherosclerosis; Subjects 53-014 and 72-006: angina pectoris and Subject 69-021: myocardial ischemia) had cardiac histories and/or pre-existing comorbid risk factors for the development of MACEs. Overall, review of these data does not reveal a discernable pattern of MACEs to have occurred in patients participating in DFC-010 as a result of exposure to DIC075V, however, if approved the drug label will contain the current mandatory NSAID class box warning for the increase in risk of cardiovascular events to guide healthcare providers who might prescribe this drug.

Table 64 – Overall Incidence of Cardiovascular Events in the Multiple Dose Pain Studies (Safety Population)

		DIC075V 37.5 mg and 50 mg[a]		
MedDRA Preferred Term	Placebo[b] (N=126) n (%)	DFC-004/DFC-005 (N=187) n (%)	DFC-010 (N=969) n (%)	Total (N=1156) n (%)
Cardiac failure congestive	1 (0.8)	0	2 (0.2)	2 (0.2)
Angina pectoris	0	0	2 (0.2)	2 (0.2)
Myocardial infarction	0	0	2 (0.2)	2 (0.2)
Pulmonary oedema	0	0	2 (0.2)	2 (0.2)
Arteriosclerosis coronary artery	0	0	1 (0.1)	1 (0.1)
Myocardial ischaemia	0	0	1 (0.1)	1 (0.1)

Source: Appendix 13.5, Table 3.11.1.4

a The DIC075V 37.5 mg and 50 mg dose groups are included in this analysis (b) (4)

b Includes subjects in the placebo group that match subjects in the DIC075V group who received the proposed dose.

Adapted Sponsor's Table 4-47; p. 156.

For completeness, cardiac AE data by pooled dose treatment group was also examined for any potential dose-dependent relationships. The proportions of patients were reported cardiac AEs were comparable for all three dose groups of DIC075V and placebo ranging from 0.7 to 0.8%. No cardiac AEs occurred in patients treated with 30 mg of ketorolac. No dose-dependent patterns for cardiac AEs were identified on review of these data (data not shown).

The safety database submitted in support of DIC075V contained a total of 12 cases of thromboembolic events that occurred in patients treated with this drug in addition to 2 cases of pulmonary embolism that occurred in 1 placebo patient (Subject 08-033) and 1 ketorolac patient (Subject 01-049). Of the 12 cases of thromboembolic events that occurred in patients treated with DIC075V, 6 cases were reports of patients who developed pulmonary emboli and 6 cases were reports of deep venous thrombosis

(DVT) in subjects who received the drug while participating in the two controlled trials and the open-label trial. Table 65 is a tabular summary of these 14 patients who developed thromboembolic events. Four out of the 12 patients treated with DIC075V who developed thromboembolic events were receiving prophylactic anticoagulant therapy when these events occurred since they had multiple risk factors that increased their risk (e.g., orthopedic surgery involving the lower extremity, prior history of DVT, malignancy, and/or obesity). Review of the remaining 8 cases of thromboembolic events in patients treated with DIC075V who did not receive anticoagulation therapy reveals that the majority of these patients had also undergone surgical procedures (e.g., orthopedic procedure involving the lower extremity or abdominal surgery) that increased their risk for developing a thromboembolic event in addition to having co-morbid risk factors that increased their risk for these events (e.g., obesity, oral contraceptive use, varicose veins, and atrial fibrillation) or had a medical contraindication for anticoagulant therapy (e.g., history of cerebrovascular accident). The thromboembolic events experienced by the two subjects with atrial fibrillation (Subjects 04-034 and 72-019) occurred while they were inadequately anticoagulated following the re-initiation of their chronic Coumadin therapy following surgery. One patient (Subject 13-072) who was at high risk for a thromboembolic event due to a prior history of DVT died as a result of having a pulmonary embolism despite receiving prophylactic anticoagulation therapy in addition to using TED hose and athrombic pumps. (Refer to Section 7.3.1 Deaths.) These 12 thrombolembolic events should not be attributed to DIC075V since they occurred in patients at high risk for developing these types of events as a result of having multiple comorbid risk factors.

Table 65 – Tabular Summary of Thromboembolic Events in Patients Who Participated in the Multidose Phase 3 Pain Trials (Safety Population)

Subject Number	Age/Sex	Dose	Event	Time from First Dose to Onset	Risk Factors
DFC-004					
01-049	26 yo/F	30 mg ketorolac	Pulmonary Embolism	Day 10	S/P cholestectomy (mini-laporotomy), H/O oral contraceptives, S/P thrombophlebitis of IV site
DFC-005					
08-033	26 yo/M	Placebo	Pulmonary Embolism	Day 12	H/O Varicose veins, S/P orthopedic procedure
04-034	73 yo/F	18.75 mg DIC075V	DVT	Day 4 (2 days after restarting warfarin therapy)	S/P Orthopedic procedure, H/O atrial fibrillation, probable inadequate anticoagulation
05-108	63 yo/F	50 mg DIC075V	DVT	Day 21	S/P Orthopedic procedure, obesity
08-036	37 yo/F	50 mg DIC075V	DVT	Day 20	S/P Orthopedic procedure, obesity
DFC-010					
13-072[a]	71 yo/M	37.5 mg DIC075V	Pulmonary Embolism	Day 2	H/O DVT, S/P orthopedic procedure
33-003	56 yo/M	37.5 mg DIC075V	Pulmonary Embolism	Day 2	S/P Repair of fascial dehiscence due to colectomy
47-014	67yo/M	50 mg DIC075V	Pulmonary Embolism	Day 3	H/O Prostate cancer, obesity, S/P orthopedic procedure
72-019	75 yo/M	37.5 mg DIC075V	Pulmonary Embolism	Day 4	S/P Orthopedic procedure, H/O atrial fibrillation, inadequate anticoagulation
51-002[b]	52 yo/F	37.5 mg DIC075V	Pulmonary Embolism	Day 16	S/P orthopedic procedure, H/O CVA
54-002	58 yo/F	50 mg DIC075V	Pulmonary Embolism	Day 23	S/P orthopedic procedure, obesity
51-013	56 yo/M	50 mg DIC075V	DVT	Day 10	S/P Orthopedic procedure, Obesity
13-030	39 yo/F	50 mg DIC075V	DVT	Day 26	S/P Orthopedic procedure, Obesity
48-018	50 yo/M	50 mg DIC075V	DVT	Day 27	S/P Orthopedic procedure, Obesity

S/P = Status-post; H/O = History of; CVA =cerebrovascular accident
[a] This patient died as a result of having a pulmonary embolism.
[b]This patient had a rotator cuff repair.

b. Arrhythmic Events

The Applicant also examined the database for the occurrence of arrhythmic events by MedDRA preferred term (Table 66). The most commonly reported arrhythmic event during the combined controlled trials was tachycardia which is commonly observed in patients following surgery due to fluid volume shifts. During DFC-004 and 005, a higher proportion of patients (4.8%) in the combined placebo group experienced tachycardia as compared to patients (1.1%) in the combined 37.5 mg and 50 mg DIC075V group. Due to the paucity of arrhythmic events that occurred during the controlled trials, no potential safety signals were identified on review of these data.

Table 66 - Overall Incidence of Arrhythmic Events in the Multiple Dose Pain Studies (Safety Population)

		DIC075V 37.5 mg and 50 mg[a]		
MedDRA Preferred Term	Placebo[b] (N=126) n (%)	DFC-004/DFC-005 (N=187) n (%)	DFC-010 (N=969) n (%)	Total (N=1156) n (%)
Tachycardia	6 (4.8)	2 (1.1)	32 (3.3)	34 (2.9)
Bradycardia	1 (0.8)	1 (0.5)	10 (1.0)	11 (1.0)
Atrial fibrillation	0	0	9 (0.9)	9 (0.8)
Sinus tachycardia	0	0	4 (0.4)	4 (0.3)
Sinus bradycardia	0	0	3 (0.3)	3 (0.3)
Syncope	0	0	3 (0.3)	3 (0.3)
Palpitations	0	1 (0.5)	1 (0.1)	2 (0.2)
Arrhythmia	0	0	2 (0.2)	2 (0.2)
Supraventricular extrasystoles	0	0	2 (0.2)	2 (0.2)
Electrocardiogram QT prolonged	0	0	2 (0.2)	2 (0.2)
Heart rate irregular	0	0	2 (0.2)	2 (0.2)
Bundle branch block left	0	0	1 (0.1)	1 (0.1)
Bundle branch block right	0	0	1 (0.1)	1 (0.1)
Cardio-respiratory arrest	0	0	1 (0.1)	1 (0.1)
Heart rate increased	1 (0.8)	0	1 (0.1)	1 (0.1)
Loss of consciousness	0	0	1 (0.1)	1 (0.1)
Heart rate abnormal	1 (0.8)	0	0	0

Source: Appendix 13.5, Table 3.11.2.4

a The DIC075V 37.5 mg and 50 mg dose groups are included in this analysis (b) (4) (b) (4)

b Includes subjects in the placebo group that match subjects in the DIC075V group who received the proposed dose.

Adapted Sponsor's Table 4-48; p. 158.

Table 66 shows that the most commonly reported arrhythmic events in DFC-010 were as follows: tachycardia (3.3%), bradicardia (1.0%), and atrial fibrillation (0.9%). Review of the cases of atrial fibrillation revealed that many of them had histories of controlled or paroxysmal atrial fibrillation or risk factors (e.g. pre-existing coronary disease or thyroid disease). There was one patient in the open label study DFC-010 who had a

cardiopulmonary arrest following the last dose of study medication (50 mg of DIC075V). This subject was a 62 year old female with history of obesity, sleep apnea, hypothyroidism, arthritis, hypertension and hyperlipidemia who became unresponsive and cyanotic after she had received 2 mg IV morphine via PCA. This patient was successfully resuscitated following the administration of 0.2 mg of narcan IV. This event was most likely due to an accidental morphine overdose. Although a small number of arrhythmic events were observed during this trial, the lack of a placebo control arm in the open label study makes it impossible to determine with certainty that a potential safety signal does not exist in this post surgical population.

For completeness, arrhythmic AE data by pooled dose treatment group was also examined for any potential dose-dependent relationships. Higher proportions of patients receiving 37.5 mg (6.0%) and 50 mg (6.2%) of DIC075V were reported to have arrhythmic events compared to patients receiving 18.75 mg (3.8%) of the drug. No dose-dependent patterns for arrhythmic AEs were identified on review of these data (data not shown).

c. Bleeding-Related Events

NSAIDs reversibly inhibit platelet cyclooxygenase which can cause prolongation of bleeding time due to impairment of thromboxane-dependent platelet aggregation. In view of this class effect, the Applicant searched the DIC075V safety database for bleeding-related events in order to determine if there was an increase in risk for bleeding events to occur in post-surgical patients treated with DIC075V. Table 67 is a tabular summary of the MedDRA preferred AE terms for bleeding-related events for patients who participated in the combined controlled trials (DFC-004 and 005) as well as in the open label trial (DFC-010). Overall, the proportions of bleeding-related events were similar for both the combined placebo and the combined 37.5 and 50 mg DIC075V treatment groups in DFC-004 and 005 (refer to Table 62). Examination of these data as shown in Table 67 did not reveal any pattern of bleeding-related AEs due to the small number of cases observed in the controlled studies.

Table 67 – Overall Incidence of Bleeding-Related Events in the Combined Controlled and Open Label Multiple Dose Pain Studies (Safety Population)

		DIC075V 37.5 mg and 50 mg[a]		
MedDRA Preferred Term	Placebo[b] (N=126) n (%)	DFC-004/DFC-005 (N=187) n (%)	DFC-010 (N=969) n (%)	Total (N=1156) n (%)
Prothrombin time prolonged	0	0	14 (1.4)	14 (1.2)
Activated partial thromboplastin time prolonged	0	0	8 (0.8)	8 (0.7)
Incision site haemorrhage	0	0	7 (0.7)	7 (0.6)
Post procedural haemorrhage	0	0	4 (0.4)	4 (0.3)
Epistaxis	0	2 (1.1)	2 (0.2)	4 (0.3)
International normalised ratio increased	0	0	3 (0.3)	3 (0.3)
Haemorrhagic anaemia	0	0	3 (0.3)	3 (0.3)
Haematochezia	0	0	3 (0.3)	3 (0.3)
Haematuria	0	0	3 (0.3)	3 (0.3)
Haematoma	0	1 (0.5)	2 (0.2)	3 (0.3)
Wound haemorrhage	0	0	3 (0.3)	3 (0.3)
Rectal haemorrhage	0	1 (0.5)	1 (0.1)	2 (0.2)
Incision site haematoma	0	0	2 (0.2)	2 (0.2)
Infusion site haematoma	0	0	2 (0.2)	2 (0.2)
Anal haemorrhage	0	0	1 (0.1)	1 (0.1)
Anastomotic haemorrhage	0	0	1 (0.1)	1 (0.1)
Blood urine present	0	0	1 (0.1)	1 (0.1)
Ecchymosis	0	0	1 (0.1)	1 (0.1)
Fibrin D dimer increased	0	0	1 (0.1)	1 (0.1)
Haematemesis	0	0	1 (0.1)	1 (0.1)
Haematocrit decreased	0	0	1 (0.1)	1 (0.1)
Haematoma infection	0	0	1 (0.1)	1 (0.1)
Infusion site haemorrhage	0	0	1 (0.1)	1 (0.1)
Injection site haemorrhage	0	0	1 (0.1)	1 (0.1)
Upper gastrointestinal haemorrhage	0	0	1 (0.1)	1 (0.1)
Vaginal haemorrhage	2 (1.6)	0	1 (0.1)	1 (0.1)
Haemarthrosis	0	1 (0.5)	0	1 (0.1)
Haemorrhagic ovarian cyst	1 (0.8)	0	0	0

Source: Appendix 13.5, Table 3.11.4.4

a The DIC075V 37.5 mg and 50 mg dose groups are included in this analysis (b) (4) (b) (4)

b Includes subjects in the placebo group that match subjects in the DIC075V group who received the proposed dose.

Adapted Sponsor's table 4-49; p. 160.

The rate of bleeding-related events was previously noted to be higher (5.8%) in the open-label trial DFC-010 than in the combined pivotal controlled trials in patients who received 37.5 mg or 50 mg of DIC075V (2.7%). The most commonly reported bleeding-related AEs in DFC-010 were as follows: prolonged prothrombin time (1.4%), activated

partial thromboplastin time (0.8%), incision site hemorrhage (0.7%), and post procedural hemorrhage (0.4%). It is not surprising that prolongations in the prothrombin time and partial thromboplastin time were observed since the protocol for DFC-010 permitted the concomitant administration of prophylactic anticoagulant therapy post-surgery. Due to the small numbers of bleeding related AEs that occurred during the open label study, no discernable pattern for a potential safety signal was identified on review of the data in Table 67.

For completeness, bleeding-related AE data by pooled dose treatment group was also examined for any potential dose-dependent relationships. Higher proportions of patients receiving 37.5 mg (5.2%) and 50 mg (5.4%) of DIC075V were reported to have bleeding events compared to patients receiving 18.75 mg (3.0%) of the drug. No dose-dependent patterns for bleeding related events were identified on review of these data with the exception of gastrointestinal disorders where the rate of gastrointestinal bleeding was 0.5% for patients receiving 37.5 mg as compared to 1.1% for patients receiving 50 mg of DIC075V.

Since prophylactic anticoagulant therapy to prevent life threatening thromboembolic events is recommended for post-surgical patients particularly following major orthopedic procedures, the Applicant also conducted an analysis to evaluate the potential impact of anticoagulant therapy (e.g., heparin, low molecular weight heparin or warfarin) on the incidence of bleeding events in the DIC075V safety database. A total of 625 subjects were identified as recieving anticoagulant therapy that was initiated immediatedly after treatment with DIC075V was completed as follows: 24 subjects who received either 37.5 mg or 50 mg while participating in DFC-004 or 005, 17 matched placebo controlled patients from these trials, and 601 patients who received either 37.5 mg or 50 mg of DIC075V in DFC-010. Table 68 lists the results of this anticoagulated subcohort analysis by MedDRA preferred term. There were a total of 2 cases of bleeding-related events (e.g., epistaxis and rectal bleeding) experienced by patients in the combined 37.5mg or 50 mg DIC075V anticoagulated subcohort in the controlled trials that resulted in an 8.3% incidence of bleeding events as compared to 0% incidence of bleeding events in the matched placebo controlled group.

The most frequently reported bleeding-related AEs in the anticoagulated subcohort for DFC-010 were as follows: prolonged prothrombin time (1.7%), incision site hemorrhage (1.0%), and prolonged activated partial thromboplastin time (1.0%). Although 62% of the subjects in the open label study DFC010 received anticoagulant therapy upon completion of study treatment with DIC075V, the overall incidence of bleeding events in these patients who were treated with either 37.5 mg or 50 mg of DIC075V was 5.5% which was lower than that observed in patients treated with DIC075V during the controlled studies (8.3%) discussed previously. The incidence of bleeding events observed in the open label safety study is similar to that reported in a published meta-analysis of preventative thromboembolism trials conducted in general surgery patients

in which patients treated prophylactically with low-dose unfractionated heparin (LDUH) (≤ 3,400 U daily) had an incidence of rate of bleeding events of 5.4% as compared to 3.8% for patients treated with low molecular weight heparin (LMWH)[1]. The results from this meta-analysis were confirmed by a second meta-analysis that also showed that higher doses of these agents resulted in more bleeding events (7.9% versus 5.3%, respectively; odds ratio 1.5)[2] Pooled rates of major bleeding events in patients following orthopedic surgery were reported to be 3.3% with concomitant vitamin K antagonists such as warfarin and 5.3% in patients who received LMWH[3]. Comparable rates for bleeding events in patients post hip or knee replacement following treatment with the LMWH enoxaprin are reported in that agent's current label.

References:

[1]Mismetti P, Laporte S, Darmon JY, et al. Meta-analyses of low molecular weight heparin in the prevention of venous thromboembolism in general surgery. Br. J of Sur 2001;88:913-930.
[2]Koch A, Bouges S., Ziegler S, et al. Low molecular weigh heparin and unfractionated heparin in thrombosis prophylaxis after major surgical intervention: update of previous meta-analyses. Br J Surg 1997; 84;750-759.
[3]Geerts WH, Pinea GF, Heit JA, Bergqvist D, Lassen MR, Colwell CW, et al. Prevention of venous thromboembolism. The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126(3)338S-4000S.

Table 68 - Overall Incidence of Bleeding-Related Events in Subjects Receiving Concomitant Anticoagulant Therapy in the Multiple Dose Pain Studies (Safety Population)

		DIC075V 37.5 mg and 50 mg[a]		
MedDRA System Organ Class/ Preferred Term	Placebo[b] (N=17) n (%)	DFC-004/ DFC-005 (N=24) n (%)	DFC-010 (N=601) n (%)	Total (N=625) n (%)
Subjects with Any Bleeding-Related Events	0	2 (8.3)	33 (5.5)	35 (5.6)
Prothrombin time prolonged	0	0	10 (1.7)	10 (1.6)
Incision site haemorrhage	0	0	6 (1.0)	6 (1.0)
Activated partial thromboplastin time prolonged	0	0	6 (1.0)	6 (1.0)
Epistaxis	0	1 (4.2)	2 (0.3)	3 (0.5)
Wound haemorrhage	0	0	3 (0.5)	3 (0.5)
International normalised ratio increased	0	0	2 (0.3)	2 (0.3)
Haematuria	0	0	2 (0.3)	2 (0.3)
Rectal haemorrhage	0	1 (4.2)	0	1 (0.2)

Source: Appendix 13.5, Table 3.12.1.2.2.
a The DIC075V 37.5 mg and 50 mg dose groups are included in this analysis (b) (4) (b) (4)
b Includes subjects in the placebo group that match subjects in the DIC075V group who received the proposed dose.
Adapted Sponsor's table 4-50; p. 162.

d. Renal Events

Renal toxicity associated with NSAIDs occurs via a reduction in prostaglandin synthesis that can result in a hemodynamically-mediated decrease in function that may result in

acute renal failure in patients with underlying risk factors such as volume depletion, congestive heart function, cirrhosis, and diabetic or hypertensive renal disease. The induction of anesthesia is also considered to be a low-to-moderate risk factor for NSAID induced renal toxicity. In view of this, the Applicant searched the safety database for renal-related events in order to determine if there was an increase in risk for renal toxicity to occur in post-surgical patients treated with DIC075V. Table 69 is a tabular summary of the MedDRA preferred AE terms for renal-related events for patients who participated in the combined controlled trials (DFC-004 and 005) as well as in the open label trial (DFC-010). There was only one case of oliguria that occurred in a patient from the combined 37.5 mg and 50 mg DIC075V treatment group as compared to one placebo patient who developed acute renal failure due to renal tubular necrosis during studies DFC-004 and 005. Examination of these data as shown in Table 69 did not reveal any pattern of renal toxicity in post-surgical patients in the controlled studies.

Table 69 – Tabular Summary of Renal Events in Patients Who Participated in the Controlled and Open Label Multidose Phase 3 Trials (Safety Population)

		DIC075V 37.5 mg and 50 mg[a]		
MedDRA Preferred Term	Placebo[b] (N=126) n (%)	DFC-004/DFC-005 (N=187) n (%)	DFC-010 (N=969) n (%)	Total (N=1156) n (%)
Urine output decreased	0	0	10 (1.0)	10 (0.9)
Blood creatinine increased	0	0	10 (1.0)	10 (0.9)
Renal failure acute	1 (0.8)	0	7 (0.7)	7 (0.6)
Oliguria	0	1 (0.5)	2 (0.2)	3 (0.3)
Renal failure	0	0	3 (0.3)	3 (0.3)
Blood urea increased	0	0	2 (0.2)	2 (0.2)
Creatinine renal clearance decreased	0	0	1 (0.1)	1 (0.1)
Renal tubular necrosis	1 (0.8)	0	1 (0.1)	1 (0.1)
Anuria	0	0	1 (0.1)	1 (0.1)
Azotaemia	0	0	1 (0.1)	1 (0.1)

Source: Appendix 13.5, Table 3.11.5.4

a The DIC075V 37.5 mg and 50 mg dose groups are included in this analysis (b) (4) (b) (4)

b Includes subjects in the placebo group that match subjects in the DIC075V group who received the proposed dose.

Adapted Sponsor's Table 4-51; p. 164.

As noted previously (Table 62), the incidence of renal events in patients treated with either 37.5 mg or 50 mg of DIC075V in the open label trial DFC-010 (2.8%) was higher than that observed in the combined placebo controlled group (0.5%). The above Table 69 shows that the most commonly reported renal events in DFC-010 were as follows: decreased urine output (1.0%), increased blood creatinine (1.0%), acute renal failure (0.7%) and renal failure (0.3%) (total of 10 cases [1%] renal failure). Review of these 10 cases of renal failure revealed that none of these patients required dialysis and these events resolved over time with fluid and blood volume repletion and diuretic therapy. In order to assess the magnitude of risk for renal toxicity associated with DIC075V in the

post-operative setting, the Applicant also conducted an analysis of patients with renal impairment at baseline which will be discussed in section 7.5.4.

For completeness, renal AE data by pooled dose treatment group was also examined for any potential dose-dependent relationships. A higher proportion of patients receiving 37.5 mg (2.8%) as compared to patients who received 50 mg (1.6%) and 18.75 mg (0.8%) of DIC075V were reported to have renal events. No patients who received ketorolac developed renal failure, however, the proportion of patients who developed oliguria (1.6%) following treatment with 30 mg of ketorolac was higher than the proportion of patients with oliguria following treatment with 37.5 mg (0.4%) and 50 mg (0%) of DIC075V. No dose-dependent patterns for renal events were identified on review of these data (data not shown).

e. Hepatobiliary Events

Since class labeling for NSAIDs includes a warning regarding hepatic toxicity, the Applicant searched the safety database for hepatobiliary events in order to determine if there was an increase in risk for hepatic toxicity to occur in post-surgical patients treated with DIC075V. Table 70 is a tabular summary of the MedDRA preferred AE terms for hepatobiliary events for patients who participated in the combined controlled trials (DFC-004 and 005) as well as in the open label trial (DFC-010). As noted previously the overall incidence of hepatobiliary events was lower in the combined 37.5 mg and 50 mg treatment group (2.7%) as compared to the placebo group (4.8%) in the controlled trials DFC-004 and 005. The most commonly reported hepatobiliary events in the combined 37.5 mg and 50 mg treatment group were increased ALT (2.7%) and increased AST (2.1%) both of which occurred less frequently as compared to the placebo group (4.0% and 4.0%, respectively). There were no serious cases of hepatobiliary AEs reported during the controlled studies. Examination of these data from the controlled trials did not reveal any new hepatotoxicity safety signals associated with the parenteral administration of DIC075V.

Table 70-Tabular Summary of Hepatobiliary Events in Patients Who Participated in the Controlled and Open Label Multidose Phase 3 Trials (Safety Population)

MedDRA Preferred Term	Placebo[b] (N=126)	DIC075V 37.5 mg and 50 mg[a]		
		DFC-004 and DFC-005 (N=187)	DFC-010 (N=969)	Total (N=1156)
Number of Subjects with Any Hepatobiliary Events:	6 (4.8%)	5 (2.7%)	38 (3.9%)	43 (3.7%)
Gastrointestinal Disorders:	0	0	1 (0.1%)	1 (0.1%)
Ascites	0	0	1 (0.1%)	1 (0.1%)
Investigations:	6(4.8%)	5 (2.7%)	33 (3.4%)	38 (3.3%)
Prothrombin Time Prolonged	0	0	14 (1.45)	14 (1.2%)
ALT Increased	5 (4.0%)	5 (2.7%)	5 (0.5%)	10 (0.9%)
AST Increased	5 (4.0%)	4 (2.1%)	4 (0.4%)	8 (0.7%)
Liver Function Test Abnormal	0	0	6 (0.6%)	6 (0.5%)
GGTP Increased	2 (1.6%)	0	3 (0.3%)	3 (0.3%)
Blood Bilirubin Increased	1 (0.8%)	0	3 (0.3%)	3 (0.3%)
INR Ratio Increased	0	0	3 (0.3%)	3 (0.3%)
Blood Akaline Phosphatase Inc.	3 (2.4%)	0	1 (0.1%)	1 (0.1%)
Hepatic Enzyme Increaed	0	0	1 (0.1%)	1 (0.1%)
Metabolism and Nutrition Disorders:	0	0	4 (0.4%)	4 (0.3%)
Hypoalbuminemia	0	0	4 (0.4%)	4 (0.3%)

[a]The DIC075V 37.5 mg and 50 mg dose groups are included in this analysis (b) (4)

[b]Includes subjects in the placebo group that match subjects in the DIC075V group who received the proposed dose
Adapted Sponsor's Table 3.11.6.4; p.

In the open-label study DFC-010, the overall incidence of hepatobiliary events increased to 3.9% (Table 70). This increase in events was mainly due to 14 cases (1.4%) of prolongation of prothrombin time. Prolongation of prothrombin time should not be attributed to DIC075V since patients were prophylactically anticoagulated postoperatively in this trial in accordance to standard of care practices. There was 1 case of ascites reported in DFC-010. This involved a 55 year-old male with retroperitoneal sarcoma and spindle cell sarcoma who underwent an exploratory laporotomy and colonic resection due to his malignancies. On his fifth postoperative day (four days after having completed study treatment) he was found to have abdominal pain and distention. CT of the abdomen and pelvis revealed a mass with ascites associated with fluid in the colon that was attributed to his malignancies. This case of ascites should not be attributed to DIC075V in view of the patient's underlying malignancies. The cases of hepatobilary events reported to have occurred in DFC-010 were also reviewed for the occurrence of serious AEs. This search identified 1 case of serious hepatobiliary AE involving a 76 year-old female with hyperlipidemia who developed elevation of her liver function tests 24 hours after her last dose of 37.5 mg of DIC075V. Review of her concomitant meds revealed that she had been anesthetized with sevoflurane for her prestudy surgical procedure, had restarted ezetimibe (Zetia) for

her hyperlidemia and was taking 500 mg every 6 hours of acetaminophen for analgesic relief following completion of the trial. Her LFT's return to normal 5 days later following the discontinuation of the Zetia and acetaminophen which are known to be hepatoxic agents as is sevoflurane. This case of elevated LFT's should not be attributed to DIC075V in view of the concomitant use of 3 other hepatotoxic agents which confound this case. Overall, the cases of heptotoxicity observed in the open-label study of DIC075V are consistent with the known safety profile of orally administered diclofenac.

For completeness, hepatobiliary AE data by pooled dose treatment group was also examined for any potential dose-dependent relationships. A higher proportion of patients receiving 37.5 mg (4.1%) as compared to patients who received 50 mg (3.0%) and 18.75 mg (2.3%) of DIC075V were reported to have hepatobiliary events. A comparable proportion of patients treated with 30 mg of ketorolac developed hepatobiliary AEs (3.2%). No dose-dependent patterns for renal events were identified on review of these data (data not shown).

In order to assess the magnitude of risk for hepatic toxicity associated with DIC075V in the post-operative setting, the Applicant also conducted an analysis of patients with hepatic impairment at baseline discussed in section 7.5.4 and liver function test results discussed in section 7.4.2.

f. Infusion Site-Related Events

A search of the safety database for toxicity related to DIC075V's route of administration (i.e., 15-second IV bolus) was conducted by the Applicant. Table 71 lists the results of this search by MedDRA preferred term for infusion site-related events. As discussed previously the overall incidence of infusion-site related events in the combined 37.5 mg and 50 mg treatment group (17.1%) was comparable to that observed in the placebo group (15.9%) in the controlled trials DFC-004 and 005. The most commonly reported infusion-site related events in the combined 37.5 mg and 50 mg treatment group were infusion site pain (10.2%), infusion site extravasation (3.2%), and peripheral edema (2.1%) which occurred at higher rates as compared to the placebo group (7.9%, 0.8% and 0.8%, respectively). However, the proportion of placebo patients who develop infusion site thrombosis (3.2%), thrombophlebitis (4.8%) and infusion site phlebitis (0.8%) were all higher as compared to the combined 37.5 mg and 50 mg DIC075V treatment group (1.1%, 0.5% and 0%, respectively) in the controlled studies.

Table 71 - Tabular Summary of Infusion Site-Related Events in Patients Who Participated in the Controlled and Open Label Multidose Phase 3 Trials (Safety Population)

		DIC075V 37.5 mg and 50 mg[a]		
MedDRA Preferred Term	Placebo[b] (N=126) n (%)	DFC-004/DFC-005 (N=187) n (%)	DFC-010 (N=969) n (%)	Total (N=1156) n (%)
Infusion site pain	10 (7.9)	19 (10.2)	50 (5.2)	69 (6.0)
Oedema peripheral	1 (0.8)	4 (2.1)	37 (3.8)	41 (3.5)
Infusion site extravasation	1 (0.8)	6 (3.2)	14 (1.4)	20 (1.7)
Infusion site thrombosis	4 (3.2)	2 (1.1)	6 (0.6)	8 (0.7)
Infusion site erythema	3 (2.4)	2 (1.1)	4 (0.4)	6 (0.5)
Infusion site swelling	1 (0.8)	0	4 (0.4)	4 (0.3)
Infusion site oedema	0	0	3 (0.3)	3 (0.3)
Infusion site haematoma	0	0	2 (0.2)	2 (0.2)
Infusion site irritation	0	0	2 (0.2)	2 (0.2)

Source: Appendix 13.5, Table 3.11.7.4

a The DIC075V 37.5 mg and 50 mg dose groups are included in this analysis (b) (4) (b) (4)

b Includes subjects in the placebo group that match subjects in the DIC075V group who received the proposed dose.

Adapted Sponsor's table 4-53; p. 166.

In the open-label study DFC-010, the overall incidence of infusion-site related events was lower (11.7%) as compared to the combined controlled trials (17.1%) (Table 62). Further examination of the data shown in Table 71 shows that the proportions of the most commonly reported infusion-site related events in this trial were also lower as follows: infusion site pain (5.2%), peripheral edema (3.8%), infusion site extravasation (1.4%) and infusion site thrombosis (0.6%). There were no cases of thrombophlebitis or infusion site phlebitis observed in the open label safety trial.

For completeness, injection site related AE data by pooled dose treatment group was also examined for any potential dose-dependent relationships. A higher proportion of patients receiving 18.75 mg (22.6%) as compared to patients who received 37.5 mg (12.2%) and 50 mg (13.2%) of DIC075V reported to having injection site related AEs which was to comparable the proportion of patients treated with 30 mg of ketorolac who developed injection site AEs (25.8%). A higher proportion of patients treated with 50 mg of DIC075V (5.9%) as compared to patients treated with 18.75 mg (4.5%) and 37.5 mg (2.4%) of DIC075V developed peripheral edema, however, no other dose-dependent patterns for renal events were identified on review of these data (data not shown).

Evaluations for thrombophlebitis were also performed as part of the safety evaluations in the Phase 3, multidose, postsurgical pain studies submitted in support of this application. The majority (i.e., $\geq$ 90%) of the subjects who participated in these trials did not have symptoms at the end of study treatment consistent with phlebitis on comparison of dose treatment groups. Additionally, the proportions of patients who had tenderness along the vein or continuous tenderness/pain with redness were comparable

on cross group comparison. A potential safety signal was also not identified on review of these data (data not shown).

g. Gastrointestinal Events

NSAID class labeling also includes warnings regarding the occurrence of serious and potentially fatal gastrointestinal (GI) reactions associated with the use of these drugs. The Applicant searched the safety database for GI events in order to determine if there was an increase in risk for GI toxicity to occur in post-surgical patients treated intravenously with DIC075V.

Table 72 is a tabular summary of the MedDRA preferred AE terms for GI events for patients who participated in the combined controlled trials (DFC-004 and 005) as well as in the open label trial (DFC-010). The most commonly reported GI events in the combined DIC075V treatment group for the controlled studies were nausea (24.1%), constipation (13.4%), vomiting (6.4%) and flatulence (8.0%) all of which occurred less frequently as compared to the placebo group (39.7%, 11.1%, 18.3% and 15.9%, respectively).

For completeness the data in Table 72 was examined for GI bleeding events in the controlled trials which resulted in the identification of 1 case of rectal hemorrhage (0.5%) that occurred in a patient in the combined DIC75V treatment group as compared to no cases of GI bleeding observed in the placebo group. Broadening this definition to include GI symptoms of irritation or potential ulceration yielded 1 case of abdominal pain (0.5%) and 2 cases of dyspepsia (1.1%) in the combined DIC075V treatment group as compared to 2 cases of abdominal pain (1.6%) and 2 cases of dyspepsia (1.6%) observed in the placebo group. The small number of GI bleeding cases observed in the controlled trials may be the result of the short duration of exposure to DIC075V in these studies, as well as protocol mandated adjustment in the default study dosing regimens for high risk patients who participated in DFC-005.

Table 72 - Tabular Summary of Gastrointestinal Events in Patients Who Participated in the Controlled and Open Label Multidose Phase 3 Trials (Safety Population)

MedDRA Preferred Term	Placebo[b] (N=126)	DIC075V 37.5 mg and 50 mg[a]		
		DFC-004 and DFC-005 (N=187)	DFC-010 (N=969)	Total (N=1156)
Number of Subjects with Any Gastrointestinal Events:	**71 (56.3%)**	**71 (38.0%)**	**513 (52.9%)**	**584 (50.4%)**
Nausea	50 (39.7%)	45 (24.1%)	360 (37.2%)	405 (35.0%)
Constipation	14 (11.1%)	25 (13.4%)	180 (18.6%)	205 (17.7%)
Vomiting	23 (18.3%)	12 (6.4%)	83 (8.6%)	95 (8.2%)
Flatulence	20 (15.9%)	15 (8.0%)	38 (3.9%)	53 (4.6%)
Dyspepsia	2 (1.6%)	2 (1.1%)	36 (3.7%)	38 (3.3%)
Diarrhea	4 (3.2%)	3 (1.6%)	27 (2.8%)	30 (2.6%)
Abdominal Distension	2 (1.6%)	3 (1.6%)	16 (1.7%)	19 (1.6%)
Abdominal Pain	2 (1.6%)	1 (0.5%)	8 (0.8%)	9 (0.8%)
Abdominal Discomfort	0	0	6 (0.6%)	6 (0.5%)
Small Intestine Obstruction	0	1 (0.5%)	3 (0.3%)	4 (0.3%)
Gastroesophageal Reflux Dis.	0	0	4 (0.4%)	4 (0.3%)
Chest Pain	0	1 (0.5%)	2 (0.2%)	3 (0,3%)
Hematochezia	0	0	3 (0.3%)	3 (0.3%)
Ileus	0	1 (0.5%)	1 (0.1%)	2 (0.2%)
Rectal Hemorrhage	0	1 (0.5%)	1 (0.1%)	2 (0.2%)
Retching	1 (0.8%)	0	2 (0.2%)	2 (0.2%)
Gastritis	0	0	2 (0.2%)	2 (0.2%)
Non-Cardiac Chest Pain	1 (0.8%)	1 (0.5%)	1 (0.1%)	2 (0.2%)
Procedural Nausea	0	0	2 (0.2%)	2 (0.2%)
Ileus Paralytic	1 (0.8%)	0	1 (0.1%)	1 (0.1%)
Abdominal Pain Upper	0	0	1 (0.1%)	1 (0.1%)
Abdominal Tenderness	0	0	1 (0.1%)	1 (0.1%)
Anal Hemorrhage	0	0	1 (0.1%)	1 (0.1%)
Anal Ulcer	0	0	1 (0.1%)	1 (0.1%)
Enterocutaneous Fistula	0	0	1 (0.1%)	1 (0.1%)
Epigastric Discomfort	0	0	1 (0.1%)	1 (0.1%)
Eructation	0	0	1 (0.1%)	1 (0.1%)
Gastrointestinal Pain	0	0	1 (0.1%)	1 (0.1%)
Hematemesis	0	0	1 (0.1%)	1 (0.1%)
Intestinal Perforation	0	0	1 (0.1%)	1 (0.1%)
Peritionitis	0	0	1 (0.1%)	1 (0.1%)
Upper Gastrointest. Hemorrhage	0	0	1 (0.1%)	1 (0.1%)
Early Satiety	0	0	1 (0.1%)	1 (0.1%)
Abdominal Wall Abscess	0	0	1 (0.1%)	1 (0.1%)
Anastomotic Hemorrhage	0	0	1 (0.1%)	1 (0.1%)
Procedural Vomiting	0	0	1 (0.1%)	1 (0.1%)
Hypovolemia	0	0	1 (0.1%)	1 (0.1%)
Colonic Stenosis	1 (0.8%)	0	0	0

[a]The DIC075V 37.5 mg and 50 mg dose groups are included in this analysis (b) (4)

[b]Includes subjects in the placebo group that match subjects in the DIC075V group who received the proposed dose
Adapted Sponsor's Table 4-56; p. 169.

Further examination of the data shown in Table 72 shows that the proportions of the most commonly reported GI related events in the open label trial were also higher as follows: nausea (37.2%), constipation (18.6%), vomiting (8.6%) and flatulence (3.9%). An additional search of the data from the open-label trial revealed 11 cases (1.1%) of GI bleeding: 3 cases of hematochezia (0.3%), 2 cases of gastritis, 1 case of rectal hemorrhage (0.1%), 1 case of anal hemorrhage (0.1%), 1 case of hematemesis (0.1%), 1 case of intestinal perforation (0.1%), 1 case of upper GI hemorrhage (0.1%) and 1 case of anastomotic hemorrhage (0.1%). Broadening the definition to include GI irritation or potential ulceration identified another 52 cases (5.3%): 36 cases of dyspepsia (3.7%), 8 cases of abdominal pain (0.8%), 6 cases of abdominal discomfort (0.6%), 1 case of upper abdominal pain (0.1%), and 1 case of GI pain (0.1%). These types of GI events are consistent with what has been reported with other systemically administered formulations of diclofenac, however, if approved DIC075V potentially will be used with prophylactic anticoagulation therapy administered as standard of care following orthopedic, pelvic and abdominal surgery to prevent thromboembolic events. Appropriate cautionary language regarding the potential increase in risk for GI bleeding events needs to be included in the drug's label.

For completeness, GI related AE data by pooled dose treatment group was also examined for any potential dose-dependent relationships particularly bleeding events. Surprisingly no dose-dependent patterns for GI events were identified on review of these data including bleeding events (total bleeding events: 6.3% for 37.5 mg dose group versus 5.1% for the 50 mg dose group of DIC075V).

h. Wound Healing

During the controlled trials DFC-004 and 005, the rate of wound healing impairment was higher in patients treated with DIC075V (7.5% for combined DIC075V treated patients) and ketorolac (6.3%) as compared to placebo controlled patients (4.1%). Additional wound assessments were performed as part of the safety evaluations in DFC-005 and 010 submitted in support of this application because of concerns related to a possible delay in wound healing due to DIC075V's anti-inflammatory capabilities. The results from these pooled assessments by dose are presented in Table 73. A potential safety signal was not identified on review of these data.

Table 73 – Tabular Summary of Wound Healing at Study Discharge and the Final Visit for Subjects Participating in the Multidose Phase 3 Trials DFC-005 and 010 (Safety Population)

		DIC075V				Ketorolac	
Parameter[a] / Timepoint	Placebo (N=72) n (%)	18.75 mg (N=47) n (%)	37.5 mg (N=699) n (%)	50 mg (N=370) n (%)	Total (N=1116) n (%)	15 mg (N=18) n (%)	30 mg (N=42) n (%)
Antibiotics prescribed for definite infection							
Study Discharge	1 (1.4)	0	0	1 (0.3)	1 (0.1)	0	0
Final Visit	1 (1.4)	0	3 (0.4)	2 (0.5)	5 (0.4)	0	0
Extent and degree of inflammation much more than expected							
Study Discharge	0	0	0	0	0	0	0
Final Visit	0	0	2 (0.3)	0	2 (0.2)	0	0
Extent of drainage much more than expected							
Study Discharge	0	0	1 (0.1)	0	1 (0.1)	0	0
Final Visit	0	0	1 (0.1)	2 (0.5)	3 (0.3)	0	0
Extent of healing much slower than expected							
Study Discharge	0	0	0	0	0	0	0
Final Visit	0	0	1 (0.1)	0	1 (0.1)	0	0
Abscess or gross cellulitis at the surgical site							
Study Discharge	0	0	0	0	0	0	0
Final Visit	0	0	1 (0.1)	1 (0.3)	2 (0.2)	0	0
Surgical incision mostly separated							
Study Discharge	0	0	0	0	0	0	0
Final Visit	0	0	1 (0.1)	1 (0.3)	2 (0.2)	0	0

Source: Appendix 13.5, Table 3.22.1.
a Wound healing data from Studies DFC-005 and DFC-010 were included.

Adapted Sponsor's Table 4-65; p. 189.

For completeness, the Applicant conducted a search for AEs related to wound healing events by MedDRA preferred term which is presented in Table 74. The rates of wound healing AEs were similar in both the DIC075V 37.5 mg (8.8%) and 50 mg (8.1%) treatment groups, however, these rates were higher than those observed in placebo treated patients (3.4%), or in patients treated with either 18.75 mg of DIC075V (3.8%) or ketorolac 30 mg (6.5%). A dose dependent relationship for wound healing was not observed on comparison of the pooled dose treatment groups for any of the wound healing AEs listed in this table.

These cases were also examined for serious AEs related to wound healing. There were a total of 9 serious cases that involved the surgical incision site [0 cases in patients treated with 18.75 mg of DIC075V, 7 cases (0.9%) in patients treated with 37.5 mg and 2 cases (0.5%) in patients treated with 50 mg] and a total of 19 serious cases of infections that involved the surgical incision site [11 cases (1.4%) in patients treated with 37.5 mg and 8 cases (2.1%) in patients treated with 50 mg of DIC075V). The latter is suggestive of a trend in dose dependent serious wound infections, however, no

patterns emerged on examination of these serious cases since they involved single events with the exception of wound infection in which 2 cases were reported in patients from each of the 37.5 mg and 50 mg groups. Although the number of cases of wound healing AEs contained in this safety database is low, the rates of wound healing impairment were higher in patients who had received either DIC075V or ketorolac as compared to placebo patients. This is consistent with NSAID-related class effects and should be conveyed to prescribers in the drug's label.

Table 74: Tabular Summary of Incidence of Treatment-Emergent Adverse Events Related to Wound Healing Occurring in at Least 2 Subjects Treated with DIC075V During the Multidose Phase 3 Controlled and Open Label Postsurgical Pain Trials (Safety Population)

		DIC075V				Ketorolac	
MedDRA System Organ Class / Preferred Term	Placebo (N=148) n (%)	18.75 mg (N=133) n (%)	37.5 mg (N=786) n (%)	50 mg (N=370) n (%)	Total (N=1289) n (%)	15 mg (N=18) n (%)	30 mg (N=124) n (%)
At least 1 wound healing event	5 (3.4)	5 (3.8)	69 (8.8)	30 (8.1)	104 (8.1)	1 (5.6)	8 (6.5)
Infections and infestations	4 (2.7)	5 (3.8)	33 (4.2)	15 (4.1)	53 (4.1)	1 (5.6)	2 (1.6)
Postoperative wound infection	4 (2.7)	3 (2.3)	7 (0.9)	4 (1.1)	14 (1.1)	0	1 (0.8)
Wound infection	0	1 (0.8)	9 (1.1)	4 (1.1)	14 (1.1)	0	0
Cellulitis	0	1 (0.8)	4 (0.5)	2 (0.5)	7 (0.5)	1 (5.6)	0
Incision site infection	0	0	6 (0.8)	0	6 (0.5)	0	0
Incision site abscess	0	0	2 (0.3)	2 (0.5)	4 (0.3)	0	0
Incision site cellulitis	0	0	2 (0.3)	1 (0.3)	3 (0.2)	0	0
Wound infection staphylococcal	0	0	2 (0.3)	0	2 (0.2)	0	0
Injury, poisoning and procedural complications	1 (0.7)	0	36 (4.6)	17 (4.6)	53 (4.1)	0	8 (6.5)
Incision site complication	0	0	10 (1.3)	5 (1.4)	15 (1.2)	0	0
Wound dehiscence	0	0	6 (0.8)	3 (0.8)	9 (0.7)	0	2 (1.6)
Post procedural discharge	0	0	6 (0.8)	2 (0.5)	8 (0.6)	0	0
Incision site haemorrhage	0	0	4 (0.5)	3 (0.8)	7 (0.5)	0	0
Procedural site reaction	0	0	4 (0.5)	1 (0.3)	5 (0.4)	0	2 (1.6)
Post procedural haemorrhage	0	0	4 (0.5)	0	4 (0.3)	0	0
Seroma	0	0	2 (0.3)	2 (0.5)	4 (0.3)	0	1 (0.8)
Incision site haematoma	0	0	1 (0.1)	1 (0.3)	2 (0.2)	0	3 (2.4)
Postoperative wound complication	0	0	2 (0.3)	0	2 (0.2)	0	0
Wound secretion	0	0	0	2 (0.5)	2 (0.2)	0	0
Vascular disorders	0	0	3 (0.4)	3 (0.8)	6 (0.5)	0	0
Haematoma	0	0	2 (0.3)	1 (0.3)	3 (0.2)	0	0
Wound haemorrhage	0	0	1 (0.1)	2 (0.5)	3 (0.2)	0	0

Source: Appendix 13.5, Table 3.22.2.1.

Adapted Sponsor's Table 4-66; p. 191.

i. Follow-On Analgesic Medications

At the EOP2 meeting, the Applicant was told that they also had to assess the risk for cumulative toxicity associated with oral NSAIDs or possible acetaminophen-associated hepatotoxicity post-treatment with DIC075V. Pursuant to this, the Applicant performed a number of analyses to evaluate the magnitude of these risks. A total of 1,199 patients out of the 1289 patients (93%) treated with DIC075V in the multidose, Phase 3 postsurgical pain trials reported taking follow-on analgesics during the follow-up period. Of these 1199 subjects, 607 subjects reported taking an opioid or opioid combination only (without an NSAID) while the remaining 499 subjects took an NSAID and opioid or opioid combination. Overall, 375 patients (31.3%) who received DIC075V during these trials reported at least 1 AE during the follow-up phase and received follow-on analgesics as compared to 12 subjects (13.5%) who did not take follow-on analgesics. The overall incidences of AEs ranged from 28-32% in the active treatment groups and placebo with higher rates observed in patients with increasing background risk (36% and 61%). The most commonly reported AEs in patients who had been treated with DIC075V were constipation (4.1%), nausea (3.8%) and insomnia (2.7%) which were also commonly reported during the treatment phase of these trials. Nausea and insomnia are AEs that have been reported associated with the use of oral diclofenac. The high rate of constipation is not unexpected in this postsurgical population and may also have been related to the administration of prior and follow-up opioid analgesics.

In view of concerns of additive risk for gastrointestinal (i.e., bleeding events), hepatic, and renal AEs to occur with follow-on analgesics, these data were examined further for these type of events. There were a total of 22 gastrointestinal AEs of special interest reported in the follow-up period by patients taking follow-on analgesics who had been treated with DIC075V as follows: abdominal pain (8 subjects, 0.7%), dyspepsia (8 subjects, 0.7%), rectal hemorrhage (2 subjects, 0.2%), anal ulcer (1 subject, 0.1%), gastritis (1 subject, 0.1%), gastrointestinal pain (1 subject, 0.1%), hematochezia (1 subject, 0.1%). For hepatic events of interest there were a total of 9 AEs reported in the follow-up period by subjects taking follow-on analgesics who had been treated with DIC075V as follows: increased AST (4 subjects, 0.3%), increased ALT (2 subjects, 0.2%), increased alkaline phosphatase (1 subject, 0.2%), prolonged activated partial thromboplastin time (1 subject, 0.2%), abnormal liver function test (1 subject, 0.1%). These data were also examined for evidence of renal AEs associated with follow-up analgesics. Only 1 case of acute renal failure (1 subject, 0.1%) was identified in a patient who had been previously treated with 37.5 mg of DIC075V. None of the 90 subjects treated with DIC075V who did not take follow-on analgesics were observed to have experienced a gastrointestinal, hepatic or renal AEs of interest. The observed events are consistent with drug class effect. No increase in frequency or severity due to cumulative effect was observed.

The Applicant also looked at the incidence of AEs in patients taking follow-on analgesics by the type of analgesic (e.g., NSAID and opioid or opioid combination versus opioid or opioid combination without NSAID). The results of this analysis showed that the rates of AEs in subjects treated with DIC075V were comparable for those who took NSAID and opioid combination (33.9%; 169 subjects) versus opioid without NSAID (31%; 188 subjects). These data were reviewed for AEs of special interest. There were a total of 6 cases of gastrointestinal AEs of special interest reported by patients taking follow-on NSAID and opioid combination therapy [4 cases of abdominal pain (0.8%), 1 case of gastritis (0.2%), 1 case of dyspepsia (0.2%)] versus 16 cases reported in the opioid without NSAID group [4 cases of abdominal pain (0.7%), 6 cases of dyspepsia (1%), 1 case of anal ulcer (0.2%), 1 case of gastrointestinal pain (0.2%), 1 case of hematochezia (0.2%), and 2 cases of rectal hemorrhage (0.3%)]. In terms of hepatic events of special interest, a total of 4 cases were reported by patients who took NSAID and opioid combination follow-up analgesics [1 case of prolonged activated partial thromboplastin time (0.2%), 1 case of increased AST (0.2%), 1 case of abnormal liver function test (0.2%), and 1 case of prolonged prothrombin time (0.2%)] as compared to 6 cases of AEs for patients treated with an opioid without NSAID [3 cases of increased ALT (0.5%), 2 cases of increased ALT (0.3%) and 1 case of increased alkaline phosphatase (0.2%)]. Again there was only 1 patient treated with opioid without NSAID who developed acute renal failure (0.2%).

Based on these results, there does not appear to be an increase in additive risk for gastrointestinal (i.e., bleeding events), hepatic, and renal AEs to occur with follow-on analgesics in patients who had been treated with DIC075V during the multidose, Phase 3 postsurgical pain trials.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 75 summarizes the most commonly reported AEs reported by patients at a frequency higher than 1% in the controlled trials DFC-004 and 005 and the open label trial DFC-010. The AEs by MedDRA preferred term most commonly reported by patients treated with 37.5 mg and 50 mg of DIC075V in the controlled trials were: nausea (24.1%), constipation (13.1%), increased blood CPK (10.7%), headache (10.2%), and infusion site pain (10.2%). These rates were comparable to those seen placebo treated patient with the exception of nausea and headache which were higher in the placebo group (39.7% and 24.1%, respectively). The placebo group also had a lower rate of increased blood CPK (7.1%). Patients treated with 37.5 mg and 50 mg during the controlled studies also experienced higher rates of dizziness (8.0%), peripheral edema (2.1%), oropharyngeal pain (1.6%), urinary retention (1.6%), incision site complication (1.1%) and infusion site extravasation (3.2%) as compared to placebo

patients (dizziness 1.6%, peripheral edema 0.8%, oropharyngeal pain 1.6%, urinary retention 1.6%, incision site complication 0%, and infusion site extravasation 0.8%). No other patterns of adverse events were noted on further review of these data from the controlled trials.

Review of the data generated from open label safety trial DFC-010 displayed in Table 75 below shows that the most commonly reported AEs reported by patients at a frequency higher than 1% during this trial were similar to that observed in patients treated with DIC075V during the controlled studies but occurred at much higher rates as follows: nausea (37.2%), postoperative anemia (22.5%), constipation (18.6%), insomnia (13.4%), pruritus (12.9%) and vomiting (8.6%). Further examination of the data shown in Table 75 revealed that anemia was coded under the preferred terms postoperative anemia and anemia. When these preferred terms were combined the rate of anemia overall increased to 23.9% in DFC-010 as compared to 4.2% for the combined DIC075V treated patients and 7.1% for placebo patients in the controlled studies.

Table 75 -Tabular Summary of Treatment Emergent Adverse Events Commonly Occurring in ≥ 1% Subjects Treated With DIC075V 37.5 mg and 50 mg Compared to Placebo in Multiple Dose Phase 3 Pain Trials (Safety Population)

		DIC075V 37.5 mg and 50 mg[a]		
MedDRA Preferred Term	Placebo[b] (N=126) n (%)	DFC-004/DFC-005 (N=187) n (%)	DFC-010 (N=969) n (%)	DIC075V Total (N=1156) n (%)
Nausea	50 (39.7)	45 (24.1)	360 (37.2)	405 (35.0)
Anaemia postoperative	2 (1.6)	2 (1.1)	218 (22.5)	220 (19.0)
Constipation	14 (11.1)	25 (13.4)	180 (18.6)	205 (17.7)
Insomnia	12 (9.5)	11 (5.9)	130 (13.4)	141 (12.2)
Pruritus	10 (7.9)	9 (4.8)	125 (12.9)	134 (11.6)
Vomiting	23 (18.3)	12 (6.4)	83 (8.6)	95 (8.2)
Blood creatine phosphokinase increased	9 (7.1)	20 (10.7)	63 (6.5)	83 (7.2)
Headache	20 (15.9)	19 (10.2)	55 (5.7)	74 (6.4)
Infusion site pain	10 (7.9)	19 (10.2)	50 (5.2)	69 (6.0)
Hypotension	6 (4.8)	9 (4.8)	59 (6.1)	68 (5.9)
Pyrexia	13 (10.3)	8 (4.3)	58 (6.0)	66 (5.7)
Dizziness	2 (1.6)	15 (8.0)	49 (5.1)	64 (5.5)
Flatulence	20 (15.9)	15 (8.0)	38 (3.9)	53 (4.6)
Oedema peripheral	1 (0.8)	4 (2.1)	37 (3.8)	41 (3.5)
Dyspepsia	2 (1.6)	2 (1.1)	36 (3.7)	38 (3.3)
Hypokalaemia	5 (4.0)	1 (0.5)	37 (3.8)	38 (3.3)
Muscle spasms	0	2 (1.1)	34 (3.5)	36 (3.1)
Tachycardia	6 (4.8)	2 (1.1)	32 (3.3)	34 (2.9)
Hypertension	0	1 (0.5)	33 (3.4)	34 (2.9)
Oropharyngeal pain	1 (0.8)	3 (1.6)	30 (3.1)	33 (2.9)
Diarrhoea	4 (3.2)	3 (1.6)	27 (2.8)	30 (2.6)
Asthenia	0	0	25 (2.6)	25 (2.2)
Urinary retention	1 (0.8)	3 (1.6)	21 (2.2)	24 (2.1)
Anxiety	0	2 (1.1)	22 (2.3)	24 (2.1)
Urinary tract infection	1 (0.8)	1 (0.5)	20 (2.1)	21 (1.8)
Anaemia	7 (5.6)	6 (3.2)	14 (1.4)	20 (1.7)
Infusion site extravasation	1 (0.8)	6 (3.2)	14 (1.4)	20 (1.7)
Abdominal distension	2 (1.6)	3 (1.6)	16 (1.7)	19 (1.6)
Pain in extremity	1 (0.8)	2 (1.1)	17 (1.8)	19 (1.6)
Cough	1 (0.8)	2 (1.1)	14 (1.4)	16 (1.4)
Dyspnoea	0	0	16 (1.7)	16 (1.4)
Incision site complication	0	2 (1.1)	13 (1.3)	15 (1.3)
Hypoaesthesia	0	2 (1.1)	12 (1.2)	14 (1.2)
Prothrombin time prolonged	0	0	14 (1.4)	14 (1.2)
Chills	1 (0.8)	1 (0.5)	12 (1.2)	13 (1.1)
Leukocytosis	0	1 (0.5)	12 (1.2)	13 (1.1)
Wound infection	0	1 (0.5)	12 (1.2)	13 (1.1)

Table 75 (cont.) – Tabular Summary of Treatment Emergent Adverse Events Commonly Occurring in ≥ 1% Subjects Treated with DIC075V 37.5 mg and 50 mg Compard to Placebo in the Multiple Dose Phase 3 Pain Trials (Safety Population)

		DIC075V 37.5 mg and 50 mg[a]		
MedDRA Preferred Term	Placebo[b] (N=126) n (%)	DFC-004/DFC-005 (N=187) n (%)	DFC-010 (N=969) n (%)	DIC075V Total (N=1156) n (%)
Hyperglycaemia	0	0	13 (1.3)	13 (1.1)
Hyponatraemia	0	0	13 (1.3)	13 (1.1)
Back pain	3 (2.4)	5 (2.7)	7 (0.7)	12 (1.0)
Dry mouth	2 (1.6)	1 (0.5)	11 (1.1)	12 (1.0)
Nasal congestion	0	1 (0.5)	11 (1.1)	12 (1.0)
Hypothermia	0	0	12 (1.2)	12 (1.0)
Postoperative wound infection	4 (3.2)	5 (2.7)	6 (0.6)	11 (1.0)
Bradycardia	1 (0.8)	1 (0.5)	10 (1.0)	11 (1.0)
Blister	1 (0.8)	0	11 (1.1)	11 (1.0)
Post procedural oedema	0	0	11 (1.1)	11 (1.0)

Source: Appendix 13.5, Table 3.2.2.1.1.

a The DIC075V 37.5 mg and 50 mg dose groups are included in this analysis (b) (4) (b) (4)

b Includes subjects in the placebo group that match subjects in the DIC075V group who received the proposed dose.

Adapted Sponsor's table 4-20; p. 83-4.

7.4.2 Laboratory Findings

Laboratory data from the three multidose, Phase 3, postsurgical trials were presented as follows: actual values and change from baseline by parameter and the incidence of treatment-emergent shifts from normal range relative to baseline. The Applicant provided normal range of values for each lab parameter assessed. These were reviewed and the clinically acceptable range for normal appeared appropriate. Since diclofenac is known to cause hematopoietic, hepatic and renal toxicities, this review will focus on analyses of lab assessments for these organ systems. (Note: The Applicant also assessed serum CPK levels in patients who participated in these trials which were found to be elevated as to be expected due to muscle trauma following surgery. Since isoenzyme determination was not performed to confirm that these elevations were due to other causes besides muscle trauma, they will not be discussed further in this review.) The findings from the three areas of interest for lab parameter analyses are as follows:

a. Hematology –

Since the three multidose, Phase 3 pain trials were conducted in a postsurgical patient population, decreases in red cell indices were expected to be seen as a result of surgical blood loss. Mean decreases in hemoglobin, hematocrit and erythrocytes from

baseline values were observed at the final visit of the treatment period for the placebo, DIC075V (i.e., 18.75 mg, 37.5 mg and 50 mg dose groups) and ketorolac treatment groups comprising the pooled safety population. However, further examination revealed that these decreases from baseline values increased with increasing doses of DIC075V in a dose-dependent manner on cross group comparison (Table 76).

Table 76 – Tabular Summary of Change in Baseline of Hematology Parameters by Dose Treatment Group for Multidose Phase 3 Trials (Safety Population)

		DIC075V				Ketorolac	
Parameter	Placebo (N=148)	18.75 mg (N=133)	37.5 mg (N=786)	50 mg (N=370)	Total (N=1289)	15 mg (N=18)	30 mg (N=124)
Hemoglobin (g/L)							
Baseline (N)	146	129	762	354	1245	17	123
Mean (SD)	137.53 (15.62)	137.10 (13.22)	134.83 (15.03)	140.13 (16.53)	136.57 (15.47)	132.94 (9.11)	137.63 (15.69)
Median	136.50	137.00	135.00	141.00	137.00	134.00	137.00
Min-Max	98.0-175.0	102.0-168.0	86.0-180.0	73.0-183.0	73.0-183.0	112.0-155.0	91.0-170.0
Change from Baseline (N)	121	114	670	306	1090	13	110
Mean (SD)	-11.85 (11.78)	-16.30 (11.54)	-25.77 (15.20)	-28.52 (14.77)	-25.55 (15.11)	-22.54 (7.74)	-16.84 (12.79)
Median	-9.00	-14.00	-24.50	-29.00	-25.00	-23.00	-16.00
Min-Max	-45.0-10.0	-50.0-5.0	-77.0-13.0	-79.0-19.0	-79.0-19.0	-36.0--7.0	-73.0-4.0
Hematocrit							
Baseline (N)	145	129	750	349	1228	17	123
Mean (SD)	0.408 (0.043)	0.407 (0.037)	0.402 (0.039)	0.418 (0.041)	0.407 (0.040)	0.393 (0.028)	0.410 (0.045)
Median	0.402	0.405	0.402	0.417	0.408	0.395	0.404
Min-Max	0.30-0.51	0.33-0.50	0.28-0.51	0.29-0.53	0.28-0.53	0.33-0.45	0.28-0.51
Change from Baseline (N)	121	112	637	293	1042	13	109
Mean (SD)	-0.036 (0.037)	-0.049 (0.035)	-0.073 (0.045)	-0.081 (0.044)	-0.072 (0.045)	-0.068 (0.029)	-0.050 (0.040)
Median	-0.030	-0.047	-0.069	-0.086	-0.072	-0.065	-0.044
Min-Max	-0.13-0.04	-0.15-0.02	-0.23-0.04	-0.27-0.09	-0.27-0.09	-0.12--0.01	-0.23-0.00
Erythrocytes (10^{12}/L)							
Baseline (N)	146	129	762	354	1245	17	123
Mean (SD)	4.508 (0.464)	4.530 (0.399)	4.473 (0.471)	4.697 (0.465)	4.543 (0.473)	4.285 (0.286)	4.567 (0.518)
Median	4.510	4.500	4.465	4.710	4.540	4.350	4.490
Min-Max	3.32-5.97	3.50-5.92	3.09-6.34	3.22-5.96	3.09-6.34	3.70-4.89	3.55-7.60
Change from Baseline (N)	121	114	670	306	1090	13	110
Mean (SD)	-0.404 (0.398)	-0.552 (0.372)	-0.847 (0.496)	-0.952 (0.476)	-0.846 (0.491)	-0.741 (0.263)	-0.568 (0.420)
Median	-0.360	-0.515	-0.820	-0.980	-0.840	-0.760	-0.520
Min-Max	-1.49-0.35	-1.55-0.15	-2.62-0.85	-2.45-0.61	-2.62-0.85	-1.21--0.19	-2.28-0.06

Modified Sponsor's Table 4-78; p. 220.

As displayed in Table 77, more patients in the DIC075V dose treatment groups experienced shifts in hemoglobin from normal to low value at baseline in a dose dependent manner (18.75 mg: 36.8%; 37.5 mg: 61.2%; 50 mg: 68.0%) as compared to patients treated with placebo (21.5%) or 30 mg of ketorolac (35.5%). This dose-dependent trend raises the concern of a possible increase in risk for postoperative bleeding to have occurred in patients treated with higher doses of DIC075V in view of the drug's effect on platelets. Review of platelet count data revealed no meaningful trends on change from baseline to final visit, however, a dose-dependent trend in shift to lower platelet counts was observed on shift table analysis for this indice (Table 77).

Table 77 – Tabular Summary of Shifts from Baseline to Final Visit in Hematology Parameters for Subjects Participating in the Multidose, Phase 3 Pain Trials (Safety Population)

			DIC075V				Ketorolac	
Parameter	Shift	Placebo (N=148) n/N (%)[a]	18.75 mg (N=133) n/N (%)[a]	37.5 mg (N=786) n/N (%)[a]	50 mg (N=370) n/N (%)[a]	Total (N=1289) n/N (%)[a]	15 mg (N=18) n/N (%)[a]	30 mg (N=124) n/N (%)[a]
Hemoglobin	Shift to High[b]	0	0	0	0	0	0	0
	Shift to Low[c]	26/121 (21.5)	42/114 (36.8)	410/670 (61.2)	208/306 (68.0)	660/1090 (60.6)	9/13 (69.2)	39/110 (35.5)
Leukocytes	Shift to High[b]	18/121 (14.9)	10/114 (8.8)	51/636 (8.0)	21/293 (7.2)	82/1043 (7.9)	1/13 (7.7)	17/110 (15.5)
	Shift to Low[c]	0	0	7/636 (1.1)	1/293 (0.3)	8/1043 (0.8)	0	1/110 (0.9)
Platelets	Shift to High[b]	1/120 (0.8)	0	1/626 (0.2)	3/289 (1.0)	4/1028 (0.4)	0	0
	Shift to Low[c]	1/120 (0.8)	2/113 (1.8)	24/626 (3.8)	14/289 (4.8)	40/1028 (3.9)	1/13 (7.7)	0
Neutrophils	Shift to High[b]	25/117 (21.4)	9/107 (8.4)	10/128 (7.8)	2/33 (6.1)	21/268 (7.8)	1/13 (7.7)	16/99 (16.2)
	Shift to Low[c]	0	0	0	0	0	0	0
Lymphocytes	Shift to High[b]	0	0	0	1/33 (3.0)	1/269 (0.4)	0	0
	Shift to Low[c]	17/117 (14.5)	12/107 (11.2)	7/129 (5.4)	5/33 (15.2)	24/269 (8.9)	4/13 (30.8)	7/101 (6.9)

Source: Appendix 13.5, Table 3.16.2.1.1.
a n=number of subjects with shift, N=total number of subjects included in analysis.
b Shift from normal or low value at baseline to a high value on study.
c Shift from normal or high value at baseline to a low value on study.
Adapted Sponsor's Table 4-78; p. 220.

Examination of WBC and differential counts data revealed no meaningful trends on change from baseline to final visit or on shift table analysis excepted that a higher proportion of placebo treated patients had a shift to higher leukocyte (13.5%) and neutrophil (20.0%) counts as compared to DIC075V treated patients (8.5% and 7.5%, respectively) (Table 77).

b. Liver Function Tests (LFTs):

Diclofenac is known to cause hepatotoxicity ranging from elevations in liver function tests to fulminant hepatic failure. A search of the safety database submitted in support of this application failed to identify any subject who met the criteria for Hy's Law. In general, the mean changes from baseline to final visit values for ALT, AST, alkaline phosphatase, and total bilirubin were small and not clinically meaningful across all dose groups of DIC075V, as well as for the placebo and ketorolac 30 mg treatment groups in the multidose, Phase 3 postsurgical pain trials. Review of shift tables by dose treatment group for DIC075V (Table 78) was remarkable for a higher rate of treatment emergent elevations in total bilirubin in patients treated with 50 mg (4.1%) as compared to 37.5 mg (1.6%) and 18.75 mg (2.3%) but did not reveal any dose-dependent treatment elevations in the other liver function tests

Table 78- Tabular Summary of Treatment-Emergent Elevations in Hepatic Function for Subjects Participating in the Multidose, Phase 3 Pain Trials (Safety Population)

		DIC075V				Ketorolac	
Elevation Test	Placebo (N=148) n (%)	18.75 mg (N=133) n (%)	37.5 mg (N=786) n (%)	50 mg (N=370) n (%)	Total (N=1289) n (%)	15 mg (N=18) n (%)	30 mg (N=124) n (%)
ALT (IU/L)							
> 1 to < 3 times ULN	13 (8.8)	8 (6.0)	50 (6.4)	15 (4.1)	73 (5.7)	0	13 (10.5)
3 to < 8 times ULN	5 (3.4)	4 (3.0)	12 (1.5)	0	16 (1.2)	0	0
≥ 8 times ULN	0	0	2 (0.3)	0	2 (0.2)	0	0
AST (IU/L)							
> 1 to < 3 times ULN	21 (14.2)	9 (6.8)	78 (9.9)	26 (7.0)	113 (8.8)	0	13 (10.5)
3 to < 8 times ULN	2 (1.4)	4 (3.0)	9 (1.1)	1 (0.3)	14 (1.1)	0	1 (0.8)
≥ 8 times ULN	1 (0.7)	0	2 (0.3)	0	2 (0.2)	0	0
Alk Phos (IU/L)							
> 1 to < 3 times ULN	6 (4.1)	4 (3.0)	24 (3.1)	6 (1.6)	34 (2.6)	0	0
3 to < 8 times ULN	0	0	0	0	0	0	0
≥ 8 times ULN	0	0	0	0	0	0	0
Total bilirubin (μmol/L)							
> 1 to < 1.5 times ULN	2 (1.4)	1 (0.8)	8 (1.0)	11 (3.0)	20 (1.6)	0	1 (0.8)
1.5 to < 2 times ULN	0	1 (0.8)	5 (0.6)	3 (0.8)	9 (0.7)	0	0
2 to < 2.5 times ULN	1 (0.7)	0	0	1 (0.3)	1 (0.1)	0	0
2.5 to < 3 times ULN	0	1 (0.8)	0	0	1 (0.1)	0	0
≥ 3 times ULN	0	0	0	0	0	0	0

Modified Sponsor's table 3.18.1.1; p. 2904.

c. Renal Function:

In addition to causing acute renal failure, diclofenac is known to cause renal impairment via its ability to inhibit renal prostaglandin synthesis. Additionally, patients are at risk for developing acute renal failure due to shock kidney following surgery. Examination of the mean changes from baseline to final visit values for creatinine and BUN showed small declines in both parameters that were not clinically meaningful across all dose groups of DIC075V, as well as for the placebo and ketorolac 30 mg treatment groups in the multidose, Phase 3 postsurgical pain trials. However, shift table analyses for these parameters (Table 79) revealed dose dependent treatment-emergent elevations for DIC075V treated patients in creatinine (18.75 mg: 1.6%; 37.5 mg: 2.8%; and 50 mg: 4.7%) as well as BUN (18.75 mg: 1.6%; 37.5 mg: 2.8%; and 50 mg: 7.3%) as compared to placebo treated patients (creatinine: 0.7%; BUN: 1.4%) and patients treated with ketorolac 30 mg (creatinine: 0%; BUN: 1.6%). This observation is consistent with what has been observed previously with other members of this drug class.

Table 79 – Tabular Summary of Treatment-Emergent Elevations in Renal Function for Subjects Participating in the Multidose, Phase 3 Pain Trials (Safety Population)

		DIC075V				Ketorolac	
Elevation Test	Placebo (N=148) n (%)	18.75 mg (N=133) n (%)	37.5 mg (N=786) n (%)	50 mg (N=370) n (%)	Total (N=1289) n (%)	15 mg (N=18) n (%)	30 mg (N=124) n (%)
Creatinine (µmol/L)							
> 1 to < 1.5 times ULN	0	1 (0.8)	10 (1.3)	11 (3.0)	22 (1.7)	2 (11.1)	0
1.5 to < 3 times ULN	1 (0.7)	1 (0.8)	12 (1.5)	5 (1.4)	18 (1.4)	0	0
≥ 3 times ULN	0	0	0	1 (0.3)	1 (0.1)	0	0
BUN (mmol/L)							
> 1 to < 1.5 times ULN	2 (1.4)	1 (0.8)	16 (2.0)	21 (5.7)	38 (2.9)	1 (5.6)	2 (1.6)
1.5 to < 3 times ULN	0	1 (0.8)	6 (0.8)	6 (1.6)	13 (1.0)	0	0
≥ 3 times ULN	0	0	0	0	0	0	0

Source: Appendix 13.5, Table 3.18.1.1
Modified Sponsor's table 3.18.1.1; p. 2904.

7.4.3 Vital Signs

According to the protocols for the three multidose, Phase 3, postsurgical pain trials, patients were mandated to undergo measurements of systolic and diastolic blood pressure, pulse, respiratory rate and temperature prior to the first dose of study medication and at one post baseline time point (e.g, during treatment, at discharge or at the follow-up visit).

Vital signs from the pooled safety databases for the three multidose Phase 3 postsurgical pain trials were presented as follows: baseline values and change from baseline by parameter, the incidence of shifts from normal range relative to baseline, and any significant observations (i.e., values meeting pre-specified criteria for possible clinical significance and/or reported as AEs such as tachycardia). The Applicant's listing of normal ranges of values for each vital sign parameter was reviewed and the clinically acceptable range for normal appeared appropriate. Examination of the vital sign data revealed no clinically meaningful trends on change from baseline or on analyses of shift tables for any of the assessed parameters except for a higher proportion of subjects (15.7%) treated with 50 mg DIC075V who had a shift from a normal or low value to a high value in their systolic blood pressure as compared to placebo treated patients (9.5%) or with 37.5 mg of DIC075V (10.5%) suggestive of a dose-dependent effect. Elevations in blood pressure are known to occur in patients treated with NSAIDs due to their ability to inhibit renal prostaglandins and cause salt and fluid retention. (Note: The Applicant did not do a shift analysis for temperature due to DIC075V's antipyretic activity.)

Overall, no new safety signal associated with the use of DIC075V was identified on review of the vital sign data collected during the controlled and open label trials.

7.4.4 Electrocardiograms (ECGs)

The Applicant conducted a formal QT/QTc interval study (DFC-011) in support of DIC075V safety profile. DFC-011 was a randomized, double-blind, 4-way, 4-period cross-over study that evaluated two doses of DIC075V (37.5 mg and 75 mg) versus moxifloxacin as a positive control for QTc prolongation in 70 healthy volunteers. Results of this study showed that neither dose of DIC075V caused QTc prolongation beyond 5 msec consistent with a negative study.

According to the protocols for the three multidose Phase 3 postsurgical pain trials, patients were mandated to have ECGs done at screening, baseline, 24 hours post-initiation of study therapy and at the follow-up safety visit on Day 5-9 for DFC-004 and 005 and at screening, baseline and study discharge for DFC-010.

Since more ECG data was collected from patients participating in the controlled trials DFC-004 and 005, the Applicant submitted a pooled analysis of ECG data from these trials consisting of baseline and final values, and change from baseline for heart rate, QTc, QT, QRS, and PR intervals. The Applicant's listing of normal ranges of values for each interval was reviewed and the clinically acceptable range for normal appeared appropriate. Examination of the ECG data revealed no clinically meaningful trends on change from baseline for any of the assessed parameters.

The Applicant also conducted a dose-based analysis of the incidence of shifts from normal range relative to baseline of ECGs collected from the three multidose, Phase 3, postsurgical pain trials. Review of the results from this analysis which are presented in Table 80 did not reveal any meaningful trends in changes from baseline or clinically significant changes due to exposure to DIC075V.

Table 80 – Tabular Summary of ECG Shifts from Baseline for Subjects Who Participated in the Multiple Dose Phase 3 Trials (Safety Population)

			DIC075V				Ketorolac	
Baseline ECG Interpretation	Final Interpretation	Placebo (N=148) n/N (%)[a]	18.75 mg (N=133) n/N (%)[a]	37.5 mg (N=786) n/N (%)[a]	50 mg (N=370) n/N (%)[a]	Total (N=1289) n/N (%)[a]	15 mg (N=18) n/N (%)[a]	30 mg (N=124) n/N (%)[a]
Normal	Abnormal NCS	19/143 (13.3)	19/124 (15.3)	74/748 (9.9)	31/343 (9.0)	124/1215 (10.2)	0	12/120 (10.0)
Normal	Abnormal CS	0	0	3/748 (0.4)	0	3/1215 (0.2)	0	0
Abnormal NCS	Abnormal CS	0	0	3/748 (0.4)	0	3/1215 (0.2)	0	0

Source: Appendix 13.5, Table 3.20.2.
Abbreviations: NCS = not clinically significant; CS = clinically significant.
a n=number of subjects with shift, N=total number of subjects included in analysis.

Adapted Sponsor's table 4-101; p. 274.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were requested, required or conducted for DIC075V.

7.4.6 Immunogenicity

Not applicable for this application since DIC075V is a small molecular entity that does not contain proteins or protein derivatives that would elicit an immunogenic response.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

NSAID toxicity is a dose dependent phenomena. Since a dose dependent relationship was observed for certain AEs over the course of this review of the pooled data from the multidose, Phase 3 postsurgical pain trials, safety data within individual multi-dose studies generated from DFC-005 and DFC-010 were also examined for the possible occurrence of dose dependent AEs. Table 81 displays treatment emergent AEs for non-high risk and high weight subjects in DFC-005 by dose group that highlights specific AEs where a difference in the rate of occurrence was identified between the 37.5 mg and 50 mg DIC075V treatment groups. Overall, a higher proportion of non-high risk subjects treated with 37.5 mg of DIC075V (75.4%) experienced AEs as compared to high weight subjects treated with 50 mg of the drug. However, rates of treatment emergent AEs were notably higher for the 50 mg treatment group in the following five organ classes: gastrointestinal disorders, injury, poisoning and procedural complications, investigations, nervous system disorders, renal function and vascular disorders.

The higher rate of treatment emergent AEs seen in the gastrointestinal disorders is due to higher rates of nausea (34.3%), constipation (11.4%) and vomiting (8.6%) experienced by subjects treated with 50 mg of DIC075V as compared to subjects treated with 37.5 mg (nausea: 16.9%, constipation: 7.7%, and vomiting: 6.2%). The higher rate of injury, poisoning and procedural complications is attributable to a higher rate of postoperative anemia (5.7%) in the 50 mg treatment group as compared to 0% in the 37.5 mg group. A higher proportion of subjects treated with 50 mg of DIC075V experienced increases in their serum creatinine (20.0%) as compared to subjects who were treated with 37.5 mg of the drug (10.8%). The higher rate of nervous disorders observed in the 50 mg treatment group is attributable to a higher rate of headaches experienced by patients in this group as compared to the 37.5 mg treatment group (10.8%). A higher rate of hypotension experienced by subjects in the 50 mg treatment group (8.6%) as compared to the 37.5 mg group (3.1%) accounts for the imbalance in vascular disorders. The observation of higher rates for these AEs in the 50 mg DIC075V

group is consistent with dose-dependent toxicity known to occur with the NSAID class of drugs.

Table 81 - Tabular Summary of Treatment Emergent AEs for Non-High Risk and High Weight Subjects in Study DFC-005 (Safety Population)

	DIC075V	
	37.5 mg (N=65)	**50 mg (N=35)**
Number (%) of Subjects with Any AEs:	49 (75.4%)	24 (68.9%)
Gastrointestinal Disorders:	17 (26.2%)	14 (40.0%)
Constipation	5 (7.7%)	4 (11.4%)
Diarrhea	3 (4.6%)	0
Nausea	11 (16.9%)	12 (34.3%)
Vomiting	4 (6.2%)	3 (8.6%)
Rectal hemorrhage	0	1 (2.9%)
Injury, Poisoning and Procedural Complications:	7 (10.8%)	7 (20.0%)
Procedural Site Reaction	6 (9.2%)	1 (2.9%)
Anemia Postoperative	0	2 (5.7%)
Investigations:	9 (13.8%)	7 (20.0%)
Blood Creatinine Increased	7 (10.8%)	7 (20.0%)
Nervous System Disorders:	17 (26.2%)	13 (37.1%)
Dizziness	7 (10.8%)	4 (11.4%)
Headache	7 (10.8%)	5 (14.3%)
Vascular Disorders:	4 (6.2%)	5 (14.3%)
Hypotension	2 (3.1%)	3 (8.6%)

Modified Sponsor's Table A14.3.5.1; p1131.

Since dose-dependent NSAID toxicity is frequently observed in liver and renal AEs, serial lab test data collected from DFC-005 and DFC-010 were also examined separately to determine if there were any potential safety signals. Table 82 summarizes on-treatment elevations of renal and liver function tests for subjects who participated in the open-label safety trial DFC-010. Review of these data reveals dose-dependent increases in serum creatinine, BUN, GGTP, and total bilirubin in this study consistent with the safety signal observed on review of the shift table analyses for renal function discussed in section 7.4.2.

Table 82 -Tabular Summary of On-Treatment Elevations of Renal and Liver Function Test for Subjects Participating in DFC-010 (Safety Population)

Test	DIC075V	
	37.5 mg (N=634)	**50 mg (N=335)**
Serum Creatinine (total):	**25 (3.9%)**	**21 (6.2%)**
>1 to <3 x ULN	13 (2.1%)	14 (4.2%)
3 to <10 xULN	12 (1.9%)	6 (1.8%)
≥ 10 x ULN	0	1 (0.3%)
BUN (total):	**29 (4.6%)**	**27 (8.1%)**
>1 to <3 x ULN	22 (3.5%)	19 (5.7%)
3 to <10 xULN	7 (1.1%)	8 (2.4%)
≥ 10 x ULN	0	0
ALT (total):	**39 (6.2%)**	**16 (4.8%)**
>1 to <3 x ULN	29 (4.6%)	16 (4.8%)
3 to <10 xULN	9 (1.4%)	0
≥ 10 x ULN	1 (0.2%)	0
AST (total):	**59 (9.3%)**	**26 (7.8%)**
>1 to <3 x ULN	51 (8.0%)	25 (7.5%)
3 to <10 xULN	6 (0.9%)	1 (0.3%)
≥ 10 x ULN	2 (0.3%)	0
GGTP (total):	**59 (9.3%)**	**37 (11.0%)**
>1 to <3 x ULN	40 (6.3%)	32 (9.6%)
3 to <10 xULN	19 (3.0%)	5 (1.5%0
≥ 10 x ULN	0	0
Total Bilirubin (total):	**17 (2.3%)**	**15 (4.3%)**
>1 to <3 x ULN	12 (1.9%)	11 (3.3%)
3 to <10 xULN	5 (0.8%)	3 (0.9%)
≥ 10 x ULN	0	1 (0.3%)

Modified Sponsor's Table 14.3.3.4.3; p.

7.5.2 Time Dependency for Adverse Events

In support of DIC075V's safety profile, the Applicant conducted two time dependency analyses for the occurrence of AEs. Since this drug was administered as an IV bolus every 6 hours over 1-5 days to patients who participated in the three Phase 3 multidose postsurgical pain trials, the Applicant first looked at AEs reported to have occurred within 45 minutes of study drug administration to determine if there was an increase in rate of AEs associated with peak plasma drug concentration levels. The results from this analysis showed that ≥ 94% of subjects treated with either 37.5 mg or 50 mg of DIC075V did not experience an AE within 45 minutes after the administration of any dose of this drug. Additionally no increase in the rate of AEs reported to have occurred within the first 45 minutes following administration of DIC075V was noted on review of these data. Nausea was the most commonly reported AE that occurred within 45 minutes of administration of the first dose of study medication by 2% of subjects in the combined 37.5 mg and 50 mg DIC075V group as compared to 6.3% of placebo patients. The rate of nausea increased to 12% in the DIC075V subjects and 18.3% in

placebo patients within the time period of 45 minutes to 6 hours post administration of first dose of study medication.

Since patients were treated for 1-5 days during the multidose Phase 3 trials, the Applicant also looked at the rate of AEs by extent of study drug exposure. The number of patients who received 37.5 mg or 50 mg of DIC075 and reported any AE was 73.2% on Day 1, 25.4% on Day 2, 20.0% on Day 3 and 15.3% on Days 4-5 postsurgical procedure. No increase in the rate of common AEs or NSAID-related AEs of special interest (i.e., GI bleeding, renal failure or cardiovascular events) associated with increasing exposure to DIC075V for up to 5 days were observed on review of the results generated from this safety analysis. However, the validity of this finding is questionable in view of the small number of patients who were exposed to DIC075V for ≥ 3 days or more.

7.5.3 Drug-Demographic Interactions

Subgroup analyses on AEs were conducted on pooled data generated from the three multidose, Phase 3 postsurgical pain trials in order to determine if there were any drug-demographic interactions. Since the protocol for DFC-004 prohibited the enrollment of subjects ≥ 65 years old and patients over 65 years of age received a reduced dose of 18.75 mg of DIC075V in DFC-005 in order to minimize the risk for NSAID-induced toxicity in this age group, the analysis for AEs by age shown in Table 83 focuses on specific AEs where a difference in the rate of occurrence was identified for subjects age < 65 years and ≥ 65 years for the safety population of the open label trial DFC-010 in which both groups were enrolled and the to be marketed doses of 37.5 mg and 50 mg of DIC075V were evaluated. The increased rate of atrial fibrillation observed in patients ≥ 65 years old compared to patients < 65 years of age may not be related to DIC075V exposure but rather to underlying age-related coronary artery disease in this subgroup. The increased occurrence of hypotension and anemia postoperative in the elderly may be secondary to the surgical procedures these individuals underwent prior to study entry in view of the small number of cases of GI hemorrhage that occurred in this trial. Constipation and peripheral edema are probably not a drug-age demographic AEs since a higher rate of constipation and peripheral edema was also seen in patients ≥ 65 years in the placebo group (33.3% and 8.3%, respectively) as compared to younger patients (11.3% and 0.8%, respectively) in the controlled trials DFC-004 and 005. Other than the increase frequency in dyspepsia, elevated serum creatinine and acute renal failure, there were no clinically meaningful differences in the safety profile of DIC075V in patients <65 years old compared to patients ≥ 65 years old. Dyspepsia (5.1%), increased blood creatinine (1.9%) and acute renal failure (1.6%) were observed more frequently in older patients as compared to younger patients (2.8%, 0.5%, and 0.2% , respectively) treated with DIC075V and are consistent with the well documented NSAID-class toxicity that has been observed in this age group. Additional review of the AEs observed in patients ≥ 65 years did not reveal a dose dependent relationship for these events.

Table 83 – Tabular Summary of Treatment Emergent AEs by Preferred Term and Age for DFC-010 (Safety Population)

MedDRA Preferred Term	DFC-010 (DIC075V 37.5 mg and 50 mg)	
	<65 years (N=602)	≥65years (N=396)
Atrial Fibrillation	2 (0.3%)	7 (1.9%0
Constipation	98 (16.3%)	83(22.5%)
Dyspepsia	17 (2.8%)	19 (5.1%)
Peripheral Edema	18 (3.0%)	19 (5.1%)
Anemia Postoperative	110 (18.3%)	108 (29.3%)
Increased Blood Creatinine	3 (0.5%)	7 (1.9%)
Acute Renal Failure	1 (0.2%)	6 (1.6%)
Hypotension	28 (4.7%)	32 (8.7%)

Modified Sponsor's Table 4-37; p. 117.

The results of an analysis of AEs by gender (Table 84) demonstrate that the rates of nausea (40.5%), flatulence (5.6%), pruritus (13.4%), and headache (7.9%) were higher in female patients treated with DIC075V as compared to male patients (nausea: 25.1%, flatulence: 2.7%, pruritus: 8.4%, and headache: 3.7%). More male subjects treated with DIC075V experienced insomnia (17.4%) and muscle spasm (4.9%) than female subjects (9.3% and 2.1%, respectively). Infusion site pain is probably not a drug-gender demographic AE since the rate of this AE was similar in female and male patients treated with placebo in the controlled trials. Overall, there were no clinically meaningful differences in the safety profile of DIC075V in females compared to males.

Table 84 – Tabular Summary of Treatment Emergent AEs by Preferred Term and Gender for the Pooled Phase 3 Multidose Trials (Safety Population)

MedDRA Preferred Term	DIC075V 37.5 mg and 50 mg	
	Male (N=407)	Female (N=749)
Nausea	102 (25.1%)	303 (40.5%)
Flatulence	11 (2.7%)	42 (5.6%)
Infusion Site Pain	15 (3.7%)	54 (7.2%)
Pruritus	34 (8.4%)	100 (13.4%)
Headache	15 (3.7%)	59 (7.9%)
Insomnia	71 (17.4%)	70 (9.3%)
Muscle Spasm	20 (4.9%)	16 (2.1%)

Modified Sponsor's Table 4-38; p. 122.

The results of analysis by race are displayed in Table 85. Since the majority of the subjects who participated in the multidose Phase 3 postsurgical pain trials for DIC075V were Caucasian (86%), followed by Black (10%), Asian (1%) and Other (3%) the

analysis for AEs by age shown in Table 86 focuses on specific AEs where a difference in the rate of occurrence that was identified for subjects who were White and Black in view of the small number of subjects of other races who participated in these trials. The results of this analysis of AEs by race demonstrates that the rates of constipation (18.8%), anemia postoperative (19.8%), insomnia (12.9%), dizziness (6.1%), oropharyngeal pain (3.2%) and muscle spasms (3.5%) were higher in White patients treated with DIC075V as compared to Black patients (nausea: 9.5%, anemia postoperative:12.1%, insomnia: 6.0%, dizziness: 0.9%, oropharyngeal pain: 0%, and muscle spasms: 0%). More Black subjects treated with DIC075V experienced flatulence (7.8%) than White subjects (4.3%). Overall, there were no clinically meaningful differences in the safety profile of DIC075V in White patients compared to Black patients.

Table 85 - Tabular Summary of Treatment Emergent AEs by Preferred Term and Race for the Pooled Phase 3 Multidose Trials (Safety Population)

MedDRA Preferred Term	DIC075V 37.5 mg and 50 mg	
	White (N=997)	Black (N=116)
Constipation	187 (18.8%)	11 (9.5%)
Flatulence	43 (4.3%)	9 (7.8%)
Anemia Postoperative	197 (19.8%)	14 (12.1%)
Insomnia	129 (12.9%)	7 (6.0%)
Dizziness	61 (6.1%)	1 (0.9%)
Oropharyngeal Pain	32 (3.2%)	0
Muscle Spasms	35 (3.5%)	0

Modified Sponsor's Table 4-41; p. 130.

7.5.4 Drug-Disease Interactions

In view of the nephrotoxic and hepatotoxic effects of diclofenac, the Applicant looked in detail at the incidence of treatment-emergent AEs by renal and hepatic impairment status (impaired/not impaired) for patients in the multidose, Phase 3, postsurgery pain trials. A total of 76 patients with renal impairment defined as a blood creatinine > upper limits of normal (ULN) at screening evaluation participated in these trials, out of which 68 patients were treated with DIC075V while the remaining 8 subjects were treated with placebo. The results of this analysis by dose treatment group are shown in Table 86 and focuses on specific AEs where a difference in the rate of occurrence was identified for subjects treated with DIC075V with renal impairment versus non-impaired renal function. Overall, the rate of AEs experienced by patients with renal impairment (80.9%) was comparable to that of non-impaired patients (83.6%) treated with DIC075V, and these rates of AEs were similar to those experienced by placebo treated patients with impaired (87.5%) and non-impaired renal function (82.7%). Higher rates of AEs were reported by renal impaired subjects treated with DIC075V for the following system

organ classes: gastrointestinal disorders (55.9%), infections and infestations (13.2%), investigations (25%), and renal and urinary disease (7.4%). Further examination of these data by preferred term reveals that the higher rates of gastrointestinal disorders were due to higher rates of nausea (44.1%), constipation (22.1%) and vomiting (11.8%) reported by renal impaired subjects treated with DIC075V as compared to non-impaired subjects (nausea: 33.8%, constipation: 17.8%, and vomiting: 8%). With the exception of nausea, these rates of gastrointestinal AEs were similar to that observed in renally impaired subjects treated with placebo (nausea: 25.0%, constipation: 25.0%, and vomiting: 25.0%). The rate of nausea in renally impaired subjects treated with DIC075V increased with increasing drug exposure (38.9% for 37.5 mg group versus 54.2% for 50 mg group) suggestive of dose-effect. Overall, the rates of AEs were comparable between impaired and not impaired, however, as expected patients with impaired renal function experienced more renal events particularly renal failure (3 cases [4.4%]) as compared to non impaired patients (8 cases [0.66%]) . Although patients with moderate renal impairment were treated with a lower dose of DIC075V (e.g., 18.75 mg), the dose reduction did not result in a reduction in events that was most likely due to increase in background risk and more vulnerability upon exposure to DIC075V in the postoperative setting.

Table 86 – Tabular Summary of Most Common AEs (≥ 1% Total DIC075V Subjects) by Renal Impairment Status and Dose Treatment Group for the Phase 3 Multidose Pain Trials (Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo		DIC075V				
	Not Impaired (N= 139)	Impaired (N=8)	18.75 mg Impaired (N=8)	37. 5 mg Impaired (N=36)	50 mg Impaired (N=24)	Total Impaired (N=68)	Total Not Impaired (N=1216)
Number (%) of Subjects with Any AE:	115 (82.7%)	7 (87.5%)	8 (100%)	28 (77.8%)	19 (79.2%)	55 (80.9%)	1016(83.6%)
Gastrointestinal Disorders:	78 (56.1%)	6 (75.0%)	5 (62.5%)	18 (50.0%)	15 (62.5%)	38 (55.9%)	621(51.1%)
Nausea	53 (38.1%)	2 (25.0%)	3 (37.5%)	14 (38.9%)	13 (54.2%)	30 (44.1%)	411 (33.8%)
Constipation	20 (14.4%)	2 (25.0%)	2 (25.0%)	10 (27.8%)	3 (12.5%)	15 (22.1%)	217 (17.8%)
Vomiting	23 (16.5%)	2 (25.0%)	1 (12.5%)	4 (11.1%)	3 (12.5%)	8 (11.8%)	97 (8.0%)
Infections and Infestat.:	9 (6.5%)	0	2 (25.0%)	4 (11.1%)	3 (12.5%)	9 (13.2%)	107 (8.8%)
Urinary Tract Infection	1 (0.7%)	0	1 (12.5%)	1 (2.8%)	1 (4.2%)	4 (4.4%)	20 (1.6%)
Injury, Poisoning, and Procedural Complic.	7 (5.0%)	1 (12.5%)	1 (12.5%)	11 (30.6%)	5 (20.8%)	17 (25.0%)	293 (24.1%)
Anemia Postoperative	2 (1.4%)	1 (12.5%)	1 (12.5%)	8 (22.2%)	5 (20.8%)	14 (20.6%)	210 (17.3%)
Renal and Urinary Dis.:	4 (2.9%)	0	1 (12.5%)	3 (8.3%)	1 (4.2%)	5 (7.4%)	56 (4.6%)
Renal failure	1 (0.7%)	0	1 (12.5%)	2 (5.6%)	0	3 (4.4%)	8 (0.66%)

Modified Sponsor's Table 3.6.1.1; p. 1646.

A similar analyses for hepatic impairment defined as a bilirubin > ULN at the screening evaluation was also performed by the Applicant (Table 87). Of the 36 patients with hepatic impairment who participated in these trials, 34 patients were treated with DIC075V while the remaining 2 subjects were treated with placebo. Overall, the rate of

AEs experienced by patients with hepatic impairment (94.1%) was higher compared to that of non-impaired patients (83.1%) treated with DIC075V, and these rates of AEs were similar to those experienced by placebo treated patients with impaired (100%) and non-impaired hepatic function (82.1%). As expected, higher rates of hepatically-related AEs were observed in patients with mild hepatic impairment treated with 37.5 mg or 50 mg doses of DIC075V compared with non-impaired patients treated with the same doses. The rates of vomiting (25.0%), peripheral edema (12.5%) and oropharyngeal pain (12.5%) in hepatically impaired patients increased with increasing drug exposure (12.5%, 4.2%, and 8.3%, respectively) suggestive of a dose effect. Differences in the designs of the various trials which mandated a reduction in dose for patients with moderate hepatic impairment defined as Child-Pugh score of 6-9 (protocol DFC-005), prohibiting the entry of patients with serum ALT or AST >1.5 and/or bilrubin >1.0 times the ULN (protocol DFC-004) or with a serum bilrubin >2.5 mg/dL and/or a prothrombin time of no more than 20% above the ULN (protocol DFC-010) may be responsible for the paucity of dose dependent AEs in the hepatically impaired population. Since there were only 2 subjects with moderate hepatic impairment treated with the 18.75 mg dose as a result of the randomization procedure used in DFC-005, it is impossible to assess the safety of this dose in patients with hepatic impairment which appears to be worse than the two higher doses of DIC075V in this subpopulation as presented in Table 87 due to the small numbers of patients treated with the lower dose.

Table 87 - Tabular Summary of Most Common AEs (≥ 1% Total DIC075V Subjects) by Hepatic Impairment Status and Dose Treatment Group for the Phase 3 Multidose Pain Trials (Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo		DIC075V				
	Not Impaired (N= 145)	Impaired (N=2)	18.75 mg Impaired (N=2)	37. 5 mg Impaired (N=24)	50 mg Impaired (N=8)	Total Impaired (N=34)	Total Not Impaired (N=1250)
Number (%) of Subjects with Any AE:	120(82.1%)	2 (100%)	2 (100%)	23 (95.8%)	7 (87.5%)	32 (94.1%)	1039(83.1%)
Gastrointestinal Disorders:	83 (57.2%)	1 (50.0%)	2 (100.0%)	15 (62.5%)	5 (62.5%)	22 (64.7%)	637(51.0%)
Nausea	54 (37.2%)	1 (50.0%)	1 (50.0%)	12 (50.0%)	3 (37.5%)	16 (47.1%)	425(34.0%)
Constipation	22 (15.2%)	0	1 (50.0%)	5 (20.8%)	0	6 (17.6%)	226(18.1%)
Vomiting	25 (17.2%)	0	0	3 (12.5%)	2 (25.0%)	5 (14.7%)	100 (8.0%)
Gen. Disord. and Adm. Site Conditions:	41 (28.1%)	0	1 (50.0%)	5 (20.8%)	3 (37.5%)	9 (26.5%)	273 (21.8%)
Edema Peripheral	3 (2.1%)	0	0	1 (4.2%)	1 (12.5%)	2 (5.9%)	45 (3.6%)
Investigations:	27 (18.6%)	1 (50.0%)	0	7 (29.2%)	0	7 (20.6%)	186 (14.9%)
ALT Inc.	4 (2.8%)	1 (50.0%)	0	3 (12.5%)	0	3 (8.8%)	10 (0.8%)
AST Inc.	4 (2.8%)	1 (50.0%)	0	3 (12.5%)	0	3 (8.8%)	8 (0.6%)
Renal and Urinary Dis.	4 (2.8%)	0	0	3 (12.5%)	1 (12.5%)	4 (11.8%)	57 (4.6%)
Urinary Retention	1 (0.7%)	0	0	3 (12.5%)	0	3 (8.8%)	25 (2.0%)
Resp., Thoracic, and Mediastinal Dis.:	6 (4.1%)	0	0	4 (16.7%)	2 (25.0%)	6 (17.6%)	107 (8.6%)
Oropharyngeal Pain	2 (1.4%)	0	0	2 (8.3%)	1 912.5%)	3 (8.8%)	33 (2.6%)

Modified Sponsor's Table 3.6.2.1; p. 1752.

7.5.5 Drug-Drug Interactions

No formal drug-drug interaction studies were conducted by the Applicant in support of DIC075V's safety. Review of the database did not identify any AEs that appeared related to an interaction with concomitant medications. The Applicant referenced the current product labeling for both the RD Cataflam (diclofenac potassium) (NDA 20-142) and for Sporanox (itraconazole) Injection (NDA 20-966) for background information on drug-drug interactions with diclofenac potassium and HPβCD, respectively.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

There were no reports of malignancy associated with the use of DIC075V in the safety database submitted in support of this indication by the Applicant. Human carcinogenicity studies were not required due to the acute exposure to DIC075V for the indicated use.

7.6.2 Human Reproduction and Pregnancy Data

No pregnant women were inadvertently exposed to DIC075V during the course of its development. In lieu of conducting formal studies in humans of the effects of DIC075V on reproduction or pregnancy, the Applicant referenced the current product labeling for the RD Cataflam (diclofenac potassium) (NDA 20-142) for background information on pregnancy, birth and lactation effects of diclofenac.

7.6.3 Pediatrics and Assessment of Effects on Growth

This application did not contain any data generated from assessments of DIC075V's effect on growth since the Applicant has not conducted a study in children or adolescents.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No overdoses occurred with DIC075V over the course of its development. DIC075V is a parenteral NSAID that was developed for use in the hospital setting for administration by trained medical personnel. Symptoms following acute overdoses of NSAIDs include lethargy, drowsiness, nausea, vomiting and epigastric pain. Gastrointestinal bleeding has been reported to occur as well. Rare cases of hypertension, acute renal failure, respiratory depression, and coma associated with NSAID overdoses have also been reported. Anaphylactoid reactions associated with therapeutic injections of NSAIDs may occur following an overdose. Since there are no specific antidotes for the treatment of NSAID overdoses, patients should be managed by symptomatic and supportive care.

Diclofenac also has no known potential for abuse, withdrawal or rebound effects. In support of this, the Applicant referenced the current product labeling for the RD Cataflam (diclofenac potassium) (NDA 20-142) for background information on overdose, abuse potential, withdrawal or rebound effects of diclofenac.

7.7 Additional Submissions / Safety Issues

Additional safety information that was contained in the Applicant's 120-day safety update submitted on March 3, 2010 has been incorporated into the postmarketing and literature review subsections of this review.

8 Postmarket Experience

In support of DIC075V's safety profile as a treatment for acute postsurgical pain, the Applicant submitted the results of a postmarketing review they conducted of AEs reports associated with any systemic formulation and dose of diclofenac that had been spontaneously submitted to the FDA's Adverse Event Reporting System (AERS database) for the time period from January 1, 2004 through March 31, 2009. A total of 82,759 AE reports were identified during this search in which diclofenac was listed as the primary or secondary suspect drug. (Note: This number of reports may contain duplicate reports of the same AE.) The most commonly reported postmarketing AEs associated with diclofenac identified on this search were pyrexia, vomiting, dyspnea, nausea, acute renal failure, diarrhea, increased ALT, increased AST, drug interaction, anemia, decreased hemoglobulin, malaise, increased blood creatinine, pneumonia, headache, dizziness, pain, aggravated condition, abdominal pain and rash. No new safety signals were identified on review of these data in view of diclofenac's well documented safety profile as a result of its availability in this country as an enteric coated, sodium salt and potassium salt since 1988 and 1993, respectively.

The Applicant also submitted the results of another search they conducted of the AERS database for the same time period of postmarketing AEs associated with the parental administration of diclofenac which is currently an unapproved route for this drug in this country. This second search identified a total of 2,334 AEs for parental formulations of diclofenac. The most common AEs associated with parenterally administered diclofenac identified on this second search were as follows: injection site necrosis, injection site pain, embolia cutis medicamentosa, acute renal failure, dyspnea, necrotizing fasciitis and multi-organ failure. The results generated from this second postmarketing AE search were also reviewed for AEs of special interest. Based on their review of these postmarketing data, the Applicant identified a total of 542 AEs of special interest for parenterally administered diclofenac. Gastrointestinal (122 AEs), hepatobiliary (114 AEs) and renal events (102 AEs) were the most commonly reported AEs of special interest for diclofenac.

The Applicant also conducted a postmarketing review of AEs associated with parenterally administered diclofenac collected by the World Health Organization's (WHO) Vigibase for the time period from 1979 through October 1, 2009. This postmarketing summary of safety contained 4,691 reports associated with the intravenous (IV) or intramuscular (IM) administration of diclofenac that had been collected from 62 countries. Review of the results generated from this postmarketing review which were presented in summarized format by MedDRA system organ class (SOC) failed to identify any new potential safety signals associated with the IV or IM administration of diclofenac.

Since October 2009, Dyloject® has been marketed in the United Kingdom (UK) for the treatment of acute pain due to renal colic, osteoarthritis, rheumatoid arthritis, back pain, gout, trauma, fractures and post-operative pain when administered via IM route and for the treatment and prevention of post-operative pain in supervised healthcare settings when administered via IV route. It has been estimated based on sales of the drug from the time of initial approval through October 29, 2009, that approximately (b) (4) patients have been exposed to Dyloject® in that country. For completeness, the Applicant submitted the first three Annual Periodic Safety Updates (PSURs) that covered the time period from October 30, 2007 through April 29, 2009 that reviewed all relevant Adverse Drug Reactions (ADRs) received from any source associated with Dyloject®. Included in the 120-day safety update was the updated fourth PSUR which covered the 6-month period from April 30, 2009 through October 29, 2009. A cumulative total of 35 spontaneous case reports, 2 literature reports and 9 clinical clinical study case reports of ADRs were received and reviewed in these PSURs. These data were reviewed by this reviewer an no particular safety issues or concerns were identified for Dyloject® and the risk-benefit balance for this drug continues to remain favorable.

9 Appendices

9.1 Literature Review/References

The Applicant conducted a review of the worldwide literature via the search engine Ovid of the MEDLINE database that identified 428 published articles, out of which 117 publications contained safety information regarding the acute administration (i.e., 7 days or less) of various formulations of diclofenac that were reviewed in support of safety for this application as follows: 45 placebo controlled studies; 31 controlled studies with only an active comparator; 5 uncontrolled retrospective trials or case series, and 36 case reports or case series of SAEs or deaths. The Applicant updated this literature review for the 120-day safety update of this application. Three active-controlled and 2 uncontrolled retrospective newly published studies were thus identified and included in the 120-day safety update. Articles that described clinical studies (14 placebo controlled, 7 active controlled studies and 4 uncontrolled retrospective trials) or case reports (6 cases) in which diclofenac was administered orally or the route of administration was unspecified were excluded since the focus of this review was to identify potential safety issues associated with the parenteral administration of diclofenac. The remaining citations contained safety data associated with parenterally administered diclofenac via the intramuscular (IM) or intravenous (IV) routes as follows: IM route: 25 placebo-controlled, 18 active-controlled, and 1 uncontrolled retrospective studies with 29 case reports; IV route: 6 placebo-controlled, 4 active controlled, and 2 uncontrolled retrospective trials with 1 case report. There were also a total of 3 active-controlled published studies where diclofenac was administered via the IV and oral routes (1 trial), via IV and IM routes (1 trial) and via IM and oral routes (1 trial). (b) (4)

The majority of the published trials that described safety data associated with parenteral formulations of diclofenac involved the administration of single or multiple doses ranging from 1 mg/kg to 75 mg of the drug. The most commonly reported AEs were gastrointestinal complaints (i.e., nausea, vomiting, and dyspepsia), injection site irritation (including rare cases of thrombophlebitis) and headache. Serious gastrointestinal AEs included perforated gastrointestinal ulcer. Overall, the adverse events reported in the published trials were similar to that observed in the safety base generated from the Phase 3 clinical trials that evaluated DIC075V.

Only one out of the 30 case reports described a serious adverse event following the IV administration of diclofenac. This report involved a 74 year old female undergoing a hemiglossectomy for squamous cell carcinoma who had a respiratory arrest following the administration of 60 mg of verapamil followed by 50 mg of diclofenac via a central

line. Neurologic and cardiovascular work-up were unremarkable. She eventually recovered after a protracted hospital course that included mechanical ventilation and treatment for methicillin-resistent staphylococcus aureus (MRSA). The remaining 29 case reports of serious adverse events occurred following the IM administration of diclofenac involving doses ranging from 1mg/kg to 75 mg of the drug. These reports included local hypersensitivity reactions, fatal cases of anaphylaxis and fulminant hepatitis, tissue necrosis at the site of IM injection (Nicolau syndrome) attributed to microembolism of small arteries by an earlier formulation of injectable diclofenac, injection site necrosis, necrotizing fasciitis, gas gangrene initiated at an injection site, injection site abscesses, injection-related tumor formation, contraction of fetal ductus arteriosus, and gastric erosions associated with hemolytic anemia and thrombocytopenia.

9.2 Labeling Recommendations

Based on the review of data submitted in support of this application, this medical officer has the following recommendations for the product's label:

1. The tradename Dyloject® is acceptable. It has been deemed acceptable by both DMETS and the Division
2. The CLINICAL STUDIES section of the label should only contain descriptions of the efficacy results from the two randomized, controlled pivotal trials DFC-004 and -005
3. The primary endpoint analysis of the long term stay subcohort of DFC-005 should be presented (b) (4)
4. The primary endpoint analysis for the two pivotal trials should be presented at the 48 hour time point as discussed with the Applicant at the EOP2 meeting
5. Since no correction for multiplicity was applied during the analyses of the secondary endpoints for both pivotal trials, these results should not be included other than to communicated information that may be clinically useful to health care providers such as opiate sparing effects
6. (b) (4)
7. (b) (4)
8. (b) (4)

(b) (4)

9. The drug label should contain information to prescribers regarding DIC075V's ability to impair wound healing
10. Based on review of the efficacy and safety data submitted in support of this application, the recommended dosing for special subpopulations including mild renal and mild hepatically impaired, and elderly patients age ≥ 65 years should be 37.5 mg every 6 hours not to exceed a maximum dose of 150 mg in 24 hours with adequate labeling/class warning
11. Additional cautionary language that DIC075V should not be used in patients with moderate to severe renal and/or hepatic impairment
12. (b) (4)
13. Inclusion of information regarding the postmarketing cases of hypersensitivity and anaphylaxis reported in the U.K.

9.3 Advisory Committee Meeting

No advisory committee meeting was conducted for this application.

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/

ROSEMARIE NEUNER
09/03/2010

LARISSA LAPTEVA
09/03/2010

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 22-396 **Applicant:** Javelin Pharmaceuticals Inc. **Stamp Date:** December 22, 2009

Drug Name: Dyloject™ (diclofenac sodium) Injection **NDA/BLA Type:** Standard

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505(b)(2); RLDs: NDA 20-142 Cataflam NDA 20-966 Sporanox
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: DFC-PK-006 Study Title: An open-label, randomized, single center study to compare the PK of IV diclofenac sodium (18.75 and 37.5 mg) vs oral diclofenac potassium (50mg) in healthy adult volunteers following single and multiple dose administration Sample Size: 36 subjects Arms: 3 Location in submission: Module 5.3.1.1	X			Also submitted results from Studies DFC-PK-008 and -009 which assessed the drug's PK profile based on age and weight as well as in renal and hepatic impaired subjects
EFFICACY					
14.	Do there appear to be the requisite number of adequate and	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	well-controlled studies in the application? Pivotal Study #1: DFC-004: Randomized controlled study for the treatment of moderate to severe post-op pain S/P abdominal or pelvic surgery Indication: analgesia Pivotal Study #2: DFC-005: Randomized controlled study for the treatment of moderate to severe post-op pain S/P ortho surgery Indication: analgesia				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			Submitted the results from Study DFC-011 which showed no QTc prolongation at either dose (e.g., 37.5 mg and 75 mg) tested
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			Division told sponsor at EOP2 meeting they needed 1000 patients exposed to drug
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Sponsor is requesting a waiver for infants (b) (4) and a deferral for children (b) (4)
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	This is an NSAID (drug class not associated with abuse liability)
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	IRB and with adequate informed consent procedures?				

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ____Yes___

If the Application is not fileable from the clinical 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.

1. In your draft product label, Table 1 includes adverse events that occurred more frequently with placebo than Dyloject™. Events that occurred more frequently with placebo than with Dyloject™ may not represent adverse reactions associated with the drug. Reformat Table 1 to exclude AEs that occurred more frequently in the placebo controlled group as compared to the Dyloject™ group.
2. (b) (4)

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

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

/s/

ROSEMARIE NEUNER
02/04/2010

JEFFREY N SIEGEL
02/05/2010