

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-165

MEDICAL REVIEW(S)

MEMORANDUM

DATE: October 27, 2008

FROM: Division Director
Division of Neurology Products/HFD-120

TO: File, NDA 22-165

SUBJECT: Action Memo for NDA 22-165, for the use of diclofenac potassium 50 mg powder sachet for the acute treatment of migraine

NDA 22-165, for the use of diclofenac potassium, a nonsteroidal anti-inflammatory drug (NSAID), 50 mg powder sachet for the acute treatment of migraine, was submitted by ProEthic Pharmaceuticals. This application was submitted as a 505(b)(2) application, with the referenced drugs being Cataflam (diclofenac potassium), and Voltaren and Voltaren XR (diclofenac sodium products). These drugs are approved in oral formulations for osteo- and rheumatoid arthritis, (Voltaren, Voltaren XR, Cataflam), ankylosing spondylitis (Voltaren), and primary dysmenorrhea or mild to moderate pain (Cataflam), and as an ophthalmologic solution for several ophthalmologic indications (Voltaren). The division originally refused to file the application because of issues related to right of reference and format. The application was ultimately filed on 9/28/07, and the review clock was extended due to a major amendment submitted on 5/8/08.

The application contains reports of two randomized controlled trials in patients with acute migraine, several Phase 1 studies including comparative bioavailability studies between this product and Cataflam, and CMC information. The application has been reviewed by Dr. Ron Farkas, medical officer, Dr. Julia Luan, statistician, Carol Noory, Office of Clinical Pharmacology, Dr. Shastri Bhamidipati, ONDQA, Dr. Ramesh Hood, ONDQA, Dr. Charles Thompson, pharmacologist, Dr. Lois Freed, pharmacology team leader, Dr. Antoine El-Hage, Division of Scientific Investigations, and Dr. Eric Bastings, Deputy Director, DNP. Dr. Bastings recommends that the sponsor be sent a Complete Response letter.

As various reviewers describe, the sponsor has submitted two controlled trials, one performed in the US, one in Europe. Each study evaluated the effects of a single 50 mg dose of diclofenac in patients with an acute migraine attack. The US study was a parallel group, placebo controlled study, while the European trial was a three-way cross-over study comparing single doses of diclofenac 50 mg sachet, Cataflam 50 mg, and placebo. Each study yielded statistically significant results on the required outcome measures (proportion of patients at 2 hours who were: pain free, nausea-free, photophobia-free, and phonophobia-free). The adverse event profile yielded no significant adverse events not previously known to occur with diclofenac or other NSAIDs.

As noted by Ms. Noory, the comparative bioavailability studies established that the Cmax of this product, in the fasted state, was about 45% greater than that of Cataflam (upper limit of the 90% confidence interval of the ratio of Cmax of about 175), and about 40% less than that of Cataflam in the fed state. Ordinarily, a significantly greater Cmax than a referenced marketed product would give rise to safety concerns, but as noted by Drs. Farkas and Bastings, diclofenac products are already marketed at 100 mg acute doses in similar populations, and the levels achieved in the fasted state with this product are not expected to be greater than those achieved with a 100 mg dose of the marketed product. For this reason, the elevated fasting Cmax is of no concern. Further, as Dr. Farkas notes, most patients are not expected to treat a migraine on a completely empty stomach. In addition, the low Cmax in the fed state could give rise to efficacy concerns. However, as Dr. Farkas notes, most patients will not have just eaten the equivalent of an FDA high fat meal at the time of treating their migraine. Also, in the US controlled trial, which was clearly positive, patients treated acute migraine attacks that bore no specific temporal relationships to a meal. For these reasons, I do not believe that the significant changes between Cmax's with and without food will have significant clinical consequences.

As noted by Drs. Thompson and Freed, we have recently become aware that there are literature reports that diclofenac may be associated with teratogenic effects in animals. These effects are not noted in the labeling of the referenced listed drugs, so we cannot write final labeling until the sponsor performs a complete literature review and we fully evaluate this issue.

Also, the sponsor's proposed tradename, Cambia, is still under review by Agency staff.

Finally, because diclofenac is an NSAID, it will be necessary for the sponsor to produce and distribute a Medication Guide describing the risks of cardiovascular adverse events with long-term use of these drugs, similar to those already in use for other NSAIDs. Under the FDA Amendments Act (FDAAA), the sponsor will need to submit a Risk Evaluation and Mitigation Strategy (REMS), which will include the Medication Guide and the required evaluation of their efforts to distribute the Medication Guide, as well as required evaluations of the success of the Medication Guide in informing patients of these risks, at the prescribed time points post approval.

For the reasons stated above, then, I will issue the attached Complete Response letter with attached draft labeling.

Russell Katz, M.D.

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/s/

Russell Katz
10/27/2008 07:09:50 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type NDA
Submission Number 22165

Letter Date 28 September 2007
PDUFA Goal Date October 27, 2008

Reviewer Name Ronald Farkas, MD, PhD
Review Completion Date September 2008

Established Name Diclofenac potassium
(Proposed) Trade Name Cambia
Therapeutic Class NSAID
Applicant ProEthic Pharmaceuticals

Priority Designation S

Formulation Powder for solution
Dosing Regimen 1 sachet for acute migraine
Indication Acute Migraine
Intended Population Adults

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EXECUTIVE SUMMARY

Migraine is a common disorder characterized by intermittent attacks of head pain associated with nausea, photophobia, and phonophobia. Migraine symptoms can be severe and disabling.

PRO-513 is intended for acute treatment of migraine. The active moiety in PRO-513 is diclofenac potassium (50 mg), which is approved in the U.S for several indications in rheumatic disease and pain. In contrast to currently approved diclofenac formulations, PRO-513 is a powder for oral solution, which the sponsor indicates is intended to provide a faster onset of action and to achieve higher peak plasma concentrations of diclofenac than tablet forms.

The PRO-513 NDA is submitted as a 505b(2), with the sponsor specifically, but not exclusively referring to FDA's previous findings of safety and efficacy for the following diclofenac products: NDA 20-142, Cataflam®; NDA 19-201, Voltaren®; and NDA 20-254, Voltaren® XR.

1.1 Recommendation on Regulatory Action

Approval is recommended.

1.2 Recommendation on Postmarketing Actions

None.

1.2.1 Risk Management Activity

No special risk management activity is recommended beyond that expected for any new drug.

1.2.2 Required Phase 4 Commitments

ProEthic requested a waiver from any requirement to do pediatric migraine studies in children less than 12 years of age. This request was based on the low incidence of migraine attacks in children under the age of 12. ProEthic requested deferral until post NDA approval for any requirement for pediatric studies.

Reviewer: If safety and efficacy of PRO-513 is established in children age 12-17 years, studies in children age 6-12 years should be conducted.

1.2.3 Other Phase 4 Requests

None.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Five clinical trials were submitted in this NDA. In the 3 trials conducted by Novartis the new drug was called (b) (4) while in the 2 studies conducted by ProEthic the new drug was called PRO-513. The sponsor indicates that (b) (4) and PRO-513 were of identical composition.

Two phase 1 studies (CAT458C2101 and PRO-513101) compared the bioavailability of PRO-513 to Cataflam 50 mg diclofenac tablets.

Two phase 3 studies were conducted in migraine, CAT458C2301 at 21 centers in Europe, and PRO-513301 at 23 centers in the U.S. The European study was a single dose, 3-way crossover design comparing PRO-513 to both Cataflam 50 mg tablets and to placebo. The U.S. study was a single dose parallel group study comparing PRO-513 to placebo.

The sponsor also submitted an additional supportive single-dose phase 3 study of PRO-513 in dental pain (Study CAT4582302).

No long term safety study of PRO-513 was conducted.

The sponsor argues that the exposure, indication, and patient population for PRO-513 are similar enough to approved formulations of diclofenac that previous FDA findings of safety combined with safety data from the new studies are adequate for approval of PRO-513.

Reviewer: For consistency in this review the new drug is referred to by a single name, PRO-513, used by the current sponsor ((b) (4) is used in some tables and figures generated by the sponsor).

1.3.2 Efficacy

This review finds PRO-513 effective in acute migraine.

The four co-primary endpoints for efficacy in acute migraine were pain-free, nausea-free, photophobia-free, and phonophobia-free at 2 hours ($p \leq 0.05$ for all 4). In both phase 3 studies the co-primary endpoints were met.

The key secondary endpoint was reduction of migraine recurrence within 24 hours of dosing, with migraine recurrence defined as reduction in pain from moderate or severe to none at 2 hours after dosing, followed by any increase in pain or the patient taking a backup pain medication within 24 hours of dosing. In the US phase 3 study this key secondary endpoint was met. In the European phase 3 study, this endpoint was analyzed as one of multiple exploratory secondary endpoints, and included about 10% of patients with mild pain at baseline. However, with these limitations, the endpoint was positive.

The sponsor makes the additional claim that the 3-way crossover European phase 3 study demonstrated superiority in migraine of PRO-513 to Cataflam tablets (50 mg diclofenac potassium). This review does *not* find this endpoint either to be acceptable or to have been met. Among several issues, the endpoint is not acceptable because Cataflam is not known to be effective for migraine, and a superiority claim versus a product not known to be effective is not meaningful (see section 6.1.6, Efficacy Conclusions).

1.3.3 Safety

This review finds PRO-513 acceptably safe in acute migraine based on previous FDA findings of safety for diclofenac tablets, combined with additional safety data in the studies submitted in this NDA.

FDA previously found diclofenac tablets safe in populations and indications similar to migraine. Bioavailability of PRO-513 is similar enough to diclofenac tablets to conclude that previous FDA findings of safety for the tablets should also apply to PRO-513.

- The exposure, indication, and patient population for PRO-513 in migraine are similar to those for diclofenac tablets.
 - The primary dysmenorrhea population is particularly similar in age and gender to the migraine population, and uses diclofenac on a similar chronic intermittent schedule. Diclofenac is also approved for ‘pain’ which would encompass a broad population inclusive of patients similar to the migraine population that in some circumstances use the drug on a chronic intermittent schedule.
- Diclofenac exposure from PRO-513 is similar to that from a single 50 mg diclofenac tablet, and is likely always less than the exposure from *two* 50 mg diclofenac tablets, a higher dose that is also approved for primary dysmenorrhea and pain.
 - PRO-513 is bioequivalent to 50 mg diclofenac tablets in terms of AUC. C_{max} from PRO-513 can be up to 50% *higher* under fasted conditions, and up to 40% *lower* under fed conditions. While not directly examined, in acute migraine it is likely that the extreme fasted and fed conditions in the bioavailability studies rarely occur, such that C_{max} is more similar between PRO-513 and 50 mg diclofenac tablets than suggested by the bioavailability studies.
 - While not directly examined, even under fasted conditions C_{max} from PRO-513 is likely lower than C_{max} from *two* 50 mg diclofenac tablets, an FDA approved dose in primary dysmenorrhea and pain. This conclusion is based on previous published findings that the pharmacokinetics of diclofenac is dose-proportional¹. Since FDA found 100 mg Cataflam safe for pain and primary dysmenorrhea, this review concludes FDA should find the predicted lower C_{max} from PRO-513 to be safe for migraine.

The safety of PRO-513 in migraine is also supported by analysis of adverse events data in new bioavailability and efficacy studies submitted with this NDA. Two phase 3 efficacy studies, one

¹ John, VA (1979) The pharmacokinetics and metabolism of diclofenac (Voltaren) in animals and man. Rheumatol Rehab. Supple 2:22-37.

in the US and one in Europe, exposed about 600 migraine patients to a single dose of PRO-513. New adverse events data was also provided by two bioavailability studies exposing about 50 healthy volunteers to 2- to 4 doses of PRO-513, and by a supportive phase 3 dental pain study that exposed 74 patients to a single dose of PRO-513. Of note, in the European migraine study and the dental pain study, adverse events collection was overly reliant on patient recall, and the European migraine study failed to adequately document events in patients that took rescue medication. However, despite such limitations, overall the new adverse events data provided by the above studies did not raise significant new safety concerns about PRO-513 and was reassuring of safety.

1.3.4 Dosing Regimen and Administration

Reviewer:

The recommended dosing of PRO-513 is one sachet containing 50 mg diclofenac for the acute treatment of migraine.

No data was collected regarding the efficacy of repeat dosing of PRO-513. For pain or primary dysmenorrhea the recommended dosing of Cataflam 50 mg is t.i.d., although Cataflam labeling states that an initial dose of 100 mg followed by 50 mg doses (200 mg/24 hours) may also be considered for patients in whom better relief is provided. Since there is no efficacy evidence for more than 1 dose of PRO-513, this review recommends that based solely on safety considerations, daily dosing for PRO-513 be limited to t.i.d. Similarly, since no data was available from the PRO-513 development program regarding long-term repeat-dose safety of PRO-513, this review recommends that, as labeled for Cataflam 50 mg, longer term use of PRO-513 should be limited to “the lowest effective dose for the shortest duration consistent with individual patient treatment goals.”

1.3.5 Drug-Drug Interactions

No drug interaction studies were conducted for PRO-513 because such interactions were not expected to be different from those of diclofenac tablets.

The sponsor proposes that the prescribing information for PRO-513 include those interactions currently listed in the prescribing information for diclofenac tablets.

Reviewer: This is generally acceptable.

1.3.6 Special Populations

The sponsor proposes that use of PRO-513 in special populations should follow current labeling for diclofenac tablets.

Reviewer: This is generally acceptable.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

PRO-513 contains diclofenac potassium, an NSAID currently approved in the U.S. for several indications related to pain and inflammation, in products including oral, ocular, and topical routes of delivery. PRO-513 is intended for the acute treatment of migraine with or without aura in adults. PRO-513 is a powder for oral solution containing 50 mg diclofenac, to be mixed with 1- to 2 ounces of water immediately prior to use.

(b) (4)

Diclofenac potassium, like other NSAIDS, appears to exert its principal effect by inhibition of cyclo-oxygenases.

Diclofenac, as either the potassium or sodium salt, is marketed in the following products and their generic equivalents:

- Cataflam® (diclofenac potassium) Tablets
- Voltaren® (diclofenac sodium) Delayed Release Tablets and Ophthalmic Drops,
- Voltaren® XR (diclofenac sodium) Extended Release Tablets
- Solaraze® (diclofenac sodium) Topical Gel.

Table 1 summarizes indications and dosing for FDA approved diclofenac products.

Table 1: Diclofenac Products

Route: Disease/Condition	Marketed Formulation(s)	Treatment Regimens
<i>Diclofenac Sodium</i>		
Topical: Actinic keratosis	Solaraze® Gel, 3% (Doak Dermatologics)	Apply topically to lesions BID for 60–90 days
Ocular: Postoperative ocular inflammation following cataract extraction	Voltaren® Ophthalmic Solution, 0.1% (Novartis Ophthalmics)	Instill one drop in the affected eye(s) four times daily, starting 24 hours after cataract surgery and continuing for two weeks.
Reduction of photophobia and ocular pain following corneal refractive surgery	Voltaren® Ophthalmic Solution, 0.1% (Novartis Ophthalmics)	Instill one to two drops in the affected eye(s) within one hour prior to surgery, then one to two drops 15 minutes after surgery and then QID beginning four to six hours after surgery and continuing for up to three days as needed
Oral: Osteoarthritis	Voltaren® (25, 50, and 75 mg tablets) or Voltaren®-XR (100 mg tablet) (Novartis)	VOLTAREN: 50 mg PO two BID/TID or 75 mg PO BID. Dosages > 150 mg/day are not recommended; VOLTAREN-XR: 100 mg PO QD for chronic therapy. Dosages > 150 mg/day PO are not recommended.
Rheumatoid arthritis	Voltaren® (25, 50, and 75 mg tablets) or Voltaren®-XR (100 mg tablet) (Novartis)	VOLTAREN: 50 mg PO TID/QID or 75 mg PO QD. Dosages > 225 mg/day PO are not recommended; VOLTAREN-XR: 100 mg PO QD for chronic therapy. In the rare cases where 100 mg/day is unsatisfactory, the dose may be increased to 100 mg PO BID if the benefits outweigh the risks. Dosages > 225 mg/day PO are not recommended.
Ankylosing spondylitis	Voltaren® (25, 50, and 75 mg tablets) (Novartis)	VOLTAREN: 100–125 mg/day PO in 4–5 divided doses. Usually 25 mg PO QID with an additional 25 mg dose at bedtime, if needed. When a satisfactory response is achieved, the dosage should be reduced to the minimum required to provide relief of symptoms. The safe and effective use of doses exceeding 125 mg/day PO has not been established for ankylosing spondylitis.
Osteoarthritis or rheumatoid arthritis in patients at high risk of developing NSAID-induced gastric/duodenal ulcers	Arthrotec® 50 (50 mg diclofenac sodium/200 mcg misoprostol) or Arthrotec® 75 (75 mg diclofenac sodium/200 mcg misoprostol) (Pfizer)	Osteoarthritis: ARTHROTEC 50 TID. For patients who experience intolerance, ARTHROTEC 75 bid or ARTHROTEC 50 bid can be used, but are less effective in preventing ulcers. Rheumatoid arthritis: ARTHROTEC 50 TID or QID. For patients who experience intolerance, ARTHROTEC 75 bid or ARTHROTEC 50 bid can be used, but are less effective in preventing ulcers.
<i>Diclofenac Potassium</i>		
Oral: Osteoarthritis	Cataflam® (50 mg tablet) (Novartis)	50 mg PO BID/TID. Dosages > 150 mg/day PO are not recommended
Rheumatoid arthritis	Cataflam® (50 mg tablet) (Novartis)	50 mg PO TID/QID. Dosages > 225 mg/day PO are not recommended
Primary dysmenorrhea or for mild to moderate pain	Cataflam® (50 mg tablet) (Novartis)	50 mg PO TID. For better relief, give 100 mg PO initially, and then follow with 50 mg doses. After the first day of therapy with a maximum dose of 200 mg PO, total doses should generally not exceed 150 mg/day.
<i>Diclofenac Epolamine</i>		
Topical: Acute pain due to minor strains, sprains, and contusions	Flector® Patch, 1.3% (Institut Biochimique)	1 patch applied to the most painful area BID

2.2 Currently Available Treatment for Indications

Currently 17 drugs are FDA approved for acute migraine, including both prescription and over-the-counter products. Most of the prescription drugs are 5- hydroxytryptamine (5-HT) receptor agonists, or “triptans,” and include naratriptan, almotriptan, frovatriptan, sumatriptan, rizatriptan, elatriptan, and zolmitriptan. A combination of sumatriptan and naproxen is also approved. Ergotamines are also available by prescription but are generally considered second-line therapy. Ibuprofen is approved as an OTC treatment for acute migraine, as is the combination of acetaminophen, aspirin and caffeine (Excedrin). Aspirin is approved for pain of migraine only.

Rapid availability of drug at the site of action might lead to faster relief from migraine². Fast relief from symptoms is a desired by migraine patients. A number of triptans are available in subcutaneous, intra-nasal, or rapid-release oral formulations. Ibuprofen is available as a rapid release liquigel formulation. Ergotamines are available in intranasal, sublingual, rectal suppository, and injectable formulations.

2.3 Availability of Proposed Active Ingredient in the United States

Diclofenac is available worldwide in a number of dosage forms for oral, rectal, intramuscular or topical administration. Extended-release forms of diclofenac are also available. Generic diclofenac potassium 50 mg tablets are available in the U.S. Diclofenac products are available only by prescription.

2.4 Important Issues With Pharmacologically Related Products

Relevant pharmacologically related products for PRO-513 include both those containing diclofenac, and also NSAIDs as a class. As a 505b(2) NDA application, the safety of PRO-513 is based in part on previous FDA findings of safety for diclofenac, particularly for Cataflam 50 mg tablets. Safety issues from diclofenac labeling are included in PRO-513 labeling.

2.5 Presubmission Regulatory Activity

PRO-513 was developed under IND 73,073.

FDA refused to file the sponsor’s June 25, 2007 NDA. FDA found the NDA not sufficiently complete to permit a substantive review due to the following: [REDACTED] (b) (4) [REDACTED] inadequate organization of the submission. The sponsor’s NDA submission of September 28, 2007 was filed by FDA. On May 8, 2008, a date within 3 months of the user fee goal date, FDA received a major amendment to the application regarding statistical analysis methods, and extended the goal date by 3 months to October 27, 2008.

2 Tfelt-Hansen, P. (2007). Parenteral vs. oral sumatriptan and naratriptan: plasma levels and efficacy in migraine. J. Headache Pain. 8:273-6.

Listed below are key issues from meetings between FDA and the sponsor.

Pre-NDA meeting (2007)

Safety

FDA noted that PRO-513 appears to have a shorter T_{max} than Cataflam, and that the sponsor should therefore provide evidence that the apparent faster rate of absorption did not lead to a worse safety profile than the approved product. FDA also noted that the sponsor would need to provide evidence that given the differences in the products, the existing long-term experience with diclofenac is relevant for PRO-513.

FDA also noted an apparent higher rate of psychiatric adverse events with PRO-513 than with placebo in Study PRO-513301.

Efficacy

The original analysis conducted for the phase 3 pivotal study conducted in Europe did not incorporate migraine-associated phonophobia, photophobia, and nausea as co-primary outcomes with migraine pain. A post-hoc analysis of the study with migraine-associated symptoms as co-primary endpoints appeared to be acceptable to FDA.

Pediatric Studies

The division indicated it could accept the sponsor's requests for a pediatric waiver in children less than 12 years of age, and for deferral until phase 4 of studies of adolescents between 12 and 17 years of age.

Type A meeting (2006)

Efficacy

FDA agreed that recurrence rate was an acceptable endpoint for description in labeling.

Sponsor response to FDA letter dated 9/24/2006

Efficacy

The sponsor proposed a single secondary endpoint, migraine recurrence rate within the first 24 hours of dosing. Recurrence was defined as reduction in pain from moderate or severe to none at 2 hours after taking study medication, followed by 1) an increase to mild, moderate or severe pain within 24 hours after taking the study medication, or 2) taking a backup pain medication within 24 hours after taking the study medication.

FDA responded that for this secondary endpoint to be considered valid, the study must incorporate a procedure to maintain the overall study-wise type I error for the primary endpoint(s) and the secondary endpoint(s) at the 0.05 level. FDA further noted that a statistically significant drug effect on the secondary endpoint must be demonstrated in at least two studies.

Special Protocol Assessment (U.S. study PRO-513301)

Key FDA comments about the proposed study included the following:

Efficacy

- To support re-dosing, safety and efficacy of re-dosing would need to be demonstrated, i.e. by re-randomizing non-responders to a second dose of study medication. In the absence of such data, approval would be limited to a single dose of drug per migraine attack.
- Exploration of the dose response relationship of PRO-513, with identification of a no-effect dose, should be part of the drug development program, or 50mg should be otherwise supported as the lowest effective dose.

Pre-IND Meeting (2005)

Efficacy

The acceptability of the completed European study was discussed, given that the migraine-associated symptoms of photophobia, phonophobia, and nausea were not originally analyzed as co-primary outcome variables along with headache pain.

Safety

FDA noted that data collection in the European trial appeared not to extend to the 24-hour time point typically required for migraine trials.

2.6 Other Relevant Background Information

None.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC

The CMC review was conducted by Shastri Bhamidipati, PhD.

The CMC review concludes that the products used in the U.S. and European phase 3 trials had the same formulation and contents.

3.2 Animal Pharmacology/Toxicology

The pharmacology review was conducted by Donald Charles Thompson

PRO-513 was submitted as a 505b(2), without new non-clinical data. The sponsor is relying on the previously approved NDAs for Cataflam and Voltaren.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Clinical data was provided by 5 clinical studies of PRO-513, and previous FDA findings of safety and efficacy for diclofenac.

4.2 Tables of Clinical Studies

Table 2: Bioavailability Studies

Study ID	Design	Treatment	Objective	Subjects	Duration
CAT458C2101	Phase I, open-label, randomized, two-way, single crossover study with 7-day washout	(b) (4) [PRO-513] (50 mg diclofenac-K sachet 50 mg Cataflam	Compare bioavailability and tolerability of (b) (4) [PRO-513] to Cataflam	24 per arm	2 study periods of 24 hours each separated by a 7-day washout period; single dose in each period
PRO-513101	Phase I, open-label, randomized, 4-period crossover, PK study	PRO-513 (50 mg diclofenac-K sachet 50 mg Cataflam	Compare bioavailability of PRO-513 to diclofenac-K tablets under fed and fasting conditions	35 PRO-513 36 Cataflam	4 treatment periods in which each subject received each test article once after fasting and once after being fed

Table 3: Phase 3 Studies in Migraine

Study ID	Diagnosis	Centers	Study Design	Treatment	Subjects	Duration
CAT458C2301	Migraine	21 in Europe	Phase 3 Double blind, double dummy, randomized, multicenter, crossover, safety and efficacy	(b) (4) [PRO-513] 50 mg Cataflam Placebo	291 (b) (4) [PRO-513] 298 Cataflam 299 Placebo	Single dose treatment of up to 3 migraines over a 2-month period
PRO-513301	Migraine	23 in US	Phase 3 prospective, randomized, double blind, parallel group, single-dose, placebo controlled, multicenter, safety and efficacy study	PRO-513 Placebo	343 PRO-513 347 Placebo	Single dose treatment of 1 migraine attack over 8 weeks

Table 4: Supportive Phase 3 Study in Pain

CAT4582302	Pain following tooth extraction	13 in Europe	Phase 3, Double blind, double dummy, randomized, multi-center, parallel group, safety and efficacy study	(b) (4) [PRO-513] 50 mg Cataflam Placebo	74 (b) (4) [PRO-513] 71 Cataflam 39 Placebo	Single dose of study medication
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4.3 Review Strategy

Clinical safety and efficacy were reviewed by Ronald Farkas, MD, PhD.

4.4 Data Quality and Integrity

The sponsor describes procedures followed to maintain data quality and integrity, as briefly described below:

Data was entered on triplicate Case Report Forms (CRFs), and field monitors reviewed the CRFs for completeness and accuracy. The original copy of the CRF was forwarded to the Data Management CRO, the second copy was retained by the field monitor, and the third copy remained at the investigational site. Once the CRFs were received by the Data Management CRO, receipt was recorded, the original copy was placed in Central Files and a working copy was made and forwarded to the responsible data management staff for processing.

Screened patients who discontinued prior to randomization were recorded as screen failures, and entered into a screening log, a separate CRF-like document. It was processed like any other CRF page.

Data items from the CRFs were entered into the study database using double data entry with verification upon second entry. Entered data were systematically checked by data management staff, using error messages printed from validation programs and database listings. Obvious errors were corrected by data management staff based on an Obvious Correction Document agreed prior to start of study. Other errors or omissions were entered on Data Query Forms, which were returned via the field monitors to the investigational site for resolution. A copy of the signed Data Query Form was kept with the CRFs at the investigational site, and once the original was received at the Data Management CRO, the database was corrected according to the resolutions.

Quality control audits of all key safety and efficacy data in the database were made after completion of data entry.

When the database was declared to be complete and accurate, the database was locked and unblinded. Any changes to the database after that time could only be made by joint written agreement between the Clinical Program Leader, the Trial Statistician and the Data Manager.

Reviewer: Procedure for maintaining data quality and integrity appear adequate.

4.5 Compliance with Good Clinical Practices

The sponsor indicates that studies were conducted in adherence to Good Clinical Practices, and to ensure the protection of patients as per the Declaration of Helsinki, the directives governing medicinal products in the European Community, and U.S. Code of Federal Regulations.

Reviewer: Sponsor compliance with Good Clinical Practice appears adequate.

4.6 Financial Disclosures

The sponsor certified on form FDA 3454 that the clinical investigators did not participate in any financial arrangement with the sponsor whereby the compensation to the investigator could be affected by the outcome of the study, had no proprietary interest in the product, and did not receive significant payments of other sorts.

5 CLINICAL PHARMACOLOGY

The clinical pharmacology review was conducted by Carol Noory, PhD.

Two bioavailability studies were conducted. Both studies were open-label, randomized, single-dose, crossover studies in healthy volunteers. In both studies, the bioavailability of PRO-513 (diclofenac potassium 50 mg sachets) was compared to the regionally marketed version of diclofenac potassium tablet 50 mg (Cataflam) under fasting conditions. The U.S. study also examined the effect of food on absorption of diclofenac from the sachet and tablet dosage forms.

5.1 Pharmacokinetics

Table 5 and Table 6 show mean pharmacokinetic parameters for PRO-513 versus Cataflam 50 mg tablets for the U.S. and the European bioavailability studies respectively.

Table 5: Pharmacokinetics, US Bioavailability Study

Table 11.4.2-1: Mean Pharmacokinetic Parameters by Treatment

PK Parameters	PRO-513-Fasting	Cataflam [®] -Fasting	PRO-513-Fed	Cataflam [®] -Fed
	Mean ± SD (N)			
AUC _{0-inf} [ng*hr/mL]	1254.6 ± 305.9 (33)	1097.9 ± 271.7 (33)	1084.2 ± 245.0 (28)	1071.4 ± 257.8 (33)
AUC _{0-t} [ng*hr/mL]	1236.9 ± 298.0 (34)	1078.5 ± 268.6 (34)	1054.6 ± 249.7 (35)	1062.2 ± 251.9 (35)
C _{max} [ng/mL]	1618.3 ± 538.4 (34)	1160.7 ± 451.6 (34)	505.5 ± 305.4 (35)	835.3 ± 448.9 (35)
T _{max} (hr) Median (Min, Max)	0.25 (0.17, 0.67) (34)	0.50 (0.25, 4.00) (34)	0.17 (0.08, 4.00) (35)	1.25 (0.33, 8.00) (35)
K _{el} [1/hr]	0.56 ± 0.17 (33)	0.59 ± 0.18 (33)	0.39 ± 0.16 (28)	0.49 ± 0.15 (33)
T _{1/2} [hr]	1.35 ± 0.40 (33)	1.29 ± 0.37 (33)	2.15 ± 0.94 (28)	1.56 ± 0.55 (33)

Source Data: [Appendix 15.2.2](#).**Table 6: Pharmacokinetics, European Bioavailability Study****Table 7-3 Summary statistics on pharmacokinetic parameters**

Treatment		Diclofenac-K tablets				Diclofenac-K sachets			
Parameter		N	Mean*	SD	Median (Range)	N	Mean*	SD	Median (Range)
C _{max}	ng/mL	24	855	580	782 (148-2430)	24	1620	872	1510 (367-3610)
t _{max}	h	24	0.864	0.624	0.50 (0.33-2.50)	24	0.233	0.0751	0.25 (0.08-0.37)
	(min)	24	51.8	37.4	30.0 (20.0-150)	24	14.0	4.51	15.0 (5.00-22.2)
t _{lag}	h	24	0.0925	0.0473	0.08 (0.00-0.18)	24	NE	NE	0.00 (0.00-0.00)
	(min)	24	5.55	2.84	5.00 (0.00-10.0)	24	NE	NE	0.00 (0.00-0.00)
AUC _{0-t}	ng.h/mL	24	945	384	910 (440-1650)	24	1010	429	1040 (447-1970)
AUC _{0-∞}	ng.h/mL	24	952	384	913 (453-1660)	24	1020	430	1050 (451-1980)
t _{1/2}	h	24	2.07	0.435	2.07 (1.25-2.94)	24	2.20	0.494	2.16 (1.00-3.36)

*Arithmetic means

SD: Standard deviation

NE: not estimable

The sponsor asserts that the relative bioavailability of PRO-513 versus Cataflam indicates that both formulations are bioequivalent in terms of extent of absorption, since the 90% confidence interval for AUC_{0-inf} was contained within the 80–125% limits of bioequivalence.

Reviewer: Agree.

The sponsor further asserts that the absorption rate for study drug was significantly faster ($p < 0.0001$) than CATAFLAM tablets, as indicated by shorter t_{lag} and t_{max} .

Reviewer: Agree.

The sponsor indicates that under fasting conditions peak plasma concentration (C_{max}) was significantly higher for the PRO-513 sachet versus Cataflam, but food decreased peak diclofenac concentrations from PRO-513 by 72% while reducing peak concentrations for Cataflam tablets by only 33%.

The sponsor also concludes that food has no effect on the extent of absorption of diclofenac from the PRO-513 sachet or CATAFLAM tablets.

Reviewer:

Peak Plasma Concentration

Under fasting conditions, peak plasma concentration of diclofenac was higher for PRO-513 than for Cataflam tablets (1618 ng/ml versus 1160 ng/ml in the US study, and 1620 ng/ml versus 855 ng/ml in the European study). The higher peak plasma concentration raised FDA concern that the safety profile of PRO-513 might be different/worse than that of Cataflam tablets. However, this review concludes that the relative C_{max} of the two formulations of diclofenac may be more similar in clinical practice than suggested by fasting conditions.

Migraineurs may have delayed gastric emptying even when not experiencing migraine,³ and gastric stasis occurs during migraine attacks. Thus, even for migraine with nocturnal onset, fasting conditions might not be met. Recent evidence suggests that peak incidence of migraine might actually occur in the middle of the day⁴, potentially within a few hours of eating. In the U.S. phase 3 study, about 1/3rd of patients reported eating within 1 hour before taking study medication, and a large majority of migraines had onset during the day, potentially within a few hours of eating (Figure 1).

In contrast to fasting conditions, under fed conditions C_{max} was higher for Cataflam than for PRO-513 (835 ng/ml versus 506 ng/ml respectively), although T_{max} was still earlier for PRO-513. While fed state in a bioavailability study, like fasted, may poorly approximate clinical use, it seems reasonable to conclude that PK parameters in clinical use would often fall between fed and fasted state, such that C_{max} might be more similar for PRO-513 and Cataflam 50 mg tablets than suggested by the bioavailability studies.

While not directly examined, C_{max} of diclofenac from PRO-513 is likely always lower than C_{max} from two 50 mg diclofenac tablets, an FDA approved dose. This conclusion is based on previous published findings that the pharmacokinetics of diclofenac is generally dose-proportional⁵.

³ Aurora, S et al., 2007. Gastric stasis occurs in spontaneous, visually induced, and interictal migraine. *Headache* 47:1443-1446.

⁴ Alstadhaug et al., 2007. 24-hour distribution of migraine attacks. *Headache* 48:95-100.

⁵ John, VA (1979) The pharmacokinetics and metabolism of diclofenac (Voltaren) in animals and man. *Rheumatol Rehab. Supple* 2:22-37.

Figure 1: Time of Headache Onset

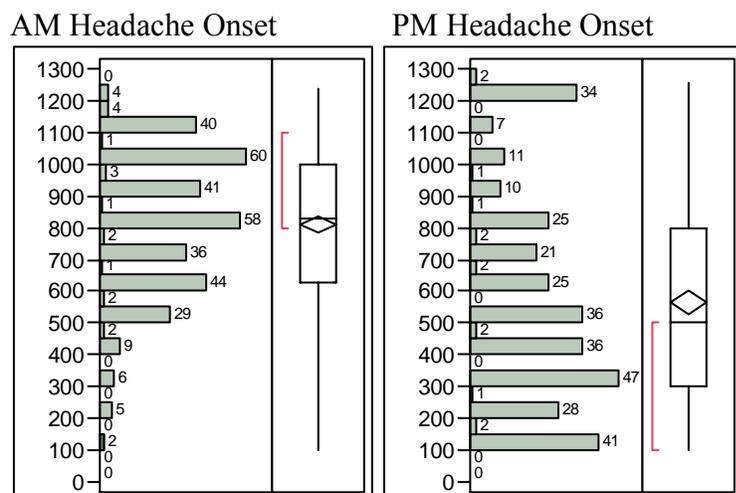


Figure 1: Histogram of time of onset of migraine in the U.S. phase 3 study. While roughly 20% of migraines had onset before or near the time most people might eat a first meal of the day, most migraines had onset not longer than a few hours after usual meal times. (Note that the high incidence of migraine onset at ‘12 PM’ and low onset at ‘12 AM’ suggests time recording error due to the switch from AM to PM at noon and midnight).

Absorption Rate

PRO-530 was significantly more rapidly absorbed than Cataflam: mean 0.25 hours versus 0.50 hours under fasted conditions, and 0.17 hours versus 1.25 hours under fed conditions.

Reviewer: Particularly in the fed state, the difference in T_{max} is large, and might plausibly lead to clinically meaningful effects in migraine.

Metabolism and Elimination

Diclofenac is eliminated through metabolism with less than 1% of the drug excreted unchanged. Diclofenac undergoes extensive first-pass metabolism with approximately 60% of the administered dose reaching systemic circulation.

Diclofenac is metabolized by Cytochrome P450 enzymes including CYP2C9, CYP3A4, and CYP2C8, and by glucuronidation by UGT-2B7.

The sponsor notes that the pharmacokinetics of diclofenac sodium does not appear to be influenced by age, renal impairment, or chronic active hepatitis. Alcoholic cirrhosis increased total exposure to diclofenac approximately 3-fold compared to healthy volunteers.

Metabolic Enzyme Inhibition

The sponsor notes that *in-vitro* studies have not found a consistent inhibitory effect of diclofenac on CYP2C9 or CYP3A4. The sponsor also notes that two *in-vivo* studies have not demonstrated clinically relevant interactions of diclofenac with either CYP2C9 or CYP3A4.

5.2 Pharmacodynamics

The following is from Cataflam labeling:

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

5.3 Exposure-Response Relationships

The sponsor did not collect exposure-response data; no dose-response studies of PRO-513 were conducted in migraine, and no diclofenac blood level data was collected in studies of patients with headache.

The sponsor concludes that 50 mg is the optimal dose of PRO-513 based on 3 previous efficacy trials conducted by Novartis, and a phase 1 food effect trial conducted by the sponsor, arguing as follows:

- **Diclofenac Potassium/Sumatriptan Migraine Study (1999)⁶**
 - 50 and 100 mg Cataflam tablets were compared to 100 mg sumatriptan and placebo in a randomized, double-blind, complete, crossover trial in 144 patients suffering from acute migraine attacks
 - The 50 and 100 mg doses of Cataflam and sumatriptan 100 mg were found to be superior to placebo ($p < 0.001$) with respect to headache response at 2 hours as measured on a 100 mm VAS (Table 7).
 - The sponsor states that 100 mg Cataflam tablets reached statistical significance compared to placebo in phonophobia and nausea ($p < 0.05$) and approached significance in the treatment of photophobia at 2 hours vs. placebo.
 - The sponsor states that 50 mg Cataflam tablets reached statistical significance compared to placebo only for nausea.

⁶ Diclofenac-K/Sumatriptan Migraine Study Group (1999) Acute treatment of migraine attacks: efficacy and safety of a nonsteroidal anti-inflammatory drug, diclofenac-potassium, in comparison to oral sumatriptan and placebo. *Cephalgia* 19:232-40

Table 7: 50 vs. 100 mg Cataflam, Pain at 2 hours

Table 1. Pain on 100 mm VAS at 2 h after dosing.

Treatment comparison	Estimated difference (mm)	p-value	95% confidence interval
Diclofenac-K 50 mg vs placebo	-17.0*	<0.001	(-23.7; -10.3)
Diclofenac-K 100 mg vs placebo	-18.6*	<0.001	(-25.4; -11.8)
Sumatriptan 100 mg vs placebo	-14.5*	<0.001	(-21.1; -7.9)
Diclofenac-K 50 mg vs sumatriptan 100 mg	-2.5	0.46	(-9.1; 4.1)
Diclofenac-K 100 mg vs sumatriptan 100 mg	-4.1	0.23	(-10.9; 2.7)

Primary patient population.

*Significant result.

Confidence intervals below 0 indicate a significant result in favor of the first treatment.

Reviewer: While the efficacy of 50 and 100 mg Cataflam appear not to be *statistically* distinguishable in this study, the results do suggest that the 50 mg Cataflam dose is potentially less effective than the 100 mg dose. Since 50 mg Cataflam was not positive for all key migraine symptoms, the study potentially suggests that a lower dose of diclofenac might not be effective.

Of note, the safety profile appeared no better for 50 mg versus 100 mg Cataflam (in fact, almost twice as many adverse event occurred with 50 mg), and for a variety of adverse events the imbalance was even more striking (for example somnolence in 6% of patients for 50 mg vs. only 1% for 100 mg)(Table 8). This may illustrate the range of apparently random effects on adverse events in studies of diclofenac in migraine.

Table 8: Safety, 50 vs. 100 mg Cataflam in Migraine

Table 4. Adverse events.

Adverse events	Diclofenac-K	Diclofenac-K	Sumatriptan	Placebo
	50 mg (n=131)*	100 mg (n=122)		
	N (%)†	N (%)†	N (%)†	N (%)†
Asthenia	1 (1%)	1 (1%)	4 (3%)	2 (1.5%)
Fatigue	5 (4%)	1 (1%)	7 (5%)	4 (3%)
Chest pain	0	0	4 (3%)	1 (1%)
Dizziness	1 (1%)	0	7 (5%)	3 (2%)
Paresthesia	2 (1.5%)	0	5 (4%)	1 (1%)
Somnolence	8 (6%)	1 (1%)	3 (2%)	3 (2%)
Dyspepsia	3 (2%)	3 (2%)	1 (1%)	1 (1%)
Nausea	3 (2%)	1 (1%)	3 (2%)	5 (4%)
Abdominal pain	1 (1%)	6 (5%)	6 (5%)	4 (3%)
Vomiting	0	0	0	4 (3%)
Tachycardia	2 (1.5%)	1 (1%)	7 (5%)	2 (1.5%)
Anxiety	1 (1%)	0	3 (2%)	0

*Number of patients receiving treatment.

†Number of AEs occurring in $\geq 2\%$ of patients for at least one treatment, regardless of relationship to trial drug.

- ***Efficacy and Safety of Cataflam 50 mg, Cafergot (2 mg ergotamine + 200 mg caffeine) and Placebo in Patients with Migraine Attacks***

- 430 patients were treated in a double-blind, double-dummy, parallel-group trial to assess the efficacy and tolerability of 50 mg Cataflam versus Cafergot for migraine. Patients were to treat 2 consecutive migraine attacks with the assigned treatment using up to 4 doses per attack if necessary, whereby the 2nd, 3rd, and 4th doses contained either 50 mg Cataflam or Cafergot.
- The primary efficacy variable was pain intensity as measured on a 100 mm VAS 2 hours after treatment. Nausea, photophobia, and phonophobia were secondary efficacy targets.
- The sponsor states that both Cataflam 50 mg and Cafergot were significantly more effective than placebo with respect to migraine relief at 2 hours.
- The sponsor states that Cataflam 50 mg was generally more effective than placebo and Cafergot in reducing the severity of accompanying symptoms; however, neither Cataflam nor Cafergot was significantly superior to placebo in treating the accompanying symptoms of migraine (at all time points assessed).

Reviewer: As in the above study, since 50 mg Cataflam was not superior to placebo in treating accompanying symptoms of migraine, this study is consistent with the hypothesis that 50 mg diclofenac may be too low a dose for migraine.

- **European phase 3 Trial (CAT458c2301) [submitted in this NDA]**

- This was a 3-arm placebo-controlled parallel group study in 328 patients comparing the 50 mg dose of PRO-513 to 50 mg Cataflam and to placebo.
- The sponsor states that both PRO-513 and Cataflam were significantly superior to placebo with respect to proportion of subjects pain free at 2 hours ($p < 0.0001$ and $p = 0.0040$, respectively).
- The sponsor states that PRO-513 was also significantly superior to Cataflam with respect to the proportion of subjects pain free at 2 hours ($p = 0.0035$).
- The sponsor states that PRO-513 was significantly more effective than placebo for relief of the associated symptoms, photophobia, phonophobia, and nausea ($p = 0.0273$, $p = 0.0035$, and $p = 0.0093$, respectively). Cataflam 50 mg tablets reached statistical significance only for phonophobia ($p = 0.0024$) and not for the other associated symptoms of migraine.

Reviewer: Similar to the above studies, since 50 mg Cataflam was not superior to placebo for all 4 key migraine symptoms, the study is consistent with the hypothesis that 50 mg diclofenac may be too low a dose for migraine. Some degree of ‘assay sensitivity’ is provided by the positive result for PRO-513 in this study, although the study still clearly does not directly address if lower doses of PRO-513 would be effective.

- **Food-Effect Study [submitted in this NDA]**

- This was the U.S. bioavailability study described above.
- The sponsor states that the study demonstrated that PRO-513 was bioequivalent to Cataflam with respect to extent of absorption when administered as a single oral dose under fasting and fed conditions, and that under both fasting and fed conditions, PRO-513 was more rapidly absorbed than Cataflam®. The sponsor

also states that the C_{max} for PRO-513 remained significantly higher than that for Cataflam under high-fat conditions. [reviewer note: this appears to be true only for fasting conditions, not fed/high-fat conditions]

Reviewer: The bioavailability trial provides the plausible explanation that differences in PK profile between PRO-513 and Cataflam 50 mg (particularly faster T_{max} for PRO-513) could account for PRO-513 being effective in all 4 migraine endpoints in phase 3 studies, while Cataflam 50 mg was not.

The sponsor summarizes the argument as follows regarding potential development of a (b) (4)

“Consideration was given to developing a (b) (4) which, in terms of C_{max}, would have a fasted pharmacokinetic profile similar to that of a 50 mg CATAFLAM tablet. The randomized, double-blind trial data, however, suggests that a 50 mg CATAFLAM tablet would not be likely to reach statistical significance in all four co-primary endpoints included in Study PRO-513301 even if the study was appropriately powered. In addition, under fed conditions, (b) (4) would not likely result in high enough plasma concentrations to result in efficacy for any of the primary endpoints. Thus, the available evidence suggests that a (b) (4) would be sub-therapeutic.”

Reviewer Conclusions, Dose:

In multiple studies (including the European phase 3 study submitted to this NDA) 50 mg Cataflam was not shown to be effective in all 4 key primary outcome variables of migraine. The diclofenac exposure from PRO-513 appears, overall, to be similar enough to diclofenac exposure from Cataflam tablets that a reduction of PRO-513 exposure by even 50% would plausibly be less effective in migraine than Cataflam 50 mg, and would therefore plausibly be ineffective.

Diclofenac is approved for analgesia/primary dysmenorrhea at an initial dose of 50 mg. Current Cataflam labeling indicates that an initial dose of 100 mg followed by 50 mg doses will provide better relief. This dosing information, while not derived from migraine, nonetheless suggests that the 50 mg dose is a reasonably low dose.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

PRO-513 is intended for acute treatment of migraine with or without aura in adults.

For the European phase 3 study, International Headache Society (IHS) criteria for migraine from 1988 were used (Table 9), while for the US study, which was conducted several years later, IHS criteria for migraine revised in 2005 were used (Table 10).

Reviewer: Changes to the IHS classification of migraine would not have affected the appropriateness of patient selection or outcome variables of the two efficacy studies.

Table 9: IHS Migraine Classification, 1988

[From ISS]

Table 1.-1: International Classification of Headache Disorders-1

Migraine Without Aura	Migraine With Aura
<p>A. At least five headache attacks lasting 4 – 72 hours (untreated or unsuccessfully treated), which have at least two of the four following characteristics:</p> <ul style="list-style-type: none"> • Unilateral location; • Pulsating quality; • Moderate or severe intensity (inhibits or prohibits daily activities); • Aggravated by walking up stairs or similar routine physical activity <p>B. During headache, at least one of the two following symptoms occur:</p> <ul style="list-style-type: none"> • Phonophobia and photophobia; • Nausea and/or vomiting 	<p>A. At least two attacks with at least three of the following:</p> <ul style="list-style-type: none"> • One or more fully reversible aura symptoms indicating focal cerebral cortical and/or brain stem functions; • At least one aura symptom develops gradually over more than four minutes, or two or more symptoms occur in succession; • No aura symptom lasts more than 60 minutes; if more than one aura symptom is present, accepted duration is proportionally increased; • Headache follows aura with free interval of at least 60 minutes (it may also simultaneously begin with the aura) <p>B. At least one of the following aura features establishes a diagnosis of migraine with typical aura:</p> <ul style="list-style-type: none"> • Homonymous visual disturbance; • Unilateral paresthesias and/or numbness; • Unilateral weakness; • Aphasia or unclassified speech difficulty

Table 10: IHS Migraine Classification, 2005 Revision

[From ISS]

Table 1.-2: International Classification of Headache Disorders-2	
Migraine Without Aura	Migraine With Aura
<p>A. At least five attacks that fulfill criteria B-D</p> <p>B. Headache lasting 4 – 72 hours (untreated or unsuccessfully treated)</p> <p>C. Headache has at least two of the following characteristics:</p> <ul style="list-style-type: none"> • Unilateral location; • Pulsating quality; • Moderate or severe pain intensity; • Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs) <p>D. During headache, at least one of the following occurs:</p> <ul style="list-style-type: none"> • Nausea and/or vomiting; • Photophobia and phonophobia <p>E. Not attributed to another disorder</p>	<p>A. At least two attacks fulfilling criteria B-D</p> <p>B. Aura consisting of at least one of the following, but no motor weaknesses:</p> <ul style="list-style-type: none"> • Fully reversible visual symptoms including positive features (e.g., flickering lights, spots, or lines) and/or negative features (i.e., loss of vision); • Fully reversible sensory symptoms including positive features (i.e., pins and needles) and/or negative features (i.e., numbness); • Fully reversible dysphasic speech disturbance <p>C. At least two of the following:</p> <ul style="list-style-type: none"> • Homonymous visual symptoms and/or unilateral sensory symptoms; • At least one aura symptom develops gradually over ≥ 5 minutes and/or different aura symptoms occur in succession over ≥ 5 minutes; • Each symptom lasts ≥ 5 minutes and ≤ 60 minutes <p>D. Headache fulfilling criteria B-D for Migraine Attack Without Aura begins during the aura or follows aura within 60 minutes</p> <p>E. Not attributable to another disorder</p>

6.1.1 Methods

Primary and secondary endpoints were analyzed for both phase 3 migraine studies.

6.1.2 General Discussion of Endpoints

Migraine Endpoints

Migraine syndrome involves the following symptoms in addition to pain: photophobia, phonophobia, and nausea. FDA generally requires efficacy in migraine to be based on these 4 symptoms as co-primary endpoints (at $p \leq 0.05$) at 2 hours.

During development the sponsor proposed a single secondary endpoint, migraine recurrence rate within the first 24 hours of dosing. Recurrence was defined as reduction in pain from moderate or severe to none at 2 hours after taking study medication, followed by 1) an increase to mild, moderate or severe pain within 24 hours after taking the study medication, or 2) taking a backup pain medication within 24 hours after taking the study medication. FDA responded that for this secondary endpoint to be considered valid, the study must incorporate a procedure to maintain the overall studywise type 1 error for the primary endpoint and the secondary endpoint at the

0.05 level. FDA further noted that a statistically significant drug effect on the secondary endpoint must be demonstrated in at least two studies.

Reviewer: The above primary and key secondary endpoints are typical for migraine studies in support of FDA approval, and are acceptable.

Comparative Endpoint

The European phase 3 study, in addition to comparing PRO-513 to placebo, compared PRO-513 to Cataflam 50 mg. (b) (4)

(b) (4) The sponsor notes that Cataflam is approved for migraine in Europe

Reviewer: Comparison between study drug and Cataflam 50 mg for efficacy in migraine is not appropriate because Cataflam is not FDA approved for migraine; no meaningful superior effectiveness claim could be based on comparison to a drug that isn't known to be effective. In fact, Cataflam 50 mg was *not* shown to be effective in migraine in several studies (see section 5.3 for details), including the European phase 3 study submitted to this NDA (CAT458c2301), in which Cataflam 50 mg tablets did not reach statistically significant superiority to placebo for photophobia or nausea.

6.1.3 Study Design

Two phase 3 efficacy studies were conducted to support the indication in migraine. The first study, CAT458C2301, was conducted in multiple centers in Europe (Germany, Hungary, Italy, the Netherlands, and Poland), and the second study, PRO-513301, was conducted in multiple centers in the U.S.

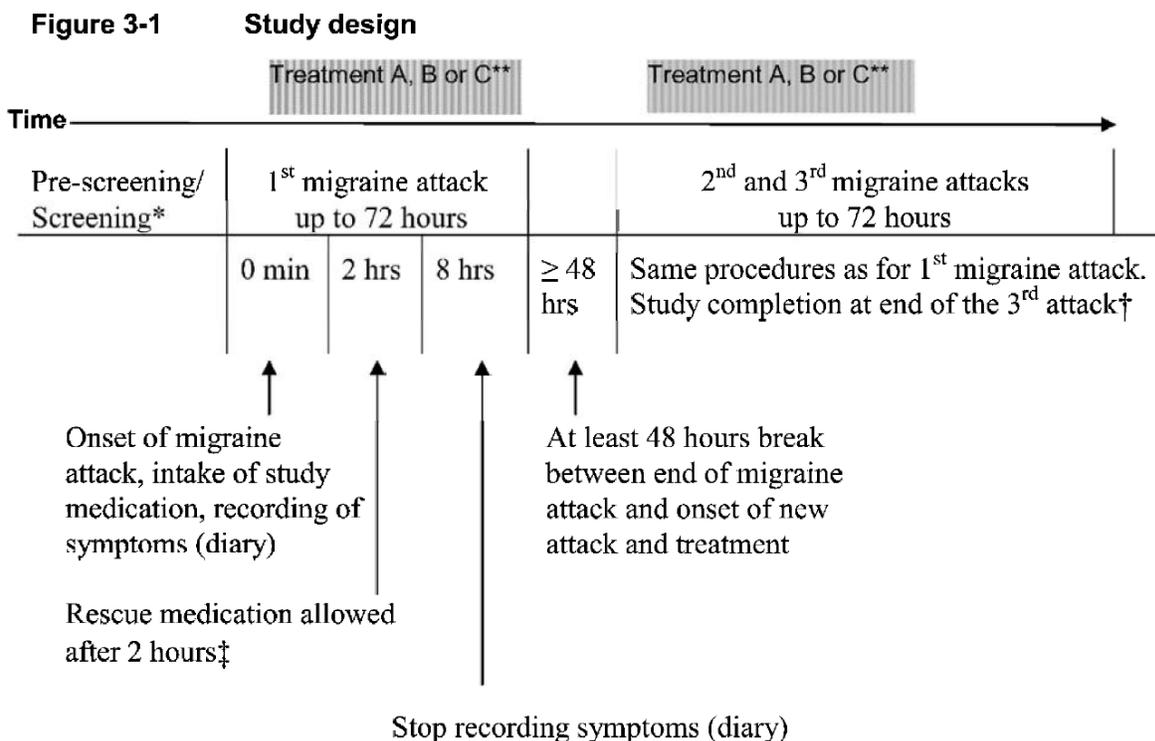
European Phase 3 Trial, CAT458C2301

Title:

A double-blind, double-dummy, randomized, multi-center, cross-over study to assess the efficacy and tolerability of single doses of (b) (4) PRO-513] sachets (50 mg diclofenac-K powder for oral solution) as an acute treatment for adult patients with migraine attacks in comparison with placebo and Cataflam (50 mg diclofenac-K tablets)

This was a 3-arm, phase 3, double-blind, double-dummy crossover study to assess the efficacy of a single dose of PRO-513 in acute migraine compared to both placebo and Cataflam 50 mg tablets (Figure 2).

Figure 2: CAT458c2301 Study Design



- * Pre-screening up to 4 weeks before screening; patients were randomized and study medication was dispensed at the screening visit (Visit 1); up to three subsequent visits occurred.
- ** Patients took treatments in randomized sequence in a double-blind, double-dummy, cross-over design:
 - A = one 50 mg diclofenac-K sachet and one placebo tablet matching diclofenac-K tablets
 - B = one 50 mg diclofenac-K tablet and one placebo diclofenac-K sachet
 - C = one placebo diclofenac-K sachet and one placebo tablet matching diclofenac-K tablets.
- † Final assessment performed after the 3rd migraine attack. The final visit should not take place until three attacks had been treated.
- ‡ The supplied rescue medication consisted of two doses of paracetamol (2 x 500 mg).

Subjects were to treat three migraine attacks over a two-month period using a different combination of study medications for each treatment as determined by randomization (bottom of Figure 2).

Paracetamol (500 mg tablets) was provided as rescue medication for each of the three attacks if at ≥ 2 hours relief of symptoms was inadequate. In addition, at the discretion of the investigator, other rescue medications could be provided. Patients were instructed not take rescue medication within 2 hours of treatment unless absolutely necessary.

Between the end of one migraine attack and the start of another, a minimum of 48 hours must have elapsed. Additionally, during the inter-attack period, subjects must have been pain free and must not have used any form of rescue medication.

Study medication was self-administered by the patient as soon as they were certain they were experiencing symptoms of a migraine attack (regardless of headache severity).

Medications were to be taken preferably before meals or on an empty stomach.

Reviewer: Since in normal clinical practice acute migraine would not be treated on an empty stomach, this aspect of the study decreases generalizability:

- Particularly given the higher C_{max} of PRO-513 under fasting versus fed conditions, PRO-513 efficacy (versus placebo) plausibly might depend on fed state
- The *relative* efficacy of PRO-513 versus Cataflam 50 mg tablets might vary depending on fed state [while not an endpoint acceptable to FDA, this aspect of study design weakens the comparative efficacy argument further]. The C_{max} of PRO-513 in the US bioavailability study was higher than Cataflam under fasting conditions, but lower than Cataflam under fed conditions.

Major inclusion criteria

- Male or female, 18-65 years of age
- Meeting IHS diagnostic criteria for migraine with or without aura,
- Disease duration of >1 year
- 2-6 migraine attacks per month over the last 3 months.

Major exclusion criteria

- Suffering from interval headaches, or other types of migraine.
- Receiving prohibited medication
- Known hypersensitivity to the active substance or its excipients or other chemically closely related substances, particularly acetylsalicylic acid and in general other analgesics, antipyretics and NSAIDs.
- In whom attacks of asthma, urticaria, or acute rhinitis were precipitated by acetylsalicylic acid or other drugs with prostaglandin-synthetase inhibiting activity.
- With severe cardiac, liver or acute renal insufficiency, with active peptic ulcer disease or a history of significant gastrointestinal disease or gastrointestinal bleeding over the past year.
- With phenylketonuria, porphyria, active blood dyscrasia, bone marrow depression or clinically significant findings on an electrocardiogram (ECG).
- With a history of non-compliance or involved in health-related litigation or treated with an investigational drug within 30 days prior to study entry.

Concomitant medications

Prophylactic treatment for migraine was permitted provided patients had been on a constant dosing regimen for at least the previous 3 months with no more than one prophylactic agent. The dose must remain unchanged throughout the study period. For patients who stopped prophylactic treatment, a washout period of 1 month before study entry was required.

Concomitant medications which were considered necessary for the patient's welfare and which do not interfere with the study medications could be given at the discretion of the investigator.

Efficacy Assessments

- Migraine pain (on a 4-point scale) and presence or absence of accompanying migraine symptoms (nausea, vomiting, photophobia, phonophobia) at 1, 2, 4, 6, and 8 hours after dosing.
- Headache intensity on a 100-point visual analog scale
- Sustained pain free, defined as pain free at 2 hours and no recurrence of headache and intake of rescue medication within 24 hours post-dose
- Sustained headache response, defined as headache response at 2 hours (pain free or reduction in headache intensity from moderate or severe to mild) and no recurrence/worsening of headache and intake of rescue medication within the 24 hours post-dose.
- Time at which migraine attack was completely resolved
- Time of migraine attack recurrence within 48 hours
- Working ability (normal, mild impairment, severe impairment, or bed rest required)
- Use of rescue medication in the first 8 hours
- Global evaluation of medication by patient (very poor, poor, no opinion, good, very good)

Primary endpoint

The primary endpoint of the original statistical analysis plan was proportion of subjects pain free at two hours. A *post-hoc* analysis was performed for the regulatory submission to FDA in which photophobia-free, phonophobia-free, and nausea-free were considered as additional co-primary endpoints.

Reviewer: The *post-hoc* addition of co-primary endpoints, with all endpoints needing to be positive at $p \leq 0.05$ does not inflate type-1 error, and is acceptable.

Key Secondary Efficacy Variables

- Sustained pain free (pain free at 2 hours and no recurrence or rescue medication within 24 hours)

Additional Secondary Efficacy Variables

- Sustained headache response (no recurrence/worsening or rescue medication within 24 hours)
- Time to onset of analgesic effect assessed using a VAS of headache intensity
- Headache response at 2 hours post-dose (pain free or reduction from moderate or severe to mild)
- Reduction of VAS headache intensity from baseline at single time points to 8 hours post-dose
- Average reduction of VAS headache intensity during the first 2, 4, and 8 hours post-dose
- Change of headache intensity from baseline on a verbal scale at 1, 2, and 8 hours post-dose
- Presence of nausea, vomiting, photophobia, and phonophobia at 1, 2, 4, 6, and 8 hours post-dose

- Working / functional ability evaluated on a verbal scale at 2 and 8 hours post-dose
- Use of rescue medication within 8 hours post-dose and time to use of rescue medication
- Time to attack completely resolved
- Recurrence of attack within 24 and 48 hours
- Patient's global evaluation of medication.
- As a summary measure, the average reduction of headache intensity from baseline during hours 0-2, 0-4, and 0-8 was calculated as area under the curve (AUC) divided by the length of time.

Safety Assessments, European Phase 3 Study

- Recording of adverse events:
The protocol specifies that “at the final assessment for each of the three migraine treatment periods, the patient will record in the patient diary any adverse events during the 8 hours following the dose of medication with their time of onset, duration, and severity. At each visit except Visit 1 the investigator will record any adverse events occurring since the previous visit on the CFS. This will include those recorded in the patient diary and any information about adverse experiences elicited or volunteered from the patient verbally, including all other adverse experiences that have occurred since the previous visit.”

The Patient diary gives the patient the following instructions:

- Please make a note of any adverse experiences in the 8-hours after taking the study medication.
- If you have taken rescue medication, please make a note of any adverse experiences until time of rescue medication intake.

Reviewer: Recording adverse events by recall from the previous 8 hours is likely less accurate than recording adverse events at the time of occurrence. Similarly, adverse events occurring more than 8 hours after dosing might not have been accurately recorded due to recall issues at the study clinic visit. Importantly, the instruction to patients to “make a note of any adverse experiences *until time of rescue medication*” would have excluded recording of adverse events after taking rescue medication that might have been due to study medication.

- All other safety assessments were performed for screening only (Hematology, blood chemistry, urine laboratory assessments, vital signs, pregnancy test, ECG, physical examination)(Table 11)
- No pharmacokinetic assessments were made.

Table 11: Study schedule, European Phase 3 Study

Table 3-2 Evaluation and visit schedule

Period	Pre-screening	Double-blind treatment of three migraine attacks separated by ≥ 48 hours			
		1	2	3	Final
Visit					
Informed consent	X				
Check inclusion/exclusion criteria	X	X			
Perform ECG and laboratory evaluations*	X				
Urine pregnancy test**	X	X			
Distribute practice/patient diary and instruct on use	X	X			
Demographic data		X			
Complete physical examination including vital signs		X			
Medical history		X			
Previous/concomitant medication or non-drug therapy		X	X	X	X
Assign randomization number		X			
Supply study medication and rescue medication		X			
Prescribe add. medication for pain relief, if necessary†		X	X	X	
Collect and check practice/patient diary		X	X	X	X
Record adverse events in CRF			X	X	X
Compliance check			X	X	X
Termination Sheet					X
Pre-screening activities could occur within 4 weeks prior to Visit 1. * ECGs performed up to 6 months prior to pre-screening could be used to assess patient inclusion. ** A positive urine pregnancy test was to be confirmed by a serum test. † Additional/alternative rescue medications for pain relief could be prescribed by the investigator, if paracetamol was considered inadequate. The final visit could also be at Visit 2 or Visit 3 if three migraine attacks had been treated with study medication at this time.					

The study was terminated before all randomized patients had treated three migraine attacks. Patients who had not treated three migraine attacks were classified as 'prematurely discontinued' for administrative problems.

Unites States Phase 3 Trial, PRO-513301

Title

A multi-center, prospective, randomized, double-blind, parallel group, single dose, placebo controlled study of the efficacy and safety of PRO-513 (50 mg diclofenac potassium powder for oral solution) compared to placebo in adult subjects with migraine attacks.

PRO-513301 was a Phase 3, multi-center (23 US centers), prospective, randomized, double-blind, parallel group, single dose, placebo-controlled study comparing PRO-513 to placebo.

Subjects treated one migraine attack fulfilling IHS criteria, and of at least moderate pain intensity.

Major inclusion criteria

- Male and female subjects 18 – 65 years of age
- Diagnosis of either migraine attack with or without aura, presenting before age 50
- A history, on average, of at least 1 migraine attack per month and an average of not more than 6 migraine attacks per month during the previous year.
- The migraine attack when left untreated was to be of at least moderate headache pain intensity

Major exclusion criteria

- A history of vomiting $\geq 20\%$ of the time during migraine attacks, or were usually so incapacitated as to require bed rest during the attack [**Reviewer:** roughly a third to one half of migraineurs require bed rest for a typical migraine attack].
- Female subjects who were taking oral contraceptives or who received progestin injections/implants and who, in addition, smoked and had experienced migraine attack with aura [**Reviewer:** a group with such increased risk of stroke that smoking cessation might reasonably be undertaken before any enrollment in a drug study]
- Subjects who, within one year, had a clinically significant medical history of gastric or peptic ulcer; gastrointestinal bleeding; bleeding problems; coagulation abnormalities; hemorrhagic disease; anemia; bone marrow suppression; immunosuppression; motility dysfunction, or any condition that could interfere with the absorption, distribution, metabolism, or excretion of the study medication.
- Subjects who were HIV+.
- Subjects who were diagnosed and/or treated for inflammatory bowel disease or pancreatic disease; serious cardiovascular disease or history of serious cardiovascular disease or stroke, renal, hepatic, endocrine, pulmonary, neurologic disease; Type I or II diabetes mellitus, uncontrolled hypertension; or malignancy not in remission
- Subjects with concurrent medical condition(s) that required the chronic use of analgesics, narcotic analgesics, steroidal or non-steroidal anti-inflammatory agents, tranquilizers, sedatives-hypnotics, antipsychotics, or nitrates or their use for prevention of migraine attacks. [**Reviewer:** PRO-513 would seemingly not be effective for migraine in patients already on chronic NSAID treatment.]
- Subjects who were taking any prescription drugs for anticoagulation (“thinning the blood”), gout or arthritis
- Subjects who were currently taking monoamine oxidase inhibitors or lithium

Reviewer: The study inclusion criteria might have led to recruitment of patients with less severe migraine symptoms than the overall migraine population. This could decrease ability to understand efficacy and safety in severely affected patients. However, as discussed in the results section below, almost 1/3 of study patients treated a headache characterized by severe pain, suggesting speculatively that the study population may be fairly representative of the overall migraine population.

Concomitant medications

Subjects could be taking migraine prophylactic medication if on a stable dose for 3 months; however, patients taking ergot alkaloids either for prophylaxis or acute migraine treatment were excluded.

Subjects were excluded who were taking medications which, in the opinion of the Investigator, could potentially confound the quantification of analgesia; or that could interfere with the absorption, distribution, metabolism, or excretion of the study medication

Subjects were to use no rescue medication prior to 2 hours. If the subject had inadequate relief from the study medication, they could take a medication that they would normally take to treat a migraine attack or a medication that the investigator recommended or prescribed.

Efficacy Assessments

- Headache pain and associated symptoms of nausea, photophobia, and phonophobia, on 4-point severity scale, just prior to dosing, and after taking study medication at 15, 30, and 45 minutes, and 1, 1.5, 2, 2.5, 3, 4, 8, 16, and 24 hours (recorded in patient diary).
- Vomiting (yes/no)
- Functional ability with regard to daily activities (on 5-point scale)

Primary endpoint

The 4 co-primary efficacy endpoints were percent of subjects who had no headache pain, nausea, photophobia, or phonophobia at 2 hours post-dosing (each at $p \leq 0.05$).

Key Secondary Endpoint

- Sustained pain-free rate (no headache pain from 2 to 24 hours post-dose and no use of rescue medication within 24 hours post-dose)

Additional Secondary Endpoints

- Headache recurrence rate (no headache pain at 2 hours post-dose and mild, moderate or severe headache pain and/or use of rescue medication within 24 hours post-dose)
- Time to headache recurrence
- Pain intensity difference (PID+) at each evaluation (15, 30 and 45 minutes and 1, 1.5, 2, 2.5, 3, 4, 8, 16 and 24 hours post-dose)
- Headache pain intensity at each evaluation time-point
- Intensity of nausea, photophobia and phonophobia at each evaluation time-point
- Presence or absence of vomiting at each evaluation time-point
- Functional ability with regard to daily activities at each evaluation time-point.

Safety Assessments

Subjects recorded all adverse events occurring subsequent to dosing and through the 24-hour post-dosing period in their headache diary. Adverse event information was also elicited at the follow-up visit.

Reviewer: Adverse event recording in the US study described above is likely more accurate than the adverse event recording in the European study, in which adverse events occurring more than 8 hours after dosing were not recorded until the follow-up clinic visit.

Additional safety assessments are listed in the study schedule (Table 12). Clinical laboratory evaluations were not performed.

Table 12: Study Schedule, US Phase 3 Study

Table 9.5.1-1: Evaluation and Visit Schedule

Assessment	Visit 1 Subject Selection	At Home	Treatment/Evaluation Phase (at Home)													Visit 2 Follow-up
			Pre	15 m	30 m	45 m	1 hr	1.5 hr	2 hr	2.5 hr	3 hr	4 hr	8 hr	16 hr	24 hr	
Informed Consent	X															
Demographic Data	X															
Physical Exam	X															
Medical History	X															
Brief Neurological Exam	X															
Prior and Concomitant Medications	X															
Inclusion/Exclusion Criteria	X															
Urine Pregnancy Test (females)	X															
Subject Training *	X															
Issue Headache Diary	X															
Issue Study Medication	X															
Telephone Follow-up **		X														
Use Study Medication		X	X													
Headache Diary		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Schedule Follow-up Visit															X	
Review Headache Diary																X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Collect/Inventory Study Medication																X

*The subjects were instructed that at the end of the treatment phase (24 hours after dosing) to call the investigational site to schedule a follow-up visit as soon as possible, but within approximately 1 week after dosing. The subjects were instructed to return to the investigational site if study medication was not used within approximately 8 weeks of enrollment. At the discretion of the Investigator, this 8-week treatment window could be extended to 12 weeks.

**The Investigator or designee was to contact the subject approximately every 2 weeks following Visit 1 to assess if the subject had treated a migraine attack.

Number of Subjects

- 690 subjects
 - PRO-513 343
 - Placebo 347

6.1.4 Efficacy Findings

European Phase 3 Study

Study Execution

In this 3-arm crossover study, 328 patients were randomized, with exposure of 291 to PRO-513, 298 to Cataflam 50 mg, and 299 to placebo. 274 patients treated all three migraine attacks.

Of 337 patients screened, 328 were randomized, and only 11 randomized were not treated.

In each arm, about 7% of doses had at least one major protocol violation. About 2% of subjects in each arm took study medication within 48 hours after end of last migraine attack. There was a low percentage of missing pain assessments at baseline and after drug intake, about 1%, but about 1/3 of diaries had at least one missing diary assessment in each arm.

Reviewer: Study execution appears acceptable.

Baseline Migraine Characteristics

Table 13 shows predose migraine characteristics of the 3 arms.

Table 13: Predose Migraine Characteristics, European Phase 3 Study

	(b) (4) (N = 291)	CATAFLAM (N = 298)	Placebo (N = 299)
Early migraine symptoms			
Yes - n (%)	205 (70.4)	208 (69.8)	201 (67.2)
Time prior to drug intake (min) - mean (SD) ^b	210 (339)	222 (353)	238 (452)
Median (Q25 -Q75) ^b	90 (30-240)	90 (30-245)	90 (30-247)
Migraine aura symptoms			
Yes - n (%)	54 (18.6)	52 (17.4)	57 (19.1)
Time prior to drug intake (min) - mean (SD) ^b	315 (782)	271 (528)	277 (531)
Median (Q25 -Q75) ^b	90 (30-330)	80 (40-235)	90 (20-240)
Accompanying symptoms - n (%)			
Nausea	167 (57.4)	166 (55.7)	168 (56.2)
Vomiting	23 (7.9)	24 (8.1)	26 (8.7)
Photophobia	184 (63.2)	188 (63.1)	183 (61.2)
Phonophobia	160 (55.0)	167 (56.0)	158 (52.8)
None	38 (13.1)	48 (16.1)	39 (13.0)
Missing data	6 (2.1)	5 (1.7)	2 (0.7)
Headache intensity			
VAS (mm) - mean (SD)	67.2 (22.9)	67.3 (23.2)	67.7 (24.0)
VAS (mm) - range	0-100	8-100	8-100
Verbal scale: None - n (%)	1 (0.3)	0 (0.0)	0 (0.0)
Verbal scale: Mild - n (%)	23 (7.9)	30 (10.1)	40 (13.4)
Verbal scale: Moderate - n (%)	153 (52.6)	146 (49.0)	133 (44.5)
Verbal scale: Severe - n (%)	112 (38.5)	119 (39.9)	124 (41.5)
Verbal scale: Missing - n (%)	2 (0.7)	3 (1.0)	2 (0.7)
Working ability - n (%)			
Normal	14 (4.8)	15 (5.0)	25 (8.4)
Mild impairment	117 (40.2)	116 (38.9)	100 (33.4)
Severe impairment	115 (39.5)	108 (36.2)	113 (37.8)
Bed rest required	34 (11.7)	54 (18.1)	55 (18.4)
Missing assessment	11 (3.8)	5 (1.7)	6 (2.0)

^a (b) (4) is the name used for the PRO-513 formulation in the Novartis-conducted studies.

^b Considering patients with symptoms only. Q25 / Q75 = 25% / 75% quantile, respectively.

Reviewer:

Predose migraine characteristics were similar among the 3 arms. While the European phase 3 study did not require pain to be at least moderate intensity before treating a headache with study medication, more than 85% of treated headaches were of moderate or severe pain intensity when treated. This is reassuring that treated headaches were similar to those that would be treated in practice if the drug is approved.

Primary Outcome Variable

Table 14 shows the sponsor's analysis of PRO-513 versus placebo, conducted according to the FDA request in the April 18, 2008 teleconference for re-analysis taking into consideration possible effects of the crossover design.

Reviewer: The 2-hour key efficacy outcomes appear positive, without significant effects from study sequence.

Table 14: Sequence and Period Outcomes in Two-Way Crossover with (b) (4) and Placebo

[from statistical-analysis-response-to-2008418-fda-teleconference.pfd, page 7 of 13, table 2]

Pain free:

Placebo	(b) (4)	P-value
11.7% (35/299)	24.7% (72/291)	
	$\Delta=13.0\%$	<0.0001

P-value for sequence effect = 0.2866

Nausea free:

Placebo	(b) (4)	P-value
54.8% (164/299)	63.9% (186/291)	
	$\Delta=9.1\%$	0.0169

P-value for sequence effect = 0.4013

Photophobia free:

Placebo	(b) (4)	P-value
48.5% (145/299)	57.7% (168/291)	
	$\Delta=9.2\%$	0.0023

P-value for sequence effect = 0.9376

Phonophobia free:

Placebo	(b) (4)	P-value
52.8% (158/299)	63.9% (186/291)	
	$\Delta=11.1\%$	0.0015

P-value for sequence effect = 0.3963

Primary Efficacy Endpoints in First Study Period

Reviewer: The first period of the crossover study was analyzed separately from the remaining periods, which is equivalent to a parallel arm study 1/3rd the size of the whole trial. The first study period alone is thus expected to be statistically underpowered. First-period analysis by the FDA statistical reviewer showed numerical superiority for PRO-513 for all 4 key primary endpoints, and statistical superiority at $p \leq 0.05$ for pain and phonophobia. This result, free of any potential carry-over effects from the crossover design, supports the efficacy findings of the overall crossover study.

Descriptive Statistics: Primary Efficacy Endpoints by Sequence and Period

Reviewer: The percent of patients symptom-free was numerically higher for PRO-513 than for placebo for all 4 key-primary endpoints for each treatment sequence and time period (Table 15

and Table 16). This supports overall study efficacy, and argues against confounding sequence and period effects.

Table 15: Percent Symptom-Free by Sequence

Symptoms	Sequence	PRO-513	Placebo
Pain	S/T/P	28.0%	13.7%
	T/P/S	24.4%	14.9%
	P/S/T	21.3%	6.8%
Nausea	S/T/P	64.4%	59.1%
	T/P/S	69.5%	50.6%
	P/S/T	60.7%	54.9%
Photophobia	S/T/P	57.8%	54.6%
	T/P/S	56.1%	42.9%
	P/S/T	61.9%	52.7%
Phonophobia	S/T/P	66.7%	58.0%
	T/P/S	64.6%	47.2%
	P/S/T	63.1%	51.6%

Source; Statistical Reviewer’s Analysis

Table 16: Percent Symptom-Free by Period

Symptoms	Period	PRO-513	Placebo
Pain	1	28.0%	6.8%
	2	21.3%	14.9%
	3	24.2%	13.7%
Nausea	1	64.4%	54.9%
	2	60.7%	50.6%
	3	69.5%	59.1%
Photophobia	1	57.8%	52.7%
	2	61.9%	42.9%
	3	56.1%	54.6%
Phonophobia	1	66.7%	51.6%
	2	63.1%	47.3%
	3	64.6%	58.0%

Source: Statistical Reviewer’s Analysis

Study Site Effects

Reviewer: The ‘Pain free at 2 hours’ endpoint was examined by study sited by this reviewer to identify potential site effects (Table 17). Study results were consistent across sites: no sites showed more patients with no pain for placebo than for drug, and six sites showed the same number with no pain in each arm. There was no indication that these differences among centers arose other than by chance. (Note: centers with relatively large drug benefit are in bold).

Table 17: Pain Free at 2 Hours by Study Site, European Phase 3 Study

[From A-SECND]

Center 20

	Drug	Placebo
none	0	0
>none	7	11

Center 22

	Drug	Placebo
none	1	1
>none	4	5

Center 23

	Drug	Placebo
none	2	0
>none	9	12

Center 24

	Drug	Placebo
none	6	4
>none	15	16

Center 25

	Drug	Placebo
none	1	1
>none	20	18

Center 30

	Drug	Placebo
none	3	3
>none	14	14

Center 31

	Drug	Placebo
none	7	3
>none	11	15

Center 32

	Drug	Placebo
none	7	5
>none	17	19

Center 33

	Drug	Placebo
none	2	1
>none	6	6

Center 35

	Drug	Placebo
none	4	3
>none	8	9

Center 41

	Drug	Placebo
--	------	---------

none	4	1
>none	12	16

Center 42

	Drug	Placebo
none	6	3
>none	13	15

Center 43

	Drug	Placebo
non	5	1
>none	16	22

Center 44

	Drug	Placebo
none	2	0
>none	5	6

Center 50

	Drug	Placebo
none	0	0
>none	1	4

Center 52

	Drug	Placebo
none	2	1
>none	16	17

Center 60

	Drug	Placebo
none	3	1
>none	7	9

Center 61

	Drug	Placebo
none	3	1
>none	8	10

Center 62

	Drug	Placebo
none	3	3
>none	5	7

Center 63

	Drug	Placebo
none	8	3
>none	16	21

Center 64

	Drug	Placebo
none	3	0
>none	9	12

KEY SECONDARY OUTCOME VARIABLE EFFICACY

For the key secondary outcome of ‘sustained pain free at 24 hours’(pain free at 2 hours and no recurrence of headache and intake of rescue medication within 24 hours post-dose) the sponsor reports superiority for study drug versus placebo: 22.3% of study drug patients meeting criteria versus 9.4% for placebo, $p < 0.0001$.

Efficacy by Demographics

Table 18 shows the sponsor’s analysis of the primary outcome by age, gender, and presence of Aura. Most, but not all endpoints were positive for each subgroup analyzed.

Table 18: Efficacy by Age, Gender, and Presence of Aura, European Phase 3 Study**Table 3.3.3-1: Analysis of the Migraine Variables by Subgroup in Study CAT458C2301 (ITT Subjects)**

	Males		Females	
	(b) (4)	Placebo	(b) (4)	Placebo
Number of Subjects	41	42	250	257
No Headache Pain ^a	9 (22.0%)	4 (9.5%)	63 (25.2%)	31 (12.1%)
No Nausea ^a	32 (78.0%)	27 (64.3%)	154 (61.6%)	139 (54.1%)
No Photophobia ^a	22 (53.7%)	24 (57.1%)	147 (58.8%)	123 (47.9%)
No Phonophobia ^a	27 (65.9%)	25 (59.5%)	160 (64.0%)	134 (52.1%)
	Age: (< 39 Years)		Age: (≥ 39 Years)	
	(b) (4)	Placebo	(b) (4)	Placebo
Number of Subjects	148	146	143	153
No Headache Pain ^a	42 (28.4%)	18 (12.3%)	30 (21.0%)	17 (11.1%)
No Nausea ^a	93 (62.8%)	88 (60.3%)	93 (65.0%)	78 (51.0%)
No Photophobia ^a	89 (60.1%)	71 (48.6%)	80 (55.9%)	76 (49.7%)
No Phonophobia ^a	98 (66.2%)	81 (55.5%)	89 (62.2%)	78 (51.0%)
	With Aura		Without Aura	
	(b) (4)	Placebo	(b) (4)	Placebo
Number of Subjects	54	57	233	240
No Headache Pain ^a	18 (33.3%)	8 (14.0%)	54 (23.2%)	27 (11.3%)
No Nausea ^a	30 (55.6%)	32 (56.1%)	156 (67.0%)	134 (55.8%)
No Photophobia ^a	26 (48.1%)	26 (45.6%)	143 (61.4%)	119 (49.6%)
No Phonophobia ^a	31 (57.4%)	26 (45.6%)	155 (66.5%)	131 (54.6%)

^a Based on assessments at two-hours post-dose

Additional Secondary Efficacy Endpoints

Reviewer: The following secondary efficacy endpoints are supportive and/or exploratory endpoints.

- Sustained headache response (no recurrence/worsening or rescue medication within 24 hours)(Table 19)

The sponsor finds that for headache response at 2 hours (pain free at 2 hours or pain reduction from moderate or severe at baseline to mild at 2 hours) both PRO-513 and Cataflam 50 mg tablets showed clear, statistically significant superiority over placebo.

Reviewer: This endpoint is similar to the key secondary endpoint, except that it includes more patients than that endpoint by counting patients with a *reduction* in pain at 2 hours, not necessarily *pain free* at 2 hours. ('Headache response' also refers only to pain, and not to associated symptoms). The endpoint has a p-value <0.05 for study drug versus placebo, and appears supportive of the key secondary endpoint.

The sponsor also compared Cataflam to placebo, and compared PRO-513 to Cataflam, and found p-values <0.05 for both. Comparison of PRO-513 to Cataflam in this endpoint and those that follow is problematic because Cataflam is not approved for migraine; superiority of study drug to a drug that is not known to be effective in migraine is not clinically meaningful. In addition, this study specified dosing before meals or on an empty stomach, an unrealistic condition for acute migraine therapy. The relative efficacy of study drug and Cataflam might depend on fed status, as suggested by differences in PK of both drugs in fed and fasted state.

Table 19: Sustained Headache Response, European Phase 3 Study

[from cat458c2301-legacy-report.pdf]

Table 9-2 Number (%) of patients with headache response at 2 hours post-dose, sustained headache response, and sustained pain free (ITT population)

Variable	Treatment ^a / Treatment contrast ^b	N	Number (%) of patients		p-value ^c
			n (%)	95% CI (%)	
Headache response at 2 hours	Dic-K Sachet	291	134 (46.0)	40.2 – 52.0	-
	Dic-K Tablet	298	124 (41.6)	36.0 – 47.4	-
	Placebo	299	72 (24.1)	19.3 – 29.3	-
	Dic-K Sachet – Placebo	279	59 (21.1)	14.1 – 28.2	<0.0001
	Dic-K Sachet – Dic-K Tablet	281	14 (5.0)	-2.0 – 11.9	0.1156
	Dic-K Tablet – Placebo	285	49 (17.2)	10.5 – 23.9	<0.0001
Sustained headache response	Dic-K Sachet	291	107 (36.8)	31.2 – 42.6	
	Dic-K Tablet	298	92 (30.9)	25.7 – 36.5	
	Placebo	299	55 (18.4)	14.2 – 23.3	
	Dic-K Sachet – Placebo	279	51 (18.3)	11.9 – 24.7	<0.0001
	Dic-K Sachet – Dic-K Tablet	281	17 (6.0)	-0.5 – 12.6	0.0227
	Dic-K Tablet – Placebo	285	36 (12.6)	6.7 – 18.6	<0.0001
Sustained pain free	Dic-K Sachet	291	65 (22.3)	17.7 – 27.6	
	Dic-K Tablet	298	45 (15.1)	11.2 – 19.7	
	Placebo	299	28 (9.4)	6.3 – 13.2	
	Dic-K Sachet – Placebo	279	36 (12.9)	7.8 – 18.0	<0.0001
	Dic-K Sachet – Dic-K Tablet	281	22 (7.8)	2.1 – 13.6	0.0005
	Dic-K Tablet – Placebo	285	15 (5.3)	0.4 – 10.1	0.0077

Headache response at 2 hours = pain free at 2 hours or pain reduction from moderate or severe at baseline to mild at 2 hours

Sustained headache response = headache response at 2 hours and no recurrence/worsening of headache and intake of rescue medication within 24 hours post-dose

Sustained pain free = pain free at 2 hours and no recurrence of headache and intake of rescue medication within 24 hours post-dose

CI = confidence interval

^a considering all patients on the respective treatment

^b considering only those patients who received both of the compared treatments, n is the difference of the number of responders

^c two-sided for pairwise treatment comparison, derived from a logistic regression analysis with explanatory variables treatment, period, patient, and baseline VAS headache intensity

- Time to onset of analgesic effect assessed using a VAS of headache intensity

The sponsor states that time to onset of analgesic effect defined as first significant difference to placebo on the VAS was at 15 minutes for diclofenac-K sachets and at 60 minutes for diclofenac-K tablets. Diclofenac-K sachets were also statistically significantly more effective than diclofenac-K tablets regarding the VAS headache reduction between 15 and 90 minutes post-dose and were only slightly above the significance level at 2 and 3 hours post-dose. Thereafter the difference between sachets and tablets diminished but the mean headache reduction was always highest on diclofenac-K sachets.

Reviewer: This might be consistent with earlier T_{max} of PRO-513 versus the diclofenac tablets. While apparently statistically significant, the VAS differences between study drug and diclofenac tablets were not large and are of uncertain clinical meaning.

- Headache response at 2 hours post-dose (pain free or reduction from moderate or severe to mild)

The sponsor notes that headache response at 2 hours post-dose was 46% for PRO-513, 41.6% for Cataflam, and 24.1% for placebo. The difference between PRO-513 and Cataflam was not statistically significant.

Reviewer: This supports the primary endpoint which considered (as one of 4 co-primary endpoints) pain-free at 2 hours. The comparison between PRO-513 and Cataflam shows similar efficacy for headache pain response at 2 hours.

[note: the following two endpoints considered together]

- Reduction of VAS headache intensity from baseline at single time points to 8 hours post-dose
- Average reduction of VAS headache intensity during the first 2, 4, and 8 hours post-dose

The sponsor states that PRO-513 had during each time period the highest average VAS headache reduction, which was also statistically significant in comparison to diclofenac-K tablets during the first 2 and 4 hours but not throughout the entire 8-hour post-dose period.

Reviewer: This might be consistent with later T_{max} of the diclofenac tablets versus PRO-513.

- Change of headache intensity from baseline on a verbal scale at 1, 2, and 8 hours post-dose

The sponsor notes improvements over placebo were also observed for both PRO-513 and diclofenac-K tablets at all time points (the percentage of patients who had improved from baseline at 2 hours post-dose was 58.4% for PRO-513, 53.5% for Cataflam tablets and 33.2% for placebo)(Table 20).

Reviewer: This endpoint generally supports the primary efficacy endpoint finding.

Table 20: Headache Intensity on 4-point Scale, US Phase 3 Study

Table 9-5 Change of headache intensity from baseline, as evaluated on a verbal scale at 1, 2, and 8 hours post-dose (ITT population)

Treatment	Time point	N	Number (%) of patients				Change from baseline		
			Headache intensity				Improved	None	Worse
			None	Mild	Moderate	Severe			
Dic-K Sachets	Predose	289	1 (0.3)	23 (8.0)	153 (52.9)	112 (38.8)			
	1 hour	257	31 (12.1)	80 (31.1)	91 (35.4)	55 (21.4)	125 (48.6)	118 (45.9)	14 (5.4)
	2 hour	255	63 (24.7)	73 (28.6)	68 (26.7)	51 (20.0)	149 (58.4)	88 (34.5)	18 (7.1)
	8 hour ^a	144	86 (59.7)	23 (16.0)	20 (13.9)	15 (10.4)	115 (79.9)	19 (13.2)	10 (6.9)
Dic-K Tablets	Predose	295	0 (0.0)	30 (10.2)	146 (49.5)	119 (40.3)	-	-	-
	1 hour	252	21 (8.3)	62 (24.6)	99 (39.3)	70 (27.8)	103 (40.9)	122 (48.4)	27 (10.7)
	2 hour	258	48 (18.6)	76 (29.5)	69 (26.7)	65 (25.2)	138 (53.5)	92 (35.7)	28 (10.9)
	8 hour ^a	163	85 (52.1)	31 (19.0)	25 (15.3)	22 (13.5)	120 (73.6)	36 (22.1)	7 (4.3)
Placebo	Predose	297	0 (0.0)	40 (13.5)	133 (44.8)	124 (41.8)			
	1 hour	267	12 (4.5)	63 (23.6)	97 (36.3)	95 (35.6)	66 (24.8)	172 (64.7)	28 (10.5)
	2 hour	267	34 (12.7)	58 (21.7)	74 (27.7)	101 (37.8)	88 (33.2)	141 (53.2)	36 (13.6)
	8 hour ^a	129	55 (42.6)	27 (20.9)	20 (15.5)	27 (20.9)	85 (65.9)	33 (25.6)	11 (8.5)

^a 8 hour or early termination

- Presence of nausea, vomiting, photophobia, and phonophobia at 1, 2, 4, 6, and 8 hours post-dose

The sponsor states that overall at 2 hours post-dose nausea, vomiting, photophobia, and phonophobia were reduced with both PRO-513 and Cataflam tablets when compared to placebo, and treatment differences were slightly in favor of PRO-513 compared to Cataflam tablets for presence of nausea, vomiting and photophobia (Table 21). A marked placebo effect for reduction in nausea and photophobia was also observed. Over the remaining post-dose treatment period (up to 8 hours) there remained an overall trend for a greater reduction in the presence of accompanying symptoms with PRO-513 and Cataflam tablets than for placebo

Table 21: Associated Migraine Symptoms, 1, 2, and 8 Hours Post Dose, US Phase 3 Study

Table 9-6 Presence of nausea, vomiting, photophobia and phonophobia at predose, 1, 2 and 8 hours post-dose and after drug intake (ITT population)

Treatment	Time point	N	Number (%) of patients				
			Nausea	Vomiting	Photophobia	Phonophobia	None
Dic-K Sachets	Predose	285	167 (58.6)	23 (8.1)	184 (64.6)	160 (56.1)	38 (13.3)
	1 hour	253	104 (41.1)	20 (7.9)	125 (49.4)	104 (41.1)	72 (28.5)
	2 hour	253	87 (34.4)	16 (6.3)	104 (41.1)	89 (35.2)	106 (41.9)
	8 hour ^a	147	25 (17.0)	8 (5.4)	27 (18.4)	27 (18.4)	100 (68.0)
	After drug intake ^b	282 ^c	127 (45.0)	33 (11.7)	146 (52.0)	126 (44.8)	82 (29.1)
Dic-K Tablets	Predose	293	166 (56.7)	24 (8.2)	188 (64.2)	167 (57.0)	48 (16.4)
	1 hour	255	118 (46.3)	21 (8.2)	134 (52.5)	107 (42.0)	70 (27.5)
	2 hour	259	101 (39.0)	20 (7.7)	112 (43.2)	90 (34.7)	105 (40.5)
	8 hour ^a	162	20 (12.3)	7 (4.3)	37 (22.8)	31 (19.1)	115 (71.0)
	After drug intake ^b	291	144 (49.5)	32 (11.0)	156 (53.6)	130 (44.7)	76 (26.1)
Placebo	Predose	297	168 (56.6)	26 (8.8)	183 (61.6)	158 (53.2)	39 (13.1)
	1 hour	257	128 (49.8)	26 (10.1)	137 (53.3)	127 (49.4)	59 (23.0)
	2 hour	270	123 (45.6)	26 (9.6)	137 (50.7)	129 (47.8)	80 (29.6)
	8 hour ^a	135	30 (22.2)	8 (5.9)	41 (30.4)	32 (23.7)	81 (60.0)
	After drug intake ^b	294	159 (54.1)	39 (13.3)	164 (55.8)	158 (53.7)	59 (20.1)

^a 8 hour or early termination

^b presence of a symptom on at least 1 post-dose time point reported in the diary or as AE within 8-72 hours post-dose (or the absence from all symptoms after taking study medication).

^c N = 281 for vomiting, photophobia, and phonophobia

Reviewer: This endpoint generally supports the primary efficacy endpoint finding. Efficacy of PRO-513 versus Cataflam tablets for these migraine-associated symptoms was similar, with any efficacy advantage of study drug of questionable clinical meaning.

- Working / functional ability evaluated on a verbal scale at 2 and 8 hours post-dose

The sponsor states that the total proportion of patients with mild impairment, severe impairment and bed rest required was roughly similar at baseline, with slightly greater improvements in the proportion of normal patients on treatment with PRO-513 than on treatment with diclofenac-K tablets at 2 hours and 8 hours post-dose. The worst treatment results were seen on placebo (Table 22).

Table 22: Working Ability, US Phase 3 Study

Treatment	Time point	N	Number (%) of patients			
			Normal	Mild impairment	Severe impairment	Bed rest required
Dic-K Sachets	Predose	280	14 (5.0)	117 (41.8)	115 (41.1)	34 (12.1)
	2 hour	251	84 (33.5)	88 (35.1)	60 (23.9)	19 (7.6)
	8 hour ^a	140	88 (62.9)	26 (18.6)	17 (12.1)	9 (6.4)
Dic-K Tablets	Predose	293	15 (5.1)	116 (39.6)	108 (36.9)	54 (18.4)
	2 hour	257	74 (28.8)	84 (32.7)	60 (23.3)	39 (15.2)
	8 hour ^a	164	92 (56.1)	37 (22.6)	22 (13.4)	13 (7.9)
Placebo	Predose	293	25 (8.5)	100 (34.1)	113 (38.6)	55 (18.8)
	2 hour	264	53 (20.1)	78 (29.5)	78 (29.5)	55 (20.8)
	8 hour ^a	130	73 (56.2)	19 (14.6)	16 (12.3)	22 (16.9)

^a 8 hour or early termination

Reviewer: This endpoint generally supports the primary efficacy finding.

- Use of rescue medication within 8 hours post-dose and time to use of rescue medication

The sponsor states that intake of rescue medication for PRO-513 and diclofenac-K tablets was generally comparable and was clearly lower than for placebo at all time points after 2 hours (Table 23).

Table 23: Use of Rescue Medication, US Phase 3 Study

Variable	Dic-K Sachet (N = 291)	Dic-K Tablet (N = 298)	Placebo (N = 299)
Number (%) of patients with rescue med. up to Hour 1	1 (0.3)	3 (1.0)	0 (0.0)
Number (%) of patients with rescue med. up to Hour 2	16 (5.5)	24 (8.1)	26 (8.7)
Number (%) of patients with rescue med. up to Hour 3	50 (17.2)	63 (21.1)	83 (27.8)
Number (%) of patients with rescue med. up to Hour 4	72 (24.7)	76 (25.5)	111 (37.1)
Number (%) of patients with rescue med. up to Hour 5	83 (28.5)	89 (29.9)	128 (42.8)
Number (%) of patients with rescue med. up to Hour 6	89 (30.6)	96 (32.2)	135 (45.2)
Number (%) of patients with rescue med. up to Hour 7	95 (32.6)	102 (34.2)	145 (48.5)
Number (%) of patients with rescue med. up to Hour 8	102 (35.1)	108 (36.2)	150 (50.2)
Time to first intake of rescue medication (min) ^a			
Mean (SD)	214.5 (100.6)	205.2 (104.9)	204.3 (94.7)
Median	183.0	172.5	180.0
Range	30 – 480	27 – 480	70 – 480

^a considering only those patients who used rescue medication, for 1 patient (Dic-K Sachet) the time was unknown

Reviewer: This endpoint generally supports the primary efficacy findings.

- Time to attack completely resolved

The sponsor states that median times to attack resolution were 330, 385, and 475 minutes on PRO-513, diclofenac-K tablets, and placebo, respectively

Reviewer: This endpoint generally supports the primary efficacy findings.

- Recurrence of attack within 24 and 48 hours

The sponsor states that recurrence rates within 48 hours after attack resolution were 15.5%, 21.8%, and 21.1% on PRO-513, diclofenac-K tablets, and placebo, respectively.

Reviewer: This endpoint generally supports the primary efficacy findings.

- Patient's global evaluation of medication.

The sponsor states that a higher percentage of patients receiving PRO-513 than either diclofenac-K tablets or placebo assessed their study medication as "good or "very good" (37.1%, 29.2% and 19.4% for diclofenac-K sachets, diclofenac-K tablets and placebo, respectively).

Reviewer: This endpoint generally supports the primary efficacy findings.

U.S. Phase 3 Study

Study Execution

Of 861 subjects screened, 834 were enrolled in the study, and 807 were randomized, 404 to PRO-513 and 403 to placebo.

Table 24 shows protocol deviations that excluded subjects from the intent-to-treat and/or per protocol population.

Table 24: Protocol Deviations, US Phase 3 Study

[from 513301.pdf]

Table 10.2-1: Summary of Protocol Deviations that Excluded Subjects from the Intent-to-Treat and/or Per-Protocol Population

	<u>PRO-513</u>	<u>Placebo</u>
Number of Subjects Randomized	404	403
<u>Intent-to-Treat</u>		
Number of Subjects Excluded from the ITT Population	61	56
Reason for Exclusion		
Did Not Treat a Headache	61	56
<u>Per-Protocol</u>		
Number of Subjects Excluded from the PP Population	15	19
Primary Exclusionary Deviation ^a		
Inappropriate Enrollment	0	1
Headache treated was not an eligible migraine attack	2	6
Subject used rescue medication within 2 hours of treatment	0	1
Subject used prohibited medication	2	2
Subject did not return to clinic following treatment	0	1
2-hour post-dose assessment off-schedule by more than 15 minutes	7	7
2-hour post-dose assessment was missing	3	1
Assessment times were not recorded after 30 minutes	1	0

^a Subjects may have more than one exclusionary deviation. A primary exclusionary deviation was assigned according to the deviation that had the greatest impact on clinical evaluations.

Reviewer: The number of patients with ‘per protocol’ violations was relatively small, suggesting that study execution was acceptable.

Baseline Migraine Characteristics

Table 25 shows pre-dose migraine characteristics for the US phase 3 study (not shown in the table is that 2% of PRO-513 arm patients experienced vomiting before dosing, versus 3.2% of placebo patients).

Table 25: Predose Migraine Characteristics, US Phase 3 Study

	PRO-513 (N=343)	Placebo (N=347)
Table 1.3.3-5: Predose Migraine Attack Characteristics for Subjects in PRO-513301		
Primary Migraine Diagnosis		
Migraine without aura	303 (88.3%)	297 (85.6%)
Migraine with aura	40 (11.7%)	50 (14.4%)
Headache Pain		
Moderate	250 (72.9%)	242 (69.7%)
Severe	93 (27.1%)	105 (30.3%)
Nausea		
None	119 (34.7%)	123 (35.4%)
Mild	146 (42.6%)	138 (39.8%)
Moderate	66 (19.2%)	78 (22.5%)
Severe	12 (3.5%)	8 (2.3%)
Photophobia		
None	10 (2.9%)	17 (4.9%)
Mild	105 (30.6%)	105 (30.3%)
Moderate	178 (51.9%)	162 (46.7%)
Severe	50 (14.6%)	63 (18.2%)
Phonophobia		
None	31 (9.0%)	17 (4.9%)
Mild	109 (31.8%)	106 (30.5%)
Moderate	156 (45.5%)	166 (47.8%)
Severe	47 (13.7%)	58 (16.7%)

Reviewer: While the US phase 3 study excluded from enrolment patients whose migraine was usually so severe as to require bed rest, or who normally experienced vomiting in more than 20% of headaches, still almost 1/3 of treated headaches were of severe pain intensity, and about 1/4 of treated headaches were accompanied by at least moderate nausea. This suggests that efficacy of study drug was tested in a relatively large number of more severe migraine attacks, even though some patients with the most severe symptoms might have been excluded from study participation.

Primary Outcome Variable

The sponsor indicates that all 4 co-primary outcomes were positive:

- Pain:
 - The percent of subjects in the PRO-513 group who had no headache pain at two-hours postdose was 25% compared to 10% in the placebo group (p<0.001)
- Nausea
 - The percent of subjects in the PRO-513 group who had no nausea at two-hours post-dose was 65% compared to 53% in the placebo group (p=0.002)
- Photophobia
 - The percent of subjects in the PRO-513 treatment group who had no photophobia at two hours post-dose was 41% compared to 27% in the placebo group (p<0.001)
- Phonophobia

- The percent of subjects in the PRO-513 group who had no phonophobia at two-hours postdose was 44% compared to 27% in the placebo group ($p < 0.001$).

Reviewer: The findings of the FDA statistical reviewer are in general agreement with the above calculations.

Key Secondary Outcome Variable

The sponsor indicates that the secondary outcome, pain-free response through 24 hours, was positive. In the PRO-513 group 19% of subjects met this endpoint compared to 7% in the placebo treatment group, $p < 0.001$.

Reviewer: The FDA statistical reviewer is in general agreement with the above calculations.

Efficacy by Demographics

Table 26 shows the sponsor's analysis of the primary outcome by age (less than or greater than median age), gender, and presence of Aura. Most, but not all endpoints were positive for each subgroup analyzed. In the US study, 80% of subjects were white, 16% African American, and 4% Asian, Native American, or other, preventing clear efficacy conclusions for non-white ethnicity.

Table 26: Efficacy by Age, Gender, and Presence of Aura, US Phase 3 Study

Table 3.3.3-2: Analysis of the Migraine Variables by Subgroup in Study PRO-513301 (ITT Subjects)				
	Males		Females	
	PRO-513	Placebo	PRO-513	Placebo
Number of Subjects	50	55	293	292
No Headache Pain ^a	11 (22.0%)	9 (16.4%)	75 (25.6%)	26 (8.9%)
No Nausea ^a	35 (70.0%)	36 (65.5%)	187 (63.8%)	147 (50.3%)
No Photophobia ^a	19 (38.0%)	17 (30.9%)	120 (41.0%)	78 (26.7%)
No Phonophobia ^a	19 (38.0%)	20 (36.4%)	133 (45.4%)	75 (25.7%)
	Age: (< 41 Years)		Age: (≥ 41 Years)	
	PRO-513	Placebo	PRO-513	Placebo
Number of Subjects	165	167	178	180
No Headache Pain ^a	41 (24.8%)	17 (10.2%)	45 (25.3%)	18 (10.0%)
No Nausea ^a	108 (65.5%)	91 (54.5%)	114 (64.0%)	92 (51.1%)
No Photophobia ^a	67 (40.6%)	46 (27.5%)	72 (40.4%)	49 (27.2%)
No Phonophobia ^a	74 (44.8%)	44 (26.3%)	78 (43.8%)	51 (28.3%)
	With Aura		Without Aura	
	PRO-513	Placebo	PRO-513	Placebo
Number of Subjects	44	43	297	297
No Headache Pain ^a	4 (9.1%)	5 (11.6%)	81 (27.3%)	27 (9.1%)
No Nausea ^a	19 (43.2%)	21 (48.8%)	201 (67.7%)	156 (52.5%)
No Photophobia ^a	9 (20.5%)	12 (27.9%)	128 (43.1%)	78 (26.3%)
No Phonophobia ^a	7 (15.9%)	10 (23.3%)	144 (48.5%)	80 (26.9%)

^a Based on assessments at two-hours post-dose

Reviewer: While all co-primary endpoints were not positive for all subgroups examined, there is little indication that such differences arose other than by chance.

Reviewer: The ‘Pain free at 2 hours’ endpoint was examined by study sited by this reviewer to identify potential site effects (Table 27). At 4 sites in the US study the number of patients with no pain in the placebo group was larger than the number with no pain in the drug group. Overall, study results for this key outcome variable across sites appeared consistent with random variation. (Centers with relatively large drug benefit are in bold).

Table 27: Pain Free at 2 Hours by Study site, US Phase 3 Study

[From ADEFF, HAPN2HR by RXCODEN by INV, 2 hour pain: 1= no pain; 2=pain]

Center 2

	Drug	Placebo
No pain	1	0
Pain	5	10

Center 3

	Drug	Placebo
No pain	7	1
Pain	20	25

Center 4

	Drug	Placebo
No pain	2	3
Pain	13	14

Center 5

	Drug	Placebo
No pain	4	0
Pain	5	8

Center 6

	Drug	Placebo
No pain	2	3
Pain	9	9

Center 7

	Drug	Placebo
No pain	5	1
Pain	5	6

Center 8

	Drug	Placebo
No pain	2	0
Pain	2	4

Center 9

	Drug	Placebo
No pain	0	1
Pain	4	4

Center 10

	Drug	Placebo
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No pain	3	1
	7	10

Center 11

	Drug	Placebo
No pain	12	3
Pain	20	31

Center 12

	Drug	Placebo
No pain	0	1
Pain	1	0

Center 13

	Drug	Placebo
No pain	2	1
Pain	16	15

Center 14

	Drug	Placebo
No pain	5	2
	8	15

Center 15

	Drug	Placebo
No pain	2	2
Pain	15	15

Center 16

	Drug	Placebo
No pain	3	0
Pain	20	19

Center 17

	Drug	Placebo
No pain	4	3
Pain	28	30

Center 18

	Drug	Placebo
No pain	0	0
Pain	3	3

Center 19

	Drug	Placebo
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No pain	12	3
Pain	15	21

Center 20

	Drug	Placebo
No pain	2	1
Pain	11	11

Center 21

	Drug	Placebo
No pain	10	9
Pain	21	24

Center 22

	Drug	Placebo
No pain	4	2
Pain	22	25

Center 23

	Drug	Placebo
No pain	0	0
Pain	0	1

Center 25

	Drug	Placebo
No pain	4	0
Pain	4	8

Additional Secondary Endpoints

Reviewer: The following secondary efficacy endpoints are supportive and/or exploratory endpoints.

- Time to headache recurrence

The sponsor states that for the subjects who were pain free at 2 hours post-dose, 24% (21/86) in the PRO-513 treatment group had a recurrence, defined as mild, moderate or severe pain and/or taking rescue medication within 24 hours, compared with 29% (10/35) in the placebo treatment group. For both treatment groups, the median time to recurrence was >24 hours.

Reviewer: This endpoint generally supports the primary efficacy findings.

- Pain intensity difference (PID+) at each evaluation (15, 30 and 45 minutes and 1, 1.5, 2, 2.5, 3, 4, 8, 16 and 24 hours post-dose)

The sponsor states that results for pain intensity differences (PIDs: pre-dose minus post-dose) were statistically significantly different between study drug and placebo starting at 30 minutes post-dose.

Reviewer: This endpoint generally supports the primary efficacy findings.

[note: next two endpoints considered together]

- Headache pain intensity at each evaluation time-point
- Intensity of nausea, photophobia and phonophobia at each evaluation time-point

Reviewer: The average migraine symptoms at each evaluation (Table 28) generally support the primary efficacy findings.

Table 28: Headache Pain, Nausea, Photophobia, and Phonophobia, US Phase 3 study

Table 11.4.1-5: Summary of Headache Pain, Nausea, Photophobia and Phonophobia Intensity Each Evaluation (Intent-to-Treat Subjects)

	PRO-513 (N=343)				Placebo (N=347)			
	Headache		Photo-	Phono-	Headache		Photo-	Phono-
	<u>Pain</u>	<u>Nausea</u>	<u>phobia</u>	<u>phobia</u>	<u>Pain</u>	<u>Nausea</u>	<u>phobia</u>	<u>phobia</u>
Pre-dose	2.3	0.9	1.8	1.6	2.3	0.9	1.8	1.8
15 Minutes	2.1	0.9	1.7	1.6	2.2	0.9	1.7	1.7
30 Minutes	1.9	0.8	1.5	1.4	2.0	0.9	1.6	1.6
45 Minutes	1.7	0.7	1.3	1.2	1.9	0.8	1.5	1.5
1 Hour	1.5	0.6	1.2	1.1	1.8	0.8	1.4	1.3
1.5 Hours	1.3	0.5	1.0	0.9	1.7	0.7	1.3	1.3
2 Hours	1.2	0.5	0.9	0.8	1.7	0.7	1.2	1.2
2.5 Hours	1.1	0.5	0.9	0.8	1.7	0.7	1.2	1.2
3 Hours	1.1	0.4	0.8	0.7	1.7	0.7	1.2	1.2
4 Hours	1.0	0.4	0.8	0.7	1.7	0.8	1.3	1.2
8 Hours	1.0	0.4	0.8	0.7	1.6	0.8	1.3	1.2
16 Hours	1.0	0.5	0.8	0.7	1.6	0.8	1.2	1.2
24 Hours	1.0	0.5	0.8	0.7	1.6	0.8	1.2	1.2

^a P-Value from an analysis of variance with factors of treatment and analysis center.

- Presence or absence of vomiting at each evaluation time-point

Reviewer: A low proportion of patients, from <1% to about 5%, experienced vomiting at each individual evaluation. Vomiting appeared similar for PRO-513 and placebo through 2 hours, with a possible trend of less vomiting in the PRO-513 arm at later time points through 24 hours. This generally supports the primary efficacy findings.

- Functional ability with regard to daily activities at each evaluation time-point.

Reviewer: This endpoint generally supports the primary efficacy endpoint findings. For example, at 2 hours, 5.5% of PRO-513 patients reported inability to perform daily activities compared to 10.1% for placebo.

6.1.5 Clinical Microbiology

Not applicable

6.1.6 Efficacy Conclusions

This review finds that the efficacy of PRO-513 has been adequately demonstrated in both the European and US phase 3 studies for the 4 co-primary endpoints and for the single key secondary endpoint:

- Co-primary endpoints: free of migraine pain, nausea, photophobia, and phonophobia at 2 hours
- Key secondary endpoint: Sustained pain free (pain free at 2 hours and no recurrence or rescue medication within 24 hours)

In contrast, this review does not find valid the claim that study drug is superior to Cataflam 50 mg, for the following reasons:

- Cataflam 50 mg is not FDA approved for migraine. A superiority claim versus a product not known to be effective in migraine is not meaningful. Multiple studies, including the current European phase 3 study, failed to demonstrate the efficacy of Cataflam 50 mg in migraine at the key co-primary endpoint of pain, nausea, photophobia, and phonophobia at 2 hours. While negative results are always difficult to interpret, available data thus suggests that Cataflam 50 mg may be ineffective in migraine.
- A superiority claim in migraine would need to establish *clinically meaningful* superiority for all 4 key migraine symptoms; the sponsor's VAS comparison for migraine pain does not adequately address either clinical meaningfulness of differences in the VAS for pain, and does not address nausea, photophobia, and phonophobia at all.
- A superiority claim for a symptomatic condition would generally need to be supported by 2 adequate studies; the current superiority comparison is based only on the European phase 3 study.
- Statistical analysis of the superiority claim in the European phase 3 study did not appear adequate to protect overall study alpha; a step-down procedure for secondary outcome variables may have been implied, but did not appear to be clearly pre-specified.
- In the study comparing efficacy of PRO-513 to Cataflam 50 mg, patients were instructed to take drug/placebo before meals or on an empty stomach. Such a dosing condition for an acute migraine treatment is inappropriate because onset of migraine is unpredictable, and patients would often take acute migraine treatment not on an empty stomach. The C_{max} of PRO-513 in PK studies was higher than Cataflam 50 mg in the fasted state, but lower in the fed state. Relative efficacy for PRO-513 might therefore have been exaggerated in this study compared to what would be expected in clinical practice.

Limitations of Available Data and Generalizability

Migraine severity

The US phase 3 study excluded patients whose usual migraine was severe enough to require bed rest or caused vomiting in 20% or more of attacks. Efficacy data from patients with more severe migraine might thus be relatively underrepresented in the US study. However, the impact of this exclusion on overall generalizability of efficacy findings is likely mitigated by the following:

- In the European phase 3 study such a condition was not imposed, such that patients with history of more severe symptoms should have been represented in the overall drug development program.
- Given the subjective nature of ‘need for bed rest’ the exclusion criteria likely did not effectively separate migraine severity sub-populations. The severity of baseline symptoms of patients in the US study generally reflected those expected of migraine patients in general.
- The attempt to exclude patients that regularly vomit from migraine may be clinically reasonable for an oral migraine therapy.

Fed status

The European phase 3 study specified that patients should take study drug/placebo on an empty stomach or before meals. This condition is unrealistic for acute migraine treatment, which would be needed at unpredictable times. The pharmacokinetics of PRO-513 is affected by fed state, in particular with a higher C_{max} in the fasted versus the fed state. While the importance of C_{max} on efficacy is unknown, there might be concern that the lower C_{max} in fed state could adversely affect efficacy. However, to speculate, just as taking acute migraine treatment on an empty stomach is unrealistic in a normal clinical setting, it was probably poorly adhered to in the European study. While time of eating wasn’t recorded, headache onset was spread fairly evenly across normal waking hours (not shown: data table ASS, column ASS1T), suggesting that study drug would likely often have been taken within a few hours or less of eating. Thus, the European study could be speculated to represent more closely normal clinical than suggested by the study protocol.

The US phase 3 study, in contrast to the European study, did not specify that study drug/placebo should be taken on an empty stomach or before meals. The fact that PRO-513 was effective in the US study is also reassuring that the drug is effective even if not taken on an empty stomach.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

No deaths were reported during any of the 5 clinical trials submitted in this NDA.

7.1.2 Other Serious Adverse Events

No serious adverse events were reported during any of the 5 clinical trials submitted in this NDA.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The phase 3 studies exposed patients to only a single dose of PRO-513, and therefore by definition had no dropouts of patients who had received PRO-513 (one patient in the US phase 3 study was lost to follow-up after taking 1 dose of placebo). However, since the European phase 3 migraine study was a crossover study in which 3 migraine attacks were treated (with PRO-513, Cataflam 50 mg, or placebo) the following dropouts occurred:

- 28 patients did not experience 3 migraine attacks and were considered as discontinuations
- 6 patients withdrew consent, 3 of whom had been treated with PRO-513
- 6 patients withdrew due to adverse events, 2 of whom had been treated with PRO-513. These two patients discontinued due to urticaria (1 patient) and vomiting (1 patient, immediately after taking study medication). The 3 Cataflam patients discontinued due to vomiting (1 patient), hematuria (1 patient), and urticaria (1 patient). One placebo patient withdrew due to eye swelling.
- 3 patients treated with placebo were lost to follow-up

In the bioavailability study CAT458C2101, there were 3 dropouts characterized by the sponsor as ‘subject refusal’ for ‘personal reasons that were unrelated to the conduct of the trial.’ (There were no dropouts in the other bioavailability study).

Reviewer:

Mainly single-dose exposure of patients to PRO-513 limits dropout data. Urticaria and vomiting, the two adverse events linked most closely to dropout of patients treated with PRO-513, are adverse events listed in current Cataflam labeling. Vomiting is also common in patients with migraine, and this patient had nausea as part of the treated migraine attack. Patient narratives for these dropouts were otherwise unremarkable.

7.1.3.2 Adverse events associated with dropouts

See 7.1.3.1

7.1.3.3 Other significant adverse events

A larger number of non-serious psychiatric adverse events occurred in PRO-513 than placebo treated patients in the US phase 3 study, 9 events versus 1. This imbalance in psychiatric events was not observed in the other studies:

- In the European phase 3 study, there were no psychiatric adverse events in any arm (see also listing of common adverse events, Section 7.1.5).
- In the bioavailability study CAT458C2101 (N = 24, 2 doses each subject), there were no psychiatric events in the (b) (4) arm, and one in the Cataflam arm (insomnia).
- In the bioavailability study PRO-513101 (N = 34-35, 4 doses each subject), there was one psychiatric event in the PRO-513 arm (aggression) and none in the Cataflam arm.
- In the dental pain study (CAT458C2302) there were no psychiatric adverse events in any arm.

The psychiatric adverse events in the US phase 3 study were as follows:

PRO-513 arm

- Agitation (2 patients)
- Anxiety (1 patient)
- Confusional state (1 patient)
- Déjà vu (1 patient)
- Insomnia (3 patients)
- Nervousness (1 patient)
- Restlessness (3 patients)

Placebo arm

- Disorientation (1 patient)

The sponsor notes that these psychiatric events were still rare, and with the exception of agitation, déjà vu, disorientation, and restlessness are described in current Cataflam labeling.

Reviewer:

- The psychiatric adverse events were in most cases of mild or moderate severity (only 1 event, insomnia, was severe in 1 patient), and resolved spontaneously within a few hours. The events appear to fall within acceptable risk/benefit considerations for acute migraine therapy.
- Most of the events correspond to “additional adverse experiences” listed in current Cataflam labeling⁷. Potentially both PRO-513 and Cataflam may be associated with a higher incidence of non-serious psychiatric adverse events than placebo.
- In the diclofenac/sumatriptan study (Section 5.3, page 22), psychiatric adverse events were more frequent in the 50 mg versus the 100 mg diclofenac arms; since it seems

⁷ Additional adverse experiences reported occasionally include: *Nervous System*: anxiety, asthenia, confusion, depression, dream abnormalities, drowsiness, insomnia, malaise, nervousness, paresthesia, somnolence, tremors, vertigo

unlikely that 50 mg diclofenac is truly associated with more psychiatric adverse events than 100 mg diclofenac, this may illustrate that the findings in the present study of PRO-513 fall within that expected for random effects in this population.

7.1.4 Other Search Strategies

None.

7.1.5 Common Adverse Events

Reviewer: The European phase 3 study collected adverse events data potentially less accurately than the US study (described under ‘Study Design,’ section 6.1.3. Therefore, adverse events rates are analyzed separately for each study.

European Phase 3 Study

The sponsor states that the overall rate of AEs was low, that events tended to be of mild or moderate severity, and that the most common adverse events were not unexpected given current Cataflam labeling. The sponsor concludes that PRO-513 was safe and well-tolerated.

Table 29 shows adverse events in the European Phase 3 study by system organ class, and Table 30 shows adverse events by preferred term.

Reviewer: The number and type of adverse events were similar for all three treatments, PRO-513, Cataflam, and placebo. No safety signals or safety differences among arms were apparent from single dose treatment.

Table 29: AEs by System Organ Class, European Phase 3 Study

Table 10-1 Number (%) of patients with AEs overall and by MedDRA system organ class (safety population)

	Dic-K Sachet n (%)	Dic-K Tablet n (%)	Placebo n (%)
Patients studied			
Total no. of patients	291 (100.0)	298 (100.0)	299 (100.0)
Total no. with AEs	14 (4.8)	15 (5.0)	22 (7.4)
MedDRA system organ class			
Gastrointestinal disorders	10 (3.4)	7 (2.3)	13 (4.3)
Nervous system disorders	5 (1.7)	2 (0.7)	5 (1.7)
Skin and subcutaneous tissue disorders	2 (0.7)	2 (0.7)	2 (0.7)
Infections and infestations	1 (0.3)	0 (0.0)	2 (0.7)
Cardiac disorders	0 (0.0)	1 (0.3)	0 (0.0)
Ear and labyrinth disorders	0 (0.0)	1 (0.3)	2 (0.7)
Eye disorders	0 (0.0)	1 (0.3)	2 (0.7)
General disorders and administration site conditions	0 (0.0)	1 (0.3)	1 (0.3)
Investigations	0 (0.0)	0 (0.0)	1 (0.3)
Renal and urinary disorders	0 (0.0)	1 (0.3)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	1 (0.3)	2 (0.7)

Patients are only counted once per treatment in each MedDRA system organ class regardless of the number of AEs experienced in that organ class. AEs were assigned according to their date of onset to the last treatment taken within 72 hours post-dose. Accompanying symptoms (nausea, vomiting, photophobia, phonophobia) experienced within 8 hours post-dose were not recorded as AEs, only if they continued over the 8 hour time period.

Source: PT table 10.1-1

Table 30: AEs by Preferred Term, European Phase 3 Study

CCAT458C 2301

Post-text table 10.1-1 (Page 1 of 3)
Number of patients with adverse events, summarized by MedDRA system organ class and preferred term
Population: Safety population

MedDRA system organ class MedDRA preferred term	Dic Sachet (N=291)		Dic Tablet (N=298)		Placebo (N=299)	
	n	(%)	n	(%)	n	(%)
No. of patients with at least one adverse event	14	(4.8)	15	(5.0)	22	(7.4)
Gastrointestinal disorders	10	(3.4)	7	(2.3)	13	(4.3)
Vomiting	3	(1.0)	1	(0.3)	1	(0.3)
Abdominal pain upper	2	(0.7)	0	(0.0)	3	(1.0)
Dyspepsia	2	(0.7)	1	(0.3)	1	(0.3)
Diarrhoea	1	(0.3)	1	(0.3)	4	(1.3)
Dry mouth	1	(0.3)	1	(0.3)	1	(0.3)
Hypoaesthesia oral	1	(0.3)	0	(0.0)	0	(0.0)
Nausea	1	(0.3)	1	(0.3)	3	(1.0)
Abdominal pain	0	(0.0)	1	(0.3)	1	(0.3)
Gastritis	0	(0.0)	0	(0.0)	1	(0.3)
Glossitis	0	(0.0)	1	(0.3)	0	(0.0)
Nervous system disorders	5	(1.7)	2	(0.7)	5	(1.7)
Dizziness	2	(0.7)	1	(0.3)	0	(0.0)
Ageusia	1	(0.3)	0	(0.0)	0	(0.0)
Paraesthesia oral	1	(0.3)	0	(0.0)	0	(0.0)
Somnolence	1	(0.3)	1	(0.3)	3	(1.0)
Tremor	1	(0.3)	0	(0.0)	1	(0.3)
Paraesthesia	0	(0.0)	0	(0.0)	1	(0.3)
Skin and subcutaneous tissue disorders	2	(0.7)	2	(0.7)	2	(0.7)
Hyperhidrosis	1	(0.3)	1	(0.3)	1	(0.3)
Urticaria	1	(0.3)	1	(0.3)	0	(0.0)
Skin reaction	0	(0.0)	0	(0.0)	1	(0.3)

Patients are only counted once per treatment in each MedDRA system organ class regardless of the number of AEs experienced in that organ class. AEs were assigned according to their date of onset to the last treatment taken within 72 hours post-dose. Accompanying symptoms (nausea, vomiting, photophobia, phonophobia) experienced within 8 hours post-dose were not recorded as AEs, only if they continued over the 8 hour time period.

CCAT458C 2301

Post-text table 10.1-1 (Page 2 of 3)
Number of patients with adverse events, summarized by MedDRA system organ class and preferred term
Population: Safety population

MedDRA system organ class MedDRA preferred term	Dic Sachet (N=291)		Dic Tablet (N=298)		Placebo (N=299)	
	n	(%)	n	(%)	n	(%)
Infections and infestations	1	(0.3)	0	(0.0)	2	(0.7)
Dysentery	1	(0.3)	0	(0.0)	1	(0.3)
Nasopharyngitis	0	(0.0)	0	(0.0)	1	(0.3)
Cardiac disorders	0	(0.0)	1	(0.3)	0	(0.0)
Tachycardia	0	(0.0)	1	(0.3)	0	(0.0)
Ear and labyrinth disorders	0	(0.0)	1	(0.3)	2	(0.7)
Tinnitus	0	(0.0)	0	(0.0)	1	(0.3)
Vertigo	0	(0.0)	1	(0.3)	1	(0.3)
Eye disorders	0	(0.0)	1	(0.3)	2	(0.7)
Eye irritation	0	(0.0)	1	(0.3)	0	(0.0)
Eye swelling	0	(0.0)	0	(0.0)	1	(0.3)
Vision blurred	0	(0.0)	0	(0.0)	1	(0.3)
General disorders and administration site conditions	0	(0.0)	1	(0.3)	1	(0.3)
Fatigue	0	(0.0)	1	(0.3)	0	(0.0)
Rigors	0	(0.0)	0	(0.0)	1	(0.3)
Investigations	0	(0.0)	0	(0.0)	1	(0.3)
Blood pressure decreased	0	(0.0)	0	(0.0)	1	(0.3)
Renal and urinary disorders	0	(0.0)	1	(0.3)	0	(0.0)
Haematuria	0	(0.0)	1	(0.3)	0	(0.0)

Patients are only counted once per treatment in each MedDRA system organ class regardless of the number of AEs experienced in that organ class. AEs were assigned according to their date of onset to the last treatment taken within 72 hours post-dose. Accompanying symptoms (nausea, vomiting, photophobia, phonophobia) experienced within 8 hours post-dose were not recorded as AEs, only if they continued over the 8 hour time period.

CCAT458C 2301

Post-text table 10.1-1 (Page 3 of 3)
 Number of patients with adverse events, summarized by MedDRA system organ class and preferred term
 Population: Safety population

MedDRA system organ class MedDRA preferred term	Dic Sachet (N=291)		Dic Tablet (N=298)		Placebo (N=299)	
	n	(%)	n	(%)	n	(%)
Respiratory, thoracic and mediastinal disorders	0	(0.0)	1	(0.3)	2	(0.7)
Nasal mucosal disorder	0	(0.0)	0	(0.0)	1	(0.3)
Respiratory disorder	0	(0.0)	1	(0.3)	1	(0.3)

US Phase 3 Study

The sponsor states that 66 subjects in the PRO-513 treatment group and 52 subjects in the placebo treatment group reported adverse events subsequent to dosing. Most events (149) were mild to moderate in intensity, while 9 events were severe.

Table 31 shows adverse events in the European Phase 3 study by system organ class, and Table 32 shows adverse events by preferred term.

Table 31: AEs by System Organ Class, US Phase 3 Study

**Table 12.2.2-1: Summary of System Organ Classes with an Incidence $\geq 1\%$
 (Adverse Events with Onset Subsequent to Dosing)
 (Safety Subjects)**

Adverse Event ^a	PRO-513 (N=343)	Placebo (N=347)	P-Value ^b
Gastrointestinal disorders	41 (12.0%)	35 (10.1%)	0.467
General disorders and administration site conditions	5 (1.5%)	3 (0.9%)	0.503
Nervous system disorders	14 (4.1%)	14 (4.0%)	1.000
Psychiatric disorders	9 (2.6%)	1 (0.3%)	0.011

^a Counts reflect numbers of subjects reporting one or more adverse events classified to MedDRA (Version 9.1) system organ classes. At each level of summarization, subjects are only counted once.

^b Fisher's Exact test was used to compare the proportion of subjects in each treatment group who reported events, by system organ class, and by preferred term for those adverse events that were reported by at least one percent of the subjects in any treatment group.

Table 32: AEs by Preferred Term, US Phase 3 Study

Table 14.3.1.2.2: Summary of Adverse Events by System Organ Class and Preferred Term
(Adverse Events that Occurred Subsequent to Dosing)
(Safety Subjects)
(Page 1 of 3)

Adverse Event*	PRO-513 (N=343)	Placebo (N=347)
Ear and labyrinth disorders	0 (0.0%)	3 (0.9%)
Ear discomfort	0 (0.0%)	1 (0.3%)
Tinnitus	0 (0.0%)	2 (0.6%)
Gastrointestinal disorders	41 (12.0%)	35 (10.1%)
Abdominal distension	1 (0.3%)	1 (0.3%)
Abdominal pain	1 (0.3%)	1 (0.3%)
Abdominal pain upper	3 (0.9%)	1 (0.3%)
Diarrhoea	2 (0.6%)	4 (1.2%)
Dry mouth	2 (0.6%)	5 (1.4%)
Dyspepsia	5 (1.5%)	5 (1.4%)
Flatulence	0 (0.0%)	1 (0.3%)
Glossitis	1 (0.3%)	0 (0.0%)
Nausea	24 (7.0%)	15 (4.3%)
Stomach discomfort	1 (0.3%)	1 (0.3%)
Vomiting	5 (1.5%)	4 (1.2%)
General disorders and administration site conditions	5 (1.5%)	3 (0.9%)
Asthenia	1 (0.3%)	0 (0.0%)
Chest discomfort	0 (0.0%)	1 (0.3%)
Chest pain	0 (0.0%)	1 (0.3%)
Fatigue	1 (0.3%)	1 (0.3%)
Feeling abnormal	2 (0.6%)	0 (0.0%)

* Counts reflect numbers of subjects reporting one or more adverse events classified to MedDRA (Version 9.1) system organ classes and preferred terms. At each level of summarization (system organ class or preferred term) subjects are only counted once.

Table 14.3.1.2.2: Summary of Adverse Events by System Organ Class and Preferred Term
(Adverse Events that Occurred Subsequent to Dosing)
(Safety Subjects)
(Page 2 of 3)

Adverse Event*	PRO-513 (N=343)	Placebo (N=347)
General disorders and administration site conditions (continued)		
Irritability	1 (0.3%)	0 (0.0%)
Infections and infestations	1 (0.3%)	1 (0.3%)
Lower respiratory tract infection	0 (0.0%)	1 (0.3%)
Sinusitis	1 (0.3%)	0 (0.0%)
Injury, poisoning and procedural complications	1 (0.3%)	0 (0.0%)
Arthropod sting	1 (0.3%)	0 (0.0%)
Investigations	1 (0.3%)	0 (0.0%)
Heart rate increased	1 (0.3%)	0 (0.0%)
Musculoskeletal and connective tissue disorders	1 (0.3%)	1 (0.3%)
Musculoskeletal chest pain	1 (0.3%)	0 (0.0%)
Myalgia	0 (0.0%)	1 (0.3%)
Nervous system disorders	14 (4.1%)	14 (4.0%)
Dizziness	5 (1.5%)	7 (2.0%)
Dysgeusia	3 (0.9%)	2 (0.6%)
Headache	1 (0.3%)	1 (0.3%)
Hyperaesthesia	1 (0.3%)	0 (0.0%)
Paraesthesia	2 (0.6%)	0 (0.0%)
Parosmia	0 (0.0%)	1 (0.3%)
Sedation	0 (0.0%)	1 (0.3%)
Sommolence	3 (0.9%)	5 (1.4%)

* Counts reflect numbers of subjects reporting one or more adverse events classified to MedDRA (Version 9.1) system organ classes and preferred terms. At each level of summarization (system organ class or preferred term) subjects are only counted once.

Table 14.3.1.2.2: Summary of Adverse Events by System Organ Class and Preferred Term
(Adverse Events that Occurred Subsequent to Dosing)
(Safety Subjects)
(Page 3 of 3)

Adverse Event*	PRO-513 (N=343)	Placebo (N=347)
Psychiatric disorders	9 (2.6%)	1 (0.3%)
Agitation	2 (0.6%)	0 (0.0%)
Anxiety	1 (0.3%)	0 (0.0%)
Confusional state	1 (0.3%)	0 (0.0%)
Deja vu	1 (0.3%)	0 (0.0%)
Disorientation	0 (0.0%)	1 (0.3%)
Insomnia	3 (0.9%)	0 (0.0%)
Nervousness	1 (0.3%)	0 (0.0%)
Restlessness	3 (0.9%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	2 (0.6%)	1 (0.3%)
Cough	1 (0.3%)	0 (0.0%)
Epistaxis	0 (0.0%)	1 (0.3%)
Throat irritation	1 (0.3%)	0 (0.0%)
Skin and subcutaneous tissue disorders	1 (0.3%)	3 (0.9%)
Erythema	1 (0.3%)	1 (0.3%)
Pruritus	0 (0.0%)	1 (0.3%)
Rash	0 (0.0%)	1 (0.3%)
Vascular disorders	2 (0.6%)	0 (0.0%)
Flushing	2 (0.6%)	0 (0.0%)

* Counts reflect numbers of subjects reporting one or more adverse events classified to MedDRA (Version 9.1) system organ classes and preferred terms. At each level of summarization (system organ class or preferred term) subjects are only counted once.

The sponsor notes that for psychiatric adverse events there was a statistically significant difference between treatment groups.

The sponsor concludes that PRO-513 was safe and well-tolerated.

Reviewer:

- Adverse events data in the US study was collected by methods likely more reliable (e.g. real-time entry into headache diary) than those used in the European study. Adverse events data from the US study alone (not averaged with the European data) is recommended to be used in PRO-513 labeling.
- Psychiatric adverse events were more common in PRO-513 versus placebo, and are discussed above in Section 7.1.3.3, Other Significant Adverse Events.
- The incidence of nausea as an adverse event was higher for PRO-513 than for placebo, 7% versus 4.3% respectively. Nausea, a co-primary efficacy endpoint, was only counted as an adverse event beginning 8 hours after study treatment dosing. The fact that nausea as an adverse event was higher in the treatment arm after 8 hours suggests that nausea might be increased by PRO-513 past 8 hours (nausea is a known common adverse effect of diclofenac). In fact, while *average* nausea in the PRO-513 arm decreased steadily between 15 minutes after dosing (0.9 on zero- to 3 scale) through 8 hours (0.4), there was a slight increase of nausea to 0.5 at hours 16 and 24. Importantly, this was still lower than the average nausea of 0.8 in the placebo arm at 24 hours.

Bioavailability study CAT458C2102

24 healthy adult subjects were dosed once, alternately, with PRO-513 and 50 mg diclofenac potassium tablet (CATAFLAM). There was a one week washout between treatments. Adverse events are shown in Table 33. The sponsor indicates that the single adverse event of ‘syncope vasovagal’ in the Cataflam arm did not result in loss of consciousness or meet the definition of serious AE.

Reviewer: This small study did not reveal safety differences between (b) (4) and Cataflam.

Table 33: Adverse Events, Bioavailability Study CAT458C2101

Table 2.1.1.1-2: Adverse Events Reported in Study CAT458C2101

Adverse Event ^a	(b) (4) (N=24)	CATAFLAM (N=24)
Gastrointestinal disorders	0 (0.0%)	1 (4.2%)
Loose stools	0 (0.0%)	1 (4.2%)
General disorders and administ	0 (0.0%)	2 (8.3%)
Influenza like illness	0 (0.0%)	2 (8.3%)
Musculoskeletal and connective	1 (4.2%)	0 (0.0%)
Flank pain	1 (4.2%)	0 (0.0%)
Nervous system disorders	3 (12.5%)	4 (16.7%)
Headache	2 (8.3%)	2 (8.3%)
Somnolence	1 (4.2%)	1 (4.2%)
Syncope vasovagal	0 (0.0%)	1 (4.2%)
Psychiatric disorders	0 (0.0%)	1 (4.2%)
Insomnia	0 (0.0%)	1 (4.2%)
Respiratory, thoracic and medi	0 (0.0%)	1 (4.2%)
Cough	0 (0.0%)	1 (4.2%)
Skin and subcutaneous tissue d	0 (0.0%)	2 (8.3%)
Ecchymosis	0 (0.0%)	1 (4.2%)
Pruritus	0 (0.0%)	1 (4.2%)

^a Counts reflect numbers of subjects reporting one or more adverse events classified to MedDRA (Version 9.1) system organ classes and preferred terms. At each level of summarization (system organ class or preferred term) subjects are only counted once.

Bioavailability study PRO-513101

36 healthy adult subjects were exposed twice to PRO-513 and twice to Cataflam 50 mg. The sponsor notes that for two patients after taking Cataflam the AE of ‘bleeding time prolongation’ was not further investigated by diagnostic tests. The sponsor states that increased bleeding time is a common adverse event for diclofenac and other NSAIDs. Adverse events are shown in Table 34.

Table 34: Adverse Events, US Bioavailability Study**Table 2.1.1.2-2: Adverse Events Reported in Study PRO-513101**

System Organ Class Preferred Term	Treatments			
	PRO-513 Fast (N=34)	CATAFLAM Fast (N=35)	PRO-513 Fed (N=35)	CATAFLAM Fed (N=35)
	Number (%) of Subjects			
Number of Subjects with an AE	4 (11.8)	7 (20.0)	3 (8.6)	6 (17.1)
Investigations	4 (11.8)	2 (5.7)	0 (0.0)	3 (8.6)
Red blood cells urine positive	1 (2.9)	1 (2.9)	0 (0.0)	1 (2.9)
Bleeding time prolonged	0 (0.0)	1 (2.9)	0 (0.0)	1 (2.9)
Heart rate decreased	1 (2.9)	0 (0.0)	0 (0.0)	1 (2.9)
Blood amylase increased	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)
Blood pressure decreased	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)
Blood uric acid increased	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)
Haemoglobin decreased	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)
Protein urine present	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	0 (0.0)	3 (8.6)	0 (0.0)	2 (5.7)
Catheter site pain	0 (0.0)	2 (5.7)	0 (0.0)	2 (5.7)
Catheter site erythema	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)
Infections and infestations	1 (2.9)	0 (0.0)	1 (2.9)	1 (2.9)
Ear infection	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)
Scarlet fever	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)
Upper respiratory tract infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)
Musculoskeletal and connective tissue disorders	0 (0.0)	1 (2.9)	1 (2.9)	0 (0.0)
Arthralgia	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)
Pain in extremity	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)
Scratch	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)
Nervous system disorders	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)
Hypoaesthesia	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)
Psychiatric disorders	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)
Aggression	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)
Cough	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)
Nasal congestion	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)
Pruritus	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)
Vascular disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)
Hot flush	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)

Reviewer: This small study did not reveal safety differences between PRO-513 and Cataflam.

Dental Pain Study CAT458C2302

In this single dose study, 74 dental patients were exposed to PRO-513. Adverse events were not recorded in patient diaries, but were collected only at 24 hours post-dose at the final clinical assessment. A single adverse event, 'post-procedural pain,' was reported in the PRO-513 arm.

Reviewer: The study did not reveal any safety differences between (b) (4) and placebo, but interpretation of safety was hindered by over-dependence of adverse events recording on patient recall.

7.1.5.1 Eliciting adverse events data in the development program

As noted in the descriptions of the phase 3 protocols in Section 6, Integrated Review of Efficacy, the US phase 3 study recorded adverse events in the patient diary as they occurred through 24 hours after dosing, while in contrast the European phase 3 study recorded adverse events in the patient at the 8 hour time point, and only recorded subsequent adverse events at the follow-up clinic visit. In addition, in the patient diary in the European phase 3 study, instructions were given that would have limited adverse events reporting in patients who took rescue medication to the period before rescue medication was taken. The supportive dental pain study recorded adverse events only at the 24-hour post dose clinic visit.

Reviewer: Adverse event recording in the European migraine study and in the dental pain study was overly dependent on patient recall, weakening confidence in the accuracy and completeness of safety findings. In the European migraine study instructions in the patient diary limited adverse events collection to the time period before rescue medication was taken, thus potentially missing adverse events related to PRO-513 occurring after rescue medication was taken.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Reviewer: The preferred terms used for verbatim terms were acceptable.

7.1.5.3 Incidence of common adverse events

See under main section 7.1.5

7.1.5.4 Common adverse event tables

See under main section 7.1.5

7.1.5.5 Identifying common and drug-related adverse events

See under main section 7.1.5

7.1.5.6 Additional analyses and explorations

None

7.1.6 Less Common Adverse Events

All non-serious adverse events are discussed under section 7.1.5.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Laboratory testing was conducted only in the two phase 1 studies, CAT458C2101 and PRO-513101. Subjects in CAT458C2101 were dosed in cross-over fashion once each with PRO-513 and Cataflam 50 mg. In Study PRO-513101, subjects took PRO-513 and Cataflam on two separate occasions after fasting and on two additional occasions under fed conditions. In both studies, clinical laboratory evaluations were conducted at all study visits.

In 3 subjects, urinalysis became positive for blood, and in one subject urinalysis became positive for protein.

Slightly elevation of serum amylase occurred in three subjects and elevation of uric acid occurred in one.

Small changes in hematological parameters occurred, including mildly decreased hemoglobin in four subjects. Decreased hemoglobin occurred in one female patient, but on retest 7 days later was normal. Two subjects reported as AEs having 'bled longer than usual,' but bleeding time was not further investigated in these patients.

The sponsor concludes that clinical laboratory findings from the two phase I bioavailability studies indicate that PRO-513 is safe and, from the standpoint of clinical chemistry, hematologic, and urinalysis findings is similar to other NSAIDs. The sponsor states that the relatively few abnormal changes in laboratory variables generally were not clinically significant, not treatment related, transient, and resolved without the need for concomitant therapy.

Reviewer: Diclofenac can be associated with bleeding and renal and pancreatic damage. Limited laboratory data was collected in these studies, diminishing interpretability of the abnormalities identified. No new safety concerns for PRO-513 were identified.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

See section 7.1.7.1.

7.1.7.3 Standard analyses and explorations of laboratory data

See section 7.1.7.1.

7.1.7.3.1 Analyses focused on measures of central tendency

Reviewer: Analyses of central tendency for laboratory data were unremarkable

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Reviewer: Analyses on outliers/shifts were unremarkable.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

One subject discontinued due to hematuria after treatment with Cataflam.

Reviewer: Outlier and dropout analysis did not reveal interpretable safety concerns for PRO-513.

7.1.7.4 Additional analyses and explorations

None.

7.1.7.5 Special assessments

None.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs were collected near drug exposure only in study PRO-513101. In the phase 3 studies in migraine, vital signs were obtained only at baseline.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

See section 7.1.8.1.

7.1.8.3 Standard analyses and explorations of vital signs data

In study PRO-513101, vital signs data was collected at baseline, after each dose of study medication, and at study exit. Decreased pulse rate occurred in two patients, and an AE of decrease in blood pressure occurred in a third patient.

- Subject 012, PRO-513: pulse rate 47, 20 year old male, baseline rate 62, exit rate 55
- Subject 019, Cataflam: pulse rate 48, 21 year old male, baseline rate 52, exit rate 54
- Subject 20, PRO-513: decrease in blood pressure to 88/62, 24 year old female, baseline pressure 105/69, exit pressure 98/66

Reviewer: Analysis of the limited vital signs data available did not reveal interpretable safety concerns for PRO-513.

7.1.8.3.1 Analyses focused on measures of central tendencies

Reviewer: Vital sign central tendencies were unremarkable.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

Reviewer: Outlier/shift analysis was unremarkable.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

None.

7.1.8.4 Additional analyses and explorations

None.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

ECGs were obtained at study entry and exit only in the bioavailability study CAT458C2101. In no studies were ECGs obtained near drug dosing.

Reviewer: No clinically meaningful adverse effects of PRO-513 on ECG were detected.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

See section 7.1.9.1

7.1.9.3 Standard analyses and explorations of ECG data

See section 7.1.9.1

7.1.9.3.1 Analyses focused on measures of central tendency

See section 7.1.9.1

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

See section 7.1.9.1

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

None.

7.1.9.4 Additional analyses and explorations

7.1.10 Immunogenicity

No studies were conducted.

7.1.11 Human Carcinogenicity

No studies were conducted.

7.1.12 Special Safety Studies

No studies were conducted.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No studies were conducted.

7.1.14 Human Reproduction and Pregnancy Data

No studies were conducted.

7.1.15 Assessment of Effect on Growth

No studies were conducted.

7.1.16 Overdose Experience

There is no overdose experience for PRO-513.

Reviewer: From the available data on PRO-513 there is no indication that overdose would differ from Cataflam 50 mg.

7.1.17 Postmarketing Experience

The sponsor states the following regarding postmarketing safety experience with a formulation of powdered diclofenac-K similar to PRO-513, Voltfast/Catafast, that has been marketed in Italy and Egypt for about 10 years:

“A search of the Novartis safety database on the formulation marketed in Italy and Egypt from launch up to 21 February 2007 yielded 60 adverse events reported by 29 patients. Of the reported events the majority were classified as gastrointestinal disorders and included stomatitis, abdominal pain, duodenal ulcer, bleeding gastric ulcer, hematemesis, pancolitis, and dyspepsia. Overall, a medical evaluation of the reported cases did not show a trend towards an increase in unexpected or more serious side effects for the VOLTFAST/CATAFAST formulation. Further, the postmarketing surveillance data indicates that the safety experience with VOLTFAST/CATAFAST in the general population is similar to what was observed in the clinical studies conducted with PRO-513. Unexpected reactions were not seen with VOLTFAST/CATAFAST, and, in general, all of the treatment-related events reported for PRO-513 were expected.”

“In approximately (b) (4) treatment periods encompassing over (b) (4) patient years of exposure, only two cases classified as cardiac disorder associated with VOLTFAST/CATAFAST have emerged.”

Reviewer: Data about postmarketing experience for Voltfast/Catafast is not presented in enough detail to assess adequately the sponsor’s findings or conclusions.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

767 subjects were exposed to PRO-513 within the five clinical trials. Exposure was to a single dose of PRO-513 in the phase 3 trials.

7.2.1.2 Demographics

In the two phase 3 migraine studies combined, the subjects were primarily female (85%), average of 40 years of age, and Caucasian (86.2%) or African American (11.1%)(Table 35). Median body weight was about 7 lbs higher in the US versus the European study.

Table 35: Demographics, Phase 3 Migraine Studies

Table 3.1-3: Demographics for Subjects who Used Study Medication in Studies CAT458C2301 and PRO-513301 (Combined, ITT)

	PRO-513/ (b) (4) ^a (N=634)	Placebo (N=646)	CATAFLAM (N=298)	Total ^b (N=1007)
Age (years)				
Mean	39.9	39.7	39.3	39.9
Median	40.0	40.5	39.0	41.0
STD	11.5	11.3	11.5	11.4
Range	18.0-65.0	18.0-65.0	18.0-64.0	18.0-65.0
Gender				
Male	91 (14.4%)	97 (15.0%)	43 (14.4%)	151 (15.0%)
Female	543 (85.6%)	549 (85.0%)	255 (85.6%)	856 (85.0%)
Ethnicity				
Hispanic/Latino	33 (9.6%)	33 (9.5%)	0 (0.0%)	66 (9.6%)
Not Hispanic/Latino	310 (90.4%)	314 (90.5%)	0 (0.0%)	624 (90.4%)
Race				
American Indian/Alaska Native	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)
Asian	3 (0.5%)	3 (0.5%)	0 (0.0%)	6 (0.6%)
Black/African American	53 (8.4%)	60 (9.3%)	1 (0.3%)	112 (11.1%)
Native Hawaiian/Other Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
White	566 (89.3%)	574 (88.9%)	297 (99.7%)	868 (86.2%)
Other	12 (1.9%)	8 (1.2%)	0 (0.0%)	20 (2.0%)

^a (b) (4) is the name used for the PRO-513 formulation in the Novartis-conducted studies.

^b The total column represents all subjects who were randomized in the two studies combined. Because Study CAT458C2301 utilized a crossover design, subjects in that study were treated with all three test articles. Therefore, these subjects contributed to the demographic counts for each treatment group represented in the table. The subject numbers by treatment group, therefore, exceed the combined number of subjects enrolled in the two studies.

Table 1.3.3-3: Summary of Demographics for Studies CAT458C2301 and PRO-513301 (Combined)
(Page 2 of 2)

	(b) (4) PRO-513 ^a (N=634)	Placebo (N=646)	CATAFLAM (N=298)	Total ^b (N=1007)
Weight (pounds)				
Mean	157.8	158.0	145.9	161.1
Median	150.5	150.0	143.3	154.3
STD	37.2	37.4	27.4	38.9
Range	86.0-325.0	86.0-359.0	86.0-260.1	86.0-359.0
Height (inches)				
Mean	65.6	65.7	65.9	65.6
Median	65.0	65.4	65.7	65.0
STD	3.4	3.2	3.1	3.3
Range	55.0-77.0	54.0-75.6	59.1-75.6	54.0-77.0
Pulse (bpm)				
Mean	72.6	72.9	72.6	72.7
Median	72.0	72.0	72.0	72.0
STD	9.0	9.3	7.9	9.5
Range	44.0-115.0	47.0-111.0	48.0-111.0	44.0-115.0
Systolic Blood Pressure (mm HG)				
Mean	117.4	118.0	118.0	117.6
Median	118.0	120.0	120.0	118.0
STD	12.7	13.8	13.1	13.3
Range	80.0-180.0	80.0-185.0	80.0-180.0	80.0-185.0
Diastolic Blood Pressure (mm HG)				
Mean	75.2	75.6	74.6	75.5
Median	76.0	76.0	75.0	76.0
STD	9.1	9.5	8.3	9.6
Range	52.0-108.0	52.0-110.0	52.0-95.0	52.0-110.0

^a (b) (4) is the name used for the PRO-513 formulation in the Novartis-conducted studies.

^b The total column represents all subjects who were randomized in the two studies combined. Because Study CAT458C2301 utilized a crossover design, subjects in that study were treated with all three test articles. Therefore, these subjects contributed to the demographic counts for each treatment group represented in the table. The subject numbers by treatment group, therefore, exceed the combined number of subjects enrolled in the two studies.

7.2.1.3 Extent of exposure (dose/duration)

Exposure was to a single dose of PRO-513 in the phase 3 trials.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

None.

7.2.2.2 Postmarketing experience

See section 7.1.17

7.2.2.3 Literature

See section 8.6

7.2.3 Adequacy of Overall Clinical Experience

Reviewer: The overall clinical experience was adequate.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Reviewer: Not applicable.

7.2.5 Adequacy of Routine Clinical Testing

Reviewer: Routine clinical testing was adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Reviewer: Previous FDA findings of safety and efficacy for diclofenac combined with current additional pharmacokinetic data for PRO-513 suggest adequate metabolic, clearance, and interaction workup.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Reviewer: Evaluation for adverse events was adequate.

7.2.8 Assessment of Quality and Completeness of Data

Reviewer: The quality and completeness of data was adequate.

7.2.9 Additional Submissions, Including Safety Update

None.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Selected Drug-Related Adverse Events

See section 7.1.3.3

Important Limitations of Data

Reviewer: The phase 3 studies were single dose, and no long-term exposure study was conducted. The current NDA therefore depends in large part on previous FDA findings of safety for Cataflam.

Conclusions

The sponsor concludes that the overall safety profile of PRO-513 is similar to that of the currently marketed diclofenac potassium tablet formulation that contains the same active ingredient at the same strength. The sponsor's overall conclusion is that PRO-513 is safe and well-tolerated by adults when used for the acute treatment of migraine attacks with and without aura.

Reviewer: Agree. See discussion in Section 1.3.3, Safety.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Reviewer: Given the small size of the safety database and differences in study design, data pooling was not conducted.

7.4.1.2 Combining data

Reviewer: Given the small size of the safety database and differences in study design, data was not combined.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Reviewer: A single dose was studied, such that no data was available from this development program for dose-dependency for adverse events. The overall database suggests that PRO-513 is similar enough to Cataflam to conclude that dose dependency for adverse findings may be similar.

7.4.2.2 Explorations for time dependency for adverse findings

Reviewer: Only single-dose phase 3 studies were conducted. The overall database suggests that PRO-513 is similar enough to Cataflam to conclude that time dependency for adverse findings may be similar.

7.4.2.3 Explorations for drug-demographic interactions

The sponsor indicates that diclofenac potassium-containing products have been available for over 20 years, and there is no evidence in the literature to suggest that ethnicity plays a role in treatment effect.

Reviewer: In the US phase 3 study, 111 of 690 patients were African American. Analysis by the statistical reviewer indicates similar response rates between African Americans and Caucasians (data not shown).

7.4.2.4 Explorations for drug-disease interactions

Reviewer: The database for PRO-513 does not suggest drug-disease interactions.

7.4.2.5 Explorations for drug-drug interactions

Reviewer: The overall database for PRO-513 suggests that drug-drug interactions for diclofenac also apply to PRO-513.

7.4.3 Causality Determination

Reviewer: The current safety database is consistent with a safety profile of PRO-513 similar to that of Cataflam.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

See section 5.3, Exposure-Response Relationship.

8.2 Drug-Drug Interactions

No additional drug interaction studies were conducted with PRO-513.

8.3 Special Populations

No studies in special populations were conducted.

8.4 Pediatrics

No pediatric studies were conducted.

8.5 Advisory Committee Meeting

No advisory committee meeting was held.

8.6 Literature Review

Reviewer: Literature review revealed few reports of psychiatric adverse events related to diclofenac. Reported psychiatric adverse events included mainly depression, paranoia, and disturbed cognition, mainly in patients with underlying psychiatric disease. No clear relationship exists between these literature reports and the observed higher incidence of psychiatric adverse events in the US phase 3 study.

8.7 Postmarketing Risk Management Plan

Not applicable.

8.8 Other Relevant Materials

Unconnected with the PRO-513 NDA application, a CDER Regulatory Briefing was held on February 1, 2008, to discuss diclofenac hepatotoxicity and product labeling changes for diclofenac products (background document and presentations can be found at http://cdernet.cder.fda.gov/ocd/regulatory_brief.htm). Labeling changes related to this regulatory briefing are incorporated into the Line-by-Line Labeling Review, section 10.2

9 OVERALL ASSESSMENT

9.1 Conclusions

Reviewer: The safety and efficacy of PRO-513 have been adequately demonstrated in migraine.

9.2 Recommendation on Regulatory Action

Reviewer: Approval.

9.3 Recommendation on Postmarketing Actions

Reviewer: None

9.3.1 Risk Management Activity

Reviewer: None

9.3.2 Required Phase 4 Commitments

Reviewer: None

9.3.3 Other Phase 4 Requests

Reviewer: Pediatric studies

9.4 Labeling Review

Reviewer: See Line-by-Line Labeling Review, Section 10.2.

9.5 Comments to Applicant

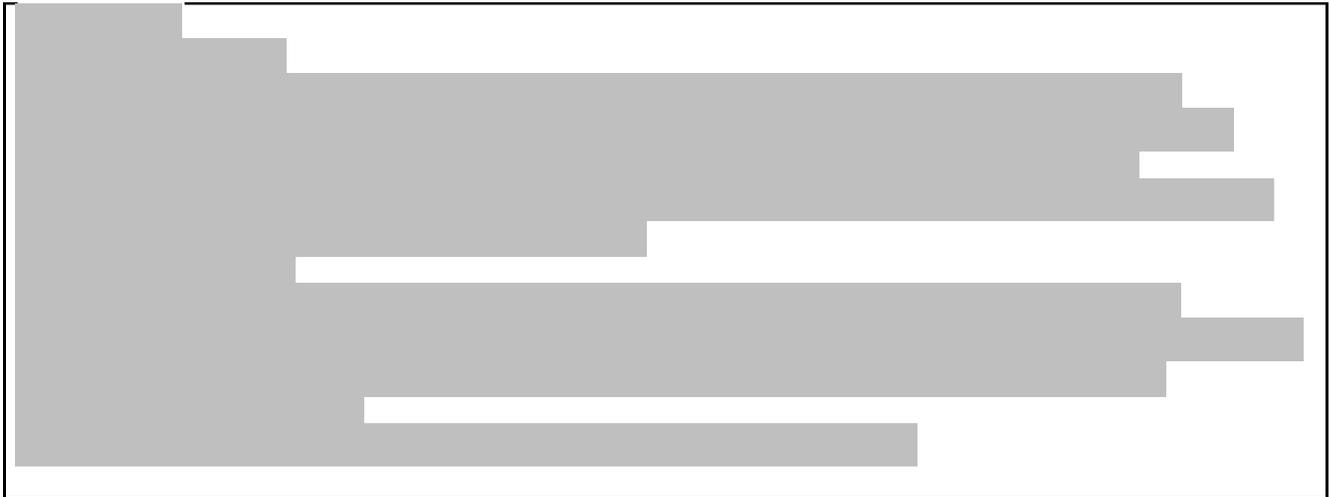
10 APPENDICES

10.1 Review of Individual Study Reports

See main body of review.

10.2 Line-by-Line Labeling Review

(b) (4)

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(TS/CCI) - Draft Labeling

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

/s/

Ronald Farkas
10/24/2008 01:44:48 PM
MEDICAL OFFICER

Eric Bastings
10/24/2008 01:58:55 PM
MEDICAL OFFICER

I concur that safety and efficacy have been established.
Please see my CDTL memo for further comments
on this application.