European Medicines Agency

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SCIENTIFIC DISCUSSION
FOR
DYNASTAT

International non-proprietary name: parecoxib

Procedure No: EMEA/H/C/000381/II/0032

Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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SCIENTIFIC DISCUSSION

1. Introduction

Dynastat (parecoxib) is a parenteral cyclooxygenase-2 (COX-2) selective inhibitor with the therapeutic indication '*for the short-term treatment of post-operative pain'*. Parecoxib is the parenteral pro-drug of the active substance valdecoxib.

Dynastat is supplied as 20 mg and 40 mg powder vials and solvent solution for intravenous and intramuscular injection. The recommended dose is 40 mg, followed every 6 to 12 hours by 20 mg or 40 mg as required, not to exceed 80 mg/day.

In June 2008, the Marketing Authorisation Holder (MAH) applied initially for an extension of indication for Dynastat to include *the reduction of opioid use and patient-reported opioid-related adverse effects when used in conjunction with opioids*. In addition, the MAH proposed specific information on opioid sparing benefits in sections 4.2 "Posology and method of administration" and 5.1 "Pharmacodynamic properties" of the Summary of Product Characteristics (SPC).

In addition to the extended indication on opioid sparing effects with associated Product Information changes, the MAH also proposed changes in SPC section 4.2 related to cardiovascular and renal safety, as well as some amendments in the Package Leaflet (PL).

2. CLINICAL EFFICACY

Background

The initial EU Marketing Authorisation Application (MAA) also sought approval for an opioid-sparing indication, but this part of the proposed indication was not approved when the Marketing Auhorisation (MA) was granted in 2002. Efficacy results from studies comparing treatment with parecoxib plus opioids versus treatment with opioids alone, demonstrated equivalent or superior pain relief of the combined treatment, as well as significant opioid sparing, in 4 post-surgical settings: orthopedic hip surgery (Study 028); gynecologic surgery (Study 029); orthopedic knee surgery (Study 033); and Coronary Artery Bypass Graft (CABG) surgery (Study 035).
At that time it was concluded that even though the initially submitted studies 029 and 035 did not unequivocally demonstrate opioid-sparing effect, studies 028 and 033 did show approximately 20-40% reduction in opioid consumption. However, the opioid-sparing effect did not appear to be associated with a reduction in the adverse effects of morphine, meaning that the combined use of the two drugs was not demonstrated to translate into symptomatic benefit for the patient.
However, the following information was included (and has remained unchanged) in section 4.5 Interactions of the SPC: *"Dynastat may be co-administered with opioid analgesics. When Dynastat was co-administered with morphine, a smaller dose (by 28-36%) of morphine could be used to achieve the same clinical level of analgesia."*

Since that time, additional opioid-sparing studies have been performed in various surgical models with similar results, including general surgery (Study 069), CABG surgery (Study 071), and orthopedic surgery of the hip (Study 080), as well as laparoscopic cholecystectomy (Study 044) and bunionectomy (Study 077). The MAH considers studies 069 and 071 as pivotal and study 080 as supportive for this variation application.
It is noted that study 069 included treatment groups with valdecoxib, a medicinal product which is no longer available on the market.

In addition to the opioid-sparing studies, further Phase III clinical pain studies have also been conducted, giving a total of 25 double-blind, randomised, controlled studies of the analgesic efficacy of parecoxib in which a total 8,661 patients undergoing a variety of surgical procedures were treated with study medication, including 4,943 patients randomised to receive parecoxib.

Analysis of the clinical data submitted

Main studies

Table 1. Listing of Controlled Clinical Studies Pertinent to the Claimed Indication

Protocol No.	Study Design and Objective	Treatment Groups	No. of Subjects (by Treatment Group)	Demographics (by Treatment Group)
Pivotal studies				
I93-01-02-**069**	Phase 3, multi-center, multiple-dose, randomised, double-blind, placebo-controlled, parallel-group study involving patients who had undergone major orthopedic or general surgery **Objectives:** Safety, Analgesic Efficacy, and Effect on Health Outcome Measures.	▪ Parecoxib 40 mg IV after recovery from anaesthesia, followed later the same day by 20 mg IV; thereafter parecoxib 20 mg IV/IM q 12h for at least a total of 6 doses, followed by valdecoxib 20 mg every 12-hour. ▪ Placebo given as above	Randomised: 533 Treated: 525 Completed: 467 Randomised: 529 Treated: 525 Completed: 467	Sex: 216 M/317 F Mean/Median Age (min/max): 53.8/55.2 (18 - 81) years Race: W/B/O: 502/24/7 Sex: 223 M/306 F Mean/Median Age (min/max): 52.9/53.2 (19 - 81) years Race: W/B/O: 486/23/20
PARA-0505-**071**	Phase 3, multi-center, multiple-dose, randomised, double-blind, placebo-controlled, parallel-group study involving patients undergoing primary isolated CABG surgery. **Objectives:** Safety, Analgesic Efficacy, and Effect on Health Outcome Measures.	▪ Day after surgery, parecoxib 40 mg IV followed later the same day by 20 mg IV; thereafter parecoxib 20 mg IV every 12 hours for at least a total of 6 doses, followed by valdecoxib 20 mg every 12 hours. ▪ Placebo given as above for parecoxib, followed by valdecoxib as given above. ▪ Placebo given as above for parecoxib, followed by placebo for valdecoxib as given above.	Randomised: 555 Treated: 544 Completed: 487 Randomised: 556 Treated: 544 Completed: 471 Randomised: 560 Treated: 548 Completed: 480	Sex: 475 M/80 F Mean/Median Age (min/max): 62/62.5 (36-79) years Race: W/B/O: 524/6/25 Sex: 479 M/77 F Mean/Median Age (min/max): 61.6/61.3 (37-81) years Race: W/B/O: 521/10/25 Sex: 477 M/83 F Mean/Median Age (min/max): 62.1/62.1 (38-80) years Race: W/B/O: 514/14/32

Supportive Study				
PARA-0505-**080**	Phase 3b, multi-center, multinational, multiple-dose, randomised, double-blind, placebo-controlled, parallel-group, 48-hour study after patient underwent hip arthroplasty and was designed to evaluate the morphine-sparing effect of parecoxib versus propacetamol, the combination of parecoxib and propacetamol, or placebo. **Objectives:** Pain relief with parecoxib versus propacetamol and the combination of parecoxib and propacetamol. Safety and tolerability of multiple doses of parecoxib.	▪ Parecoxib 40 mg IV BID ▪ Propacetamol 2 grams IV QID ▪ Parecoxib 40 mg IV BID + propacetamol 2 grams IV QID ▪ Placebo	Randomised: 72 Treated: 72 Completed: 64 Randomised: 71 Treated: 71 Completed: 63 Randomised: 72 Treated: 72 Completed: 69 Randomised: 38 Treated: 38 Completed: 33	Sex: 30 M/42 F Mean/Median Age (min/max): 65.6/67.3 (41 - 84) years Race: W/B/O: 70/1/1 Sex: 30 M/ 41 F Mean/Median Age (min/max): 66.9/68.7 (39- 86) years Race: W/B/O: 71/0/0 Sex: 29 M/ 43 F Mean/Median Age (min/max): 66.6/68.2 (28 – 84) years Race: W/B/O: 71/1/0 Sex: 19 M/ 19F Mean/Median Age (min/max): 67.7/70.8 (48 – 82) years Race: W/B/O: 38/0/0

Note: No = Number; M = Male; F = Female; W = White; B = Black; O = Other; BID = Twice daily; QID = Four times daily; IV = Intravenous; IM = Intramuscular.

The two pivotal studies (069 and 071) include a reasonable number of patients, with the main objective to measure safety outcomes. Study 069 is clearly relevant for the target population of the proposed extended indication, whereas the other pivotal study 071 may have less relevance as that study population only includes CABG-surgery patients, for whom parecoxib is contraindicated in the SPC.

Study I93-01-02-069: A Double-Blind Multicenter Study of the Safety and Efficacy of Parecoxib Followed by Valdecoxib Compared to Placebo in General Surgery Patients for Treatment of Post-Surgical Pain

Protocol No.	Study Design and Objective	Treatment Groups	No. of Subjects (by Treatment Group)	Demographics (by Treatment Group)
I93-01-02-**069**	Phase 3, multi-center, multiple-dose, randomised, double-blind, placebo-controlled, parallel-group study involving patients who had undergone major orthopedic or general surgery **Objectives:** Safety, Analgesic Efficacy, and Effect on Health Outcome Measures.	▪ Parecoxib 40 mg IV after recovery from anaesthesia, followed later the same day by 20 mg IV; thereafter parecoxib 20 mg IV/IM q 12h for at least a total of 6 doses, followed by valdecoxib 20 mg every 12-hour. ▪ Placebo given as above	Randomised: 533 Treated: 525 Completed: 467 Randomised: 529 Treated: 525 Completed: 467	Sex: 216 M/317 F Mean/Median Age (min/max): 53.8/55.2 (18 - 81) years Race: W/B/O: 502/24/7 Sex: 223 M/306 F Mean/Median Age (min/max): 52.9/53.2 (19 - 81) years Race: W/B/O: 486/23/20

Methods

- **Study participants**

A total of 1062 patients were randomised at 113 centres in 14 countries from September 2002 - February 2003.

Principal inclusion and exclusion criteria

Eligible patients were adult male or female, 18 to 80 years of age scheduled to undergo major orthopedic or general surgery. All patients were expected to require in-hospital analgesic treatment for postoperative pain for at least three days and analgesic treatment following discharge over a 10-day period following surgery. Patients participating in the study were to have an American Society of Anesthesiologists I to III grade for pre-operative health. Female patients were to be post-menopausal, surgically sterile, or using adequate contraception, not lactating, and had a negative pregnancy test at screening.

There were 16 exclusion criteria principally specifying the absence of previous major surgery, significant co-morbidity or factors such as alcohol misuse which could compromise participation in the study. Patients could also be removed from the study if surgery lasted more than four hours, and if they had a significant intra-operative or postoperative complication.

The CHMP agreed that the inclusion criteria adequately reflected the group of patients who would normally require opioid analgesia after general major surgery, and who may profit from multimodal analgesic regimens with a COX-inhibitor. The exclusion criteria were also considered reasonable and took into account labelled warnings and contraindications of parecoxib.

- **Treatments**

Parenteral parecoxib or placebo were administered to the two groups as shown in table 2.

Table 2. Groups and treatments

Treatments	Route	Dose	Dosing Interval
Group 1: Parecoxib Group 2: Placebo	IV	40 mg	Day 1 (= day of surgery), Dose 1
Group 1: Parecoxib Group 2: Placebo	IV/IM	20 mg	Day 1 (= day of surgery), Dose 2 followed by Q12h through at least Day 3
Group1: Valdecoxib Group 2: Placebo	PO	20 mg	Q12h, when patients could tolerate PO medication after Day 3 through Day 10

In addition to study medication, supplemental analgesia was allowed throughout the study in the form of morphine with patient-controlled analgesia (PCA) or bolus administration during the IV/IM treatment period and codeine/acetaminophen (paracetamol) or hydrocodone/acetaminophen (paracetamol) during the oral treatment period of the study. PCA was initiated at the time of randomisation. The PCA protocol included PCA pump on demand (no basal infusion) at 1 mg/ml administered at 1.0 ml per dose, with a blockout time of six minutes. If bolus morphine was administered in addition to PCA, the doses were included with the total morphine calculation.

The dosage complies with the current SPC. The valdecoxib treatment period has minor importance for this variation application, which means that this assessment will mainly address the data over the first 3 days, which were scheduled for parecoxib.

- **Outcomes/endpoints**

Primary Safety Endpoint:
The primary measure to assess the safety of parecoxib sodium/valdecoxib was the first occurrence of any confirmed clinically relevant adverse event (CRAE) in the following categories:

1. Cardiovascular thromboembolic CRAEs consisting of:
    - Cardiac events: myocardial infarction (MI), severe myocardial ischemia, cardiac arrest, or sudden cardiac death determined by autopsy or if, in the absence of another identifiable cause, unexpected death occurring within 60 minutes of the onset of symptoms;
    - Cerebrovascular events: acute ischemic or hemorrhagic stroke, hemorrhagic infarction, or transient ischemic attacks (TIA); and
    - Peripheral vascular events: deep venous thrombosis (DVT) or pulmonary embolism.
2. Renal CRAEs consisting of renal failure or severe renal dysfunction.
3. Upper gastrointestinal (Gastroduodenal Ulcer) CRAEs consisting of perforation, bleeding, or outlet obstruction.
4. Wound healing complication CRAEs consisting of infectious complications (superficial incisional surgical site infection (SSI), deep incisional SSI, and organ space SSI) and noninfectious wound separation or dehiscence

Secondary Endpoints:
Safety
Secondary measures for analysis of safety were:
1. Adverse events
2. Serious adverse events
3. Clinical laboratory assessments
4. Vital signs

Efficacy:
The main measures of efficacy were:
1. Rate of supplemental analgesia consumed on Days 2 through 10.
2. Summed Pain Intensity (SPI) over 24 hours (SPI 24) beginning on Day 2 through the end of the treatment period.
3. Patient's and Physician's Global Evaluation of Study Medication at time of transition from IV/IM to PO medication and Final Visit/Day 11.

Other measures of efficacy were:
1. SPI over 12 hours (SPI 12) beginning on Day 2 through the end of the treatment period.
2. Peak Pain Intensity (PPI) on Days 2 through 10.

The measures used to evaluate the effect of parecoxib sodium/valdecoxib on health outcomes included:
1. Modified Brief Pain Inventory - Short Form (mBPI-sf) on Days 2 through 10
2. Opiod-related Symptom Distress Scale (OR-SDS and also referred to in accompanying documents as the Symptom Distress Questionnaire) on Days 2 through 10
3. Hospital Length of Stay (LOS)

- **Sample size**

The sample size of 500 patients per treatment arm for this trial is based on the need to obtain multiple dosing experience with parecoxib/valdecoxib and to demonstrate safety of the drug regimen in patients undergoing a variety of surgical procedures. This sample size provides 95% power to observe at least one case of uncommon adverse events occurring with an assumed incidence of 1%. This sample size also

provides at least 80% power to detect a doubling of background (i.e., placebo group) incidence rate of 4%. Power increases if background rate increases from 4%.
The sample size would also provide at least 95% power to detect a difference in the efficacy endpoints assuming treatment effects similar to those observed in previous post-surgery studies.

The CHMP agrees that this relatively large study (compared to previous studies on co-administration with opioids) is considered to have a meaningful size for the investigation of opioid-related effects on safety and efficacy.

- **Statistical methods**

The safety analyses were performed on all randomised patients who receive at least one dose of study medication. The event rates for clinically relevant adverse events (CRAE) categories were tabulated and the incidence compared using Fisher's exact test. The 95% confidence interval (CI) was provided for the difference between treatment groups in the proportion of patients with CRAEs. The incidence of CRAEs was also tabulated by type of surgery and geographical region.

The incidence of adverse events was summarised for each treatment group and compared using Fisher's exact test. The incidence of adverse events by attribution, by opioid attribution, and by severity during the IV/IM, PO, and entire study periods were summarised. The incidence of serious adverse events was summarised for each treatment group. Withdrawals due to adverse events were summarised by treatment group and compared using Fisher's exact test.

All efficacy analyses were performed on the Modified Intent-to-Treat (MITT) population – patients who were randomised to treatment and received at least one dose of study medication. Summary statistics (N, mean, and SD) were provided to summarize the rate of analgesia (mg/h) consumed on
Days 2 through 10, during the IV/IM treatment period, and during the PO treatment period for each treatment group and the rate of analgesia (mg/h) was analyzed using analysis of variance with treatment and country as factors.

The CHMP was of the opinion that the statistical methods were appropriate.

Results

Exposure to Study Medication
Table 3 summarises the number doses of study medication for all treated patients by treatment group.

Table 3. Extent of Drug Exposure - All Treated Patients

		Treatment Group	
Sequence of Study Drug	**Statistic**	**Placebo**	**Parecoxib sodium/ Valdecoxib**
IV/IM Study Drug (parecoxib sodium)	N Mean (SD) Median Range	525 6.4 (1.43) 6.0 1-15	525 6.4 (1.30) 6.0 1-12
Oral Study Drug (valdecoxib)	N Mean (SD) Median Range	525 11.7 (4.00) 13.0 0-15	525 11.9 (3.72) 13.0 0-15

1 Parecoxib sodium/valdecoxib = parecoxib sodium 40 mg IV/IM followed by parecoxib sodium 20 mg IV/IM every 12 hours followed by valdecoxib 20 mg PO every 12 hours.

The average duration of parenteral study drug treatment was about 3 days (~6 doses), which is a clinically relevant time of exposure taking into account the SPC warning "There is limited clinical experience with Dynastat treatment beyond three days". However, the study design and the pre-set outcome measures are planned and carried out by data and estimations for the whole 2-10 days study period. Even though data are provided for separate days as well as for the full study period, it is unclear to what extent the different day data reflect use of parecoxib 20 mg BID or valdecoxib BID. Nevertheless, even though the range of parecoxib doses were 1-12, the overall average exposure appears satisfactory for providing useful 2(-3) day data (i.e. first and second postoperative day = Days 2 and 3 in this study).

The CHMP was of the opinion that focusing post-hoc on 2-3 day period outcome measures weaken the study as a support of the proposed extended indication. On the other hand, if data are supportive of clinically useful opioid-sparing effects throughout a 10-day post-operative period with parecoxib/valdecoxib, such findings may strengthen the concept even for short-term use.

Rate of Supplemental Opioids

The rate of analgesic consumption from Days 2 through 10 by treatment group is presented in Table 4. Data are presented as morphine equivalents.

Table 4. Rate of Supplemental Opioid Consumption and Total Daily Supplemental Opioid Consumption From Days 2 through 10 for Patients in the MITT Population

Treatment Group	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
Placebo									
N	519	510	500	491	484	482	473	472	469
Mean (Std) Rate (mg/hr)	0.83 (1.20)	0.41 (0.72)	0.23 (0.64)	0.14 (0.39)	0.10 (0.27)	0.09 (0.34)	0.09 (0.35)	0.07 (0.31)	0.06 (0.34)
Total Daily Consumption (mg)	19.9	9.8	5.5	3.4	2.4	2.2	2.2	1.7	1.4
Parecoxib sodium/Valdecoxib[1]									
N	520	516	502	497	490	485	480	476	473
Mean (Std) Rate (mg/hr)	0.53 (0.93)	0.29 (0.67)	0.14 (0.31)	0.10 (0.27)	0.07 (0.23)	0.07 (0.22)	0.08 (0.30)	0.07 (0.24)	0.06 (0.23)
Total Daily Consumption (mg	12.7	7.0	3.4	2.4	1.7	1.7	1.9	1.7	1.4
Treatment P-Value[2]	<0.001***	0.004**	0.002**	0.026*	0.104	0.227	0.727	0.669	0.820
Type of Surgery p-Value[3]	0.004**	0.002**	0.070	0.003**	0.270	0.254	0.889	0.080	0.162
Morphine Reduction (%)[4]	37	28	38	30	24	21	7	9	8

1 Parecoxib sodium/valdecoxib = parecoxib sodium 40 mg IV (Day 1) followed by parecoxib sodium 20 mg IV/IM every 12 hours (Days 2 through 4) and then valdecoxib
20 mg PO every 12 hours (Days 5 through 10).
2 Analysis of variance with treatment and country as factors.
3 Analysis of covariance with treatment, country and type of surgery as factors, and time from end of surgery to study medication as a covariate.
4 Morphine reduction =100% x (placebo rate – parecoxib sodium rate) / placebo rate. The rates are based on LS means.
***Significant at the 0.001 level. **Significant at the 0.01 level. *Significant at the 0.05 level.
Note: Total supplemental analgesia morphine equivalent from all the routes of administration (PCA, bolus and oral opioids).
Note: Daily Total (mg): rate (mg/hr) x 24 hr.
Note: A study day is defined as the time interval between dose 1 on the current day and dose 1 on the following day.
Note: All the statistics in each interval (day) are based on only those patients with data in the interval.

Mean opioid requirements on the first post-operative day were reduced by 7.2 mg morphine equivalents by parecoxib, which is considered as a clinically relevant difference. On the second post-operative day the corresponding difference between the two groups was 2.8 mg, which is considered as a less meaningful clinical effect. The data show that the overall need of supplemental opioids is greatest in the immediate post-operative period, which falls within the maximum recommended period of treatment with parecoxib (3 days).

These data (large SD-values) demonstrate the well-known wide variation in post-operative opioid requirements among patients. The reduction in opioid supplements produced by parecoxib in this study will therefore not provide any helpful prediction regarding the potential need of opioids in the individual patient.

The statistically significant reduction in mean morphine equivalent consumption was accompanied by superior pain control for the parecoxib treatment group (table 5).

Table 5. Time Weighted Sum of Pain Intensity Over 24 Hours: Study 069

Treatment Group	Day 2	Day 3
Placebo		
N	516	499
Mean (SD)	32.2 (16.1)	25.7 (15.2)
LS Means[a]	29.3	23.7
Parecoxib		
N	519	507
Mean (SD)	23.7 (15.3)	19.0 (15.0)
LS Means[a]	21.1	17.1
P-Value[a]	<0.001	<0.001

N = Number of patients; LS = Least squares; SD = Standard Deviation
[a] Calculated using ANOVA with treatment and country as factors.

The size of the SPIDs depends on how well post-operative analgesia generally was performed. In a recent editorial in Pain (Breivik H, Stubhaug A. Management of acute postoperative pain: Still a long way to go. Pain 2008; 137: 233-4), the reasons for under-managed pain service post-operatively are discussed. Important reasons are organizational obstacles and lack of awareness of the problem. If pain is under-treated (by sub-optimal doses of opioids), the numerical decrease in pain caused by an additional analgesic will tend to be larger when using pain intensity scales. On the other hand, if pain is adequately treated (with a pain intensity below 3 on an 11-point scale), the possible added effect produced by parecoxib is unlikely to be clinically meaningful.

The SPID data above may reflect suboptimal pain treatment. The adequacy of the overall post-operative pain treatment in the trial, as well as the clinical relevance of the numerical differences in SPID between the parecoxib and the placebo group needed to be clarified.

Therefore, in its responses to the Request for Supplementary Information, the MAH cited a study (Cepeda MS, Africano JM, Polo R et al, 2003) which suggests that a reduction of approximately 20% in a numerical pain rating or visual analogue score in a post-surgical acute pain evaluation is clinically meaningful. In Study 069 the reduction (active vs. placebo) of Sum of Pain Intensity over 24 hours was 28% on Day 1 and 27.8% on Day 2. Similar reductions were found using the modified Brief Pain Inventory- short form (mBPI-sf).

In addition, with regard to the overall quality management of pain in the immediate post operative, the MAH reassures the CHMP indicating that the experimental treatments were administered on a background of patient controlled analgesia at all investigational sites and that this is the current state of the art standard.

Modified Brief Pain Inventory-Short Form (mBPI-sf) for Days 2 (= 1 postoperative day) through 10

Across each of study Days 2 through 10 significantly fewer patients in the parecoxib sodium/valdecoxib treatment group reported having had Any Pain in the last 24 hours compared with patients in the placebo treatment group.

The mBPI-sf scores for the two first postoperative days after the day of surgery are shown in table 6.

Table 6. Pain and Pain Interference with Function, mBPI-sf : Study 069 (Day 1 is day of surgery)

Scale Item	Day 2			Day 3		
	Placebo N = 507	**Parecoxib N = 511**	**% Reduction[a]**	**Placebo N = 500**	**Parecoxib N = 510**	**% Reduction[a]**
Mean Pain Intensity						
Worst Pain	5.9	4.3	27%	4.4	3.1	30%
P-Value[b]			≤ 0.001			≤ 0.001
Average Pain	4.0	2.7	33%	2.9	2.0	31%
P-Value[b]			≤ 0.001			≤ 0.001
Mean Pain Interference With Function						
General Activity	5.0	3.6	28%	3.3	2.2	33%
P-Value[b]			≤ 0.001			≤ 0.001
Mood	3.5	2.1	40%	2.1	1.3	38%
P-Value[b]			≤ 0.001			≤ 0.001
Walking Ability	5.2	3.8	27%	3.5	2.5	29%
P-Value[b]			≤ 0.001			≤ 0.001
Relations with Others	2.3	1.3	43%	1.3	0.8	38%
P-Value[b]			≤ 0.001			≤ 0.001
Sleep	3.3	2.2	33%	2.1	1.4	33%
P-Value[b]			≤ 0.001			≤ 0.001
Coughing	2.7	1.9	30%	2.0	1.3	35%
P-Value[b]			≤ 0.001			≤ 0.001
Deep Breathing	2.2	1.4	36%	1.4	0.9	36%
P-Value[b]			≤ 0.001			≤ 0.001
Concentration	2.1	1.2	43%	1.1	0.7	36%
P-Value[b]			≤ 0.001			≤ 0.001
5-Item Composite[c]	**3.8**	**2.6**	**32%**	**2.5**	**1.6**	**36%**
P-Value[b]			≤ 0.001			≤ 0.001
8-Item Composite[c]	**3.3**	**2.2**	**33%**	**2.1**	**1.4**	**33%**
P-Value[b]			≤ 0.001			≤ 0.001

N = Number of patients (indicates numbers of patients who provided evaluable data for mBPI-sf Worst Pain; numbers of patients who provided evaluable data may vary somewhat for other items).

[a] Calculated as the absolute value of the difference between the treatment groups, divided by the value for the placebo treatment group.

[b] Statistical significance calculated based on general linear models with treatment and country as factors.

[c] 5-item composite = average general activity, mood, walking ability, relations with others, and sleep; 8-item composite = average 5-item composite items plus coughing, deep breathing, and concentration.

The (modified) BPI is designed to measure pain intensity and pain interference with life functions.

Since well-treated post-operative pain generally is low (should be 3 or lower on a 0-10 point numerical scale), any additional component to the established treatment will be unlikely to provide large improvements in pain scores. Nevertheless, possible due to inadequate analgesic treatment in the placebo group, the active treatment improved pain and interference scores as well as composite scores by about 1 point (~30%) on average, which may be clinically significant in postoperative patients with average pain scores of 4.0 and worst pain score of 5.9.
The increase by about 10%-points in the number of patients with no reported pain in the active treatment group (Item 1 in mBPI-sf) is considered clinically significant, but could reflect a suboptimal treatment in the placebo group.

Opioid-related Symptom Distress
The reduced opioid consumption was accompanied by a statistically significant reduction in OR-SDS frequency, severity, bothersomeness, and overall composite scores on first and second post-operative day (Days 2 and 3) in patients treated with parecoxib, compared to patients treated with placebo.
Additionally, the clinical benefit of opioid sparing was evident in a reduction in the risk of experiencing CMEs (results for 3 composite CME constructs are presented in Table 7).

Table 7. OR-SDS Scores and Clinically Meaningful Events: Study 069, Days 2 and 3

	Placebo	Parecoxib	
Study Day 2			
Opioid-Related Symptom Distress, mean (SD)			**% Reduction[a]**
N	509	513	
Frequency Composite Score	0.80 (0.66)	0.58 (0.56)	28% (p = 0.001)
Severity Composite Score	0.62 (0.52)	0.45 (0.45)	27% (p = 0.001)
Bothersomeness Composite Score	0.65 (0.59)	0.46 (0.49)	29% (p = 0.001)
Overall Composite Score	0.69 (0.57)	0.50 (0.49)	28% (p = 0.001)
Risk of CMEs[b]			**RR (95% CI)**
Days with ≥1 CME	378/520	307/520	0.81 (0.74, 0.89)
Days with ≥2 CME	285/520	216/520	0.76 (0.67, 0.86)
Days with ≥3 CME	186/520	132/520	0.71 (0.59, 0.86)
Study Day 3			
Opioid-Related Symptom Distress, mean (SD)			**% Reduction[a]**
N	500	506	
Frequency Composite Score	0.57 (0.57)	0.39 (0.48)	32% (p = 0.001)
Severity Composite Score	0.42 (0.42)	0.29 (0.37)	31% (p = 0.001)
Bothersomeness Composite Score	0.44 (0.47)	0.30 (0.38)	32% (p = 0.001)
Overall Composite Score	0.47 (0.47)	0.33 (0.40)	30% (p = 0.001)
Risk of CMEs[b]			**RR (95% CI)**
Days with ≥1 CME	291/505	215/512	0.73 (0.64, 0.83)
Days with ≥2 CME	177/505	116/512	0.65 (0.53, 0.79)
Days with ≥3 CME	114/505	51/512	0.44 (0.32, 0.60)

N = Number of Patients; SD = Standard Deviation; CME = Clinically Meaningful Event; RR = Relative Risk; CI = Confidence Interval.

[a] Based on mean daily scores, with % reduction calculated as the absolute value of the difference between treatment groups, divided by the value for the placebo treatment group. P-values are calculated based on general linear models with treatment and country as factors.

[b] Expressed for each treatment group as total number of patient-days with the respective number of CMEs divided by total number of patient-days of treatment; 95% CIs were constructed using Fisher's Exact Test.

Parecoxib reduced the OR-SDS scores by about 30% on the first 2 post-operative days, but the numerical differences were only about 0.20-0.15. There were wide SDs, but the large samples lead to "impressive" levels of statistical significance. It is unclear to what extent the apparently modest numerical difference reflects a clinically meaningful difference.

On the other hand, the potential clinical benefit of opioid sparing was more evident in terms of occurrence of CMEs, where the size of risk reduction appears clinically relevant. In addition, table 9 shows that CMEs affected a large proportion of patients, which means that a moderate risk reduction reflects an appreciable number of patients with less CMEs.

General conclusion on study I93-01-02-069

The study 069 is a sizable and well-conducted evaluation of the safety and efficacy of parecoxib and valdecoxib following major surgery. The study was planned and carried out prior to the removal of

valdecoxib from the market because of its dermal toxicity. However, as valdecoxib is no longer available the relevance of the study to the claimed indication at times after the parenteral dosing period becomes difficult to interpret.
On post-operative days two and three there was a 36% and a 29% reduction, respectively, in morphine consumption and this resulted in a 28% and a 30% relative reduction in the corresponding opiate related symptom distress score. However, the absolute reduction in the scores were modest and the overall scores low, about one eighth of their maximum possible value. Overall the quality of analgesia seems to have been better in the active treatment arm. This is not surprising as, in effect, patients in that arm received prophylactic analgesia compared to as needed in the placebo arm.

Study PARA-0505-071: A Double-Blind Multicenter Study of the Safety and Efficacy of Parecoxib Sodium/Valdecoxib Compared to Placebo for Treatment of Post-Surgical Pain in Patients who Have Coronary Artery Bypass Graft (CABG) via Median Sternotomy

Protocol No.	Study Design and Objective	Treatment Groups	No. of Subjects (by Treatment Group)	Demographics (by Treatment Group)
PARA-0505-**071**	Phase 3, multi-center, multiple-dose, randomised, double-blind, placebo-controlled, parallel-group study involving patients undergoing primary isolated CABG surgery. **Objectives:** Safety, Analgesic Efficacy, and Effect on Health Outcome Measures.	▪ Day after surgery, parecoxib 40 mg IV followed later the same day by 20 mg IV; thereafter parecoxib 20 mg IV every 12 hours for at least a total of 6 doses, followed by valdecoxib 20 mg every 12 hours.	Randomised: 555 Treated: 544 Completed: 487	Sex: 475 M/80 F Mean/Median Age (min/max): 62/62.5 (36-79) years Race: W/B/O: 524/6/25
		▪ Placebo given as above for parecoxib, followed by valdecoxib as given above.	Randomised: 556 Treated: 544 Completed: 471	Sex: 479 M/77 F Mean/Median Age (min/max): 61.6/61.3 (37-81) years Race: W/B/O: 521/10/25
		▪ Placebo given as above for parecoxib, followed by placebo for valdecoxib as given above.	Randomised: 560 Treated: 548 Completed: 480	Sex: 477 M/83 F Mean/Median Age (min/max): 62.1/62.1 (38-80) years Race: W/B/O: 514/14/32

Methods

- **Study participants**

A total of 1671 patients were randomised at 175 centres in 27 countries from January 2003 - January 2004.

Principal inclusion and exclusion criteria

Eligible patients were adult males or females, 18 to 80 years of age scheduled to undergo elective CABG surgery. All patients were expected to require in-hospital analgesic treatment for postoperative pain for at least three full days and analgesic treatment following discharge over a 10-day period following surgery. Patients participating in the study were required to have a pre-operative New York Heart Association Class I to III or cardiac ejection fraction ≥35%. Patients were required to have a body mass index (BMI) ≤40 kg/m^2 and must have weighed at least 55 kg. Patients were required to be treated post-operatively before the first dose of study medication with 75 to 325 mg aspirin and maintained on this daily dose of aspirin throughout the study. Female patients were to be, post-menopausal, surgically sterile, or using adequate contraception, not lactating, and have a negative pregnancy test at screening.

There were 14 exclusion criteria principally specifying the absence of previous cardiovascular surgery, significant co-morbidity or factors such as alcohol misuse which could compromise participation in the study. There were 15 post-operative to baseline exclusion criteria principally excluding patients with early post-operative complications or clinical instability.

It is noted that this study includes only patients with established cardiovascular disease, which contraindicates treatment with parecoxib as stated in the SPC. In fact, it was a former similar CABG study (Study 035) that particularly raised this concern for parecoxib. Even though the MAH describes this study as pivotal, the CHMP is of the opinion that the inclusion criteria weaken the overall relevance of this study for the present application.

- **Treatments**

Parecoxib or placebo were administered to the three groups as shown in table 8. (Day 1 means the first post-operative day in this study).

Table 8. Groups and treatments

Treatment Groups	Drug	Route	Dose	Dosing Interval	# Patients Planned
1	Parecoxib sodium	IV	40 mg	Day 1, Dose 1	500
	Parecoxib sodium	IV	20 mg	Day 1, Dose 2 followed by q12h through at least Day 3 (minimum of 6 doses of parecoxib sodium)	
	Valdecoxib	PO	20 mg	q12h, when patients can tolerate oral medication after Days 3 through 10	
2	Placebo for Parecoxib sodium	IV	0 mg (Matched to 40 mg)	Day 1, Dose 1	500
	Placebo for Parecoxib sodium	IV	0 mg (Matched to 20 mg)	q12h during parenteral dosing period (minimum of 6 doses of placebo for parecoxib sodium)	
	Valdecoxib	PO	20 mg	q12h when patients can tolerate oral medication after Days 3 through 10	
3	Placebo for Parecoxib sodium	IV	0 mg (Matched to 40 mg)	Day 1, Dose 1	500
	Placebo for Parecoxib sodium	IV	0 mg (Matched to 20 mg)	q12h during parenteral dosing period (minimum of 6 doses of placebo for parecoxib sodium)	
	Placebo for Valdecoxib	PO	0 mg (Matched to 20 mg)	q12h when patients can tolerate oral medication after Days 3 through 10	

The dosage complies with the current SPC. The valdecoxib treatment period has minor importance for this application, which means that this assessment will mainly address the data over the first 3 days, which were scheduled for parecoxib.

- **Outcomes/endpoints**

Primary Endpoint

The primary measure to assess the safety of parecoxib sodium/valdecoxib and placebo/valdecoxib was the combined incidence of the number of patients with at least 1 confirmed CRAE.

Secondary Endpoints

Safety

1. Combined incidence of the number of patients with specific confirmed CRAEs summarised according to the following categories:
    1) Cardiovascular thromboembolic CRAEs consisting of:
        a. Cardiac events: MI, severe myocardial ischemia, cardiac arrest, or sudden cardiac death;
        b. Cerebrovascular events: acute ischemic or hemorrhagic stroke, hemorrhagic infarction, or TIA; and
        c. Peripheral vascular events: vascular thrombosis (lower limb deep vein thrombosis, venous thromboses, other sites, and all peripheral arterial thromboses) or pulmonary embolism.
    2) Renal CRAEs consisting of renal failure or severe renal dysfunction.
    3) GI ulcer CRAEs consisting of perforation, bleeding, or outlet obstruction.
    4) Wound healing complication CRAEs consisting of infectious complications (superficial incisional SSI, deep incisional SSI, and organ space SSI) and non-infectious wound separation or dehiscence.
2. Combined incidence of the number of patients with at least 1 reported CRAE and the combined incidence of the number of patients with specific reported CRAEs summarised according to the categories listed above.
3. Adverse events
4. Serious adverse events

5. Clinical laboratory assessments
6. Vital signs

Efficacy
1. Rate of supplemental analgesia consumed on Days 1 through 10
2. SPI of sternotomy alone and overall body pain over 8 hours (SPI 8) on Day 1
3. SPI of sternotomy alone and overall body pain over 12 hours (SPI 12) and 24 hours (SPI 24) on Days 1 through 10
4. PPI of sternotomy alone and overall body pain on Days 1 through 10
5. Patient's and Physician's Global Evaluation of Study Medication at time of transition from IV/PO medication and Final Visit/Early Termination

Health Outcome Measures
1. Modified Brief Pain Inventory – Short Form (mBPI-sf) on Days 1 through 10
2. Opioid-Related Symptom Distress Scale (OR-SDS) on Days 1 through 10
3. Time to last PCA dose
4. Time spent to manage pain during hospitalization
5. Time from first dose of study medication to exit from critical care unit/intensive care unit.
6. Time from first dose of study medication to discharge from hospital.

The CHMP noted that the sought indication change relates to points 1 and 2 in the last passage mentioned above (mBPI-sf and OR-SDS), and is thus addressed in this study as secondary endpoint (and secondary objective) among other secondary endpoints in this study. Moreover, post-hoc analyses are confined to Days 1-3, whereas the planned analyses were scheduled for the combined parecoxib/valdecoxib 1-10 days period, i.e. the same post-hoc amendment is made as for study 069.

- **Sample size**

Based on clinical judgment and the results of a previous CABG surgery trial (parecoxib Study 035), 500 patients were to be enrolled in each treatment group. This sample size provided at least 85% power to detect the safety signal as observed in the previous CABG trial.

The CHMP agrees that this relatively large study is considered to have a satisfactory size for the investigation of opioid-related effects on safety and efficacy.

- **Statistical methods**

The statistical analyses on opioid-sparing outcome measures in study 071 are similar as described for study 069 and considered appropriate.

Results

Exposure to Study Medication

The average duration of parenteral study drug treatment was about 3 days (~6 doses), which is a clinically relevant time of exposure taking into account the SPC warning "There is limited clinical experience with Dynastat treatment beyond three days". The dosing schedule was well performed during the 3 days of treatment with parecoxib, leaving this period suitable for mBPI-sf and OR-SDS analyses.

Rate of Supplemental Opioids
The rate of analgesic consumption from Days 1 through 10 by treatment group
is presented in Table 9. Data are presented as morphine equivalents.

Table 9. Rate of Supplemental Opioid Consumption and Total Daily Supplemental Opioid Consumption From Days 1 through 10 for the MITT Population

Treatment Group	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
Placebo/Placebo										
N	548	525	507	502	493	490	488	480	476	469
Mean (SD) Rate (mg/hr)	0.74 (0.80)	0.39 (0.60)	0.22 (0.38)	0.11 (0.22)	0.08 (0.17)	0.06 (0.17)	0.04 (0.17)	0.04 (0.18)	0.04 (0.17)	0.02 (0.09)
Daily Total (mg)	17.8	9.4	5.3	2.6	1.9	1.4	1.0	1.0	1.0	0.5
Pairwise Comparison[a]	B	B	B	B	B	B	B	B	B	B
Placebo/Valdecoxib[a]										
N	543	523	512	501	493	480	475	469	457	449
Mean (SD) Rate (mg/hr)	0.68 (0.69)	0.36 (0.54)	0.20 (0.37)	0.07 (0.19)	0.04 (0.13)	0.04 (0.18)	0.03 (0.13)	0.02 (0.11)	0.03 (0.11)	0.02 (0.09)
Daily Total (mg)	16.3	8.6	4.8	1.7	1.0	1.0	0.7	0.5	0.7	0.5
Pairwise Comparison[a]	B	B	B	A	A	A, B	A, B	A	A, B	A, B
Parecoxib Sodium/Valdecoxib										
N	544	528	515	510	505	498	494	490	485	475
Mean (SD) Rate (mg/hr)	0.44 (0.58)	0.23 (0.37)	0.11 (0.23)	0.06 (0.18)	0.06 (0.19)	0.03 (0.15)	0.02 (0.09)	0.01 (0.06)	0.01 (0.05)	0.01 (0.05)
Daily Total (mg)	10.6	5.5	2.6	1.4	1.4	0.7	0.5	0.2	0.2	0.2
Pairwise Comparison[a]	A	A	A	A	A, B	A	A	A	A	A
Treatment p-Value[b]	<0.001***	<0.001***	<0.001**	<0.001**	0.003*	0.077	0.067	<0.001**	0.010*	0.113
Treatment by Country p-Value[c]	0.012*	0.351	0.302	0.175	0.724	0.147	0.107	0.005**	0.005*	0.544
Morphine Reduction (%)[d]										
Parecoxib Sodium/Valdecoxib	41	43	49	42	29	42	50	70	69	57
Placebo/Valdecoxib	9	9	8	36	48	36	32	49	31	15

[a] Treatments with the same letter (A or B) are not significantly different from each other.
[b] ANOVA with treatment and country as factors.
[c] ANOVA with treatment, country, and treatment by country interaction as factors.
[d] Percent Morphine Reduction versus placebo/placebo = 100% × (placebo/placebo rate – placebo/valdecoxib or parecoxib sodium/valdecoxib rate)/placebo/placebo rate.
*** Significant at the 0.001 level. ** Significant at the 0.01 level. * Significant at the 0.05 level.
Note: Total supplemental analgesic morphine equivalent from all the routes of administration (PCA, bolus, and oral opioids).
Note: Daily Total (mg) = Rate (mg/hr) × 24 hours.
Note: A study day is defined as the time interval between dose 1 on the current day and dose 1 on the following day.
Note: All the statistics in each interval (day) are based on only those patients with data in the interval.

Mean opioid requirements on the first post-operative day were reduced by about 6.5 mg morphine equivalents by parecoxib, which is considered as a potentially clinically relevant difference.
On the second and third post-operative day the corresponding difference was about 3.5 mg and 2.5 mg, respectively, which is considered as a less meaningful clinical effect.
The data show that the overall need of supplemental opioids is greatest in the immediate post-operative period, which falls within the maximum recommended period of treatment with parecoxib (3 days).
Similar to study 069, the data (large SD-values) demonstrate the well-known wide variation in postoperative opioid requirements among patients.

The statistically significant reduction in mean morphine equivalent consumption demonstrated above was accompanied by improved pain control in Study 071 for the parecoxib treatment group (see Table 10).

Table 10. Time Weighted Sum of Pain Intensity Over 24 Hours: Study 071

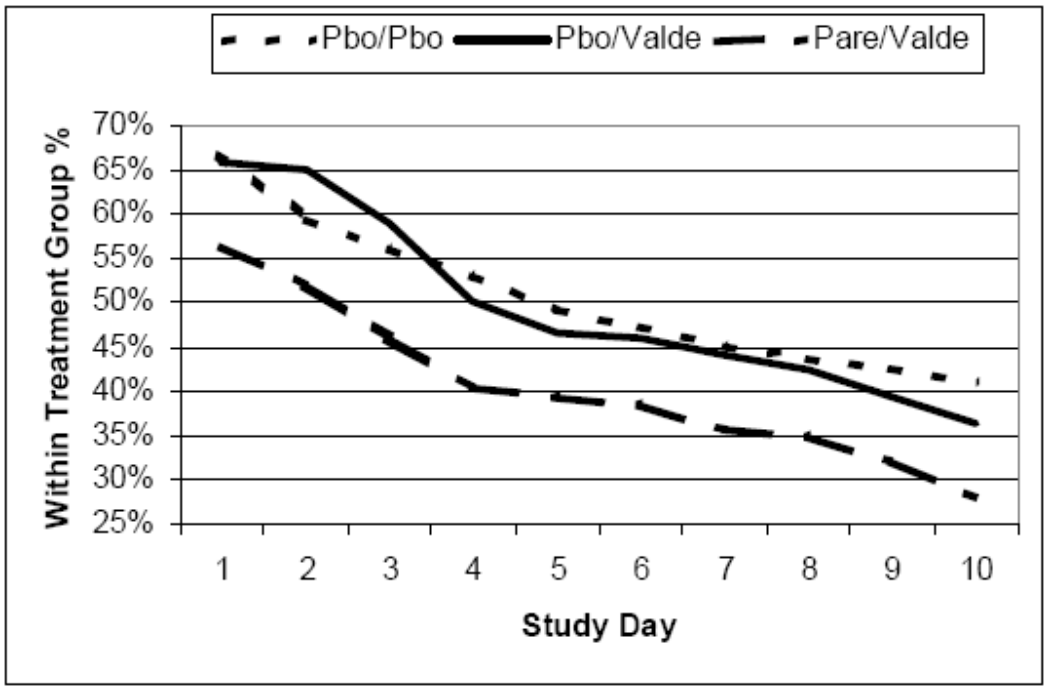
Treatment Group	**Day 1**	**Day 2**	**Day 3**
Placebo			
N	543	516	498
Mean (SD)	22.48 (16.5)	19.69 (15.4)	16.43 (14.8)
LS Means[a]	19.88	17.59	14.56
Parecoxib			
N	542	525	512
Mean (SD)	17.13 (15.1)	14.90 (14.3)	12.38 (13.3)
LS Means[a]	14.29	12.58	10.34
P-Value[a]	<0.001	<0.001	<0.001

N = Number of patients; LS = Least squares; SD = Standard Deviation
[a] Calculated using ANOVA with treatment and country as factors.

Similar concerns as raised for the study 069 (see table 6 above) pertain to the similar data produced in study 071. The SPIDs shown in the table above are smaller than those observed in study 069, however the differences may be considered clinically relevant.

Modified Brief Pain Inventory-Short Form for Days 1 (= 1. postoperative day) through 10
Across each of study Days significantly fewer patients in the parecoxib sodium/valdecoxib treatment group reported having had Any Pain in the last 24 hours compared with patients in the placebo/placebo treatment group (see figure 3).

Figure 3. Within Treatment-Group Trends in Percentage of Patients With Any Pain in the Last 24 Hours



The mBPI-sf scores for the three first post-operative days after the day of surgery are shown in table 11. Results from Study 071 show lower mean scores for pain and pain interference with function in both the parecoxib treatment group and the placebo treatment group as compared to those observed in Study 069. Nonetheless, for all pain and pain interference with function items, statistically significant reductions were observed in the parecoxib treatment group compared to the placebo treatment group.

Table 11. Pain and Pain Interference With Function, mBPI-sf: Study 071

Scale Item	Day 1				Day 2				Day 3			
	Placebo N = 519	**Parecoxib** N = 526	**% Reduction[a]**	**P-Value[b]**	**Placebo** N =517	**Parecoxib** N = 525	**% Reduction[a]**	**P-Value[b]**	**Placebo** N = 504	**Parecoxib** N = 514	**% Reduction[a]**	**P-Value[b]**
Mean Pain Intensity												
Worst Pain	4.0	2.8	30%	<0.001	3.3	2.5	24%	<0.001	2.6	1.9	27%	<0.001
Average Pain	2.5	1.6	36%	<0.001	2.1	1.4	33%	<0.001	1.7	1.2	29%	<0.001
Mean Pain Interference With Function												

General Activity	2.9	1.8	38%	<0.001	2.5	1.6	36%	<0.001	1.9	1.2	37%	<0.001
Mood	2.0	1.2	40%	<0.001	1.7	1.1	35%	<0.001	1.4	0.8	43%	<0.001
Walking Ability	2.4	1.5	38%	<0.001	2.0	1.3	35%	<0.001	1.5	1.0	33%	<0.001
Relations with others	1.3	0.7	46%	<0.001	1.1	0.8	27%	<0.001	0.9	0.6	33%	<0.001
Sleep	2.1	1.3	38%	<0.001	1.9	1.2	37%	<0.001	1.6	0.9	44%	<0.001
Coughing	2.8	2.1	25%	<0.001	2.5	1.8	28%	<0.001	2.0	1.5	25%	<0.001
Deep Breathing	3.1	2.0	35%	<0.001	2.5	1.7	32%	<0.001	1.9	1.3	32%	<0.001
Concentration	1.7	1.0	41%	<0.001	1.4	0.9	36%	<0.001	1.0	0.6	40%	<0.001
5-Item Composite[c]	**1.9**	**1.1**	**42%**	**<0.001**	**1.6**	**1.0**	**38%**	**<0.001**	**1.3**	**0.8**	**38%**	**<0.001**
8-Item Composite[c]	**2.3**	**1.4**	**39%**	**<0.001**	**2.0**	**1.3**	**35%**	**<0.001**	**1.5**	**1.0**	**33%**	**<0.001**

N = Number of patients (indicates patients who provided evaluable data for mBPI-sf Worst Pain; numbers of patients who provided evaluable data may vary for other items).

[a] Calculated as the absolute value of the difference between treatment groups, divided by the value for the placebo group.

[b] Statistical significance calculated based on analysis of variance (ANOVA) models with treatment and country as factors.

[c] 5-item composite = average general activity, mood, walking ability, relations with others, and sleep; 8-item composite = average 5-item composite items plus coughing, deep breathing, and concentration.

Source: Study Report 071, Tables T20.2; T20.4; and T20.7.1-10.

Since the post-operative pain was apparently well treated in these patients, any additional component to the established treatment will be unlikely to provide large improvements in pain scores. Accordingly, the numerical differences between the placebo group and the parecoxib group in table 14 have small clinical significance, even though the relative improvements are in the order of 30-40%, and statistical significances are high.

The increase by about 10%-points in the number of patients with no reported pain in the active treatment group (Item 1 in mBPI-sf, figure 3) may be considered clinically significant.

Opioid-related Symptom Distress (OR-SDS)

The reduced opioid consumption was accompanied by a statistically significant reduction in OR-SDS frequency, severity, bothersomeness, and overall composite scores on days 1-3 in patients treated with parecoxib, compared to patients treated with placebo. Additionally, the clinical benefit of opioid sparing was evident in a reduction in the risk of experiencing CMEs (results for 3 composite CME constructs are presented in table 12).

Table 12. OR-SDS Scores and Clinically Meaningful Events: Study 071, Days 1-3

	Placebo N = 519	Parecoxib N = 533	
Opioid-Related Symptom Distress, mean (SD)[a]			**% Reduction (P-value)**
Frequency Composite Score	1.25 (0.95)	1.08 (0.88)	14% (p = 0.003)
Severity Composite Score	0.95 (0.76)	0.82 (0.74)	14% (p = 0.004)
Bothersomeness Composite Score	0.67 (0.76)	0.54 (0.69)	20% (p = 0.004)
Overall Composite Score	0.95 (0.78)	0.80 (0.74)	16% (p = 0.003)
Risk of CMEs[b]			**RR (95% CI)**
Days with ≥1 CME	951/1580	886/1587	0.93 (0.85, 1.02)
Days with ≥2 CME	717/1580	599/1587	0.83 (0.75, 0.93)
Days with ≥3 CME	415/1580	339/1587	0.81 (0.70, 0.94)

N = Number of Patients; SD = Standard Deviation; CME = Clinically Meaningful Event; RR = Relative Risk; CI = Confidence Interval.

[a] Based on summed average score over Days 1-3, with % reduction calculated as the absolute value of the difference between treatment groups, divided by the value for the placebo treatment group. P-values are calculated based on analysis of variance (ANOVA) models with treatment and country as factors.

[b] Expressed for each treatment group as total number of patient-days with the respective number of CMEs divided by total number of patient-days of treatment; 95% CIs were constructed using Fisher's Exact Test.

Source: Clinical Study Report 071, Tables 44; T23.6; T25.2.

Parecoxib reduced the OR-SDS scores by about 16% on the first 3 post-operative days, and the numerical differences were only about 0.15. There were wide SDs, but the large samples lead to "impressive" levels of statistical significance. It is unclear to what extent the apparently modest numerical difference reflects a clinically meaningful difference.

On the other hand, the potential clinical benefit of opioid sparing was somewhat more evident in terms of occurrence of CMEs. The table shows that a large proportion of CABG patients experience a CME during the immediate post-operative period, however, such patients are not typical representatives of the general post-operative patient population, meaning that the results can not be fully extrapolated to post-operative patients in general.

Supportive Study

PARA-0505-080: Multicenter, Multinational, Double-Blind, Randomised, Placebo-Controlled Study Comparing The Efficacy And Safety Of Parecoxib Sodium Vs Propacetamol And The Combination Of Parecoxib And Propacetamol For Pain After Hip Arthroplasty

Protocol No.	Study Design and Objective	Treatment Groups	No. of Subjects (by Treatment Group)	Demographics (by Treatment Group)
PARA-0505-**080**	Phase 3b, multi-center, multinational, multiple-dose, randomised, double-blind, placebo-controlled, parallel-group, 48-hour study after patient underwent hip arthroplasty and was designed to evaluate the morphine-sparing effect of parecoxib versus propacetamol, the combination of parecoxib and propacetamol, or placebo. **Objectives:** Pain relief with parecoxib versus propacetamol and the combination of parecoxib and propacetamol. Safety and tolerability of multiple doses of parecoxib.	▪ Parecoxib 40 mg IV BID	Randomised: 72 Treated: 72 Completed: 64	Sex: 30 M/42 F Mean/Median Age (min/max): 65.6/67.3 (41 - 84) years Race: W/B/O: 70/1/1
		▪ Propacetamol 2 grams IV QID	Randomised: 71 Treated: 71 Completed: 63	Sex: 30 M/ 41 F Mean/Median Age (min/max): 66.9/68.7 (39- 86) years Race: W/B/O: 71/0/0
		▪ Parecoxib 40 mg IV BID + propacetamol 2 grams IV QID	Randomised: 72 Treated: 72 Completed: 69	Sex: 29 M/ 43 F Mean/Median Age (min/max): 66.6/68.2 (28 – 84) years Race: W/B/O: 71/1/0
		▪ Placebo	Randomised: 38 Treated: 38 Completed: 33	Sex: 19 M/ 19F Mean/Median Age (min/max): 67.7/70.8 (48 – 82) years Race: W/B/O: 38/0/0

Methods

- **Study participants**

A total of 253 patients were randomised at 18 centres in 5 countries from October 2002 - January 2004.

Principal inclusion and exclusion criteria

Eligible patients were at least 18 years old and capable of giving informed consent. If of childbearing potential, had been using effective contraception and would continue to use effective contraception during the study period, were not lactating, and had a negative pregnancy test within 24 hours prior to the first dose of study medication. Patients were in satisfactory health as determined by the investigator and were scheduled for routine total primary hip replacement surgery performed under a standardised regimen of spinal anesthesia, and were expected to experience moderate to severe post-surgical pain.

There were 17 exclusion criteria the principal ones being an emergency hip replacement procedure, a hip replacement procedure further to a trauma, or a procedure expected to last longer than 4 hours. A history of uncontrolled chronic disease or a concurrent clinically significant illness or medical condition, which in the investigator's opinion, would contraindicate study participation or confound interpretation of the

results. Receipt of investigational medication within 30 days prior to administration of study medication: previous admission to the study.

The CHMP agrees that the inclusion criteria adequately reflect the group of patients who would normally require opioid analgesia after general major surgery, and who may profit from multimodal analgesic regimes with a COX-inhibitor.

- **Treatments**

A schematic presentation of the trial is presented. The first dose of study medication was administered immediately after the last surgical stitch. For the QID regimen each subsequent dose was administered at 6-hour intervals until 42 hours, and for the BID regimen at 12-hour intervals at until 36 hours.

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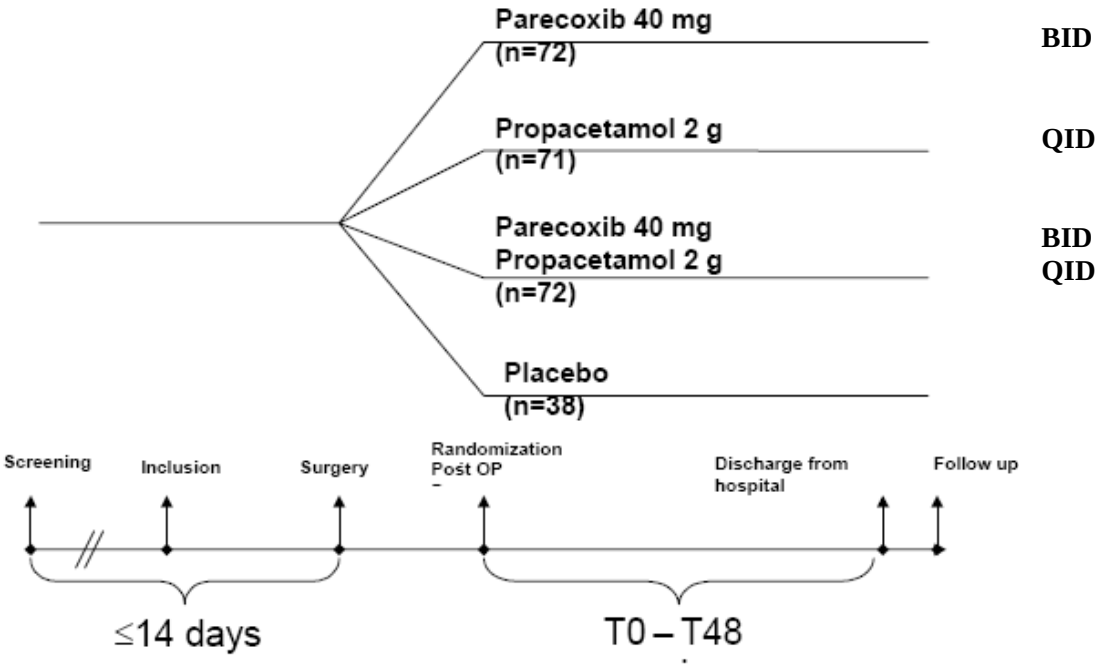


The dosage complies with the current SPC. The data for the opioid-saving results were collected on the two first post-operative days (i.e. Day 1 and Day 2).

- **Outcomes/endpoints**

Primary Endpoint:
The total cumulative amount of morphine administered (PCA and bolus) in the 24 hours after the end of surgery.

Secondary Endpoints:
1. The total cumulative amount of morphine administered (PCA and bolus) in the 48 hours after surgery.
2. Time specific pain intensity (Visual Analog Scale [VAS] and categorical scale) at 2, 4, 6, 8, 10, 12, 18, 24, 30, 36, 42, and 48 hours after the initial dose of study medication.
3. Change in pain intensity (VAS and categorical scales) after log roll.
4. Patient global assessment of analgesic experience.
5. Opiate Symptom Distress Questionnaire on Days 1-2.
6. Modified Brief Pain Inventory-Short Form (mBPI-sf) on Days 1-2.
7. Time of last Patient Controlled Analgesia (PCA) dose.

8. Pulse oximetry monitoring of hypoxemia (where available)

The sought indication relates to the primary endpoint (even though the primary objective was a non-inferiority analysis comparing parecoxib with parecoxib+propacetamol) and points 5 and 6 among the secondary endpoints.

- **Sample size**

The sample size is based on the primary efficacy criteria - amount of morphine consumed within 24 hours - and on the primary comparison: non-inferiority of parecoxib versus parecoxib + propacetamol. Parecoxib will be considered non-inferior to the combination of parecoxib and propacetamol if the one sided 95% confidence interval for the difference between treatments lies within the margin of non-inferiority. According to clinical knowledge and previous studies, the margin of non-inferiority could reasonably be fixed at 6 mg (standard deviation of 12.92 mg) and a sample size of 59 patients per treatment group is then needed to conclude non-inferiority with a power of 80%. Due to the design and objectives of the study, it is decided to equally balance the 3 active groups, and the placebo group will be in a 1:2 ratio with each active treatment group. Therefore, a total of 231 patients will be included in the study, 66 in each active treatment group and 33 in the placebo group, taking into account approximately 10% patients excluded from per protocol analysis.

The non-inferiority margin of 6 mg per 24 hours seems reasonable, and is in line with the CHMP's comments on what is considered as clinically meaningful differences in opioid consumption in studies 069 and 071.

- **Statistical methods**

The cumulative amount of morphine administered by PCA and bolus and time specific pain intensity (VAS) will be analyzed using a two-way ANOVA model with treatment and center as factors.
The individual mBPI-sf responses for worst pain intensity, least pain intensity, average pain intensity, current pain intensity, pain relief and pain interference scores will be analyzed using a general linear model with treatment and center as factors. The responses for pain in the last 24 hours (yes/no) will be analyzed using the CMH method, controlling for center.

The CHMP considers the statistical methods appropriate.

Results

- **Patient disposition**

All randomised 253 patients received at least one dose of study medication and were included in the modified intention to treat (MITT) cohort. 10 patients were excluded due to late institution of PCA, and 24 patients were withdrawn before 24 hours. 203 patients comprise the Evaluable cohort. Other reasons for subjects excluded from the Evaluable population are presented in Section 13, Appendix 3.3.1 [- not included in the submitted dossier].

It is unclear to what extent the evaluable cohort used in the non-inferiority analysis is a well-defined per-protocol population, especially with regard to per-protocol exposure of study drugs.

Rate of Supplemental Opioids
The rates of analgesic consumption during the first postoperative day are presented in table 13.

Table 13. Mean Cumulative Amount of Morphine Administered (PCA and Bolus) in the First 24 Hours After Surgery – Evaluable Population

	Parecoxib 40 mg BID	Propacetamol 2 g QID	Parecoxib 40 mg BID + Propacetamol 2 g QID	Placebo
N	58	58	59	28
Adjusted Mean (s.e)[a]	22.8 (2.00)	27.3 (1.98)	15.0 (1.97)	37.3 (2.85)
95% CI	[18.9, 26.7]	[23.4, 31.2]	[11.1, 18.9]	[31.6, 42.9]
(Change in morphine consumption vs placebo %)	(-38.9%)	(-26.8%)	(-59.8%)	
Estimates of Treatment Difference[b] - Evaluable Population				
	Difference (s.e)	95% CI	*P*-value[d]	
Primary Contrast				
Parecoxib+Propacetamol vs Parecoxib[c]	-7.80 (2.782)	[-12.40, infinity]		
Secondary Contrasts				
Parecoxib vs Propacetamol	-4.49 (2.816)	[-10.04, 1.07]	0.113	
Parecoxib vs Placebo	-14.44 (3.471)	[-21.29, -7.59]	<0.001	
Propacetamol vs Placebo	-9.95 (3.468)	[-16.79, -3.11]	0.005	
Parecoxib+Propacetamol vs Propacetamol	-12.29 (2.792)	[-17.80, -6.79]	<0.001	
Parecoxib+Propacetamol vs Placebo	-22.24 (3.457)	[-29.06, -15.43]	<0.001	

a. Least square means, adjusted for center.
b. Estimates based on comparisons of least square means.
c. Evidence showing parecoxib is noninferior to the combination of parecoxib + propacetamol is obtained if the lower 95% CI bound is greater than –6.
d. *P*-value is from a two-sided test of no difference between treatment groups.

For the primary efficacy analysis – parecoxib + propacetamol vs parecoxib – the lower bound of the 95% confidence interval included the non-inferiority limit of –6 mg, therefore, the null hypothesis could not be rejected and the non-inferority of parecoxib 40 mg BID to the combination parecoxib 40 mg BID plus propacetamol 2 g QID was not demonstrated.
For the secondary efficacy contrasts at 24 hours post surgery, parecoxib showed a numerically greater morphine reduction (38.9%) compared with propacetamol (26.8%) but this difference was not statistically significant (p=0.113). Statistically significant differences (at p<0.001) were observed for parecoxib versus placebo (38.9% reduction).
The general pattern of morphine use observed after 48 hours was similar to that observed after 24 hours.

Since analysis of the evaluable cohort clearly did not show non-inferiority for parecoxib compared to parecoxib + propacetamol, it is highly unlikely that a potentially strictly defined per-protocol population would have given a different result. Nevertheless, the primary study objective has minor relevance to the present variation application. With regard to the secondary endpoints, parecoxib gave clinically significantly reduced mean opioid-requirements compared to placebo both during 24 h post-surgery (difference 14.5 mg) and 24-48 h post-surgery (difference 13.5 mg). Again the data demonstrate a wide variation in postoperative opioid requirements among patients.

Using a 100 mm VAS scale, pain intensity was measured at two time point after surgery (table 14).
Only placebo and parecoxib data are shown.

Table 14. Pain Intensity at 24 and 48 Hours After Surgery: Study 080 [a]

	Placebo (N = 38)	Parecoxib 40mg BID (N = 72)
24 Hours		
Mean (SD)	18.8 (20.73)	11.6 (15.47)
95% CI	(11.9, 25.6)	(7.9, 15.2)
LS Mean (SE)[a]	18.8 (2.86)	11.7 (2.08)
95% CI	(13.2, 24.5)	(7.6, 15.8)
P-value[b]		0.046
48 Hours		
Mean (SD)	13.3 (19.45)	8.2 (14.37)
95% CI	(6.9, 19.7)	(4.9, 11.6)
LS Mean (SE)[a]	13.5 (2.73)	8.4 (1.99)
95% CI	(8.1, 18.9)	(4.5, 12.3)
P-value[b]		0.133

SD = Standard Deviation; CI = Confidence Interval; LS = Least squares; SE = Standard Error.

[a] LS Means were adjusted for center, and analyses were performed using data for all patients who were randomised and received at least one dose of study medication.

[b] Statistical significance calculated using a general linear model with fixed effects for treatment and center (two-sided test of no difference between treatment groups).

Modified Brief Pain Inventory-Short Form for Days 1-2

In the supportive Study 080, treatment with parecoxib alone and in combination with propacetamol significantly reduced the "Worst Pain" and "Average Pain" assessed in the mBPI-sf compared to placebo treatment at the end of 24 and 48 hours (data at 48 hours are shown in Table 15)

Table 15. Pain and Pain Interference With Function, mBPI-sf: Study 080 (48 hours)

	Placebo (N = 32)	Parecoxib 40mg BID (N = 65)	Propacetamol 2g QID (N = 64)	Parecoxib 40mg BID + Propacetamol 2g BID (N = 67)
Pain Intensity[a]				
mBPI-sf Worst	5.7	3.1	4.4	3.2
% Reduction (P-value)		46% (<0.001)	23% (0.035)	44% (<0.001)
mBPI-sf Average	2.7	1.7	2.3	1.6
% Reduction (P-value)		37% (0.003)	15% (0.285)	41% (0.001)
Pain Interference With Function[a]				
General Activity	4.5	2.0	2.6	2.0
% Reduction (P-value)		55% (<0.001)	42% (0.002)	55% (<0.001)
Mood	2.0	0.7	1.7	0.9
% Reduction (P-value)		65% (0.006)	15% (0.509)	55% (0.017)
Walking Ability	6.6	4.3	5.5	4.4
% Reduction (P-value)		35% (0.019)	17% (0.295)	33% (0.025)
Relations With Others	1.4	0.3	0.9	0.2
% Reduction (P-value)		79% (<0.001)	36% (0.112)	86% (<0.001)
Sleep	2.2	1.5	2.2	1.3
% Reduction (P-value)		32% (0.158)	0% (0.933)	41% (0.088)
Coughing	0.5	0.1	0.3	0.0
% Reduction (P-value)		80% (0.040)	40% (0.343)	100% (0.015)
Deep Breathing	0.6	0.1	0.1	0.0
% Reduction (P-value)		83% (0.004)	83% (0.010)	100% (0.002)
Concentration	1.2	0.6	1.0	0.4
% Reduction (P-value)		50% (0.104)	17% (0.572)	67% (0.022)

BID = Twice daily; QID = Four times daily; N = Number of patients (indicates patients who provided evaluable data for mBPI-sf Worst Pain; numbers of patients who provided evaluable data may vary for other items);

[a] Presented are least squares means, with % reductions calculated as the absolute value of the difference between treatment groups, divided by the value for the placebo group. P-values are calculated based general linear model with fixed effects for treatment and center (two-sided test of no difference between treatment groups).

Experience of "worst pain" is lower with parecoxib compared to placebo (mean difference 2.6 points, which is considered clinically relevant). Moreover, "general activity" and "walking ability" showed possibly clinically relevant differences compared to placebo. Other items showed small numerical differences.

Opioid-related Symptom Distress

Treatment with the combination of parecoxib and propacetamol, compared to placebo, produced the greatest reduction in OR-SDS symptom distress with significant reductions in all three distress composite scores (frequency, severity, and bothersomeness) and in the overall composite score across dimensions and symptoms for both the 0-24h and the 24-48h periods. Compared to placebo, treatment with parecoxib alone was associated with significant reductions in the bothersomeness composite score and in the overall composite score during the 0-24h period only (Table 16).

Table 16. OR-SDS Scores for Days 1 and 2 – MITT Cohort.
Only Placebo and Parecoxib data are presented

	Placebo	Parecoxib	
Study Day 1 (0-24 hours)			
Opioid-Related Symptom Distress, mean (SD)			**P-value[a]**
N	36	70	
Frequency Composite Score	0.73 (0.54)	0.57 (0.53)	p = 0.079
Severity Composite Score	0.62 (0.45)	0.49 (0.42)	p = 0.063
Bothersomeness Composite Score	0.62 (0.55)	0.46 (0.43)	p = 0.033
Overall Composite Score	0.66 (0.50)	0.51 (0.45)	p = 0.046
Study Day 2 (24-48 hours)			
Opioid-Related Symptom Distress, mean (SD)			**P-value[a]**
N	33	65	
Frequency Composite Score	0.48 (0.42)	0.41 (0.40)	p = 0.273
Severity Composite Score	0.42 (0.36)	0.32 (0.34)	p = 0.101
Bothersomeness Composite Score	0.35 (0.35)	0.27 (0.30)	p = 0.122
Overall Composite Score	0.42 (0.37)	0.33 (0.33)	p = 0.143

N = Number of Patients; SD = Standard Deviation; CI = Confidence Interval.
[a] P-values are from a 2-sided test of no difference between treatment groups.

Parecoxib reduced the Overall Composite OR-SDS score by about 23% on the first post-operative day, but the numerical differences were only 0.15. It is unclear to what extent the apparently modest numerical difference reflects a clinically meaningful difference.

Other submitted data

Validation reports for the modified Brief Pain Inventory short form (mBPI-sf) and the Opioid-Related Symptom Distress Scale (OR-SDS)

The MAH submitted validation reports of the two measurement instruments of health outcomes used in the 3 above-mentioned studies: the modified Brief Pain Inventory short form (mBPI-sf) and the Opioid-Related Symptom Distress Scale (OR-SDS)

The CHMP agrees that the overall validation of the mBPI-sf is considered satisfactory with acceptable results for construct validity, discriminant validity and responsiveness.

For the OR-SDS, the CHMP agrees that a satisfactory validation is provided for composite scores based on CME for symptoms in the OR-SDS.
However, this validation report does not evaluate or discuss the properties of OR-SDS scores, but provides a confirmation of the CME scores as a valid tool for monitoring opioid-related symptom distress. Fortunately, the estimated cut-off points for CMEs were identical in this report as in the submitted studies. The validation report does, however, question the appropriateness of including both severity and frequency for the calculation of CME scores (as done in the studies); nevertheless the arguments for simplifying the definition of CME to only symptom severity should not contradict the validity of also including the frequency item.
With regard to the OR-SDS scores (separate from the CME scores), there is no specific validation of the scale. However, such validation may not be a critical issue, since the use of OR-SDS scores may not be effective for providing clinically meaningful differences to reflect different consumptions of opioid analgesics, as commented for studies 069, 071 and 080. On the other hand, if clinically meaningful effects are claimed for apparently small differences, the existence of a satisfactory validation becomes more critical.

In its responses to the Request for Supplementary Information, the MAH argues that the OR-SDS has been validated and cited publications from 1994 and 2004. The CHMP was however of the opinion that this argument is not a robust one. A brief review of the literature suggests that the publications cited by the MAH may be the only ones relating to the score. However, this issue on validation of OR-SDS can be dealt with by appropriate wording in the SPC (see section III-4 Product Information).

2. CLINICAL SAFETY

- **Safety results of study PARA-0505-071:**

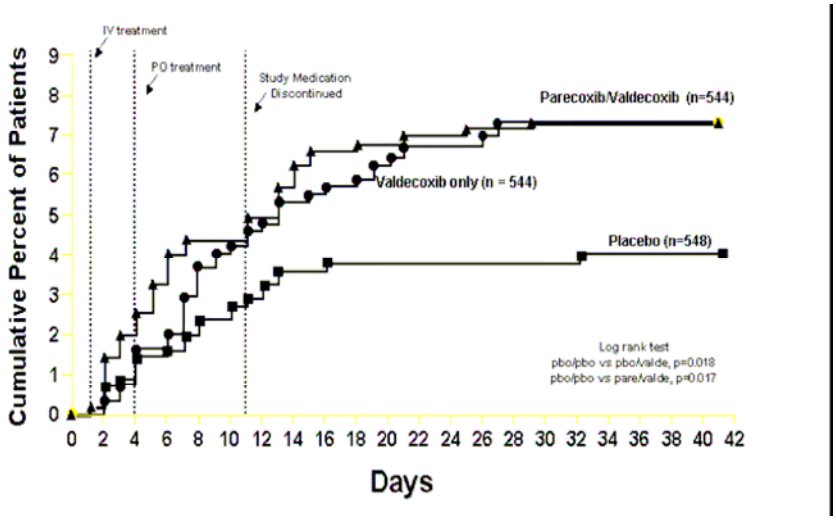
The following table 17 and figure 4 present a summary of the CRAEs over the entire study period for the 3 treatments group as well as the time to event for CRAE by treatment arm.

Table 17. Summary of CRAEs over the entire study period (primary study variable)

	Plac/Plac	Plac/Val	Par/Val
		Cardiovascular	
Myocardial infarction	0	1	1
Cardiac arrest	0	0	1
Cardiac arrest resuscitated	0	1	1
Sudden cardiac death	0	1	1
Total Cardiovascular	0		
Cardioembolic probable	1	1	2
Cardioembolic possible	1	0	0
Acute ischemic	0	1	0
TIA	0	0	3
Vascular thrombosis	1	0	0
Pulmonary embolism	1	2	2
Total Cardiovascular*[1]	**3**	**6**	**11**
		Renal dysfunction/failure	
Required dialysis	0	2	2
Persistent high serum creatinine	3	2	5
Total Renal	**3**	**4**	**7**
		Upper GI	
Haematemesis with GU/DU	0	0	1
GU/DU on endoscopy	2	3	3
Melena with GU/DU	0	0	2
Perforation	0	1	0
Total GI	**2**	**4**	**6**
		Wound complications	
Superficial incisional SSI	12	13	8
Deep incisional SSI	1	5	5
Organ/space SSI	1	1	1
Healing complication	2	8	6
Total surgical wound	**16**	**27**	**20**
No. with ≥ 1 CRAE[2]	22 (4%)	40 (7.4%)	40 (7.4%)

* as one patient may experience more than one event the numbers do not necessarily match – the primary criterion was the number of patients experiencing a qualifying CRAE and not the number of events.
1 for cardiovascular CRAEs the comparisons between both active treatment groups and placebo were statistically significant p = 0.033
2 Overall CRAEs were significantly more common in the two active treatment groups than in the placebo group p = 0.019

Figure 4. Time to event for CRAE by treatment arm



The CHMP noted the statistically significant excess of CRAEs in the two active treatment groups and particularly the time to event analysis which suggests a 'catch up' effect when the placebo for parecoxib group switches to active treatment. These safety results for Study 071 replicate those of a previous study in CABG trial (Study 035) in which there was a higher CRAE and particularly cerebrovascular thrombotic or ischemic rate in the active treatment group.

- **Other safety results**

It is noted that in study I93-01-02-069, the incidence of gastrointestinal toxicity was higher with active treatment where there were 12 clinically important events compared to 2 in the placebo group.

The MAH has provided adverse events data from 26 "Parecoxib combined surgery studies", which adequately seem to represent the patient population most likely to receive parecoxib.

Durations of exposure to parecoxib or placebo in the 26 Combined Surgery Studies are summarised in Table 18.

Table 18. Exposure to Placebo or Parecoxib: Combined Surgery Studies

Number (%) of Patients

		Parecoxib Sodium	
	Placebo	**20-60 mg TDD[a]**	**80 mg TDD[a,b]**
Day 1	3627 (100.0)[c]	3860 (100.0)	808 (100)
Day 2	2448 (67.5)	2157 (55.9)	742 (91.8)
Day 3	1890 (52.1)	1337 (34.6)	400 (49.5)
Day 4	472 (13.0)	374 (9.7)	274 (33.9)
Day 5	62 (1.7)	41 (1.1)	29 (3.6)
Day 6	5 (0.1)	9 (0.2)	0 (0.0)
Day 7	2 (<0.1)	1 (<0.1)	0 (0.0)
Day 8	1 (<0.1)	0 (0.0)	0 (0.0)
Day 9	1 (<0.1)	0 (0.0)	0 (0.0)
Day 10	0 (0.0)	0 (0.0)	0 (0.0)

TDD = Total daily dose.

[a] Data were excluded for 32 patients who were re-randomised to receive parecoxib sodium 40-60 mg TDD or parecoxib sodium 80 mg TDD in Studies 020 and 021 after first having received placebo or morphine.

[b] Excludes data for 72 patients who received parecoxib sodium in combination with propacetamol 2 g four times daily in Study 080.

[c] One patient was excluded from the placebo group due to an error in recording the study medication administration date.

It is noted that only data from the IV treatment periods of these studies are included in the table above and in the integrated summaries of adverse events.

Adverse events occurred in 46% (1776/3860) of patients treated with parecoxib 20 to 60 mg TDD and in 64% (514/808) of patients treated with parecoxib 80 mg TDD, compared to 53% (1936/3628) of patients treated with placebo (Table 19).

Table 19. Adverse Events Occurring in ≥2% of Patients in Any Treatment Group: Parecoxib Combined Surgery Studies

	Number (%) of Patients		
		Parecoxib TDD (mg)	
Body System	**Placebo**	**20-60**	**80**
Adverse Event	**N = 3628**	**N = 3860**	**N = 808**
Any Adverse Event	**1936 (53.4)**	**1776 (46.0)**	**514 (63.6)**
Autonomic Nervous System Disorders	**154 (4.2)**	**227 (5.9)**	**77 (9.5)**
Hypertension	29 (0.8)	80 (2.1)	13 (1.6)
Hypotension	65 (1.8)	75 (1.9)	54 (6.7)
Body as a Whole – General	**616 (17.0)**	**407 (10.5)**	**123 (15.2)**
Edema Peripheral	62 (1.7)	43 (1.1)	37 (4.6)
Fever	348 (9.6)	108 (2.8)	35 (4.3)
Postoperative Incisional Pain	17 (0.5)	68 (1.8)	2 (0.2)
Central & Peripheral Nervous System Disorders	**312 (8.6)**	**352 (9.1)**	**70 (8.7)**
Dizziness	152 (4.2)	196 (5.1)	34 (4.2)
Headache	116 (3.2)	124 (3.2)	18 (2.2)
Gastrointestinal System Disorders	**912 (25.1)**	**927 (24.0)**	**333 (41.2)**
Abdominal Pain	56 (1.5)	93 (2.4)	15 (1.9)
Constipation	214 (5.9)	181 (4.7)	91 (11.3)
Dyspepsia	34 (0.9)	44 (1.1)	14 (1.7)
Nausea	600 (16.5)	561 (14.5)	230 (28.5)
Vomiting	249 (6.9)	254 (6.6)	78 (9.7)
Heart Rate and Rhythm Disorders	**370 (10.2)**	**181 (4.7)**	**83 (10.3)**
Fibrillation Atrial	240 (6.6)	62 (1.6)	43 (5.3)
Tachycardia	72 (2.0)	53 (1.4)	21 (2.6)
Metabolic and Nutritional Disorders	**118 (3.3)**	**67 (1.7)**	**73 (9.0)**
Hypokalemia	28 (0.8)	11 (0.3)	21 (2.6)
Psychiatric Disorders	**338 (9.3)**	**375 (9.7)**	**86 (10.6)**
Insomnia	98 (2.7)	81 (2.1)	46 (5.7)
Somnolence	114 (3.1)	220 (5.7)	17 (2.1)
Red Blood Cell Disorders	**112 (3.1)**	**86 (2.2)**	**55 (6.8)**
Anemia	76 (2.1)	52 (1.3)	5 (0.6)
Postoperative Anemia	32 (0.9)	32 (0.8)	43 (5.3)
Respiratory System Disorders	**314 (8.7)**	**180 (4.7)**	**110 (13.6)**
Abnormal Breath Sounds	45 (1.2)	25 (0.6)	37 (4.6)
Dyspnea	41 (1.1)	24 (0.6)	17 (2.1)
Pleural Effusion	51 (1.4)	17 (0.4)	16 (2.0)
Skin and Appendages Disorders	**187 (5.2)**	**250 (6.5)**	**52 (6.4)**
Pruritus	119 (3.3)	173 (4.5)	32 (4.0)
Sweating Increased	34 (0.9)	36 (0.9)	17 (2.1)
Urinary System Disorders	**165 (4.5)**	**146 (3.8)**	**94 (11.6)**
Oliguria	42 (1.2)	35 (0.9)	48 (5.9)
Urinary Retention	44 (1.2)	36 (0.9)	24 (3.0)

TDD = Total Daily Dose

It is reasonable to believe that the parecoxib group received somewhat less post-operative opioids, however, the tabulated data do not indicate any clear difference in the occurrence of adverse events (acknowledging the difficulty to interpret the comparison with the 80 mg TDD group).

In order to assess the overall adverse events profile compared to the opioid-related events profile between treatments, the CHMP requested the MAH to provide pooled data from the three opioid-sparing studies (069, 071 and 080). Such summary data will make it possible to assess if the reduction of opioid-related CMEs was followed by an increase in other (parecoxib-related) adverse events.

However, the MAH makes the point that the clinical development plan for valdecoxib and parecoxib was designed and powered primarily to demonstrate a difference in between active and placebo treatments with respect to efficacy and not to detect safety differences, which must be based on the

differences of investigator reporting rates. No overview or meta-analysis of the adverse events were provided.
In the supporting clinical studies patients treated with morphine and parecoxib/valdecoxib experienced more frequent NSAID/COX2 adverse effects than those in the placebo arm. This is to be expected and will be known to prescribers of parecoxib. The relative contribution of valdecoxib and parecoxib to the safety profile is not evaluable and therefore it is difficult to formulate a warning or SPC wording on the issue. However, the CHMP was of the opinion that the risks are not such as to prevent the variation being approved.

3. OVERALL DISCUSSION ON CLINICAL EFFICACY AND CLINICAL SAFETY

In the three present studies - Study 069 (general surgery), Study 071 (CABG surgery), and Study 080 (orthopedic surgery of the hip) - the clinical benefit of opioid sparing was investigated using 2 instruments (questionnaires) to assess patient-reported outcomes: the Opioid Related Symptom Distress Scale (OR-SDS) (including Clinically Meaningful Events (CME) in studies 069 and 071); and a modified version of the Brief Pain Inventory short form (mBPI-sf). In addition, the amount of opioids that patients required to achieve pain control was estimated.

Study 069 is clearly relevant for the target population of the proposed extended indication, whereas the other pivotal study 071 may have less relevance as that study population only includes CABG-surgery patients, for whom parecoxib is contraindicated in the SPC.

The mBPI-sf is quite similar to the original BPI-sf, e.g. the pain severity domain is identical. The overall validation of the mBPI-sf is considered satisfactory.
The definition of clinically meaningful events (CME) is considered useful. A satisfactory validation is provided for scores based on CME for symptoms in the OR-SDS.

However, with regard to the OR-SDS scores (separate from the CME scores), there is no specific validation of the 10-point scale despite the fact that if clinically meaningful effects are claimed for apparently small differences, the existence of a satisfactory validation is important.
In its responses to the Request for Supplementary Information, the MAH argues that the OR-SDS has been validated and cited publications from 1994 and 2004. The CHMP was of the opinion that this argument is not a robust one. A brief review of the literature suggests that the publications cited by the MAH may be the only ones relating to the score. However, this issue on validation of OR-SDS can be dealt with by appropriate wording in the SPC (see section III-4 Product Information).

In all three studies, parecoxib produced statistically significant reduction in opioid consumption. However, a methodological concern is which size of reduction should be considered as clinically meaningful. In a non-inferiority analysis of opioid consumption in study 080, the MAH used a delta size of 6 mg per day, which is considered reasonable. For the two pivotal studies (069 and 071), this means that parecoxib produced a clinically meaningful morphine reduction on the first post-operative day only (mean 7.2 mg and 6.5 mg, respectively). On the second post-operative day the respective findings were 2.8 mg and 3.5 mg.
In its responses to the Request for Supplementary Information, the MAH states that in Study 069 (general surgery) the reductions of morphine is equivalent to 36% on Day 2 and 29% which are highly statistically significant. In the other pivotal study 071, the reductions for Days 1, 2, 3 were 40% 41%, 51% which are also highly significant. The CHMP agrees that the MAH is technically correct but oversimplifies the situation. The mean consumption of morphine (in mg equivalent) fell by about half on each successive post-operative day. Thus, while in Study 071 the sparing effect appears to increase with time, it actually relates to 7.2 mg on Day 1, 3.9 mg on Day 2 and 2.7 mg on Day 3. Small differences between the diminishing amounts exaggerate the differences between the treatment arms, in this case to the apparent benefit of parecoxib. However the CHMP was of the opinion that this issue could be resolved by appropriate wording of the SPC.

In the supportive study 080, the primary efficacy analysis did not show non-inferiority for parecoxib

compared to parecoxib + propacetamol. However, with regard to the secondary endpoints, parecoxib gave clinically significantly reduced mean opioid-requirements compared to placebo both during 24 h post-surgery (difference 14.5 mg) and 24-48 h post-surgery (difference 13.5 mg).

For all three studies, the data (large SD-values) demonstrate the well-known wide variation in post-operative opioid requirements among patients. The reduction in opioid supplements produced by parecoxib will therefore not provide any helpful prediction regarding the need of opioids in the individual patient.

Consequently, the CHMP does not endorse the proposed extended indication (decrease in opiod consumption) and is of the opinion that the information about the demonstrated reduction of dose-dependent adverse effects following dose-reduction of opioids should be instead included in section 5.1 “Pharmacodynamic properties” of the SPC.
The MAH agreed with this position and withdrew its request to extend the therapeutic indication. The remaining scope of the variation relates to the update of section 5.1 with information on the reduction of dose-dependent adverse effects following dose reduction of opioids and consequent updates of section 4.2 “Posology and method of administration” and 4.5 “Interaction with other medicinal products and other forms of interaction”.

With regard to pain, the MAH proposed a claim in SPC section 5.1, that parecoxib provides additional pain reduction in post-operative patients when used in combination with opioids. The CHMP wanted further reassurance to support this claim.
Indeed, the reported SPID data for studies 069 and 071 needs clarification with regard to clinical relevance of the reported differences and the clinical relevance of the differences in Pain intensity (PID data) reported in study 080 is considered questionable.
With regard to the pain data as provided with the mBPI-sf , the findings in all three studies show numerical improvements with frequently high statistically significances. However, the clinical relevance of the numerical differences may not be convincing, and will apparently depend on the quality of the general post-operative pain management at the study site.

In order to address these CHMP concerns, the MAH cited a study (Cepeda MS, Africano JM, Polo R et al, 2003) which suggests that a reduction of approximately 20% in a numerical pain rating or visual analogue score in a post-surgical acute pain evaluation is clinically meaningful. In Study 069 the reduction (active vs. placebo) of Sum of Pain Intensity over 24 hours was 28% on Day 1 and 27.8% on Day 2. For Study 071 the equivalent figures were approximately 28% to 29% for Days 1, 2, 3. For Study 080 pain reduction at 24 hours and 48 hours was judged to be 24% and 38% respectively. Similar reductions were found using the modified Brief Pain Inventory- short form (mBPI-sf).

With regard to the overall quality management of pain in the immediate post operative, the MAH reassures the CHMP indicating that the experimental treatments were administered on a background of patient controlled analgesia at all investigational sites and that this is the current state of the art standard.

Parecoxib reduced the OR-SDS scores by about 30% on the first 2 post-operative days in study 069, and by about 16% on the first 3 post-operative days in study 071, and by about 23% on the first post-operative day in study 080. However, the numerical differences were only about 0.15-0.20 in the three studies, and it is unclear to what extent the apparently modest numerical difference may reflect a clinically meaningful difference. There were wide SDs, but the large samples lead to "impressive" levels of statistical significance.
On the other hand, the potential clinical benefit of opioid sparing was more evident in terms of occurrence of CMEs (studies 069 and 071), where the size of risk reduction may appear clinically relevant. In addition, CMEs affected a large proportion of patients, which means that a moderate risk reduction reflects an appreciable number of patients with less CMEs.
Inferring from the CME data, it appears reasonable to support the MAH's claim that the use of parecoxib reduces the occurrence of opioid-related adverse events.

Regarding safety data, the MAH has provided adverse events data from 26 "Parecoxib combined surgery studies", which adequately seem to represent the patient population most likely to receive parecoxib.
It is reasonable to believe that the parecoxib groups in these data received somewhat less post-operative opioids compared to the placebo group, however, the tabulated data do not indicate any clear difference in the occurrence of adverse events (acknowledging the difficulty to interpret the comparison with the 80 mg TDD group).
In order to assess the overall adverse events profile between treatments, compared to the opioid-related events profile, the MAH should have provide pooled adverse events data from the three opioid-sparing studies (069, 071 and 080). Such summary data would have made it more feasible to assess if the reduction of opioid-related CMEs was followed with an increase in other (parecoxib-related) adverse events. Indeed, if the overall adverse events profile is not influenced by the reduction in opioid-related adverse events, the true benefit of the co-administration of parecoxib should be questioned.
However, the MAH makes the point that the clinical development plan for valdecoxib and parecoxib was designed and powered primarily to demonstrate a difference between active and placebo treatments with respect to efficacy and not to detect safety differences, which must be based on the differences of investigator reporting rates. No overview or meta-analysis of the adverse events were provided.

In the supporting clinical studies patients treated with morphine and parecoxib/valdecoxib experienced more frequent NSAID/COX2 adverse effects than those in the placebo arm. This is to be expected and will be known to prescribers of parecoxib. The relative contribution of valdecoxib and parecoxib to the safety profile is not evaluable and therefore it is difficult to formulate a warning or SPC wording on the issue. However, the CHMP was of the opinion that the risks are not such as to prevent the variation being approved.

Serious adverse events and deaths reported in the clinical studies were discussed in the recent renewal assessment report. There were no data suggesting less risk associated with the use of parecoxib compared to placebo.

4. PRODUCT INFORMATION

The MAH provided with the initial variation application a proposed revised SPC and Package Leaflet.

As detailed above (section III.4 – Overall discussion on clinical aspects), the CHMP does not endorsed the extension of indication with the proposed information on opioid sparing effects for the section 4.1 “Therapeutic indications” of the SPC as it refers to secondary end-points which may more appropriately be considered for inclusion in section 5.1 “Pharmacodynamic properties”.
Accordingly, the MAH agrees not to pursue the request to extend the indication (section 4.1) but to update the section 5.1 of the SPC with information about the demonstrated reduction of dose-dependent adverse effects following dose-reduction of opioids.

The initial SPC section 4.2 “Posology and method of administration” was updated and included *“An optimal effect is achieved when parecoxib is given prior to opioid administration”*. The CHMP disagrees with this statement as it is not supported by any data in the present variation application.
This statement was consequently deleted.

In addition the MAH also proposed changes in SPC section 4.2 related to cardiovascular and renal safety to bring it into line with the parecoxib Core Data Sheet: “*As the cardiovascular risk of cyclooxygenase-2 (COX-2) specific inhibitors may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. However, the relevance*

of these findings for the short-term use of parecoxib in the postoperative setting has not been evaluated."
The first part of the proposed text is considered acceptable, and underlines the second and third passage in the SPC section 4.4. However, the message as proposed in the last sentence appears unclear. As mentioned in the SPC, the cardiovascular events associated with COX-2 inhibitors are regarded to have relevance for the prodrug parecoxib as well, and the Renewal AR (November 2006) concludes that "It must be considered, as is currently signalled in the SPC through the contraindication to use in CABG surgery, that parecoxib like other COX-2 inhibitors has some degree of cardiotoxic potential." It was therefore agreed just to add "*As the cardiovascular risk of cyclooxygenase-2 (COX-2) specific inhibitors may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used."*

Following the CHMP disagreement to extend the indication with the reduction of opioid use and patient reported opioid related adverse effects when used in conjunction with opioids, section 5.1 was updated with the appropriate information. The initial proposed wording was amended in order to deal with the use of the lack of comprehensive validation for the OR-SDS, the clinical significance of the statistically significant reduction in opioid consumption and the lack of safety data associated with the use of parecoxib compared to placebo when used in conjunction with opioids.

It is noted that the additional proposed changes in section 4.2 for the renal safety, with a moderate strengthening of the wording, are considered reasonable: *"Renal Impairment: On the basis of pharmacokinetics, no dosage adjustment is necessary in patients with mild to moderate renal impairment (creatinine clearance of 30-80 ml/min). In patients with severe renal impairment (creatinine clearance <30 ml/min) or patients who may be predisposed to fluid retention parecoxib should be initiated at the lowest recommended dose and the patient's kidney function closely monitored (see sections 4.4 and 5.2)."*

The Package Leaflet (PL) was updated in accordance with the SPC and agreed by the CHMP. In addition, minor changes to the list of representatives were introduced.

For further details on the exact adopted wording for the SPC and PL, please refer to Attachement 1 – SPC and Package Leaflet.

5. ENVIRONMENTAL RISK ASSESSMENT

In addition to the clinical data supporting this variation and assessed above, the MAH submitted an environmental risk assessment (not previously provided for this product).

The CHMP agrees that the sections dealing with the human pharmacokinetics and pharmacodynamics of valdecoxib are accurate, and that the use of valdecoxib rather than parecoxib as the 'burden of risk' is appropriate.

The MAH has completed a series of studies which probably fulfill the technical requirements some of which seem demanding, at least in the time required to carry them out. However, the feasibility of carrying out an environmental risk evaluation for the entire EU is very doubtful; basic assumptions of the environmental exposure such as market penetration, amount of waste water per inhabitant and dilution factor are likely to be very different between the south of Spain and the west of Ireland. Consequently effects on the biosphere are likely to vary as will the amount of drug related substance retained in the physical environment.

From a simple viewpoint valdecoxib is not thought to have important hormonal side effects, is not a designed cytotoxic substance (e.g. cyclophosphamide) and is not a product of mass use; and for those reasons is unlikely to function as an important pollutant

However it is noted that the results from the water sediment study (OECD 308) demonstrate significant shifting of the drug substance to the sediment (more than 10% of the substance after 14 days is present in sediment).
Therefore the MAH was asked to provide effects studies of sediment dwelling organisms (OECD 218) as described in the harmonised guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00). Accordingly, the MAH committed to conducted a study to determine the effects of valdecoxib on sediment dwelling organisms a per OECD 218 for which the final study report will be provided 3Q09 (see Letter of Undertaking in attachment 6).

6. CONCLUSION AND BENEFIT RISK ASSESSMENT

The CHMP noted that the initially proposed extended indication (decrease in opioid consumption) includes an endpoint with is one among several endpoints generally used for evaluation of analgesia. However the SPC guideline specifies that study endpoints should not normally be included in the therapeutic indication unless such mention is specified as being appropriate for the indication in CHMP Notes for Guidance or Points to Consider documents.

All the three submitted studies (069,071, 080), parecoxib produced statistically significant reduction in opioid consumption. However, a methodological concern is which size of reduction should be considered as clinically meaningful. Indeed, small differences between the diminishing amounts exaggerate the differences between the treatment arms, leading in this case to the apparent benefit of parecoxib. However the CHMP was of the opinion that this issue could be resolved by appropriate wording of the SPC.

For all three studies, the data (large SD-values) demonstrate the well-known wide variation in post-operative opioid requirements among patients. The reduction in opioid supplements produced by parecoxib will therefore not provide any helpful prediction regarding the need of opioids in the individual patient.

Therefore, the CHMP is of the opinion that the therapeutic indication should not be extended, but that the information about the demonstrated reduction of dose-dependent adverse effects following dose-reduction of opioids should be instead included in section 5.1 “Pharmacodynamic properties” of the SPC.

Regarding safety data, no overview or meta-analysis of the adverse events for the three opioid-sparing studies were provided and it is not possible to assess the overall adverse events profile between treatments, compared to the opioid-related events profile.
In the supporting clinical studies patients treated with morphine and parecoxib/valdecoxib experienced more frequent NSAID/COX2 adverse effects than those in the placebo arm. This is to be expected and will be known to prescribers of parecoxib. However the relative contribution of valdecoxib and parecoxib to the safety profile is not evaluable and therefore it is difficult to formulate a warning or SPC wording on the issue. However, the CHMP was of the opinion that the risks are not such as to prevent the variation being approved.

Serious adverse events and deaths reported in the clinical studies were discussed in the recent renewal assessment report. There were no data suggesting less risk associated with the use of parecoxib compared to placebo.

The overall risk-benefit of Dynastat is not affected by the newly submitted data in this variation application and remains positive.

Recommendation

On 22 January 2009 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics (on sections 4.2. and 5.1) and Package Leaflet accordingly.