

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-341

MEDICAL REVIEW

**Division of Gastrointestinal and Coagulation Drug Products
Medical Officer's Consult Review**

To: Larry Goldkind MD, Deputy Director
HFD-550, Division of Anti-Inflammatory, Analgesic, and
Ophthalmological Drug Products

From: Ann Farrell MD, Medical Reviewer
HFD-180, Division of Gastrointestinal and Coagulation Drug
Products

Through: Lilia Talarico MD, Division Director
HFD-180, Division of Gastrointestinal and Coagulation Drug
Products

Re: Consult request: Please review the Valdecoxib studies for effect on
platelets.

Submission Date: January 15, 2001

Sponsor: Searle

Drug: Valdecoxib

Date Assigned: May 4, 2001

Date Completed: August 13, 2001

Summary

Searle has submitted NDA 21341 for Valdecoxib. Valdecoxib, a selective cyclooxygenase -2 inhibitor, is an oral tablet intended for use in the:

- 1) prevention and treatment of acute pain
- 2) treatment of primary dysmenorrhea
- 3) relief of the signs and symptoms of osteoarthritis and adult rheumatoid arthritis

This consult review will address the effect of valdecoxib on platelet function studies and provide labeling recommendations.

Background

The most commonly used medications to prevent and treat pain are non-steroidal anti-inflammatory drugs. Non-steroidal anti-inflammatory drugs can be categorized based on cyclooxygenase (COX) isoenzyme inhibitory activity. Theoretically, nonselective COX inhibitors possess COX-1 and COX-2 inhibitory activity, while COX-2 inhibitors possess only COX-2 inhibitory activity. Drugs such as naproxen, diclofenac, and ibuprofen are nonselective COX inhibitors. One advantage of selective COX-2 inhibitors is that COX-2 inhibitors do not interfere with platelet function, since platelets possess only the COX-1 isoenzyme. Thus, selective COX-2 inhibitors are not expected to impair hemostasis.

Platelet function and COX isoenzyme activity

Platelet function is assessed in vitro by platelet aggregation studies and clinically by a bleeding time. COX-1 activity can be assessed by measuring serum thromboxane B₂ (TXB₂). Measuring urine samples for urinary prostaglandins can assess COX-2 activity.

COX inhibitors

A nonselective inhibitor should interfere with platelet aggregation, suppress serum TXB₂ levels relative to placebo, and suppress urinary prostaglandin levels relative to placebo.

A selective COX-2 inhibitor should not prolong bleeding times, impair platelet aggregation, and suppress serum TXB₂ levels relative to placebo. However, a selective COX-2 inhibitor should decrease urinary prostaglandin levels relative to placebo.

NDA studies

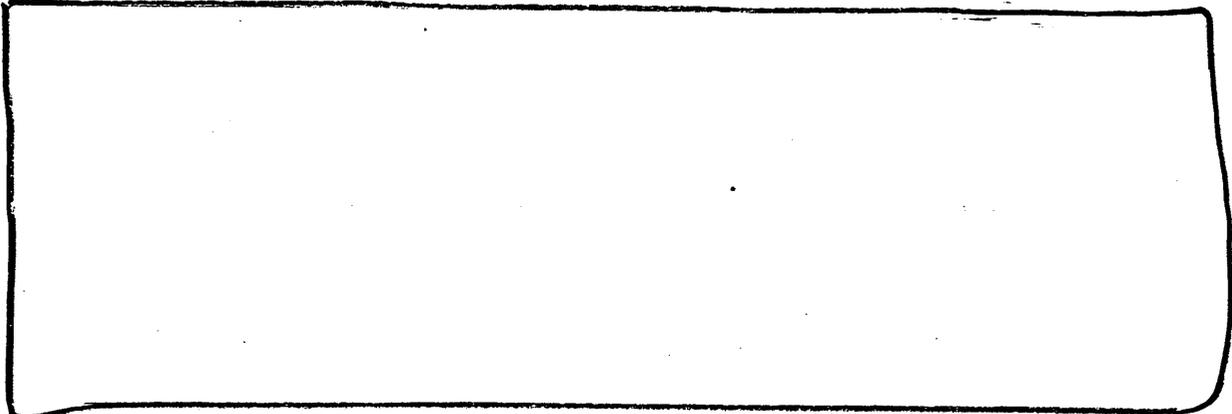
Platelet function and COX inhibition were assessed in five studies, which are listed in the table below. Review of the five studies suggests that valdecoxib is a relatively selective COX-2 inhibitor and does not interfere with platelet function. Individual study reviews are in the Appendix.

Reviewer's Comment: The sponsor has previously submitted platelet function study 93-031 for parecoxib, a prodrug of valdecoxib (NDA 21294). My previous review is reproduced in the Appendix with minor changes.

Table 14.ttt Summary of Platelet Function Studies

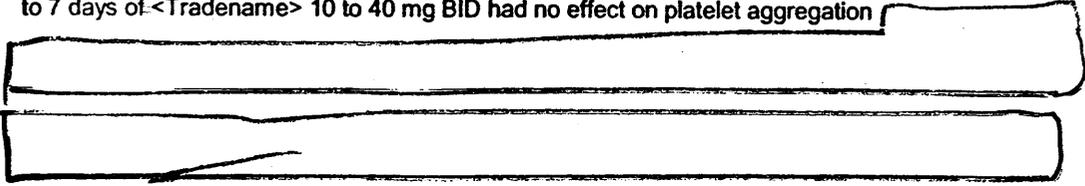
| Study Number | Design | Population | Treatment Group | Treatment Period | Outcome Measures |
|------------------|--|---------------------------------|--|------------------|---|
| 021 N = 76 | randomized double-blind, single center | healthy adults age 18-55 yrs | placebo valdecoxib 10 mg BID valdecoxib 25 mg BID naproxen 500 mg BID diclofenac 75 mg BID | 7.5 days | platelet aggregation, bleeding time, serum TxB ₂ , urinary 11- dehydro-TxB ₂ |
| 023 N = 45 | randomized double-blind, single center | healthy adults age 65-95 yrs | placebo valdecoxib 10 mg BID ibuprofen 800 mg TID | 7.5 days | platelet aggregation, bleeding time, serum TxB ₂ , urinary 11- dehydro-TxB ₂ |
| 042 N = 47 | randomized double-blind, single center | healthy adults age 65-95 yrs | placebo valdecoxib 40 mg BID ibuprofen 800 mg TID | 7.5 days | platelet aggregation, bleeding time, serum TxB ₂ , urinary 11- dehydro-TxB ₂ |
| 043 N = 62 | randomized double-blind, single center | healthy adults age 18-55 yrs | placebo valdecoxib 40 mg BID naproxen 500 mg BID diclofenac 75 mg BID | 7.5 days | platelet aggregation, bleeding time, serum TxB ₂ , urinary 11- dehydro-TxB ₂ |
| 93-031 N = 20 | randomized double-blind, single center | healthy adults age 18-55 yrs | placebo parecoxib 40 mg BID | 3.5 days | platelet aggregation, bleeding time, serum TxB ₂ |

Information derived from individual study reports. TxB₂ – serum thromboxane B₂

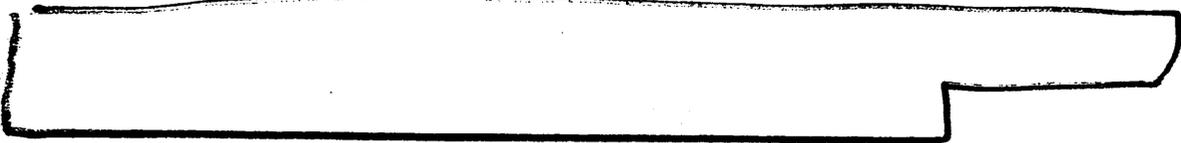


Platelets:

In four clinical trials studying young and elderly (>65 years) subjects, single and multiple doses up to 7 days of <Tradename> 10 to 40 mg BID had no effect on platelet aggregation



3) Under the Precautions section, in the hematological effects subsection, the sponsor states: "does not appear to inhibit platelet aggregation at indicated dosages". This reviewer finds the phrase acceptable.



Conclusion and Recommendation

Review of the five studies suggests that valdecoxib is a relatively selective COX-2 inhibitor and does not interfere with platelet function. The sponsor should revise the labeling as suggested above.

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Appendix

Study 021 - Title: Integrated Clinical and Statistical Report for a Double-Blind, Placebo-Controlled Study to Evaluate the Effects of SC-65872 10 mg BID, SC-65872 25 mg BID, Naproxen 500 mg BID and Diclofenac 75 mg BID on Platelet Function and Urinary Prostaglandins in Normal Healthy Subjects

Reviewer's Conclusion: *The sponsor assessed platelet aggregation, bleeding time, serum TxB₂ level, and urinary prostaglandin levels for SC-65872 in a single center, double-blind, randomized, multiple dose, positive comparator, placebo controlled, parallel-group study in healthy volunteers. The results suggest that SC-65872 administration does not interfere with platelet aggregation, bleeding time, and serum TxB₂ level consistent with lack of significant COX-1 inhibitory activity. There was a decrease in urinary prostaglandin level excretion with SC-65872 consistent with COX-2 inhibition.*

Study Description: Study 021 was a single center, double-blind, randomized, multiple dose, placebo-controlled, active comparator, parallel-group study in healthy volunteers.

Subjects:

The trial enrolled subjects meeting the inclusion and exclusion criteria listed below.

Inclusion Criteria

Subjects were enrolled in the study if they met the following criteria:

1. were male or female, between 18 to 55 years of age, inclusive;
2. if female and of childbearing potential, were using adequate contraception, not lactating and had a negative serum pregnancy tests result within 24 hours prior to receiving study medication;
3. had a physical examination during the Pretreatment Screening Visit which revealed no clinically significant abnormalities;
4. had clinical laboratory test results that were within normal limits for blood urea nitrogen (BUN), creatinine, sodium, potassium, prothrombin time (PT), and partial thromboplastin time (PTT) during the Pretreatment Screening Visit (other Screening clinical laboratory test results, if abnormal, were not clinically significant in the investigator's opinion);
5. had a negative drug toxicology screen during the Pretreatment Screening Visit;

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6. had a negative Hepatitis B surface antigen test obtained during the Pretreatment Screening Visit;
7. weighed >50 kg and were within $\pm 20\%$ of desired body weight (see Appendix 5 —of-protocol contained in Appendix 1 of this report);
8. had a $\geq 60\%$ platelet aggregation response to arachidonate and collagen performed at Baseline;
9. had an estimated GFR (Cockcroft-Gault Estimate) > 100 mL/min/1.73m², or serum creatinine ≤ 1.2 mg/dL (if male), or a serum creatinine ≤ 1.0 mg/dL (if female) at the Pretreatment Screening Visit;
10. were normotensive (BP $\leq 140/90$);
11. if male, agreed to abstain from all sexual activity from 48 hours prior to confinement to the study unit and until the end of the study period; and
12. had provided written informed consent prior to admission to this study.

Exclusion Criteria

Subjects were excluded from the study if they met any of the following criteria:

1. had a history of any clinically significant illness within the three months prior to the Pretreatment Screening Visit, or any medical condition or laboratory abnormality considered to be clinically significant, by the investigator;
2. had known hypersensitivity to NSAIDs or other cyclooxygenase inhibitor compounds, or lactose;
3. used any medication (including any use of ascorbic acid) within 14 days prior to receiving the first dose of study medication or were expected to take any medication [other than study medication, oral contraceptives, hormone replacement therapy or an occasional acetaminophen (up to 650 mg BID)] during the study;
4. had a history of clinically significant substance abuse, drug addiction or alcoholism within three years prior to admission to this study;
5. had a history of smoking or used a tobacco product within two weeks prior to the Pretreatment Screening Visit or anticipated use of tobacco products during the course of the study;
6. had a history of keloid formation or abnormal scarring;

7. had a history of frequent nosebleeds or frequent bruising, bleeding diathesis, or any clinically significant hematologic condition that would, in the investigator's opinion, preclude study participation;
8. had urinary incontinence;
9. had been diagnosed with or treated for esophageal, gastric, pyloric channel or duodenal ulceration within three months prior to receiving the first dose of study medication;
10. had received any investigational medication within 30 days prior to the Treatment Period or were scheduled to receive an investigational drug other than SC-65872 during the course of this study; or
11. had been previously admitted to this study.

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Enrollment was stratified by gender. The 76 subjects were randomized to the following groups:

- 10 mg SC-65872 (15 subjects)
- 25 mg SC-65872 (16 subjects)
- 500 mg naproxen (15 subjects)
- 75 mg diclofenac (15 subjects)
- placebo (15 subjects)

Study Plan:

Study medication was administered at approximately 0700 and 1900 daily. The sponsor's table below shows the sampling times for blood work and urine collection.

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Table 1. Schedule Of Observations And Procedures

| Procedures | Pretreatment Period | | | Treatment Period (Day) | | | | | | | |
|--|------------------------------|-----------------------|----------------------|------------------------|---|---|---|---|---|----------------|----------------|
| | Screening (Day -21 to -2) | Admission (Day -2) | Baseline (Day -1) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| Informed Consent | x | | | | | | | | | | |
| Medical History | x | | | | | | | | | | |
| Physical Exam | x ^a | | x | | | | | | | | x ^b |
| Drug/Alcohol Screen | x ^a | x ^a | | | | | | | | | |
| Hepatitis B Surface Antigen Screen | x ^a | | | | | | | | | | |
| Clinical Laboratory Tests | x ^a | | x | | | | | | | | x ^b |
| Serum Pregnancy Test | | | x | | | | | | | | |
| Renal Screen ^e | x ^{a, c} | | | | | | | | | | |
| Vital Signs | x ^a | | x | | | | | | | | x ^b |
| Signs and Symptoms | | x | x | x | x | x | x | x | x | x | x ^b |
| Concomitant Meds. | | x | x | x | x | x | x | x | x | x | x ^b |
| Admission to Unit | | x | | | | | | | | | |
| Discharge from Unit | | | | | | | | | | | x |
| Study Medication Admin. | | | | x | x | x | x | x | x | x | x ^b |
| Serum & urine for Na, Cr | | x | x | x | | | | | | x | |
| Urine for PGs | | x ^a | x ^a | x ^a | | | | | | x ^a | |
| Urine for 11-dehydro- TxB ₂ | | x ^a | x ^a | x ^a | | | | | | x ^e | |
| Platelet Aggregation | | x ^{a, f} | x | x ^g | | | | | | | x ^h |
| Simple Bleeding Time | | | x | x ^g | | | | | | | x ^h |
| Blood Specimen for Serum TxB ₂ | | | x | x ^g | | | | | | | x ^h |

a These results were not be recorded on CRFs.
b Performed on the final day of treatment or early termination.
c Cockcroft-Gault estimate of GFR or serum creatinine.
d Single morning dose only.
e 24-hour collection, beginning at 0700 hours.
f. Platelet aggregation response to arachidonate only
g Sample collected or test performed at 2, 4, and 8 hrs after morning dose on Day 1.
h Sample collected at 30 min before and 2, 4, and 8 hrs after dose on Day 8.

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Results:

Demographics:

No significant differences were noted between treatment groups.

Subject Disposition:

One female subject withdrew due to an adverse event (mild diarrhea) and was replaced by another female subject in the 25 mg SC-65872 treatment group.

Platelet aggregation:

The sponsor's table below summarizes the results in response to arachidonic acid.

Reviewer's Comment: The table below shows that, in general, the response to arachidonic acid stimulation was not statistically significantly different for SC-65872 compared with placebo. Naproxen subjects demonstrated a statistically significant decrease in response to arachidonic acid compared with placebo. Diclofenac subjects did not. The sponsor did not provide an explanation for the observed difference between the naproxen and diclofenac responses. These results are consistent with the relatively selective inhibition of COX-2 by SC-65872.

Summary Table 1. Platelet Aggregation Response to Arachidonate (Median Change from Baseline)

| | Day 1 | | | | |
|---|-------------------|-----------------------|-----------------------|------------------------|-------------------------|
| | Placebo | SC-65872 10 mg BID | SC-65872 25 mg BID | naproxen 500 mg BID | diclofenac 75 mg BID |
| Median response to arachidonate (%): | | | | | |
| Baseline [†] (Q1 - Q3) | 84.0 (79 - 88) | 86.0 (80 - 88) | 82.0 (80 - 87.5) | 87.0 (83-90) | 87.0 (81 - 91) |
| Median change from Baseline at: ‡ | | | | | |
| 2 hours | -1.0 | 0.0 [n***] | 1.0 [n***] | -79.0 [p****] | -2.0 |
| 4 hours | -2.0 | -1.0 [n***, d****] | 3.5 [n***, d****] | -85.0 [p****] | -16.0 [p****] |
| 8 hours | -4.0 | -2.0 [n****] | 1.0 [n***, p*] | -84.0 [p****] | -5.0 |
| | Day 8 | | | | |
| | Placebo | SC-65872 10 mg BID | SC-65872 25 mg BID | naproxen 500 mg BID | diclofenac 75 mg BID |
| Median response to arachidonate (%): | | | | | |
| Baseline [†] (Q1 - Q3) | 84.0 (79 - 88) | 86.0 (80 - 88) | 82.0 (80 - 87.5) | 87.0 (83-90) | 87.0 (81 - 91) |
| Median change from Baseline at: ‡ | | | | | |
| -30 minutes | -2.0 | -3.0 [n****] | 3.0 [n***, d*] | -83.0 [p****] | -3.0 |
| 2 hours | 1.0 | 0.0 [n****] | 4.0 [n****] | -83.0 [p****] | -5.0 |
| 4 hours | -3.0 | 0.0 [n***, d*] | 2.0 [n***, d**] | -83.0 [p****] | -15.0 |
| 8 hours | 0.0 | -1.0 [n****] | 3.0 [n****] | -83.0 [p****] | -2.0 |

[†] Baseline is defined as the median Day -1 measurement; Q1-Q3 is the interquartile range
[‡] Observed median changes from Baseline are shown; statistically significant pairwise comparisons of the median change from Baseline, using Wilcoxon exact test, are shown in brackets
n*** = statistically significantly different from naproxen at a level of 0.001
d****, d**, d* = statistically significantly different from diclofenac at levels of 0.001, 0.01 and 0.05, respectively
p****, p* = statistically significantly different from placebo at levels of 0.001 and 0.05, respectively
Source: Table 7

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In general, platelet aggregation testing results with collagen and adenosine diphosphate (ADP) acid were not statistically significantly different for SC-65872 compared with placebo. In general, platelet aggregation testing results with collagen and ADP were statistically significantly different for naproxen compared with placebo. Diclofenac platelet aggregation testing results with collagen were statistically significantly different from placebo at 4 hours post-dose on Day 1 and at 2 hours post dose on Day 8. Diclofenac platelet aggregation testing results with ADP were statistically significantly different from placebo at 4 hours post-dose on Days 1 and 8.

Reviewer's Comment: These results are consistent with the relatively selective inhibition of COX-2 by SC-65872.

**Summary Table 2. Platelet Aggregation Response to Collagen
(Median Change from Baseline)**

| | Day 1 [†] | | | | |
|--|--------------------|-----------------------|-----------------------|------------------------|-------------------------|
| | Placebo | SC-65872 10 mg BID | SC-65872 25 mg BID | naproxen 500 mg BID | diclofenac 75 mg BID |
| Median response to collagen (%): | | | | | |
| Baseline [†] (Q1 - Q3) | 83.0 (79 - 88) | 85.0 (82 - 89) | 84.5 (80 - 86.5) | 83.0 (80 - 90) | 83.0 (81 - 90) |
| Median change from Baseline at: ‡ | | | | | |
| 2 hours | 1.0 | 2.0 [n*] | 2.0 [n*] | -11.0 [p*] | 2.0 |
| 4 hours | 1.0 | 2.0 [n***, d**] | 1.5 [n***, d**] | -28.0 [p***] | -8.0 [p**] |
| 8 hours | -3.0 | -3.0 [n***] | -0.5 [n***] | -10.0 [p**] | -1.0 |
| | Day 8 | | | | |
| | Placebo | SC-65872 10 mg BID | SC-65872 25 mg BID | naproxen 500 mg BID | diclofenac 75 mg BID |
| Median response to collagen (%): | | | | | |
| Baseline [†] (Q1 - Q3) | 83.0 (79 - 88) | 85.0 (82 - 89) | 84.5 (80 - 86.5) | 83.0 (80 - 90) | 83.0 (81 - 90) |
| Median change from Baseline at: ‡ | | | | | |
| -30 minutes | 0.0 | 0.0 [n**] | 6.0 [n***] | -9.0 [p***] | 0.0 |
| 2 hours | 2.0 | 5.0 [n***] | 2.0 [n***] | -25.0 [p***] | 4.0 [p**] |
| 4 hours | 0.0 | 0.0 [n***] | 3.0 [n***, d*] | -33.0 [p***] | -3.0 |
| 8 hours | 1.0 | 2.0 [n***] | 2.0 [n***] | -13.0 [p***] | -2.0 |

[†] Baseline is defined as the median Day -1 measurement; Q1-Q3 is the interquartile range
[‡] Observed median changes from Baseline are shown; statistically significant pairwise comparisons of the median change from Baseline, using Wilcoxon exact test, are shown in brackets
n***, n**, n* = statistically significantly different from naproxen at levels of 0.001, 0.01, and 0.05, respectively
d**, d* = statistically significantly different from diclofenac at levels of 0.01 and 0.05, respectively
p***, p**, p* = statistically significantly different from placebo at levels of 0.001, 0.01, and 0.05, respectively
Source: Table 8

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**Summary Table 3. Platelet Aggregation Response to ADP
(Median Change from Baseline)**

| | Day 1 | | | | |
|--|-------------------|-----------------------|-------------------------|------------------------|-------------------------|
| | Placebo | SC-65872 10 mg BID | SC-65872 25 mg BID | naproxen 500 mg BID | diclofenac 75 mg BID |
| Median response to ADP (%): | | | | | |
| Baseline [†] (Q1 - Q3) | 84.0 (81 - 89) | 86.0 (84 - 90) | 83.0 (80.5-87.5) | 84.0 (79 - 88) | 87.0 (84 - 89) |
| Median change from Baseline at:[‡] | | | | | |
| 2 hours | 2.0 | -1.0 [n***] | 2.5 [n***] | -16.0 [p***] | 1.0 |
| 4 hours | -1.0 | 1.0 [n***, d****] | 4.0 [n***, d****] | -15.0 [p***] | -15.0 [p***] |
| 8 hours | -6.0 | -2.0 [n***] | 1.0 [n***, d**, p**] | -19.0 [p***] | -6.0 |
| | Day 8 | | | | |
| | Placebo | SC-65872 10 mg BID | SC-65872 25 mg BID | naproxen 500 mg BID | diclofenac 75 mg BID |
| Median response to ADP (%): | | | | | |
| Baseline [†] (Q1 - Q3) | 84.0 (81 - 89) | 86.0 (84 - 90) | 83.0 (80.5-87.5) | 84.0 (79 - 88) | 87.0 (84 - 89) |
| Median change from Baseline at:[‡] | | | | | |
| -30 minutes | -1.0 | 1.0 [n***] | 5.0 [n***, d**] | -13.0 [p***] | -1.0 |
| 2 hours | -1.0 | 0.0 [n*] | 4.0 [n**] | -13.0 [p**] | -1.0 |
| 4 hours | 3.0 | -1.0 [n***] | 5.0 [n***, d**] | -19.0 [p***] | -6.0 [p*] |
| 8 hours | -2.0 | 3.0 [n***] | 3.0 [n***, d*] | -22.0 [p***] | -1.0 |

[†] Baseline is defined as the median Day -1 measurement; Q1-Q3 is the interquartile range

[‡] Observed median changes from Baseline are shown; statistically significant pairwise comparisons of the median change from Baseline, using Wilcoxon exact test, are shown in brackets

n***, n**, n* = statistically significantly different from naproxen at levels of 0.001, 0.01, and 0.05, respectively

d***, d**, d* = statistically significantly different from diclofenac at levels of 0.001, 0.01, and 0.05, respectively

p***, p**, p* = statistically significantly different from placebo at levels of 0.001, 0.01, and 0.05, respectively
Source: Table 9

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Simplate II bleeding times

There were no statistically significant differences in bleeding times between placebo and SC-65872 for any time point on Days 1 and 8.

Serum TxB₂ concentrations

The sponsor's table below shows that subjects taking SC-65872 had serum TxB₂ levels that were statistically significantly different from naproxen and diclofenac but not from placebo. The subjects taking naproxen had serum TxB₂ levels that were statistically significantly different from placebo.

Reviewer's Comment: These results are consistent with the relatively selective inhibition of COX-2 by SC-65872.

Summary Table 5. Serum Thromboxane B₂ Concentration (Change from Baseline)

| | Day 1 | | | | |
|--|-------------------|-----------------------|-----------------------|------------------------|-------------------------|
| | Placebo | SC-65872 10 mg BID | SC-65872 25 mg BID | naproxen 500 mg BID | diclofenac 75 mg BID |
| Median Serum TxB₂ Concentration (ng/ml): | | | | | |
| Baseline [†] (Q1 - Q3) | 125.0 (45-254) | 119.0 (56.7-155) | 102.2 (24.9-155.5) | 98.5 (40.9-162) | 137.0 (54.1-162) |
| Median change from Baseline at: ‡ | | | | | |
| 2 hours | 5.0 | 9.3 [n***] | 26.0 [n***] | -74.0 [p***] | -1.0 |
| 4 hours | 32.0 | 13.0 [n***, d**] | 4.5 [n***, d**] | -98.0 [p***] | -48.4 [p*] |
| 8 hours | -1.9 | 2.0 [n***, d**] | 16.5 [n***, d**] | -98.0 [p***] | -65.4 [p*] |
| Percent change from Baseline at: ‡ | | | | | |
| 2 hours | 1.3 | 14.6 [n***] | 16.6 [n***] | -89.3 [p***] | -0.3 |
| 4 hours | 31.1 | 5.6 [n***, d***] | 2.5 [n***, d***] | -97.7 [p***] | -72.0 [p**] |
| 8 hours | -10.1 | 0.8 [n***, d**] | 11.4 [n***, d**] | -95.3 [p***] | -42.7 [p*] |
| | Day 8 | | | | |
| | Placebo | SC-65872 10 mg BID | SC-65872 25 mg BID | naproxen 500 mg BID | diclofenac 75 mg BID |
| Median serum TxB₂ concentration (ng/ml): | | | | | |
| Baseline [†] (Q1 - Q3) | 125.0 (45-254) | 119.0 (56.7-155) | 102.2 (24.9-155.5) | 98.5 (40.9-162) | 137.0 (54.1-162) |
| Median change from Baseline at: ‡ | | | | | |
| -30 minutes | -8.0 | 22.5 [n***] | -6.9 [n***] | -98.1 [p**] | -45.0 |
| 2 hours | -37.6 | 17.0 [n**] | -13.5 [n***] | -98.3 [p*] | -8.0 |
| 4 hours | -3.0 | 7.0 [n**, d*] | -3.0 [n***, d*] | -98.4 [p**] | -49.7 |
| 8 hours | -55.8 | 17.0 [n**] | -6.8 [n***] | -97.7 | -33.0 |
| Percent change from Baseline at: ‡ | | | | | |
| -30 minutes | -3.6 | 19.2 [n***] | -18.1 [n***] | -98.3 [p***] | -41.1 |
| 2 hours | -30.1 | 13.0 [n***] | -14.4 [n***] | -98.8 [p***] | -44.4 |
| 4 hours | -2.9 | 5.9 [n***, d**] | -2.5 [n***, d***] | -99.3 [p***] | -77.7 [p**] |
| 8 hours | -36.0 | 12.6 [n***] | -10.5 [n***, d*] | -98.7 [p***] | -37.2 |

[†] Baseline is defined as the median Day -1 measurement; Q1-Q3 is the interquartile range

[‡] Observed median changes from Baseline are shown; statistically significant pairwise comparisons of

the median change from Baseline, using Wilcoxon exact test, are shown in brackets

n***, n** = statistically significantly different from naproxen at levels of 0.001 and 0.01 respectively

d***, d**, d* = statistically significantly different from diclofenac at levels of 0.001, 0.01, and 0.05, respectively

p***, p**, p* = statistically significantly different from placebo at levels of 0.001, 0.01, and 0.05, respectively

Source: Table 11

Urinary Prostaglandins

In general, the table below demonstrates that urinary prostaglandin levels were decreased in SC-65872 subjects to a lesser extent than naproxen subjects were.

Reviewer's Comment: Urinary prostaglandin level assays have significant variability, making comparisons between groups difficult.

Summary Table 6. Urinary Prostaglandins PGE₂, 6-keto-PGF_{1α}, and 11-dehydro-TxB₂ (Median Change from Baseline—All Subjects)

| | Placebo | SC-65872 10 mg BID | SC-65872 25 mg BID | naproxen 500 mg BID | diclofenac 75 mg BID |
|---|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|
| Median urinary 11-dehydro TxB₂ levels (ng/day): | | | | | |
| Baseline† (Q1 - Q3) | 1974.3 (1670.3-2298.7) | 1843.9 (1619.5-2969.9) | 1918.3 (1722.1-2435.3) | 2035.7 (1813.4-2335.0) | 2100.9 (1486.6-2392.9) |
| Median change from Baseline on: | | | | | |
| Day 1 | -209.1 | -39.1 | -81.0 | -1092.7 | -519.5 |
| Day 7 | 7.0 | 83.0 | -27.8 | -1238.9 | -719.9 |
| Median urinary PGE₂ levels (ng/day): | | | | | |
| Baseline† (Q1 - Q3) | 281.0 (193.6-425.1) | 250.7 (141.8-525.7) | 247.1 (160.0-327.5) | 188.0 (159.4-326.4) | 257.4 (195.2-424.8) |
| Median change from Baseline on: ‡ | | | | | |
| Day 1 | -6.4 | -25.1 | -71.5 | -95.8 | -73.2 |
| Day 7 | -40.5 | -31.8 | -82.0 | -96.3 | -107.6 |
| Median urinary 6-keto-PGF_{1α} levels (ng/day): | | | | | |
| Baseline† (Q1 - Q3) | 39.9 (38.5-52.0) | 59.4 (38.4-69.8) | 35.9 (22.3-55.5) | 39.1 (35.3-76.1) | 45.7 (29.1-63.1) |
| Median change from Baseline on: ‡ | | | | | |
| Day 1 | -8.4 | -29.8 | -18.5 | -23.4 | -14.0 |
| Day 7 | -4.0 | -27.1 | -15.7 | -23.1 | -18.4 |

† Baseline is defined as the median Day -1 measurement; Q1-Q3 is the interquartile range

‡ Median changes from Baseline are shown

Source: Tables 12-14

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**APPEARS THIS WAY
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Study 023- Revised Integrated Clinical and Statistical Report for a Double-Blind, Placebo-Controlled Study to Evaluate the Effects of SC-65872 10 mg BID and Ibuprofen 800 mg TID on Platelet Function and Urinary Prostaglandins in Elderly Subjects

Reviewer's Conclusion: *The sponsor assessed platelet aggregation, bleeding time, serum TxB₂ level, and urinary TxB₂ levels for SC-65872 in a single center, double-blind, randomized, multiple dose, positive comparator, placebo controlled, parallel-group study in healthy elderly volunteers. The results suggest that SC-65872 administration does not interfere with platelet aggregation, bleeding time, and serum TxB₂ level consistent with lack of significant COX-1 inhibitory activity. There was a decrease in urinary prostaglandin level excretion with SC-65872 consistent with COX-2 inhibition.*

Study Description: Study 021 was a single center, double-blind, randomized, multiple dose, placebo-controlled, active comparator, parallel-group study in healthy elderly volunteers.

Subjects:

The trial enrolled 46 subjects (15 male, 31 female). The inclusion and exclusion criteria were similar to those used in study 021 except for the acceptable age range, acceptable weight range, acceptable renal function, and acceptable upper limit of normal for blood pressure.

The 46 subjects were randomized to the following groups:

- 10 mg SC-65872 BID (15 subjects)
- 800 mg ibuprofen TID (16 subjects)
- placebo (15 subjects)

Study Plan:

The schedule of observations and procedures was similar to that for Study 021.

10 mg SC-65872 subjects

These subjects received 10 mg SC-65872 at 7 a.m. and 7 p.m. and ibuprofen matching placebo at 7 a.m., 3 p.m., and 11 p.m.

Ibuprofen subjects

These subjects received SC-65872 matching placebo at 7 a.m. and 7 p.m. and ibuprofen at 7 a.m., 3 p.m., and 11 p.m.

Results:

Demographics:

No significant differences were noted between treatment groups.

Subject disposition:

One subject in the 800 mg ibuprofen treatment group withdrew due to an adverse event (maculopapular rash).

Platelet Aggregation:

The sponsor's table below summarizes the results in response to arachidonic acid.

Reviewer's Comment: The table below shows the response to arachidonic acid stimulation was not statistically significantly different for SC-65872 compared with placebo. Ibuprofen subjects

demonstrated a statistically significant decrease in response to arachidonic acid compared with placebo. These results are consistent with the relatively selective inhibition of COX-2 by SC-65872.

Summary Table 1. Platelet Aggregation Response to Arachidonate (Median Change from Baseline)

| | Day 1 | | |
|--|------------------------|------------------------|------------------------|
| | Placebo | SC-65872 10 mg BID | Ibuprofen 800 mg TID |
| Median response to arachidonate (%) | | | |
| Baseline [†] (Q1-Q3) | 84.0 (81.0 to 86.0) | 86.0 (79.0 to 88.0) | 87.0 (80.5 to 90.0) |
| Median change from Baseline at: [‡] | | | |
| 2 hours | 2.0 | -1.0 [i****] | -79.0 [p****] |
| 4 hours | 3.0 | 2.0 [i****] | -76.0 [p****] |
| 8 hours | 5.0 | 1.0 | -3.0 [p*] |
| | Day 8 | | |
| | Placebo | SC-65872 10 mg BID | Ibuprofen 800 mg TID |
| Median response to arachidonate (%) | | | |
| Baseline [†] (Q1-Q3) | 84.0 (81.0 to 86.0) | 86.0 (79.0 to 88.0) | 87.0 (80.5 to 90.0) |
| Median change from Baseline at: [‡] | | | |
| -30 minutes | 3.0 | -1.0 | -2.0 |
| 2 hours | 3.0 | -3.0 [i****] | -74.0 [p****] |
| 4 hours | 2.0 | 2.0 [i**] | -40.0 [p**] |
| 8 hours | 4.0 | -1.0 | 1.0 |

[†] Defined as the median Day -1 measurement.

[‡] Observed median changes from Baseline are shown; statistically significant pairwise comparisons of the median change from Baseline, using Wilcoxon test, are shown in brackets.

i****, i** = statistically significantly different from ibuprofen at levels of 0.001 and 0.01, respectively.

p****, p**, p* = statistically significantly different from placebo at levels of 0.001, 0.01, and 0.05, respectively. Information from Table 7.

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In general, platelet aggregation testing results with collagen and ADP were not statistically significantly different for SC-65872 compared with placebo. Some platelet aggregation testing results with collagen and ADP acid were statistically significantly different for ibuprofen compared with placebo.

Reviewer's Comment: These results are consistent with the relatively selective inhibition of COX-2 by SC-65872.

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Summary Table 2. Platelet Aggregation Response to Collagen (Median Change from Baseline)

| | Day 1 | | |
|--|------------------------|------------------------|------------------------|
| | Placebo | SC-65872 10 mg BID | Ibuprofen 800 mg TID |
| Median response to collagen (%) | | | |
| Baseline [†] (Q1-Q3) | 85.0 (84.0 to 89.0) | 86.0 (83.0 to 91.0) | 86.0 (82.0 to 90.5) |
| Median change from Baseline at:[‡] | | | |
| 2 hours | 0.0 | 1.0 [**] | -7.0 [p*] |
| 4 hours | 0.0 | -1.0 | -2.5 |
| 8 hours | 3.0 | 0.0 | 0.5 |
| | Day 8 | | |
| | Placebo | SC-65872 10 mg BID | Ibuprofen 800 mg TID |
| Median response to collagen (%) | | | |
| Baseline [†] (Q1-Q3) | 85.0 (84.0 to 89.0) | 86.0 (83.0 to 91.0) | 86.0 (82.0 to 90.5) |
| Median change from Baseline at:[‡] | | | |
| -30 minutes | 1.0 | 0.0 | 1.0 |
| 2 hours | 0.0 | 0.0 [**] | -6.0 [p***] |
| 4 hours | 0.0 | -1.0 | -5.0 [p*] |
| 8 hours | 1.0 | 0.0 | 3.0 |

[†] Defined as the median Day -1 measurement.

[‡] Observed median changes from Baseline are shown; statistically significant pairwise comparisons of the median change from Baseline, using Wilcoxon test, are shown in brackets.

i** = statistically significantly different from ibuprofen at level of 0.01.

p***, p**, p* = statistically significantly different from placebo at levels of 0.001, 0.01, and 0.05, respectively. Information from Table 8.

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Summary Table 3. Platelet Aggregation Response to ADP (Median Change from Baseline)

| | Day 1 | | |
|--|------------------------|------------------------|------------------------|
| | Placebo | SC-65872 10 mg BID | Ibuprofen 800 mg TID |
| Median response to ADP (%) | | | |
| Baseline [†] (Q1-Q3) | 84.0 (83.0 to 89.0) | 83.0 (80.0 to 88.0) | 85.5 (82.0 to 89.0) |
| Median change from Baseline at: [‡] | | | |
| 2 hours | 2.0 | 3.0 [****] | -6.5 [p****] |
| 4 hours | -1.0 | 1.0 [**] | -6.0 [p*] |
| 8 hours | 3.0 | 2.0 [*] | -5.0 [p*] |
| | Day 8 | | |
| | Placebo | SC-65872 10 mg BID | Ibuprofen 800 mg TID |
| Median response to ADP (%) | | | |
| Baseline [†] (Q1-Q3) | 84 (83.0 to 89.0) | 83 (80.0 to 88.0) | 85.0 (82.0 to 89.0) |
| Median change from Baseline at: [‡] | | | |
| -30 minutes | 0.0 | 2.0 | -1.0 |
| 2 hours | 2.0 | 0.0 [*] | -7.0 [p**] |
| 4 hours | 5.0 | 2.0 [**] | -2.0 [p*] |
| 8 hours | 3.0 | 2.0 [*] | -4.0 |

[†] Defined as the median Day -1 measurement.

[‡] Observed median changes from Baseline are shown; statistically significant pairwise comparisons of the median change from Baseline, using Wilcoxon test, are shown in brackets.

i***, i**, i* = statistically significantly different from ibuprofen at levels of 0.001, 0.01, and 0.05, respectively.
p***, p**, p* = statistically significantly different from placebo at levels of 0.001, 0.01, and 0.05, respectively.
Information from Table 9.

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Simplate II bleeding times

There were no statistically significant differences in bleeding times between placebo and SC-65872 for any time point on Days 1 and 8.

Serum TxB₂ concentrations

The sponsor's table below shows that subjects taking SC-65872 had serum TxB₂ levels that were statistically significantly different from ibuprofen, but were not statistically significantly different from placebo. The subjects taking ibuprofen had statistically significant different serum TxB₂ levels from placebo.

Reviewer's Comment: These results are consistent with the relatively selective inhibition of COX-2 by SC-65872.

Summary Table 5. Serum TxB₂ (Median Change from Baseline)

| | Day 1 | | |
|---|--------------------------|--------------------------|--------------------------|
| | Placebo | SC-65872 10 mg BID | Ibuprofen 800 mg TID |
| Median serum TxB₂ level (ng/mL) | | | |
| Baseline [†] (Q1-Q3) | 146.0 (39.3 to 198.0) | 119.0 (58.4 to 185.0) | 151.0 (84.2 to 213.0) |
| Median change from Baseline at:[‡] | | | |
| 2 hours | -21.0 | 3.1 [i***] | -149.1 [p***] |
| 4 hours | 0.0 | 13.3 [i***] | -142.2 [p***] |
| 8 hours | 5.0 | -0.1 [i***] | -126.7 [p***] |
| Percent change from Baseline at:[‡] | | | |
| 2 hours | -7.0 | 2.0 [i***] | -98.2 [p***] |
| 4 hours | 0.0 | 11.2 [i***] | -97.2 [p***] |
| 8 hours | 1.9 | -0.4 [i***] | -87.2 [p***] |
| | Day 8 | | |
| | Placebo | SC-65872 10 mg BID | Ibuprofen 800 mg TID |
| Median serum TxB₂ level (ng/mL) | | | |
| Baseline [†] (Q1-Q3) | 146.0 (39.3 to 198.0) | 119.0 (58.4 to 185.0) | 151 (84.2 to 213.0) |
| Median change from Baseline at:[‡] | | | |
| -30 minutes | -26.0 | -11.0 [i***] | -123.5 [p***] |
| 2 hours | 12.0 | -10.0 [i***] | -151.5 [p***] |
| 4 hours | -6.0 | -13.8 [i***] | -150.5 [p***] |
| 8 hours | -35.0 | -34.4 [i***] | -145.1 [p***] |
| Percent change from Baseline at:[‡] | | | |
| -30 minutes | -17.1 | -5.9 [i***] | -88.9 [p***] |
| 2 hours | 7.9 | -11.3 [i***] | -99.0 [p***] |
| 4 hours | -3.7 | -20.5 [i***] | -99.1 [p***] |
| 8 hours | -16.4 | -30.8 [i***] | -92.3 [p***] |

[†] Defined as the median Day -1 measurement.

[‡] Observed median changes from Baseline are shown; statistically significant pairwise comparisons of the median change from Baseline, using Wilcoxon test, are shown in brackets.

i*** = statistically significantly different from ibuprofen at a level of 0.001.

p*** = statistically significantly different from placebo at a level of 0.001.

Information from Table 11.

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Urinary Prostaglandin

The table below demonstrates that urinary 11-dehydro-TxB₂ levels were decreased in SC-65872 subjects to a lesser extent than in ibuprofen subjects.

Summary Table 6. Urinary 11-dehydro-TxB₂ (Median Change from Baseline—All Subjects)

| | Placebo | SC-65872 10 mg BID | Ibuprofen 800 mg TID |
|---|------------------------------|------------------------------|------------------------------|
| Median 11-dehydro-TxB₂ level (ng/day) | | | |
| Baseline [†] (Q1-Q3) | 1982.6 (1386.4 to 2098.9) | 1875.3 (1472.9 to 2379.8) | 1680.4 (1364.1 to 2408.4) |
| Median change from Baseline on:[‡] | | | |
| Day 1 | -53.6 | -182.9 | -909.0 |
| Day 7 | 240.8 | -197.7 | -1072.7 |

[†] Defined as the median Day -1 measurement.

[‡] Observed median changes from Baseline are shown.
Information from Table 12.

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Study 042- Final Report for a Double-Blind, Placebo Controlled Study To Evaluate the Effects of SC-65872 40 mg BID and Ibuprofen 800 mg TID on Platelet Function and Urinary Prostaglandins in-Elderly Subjects

Reviewer's Conclusion: *The sponsor assessed platelet aggregation, bleeding time, serum TxB₂ level, and urinary TxB₂ levels for SC-65872 in a single center, double-blind, randomized, multiple dose, positive comparator, placebo controlled, parallel-group study in healthy elderly volunteers. The results suggest that SC-65872 administration does not interfere with platelet aggregation, bleeding time, and serum TxB₂ level consistent with lack of significant COX-1 inhibitory activity. There was a decrease in urinary prostaglandin level excretion with SC-65872 consistent with COX-2 inhibition.*

Study Description: Study 042 was a single center, double-blind, randomized, multiple dose, placebo-controlled, active comparator, parallel-group study in healthy elderly volunteers.

Subjects:

The trial enrolled 47 subjects. The inclusion and exclusion criteria were similar to those used in study 021 except for the acceptable age range, acceptable weight range, acceptable renal function, and acceptable upper limit of normal for blood pressure.

The 47 subjects were randomized to the following groups:

- 40 mg SC-65872 BID (17 subjects)
- 800 mg ibuprofen TID (15 subjects)
- placebo (15 subjects)

Study Plan:

The schedule of observations and procedures was similar to that for Study 021.

40 mg SC-65872 subjects

These subjects received 40 mg SC-65872 at 7 a.m. and 7 p.m. and ibuprofen matching placebo at 7 a.m., 3 p.m., and 11 p.m.

Ibuprofen subjects

These subjects received SC-65872 matching placebo at 7 a.m. and 7 p.m. and ibuprofen at 7 a.m., 3 p.m., and 11 p.m.

Results:

Demographics:

No significant differences were noted between treatment groups.

Subject disposition:

Two subjects withdrew due to protocol non-compliance in the 40 mg SC-65872 treatment group.

Platelet Aggregation:

The sponsor's table below summarizes the results in response to arachidonic acid.

Reviewer's Comment: The table below shows the response to arachidonic acid stimulation was not statistically significantly different for SC-65872 compared with placebo. Ibuprofen subjects demonstrated a statistically significant decrease in response to arachidonic acid compared with placebo. These results are consistent with the relatively selective inhibition of COX-2 by SC-65872.

Table 9.a. Platelet Aggregation Response to Arachidonate (Median Change from Baseline)

| | Day 1 | | |
|--|------------------------|------------------------|------------------------|
| | Placebo | SC-65872 40 mg BID | Ibuprofen 800 mg TID |
| Median response to arachidonate (%) | | | |
| Baseline ¹ (Q1-Q3) | 83.0 (78.0 to 89.0) | 85.0 (78.0 to 88.0) | 81.0 (76.0 to 86.0) |
| Median change from Baseline at:² | | | |
| 2 hours | -4.0 | 0.0 [***] | -73.0 [p***] |
| 4 hours | -2.0 | -3.0 [***] | -69.0 [p***] |
| 8 hours | 0.0 | -4.0 | -9.0 |
| | Day 8 | | |
| | Placebo | SC-65872 40 mg BID | Ibuprofen 800 mg TID |
| Median response to arachidonate (%) | | | |
| Baseline ¹ (Q1-Q3) | 83.0 (78.0 to 89.0) | 85.0 (78.0 to 88.0) | 81.0 (76.0 to 86.0) |
| Median change from Baseline at:² | | | |
| -30 minutes | -3.0 | -2.0 | -1.0 |
| 2 hours | -2.0 | 1.0 [***] | -70.0 [p***] |
| 4 hours | -1.0 | 0.0 [***] | -60.0 [p***] |
| 8 hours | -2.0 | -2.0 | -1.0 |

¹ Defined as the median Day -1 measurement.

² Observed median changes from Baseline are shown; statistically significant pairwise comparisons of the median change from Baseline, using Wilcoxon test, are shown in brackets.

i*** = statistically significantly different from ibuprofen at a level of 0.001.

p*** = statistically significantly different from placebo at a level of 0.001.

Information from Tables T6.1 to T6.3.

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In general, platelet aggregation testing results with collagen and ADP were not statistically significantly different for SC-65872 compared with placebo. Some platelet aggregation testing results with collagen and ADP acid were statistically significantly different for ibuprofen compared with placebo.

Reviewer's Comment: These results are consistent with the relatively selective inhibition of COX-2 by SC-65872.

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Table 9.b. Platelet Aggregation Response to Collagen (Median Change from Baseline)

| | Day 1 | | |
|--|------------------------|------------------------|------------------------|
| | Placebo | SC-65872 40 mg BID | Ibuprofen 800 mg TID |
| Median response to collagen (%) | | | |
| Baseline [†] (Q1-Q3) | 84.0 (82.0 to 88.0) | 84.0 (81.0 to 85.0) | 83.0 (80.0 to 86.0) |
| Median change from Baseline at: [‡] | | | |
| 2 hours | 0.0 | 0.0 [i***] | -7.0 [p**] |
| 4 hours | -4.0 | -2.0 [i**] | -8.0 |
| 8 hours | 2.0 | 0.0 | 1.0 |
| | Day 8 | | |
| | Placebo | SC-65872 40 mg BID | Ibuprofen 800 mg TID |
| Median response to collagen (%) | | | |
| Baseline [†] (Q1-Q3) | 84.0 (82.0 to 88.0) | 84.0 (81.0 to 85.0) | 83.0 (80.0 to 86.0) |
| Median change from Baseline at: [‡] | | | |
| -30 minutes | -2.0 | -1.0 | -2.0 |
| 2 hours | 0.0 | 1.0 [i***] | -12.0 [p**] |
| 4 hours | -1.0 | -1.0 [i**] | -9.0 [p***] |
| 8 hours | -1.0 | 1.0 | -1.0 |

[†] Defined as the median Day -1 measurement.

[‡] Observed median changes from Baseline are shown; statistically significant pairwise comparisons of the median change from Baseline, using Wilcoxon test, are shown in brackets.

i***, i** = statistically significantly different from ibuprofen at levels of 0.001, and 0.01, respectively.

p***, p** = statistically significantly different from placebo at levels of 0.001, and 0.01, respectively.

Information from Tables T7.1 to T7.3.

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Table 9.c. Platelet Aggregation Response to ADP (Median Change from Baseline)

| | Day 1 | | |
|--|------------------------|------------------------|------------------------|
| | Placebo | SC-65872 40 mg BID | Ibuprofen 800 mg TID |
| Median response to ADP (%) | | | |
| Baseline [†] (Q1-Q3) | 90.0 (86.0 to 91.0) | 88.0 (84.0 to 90.0) | 87.0 (84.0 to 90.0) |
| Median change from Baseline at: [‡] | | | |
| 2 hours | -3.0 | 1.0 [i***] | -6.0 |
| 4 hours | -2.0 | 0.0 [i***] | -11.0 [p**] |
| 8 hours | -3.0 | 0.0 [i**] | -5.0 |
| | Day 8 | | |
| | Placebo | SC-65872 40 mg BID | Ibuprofen 800 mg TID |
| Median response to ADP (%) | | | |
| Baseline [†] (Q1-Q3) | 90.0 (86.0 to 91.0) | 88.0 (84.0 to 90.0) | 87.0 (84.0 to 90.0) |
| Median change from Baseline at: [‡] | | | |
| -30 minutes | -2.0 | 1.0 [i*] | -6.0 |
| 2 hours | -1.0 | 3.0 [i**] | -10.0 [p**] |
| 4 hours | -2.0 | 3.0 [i*] | -3.0 |
| 8 hours | -1.0 | 1.0 [i**] | -3.0 |

[†] Defined as the median Day -1 measurement.

[‡] Observed median changes from Baseline are shown; statistically significant pairwise comparisons of the median change from Baseline, using Wilcoxon test, are shown in brackets.

i***, i**, i* = statistically significantly different from ibuprofen at levels of 0.001, 0.01, and 0.05, respectively.

p** = statistically significantly different from placebo at a level of 0.01.

Information from Tables T8.1 to T8.3.

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Simplate II bleeding times

There were no statistically significant differences in bleeding times between placebo and SC-65872 for any time point on Days 1 and 8.

Serum TxB₂ concentrations

The sponsor's table below shows that subjects taking SC-65872 had serum TxB₂ levels that were statistically significantly different from ibuprofen, but were not different from placebo. The subjects taking ibuprofen had statistically significant different serum TxB₂ levels from placebo.

Reviewer's Comment: These results are consistent with the relatively selective inhibition of COX-2 by SC-65872.

Table 9.e. Serum TxB₂ (Median Change from Baseline)

| | Day 1 | | |
|---|-------------------------|--------------------------|--------------------------|
| | Placebo | SC-65872 40 mg BID | Ibuprofen 800 mg TID |
| Median serum TxB₂ level (ng/mL) | | | |
| Baseline [†] (Q1-Q3) | 71.2 (24.1 to 182.0) | 111.0 (20.5 to 169.0) | 125.0 (19.3 to 184.0) |
| Median change from Baseline at:[‡] | | | |
| 2 hours | 8.9 | 12.0 [i**] | -122.9 [p***] |
| 4 hours | 23.7 | -14.0 [i**] | -121.5 [p***] |
| 8 hours | -13.5 | -13.0 [i*] | -106.9 [p**] |
| Percent change from Baseline at:[‡] | | | |
| 2 hours | 17.8 | 5.1 [i***] | -98.0 [p***] |
| 4 hours | 24.4 | -10.6 [i***] | -95.6 [p***] |
| 8 hours | -15.8 | -5.8 [i**] | -86.9 [p**] |
| | Day 8 | | |
| | Placebo | SC-65872 40 mg BID | Ibuprofen 800 mg TID |
| Median serum TxB₂ level (ng/mL) | | | |
| Baseline [†] (Q1-Q3) | 71.2 (24.1 to 182.0) | 111.0 (20.5 to 169.0) | 125.0 (19.3 to 184.0) |
| Median change from Baseline at:[‡] | | | |
| -30 minutes | 17.7 | -22.2 [i*] | -106.8 [p***] |
| 2 hours | 9.0 | -13.4 [i**] | -122.8 [p***] |
| 4 hours | 14.7 | -30.4 [i*] | -121.8 [p***] |
| 8 hours | -2.5 | -34.5 [i*] | -105.6 [p***] |
| Percent change from Baseline at:[‡] | | | |
| -30 minutes | 15.2 | -20.4 [i**] | -91.8 [p***] |
| 2 hours | 18.0 | -12.4 [i***] | -98.1 [p***] |
| 4 hours | 40.1 | -22.5 [i***] | -97.5 [p***] |
| 8 hours | -5.0 | -28.5 [i***] | -90.5 [p***] |

[†] Defined as the median Day -1 measurement.

[‡] Observed median changes from Baseline are shown; statistically significant pairwise comparisons of the median change from Baseline, using Wilcoxon test, are shown in brackets.

i***, i**, i* = statistically significantly different from ibuprofen at levels of 0.001, 0.01, and 0.05, respectively.

p***, p** = statistically significantly different from placebo at levels of 0.001 and 0.01, respectively.

Information from Tables T10.1 to T10.5.

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Urinary TxB₂

The table below demonstrates that urinary 11-dehydro-TxB₂ levels were decreased in SC-65872 subjects to a lesser extent than in ibuprofen subjects.

Table 9.f. Urinary 11-dehydro-TxB₂ (Median Change from Baseline)

| | Placebo | SC-65872 40 mg BID | Ibuprofen 800 mg TID |
|---|------------------------------|------------------------------|------------------------------|
| Median 11-dehydro-TxB₂ level (ng/day) | | | |
| Baseline [†] (Q1-Q3) | 1767.1 (1433.3 to 2055.6) | 1688.8 (1529.3 to 2346.9) | 2025.6 (1452.5 to 2616.3) |
| Median change from Baseline on:[‡] | | | |
| Day 1 | 9.2 | -131.4 | -1149.8 |
| Day 7 | -18.0 | -150.7 | -1159.9 |

[†] Defined as the median Day -1 measurement.
[‡] Observed median changes from Baseline are shown.
Information from Tables T11.1 and T11.2.

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Study 043 -Final Report for a Double-Blind, Placebo Controlled Study To Evaluate the Effects of SC-65872 40 mg BID, Naproxen 500 mg BID, and Diclofenac 75 mg TID on Platelet Function and Urinary Prostaglandins in Normal Healthy Subjects

Reviewer's Conclusion: *The sponsor assessed platelet aggregation, bleeding time, serum TxB₂ level, and urinary TxB₂ levels for SC-65872 in a single center, double-blind, randomized, multiple dose, positive comparator, placebo controlled, parallel-group study in healthy volunteers. The results suggest that SC-65872 administration does not interfere with platelet aggregation, bleeding time, and serum TxB₂ level consistent with lack of significant COX-1 inhibitory activity. There was a decrease in urinary prostaglandin level excretion with SC-65872 consistent with COX-2 inhibition.*

Study Description: Study 043 was a single center, double-blind, randomized, multiple dose, placebo-controlled, active comparator, parallel-group study in healthy volunteers.

Subjects:

The trial enrolled 62 subjects. The inclusion and exclusion criteria were similar to those used in Study 021.

The 62 subjects were randomized to the following groups:

- 40 mg SC-65872 BID (15 subjects)
- 500 mg naproxen BID (15 subjects)
- 75 mg diclofenac BID (16 subjects)
- placebo (16 subjects)

Study Plan:

The schedule of observations and procedures was similar to that for Study 021.

Results:

Demographics:

No significant differences were noted between treatment groups.

Subject disposition:

Two subjects in the diclofenac treatment group withdrew due to protocol non-compliance. One subject in the placebo treatment group withdrew due to urticaria.

Platelet Aggregation:

The sponsor's table below summarizes the results in response to arachidonic acid.

Reviewer's Comment: The table below shows the response to arachidonic acid stimulation was not statistically significantly different for SC-65872 compared with placebo. Naproxen and diclofenac subjects demonstrated a statistically significant decrease in response to arachidonic acid compared with placebo. These results are consistent with the relatively selective inhibition of COX-2 by SC-65872.

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Table 9.a. Platelet Aggregation Response to Arachidonate (Median Change from Baseline)

| | Day 1 | | | |
|--|------------------------|------------------------|------------------------|-------------------------|
| | Placebo | SC-65872 40 mg BID | Naproxen 500 mg BID | Diclofenac 75 mg BID |
| Median response to arachidonate (%) | | | | |
| Baseline [†] (Q1-Q3) | 85.5 (82.5 to 88.5) | 84.0 (80.0 to 88.0) | 87.0 (82.0 to 89.0) | 87.0 (83.0 to 90.0) |
| Median change from Baseline at:[‡] | | | | |
| 2 hours | 3.0 | -1.0 [n***] | -82.0 [p***] | 0.0 |
| 4 hours | 1.0 | -1.0 [n***, d**] | -83.0 [p***] | -80.0 [p**] |
| 8 hours | -2.0 | 6.0 [n***, d**] | -82.0 [p***] | -18.5 [p*] |
| | Day 8 | | | |
| | Placebo | SC-65872 40 mg BID | Naproxen 500 mg BID | Diclofenac 75 mg BID |
| Median response to arachidonate (%) | | | | |
| Baseline [†] (Q1-Q3) | 85.5 (82.5 to 88.5) | 84.0 (80.0 to 88.0) | 87.0 (82.0 to 89.0) | 87.0 (83.0 to 90.0) |
| Median change from Baseline at:[‡] | | | | |
| -30 minutes | 3.0 | 4.0 [n***] | -80.0 [p***] | -3.5 |
| 2 hours | 3.0 | 3.0 [n***, d***] | -81.0 [p***] | -8.5 [p**] |
| 4 hours | 0.0 | 3.0 [n***, d**] | -79.0 [p***] | -41.0 [p*] |
| 8 hours | 2.0 | 2.0 [n***, d***] | -80.0 [p***] | -11.0 [p**] |

[†] Defined as the median Day -1 measurement. Q1=upper quartile; Q3=lower quartile.

[‡] Observed median changes from Baseline are shown; statistically significant pairwise comparisons of the median change from Baseline, using the Wilcoxon Exact test, are shown in brackets. Results from comparisons of naproxen to diclofenac are not shown.

n*** = statistically significantly different from naproxen at a level of 0.001.

d***, d**= statistically significantly different from diclofenac at a level of 0.001 and 0.01, respectively.

p***, p**, p*= statistically significantly different from placebo at a level of 0.001, 0.01, and 0.05, respectively.
Information from Tables T6.1, T6.2, and T6.3.

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In general, platelet aggregation testing results with collagen and ADP were not statistically significantly different for SC-65872 compared with placebo. Some platelet aggregation testing results with collagen and ADP were statistically significantly different for naproxen and diclofenac compared with placebo.

Reviewer's Comment: These results are consistent with the relatively selective inhibition of COX-2 by SC-65872.

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Table 9.b. Platelet Aggregation Response to Collagen (Median Change from Baseline)

| | Day 1 | | | |
|--|------------------------|------------------------|------------------------|-------------------------|
| | Placebo | SC-65872 40 mg BID | Naproxen 500 mg BID | Diclofenac 75 mg BID |
| Median response to collagen (%) | | | | |
| Baseline [†] (Q1-Q3) | 82.5 (79.5 to 85.0) | 86.0 (82.0 to 90.0) | 85.0 (83.0 to 87.0) | 82.5 (79.0 to 87.5) |
| Median change from Baseline at: [‡] | | | | |
| 2 hours | 4.0 | -3.0 [n**] | -13.0 [p***] | 1.0 |
| 4 hours | 2.5 | -1.0 [n*, d*] | -6.0 [p**] | -11.0 [p**] |
| 8 hours | 0.5 | 2.0 | -1.0 | 0.0 |
| | Day 8 | | | |
| | Placebo | SC-65872 40 mg BID | Naproxen 500 mg BID | Diclofenac 75 mg BID |
| Median response to collagen (%) | | | | |
| Baseline [†] (Q1-Q3) | 82.5 (79.5 to 85.0) | 86.0 (82.0 to 90.0) | 85.0 (83.0 to 87.0) | 82.5 (79.0 to 87.5) |
| Median change from Baseline at: [‡] | | | | |
| -30 minutes | 3.0 | 0.0 | 0.0 | 4.0 |
| 2 hours | 5.0 | 0.0 | -6.0 [p**] | 0.0 |
| 4 hours | 2.0 | -1.0 [n**] | -18.0 [p**] | -2.5 |
| 8 hours | 5.0 | -1.0 | -1.0 | -1.0 |

[†] Defined as the median Day -1 measurement. Q1=upper quartile; Q3=lower quartile.

[‡] Observed median changes from Baseline are shown; statistically significant pairwise comparisons of the median change from Baseline, using the Wilcoxon Exact test, are shown in brackets. Results from comparisons of naproxen to diclofenac are not shown.

n**, n* = statistically significantly different from naproxen at a level of 0.01 and 0.05, respectively.

d* = statistically significantly different from diclofenac at a level of 0.05.

p***, p** = statistically significantly different from placebo at a level of 0.001 and 0.01, respectively.

Information from Tables T7.1, T7.2, and T7.3.

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Table 9.c. Platelet Aggregation Response to ADP (Median Change from Baseline)

| | Day 1 | | | |
|----------------------------------|------------------------|------------------------|------------------------|-------------------------|
| | Placebo | SC-65872 40 mg BID | Naproxen 500 mg BID | Diclofenac 75 mg BID |
| Median response to ADP (%) | | | | |
| Baseline† (Q1-Q3) | 81.5 (77.5 to 85.0) | 87.0 (79.0 to 90.0) | 84.0 (77.0 to 91.0) | 85.5 (80.0 to 88.5) |
| Median change from Baseline at:‡ | | | | |
| 2 hours | 4.5 | 1.0 [n***] | -55.0 [p***] | -3.0 |
| 4 hours | 1.5 | -3.0 [n***, d**] | -39.0 [p***] | -26.0 [p***] |
| 8 hours | 1.0 | -1.0 [n***] | -48.0 [p***] | -5.0 |
| | Day 8 | | | |
| | Placebo | SC-65872 40 mg BID | Naproxen 500 mg BID | Diclofenac 75 mg BID |
| Median response to ADP (%) | | | | |
| Baseline† (Q1-Q3) | 81.5 (77.5 to 85.0) | 87.0 (79.0 to 90.0) | 84.0 (77.0 to 91.0) | 85.5 (80.0 to 88.5) |
| Median change from Baseline at:‡ | | | | |
| -30 minutes | 1.0 | -1.0 [n***] | -23.0 [p***] | -2.0 |
| 2 hours | 3.0 | -2.0 [n***] | -35.0 [p***] | -1.5 |
| 4 hours | 3.0 | -1.0 [n***] | -26.0 [p***] | -6.5 [p**] |
| 8 hours | 2.0 | 2.0 [n***] | -29.0 [p**] | 1.5 |

† Defined as the median Day -1 measurement. Q1=upper quartile; Q3=lower quartile.

‡ Observed median changes from Baseline are shown; statistically significant pairwise comparisons of the median change from Baseline, using the Wilcoxon Exact test, are shown in brackets. Results from comparisons of naproxen to diclofenac are not shown.

n*** = statistically significantly different from naproxen at a level of 0.001.

d**= statistically significantly different from diclofenac at a level of 0.01.

p***, p**= statistically significantly different from placebo at a level of 0.001, and 0.01, respectively.

Information from Tables T8.1, T8.2, and T8.3.

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Simplate II bleeding times

There were no statistically significant differences in bleeding times between placebo and SC-65872 for any time point collected on Day 1 and Day 8.

Serum TxB₂ concentrations

The sponsor's table below shows that subjects taking SC-65872 had serum TxB₂ levels that were significantly different from naproxen but not statistically significant from placebo. The subjects taking naproxen had statistically significant different serum TxB₂ levels from placebo.

Reviewer's Comment: These results are consistent with the relatively selective inhibition of COX-2 by SC-65872.

Table 9.e. Serum TxB₂ (Median Change from Baseline)

| | Day 1 | | | |
|---|--------------------------|--------------------------|--------------------------|--------------------------|
| | Placebo | SC-65872 40 mg BID | Naproxen 500 mg BID | Diclofenac 75 mg BID |
| Median serum TxB₂ level (ng/mL) | | | | |
| Baseline† (Q1-Q3) | 139.5 (64.2 to 246.0) | 149.0 (65.9 to 250.0) | 169.0 (27.7 to 201.0) | 118.7 (37.7 to 184.5) |
| Median change from Baseline at:‡ | | | | |
| 2 hours | 23.4 | 13.0 [n***] | -167.9 [p***] | 35.0 |
| 4 hours | 39.5 | 8.0 [n***, d*] | -167.1 [p***] | -67.3 [p*] |
| 8 hours | 8.8 | -3.0 [n***] | -163.0 [p***] | -13.2 |
| Percent change from Baseline at:‡ | | | | |
| 2 hours | 11.4 | 8.7 [n***] | -97.5 [p***] | 28.9 |
| 4 hours | 16.1 | 4.1 [n***, d**] | -97.6 [p***] | -88.7 [p**] |
| 8 hours | 10.1 | -1.2 [n***] | -94.6 [p***] | -7.8 |
| | Day 8 | | | |
| | Placebo | SC-65872 40 mg BID | Naproxen 500 mg BID | Diclofenac 75 mg BID |
| Median serum TxB₂ level (ng/mL) | | | | |
| Baseline† (Q1-Q3) | 139.5 (64.2 to 246.0) | 149.0 (65.9 to 250.0) | 169.0 (27.7 to 201.0) | 118.7 (37.7 to 184.5) |
| Median change from Baseline at:‡ | | | | |
| -30 minutes | -21.0 | 5.0 [n***] | -168.3 [p**] | -24.8 |
| 2 hours | 8.0 | -10.0 [n**] | -165.3 [p***] | -39.3 |
| 4 hours | 13.4 | 7.5 [n***] | -168.6 [p**] | -15.0 |
| 8 hours | 8.0 | 20.0 [n***] | -167.6 [p***] | -33.3 |
| Percent change from Baseline at:‡ | | | | |
| -30 minutes | -15.2 | 3.4 [n***] | -98.2 [p***] | -32.2 |
| 2 hours | 4.6 | -6.7 [n***] | -98.0 [p***] | -26.2 |
| 4 hours | 34.1 | 12.4 [n***] | -99.5 [p***] | -26.6 |
| 8 hours | 4.7 | 10.6 [n***] | -98.3 [p***] | -25.7 |

† Defined as the median Day -1 measurement. Q1=upper quartile; Q3=lower quartile.

‡ Observed median changes from Baseline are shown; statistically significant pairwise comparisons of the median change from Baseline, using the Wilcoxon Exact test, are shown in brackets. Results from comparisons of naproxen to diclofenac are not shown.

n***, n** = statistically significantly different from naproxen at a level of 0.001 and 0.01, respectively.

d**, d* = statistically significantly different from diclofenac at a level of 0.01 and 0.05, respectively.

p***, p**, p* = statistically significantly different from placebo at a level of 0.001, 0.01, and 0.05, respectively.

Information from Tables T10.1, T10.2, T10.3, T10.4 and T10.5.

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Urinary TxB₂

The table below demonstrates that urinary 11-dehydro-TxB₂ levels were decreased in SC-65872 subjects to a lesser extent than in naproxen and diclofenac subjects.

Table 9.f. Urinary 11-dehydro-TxB₂ (Median Change from Baseline)

| | Placebo | SC-65872 40 mg BID | Naproxen 500 mg BID | Diclofenac 75 mg BID |
|---|------------------------------|------------------------------|------------------------------|------------------------------|
| Median 11-dehydro-TxB₂ level (ng/day) | | | | |
| Baseline [†] (Q1-Q3) | 1584.3 (1335.8 to 2156.4) | 1811.7 (1665.4 to 2424.4) | 1947.9 (1362.5 to 2071.6) | 2039.6 (1390.3 to 2233.0) |
| Median change from Baseline on:[‡] | | | | |
| Day 1 | 50.9 | -113.3 | -1005.8 | -486.4 |
| Day 7 | 85.1 | -223.6 | -1132.6 | -554.0 |

[†] Defined as the median Day -1 measurement.

[‡] Observed median changes from Baseline are shown.
Information from Table T11.1.

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Study 93-031-Final Report for a Multidose, Double-Blind, Placebo Controlled Study To Determine the Effects of Co-administration of Parecoxib 40 mg IV BID and Aspirin 325 mg on Platelet Function in Normal Healthy Subjects

Reviewer's Conclusion: *The sponsor assessed platelet aggregation, bleeding time, and serum TxB₂ levels in a co-administration study of IV SC-69124A and aspirin in a single center, double-blind, randomized, multiple dose, and placebo-controlled, parallel-group study in healthy volunteers. The results of this study suggest that co-administration of IV SC-69124A and aspirin compared with co-administration of IV normal saline and aspirin produced similar results for platelet aggregation, bleeding times, and serum TxB₂ levels.*

Study Description: Study 031 was a single center, double-blind, randomized, multiple dose, placebo-controlled, and parallel-group study in healthy volunteers. The sponsor's objective is listed below.

The objective of this study was to compare the effects of coadministration of parecoxib 40 mg BID and a single dose of aspirin 325 mg versus coadministration of placebo and a single dose of aspirin 325 mg on platelet function.

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Inclusion and Exclusion Criteria:

The trial enrolled subjects meeting the inclusion and exclusion criteria listed below.

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Reviewer's Comment: These inclusion and exclusion criteria are typical for platelet aggregation studies.

6.2.1. Inclusion Criteria

To be eligible for the study, candidates had to satisfy the following criteria:

- Were between 18 and 55 years of age;
- Weighed at least 50 kg;
- If female, were not pregnant, not lactating, surgically sterilized (e.g., hysterectomy, bilateral oophorectomy, or tubal ligation), or postmenopausal for at least two years (females had to provide a negative pregnancy test prior to admission to the study);
- Had a body weight within $\pm 20\%$ of the 1983 Metropolitan Life Insurance Company Standards;
- Were in good health as determined by medical history, physical examination, and laboratory screening tests;
- Provided a negative hepatitis B surface antigen test result within two weeks prior to admission to the study;
- Had clinical laboratory test results within normal limits for PT and aPTT during the Screening Visit; and
- Provided written informed consent.

6.2.2. Exclusion Criteria

Candidates were excluded from the study for any of the following:

- Had a clinically significant history of cardiac, renal, hepatic, or endocrinologic disease, or a history of gastric or duodenal ulcer;
- Had a personal history of bruising or bleeding abnormalities (e.g., chronic rectal or hemorrhoidal bleeding, or excessive bleeding during surgery or tooth extraction), or a family history of bleeding disorders;
- Had an abnormal Baseline platelet aggregation test utilizing arachidonic acid;
- Had a history of malignancy, except basal cell carcinoma;
- Had taken any drug with known platelet effects (e.g., aspirin, aspirin[®] or salicylate-containing combination products, NSAIDs, dipyridamole, etc.) within 14 days prior to the first dose of study medication;
- Had used any medication (including ascorbic acid) within 14 days prior to the first dose of study medication, or was expected to receive any medication other than parecoxib that could confound the interpretation of study results;

- Had any abnormal Screening clinically laboratory test value (e.g., a clinically significant coagulation abnormality; a platelet count $<150 \times 10^9/L$; AST, ALT, or BUN ≥ 1.5 times the upper limit of normal; or creatinine levels ≥ 500 U/L);
- Had a clinically significant abnormality on the Screening 12-lead ECG;
- Had a history of smoking within the previous six months;
- Had a history of alcoholism and/or drug abuse, and had an admitted inability to abstain from alcohol from the 48 hours prior to the first dose of study drug to the end of the study;
- Had received any investigational medication within 30 days prior to the first dose of study medication, or was scheduled to receive an investigational drug other than parecoxib during the course of the study;
- Had a known hypersensitivity to COX inhibitors, NSAIDs, aspirin, and/or related compounds with cross-reactivity to any medication used in the study;
- Were scheduled for elective surgery or dental procedure within 14 days of the last dose of study medication;
- Had donated blood products within 30 days prior to the first dose of study medication;
- Had a positive urine drug and/or alcohol screening test prior to the first dose of study medication;
- Had any other condition that, in the Investigator's opinion, would have precluded participation in the study;
- Had a history of keloid formation or abnormal scarring; or
- Were previously admitted to the study.

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Subjects:

The 20 subjects were enrolled and randomized to the following groups:

40 mg SC-69124A BID (10 subjects)

placebo (10 subjects)

Eighteen completed the study.

Study Plan:

Treatments were administered at 0700 – 0900 and 1900-2100. All patients received aspirin on Day 4.

SC-69124A subjects

SC-69124A was given intravenously twice a day at on Days 1-3 and at 0700 on Day 4. Aspirin was administered on Day 4 at approximately 0700.

Placebo subjects

Intravenous injection of normal saline was administered twice a day at 0700-0900, and 1900-2100 on Days 1-3 and at 0700 on Day 4. Aspirin was administered on Day 4 at approximately 0700.

Samples

Blood samples for serum TxB₂, platelet aggregation, and bleeding times were measured at predose and 2 hours after the 0700 dose on Days 1. On Day 4 samples were taken 30 minutes prior to, as well as 2, 4, 8 and 24 hours after the 0700 dose of aspirin on Day 4.

Results:

Subject Disposition

Two placebo subjects did not complete the study.

Platelet aggregation

There was no statistically significant difference in the platelet aggregation studies performed on Day 1 between placebo and SC-69124A. The sponsor's table below shows the response to arachidonic acid, ADP, and collagen on Day 4.

Reviewer's Comment: Results of platelet aggregation studies performed on Day 1 did not demonstrate a statistically significant difference between SC-69124A and placebo. The co-administration of aspirin with placebo and SC-69124A demonstrated a significant decrease in platelet aggregation on Day 4 but the decrease was not statistically significant different between the comparison groups (SC-69124A and placebo).

| Mean Percent Platelet Aggregation and Mean Percent Change in Platelet Aggregation following Coadministration of Aspirin with Parecoxib or Aspirin with Placebo on Day 4 | | | | | | |
|---|---------------|----------------------------|------------------------|----------------------------|----------------------|-------|
| Stimulation | Placebo (n=9) | | Parecoxib 40 mg (n=10) | | p-Value [‡] | |
| | Mean % | Mean % Change [†] | Mean % | Mean % Change [†] | | |
| Arachidonate [‡] | 0 hr | 71.89 | --- | 79.50 | --- | - |
| | 2 hr | 1.89 | -97.71 | 2.80 | -96.63 | 0.549 |
| | 4 hr | 2.44 | -97.06 | 1.80 | -97.78 | 0.701 |
| | 8 hr | 2.22 | -93.84 | 3.90 | -95.17 | 0.696 |
| | 22 hr | 2.00 | -97.56 | 3.10 | -96.18 | 0.440 |
| ADP [‡] | 0 hr | 62.56 | --- | 61.90 | --- | - |
| | 2 hr | 56.22 | -9.94 | 56.90 | -5.87 | 0.447 |
| | 4 hr | 50.44 | -20.16 | 62.00 | 1.68 | 0.006 |
| | 8 hr | 41.00 | -35.84 | 45.50 | -27.25 | 0.458 |
| | 22 hr | 56.00 | -11.19 | 61.60 | 1.05 | 0.044 |
| Collagen [‡] | 0 hr | 70.00 | --- | 72.30 | --- | - |
| | 2 hr | 5.11 | -92.74 | 6.40 | -91.37 | 0.660 |
| | 4 hr | 4.56 | -93.53 | 10.20 | -86.47 | 0.144 |
| | 8 hr | 5.00 | -92.57 | 8.40 | -88.73 | 0.318 |
| | 22 hr | 8.67 | -88.43 | 15.60 | -79.26 | 0.196 |

[†] Relative to predose value on Day 4.
[‡] Derived from two-sample t-test comparing mean percent changes of parecoxib and placebo treatment groups.
[§] Sampling times are relative to aspirin administration.

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Simplate II Bleeding Times

The Simplate II Bleeding Times were not prolonged for either the placebo group or the SC-69124A group on Day 1 (prior to aspirin administration). The observed Simplate II Bleeding Times were prolonged at 2, 4, 8, and 22 hours after aspirin administration on Day 4.

Serum TxB₂ Levels

Serum TxB₂ concentration levels decreased in both groups on Day 1 but did not differ statistically significantly between placebo and SC-69124A.

Serum TxB₂ concentration levels did not differ between placebo and SC-69124A with aspirin co-administration on Day 4.

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