Discontinuation for Clinical AE's 6 Week Osteoarthritis Studies

	Placebo	Rofecoxib		Ibuprofen
	N=412 %	12.5 mg N=725 %	25 mg N=735 %	2400 mg N=470 %
Headache	0.5	0.0	0.1	0.0
Dizziness	0.2	0.6	0.0	0.2
Diarrhea	0.7	0.0	0.4	0.2
Abdominal pain	0.5	0.1	0.5	1.5
Dyspepsia	0.0	0.1	0.4	0.9
Epigastric discomfort	0.0	0.3	0.7	1.1
Total discontinued for AE	3.4	4.7	5.4	6.6

All groups p = *NS* compared with placebo.

Protocols 010,029,033,040,058

Laboratory AE Summary
6 Week Osteoarthritis Studies

Laboratory AE	Placebo N=412 %	Rofecoxib 12.5 mg N=725 %	Rofecoxib 25 mg N=735 %	Ibuprofen 2400 mg N=470 %
With ≥ 1 AE	5.2	10.4	7.3	11.3*
Discontinued	0.0	0.6	0.3	0.2
Serious	0.0	0.0	0.0	0.0

* $p \leq 0.05$ vs. placebo.

Clinical Experience
Rofecoxib 50 mg and Greater

	Osteoarthritis Number of Patients		Rheumatoid Arthritis Number of Patients	
Duration	50 mg	125 mg	50 mg	125 mg
Up to 6 Weeks	551	74	161	69
Up to 12 Weeks	420			60
Up to 26 Weeks	379			36
Up to 1 Year	75			9

Clinical AE's with Rofecoxib 50 mg Once Daily Four Month Placebo Controlled OA Studies

Incidence ≥ 5.0% in Any Treatment Group

Adverse Experience	Placebo N=371 %	Rofecoxib 25 mg N=390 %	Rofecoxib 50 mg N=379 %	Ibuprofen 2400 mg N=377 %
Headache	8.9	6.4	5.8	8.0
Upper respiratory infection	9.2	7.2	6.3	6.4
Diarrhea	7.8	10.5	9.2	9.3
Abdominal pain	6.7	6.7	6.9	5.0
Epigastric discomfort	5.9	6.9	6.9	13.5*
Nausea	4.0	9.0*	7.7*	9.3*
Heartburn	5.9	8.5	9.2	8.2
Vomiting	1.6	3.3	3.7	5.3*
Lower extremity edema	1.3	4.4*	5.3*	3.4
Hypertension	2.2	5.1*	9.2*	4.0

*$p < 0.05$ compared with placebo.

Protocol 044 & 045

Topics of Special Interest

- Renal safety
- Hepatic safety
- Cardiovascular safety

Renal Safety

- COX-2 is constitutively present in the kidney
- Prostaglandins involved in renal physiology
  - Glomerular filtration rate
  - Renin secretion
  - Sodium, potassium and water homeostasis

Edema Adverse Experiences

1 Week Osteoarthritis Studies

	Placebo	Rofecoxib					Ibuprofen	Nabumetone
		5 mg	12.5 mg	25 mg	50 mg	125 mg	2400 mg	1500 mg
	N=412	N=149	N=725	N=735	N=97	N=74	N=470	N=115
	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
% of Patients with Edema AE	1.9	3.4	4.3	6.1	9.3	8.1	5.7	6.1
% of Patients Discontinued	0.0	0.0	0.4	0.3	1.0	5.4	0.0	0.0

AE Terms included edema, fluid retention, hand swelling, lower extremity edema, peripheral edema, upper extremity edema.

Protocols: 010, 029,033,040,058

Hypertension Adverse Experiences

6 Week Osteoarthritis Studies

	Placebo	Rofecoxib					Ibuprofen	Nabumetone
	N=412	5 mg N=149	12.5 mg N=725	25 mg N=735	50 mg N=97	125 mg N=74	2400 mg N=470	1500 mg N=115
	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
% of Patients Hypertension AE	1.0	2.0	3.4	3.8	2.1	2.7	2.6	3.5
% of Patients Discontinued	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

AE terms included: Hypertension, blood pressure increased, borderline hypertension, diastolic hypertension, hypertension uncontrolled with medication, systolic hypertension, hypertensive crisis, uncontrolled hypertension.

Protocols 010,029,033,040,058

Hypertension Adverse Experiences
Four Month Placebo Controlled OA Studies

	Placebo N=371 %	Rofecoxib 25mg N=390 %	Rofecoxib 50mg N=379 %	Ibuprofen 2400 mg N=377 %
% of Patients Hypertension AE	3.5	5.9	10.8	4.5
% Patients Discontinued	0.0	0.3	0.5	1.1

AE terms include blood pressure increased, borderline hypertension, hypertension, hypertensive crisis, uncontrolled hypertension.

Protocol 045

Creatinine and Serum Electrolytes
Four Month Placebo-Controlled OA Studies

% of Patients with Change 2 or More Times	Placebo N=363	Rofecoxib 25 mg N=385	Rofecoxib 50 mg N=372	Ibuprofen 2400 mg N=371
Serum Creatinine (Increase ≥ 0.5 mg/dL and > ULN)	0.0	0.3	0.6	0.8
Serum Bicarbonate (Value ≤ 16 mEq/L)	0.0	0.3	0.0	0.0
Serum Chloride (Value ≥ 115 mEq/L)	0.0	0.0	0.0	0.0
Serum Potassium (Increase ≥ 0.8 mEq/L and > ULN)	0.6	1.9	1.9	0.8

Protocols 044 and 045

Serum Phosphorus and Calcium Bone Density in OA Study

Insufficient 12 Week Data

% of Patients with:	Placebo N=99	Rofecoxib 25 mg N=98	Ibuprofen 2400 mg N=107
Phosphorus below normal and decreased 1.0 mg/dL from baseline	1.0	0.0	0.9
Phosphorus below 2.0 mg/dL	1.0	0.0	1.9
Calcium below normal	0.0	0.0	0.0

Renal Safety Conclusions

- Similar to NSAIDs
  - Mild sodium retention
    - Dose related incidence of edema and hypertension
    - Few patients discontinue therapy due to these AE's
  - No clinically significant effects on serum electrolytes (potassium, sodium, bicarbonate, chloride)
- Other
  - No acute renal failure
  - No interstitial nephritis
  - No clinically significant proteinuria

Hepatic Safety

Liver Function

- In chronic administration:
  - Rofecoxib & ibuprofen do not significantly change mean ALT/AST
  - Diclofenac significantly increases mean ALT/AST
- Increases in ALT/AST > 3-fold upper limit of normal
  - Rofecoxib and Ibuprofen ~1% of patients
    - ~0.1 % of patients discontinued treatment
  - Diclofenac ~5% of patients
    - ~3% of patients discontinued treatment

Thromboembolic Cardiovascular AE's

Thromboembolic Cardiovascular AE's
All OA Studies

[illegible] Patient Years (Number of [illegible])

Placebo N=783	Rofecoxib N=3595	NSAIDs N=1565
2.9 (4)	3.0 (46)	3.0 (19)

Deaths
All Osteoarthritis Studies

	Rofecoxib N=3595	NSAIDs N=1565
Total Deaths	0.1 (2)	1.1 (7)
Cardiovascular Deaths	0.1 (2)	0.8 (5)

†There were no deaths in the placebo group.

Rofecoxib General Safety Profile Summary

- Rofecoxib safety profile
  - Generally well tolerated
  - Safety profile is maintained at 4-5 x the therapeutic dose for OA, at doses of ≥ 50 mg in patients with osteoarthritis slightly higher incidence of edema and hypertension AE's
    - However, clinical consequences are limited. Only ~0.5% patients discontinue therapy
  - Safety profile is maintained with chronic administration up to 2 years
- Fewer liver function test abnormalities compared to diclofenac

Ongoing Studies: Rofecoxib Clinical Program

- Osteoarthritis ~9600 patients
  - Phase V OA (low dose aspirin allowed)
  - Phase III OA Extensions
  - 12 month Bone Mineral Density
- Rheumatoid Arthritis ~2700 patients
  - Phase III RA (low dose aspirin allowed)
- GI Outcomes Study ~7000 patients
- Juvenile RA
- Analgesia ~820 patients
- Alzheimer's ~1900 patients

Overall Conclusions
Rofecoxib Development Program

- Rofecoxib is a COX-2 specific inhibitor
- Rofecoxib is effective in the treatment of acute pain and the signs and symptoms of osteoarthritis
- Generally safe & well tolerated
- Dose selection for osteoarthritis and acute pain supported by optimal efficacy and safety
  - Osteoarthritis - 12.5 to 25 mg once daily
  - Acute analgesia - 50 mg once daily, some patients might receive benefit beyond day 1 from 25 mg
- Confirmed the COX-2 hypothesis
  - Efficacy statistically equivalent to NSAIDs
  - GI safety is significantly better than NSAIDs