2.4 Important Issues With Pharmacologically Related Products

NSAIDs/Naproxen

Recent concerns regarding the cardiovascular safety of NSAIDs as a class have arisen. See Section 1.1, *Recommendation on Regulatory Action*, Section 1.3.3, *Safety*, and Section 8.6, *Literature Review.*

Triptans/Sumatriptan

No new issues relate to triptans as a class.

2.5 Presubmission Regulatory Activity

Clinical development of Trexima originally was under IND 60,669. A second IND, 68,436 was submitted in December 2003 to conduct clinical studies on the fixed dose combination selected for further development (Table 3).

Table 3: Presubmission Regulatory Activity

August 2000	60,669 (000), original IND Protocol MT 400-203 *Evaluation of naproxen and Imitrex, alone and in combination, in acute migraine*
October 2000	60,669(001), Addendum (002) Protocol MT 400-204 *Minor revisions to protocol MT 400-203 to address 30-day safety review issues*
December 2000	60,669 (001) Statistical review, Dr. Yeh-Fong Chen *Analysis plan for study MT 400-204*
February 2002	60669 (007) Pre-IND meeting (for new fixed dose, IND 68,436)
April 2002	60,669 Biopharmaceutical guidance from OCPB
July 2002	60,669 Pozen clarification on Pre-IND Meeting minutes
August 2003	60,669 (010) *Pilot pharmacology study to assess vasoconstrictive potential*
December 2003	68,436 (000) *Clinical studies on the fixed dose combination selected*
May 2004	68,436 End-of-phase 2 meeting
October 2004	Biopharmaceutical guidance Phase 3 efficacy studies
November 2004	68,436 FDA Comments and request for information
April 2005	68,436 Pre-NDA meeting
April 2005, HFD-860 Consult	Biopharmaceutical guidance Secondary efficacy measures
May 2005	Biopharmaceutical guidance Effect of migraine on pharmacokinetics

Below I note important issues raised during the pre-submission period, along with the associated submission or meeting. I generally limit my discussion to the clinical issues raised, but have also included important preclinical issues with direct bearing on the cardiovascular safety of Trexima.

Pre-IND meeting (60,669)[for IND 68,436, new fixed dose] **February 28, 2002**

The lack of effective dose-finding studies was discussed with Pozen at the Pre-IND meeting:

> "There were two proposed dose-ranging studies for dose selection, and it was noted that this would not evaluate all possible dose-combinations for sumatriptan and naproxen. Likewise it was not apparent from the submission how the sponsor would determine which fixed dose combination ultimately considered optimal. The sponsor responded that they would most likely "eyeball" the studies looking for the combination product with the best response."

Nonclinical issues
The Division requested a safety pharmacology study in dog to assess the effect of naproxen on the risk of sumatriptan-induced vasoconstriction of the coronary artery.

End-of-Phase 2 Meeting May 6, 2004

The Division stated data would be needed to support any statement

[redacted]

Non-Clinical
The Division did not agree that the results of the dog cardiovascular study demonstrate that there is no evidence of an interaction between sumatriptan succinate and naproxen sodium on coronary artery vasoconstriction.

FDA Clinical Guidance Letter, 68,436 (008, 011) **November 12, 2004**
"*A Double-Blind, Multicenter, Randomized, Placebo-Controlled Single Dose Study To Evaluate The Safety And Efficacy Of Trexima In The Acute Treatment Of Migraine Headaches*"

No major issues raised in this letter remain unaddressed in the NDA.

Teleconference, clarifications from End-of-phase 2 meeting **October 25, 2004**

The Division further clarified that at 2 hours a statistical advantage to Trexima on migraine associated symptoms was not required for approval, but that inferiority would suggest a 'pathological' interaction of the components.

PRE-NDA meeting ***April 20, 2005***

Selected Issues:

- The Division stated that chronic, intermittent use of naproxen may be an issue in light of the evolving cardiovascular safety concerns. DNDP is unsure how this will affect the Trexima application. The company indicated that the number of times Trexima could be used monthly might be limited by the limitations on the use of sumatriptan. DNDP suggested that the company present arguments to support the safety of chronic, intermittent administration at the level they intend for use and in the migraine population and suggested the company should include epidemiologic data in this presentation. The company noted that there are over the counter migraine products. DNDP noted that this did not speak to the question of long term use.

Changes in the Conduct of the Study or Planned Analyses

The SAP was changed between studies 301 and 302 to account for baseline imbalances in symptom severity, as follows:

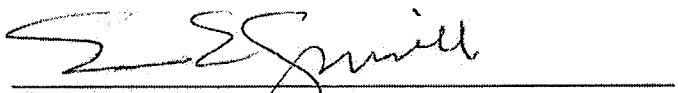
> "If any of the baseline symptoms (i.e. pain, nausea, photophobia and phonophobia) suggest a treatment imbalance, as evidenced by a p-value of <0.15 for overall treatment differences, then the primary analysis (Trexima versus placebo at 2 hours) for that symptom will be adjusted for baseline. Logistic Regression, with the baseline symptom and pooled investigator sites as covariates, will be done instead of the Cochran-Mantel-Haenszel test."

The Division was not apprised of this change at the time, thus requiring additional evidence (below) that the change to the SAP was prospective.

The Statistical Analysis Plan for MT400-302 was finalized on March 21, 2005, the database was locked on March 29, 2005 and the study unblinded to treatment assignments on March 30, 2005.

Below is the signature approving the SAP, showing a date before database lock:

Technical Approver:



Susan E. Spruill, MS
Senior Director of Biostatistics, POZEN, Inc.

3/21/2005
Date of Approval

Amendments Submitted to the Protocol

Amendments submitted to the phase III protocols are minor and do not represent review issues.

There were four amendments submitted for study 301:

Amendment 1, June 22, 2004 Prior to any subject enrollment, changed the sample size from 1200 (300 subjects per treatment arm) to 1400 (350 subjects per arm) and increased the approximate number of centers from 50 to 54. The rationale was to accommodate a higher-than-expected variability in the incidence of individual associated symptoms of migraine at baseline and to improve confidence in obtaining statistical significance for clinically meaningful changes regarding the outcome of one or more migraine endpoints.

Amendment 2, August 19, 2004 allowed those subjects who had not treated with study drug for six weeks after screening to continue in the study until they had either treated an eligible migraine or until the study was terminated. The amendment also increased the number of sites participating in the study from approximately 54 to 60. Approximately 1074 subjects were enrolled in the study after this amendment was finalized.

Amendment 3, September 23, 2004, added spermicide plus a mechanical barrier as an additional acceptable method of contraception. The amendment also added history of gastric bypass or stapling surgery as an additional exclusion criterion. Approximately 739 subjects were enrolled in the study after this amendment was finalized.

Amendment 4, January 31, 2005 added key secondary endpoints, changed the statistical methodology for analysis of key secondary endpoints and changed the size of sites to be pooled from < 25 subjects to < 20 subjects. The amendment specified time points and treatment comparisons to be used as key secondary and other supporting endpoints. Clinical disability categories were defined, and details of health outcome measures analyses were specified. The study was fully enrolled prior to finalization of this amendment.

Other key dates associated with the study included February 1, 2005, when the Statistical Analysis Plan was finalized and February 2, 2005 when the database was locked and the study unblinded to treatment assignments.

There were 3 amendments submitted for study 302:

Amendment 1, same as amendment 2 above, of August 19, 2004
Amendment 2, same as amendment 3 above, September 23, 2004
Amendment 3, dated March 8, 2005, was almost the same as amendment 4 of study 302, above. It added key secondary endpoints, changed the statistical methodology for analysis of key secondary endpoints and changed the size of sites to be pooled from < 25 subjects to < 20 subjects. The amendment specified time points and treatment comparisons to be used as key secondary and other supporting endpoints. Clinical disability categories were defined, and details of health outcome measures analyses were specified. The study was fully enrolled prior to finalization of this amendment but was still ongoing and the blind had not been broken.

2.6 Other Relevant Background Information

None

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC

See CMC review.

3.2 Animal Pharmacology/Toxicology

The two components of Trexima, sumatriptan and naproxen, are currently FDA approved, with extensive post-marketing experience. As a result, the non-clinical studies of Trexima were designed primarily to evaluate the pharmacology/toxicology of their co-administration. As agreed with the Division, no primary or secondary nonclinical pharmacology studies, pharmacodynamic drug interaction studies, or pharmacokinetic studies (excluding kinetic support to toxicology studies) were conducted for the combination. Similarly, a standard battery of safety pharmacology studies (cardiovascular, CNS and respiratory) were not conducted.

Safety pharmacology

- Coronary vasoconstrictive potential of sumatriptan combined administration with naproxen (MT400-T15 and T17).

A cardiovascular safety pharmacology study recommended by the Division examined changes in coronary and carotid artery diameter, resistance, and blood flow after intravenous administration of sumatriptan (80 µg/kg) alone and in combination with intravenous naproxen (20 mg/kg), in conscious, chronically instrumented beagle dogs. Vital signs, including blood pressure, were also evaluated.

I find these experiments indicate a possible additive interaction of naproxen and sumatriptan on arterial vasoconstriction and blood pressure.

Experimental design
The study consisted of three phases. Phase I examined the effect of sumatriptan alone.

- On Day 1, animals received a 1-minute infusion of vehicle followed by a bolus of 80 µg/kg sumatriptan.
- On Days 2 and 3, animals received only the bolus of 80 µg/kg sumatriptan.

Five days after Phase I, Phase II examined the interaction of naproxen and sumatriptan in the same animals.

- On Day 1, animals received 20 mg/kg naproxen followed by of 80 µg/kg sumatriptan.

- On Days 2 and 3, animals received only 80 μg/kg sumatriptan. Since naproxen has a long half-life in dogs (about 35 hours), the single dose during Day 1 of Phase II provided a declining daily blood level over the 3 days of the experiment.

Phase III was amended to the study design to evaluate possible interaction of naproxen with a higher dose of sumatriptan, 200 μg/kg. However, this portion of the study is uninterpretable due to design issues. An initial dose of sumatriptan was used to establish the baseline sumatriptan response, and 60 minutes later sumatriptan was readministered in combination with naproxen. Possible tachyphylaxis of the sumatriptan response was not, however, accounted for, preventing separate estimate of the contribution of naproxen.

Experimental Findings:

Vasoconstriction

Coronary Artery. Sumatriptan alone reduced coronary artery diameter by about 4%. Co-administration of naproxen and sumatriptan reduced coronary artery diameter about 8%. In 2 out of 6 animals (1101 and 1104), the *additional* reduction with the combined drugs, beyond that caused by sumatriptan alone, was almost 10% of total baseline vessel diameter (Table 4; all data tables express diameter in millimeters, not percent). Five of the 6 animals showed increased vasoconstriction from the combined drugs. Lower levels of naproxen (achieved by giving a single dose of naproxen day 1 and allowing for natural metabolism over 3 days after the initial dose) did not show this additive vasoconstrictive effect with sumatriptan (Table 5, Table 6). Corresponding to the decreased coronary vessel caliber was an increase in vessel resistance, greatest on day 1 of naproxen dosing (Table 7), and decreasing as the naproxen was metabolized over days 2 and 3 (not shown).

Table 4: Coronary artery Diameter, Day 1

(NDA application 'Study QCBW 106, Table 1.1)

Maximum Reductions in
Coronary Diameter (mm) on Day 1

	Phase I (Vehicle + 80 µg/kg Sumatriptan)			Phase II (20 mg/kg Naproxen + 80 µg/kg Sumatriptan)			
Dog ID	Baseline [a]	Minimum Diameter [b]	Change From Baseline [c]	Baseline [a]	Minimum Diameter [b]	Change From Baseline [c]	Change Phase II - Phase I
1101	3.6071	3.5633	-0.0438	3.5386	3.1785	-0.3601	-0.3163
1102	3.9718	3.8083	-0.1635	4.1781	3.7839	-0.3941	-0.2307
1104	3.2097	3.1610	-0.0487	3.4923 [d]	3.1430	-0.3493	-0.3006
1105	3.0507	2.9817	-0.0690	3.4085	3.1598	-0.2486	-0.1796
1107	3.9149	3.6082	-0.3067	3.1788	3.0694	-0.1094	0.1973
1108	2.7476	2.6101	-0.1375	2.8021	2.6460	-0.1561	-0.0185
						Mean	-0.1414
						STD	0.1976
						95% CI	(-0.3487, 0.0659)
						p-value	0.1399

[a] The baseline values were obtained by taking the mean of the data collected during the 5 minute interval immediately preceeding vehicle (Phase I) or naproxen (Phase II) administration.
[b] Minimum Coronary Diameter during the first hour after sumatriptan administration.
[c] Minimum Coronary Diameter - Baseline Coronary Diameter.
[d] An outlier value of 5.4712 mm at the one minute pre-NAP sampling time was determined to be an outlier and was excluded from calculation of the baseline value

Table 5: Coronary artery diameter, day 2

(NDA application 'Study QCBW 106, Table 1.2)

Maximum Reductions in
Coronary Diameter (mm) on Day 2

	Phase I (80 µg/kg Sumatriptan)			Phase II (80 µg/kg Sumatriptan)			
Dog ID	Baseline [a]	Minimum Diameter [b]	Change From Baseline [c]	Baseline [a]	Minimum Diameter [b]	Change From Baseline [c]	Change Phase II - Phase I
1101	3.3883	3.3797	-0.0086	3.4682	3.3657	-0.1024	-0.0938
1102	4.3101	4.0378	-0.2723	4.1128	3.9349	-0.1779	0.0943
1104	3.0521	2.9014	-0.1507	3.2629	3.1321	-0.1309	0.0199
1105	2.9889	2.8985	-0.0905	3.3656	3.2092	-0.1564	-0.0659
1107	4.0199	3.7575	-0.2624	3.1805	3.0639	-0.1166	0.1458
1108	2.7941	2.6550	-0.1391	2.6486	2.5279	-0.1207	0.0184
						Mean	0.0198
						STD	0.0913
						95% CI	(-0.0761, 0.1156)
						p-value	0.6186

[a] The baseline values were obtained by taking the mean of the data collected during the 5 minute interval immediately preceeding sumatriptan administration.
[b] Minimum Coronary Diameter during the first hour after sumatriptan administration.
[c] Minimum Coronary Diameter - Baseline Coronary Diameter.

Table 6: Coronary artery diameter, day 3

(NDA application 'Study QCBW 106, Table 1.3)

Maximum Reductions in
Coronary Diameter (mm) on Day 3

	Phase I (80 µg/kg Sumatriptan)			Phase II (80 µg/kg Sumatriptan)			
Dog ID	Baseline [a]	Minimum Diameter [b]	Change From Baseline [c]	Baseline [a]	Minimum Diameter [b]	Change From Baseline [c]	Change Phase II - Phase I
1101	3.4381	3.2512	-0.1869	3.4491	3.4023	-0.0468	0.1402
1102	3.9887	3.8669	-0.1218	4.1699	3.8438	-0.3261	-0.2044
1104	3.1713	2.9252	-0.2461	3.5305	3.2353	-0.2952	-0.0491
1105	3.0257	2.9267	-0.0990	3.3221	3.1880	-0.1340	-0.0350
1107	3.3684	3.2138	-0.1546	3.1711	3.0566	-0.1145	0.0401
1108	2.8176	2.6591	-0.1585	2.7131	2.5319	-0.1812	-0.0227
						Mean	-0.0218
						STD	0.1134
						95% CI	(-0.1408, 0.0972)
						p-value	0.6572

[a] The baseline values were obtained by taking the mean of the data collected during the 5 minute interval immediately preceeding sumatriptan administration.
[b] Minimum Coronary Diameter during the first hour after sumatriptan administration.
[c] Minimum Coronary Diameter - Baseline Coronary Diameter.

Table 7: Coronary artery Resistance

(NDA application 'Study QCBW 106, Table 2.1)

Maximum Reductions in
Coronary Resistance (mL/mmHg.min) on Day 1

	Phase I (Vehicle + 80 µg/kg Sumatriptan)			Phase II (20 mg/kg Naproxen + 80 µg/kg Sumatriptan)			
Dog ID	Baseline [a]	Minimum Resistance [b]	Change From Baseline [c]	Baseline [a]	Minimum Resistance [b]	Change From Baseline [c]	Change Phase II - Phase I
1101	0.2782	0.2626	-0.0157	0.2244	0.1809	-0.0436	-0.0279
1102	0.3623	0.3989	0.0367	0.4144	0.3088	-0.1057	-0.1423
1104	0.1496	0.1557	0.0062	0.1365	0.1057	-0.0307	-0.0369
1105	0.1337	0.1022	-0.0315	0.1420	0.1098	-0.0322	-0.0007
1107[d]	.	.	.	.	.	.	.
1108	0.1430	0.1294	-0.0136	0.1459	0.1218	-0.0241	-0.0105
						Mean	-0.0437
						STD	0.0570
						95% CI	(-0.1144, 0.0271)
						p-value	0.1617

[a] The baseline values were obtained by taking the mean of the data collected during the 5 minute interval immediately preceeding vehicle (Phase I) or naproxen (Phase II) administration.
[b] Minimum Coronary Resistance during the first hour after sumatriptan administration.
[c] Minimum Coronary Resistance - Baseline Coronary Resistance.
[d] Period (.) denotes a missing value.

Carotid artery: Similarly, coadministration of sumatriptan and naproxen appeared to have an additive vasoconstrictive effect on the dog carotid artery. Sumatriptan alone caused about a 10% constriction, while naproxen + sumatriptan caused about 20% constriction (Table 8). The additive vasconstrictive effect was present in 5 of 6 animals, and approached statistical significance ($p = 0.08$) despite the small sample size. The additive effect was about the same one day after naproxen was given (12% sumatriptan alone; 22% sumatriptan + naproxen) (Table 9), while by the third day after naproxen the additive effect was not present (12% sumatriptan alone; 16% sumatriptan + naproxen)(Table 10). The resistance of the carotid artery did not to increase as a result of the vasoconstriction (Table 11).

Table 8: Carotid Diameter, Day 1

(NDA application 'Study QCBW 106, Table 4.1)

Maximum Reductions in
Carotid Diameter (mm) on Day 1

	Phase I (Vehicle + 80 μg/kg Sumatriptan)			Phase II (20 mg/kg Naproxen + 80 μg/kg Sumatriptan)			
Dog ID	Baseline [a]	Minimum Diameter [b]	Change From Baseline [c]	Baseline [a]	Minimum Diameter [b]	Change From Baseline [c]	Change Phase II - Phase I
1101	5.1569	4.1227	-1.0342	4.9081	4.0581	-0.8500	0.1842
1102	5.9945	5.7021	-0.2924	4.2856	3.7571	-0.5285	-0.2361
1104	2.9883	2.7129	-0.2754	3.6837	2.9264	-0.7573	-0.4818
1105	7.0062	6.8267	-0.1795	6.2442	4.1210	-2.1232	-1.9437
1107	6.5184	6.4419	-0.0765	6.6695	6.2246	-0.4449	-0.3684
1108	7.2671	5.5006	-1.7665	10.8691	7.3404	-3.5287	-1.7621
						Mean	-0.7680
						STD	0.8720
						95% CI	(-1.6831, 0.1471)
						p-value	0.0835

[a] The baseline values were obtained by taking the mean of the data collected during the 5 minute interval immediately preceeding vehicle (Phase I) or naproxen (Phase II) administration.
[b] Minimum Carotid Diameter during the first hour after sumatriptan administration.
[c] Minimum Carotid Diameter - Baseline Carotid Diameter.

Table 9: Carotid Diameter, Day 2

(NDA submission 'Study QCBW 106, Table 4.2)

Maximum Reductions in
Carotid Diameter (mm) on Day 2

	Phase I (80 μg/kg Sumatriptan)			Phase II (80 μg/kg Sumatriptan)			
Dog ID	Baseline [a]	Minimum Diameter [b]	Change From Baseline [c]	Baseline [a]	Minimum Diameter [b]	Change From Baseline [c]	Change Phase II - Phase I
1101	4.8989	4.0453	-0.8536	5.0104	3.4912	-1.5192	-0.6656
1102	5.8973	5.2248	-0.6725	4.6516	4.1798	-0.4718	0.2007
1104	3.0779	2.7831	-0.2948	4.2516	3.0123	-1.2393	-0.9445
1105	5.4824	4.4615	-1.0209	5.7116	4.1349	-1.5767	-0.5559
1107	6.5983	6.0631	-0.5352	6.7288	6.3346	-0.3942	0.1410
1108	6.8887	6.2406	-0.6481	7.7285	5.5450	-2.1835	-1.5354
						Mean	-0.5599
						STD	0.6604
						95% CI	(-1.2530, 0.1331)
						p-value	0.0924

[a] The baseline values were obtained by taking the mean of the data collected during the 5 minute interval immediately preceeding sumatriptan administration.
[b] Minimum Carotid Diameter during the first hour after sumatriptan administration.
[c] Minimum Carotid Diameter - Baseline Carotid Diameter.

Table 10: Carotid Diameter, Day 3

(NDA application 'Study QCBW 106, Table 4.3)

Maximum Reductions in
Carotid Diameter (mm) on Day 3

	Phase I (80 µg/kg Sumatriptan)			Phase II (80 µg/kg Sumatriptan)			
Dog ID	Baseline [a]	Minimum Diameter [b]	Change From Baseline [c]	Baseline [a]	Minimum Diameter [b]	Change From Baseline [c]	Change Phase II - Phase I
1101	4.8403	4.2777	-0.5627	5.0929	4.1181	-0.9749	-0.4122
1102	4.0582	3.6919	-0.3663	4.6492	4.0117	-0.6374	-0.2711
1104	3.0864	2.8132	-0.2732	4.0423	3.1709	-0.8714	-0.5982
1105	6.1634	4.2834	-1.8800	5.4037	4.7223	-0.6814	1.1986
1107	6.5951	6.2973	-0.2978	6.7821	6.1394	-0.6427	-0.3449
1108	7.8122	7.0105	-0.8017	8.3397	6.7994	-1.5403	-0.7386
						Mean	-0.1944
						STD	0.7037
						95% CI	(-0.9328, 0.5441)
						p-value	0.5286

[a] The baseline values were obtained by taking the mean of the data collected during the 5 minute interval immediately preceeding sumatriptan administration.
[b] Minimum Carotid Diameter during the first hour after sumatriptan administration.
[c] Minimum Carotid Diameter - Baseline Carotid Diameter.

Table 11: Carotid Resistance

(NDA application 'Study QCBW 106, Table 5.1)

Maximum Increases in
Carotid Resistance (mL/mmHg.min) on Day 1

	Phase I (Vehicle + 80 µg/kg Sumatriptan)			Phase II (20 mg/kg Naproxen + 80 µg/kg Sumatriptan)			
Dog ID	Baseline [a]	Maximum Resistance [b]	Change From Baseline [c]	Baseline [a]	Maximum Resistance [b]	Change From Baseline [c]	Change Phase II - Phase I
1101	0.5360	0.4056	-0.1304	0.3393	0.3694	0.0300	0.1604
1102	0.2970	0.4214	0.1244	0.3583	0.3437	-0.0145	-0.1390
1104	0.3399	0.3009	-0.0390	0.3280	0.2811	-0.0468	-0.0078
1105	0.3593	0.3541	-0.0052	0.3170	0.3602	0.0432	0.0484
1107	0.2175	0.2676	0.0502	0.2255	0.1972	-0.0283	-0.0785
1108	0.3075	0.2722	-0.0354	0.3604	0.3680	0.0076	0.0430
						Mean	0.0044
						STD	0.1052
						95% CI	(-0.1060, 0.1148)
						p-value	0.9218

[a] The baseline values were obtained by taking the mean of the data collected during the 5 minute interval immediately preceeding vehicle (Phase I) or naproxen (Phase II) administration.
[b] Maximum Carotid Resistance during the first hour after sumatriptan administration.
[c] Maximum Carotid Resistance - Baseline Carotid Resistance.

Blood Pressure

The variation was very large in the response of dog mean arterial pressure to sumatriptan and naproxen. I sampled the raw blood pressure data, and find that a striking degree of baseline instability, or 'noise,' was present. Given such limitations of the data, however, strikingly 3 of 6 dogs had a large increase of blood pressure attributable to the combination (shown as 'change, phase II- phase I'), of from 18 mm Hg to more than 30 mm Hg mean arterial pressure (Table 12), and 4 of 6 had some increase.

Table 12: Mean Arterial Pressure

Study QCBW 106
Table 8.1

Maximum Increases in
MAP (mmHg) on Day 1

	Phase I (Vehicle + 80 µg/kg Sumatriptan)			Phase II (20 mg/kg Naproxen + 80 µg/kg Sumatriptan)			
Dog ID	Baseline [a]	Maximum MAP [b]	Change From Baseline [c]	Baseline [a]	Maximum MAP [b]	Change From Baseline [c]	Change Phase II - Phase I
1101	105.66	118.68	13.02	103.83	135.01	31.18	18.16
1102	115.55	129.29	13.74	113.19	125.18	11.99	-1.75
1104	117.23	135.54	18.31	108.25	129.18	20.93	2.62
1105	108.86	140.36	31.50	136.53	135.46	-1.07	-32.56
1107	136.14	154.77	18.63	112.12	155.38	43.26	24.63
1108	134.51	154.09	19.58	101.19	151.38	50.19	30.61
						Mean	6.95
						STD	23.04
						95% CI	(-17.23, 31.13)
						p-value	0.4931

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Most data, including all efficacy data, was derived from trials of Trexima conducted by Pozen. Some safety data was derived from other studies of sumatriptan and naproxen used individually.

4.2 Tables of Clinical Studies

See Table 1: Overall Clinical Development Program for Trexima, and Table 62: Phase I studies: objectives, design, patient enumeration, Table 63: Phase 2 studies: objectives, design, patient enumeration, and Table 64: Phase 3 studies: objectives, design, patient enumeration.

4.3 Review Strategy

The main efficacy trials reviewed were MT400-301 and MT400-302. Trial MT400-204 was conducted with a different formulation and dose of sumatriptan, but was used to assess safety and dose/response.

4.4 Data Quality and Integrity

4.4.1 Randomization

Treatment randomization is shown in Table 13 (study 301), and Table 14 (study 302), and was balanced within sites.

Table 13: Enrollment by site, study 301

(NDA submission Table 14.1.1, study MT400-301)

Site Number	Trexima (N=367)	Sumatriptan (N=370)	Naproxen (N=371)	Placebo (N=387)	Total Subjects (N=1495)
SITE013	4 (1%)	4 (1%)	3 (<1%)	3 (<1%)	14 (<1%)
SITE015	2 (<1%)	2 (<1%)	0	0	4 (<1%)
SITE016	5 (1%)	5 (1%)	6 (2%)	6 (2%)	22 (1%)
SITE025	6 (2%)	3 (<1%)	5 (1%)	4 (1%)	18 (1%)
SITE026	0	1 (<1%)	0	2 (<1%)	3 (<1%)
SITE027	9 (2%)	11 (3%)	10 (3%)	10 (3%)	40 (3%)
SITE028	8 (2%)	5 (1%)	7 (2%)	7 (2%)	27 (2%)
SITE091a	9 (2%)	10 (3%)	10 (3%)	9 (2%)	38 (3%)
SITE101	7 (2%)	6 (2%)	7 (2%)	6 (2%)	26 (2%)
SITE113	3 (<1%)	3 (<1%)	3 (<1%)	2 (<1%)	11 (<1%)
SITE132	6 (2%)	4 (1%)	7 (2%)	5 (1%)	22 (1%)
SITE137	8 (2%)	7 (2%)	7 (2%)	7 (2%)	29 (2%)
SITE138	9 (2%)	8 (2%)	10 (3%)	10 (3%)	37 (2%)
SITE139	3 (<1%)	4 (1%)	3 (<1%)	5 (1%)	15 (1%)
SITE142	4 (1%)	5 (1%)	5 (1%)	6 (2%)	20 (1%)
SITE146	15 (4%)	16 (4%)	17 (5%)	16 (4%)	64 (4%)
SITE153	6 (2%)	7 (2%)	7 (2%)	8 (2%)	28 (2%)
SITE173	10 (3%)	11 (3%)	11 (3%)	12 (3%)	44 (3%)
SITE175	6 (2%)	6 (2%)	5 (1%)	7 (2%)	24 (2%)
SITE179	5 (1%)	3 (<1%)	2 (<1%)	4 (1%)	14 (<1%)
SITE180	10 (3%)	9 (2%)	7 (2%)	10 (3%)	36 (2%)
SITE193	4 (1%)	3 (<1%)	6 (2%)	6 (2%)	19 (1%)
SITE197	5 (1%)	6 (2%)	5 (1%)	4 (1%)	20 (1%)
SITE201	7 (2%)	7 (2%)	7 (2%)	5 (1%)	26 (2%)
SITE203	1 (<1%)	1 (<1%)	1 (<1%)	2 (<1%)	5 (<1%)
SITE209	4 (1%)	5 (1%)	4 (1%)	4 (1%)	17 (1%)
SITE218	7 (2%)	7 (2%)	7 (2%)	5 (1%)	26 (2%)
SITE223	10 (3%)	11 (3%)	10 (3%)	11 (3%)	42 (3%)
SITE230	4 (1%)	7 (2%)	6 (2%)	7 (2%)	24 (2%)
SITE248	5 (1%)	6 (2%)	7 (2%)	6 (2%)	24 (2%)

Site Number	Trexima (N=367)	Sumatriptan (N=370)	Naproxen (N=371)	Placebo (N=387)	Total Subjects (N=1495)
SITE251	8 (2%)	7 (2%)	8 (2%)	8 (2%)	31 (2%)
SITE252	4 (1%)	4 (1%)	3 (<1%)	5 (1%)	16 (1%)
SITE256	14 (4%)	16 (4%)	14 (4%)	16 (4%)	60 (4%)
SITE258	5 (1%)	5 (1%)	3 (<1%)	5 (1%)	18 (1%)
SITE259	8 (2%)	9 (2%)	8 (2%)	9 (2%)	34 (2%)
SITE260	4 (1%)	6 (2%)	5 (1%)	6 (2%)	21 (1%)
SITE265	1 (<1%)	1 (<1%)	2 (<1%)	0	4 (<1%)
SITE267	9 (2%)	10 (3%)	9 (2%)	10 (3%)	38 (3%)
SITE272	2 (<1%)	3 (<1%)	2 (<1%)	2 (<1%)	9 (<1%)
SITE278	4 (1%)	4 (1%)	5 (1%)	6 (2%)	19 (1%)
SITE279	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	4 (<1%)
SITE281	18 (5%)	18 (5%)	17 (5%)	18 (5%)	71 (5%)
SITE284	7 (2%)	6 (2%)	4 (1%)	6 (2%)	23 (2%)
SITE293	6 (2%)	6 (2%)	7 (2%)	6 (2%)	25 (2%)
SITE296	5 (1%)	3 (<1%)	5 (1%)	4 (1%)	17 (1%)
SITE305	4 (1%)	5 (1%)	4 (1%)	4 (1%)	17 (1%)
SITE307	0	1 (<1%)	0	1 (<1%)	2 (<1%)
SITE308	7 (2%)	5 (1%)	7 (2%)	7 (2%)	26 (2%)
SITE312	10 (3%)	11 (3%)	11 (3%)	11 (3%)	43 (3%)
SITE317	8 (2%)	5 (1%)	8 (2%)	9 (2%)	30 (2%)
SITE320	11 (3%)	11 (3%)	11 (3%)	11 (3%)	44 (3%)
SITE321	2 (<1%)	4 (1%)	4 (1%)	3 (<1%)	13 (<1%)
SITE338	20 (5%)	17 (5%)	20 (5%)	20 (5%)	77 (5%)
SITE342	10 (3%)	10 (3%)	11 (3%)	10 (3%)	41 (3%)
SITE343	7 (2%)	6 (2%)	7 (2%)	6 (2%)	26 (2%)
SITE344	2 (<1%)	3 (<1%)	2 (<1%)	4 (1%)	11 (<1%)
SITE345	7 (2%)	9 (2%)	7 (2%)	7 (2%)	30 (2%)
SITE347	0	0	0	2 (<1%)	2 (<1%)
SITE361	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	4 (<1%)

Table 14: Enrollment by site, study 302

(NDA submission Table 14.1.1, study MT400-302)

POZEN, Inc. Study Number MT400-302

Table 14.1.1
Subject Enrollment
All Subjects in the Safety Population

Site Number	Trexima (N=370)	Sumatriptan (N=365)	Naproxen (N=361)	Placebo (N=365)	Total Subjects (N=1461)
SITE002	8 (2%)	9 (2%)	7 (2%)	9 (2%)	33 (2%)
SITE008	4 (1%)	3 (<1%)	3 (<1%)	3 (<1%)	13 (<1%)
SITE009	4 (1%)	4 (1%)	5 (1%)	4 (1%)	17 (1%)
SITE010	4 (1%)	5 (1%)	6 (2%)	4 (1%)	19 (1%)
SITE019	1 (<1%)	0	1 (<1%)	2 (<1%)	4 (<1%)
SITE030	7 (2%)	7 (2%)	10 (3%)	8 (2%)	32 (2%)
SITE068	3 (<1%)	4 (1%)	1 (<1%)	3 (<1%)	11 (<1%)
SITE071	8 (2%)	9 (2%)	8 (2%)	9 (2%)	34 (2%)
SITE100	17 (5%)	17 (5%)	16 (4%)	17 (5%)	67 (5%)
SITE106	4 (1%)	4 (1%)	5 (1%)	5 (1%)	18 (1%)
SITE108	11 (3%)	11 (3%)	10 (3%)	9 (2%)	41 (3%)
SITE112	9 (2%)	7 (2%)	9 (2%)	8 (2%)	33 (2%)
SITE115	8 (2%)	7 (2%)	8 (2%)	7 (2%)	30 (2%)
SITE119	4 (1%)	4 (1%)	2 (<1%)	5 (1%)	15 (1%)
SITE135	3 (<1%)	3 (<1%)	3 (<1%)	3 (<1%)	12 (<1%)
SITE140	3 (<1%)	3 (<1%)	4 (1%)	2 (<1%)	12 (<1%)
SITE143	6 (2%)	4 (1%)	6 (2%)	6 (2%)	22 (2%)
SITE149	14 (4%)	13 (4%)	12 (3%)	13 (4%)	52 (4%)
SITE174	5 (1%)	4 (1%)	2 (<1%)	3 (<1%)	14 (<1%)
SITE176	6 (2%)	6 (2%)	8 (2%)	6 (2%)	26 (2%)
SITE177	6 (2%)	5 (1%)	6 (2%)	7 (2%)	24 (2%)
SITE196	2 (<1%)	1 (<1%)	2 (<1%)	2 (<1%)	7 (<1%)
SITE222	5 (1%)	6 (2%)	7 (2%)	7 (2%)	25 (2%)
SITE227	3 (<1%)	3 (<1%)	2 (<1%)	5 (1%)	13 (<1%)
SITE232	2 (<1%)	1 (<1%)	0	2 (<1%)	5 (<1%)
SITE247	13 (4%)	13 (4%)	10 (3%)	12 (3%)	48 (3%)
SITE257	5 (1%)	5 (1%)	5 (1%)	7 (2%)	22 (2%)
SITE266	3 (<1%)	3 (<1%)	1 (<1%)	2 (<1%)	9 (<1%)
SITE268	2 (<1%)	3 (<1%)	5 (1%)	4 (1%)	14 (<1%)
SITE280	1 (<1%)	0	1 (<1%)	1 (<1%)	3 (<1%)

Site Number	Trexima (N=370)	Sumatriptan (N=365)	Naproxen (N=361)	Placebo (N=365)	Total Subjects (N=1461)
SITE297	7 (2%)	7 (2%)	7 (2%)	6 (2%)	27 (2%)
SITE298	1 (<1%)	0	2 (<1%)	0	3 (<1%)
SITE299	12 (3%)	12 (3%)	13 (4%)	13 (4%)	50 (3%)
SITE300	0	1 (<1%)	1 (<1%)	1 (<1%)	3 (<1%)
SITE301	5 (1%)	4 (1%)	4 (1%)	3 (<1%)	16 (1%)
SITE304	15 (4%)	17 (5%)	16 (4%)	15 (4%)	63 (4%)
SITE306	1 (<1%)	2 (<1%)	0	1 (<1%)	4 (<1%)
SITE309	4 (1%)	4 (1%)	4 (1%)	4 (1%)	16 (1%)
SITE319	9 (2%)	10 (3%)	6 (2%)	7 (2%)	32 (2%)
SITE322	1 (<1%)	2 (<1%)	3 (<1%)	1 (<1%)	7 (<1%)
SITE327	4 (1%)	4 (1%)	4 (1%)	4 (1%)	16 (1%)
SITE328	3 (<1%)	1 (<1%)	4 (1%)	5 (1%)	13 (<1%)
SITE334	4 (1%)	3 (<1%)	4 (1%)	4 (1%)	15 (1%)
SITE336	9 (2%)	8 (2%)	8 (2%)	5 (1%)	30 (2%)
SITE337	3 (<1%)	4 (1%)	3 (<1%)	4 (1%)	14 (<1%)
SITE339	5 (1%)	6 (2%)	6 (2%)	5 (1%)	22 (2%)
SITE340	6 (2%)	4 (1%)	5 (1%)	3 (<1%)	18 (1%)
SITE346	5 (1%)	4 (1%)	4 (1%)	5 (1%)	18 (1%)
SITE348	2 (<1%)	0	1 (<1%)	2 (<1%)	5 (<1%)
SITE351	18 (5%)	19 (5%)	18 (5%)	20 (5%)	75 (5%)
SITE352	5 (1%)	6 (2%)	5 (1%)	4 (1%)	20 (1%)
SITE353	7 (2%)	7 (2%)	10 (3%)	9 (2%)	33 (2%)
SITE354	14 (4%)	16 (4%)	14 (4%)	17 (5%)	61 (4%)
SITE355	6 (2%)	7 (2%)	6 (2%)	7 (2%)	26 (2%)
SITE357	14 (4%)	18 (5%)	12 (3%)	14 (4%)	58 (4%)
SITE358	20 (5%)	20 (5%)	20 (6%)	17 (5%)	77 (5%)
SITE362	12 (3%)	10 (3%)	10 (3%)	9 (2%)	41 (3%)
SITE364	7 (2%)	5 (1%)	5 (1%)	5 (1%)	22 (2%)
SITE365	0	0	1 (<1%)	0	1 (<1%)

4.4.2 Subject Disposition

The disposition of all subjects is shown in Table 15 (study 301) and Table 16 (study 302). The attrition between 'randomized' and 'treated' populations was about equal between groups in both studies (about 15%). Almost all treated patients submitted treatment diaries and were included in the ITT population.

Table 15: Subject Disposition, Study 301

POZEN, Inc. Study Number MT400-301

Table 14.1.2
Subject Disposition

	Trexima	Sumatriptan	Naproxen	Placebo	Total
Total Screened					1875
Total Randomized	433	434	434	435	1736
Total Treated (Safety Population)	367	370	371	387	1495
Total With Diaries	364	363	365	383	1475
Efficacy ITT [1]	362	362	364	382	1470
Per Protocol [2]	357	355	362	375	1449

[1] = Efficacy ITT includes all subjects who took study drug, recorded moderate or severe pain at baseline, and recorded at least one post-dose pain assessment.
[2] = The Per-Protocol population excludes all subjects with a major protocol violation.

Table 16: Subject Disposition, Study 302

(NDA submission Table 14.1.2, Study 302)

	Trexima	**Sumatriptan**	**Naproxen Sodium**	**Placebo**	**Total**
Screened					1768
Randomized	422	415	419	421	1677
Treated (Safety Population)	370	365	361	365	1461
Efficacy Intent-to-Treat Population 1	364	361	356	360	1441
Per Protocol Population2	355	344	343	351	1393

1Includes all subjects who took study drug, recorded moderate or severe pain at baseline and recorded at least one post-dose pain assessment 2Excludes all subjects with a major protocol violation and all subjects at site 355.

4.4.3 Examination of Major Outcome Variables by Study Site

Both study 301 and 302 were conducted at more than 50 sites each. No site in either study contributed more than 5-6% of total study enrollment.

Large site outcomes
Immediately below I examine the major outcome variables of "2 hour pain" and "Sustained Pain Free, 2-24 hrs" for the largest sites in study 301 (sites 146 and 338) and study 302 (sites 100, 304, 351, and 358). Treatment outcomes were approximately as expected from overall study averages.

Study MT400-301

- Site 146: 4-5% of total enrolment [redacted]

Pain Score 2 hours

Site 146	0	1	2	3
Naproxen	3	4	8	2
Placebo	0	5	10	1
Sumatriptan	6	3	6	1
Trexima	5	5	4	1

Sustained pain free, 2-24 hours

Site 146	No	Yes
Naproxen	15	2
Placebo	16	0
Sumatriptan	10	6
Trexima	11	4

- Site 338: 5% of total enrollment [redacted]

Pain Score 2 hours

Site 338	0	1	2	3
Naproxen	4	3	8	4
Placebo	2	3	8	6
Sumatriptan	4	1	9	3
Trexima	4	5	5	6

Sustained pain free, 2-24 hours

Site 338	No	Yes
Naproxen	15	5
Placebo	19	1

Sumatriptan	15	2
Trexima	17	3

Study MT400-302

- Site 100: 4-5% of total enrollment [redacted]

Pain Score 2 hours

Site 100	0	1	2	3
Naproxen	0	6	9	1
Placebo	3	1	9	3
Sumatriptan	5	8	3	1
Trexima	6	5	5	1

Sustained pain free, 2-24 hours

Site 100	No	Yes
Naproxen	16	0
Placebo	13	4
Sumatriptan	13	4
Trexima	13	4

- Site 304: 4-5% [redacted]

Pain Score 2 hours

Site 304	0	1	2	3
Naproxen	4	3	6	3
Placebo	3	3	6	3
Sumatriptan	1	5	7	4
Trexima	4	3	5	2

Sustained pain free, 2-24 hours

Site 304	No	Yes
Naproxen	13	3
Placebo	12	3
Sumatriptan	16	1
Trexima	12	3

- Site 351: 5% [redacted]

Pain Score 2 hours

Site 351	0	1	2	3
Naproxen	3	5	8	2
Placebo	2	3	8	6
Sumatriptan	6	3	7	3
Trexima	6	4	5	3

Sustained pain free, 2-24 hours

Site 351	No	Yes
Naproxen	16	2
Placebo	18	2
Sumatriptan	13	6
Trexima	15	3

- Site 358: 5-6%
[redacted]

Pain Score 2 hours

Site 358	0	1	2	3
Naproxen	4	4	6	6
Placebo	0	5	7	4
Sumatriptan	2	10	6	2
Trexima	3	5	7	5

Sustained pain free, 2-24 hours

Site 358	No	Yes
Naproxen	18	2
Placebo	17	0
Sumatriptan	19	1
Trexima	18	2

Outcomes at all sites

I examined for all sites the major outcome variable for satisfying the combination drug rule, "Sustained Pain Free, 2-24 hr," as shown in Table 17 and Table 18. As noted above, superiority of Trexima was not statistically driven by any single large study site. In Table 17 and Table 18, study sites with a high percentage of responders to Trexima are highlighted in red. Given the large number of study sites, substantial variation in response percentages would be expected. Highlighted sites had results relatively more important in driving overall study outcome and are listed here:

Study 301: 16, 230, 252, 342
Study 302: 176, 309, 364

Sites 343 and 364 were chosen for DSI inspection, and found to be without major violations.

Table 17: Study 301, Sustained Pain Free (2-24 hr), by Site

Site	N	Trexima		Sumatriptan		Naproxen		Placebo	
		No	Yes	No	Yes	No	Yes	No	Yes
013	14	3	1	4	0	3	0	3	0
015	4	2	0	2	0	0	0	0	0
016	22	1	4	5	0	5	1	6	0
025	18	5	1	3	0	5	0	4	0
026	3	0	0	1	0	0	0	2	0
027	40	5	4	10	1	10	0	9	1
028	27	6	2	4	1	6	1	7	0
091	38	7	2	7	3	7	3	8	1
101	26	6	1	6	0	6	1	6	0
113	11	3	0	1	2	3	0	2	0
132	22	5	1	4	0	4	3	4	1
137	29	5	3	6	1	6	1	7	0
138	37	8	1	7	1	10	0	10	0
139	15	3	0	2	2	3	0	5	0
142	20	3	1	4	1	4	1	6	0
146	64	11	4	10	6	15	2	16	0
153	28	4	2	6	1	7	0	8	0
173	44	9	1	9	2	10	1	8	4
175	24	5	1	5	1	5	0	7	0
179	14	5	0	2	1	2	0	3	1
180	36	8	2	9	0	6	1	10	0
193	19	3	1	3	0	6	0	5	1
197	20	5	0	4	2	5	0	2	2
201	26	5	2	5	2	7	0	4	1
203	5	1	0	1	0	1	0	1	1
209	17	3	1	5	0	4	0	4	0
218	26	4	3	6	1	6	1	5	0
223	42	7	3	9	2	10	0	10	1
230	24	1	3	6	1	5	1	7	0
248	24	3	2	4	2	4	3	5	1
251	31	6	2	7	0	8	0	7	1
252	16	1	3	3	1	2	1	5	0
256	60	13	1	14	2	13	1	15	1
258	18	5	0	4	1	3	0	5	0
259	34	6	2	8	1	7	1	8	1
260	21	2	2	5	1	4	1	6	0
265	4	1	0	0	1	2	0	0	0
267	38	8	1	8	2	8	1	9	1
272	9	1	1	3	0	2	0	2	0
278	19	3	1	3	1	4	1	5	1
279	4	1	0	1	0	1	0	1	0

281	71	13	5	14	4	14	3	16	2
284	23	4	3	6	0	4	0	6	0
293	25	5	1	6	0	7	0	6	0
296	17	5	0	3	0	4	1	3	1
305	17	3	1	4	1	4	0	4	0
307	2	0	0	0	1	0	0	1	0
308	26	6	1	5	0	7	0	7	0
312	43	10	0	8	3	9	2	10	1
317	30	8	0	5	0	7	1	9	0
320	44	6	5	10	1	10	1	9	2
321	13	1	1	3	1	4	0	3	0
338	77	17	3	15	2	15	5	19	1
342	41	4	6	9	1	10	1	10	0
343	26	6	1	6	0	6	1	5	1
344	11	2	0	2	1	1	1	2	2
345	30	6	1	9	0	6	1	7	0
347	2	0	0	0	0	0	0	2	0
361	4	1	0	1	0	1	0	1	0

Table 18: Study 302, Sustained Pain Free (2-24 hr), by Site

		Trexima		Sumatriptan		Naproxen		Placebo	
Site	N	No	Yes	No	Yes	No	Yes	No	Yes
002	33	7	1	8	1	6	1	9	0
008	13	3	1	2	1	2	1	3	0
009	17	4	0	1	3	5	0	4	0
010	19	2	2	2	3	4	2	4	0
019	4	1	0	0	0	1	0	2	0
030	32	6	1	6	1	8	2	8	0
068	11	2	1	4	0	1	0	3	0
071	34	6	2	7	2	7	1	9	0
100	67	13	4	13	4	16	0	13	4
106	18	4	0	4	0	3	2	3	2
108	41	7	4	9	2	8	2	9	0
112	33	7	2	5	2	9	0	8	0
115	30	6	2	7	0	4	4	7	0
119	15	2	2	3	1	1	1	1	4
135	12	1	2	2	1	3	0	3	0
140	12	3	0	2	1	4	0	2	0
143	22	3	3	3	1	6	0	5	1
149	52	9	5	12	1	12	0	12	1
174	14	4	1	4	0	2	0	2	1
176	26	3	3	6	0	5	3	6	0
177	24	5	1	4	1	6	0	7	0
196	7	2	0	1	0	2	0	2	0

222	25	3	2	6	0	7	0	7	0
227	13	2	1	3	0	2	0	5	0
232	5	2	0	1	0	0	0	1	1
247	48	11	2	12	1	8	2	11	1
257	22	5	0	4	1	4	1	6	1
266	9	1	2	1	2	1	0	2	0
268	14	2	0	3	0	5	0	4	0
280	3	1	0	0	0	1	0	1	0
297	27	5	2	6	1	7	0	6	0
298	3	1	0	0	0	2	0	0	0
299	50	10	2	8	4	13	0	12	1
300	3	0	0	0	1	1	0	0	1
301	16	3	2	4	0	3	1	3	0
304	63	12	3	16	1	13	3	12	3
306	4	1	0	1	1	0	0	1	0
309	16	1	3	3	1	4	0	3	1
319	32	7	2	8	2	5	1	7	0
322	7	0	1	2	0	3	0	1	0
327	16	2	2	3	1	4	0	3	1
328	13	2	1	1	0	4	0	3	2
334	15	2	2	1	2	4	0	4	0
336	30	8	1	7	1	7	1	5	0
337	14	2	1	4	0	3	0	4	0
339	22	5	0	3	3	4	2	5	0
340	18	5	1	2	2	5	0	3	0
346	18	4	1	3	1	4	0	4	1
348	5	0	2	0	0	1	0	2	0
351	75	15	3	13	6	16	2	18	2
352	20	2	3	6	0	4	1	3	1
353	33	4	3	6	1	8	2	9	0
354	61	11	3	15	1	13	1	15	2
355*	35	5	4	7	1	6	3	6	3
357	58	11	3	15	3	12	0	12	2
358	77	18	2	19	1	18	2	17	0
362	41	9	3	10	0	7	3	9	0
364	22	3	4	4	1	5	0	5	0
365	1	0	0	0	0	0	1	0	0

*All study subjects at site 355 were excluded from the final analysis prior to unblinding due to sponsor assessment of poor data integrity (see section 4.5, Compliance with Good Clinical Practices).

4.5 Compliance with Good Clinical Practices

Protocol Deviations

Pozen indicates that all protocol deviations were identified prior to unblinding the data.

Minor protocol deviations occurred for 31 subjects, all of whom were included in the per protocol analysis:

- Inclusion criteria deviations, 5 subjects (1 Trexima, 2 sumatriptan, 1 naproxen,1 placebo)
- Exclusion criteria deviations, 26 subjects (9 Trexima, 8 sumatriptan, 8 naproxen, 1 placebo)

Forty-eight subjects were not included in the per protocol analysis. Twenty-two of those subjects had major protocol violations:

- Took a disallowed medication prior to study drug (18 subjects)
- Used rescue medication before two hours post-dosing (4 subjects).

The other 26 subjects were enrolled at site 355. Per Pozen, the quality of data from site 355 was unreliable due to inadequate documentation and poor principal investigator oversight. Pozen therefore performed the primary efficacy analysis of the MT400-302 data with and without the data from site 355. One subject (227/6247) was not included in the ITT population as a result of treating a migraine that was not of moderate or severe pain.

Subjects with Major Protocol Violations

Major Protocol Violations (n = 22)	**Site/Subject**
Rescue medication taken before 2 hours post dosing	002/6494 257/7365 299/7913 304/6363
Disallowed medication taken prior to study drug administration*	030/6787 108/7438 115/7421 115/7422 140/6841 247/7452 327/6601 334/6475 346/6569 346/7738 348/6715 348/6716 354/6879 357/7821 358/6912 358/8079 362/7116 364/7552

*Subject 339/6761 did not return a diary card and also took a disallowed medication

4.6 Financial Disclosures

[redacted] investigator at site [redacted] for study 302, [redacted]
He owns 10,118 shares of Pozen Stock, granted in 1996. Only [redacted] patients were enrolled at this site, and outcomes were similar to overall study averages

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Pharmacokinetic studies included: MT400-101, 102, 103, 104, 105

ATTENTION: STUDY MT400-101 COMPARED TREXIMA, AN RT FORMULATION, TO THE *NON-RT* FORMULATIONS OF SUMATRIPTAN

MT400-101: Bioavailability of Trexima, each of its components and marketed versions of components

Naproxen Bioavailability: $AUC_{(0-\infty)}$ values for naproxen were similar for Trexima and marketed versions of naproxen tablets (Table 19). C_{max} was lower and the T_{max} occurred later for Trexima (Figure 1). These differences might be due to the presence of sumatriptan in Trexima, which has been reported to delay gastric emptying.

Table 19: Naproxen PK, MT400-101

(Adapted from NDA application study MT400-101, Table 7)

(Bioavailability Ratios and 90% CI)

PK Parameter	Trexima vs. Nap 500 mg	Nap 500 mg vs. Anaprox 550 mg	Trexima vs. Anaprox 550 mg
$AUC_{0-\infty}$ (hr·µg/mL)	1.04 (1.01 – 1.08)	0.94 (0.91 – 0.98)	0.98 (0.94 – 1.03)
C_{max} (µg/mL)	0.73 (0.67 – 0.79)	0.90 (0.83 – 0.97)	0.65 (0.60 – 0.72)
T_{max}* (hr)	3.21 (1.92 – 4.59)	0.08 (-0.25 – 0.84)	3.79 (1.00 – 5.75)

*median difference with 95% CI on T_{max}

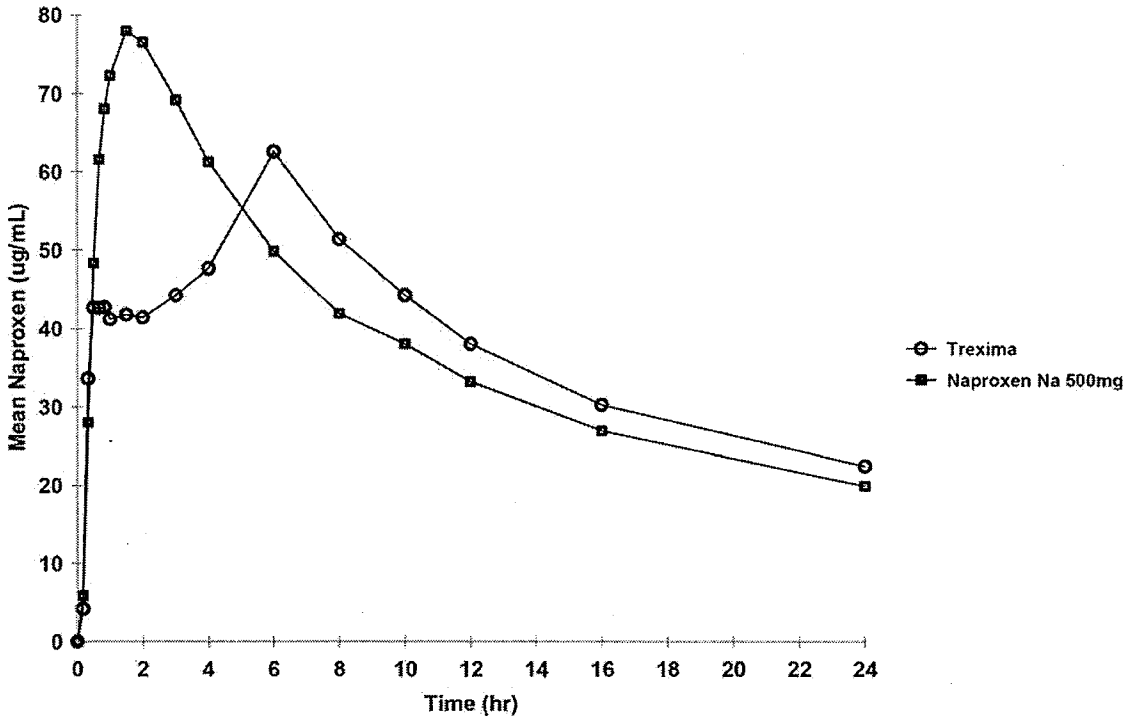


Figure 1: Naproxen mean plasma concentration: Trexima vs. Naproxen Na 500 mg

(NDA application study MT400-101, Figure 1)

The following data is included for use in interpretation of the phase II Trexima studies, but is not applicable to phase III studies.

Sumatriptan Bioavailability: C_{max} was higher for Trexima than sumatriptan 85 or 100 mg non-RT (Table 20). Sumatriptan concentrations increased faster, and peaked higher and earlier after Trexima than after sumatriptan 85 or 100 mg non-RT (Figure 2).

Table 20: Sumatriptan PK, MT 400-101

(adapted from NDA application, study MT400-101, Table 8)

(Bioavailability Ratios and 90% CI)

PK Parameter	Trexima vs. Suma 85 mg	Suma 85 mg vs. Imitrex 100 mg	Trexima vs. Imitrex 100 mg
$AUC_{0-\infty}$ (hr·ng/mL)	1.10 (1.02 – 1.18)	0.82 (0.76 – 0.88)	0.90 (0.83 – 0.98)
C_{max} (ng/mL)	1.30 (1.14 – 1.50)	0.85 (0.74 – 0.98)	1.11 (0.94 – 1.31)
T_{max} * (hr)	-0.63 (-1.67 – 0.09)	-0.17 (-1.00 – 0.50)	-0.36 (-1.67 – 0.50)

*median difference with 95% CI on T_{max}

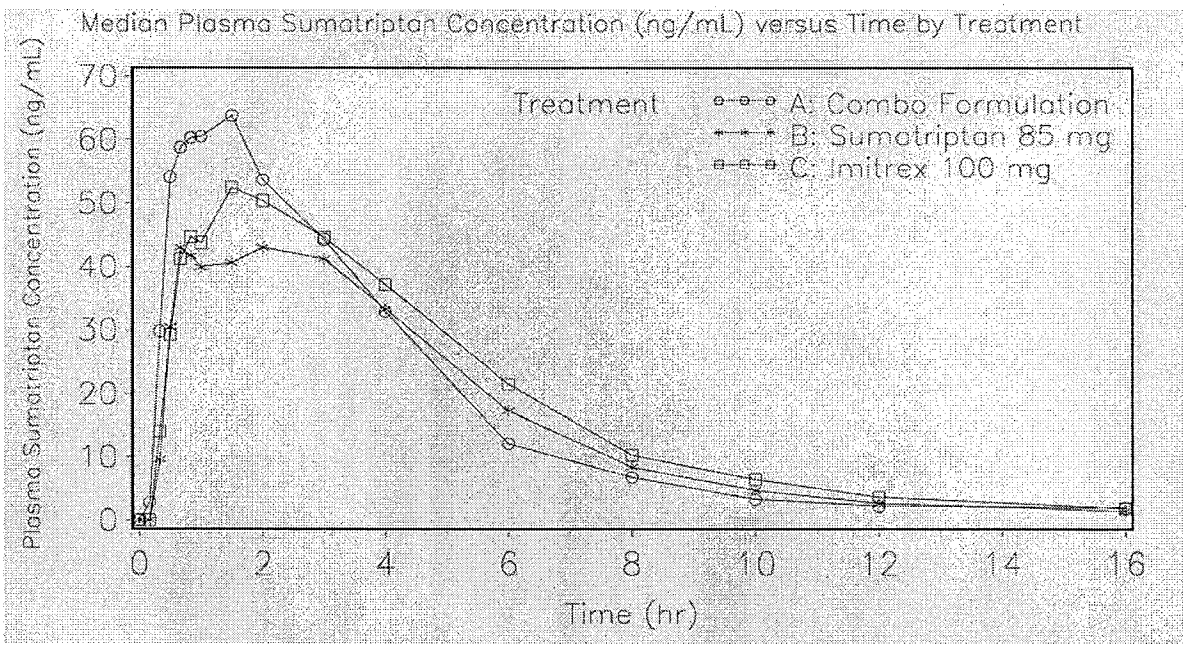


Figure 2: Sumatriptan median plasma concentration, Trexima, Sumatriptan 85 mg, Imitrex 100 mg.
(NON-RT FORMULATION OF SUMATRIPTAN AND IMITREX)(NDA submission study MT400-101, Figure 14.2.2.2)

[Reviewers comment: the sumatriptan blood level obtained after Trexima is lower than that produced by SQ sumatriptan, 6 mg: "After a single 6-mg subcutaneous manual injection into the deltoid area of the arm in 18 healthy males (age, 24 ± 6 years; weight, 70 kg), the maximum serum concentration (C_{max}) was (mean ± standard deviation) 74 ± 15 ng/mL and the time to peak concentration (T_{max}) was 12 minutes after injection (range, 5 to 20 minutes)." The AUC for sumatriptan in Trexima is, however, about 2-fold higher than for 6mg SQ sumatriptan, which might increase the risk of Trexima compared to 6 mg SQ, due to nearly as high levels, over a longer time.]

MT400-102: Effect of food on the bioavailability of Trexima in healthy volunteers, and pharmacokinetics of comparator sumatriptan

MT400-102 examined the effects of a high fat meal on the bioavailability of naproxen and sumatriptan from Trexima in healthy volunteers, and additionally compared the bioavailability of sumatriptan from Trexima to that of sumatriptan 85 mg RT.

There was almost no effect of a high fat meal on naproxen bioavailability from Trexima (Table 21). T_{max} for sumatriptan from Trexima was delayed by food by about an hour (Table 22), with a similar effect of food on sumatriptan taken alone.

The comparative bioavailability of sumatriptan from Trexima (fasted) compared to sumatriptan 85 mg (fasted) showed that the extent of absorption, based upon AUC values, was the same for both formulations. Importantly, however, the C_{max} for sumatriptan from the Trexima was on average 17% greater than from sumatriptan 85mg RT tablet (the comparator used in the phase III studies). The T_{max} values for both formulations were similar.

Table 21: Trexima PK food effect, Naproxen

(adapted from NDA application study MT400-102, Table 9)
(Bioavailability Ratios and 90% CI)

PK Parameter	Trexima fed vs. fasted
$AUC_{0-\infty}$ (hr*µg/mL)	0.98 (0.95-1.01)
C_{max} (µg/mL)	1.02 (0.96 – 1.08)
T_{max} * (hr)	0.00 (-1.00 – 1.00)

*median difference with 95% CI on T_{max}

Table 22: Trexima PK food effect, Sumatriptan

(adapted from NDA application study MT400-102, Table 11)
Sumatriptan PK (Bioavailability Ratios and 90% CI)

PK Parameter	Trexima fed vs. fasted	Trexima fasted vs. Sumatriptan fasted
$AUC_{0-\infty}$ (hr*ng/mL)	1.01 (0.95 – 1.08)	1.08 (1.01 – 1.16)
C_{max} (ng/mL)	0.98 (0.85 – 1.12)	1.17 (1.02 – 1.34)
T_{max} * (hr)	0.67 (0.25 – 1.08)	-0.09 (-0.50 – 0.09)

*median difference with 95% CI on T_{max}

MT400-103: Bioavailability of different dose combinations of sumatriptan and naproxen in healthy volunteers

Main positive findings include:

- Delay in naproxen T_{max} in Trexima, and
- TREXIMA had a 16% *lower* C_{max} for naproxen than the combination of sumatriptan RT 85 mg and naproxen sodium 500 mg given concomitantly as individual tablets. This contrasts with Trexima having a *higher* C_{max} for sumatriptan compared to a sumatriptan tablet given alone (Table 22).

MT400-104

In subjects with migraine, the rate or extent of the absorption of naproxen (Figure 3) or sumatriptan (Figure 4) is not significantly changed (see also Table 23: Trexima PK, Summary Results).

Figure 3: Mean naproxen concentrations, during and outside migraine

(NDA application Figure 2.7.10,

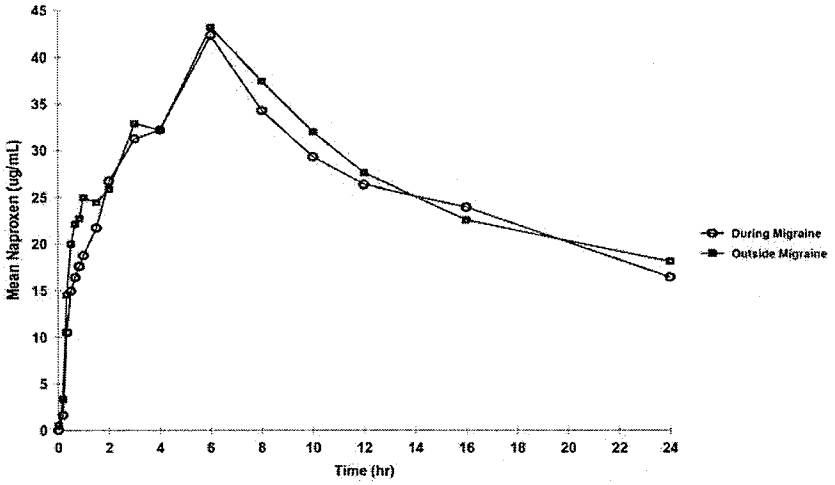
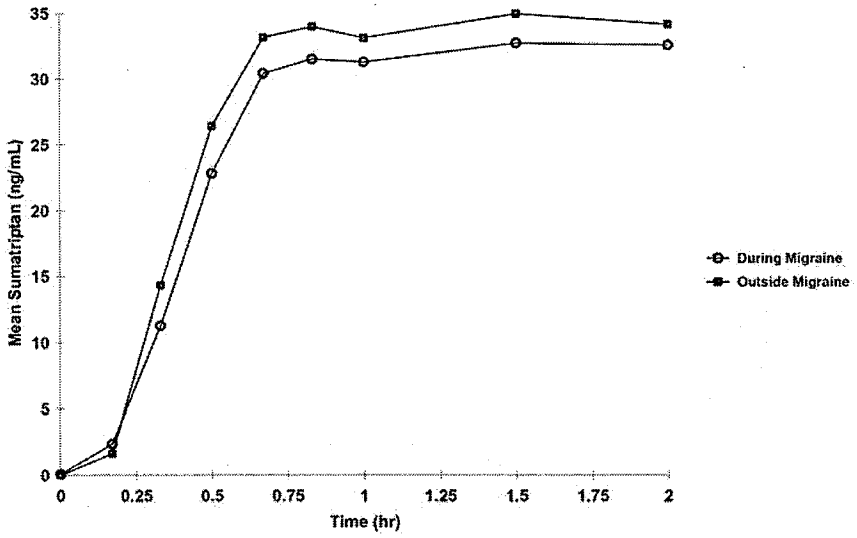


Figure 4: Mean sumatriptan concentrations, during and outside migraine



MT400-105

This study compared the PK of single dose Trexima and two single doses of a Trexima taken 2 hours apart in healthy volunteers (see also Table 23: Trexima PK, Summary Results).

- Naproxen mean C_{max} and $AUC_{0-\infty}$ values increased approximately 1.5 fold with repeated dosing at 2 hours.
- Median naproxen T_{max} and geometric mean terminal-phase half-life values were unchanged with repeated dosing at 2 hours.

- There was a dose proportional increase in AUC sumatriptan values and mean sumatriptan Cmax value increased by a factor of 1.6 with repeated dosing at 2 hours. [Note: The cardiovascular risk associated with repeat dose at 2 hours might increase in approximate proportion with PK values. There is little clinical data from which to estimate this risk].
- There was no lag time in median Tmax values for the absorption of naproxen or sumatriptan for either treatment.

Table 23: Trexima PK, Summary Results

Study Number	Treatment (Dosage Form, Dose) (Product ID)	Sumatriptan				Naproxen			
		C_{max} (ng/mL) Geo. Mean (95% CI)	T_{max} (hr) Median (Range)	$AUC_{0-\infty}$ (hr • ng/mL) Geo. Mean (95% CI)	$t_{1/2}$ (hr) Geo. Mean (95% CI)	C_{max} (mcg/mL) Geo. Mean (95% CI)	T_{max} (hr) Median (Range)	$AUC_{0-\infty}$ (hr • mcg/mL) Geo. Mean (95% CI)	$t_{1/2}$ (hr) Geo. Mean (95% CI)
MT400-104	Trexima tablet (sumatriptan 85 mg and naproxen sodium 500 mg) during a migraine (B916681)	39.8 (35.8-44.2)	1.5 (0.5 – 4.1)	193 (167-223)	2.1 (1.9-2.3)	49.4 (44.8-54.5)	6.0 (3.0 – 16.0)	1162 (1070-1261)	19.8 (18.5-21.1)
	Trexima tablet (sumatriptan 85 mg and naproxen sodium 500 mg) outside of a migraine (B916681)	42.0 (37.0-47.5)	2.0 (0.5 – 4.1)	211 (189-237)	2.1 (1.9-2.3)	48.4 (43.9-53.4)	6.0 (0.7 – 8.0)	1208 (1118-1307)	19.6 (18.3-21.0)
MT400-105	Trexima tablet (sumatriptan 85 mg and naproxen sodium 500 mg) (B916681)	54.2 (47.0-62.5)	0.9 (0.3 – 2.0)	212 (193-233)	2.0 (1.9-2.1)	53.1 (48.2-58.4)	5.0 (0.5 – 10.0)	1173 (1091-1261)	18.5 (17.5-19.6)
	Trexima tablet (sumatriptan 85 mg and naproxen sodium 500 mg) with a second tablet 2 hours apart (B916681)	51.0[1] (44.9-57.9) 79.8[2] (73.1-87.1)	1.0[1] (0.5 – 1.5) 2.8[3] (2.7 – 5.0)	456 (431-484)	2.0 (1.9-2.2)	80.5 (74.9-86.4)	8.0[4] (2.5 – 10.0)	1864 (1749-1987)	17.5 (16.5-18.6)

[1]After the first dose
[2]After the second dose
[3]0.83 hours after the second dose
[4]6 hours after the second dose
Source: of MT400-104, Sections 14.2.3 and 14.2.4; MT400-105, Sections 14.2.3 and 14.2.4

5.2 Pharmacodynamics

No pharmacodynamic studies were conducted.

5.3 Exposure-Response Relationships

No formal exposure-response studies were conducted.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Trexima is indicated for the acute treatment of migraine headache with or without aura in adults.

6.1.1 Methods

Two pivotal studies were submitted to support efficacy, MT100-301 and MT100-302.

6.1.2 General Discussion of Endpoints

Primary Endpoints/Combination Drug Requirements

To satisfy the requirements of 21 CFR §300.50, *Fixed-Combination Prescription Drugs for Humans*, Trexima demonstrated superiority versus its individual components, sumatriptan and naproxen. The agreed efficacy endpoint was '*sustained pain-free 2-24 hours,*' defined as "no pain at 2 hours and no relapse of pain (to mild, moderate or severe), and no use of rescue medication during the 24-hour period after dosing." The Division also required that Trexima not *decrease* the effectiveness of its individual components at early time points (2 hours), as measured by all 4 major migraine symptoms: pain, nausea, photophobia, and phonophobia. The Division had the additional expectation that associated symptoms would not be worsened by Trexima at 24 hours in comparison to its individual components.

Secondary endpoints

Ten secondary endpoints were analyzed as ordered below by a hierarchical stepdown procedure to control for multiplicity. Once a test exceeded $p = 0.05$, subsequent endpoints were not considered to be significant:

1. Pain-free at 2 hours for Trexima vs. placebo
2. Sustained pain relief for Trexima vs. placebo
3. Sustained pain relief for Trexima vs. sumatriptan
4. Sustained symptom-free (photophobia-free, phonophobia-free, or nausea-free) for Trexima vs. sumatriptan [this was not achieved statistically. I consider endpoints that follow to be 'not significant']
5. Use of rescue medication for Trexima vs. sumatriptan
6. Time to rescue for Trexima vs. sumatriptan
7. Pain-relief at 4 hours for Trexima vs. sumatriptan
8. Symptom-free (photophobia-free, phonophobia-free, or nausea-free) at 4 hours for Trexima vs. sumatriptan
9. Pain relief at 2 hours Trexima vs. sumatriptan
10. Symptom-free (photophobia-free, phonophobia-free, or nausea-free) at 2 hours for Trexima vs. sumatriptan

In pre-filing meetings, the Division expressed that it did not accept as a valid secondary endpoint *"sustained pain relief"* because it is not sufficiently different from "sustained pain free 2-24 hours," one of the primary outcome variables.

Basis for study endpoints

2-hour migraine relief

The Division generally requires migraine therapies to demonstrate efficacy against all 4 major migraine symptoms (pain, nausea, photophobia, phonophobia) at the 2 hour time point. Efficacy is quantified as decrease of pain from 'moderate or severe' to 'none or mild,' accompanied by elimination of all 3 associated symptoms. This standard, with small variation (mainly regarding exact degree of pain relief, to mild or to none) enjoys wide acceptance across both clinical and research settings, as reflected by the recommendations of the International Headache Society (IHS) and other professional organizations.

Sustained effectiveness

A recognized goal of migraine therapy, and significant shortcoming of current treatments, is sustained symptom relief beyond the initial 2 hour period used to judge efficacy. Ideally, symptom relief would be for 24 or even 48 hours (essentially the duration of the migraine). Sustained relief is also defined as freedom from associated migraine symptoms. This is particularly important for nausea, which can be exacerbated by migraine therapy itself. The primary endpoint of the Trexima pivotal studies was pain relief at 24 hours, with no worsening of associated symptoms.

Combination drug requirements

To fulfill the combination drug rule, documentation was required only that both components contributed substantively to some clinically important aspect of the overall drug effect. For Trexima, it was judged to be sufficient to show a contribution of the sumatriptan and naproxen combination on the single critical outcome of migraine pain relief sustained through 24 hours.

6.1.3 Study Design

Studies MT400-301 and MT400-302 were nearly identical phase 3, randomized, double-blind, parallel group, placebo-controlled, single-dose, multicenter, outpatient studies conducted concurrently at multiple sites in the U.S.

Eligible subjects were randomized (1:1:1:1) to receive Trexima, sumatriptan 85 mg RT, naproxen sodium 500 mg, or placebo, dispensed for 'at home' treatment. When the subject's next migraine attack of moderate or severe intensity occurred, subjects completed pain intensity (none, mild, moderate or severe), clinical disability, and associated symptoms (photophobia, phonophobia, nausea) assessments on a diary card immediately prior to taking study medication, every 30 minutes for the first two hours, hourly from 2-4 hours, and then hourly while awake for the next 20 hours. Subjects were allowed to take rescue medication, if necessary, no sooner than two hours after taking the study medication. The subjects had a follow-up visit to collect safety assessments and diaries.

The inclusion and exclusion criteria were chosen to enroll subjects who would be treated in accordance with the approved labeling of both sumatriptan and naproxen.

Key entry criteria, MT400-301, MT400-302:

- Diagnosis of migraine with or without aura, according to IHS criteria
- First migraine prior to age 50
- ≥ 6-month history of migraine
- Males or non-pregnant, non-lactating female
- Age 18-65 years
- Average migraine headache frequency of two to six moderate or severe attacks per month in the previous two months
- Subjects could enroll whether or not they had previously used 5-HT agonists for migraines.

Key exclusion criteria

- History of non-migraine headache frequency ≥ 15 days per month in each of the three months prior to screening.
- History of more than six migraines per month
- Basilar or hemiplegic migraine
- Cardiavascular disease or risk factors
- Excluded medications: monoamine oxidase inhibitor, any anti-coagulant, ergot-containing compounds, NSAIDs (except aspirin ≤ 325 mg per day for cardiovascular prophylaxis), methysergide, herbal preparations containing St John's Wort.
- Subjects were not to treat a migraine with study drug if they had taken NSAIDs, opioids, opioid derivatives or a 5-HT agonist within 24 hours, or any analgesic or migraine treatment within six hours of dosing with study drug.

Characteristics of Enrolled Subjects

Differences between treatment groups within each study were not statistically significant or clinically important (Table 24).

Table 24: Subject Characteristics, Study 301, 302

	Trexima N = 726	**Sumatriptan** N = 723	**Naproxen** N = 720	**Placebo** N = 742	**p-Value**
Gender– n (%)					0.932
Male	93 (13)	98(14)	90 (13)	98 (13)	
Female	633 (87)	625 (86)	630 (88)	644 (87)	
Ethnicity – n (%)					0.490
Hispanic/Latino	70 (10)	64 (9)	75 (10)	72 (10)	
Not Hispanic/Latino	656 (90)	659 (91)	645 (90)	669 (90)	
Unknown	0	0	0	1 (<1)	
Race– n (%)					0.461
White	650 (90)	635 (88)	647 (90)	656 (88)	
Black	59 (8)	70 (10)	54 (8)	63 (8)	
Asian	4 (<1)	6 (<1)	4 (<1)	3(<1)	
Native American	4 (<1)	4 (<1)	2 (<1)	8 (1)	
Pacific Islander	0	2 (<1)	1 (<1)	0	
Other	8 (1)	6 (<1)	12 (2)	11 (1)	
Unknown	1 (<1)	0	0	1 (<1)	
Smoker– n (%)					0.756
Yes	103 (14)	108 (15)	96 (13)	110 (15)	
No	623 (86)	615 (85)	624 (87)	632 (85)	
Age (years)					0.810
Mean (±SD)	39.9 (11.3)	40.2 (11.1)	39.9 (11.5)	40.3 (10.8)	
Median	40	40	40	41	
Min – Max	18 – 65	18 – 65	18 – 65	18 – 65	
Age Category (yrs)					0.060
18-35	266 (37)	263 (36)	269 (37)	242 (33)	
36-55	382 (53)	399 (55)	379 (53)	442 (60)	
>55	78 (11)	61 (8)	72 (10)	58 (8)	
Height (in)					0.771
Mean (±SD)	65.5 (3.4)	65.5 (3.2)	65.4 (3.3)	65.4 (3.3)	
Median	65	65	65	65	
Min – Max	56.0 – 77.0	56.0 – 77.0	55.5 – 77.0	56.0 – 78.0	
Weight (lb)					0.390
Mean (±SD)	163.3 (38.9)	165.9 (41.8)	162.8 (38.3)	164.5 (40.1)	
Median	156	160	156.2	155	
Min – Max	93.0 – 320	95.0 – 361	96.0 – 452	95.0 – 333	

Statistical analysis of endpoints

The primary endpoint of "sustained pain free 2-24 hours," was defined as; a) no pain at two hours, b) no relapse of pain (to mild, moderate or severe), and c) no use of rescue medication

during the 24-hour period after dosing. This analysis was done using the CMH test with two outcome categories and with pooled investigator sites as strata.

The 2 hour endpoints of pain relief and incidence of photophobia and phonophobia were analyzed using the CMH test with two outcome categories and with pooled investigator sites as strata. In contrast, the incidence of nausea was analyzed using logistic regression with pooled investigator in order to adjust for an imbalance between study arms in the percentage of patients presenting with nausea in study MT400-301. This represented a change to the original SAP, but was done prior to finalization of the plan and to database lock.

A Kaplan-Meier survival method was used to summarize time to rescue medication use. Treatment differences were tested with the logrank test without adjustment for pooled site. Each of the other analyses used the CMH test with two outcome categories and with pooled investigator sites as strata.

Baseline Differences, Characteristics of Treated Migraine
The baseline characteristics of treatment groups were generally similar (Table 25), but in both pivotal studies there was a higher incidence of baseline nausea in subjects treated with Trexima than with placebo. Also, in the MT400-301 study, there was a statistically significant baseline difference in unilateral head pain, which was reported by fewer subjects treated with Trexima than subjects in the other groups.

Table 25: Baseline Characteristics of Treated Migraine, MT400-301, MT400-302

	Trexima 85mg / 500mg n (%)	**Sumatriptan 85 mg n (%)**	**Naproxen Sodium 500 mg n (%)**	**Placebo n (%)**
Severe Pain				
MT400-301	150 (41)	143 (40)	152 (42)	152 (40)
MT400-302	137 (38)	129 (36)	128 (36)	133 (37)
Photophobia				
MT400-301	300 (83)	302 (83)	301 (83)	310 (81)
MT400-302	288 (79)	296 (82)	287 (81)	286 (79)
Phonophobia				
MT400-301	293 (81)	286 (79)	296 (81)	316 (83)
MT400-302	281 (77)	286 (79)	265 (74)	278 (77)
Nausea				
MT400-301	201 (56)	174 (48)	175 (48)	188 (49)
MT400-302	176 (48)	167 (46)	174 (49)	149 (41)
Aura				
MT400-301	70 (19)	91 (25)	95 (26)	89 (23)
MT400-302	76 (21)	86 (24)	75 (21)	86 (24)
Pain Only on 1 Side of Head				
MT400-301	238 (66)	272 (75)	253 (70)	277 (73)

In Study MT400-301, the Trexima arm treated the headache earlier than the sumatriptan arm, but at about the same time as the naproxen arm (Table 26). I find the likely impact of this difference to be small.

Table 26: Time from Headache Onset Until Study Drug Administration, MT400-301, MT400302

	Trexima 85 mg / 500 mg n (%)	**Sumatriptan 85 mg n (%)**	**Naproxen Sodium 500 mg n (%)**	**Placebo n (%)**
MT400-301				
N	362	362	364	382
Hours between headache onset and dosing				
0 to <1	140 (39)	115 (32)	144 (40)	128 (34)
1 to <2	44 (12)	52 (14)	37 (10)	48 (13)
2 to <4	45 (12)	59 (16)	44 (12)	53 (14)
4 to <6	21 (6)	20 (6)	17 (5)	17 (4)
6 to <12	14 (4)	12 (3)	14 (4)	12 (3)
12 to <24	3 (<1)	3 (<1)	7 (2)	3 (<1)
≥24	1 (<1)	1 (<1)	3 (<1)	3 (<1)
Unknown (onset while sleeping or not reported)	94 (26)	100 (28)	98 (27)	118 (31)
MT400-302				
N	364	361	356	360
Hours between headache onset and dosing				
0 to <1	112 (31)	123 (34)	118 (33)	117 (33)
1 to <2	40 (11)	50 (14)	48 (13)	47 (13)
2 to <4	63 (17)	33 (9)	47 (13)	44 (12)
4 to <6	20 (5)	12 (3)	19 (5)	19 (5)
6 to <12	10 (3)	13 (4)	11 (3)	17 (5)
12 to <24	5 (1)	5 (1)	3 (<1)	3 (<1)
≥24	1 (<1)	2 (<1)	1 (<1)	2 (<1)
Unknown (onset while sleeping or not reported)	113 (31)	123 (34)	109 (31)	111 (31)

6.1.4 Efficacy Findings

I summarized the major efficacy outcomes in section 1.3.2, '*Efficacy*' and below present the data in detail for each outcome. I present the primary endpoints first, followed by the secondary endpoints.

2 hour co-primary endpoints

The Division required that at 2 hours Trexima be superior to placebo, and at least as efficacious as the individual components (sumatriptan and naproxen), for the major migraine symptoms of pain, nausea, photophobia, and phonophobia.

Superiority to placebo was demonstrated statistically in both pivotal studies for pain, photophobia, and phonophobia, while for nausea, statistical significance was shown in only one study (302), with numerical superiority in the other (301).

- **Pain**

Trexima was superior to placebo, naproxen, and sumatriptan in percentage of pain relief at 2 hours, in both study 301 and 302

Table 27).

Table 27: Pain relief, 2 hours, Study 301, 302

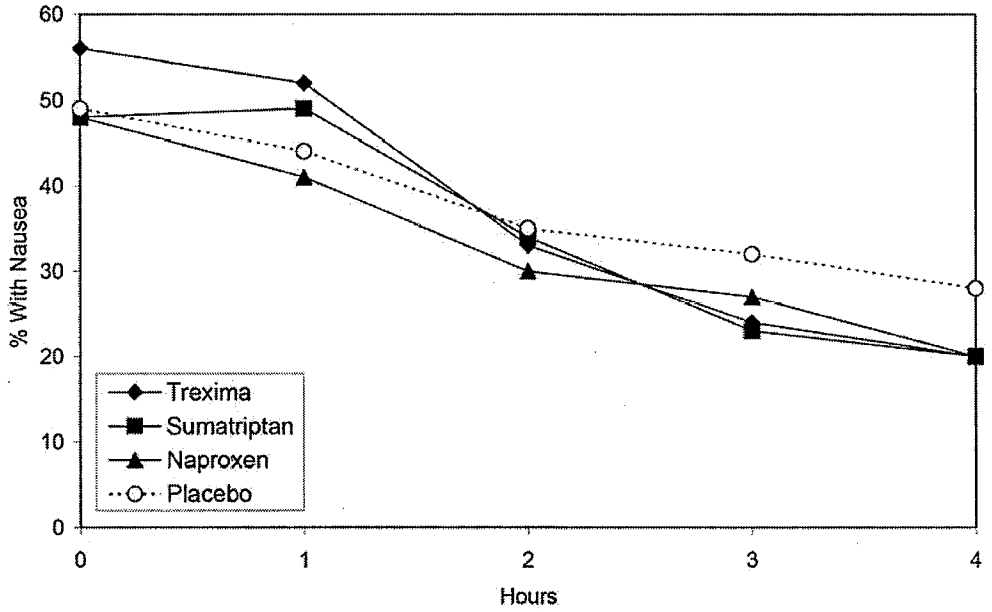
	Trexima	**Sumatriptan 85 mg**	**Naproxen Sodium 500 mg**	**Placebo**
MT400-302 ITT Population	65%* (237/364)	55% (200/361)	44% (157/356)	28% (102/360)
MT400-301 ITT Population	57%** (207/362)	50% (182/362)	43% (158/364)	29% (109/382)

*p<0.001 versus placebo; p= 0.009 versus sumatriptan
** p<0.001 versus placebo; p<0.05 versus sumatriptan

- Nausea

Trexima was not statistically superior to placebo for nausea at 2 hours in one of two pivotal studies (MT400-301). In large part, this appears to be the result of the Trexima arm having a higher initial percentage of patients with nausea (Figure 5). Between 1 and 3 hours, there was a large decrease in the percentage of Trexima patients with nausea, such that by 4 hours (but not by 2) Trexima appeared at least equally as effective as its components, and superior to placebo.

Figure 5: Incidence of Nausea, 0-4 hrs, MT400-301



Below, in Table 28, is the data from Figure 5. Trexima was not statistically superior to placebo for nausea at 2 hours (65% nausea free vs. 64% for placebo), while at 4 hours Trexima was statistically superior to placebo (73% nausea free vs. 56%). Trexima did not achieve statistical superiority to sumatriptan at 2 hours (73% nausea free vs. 69%), which was a secondary outcome measure.

Table 28: Nausea Efficacy, Study 301, 0-4 hrs.

POZEN, Inc. Study Number MT400-301

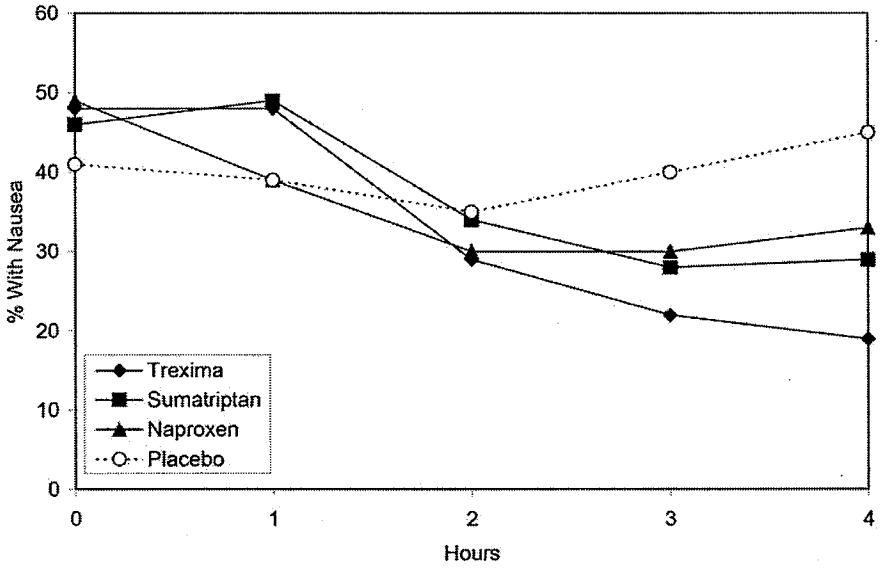
Table 14.2.5.1
Nausea by Time Post-Dose
All Subjects in the Intent-to-Treat Population

Treatment Group / Symptom	HOURS POST-DOSE 0.0	1.0	2.0	3.0	4.0
Trexima (N=362)					
Absent	161 (44%)	172 (48%)	237 (65%)	261 (72%)	266 (73%)
Present	201 (56%)	190 (52%)	125 (35%)	101 (28%)	96 (27%)
Sumatriptan (N=362)					
Absent	188 (52%)	185 (51%)	233 (64%)	250 (69%)	250 (69%)
Present	174 (48%)	177 (49%)	129 (36%)	112 (31%)	112 (31%)
Naproxen (N=364)					
Absent	189 (52%)	215 (59%)	249 (68%)	244 (67%)	247 (68%)
Present	175 (48%)	149 (41%)	115 (32%)	120 (33%)	117 (32%)
Placebo (N=382)					
Absent	194 (51%)	213 (56%)	244 (64%)	218 (57%)	213 (56%)
Present	188 (49%)	169 (44%)	138 (36%)	164 (43%)	169 (44%)
P-Values[1]					
Trexima vs. Placebo			0.711		<.001
Trexima vs. Sumatriptan			0.557		0.140

[1] P-Values are from the Cochran-Mantel-Haenszel test, with pooled investigator site as the strata.

In study 302, there was similarly an imbalance of nausea among the arms, but in this case, nausea was more prevalent in all three 'treatment' arms as compared to the control arm (Figure 6).

Figure 6: Incidence of Nausea, 0-4 hrs, MT400-302



Despite this imbalance in initial nausea in study 302, Trexima was statistically superior to placebo for nausea at 2 hours (71% nausea free vs. 65% for placebo), when analyzed using a logistic regression method (Table 29; result shown for both CMH test and logistic regression). This logistic regression method was not in the study's original analysis plan, but was changed before data unblinding (see section 2.5, *Presubmission Regulatory Activity*)