

Tingling/numbness Site 339 / Subject 2324/ increased tingling all extremities
Site 367 / Subject 2640/ numbness of hip, numbness of shoulder

Other Site 025 / Subject 2387/ bilateral heaviness of arms, jittery feeling
Site 197 / Subject 2007/ diabetes type 2

7.1.3.3 Other significant adverse events

None

7.1.4 Other Search Strategies

There is an extensive literature on the safety of sumatriptan and naproxen. See Section 8.6

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

At each visit, the subject spontaneously mentioned problems then the investigator inquired about adverse events:

- "Have you had any (other) medical problems since your last visit/assessment?"
- "Have you taken any new medicines, other than those given to you in this study, since your last visit/assessment?"

Subjects in the MT400-204 study and the three Phase 3 studies (MT400-301, MT400-302 and MT400-303) were instructed to record adverse events on diary cards.

Since migraine headaches are typically accompanied by pain, nausea, vomiting, phonophobia and photophobia, these specific signs and symptoms were not recorded as adverse events, unless the condition worsened.

Investigators were not obligated to actively seek adverse events in former study participants, but were instructed to notify Pozen if they became aware of any deaths or SAEs in any subject after sign-out from a clinical trial, when the event could have reasonably been related to study drug.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

I examined adverse events as categorized by preferred terms and combination of preferred terms (for example, 'chest pain' and 'neck pain' categories were assembled from several preferred

terms, see section 7.1.6). Adverse effects were generally not serious and reversible, and derived mainly from patient reported symptoms. Adverse events data was generally straightforward given the healthy patient population and relative tolerability of Trexima.

7.1.5.3 Incidence of common adverse events

Studies MT400-204, MT400-301 and MT400-302 were single dose efficacy studies of Trexima in an outpatient setting. Therefore, objective safety assessments followed treatment with study medication by several days, making the measures less useful for safety determinations. Subjects recorded subjective adverse events during dosing of study medication.

Phase I studies

MT400-101, 102, 103, 105 (N = 13 to 31 for each)

Common adverse events reported by healthy volunteers were dizziness, somnolence, nausea, and headache. All events were mild except for one case of moderate nausea and vomiting.

Phase II studies

MT400-204, (single-dose outpatient 'proof of concept' study)

Importantly, the dose of sumatriptan in study MT400-204 was 50 mg non-RT, instead of the 85 mg RT [REDACTED] in the final Trexima formulation. The incidences of adverse events were similar in subjects treated with MT400 and sumatriptan (23% and 24%, respectively), and higher than the incidences of adverse events with naproxen sodium (17%) and placebo (15%). Events occurring in 2% or more of subjects are listed in Table 51

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Table 51: Adverse Events in $\geq 2\%$ of subjects, MT400-204

Body System Adverse event (preferred term)	Treatment Groups			
	MT 400 (sumatriptan 50 mg non-RT + naproxen sodium 500 mg) N=251	Sumatriptan 50 mg (non-RT) N=229	Naproxen Sodium 500 mg N=250	Placebo N=242
Subjects with at least one adverse event – n (%)	58 (23)	56 (24)	43 (17)	37 (15)
Nervous System Disorders	18 (7)	25 (11)	10 (4)	11 (5)
Dizziness	9 (4)	11 (5)	4 (2)	8 (3)
Somnolence	3 (1)	6 (3)	2 (1)	0
Paresthesia	2 (1)	4 (2)	1 (<1)	1 (<1)
General Disorders	18 (7)	8 (3)	5 (2)	5 (2)
Chest tightness	5 (2)	2 (1)	4 (2)	3 (1)
Fatigue	5 (2)	1 (<1)	0	0
Gastrointestinal Disorders	14 (6)	21 (9)	20 (8)	18 (7)
Dry mouth	4 (2)	4 (2)	3 (1)	1 (<1)
Nausea aggravated	1 (<1)	3 (1)	2 (1)	4 (2)
Diarrhoea	0	4 (2)	6 (2)	3 (1)
Ear and Labyrinth Disorders	8 (3)	5 (2)	5 (2)	2 (1)
Tinnitus	6 (2)	4 (2)	4 (2)	2 (1)

Phase III studies

The most Common Treatment-Emergent Adverse Events in >2% of Subjects in the Primary Safety Population (MT400-301 and MT400-302) are shown in Table 52, while the same data with a >1% cutoff is shown in Table 53 . Adverse events are increased in Trexima and sumatriptan arms versus the other two arms. No clear distinction can be made between Trexima and sumatriptan, however.

Table 52: Common Adverse Events, >2%, MT400-301, MT400-302

(From Table 2.7.61)

	Treatment Group			
	Trexima (sumatriptan 85 mg (RT) / naproxen sodium 500 mg)	Sumatriptan 85 mg (RT)	Naproxen Sodium 500 mg	Placebo
	N = 737	N = 735	N = 732	N = 752
Any Adverse Event	197 (27)	194 (26)	100 (14)	84 (11)
Nervous System				
Any Event	89 (12)	63 (9)	37 (5)	35 (5)
Dizziness	28 (4)	16 (2)	11 (2)	16 (2)
Somnolence	24 (3)	17 (2)	12 (2)	15 (2)
Paresthesia	18 (2)	17 (2)	2 (<1)	3 (<1)
Gastrointestinal				
Any Event	69 (9)	71 (10)	32 (4)	33 (4)
Nausea	24 (3)	21 (3)	5 (<1)	10 (1)
Dry mouth	15 (2)	15 (2)	1 (<1)	8 (1)
Dyspepsia	15 (2)	14 (2)	6 (1)	5 (1)
Cardiac				
Any Event	23 (3)	26 (4)	7 (1)	6 (1)
Chest discomfort	13 (2)	10 (1)	3 (<1)	1 (<1)

Table 53: Common Adverse Events, >1%, MT400-301, MT400-302

n (%)	Treatment Group			
	Trexima (sumatriptan 85 mg (RT) / naproxen sodium 500 mg) N = 737	Sumatriptan 85 mg (RT) N = 735	Naproxen Sodium 500 mg N = 732	Placebo N = 752
Any Adverse Event¹	197 (27)	194 (26)	100 (14)	84 (11)
Nervous System disorders	89 (12)	63 (9)	37 (5)	35 (5)
Dizziness	28 (4)	16 (2)	11 (2)	16 (2)
Somnolence	24 (3)	17 (2)	12 (2)	15 (2)
Paraesthesia	18 (2)	17 (2)	2 (<1)	3 (<1)
Gastrointestinal disorders	69 (9)	71 (10)	32 (4)	33 (4)
Nausea	24 (3)	21 (3)	5 (<1)	10 (1)
Dry mouth	15 (2)	15 (2)	1 (<1)	8 (1)
Dyspepsia	15 (2)	14 (2)	6 (<1)	5 (<1)
Abdominal pain upper	5 (<1)	1 (<1)	7 (1)	2 (<1)
Vomiting	3 (<1)	6 (<1)	3 (<1)	9 (1)
Musculoskeletal and connective tissue	35 (5)	35 (5)	8 (1)	6 (<1)
Muscle tightness	10 (1)	9 (1)	0	0
Neck pain	8 (1)	4 (<1)	3 (<1)	3 (<1)
General disorders	30 (4)	27 (4)	12 (2)	9 (1)
Asthenia	8 (1)	3 (<1)	1 (<1)	1 (<1)
Cardiac disorder	23 (3)	26 (4)	7 (1)	6 (<1)
Chest discomfort	13 (2)	10 (1)	3 (<1)	1 (<1)
Palpitations	8 (1)	10 (1)	2 (<1)	5 (<1)
Respiratory, thoracic and mediastinal	21 (3)	28 (4)	4 (<1)	5 (<1)
Throat tightness	10 (1)	9 (1)	0	0
Vascular disorders	7 (<1)	14 (2)	4 (<1)	3 (<1)
Hot flush	1 (<1)	9 (1)	1 (<1)	0

¹ Total number of subjects with at least one adverse event

Source: Section 2.7.4.7.2.2

Moderate/severe ratings were reported by 8 (3%) of subjects in the Trexima treatment group, by 7 (2%) subjects in the sumatriptan group, 4 (1%) subjects in the naproxen sodium group and 3 (1%) of subjects in the placebo group.

Common adverse events in the long-term safety study (MT400-303) are shown in Table 54. I find the common adverse events to be similar to those in current sumatriptan and naproxen labeling.

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Table 54: Common Adverse Events, MT400-303

(Table 2.7.4, Safety Update)

Type of Event	Overall Safety Population N = 565 n (%)	6-Month Completers N = 414 n (%)	12-Month Completers N = 362 n (%)
Subjects With At Least One Adverse Event	374 (66.2)	228 (55.1)	246 (68.0)
Infections and Infestations			
Any Event	180 (31.9)	100 (24.2)	140 (38.7)
Nasopharyngitis	50 (8.8)	30 (7.2)	47 (13.0)
Sinusitis	46 (8.1)	23 (5.6)	34 (9.4)
Upper respiratory tract infection	25 (4.4)	13 (3.1)	23 (6.4)
Influenza	20 (3.5)	6 (1.4)	17 (4.7)
Bronchitis	14 (2.5)	7 (1.7)	11 (3.0)
Gastrointestinal Disorders			
Any Event	131 (23.2)	71 (17.1)	79 (21.8)
Nausea	44 (7.8)	21 (5.1)	21 (5.8)
Dyspepsia	29 (5.1)	15 (3.6)	19 (5.2)
Abdominal pain upper	20 (3.5)	8 (1.9)	13 (3.6)
Diarrhea	17 (3.0)	8 (1.9)	8 (2.2)
Vomiting	13 (2.3)	5 (1.2)	5 (1.4)
Musculoskeletal & Connective Tissue Disorders			
Any Event	97 (17.2)	54 (13)	62 (17.1)
Myalgia	21 (3.7)	12 (2.9)	12 (3.3)
Muscle tightness	19 (3.4)	10 (2.4)	8 (2.2)
Arthralgia	16 (2.8)	10 (2.4)	10 (2.8)
Neck pain	16 (2.8)	9 (2.2)	11 (3.0)
Back pain	15 (2.7)	10 (2.4)	9 (2.5)
Nervous System Disorders			
Any Event	94 (16.6)	52 (12.6)	56 (15.5)
Dizziness	26 (4.6)	18 (4.3)	18 (5.0)
Insomnia	16 (2.8)	5 (1.2)	14 (3.9)
Paraesthesia	13 (2.3)	8 (1.9)	9 (2.5)

(continued)

Type of Event	Overall Safety Population N = 565 n (%)	6-Month Completers N = 414 n (%)	12-Month Completers N = 362 n (%)
Respiratory, thoracic and mediastinal			
Any event	76 (13.5)	52 (12.6)	50 (13.8)
Pharyngolaryngeal pain	20 (3.5)	14 (3.4)	13 (3.6)
Cough	13 (2.3)	9 (2.2)	9 (2.5)
Nasal congestion	12 (2.1)	7 (1.7)	11 (3.0)
Sinus congestion	11 (1.9)	7 (1.7)	8 (2.2)
Injury, poisoning and procedure complications			
Any Event	53 (9.4)	34 (8.2)	39 (10.8)
Joint Sprain	8 (1.4)	6 (1.4)	8 (2.2)
Cardiac Disorders			
Any Event	23 (4.1)	12 (2.9)	12 (3.3)
Chest Discomfort	12 (2.1)	7 (1.7)	7 (1.9)
Psychiatric Disorders			
Any Event	23 (4.1)	10 (2.4)	17 (4.7)
Anxiety	12 (2.1)	6 (1.4)	9 (2.5)

Twenty-seven percent of subjects within the overall safety population reported an event judged related to Trexima by the investigator. These events were primarily from the gastrointestinal or nervous system (Table 55).

Table 55: Common Adverse Events Judged Drug-Related by Investigator, MT400-303
 (from table 2.7.63, Safety Update)

Type of Event	All Subjects N=565
	n (%)
At Least One Adverse Event	152 (27)
Gastrointestinal Disorders	
Any Event	71 (13)
Nausea	34 (6)
Dyspepsia	14 (3)
Nervous System Disorders	
Any Event	54 (10)
Dizziness	18 (3)
Paraesthesia	12 (2)
Musculoskeletal & Connective Tissue Disorders	
Any Event	35 (6)
Muscle tightness	19 (3)

7.1.5.4 Common adverse event tables

(see under heading 7.1.5.3)

7.1.5.5 Identifying common and drug-related adverse events

(see under main heading 7.1.5)

7.1.5.6 Additional analyses and explorations

None

7.1.6 Less Common Adverse Events

I examined the table of all treatment emergent adverse events for rare (<2%) but possibly significant events (Table 56).

“Cardiac disorders” (listed as ‘chest discomfort, palpitations, chest pain, cardiac flutter’) were more common, about equally, for Trexima and sumatriptan versus naproxen and placebo. These symptoms are expected given previous adverse events documented for sumatriptan alone.

	Trexima(%)	Sumatriptan(%)
• Chest discomfort	1.8	1.4
• Palpitations	1.1	1.4
• Chest pain	0.8	0.8

Similarly, muscle tightness, particularly throat and neck tightness and discomfort, occurred more commonly for Trexima and sumatriptan:

	Trexima(%)	Sumatriptan(%)
• Muscle tightness	1.4	1.2
• Neck pain	1.1	0.5
• Throat tightness	1.4	1.2
• Pharyngolaryngeal pain	0.7	0.8

[Comment: neck/throat pain should be included in labeling as a single adverse event.]

Table 56: Adverse Events, Controlled Trials

Table 2.7.4.7.2.2 Treatment Emergent Adverse Events By MedDRA System Organ Class and Preferred Term Safety Population from Studies 301 and 302				
	Trexima (N=737)	Sumatriptan (N=735)	Naproxen (N=732)	Placebo (N=752)
Subject Had at Least One Adverse Event				
No	540 (73.3%)	541 (73.6%)	632 (86.3%)	668 (88.8%)
Yes	197 (26.7%)	194 (26.4%)	100 (13.7%)	84 (11.2%)
Nervous system disorders				
Dizziness	89 (12.1%)	63 (8.6%)	37 (5.1%)	35 (4.7%)
Somnolence	28 (3.8%)	16 (2.2%)	11 (1.5%)	16 (2.1%)
Paraesthesia	24 (3.3%)	17 (2.3%)	12 (1.6%)	15 (2.0%)
Paraesthesia	18 (2.4%)	17 (2.3%)	2 (0.3%)	3 (0.4%)
Tremor	7 (0.9%)	4 (0.5%)	2 (0.3%)	0
Burning sensation	4 (0.5%)	3 (0.4%)	3 (0.4%)	0
Headache	4 (0.5%)	1 (0.1%)	1 (0.1%)	2 (0.3%)
Hyperaesthesia	3 (0.4%)	1 (0.1%)	0	0
Vertigo	3 (0.4%)	1 (0.1%)	4 (0.5%)	2 (0.3%)
Hypoaesthesia	2 (0.3%)	5 (0.7%)	0	0
Mental impairment	2 (0.3%)	0	0	0
Migraine	2 (0.3%)	0	0	1 (0.1%)
Sensory disturbance	2 (0.3%)	1 (0.1%)	0	0
Cognitive disorder	1 (0.1%)	0	0	0
Formication	1 (0.1%)	1 (0.1%)	0	0
Insomnia	1 (0.1%)	1 (0.1%)	2 (0.3%)	0
Restlessness	1 (0.1%)	0	0	0
Tension headache	1 (0.1%)	1 (0.1%)	1 (0.1%)	0
Vision blurred	1 (0.1%)	1 (0.1%)	2 (0.3%)	0
Eyelid ptosis	0	1 (0.1%)	0	0
Hypoaesthesia oral	0	2 (0.3%)	0	0
Intranasal paraesthesia	0	1 (0.1%)	0	0
Paraesthesia oral	0	1 (0.1%)	0	1 (0.1%)
Parosmia	0	1 (0.1%)	0	0
Nervous system disorders (Cont.)				
Psychomotor hyperactivity	89 (12.1%)	63 (8.6%)	37 (5.1%)	35 (4.7%)
Psychomotor skills impaired	0	0	1 (0.1%)	0
Sedation	0	1 (0.1%)	0	0
Skin burning sensation	0	1 (0.1%)	0	0
Tinnitus	0	0	1 (0.1%)	0
Gastrointestinal disorders				
Nausea	69 (9.4%)	71 (9.7%)	32 (4.4%)	33 (4.4%)
Dry mouth	24 (3.3%)	21 (2.9%)	5 (0.7%)	10 (1.3%)
Dyspepsia	15 (2.0%)	15 (2.0%)	1 (0.1%)	8 (1.1%)
Dyspepsia	15 (2.0%)	14 (1.9%)	6 (0.8%)	5 (0.7%)
Abdominal pain upper	5 (0.7%)	1 (0.1%)	7 (1.0%)	2 (0.3%)
Diarrhoea	5 (0.7%)	6 (0.8%)	5 (0.7%)	5 (0.7%)
Dysgeusia	3 (0.4%)	0	2 (0.3%)	0
Vomiting	3 (0.4%)	6 (0.8%)	3 (0.4%)	9 (1.2%)
Eructation	2 (0.3%)	0	0	0
Flatulence	2 (0.3%)	2 (0.3%)	1 (0.1%)	0
Abdominal distension	1 (0.1%)	0	0	0
Abdominal pain	1 (0.1%)	4 (0.5%)	1 (0.1%)	0
Dysphagia	1 (0.1%)	0	1 (0.1%)	0
Gastric irritation	1 (0.1%)	1 (0.1%)	0	0
Gastroesophageal reflux disease	1 (0.1%)	1 (0.1%)	0	0
Lip dry	1 (0.1%)	0	0	0
Abdominal tenderness	0	0	1 (0.1%)	0
Abnormal faeces	0	0	1 (0.1%)	0
Chapped lips	0	1 (0.1%)	0	0
Constipation	0	1 (0.1%)	0	0
Dry throat	0	1 (0.1%)	2 (0.3%)	0

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Gastrointestinal disorders (Cont.)	69 (9.4%)	71 (9.7%)	32 (4.4%)	33 (4.4%)
Gastritis	0	1 (0.1%)	0	0
Gastrointestinal pain	0	0	1 (0.1%)	0
Hiccups	0	0	1 (0.1%)	0
Loose stools	0	1 (0.1%)	0	0
Salivary hypersecretion	0	1 (0.1%)	0	0
Sensitivity of teeth	0	1 (0.1%)	0	0
Stomach discomfort	0	1 (0.1%)	0	0
Throat irritation	0	1 (0.1%)	0	0
Musculoskeletal and connective tissue	35 (4.7%)	35 (4.8%)	8 (1.1%)	6 (0.8%)
Muscle tightness	10 (1.4%)	9 (1.2%)	0	0
Neck pain	8 (1.1%)	4 (0.5%)	3 (0.4%)	3 (0.4%)
Arthralgia	5 (0.7%)	4 (0.5%)	1 (0.1%)	0
Musculoskeletal stiffness	4 (0.5%)	5 (0.7%)	0	0
Myalgia	3 (0.4%)	4 (0.5%)	2 (0.3%)	1 (0.1%)
Pain in jaw	3 (0.4%)	4 (0.5%)	0	1 (0.1%)
Muscular weakness	2 (0.3%)	2 (0.3%)	0	0
Sensation of heaviness	2 (0.3%)	4 (0.5%)	0	0
Back pain	1 (0.1%)	1 (0.1%)	0	0
Limb discomfort	1 (0.1%)	0	0	0
Muscle rigidity	1 (0.1%)	0	0	0
Musculoskeletal discomfort	1 (0.1%)	1 (0.1%)	0	0
Pain in extremity	1 (0.1%)	2 (0.3%)	0	0
Arthropathy	0	0	0	1 (0.1%)
Chest wall pain	0	0	1 (0.1%)	0
Facial pain	0	0	1 (0.1%)	1 (0.1%)
Joint stiffness	0	1 (0.1%)	0	0
Musculoskeletal and connective tissue (Cont.)	35 (4.7%)	35 (4.8%)	8 (1.1%)	6 (0.8%)
Joint swelling	0	0	0	1 (0.1%)
Muscle twitching	0	0	1 (0.1%)	0
Trismus	0	1 (0.1%)	0	0
General disorders	30 (4.1%)	27 (3.7%)	12 (1.6%)	9 (1.2%)
Asthenia	8 (1.1%)	3 (0.4%)	1 (0.1%)	1 (0.1%)
Fatigue	7 (0.9%)	6 (0.8%)	5 (0.7%)	5 (0.7%)
Feeling hot	6 (0.8%)	4 (0.5%)	0	1 (0.1%)
Lethargy	3 (0.4%)	3 (0.4%)	0	0
Feeling abnormal	2 (0.3%)	4 (0.5%)	1 (0.1%)	0
Thirst	2 (0.3%)	0	0	0
Cold sweat	1 (0.1%)	0	0	0
Feeling cold	1 (0.1%)	1 (0.1%)	1 (0.1%)	0
Feeling jittery	1 (0.1%)	1 (0.1%)	0	0
Malaise	1 (0.1%)	0	0	0
Sensation of pressure	1 (0.1%)	1 (0.1%)	0	0
Energy increased	0	0	1 (0.1%)	0
Influenza like illness	0	1 (0.1%)	0	0
Oedema peripheral	0	0	2 (0.3%)	1 (0.1%)
Pain	0	1 (0.1%)	0	0
Pyrexia	0	0	0	1 (0.1%)
Rigors	0	1 (0.1%)	1 (0.1%)	2 (0.3%)
Sensation of foreign body	0	1 (0.1%)	0	0
Sluggishness	0	1 (0.1%)	0	0
Suprapubic pain	0	1 (0.1%)	0	0

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Cardiac disorders	23 (3.1%)	26 (3.5%)	7 (1.0%)	6 (0.8%)
Chest discomfort	13 (1.8%)	10 (1.4%)	3 (0.4%)	1 (0.1%)
Palpitations	8 (1.1%)	10 (1.4%)	2 (0.3%)	5 (0.7%)
Chest pain	6 (0.8%)	6 (0.8%)	2 (0.3%)	2 (0.3%)
Cardiac flutter	0	1 (0.1%)	0	0
Respiratory, thoracic and mediastinal	21 (2.8%)	28 (3.8%)	4 (0.5%)	5 (0.7%)
Throat tightness	10 (1.4%)	9 (1.2%)	0	0
Pharyngolaryngeal pain	5 (0.7%)	6 (0.8%)	1 (0.1%)	0
Cough	3 (0.4%)	1 (0.1%)	0	0
Nasal passage irritation	2 (0.3%)	3 (0.4%)	0	0
Dyspnoea	1 (0.1%)	3 (0.4%)	0	3 (0.4%)
Hoarseness	1 (0.1%)	0	0	0
Nasal congestion	1 (0.1%)	1 (0.1%)	1 (0.1%)	1 (0.1%)
Oropharyngeal swelling	1 (0.1%)	2 (0.3%)	0	0
Postnasal drip	1 (0.1%)	0	0	0
Productive cough	1 (0.1%)	0	1 (0.1%)	0
Sinus pain	1 (0.1%)	2 (0.3%)	1 (0.1%)	1 (0.1%)
Throat irritation	1 (0.1%)	2 (0.3%)	0	0
Nasal oedema	0	1 (0.1%)	0	0
Rhinorrhoea	0	1 (0.1%)	0	0
Sneezing	0	1 (0.1%)	0	0
Wheezing	0	2 (0.3%)	0	0
Skin and subcutaneous tissue disorders	10 (1.4%)	15 (2.0%)	4 (0.5%)	4 (0.5%)
Hyperhidrosis	5 (0.7%)	5 (0.7%)	1 (0.1%)	3 (0.4%)
Cold sweat	1 (0.1%)	0	0	0
Erythema	1 (0.1%)	1 (0.1%)	0	0
Skin and subcutaneous tissue disorders (Cont.)	10 (1.4%)	15 (2.0%)	4 (0.5%)	4 (0.5%)
Night sweats	1 (0.1%)	0	0	0
Pruritus	1 (0.1%)	3 (0.4%)	2 (0.3%)	0
Rash	1 (0.1%)	2 (0.3%)	1 (0.1%)	1 (0.1%)
Acne	0	1 (0.1%)	0	0
Comedone	0	1 (0.1%)	0	0
Pruritus generalised	0	1 (0.1%)	0	0
Rash papular	0	1 (0.1%)	0	0
Skin tightness	0	1 (0.1%)	0	0
Urticaria	0	2 (0.3%)	1 (0.1%)	0
Infections and infestations	9 (1.2%)	8 (1.1%)	7 (1.0%)	4 (0.5%)
Respiratory tract infection viral	2 (0.3%)	0	0	0
Upper respiratory tract infection	2 (0.3%)	1 (0.1%)	1 (0.1%)	1 (0.1%)
Bladder infection	1 (0.1%)	0	0	0
Bronchitis	1 (0.1%)	1 (0.1%)	2 (0.3%)	0
Cystitis acute	1 (0.1%)	0	0	0
Influenza	1 (0.1%)	0	1 (0.1%)	1 (0.1%)
Tonsillitis	1 (0.1%)	0	1 (0.1%)	0
Candidiasis	0	0	0	1 (0.1%)
Herpes simplex	0	0	1 (0.1%)	0
Nasopharyngitis	0	0	0	1 (0.1%)
Oral candidiasis	0	1 (0.1%)	0	0
Otitis media	0	3 (0.4%)	0	0
Pharyngitis	0	1 (0.1%)	0	0
Sinusitis	0	1 (0.1%)	1 (0.1%)	0

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 MT400/Trexima

Psychiatric disorders	8 (1.1%)	3 (0.4%)	2 (0.3%)	1 (0.1%)
Anxiety	3 (0.4%)	0	1 (0.1%)	0
Irritability	2 (0.3%)	0	0	0
Depressed mood	1 (0.1%)	0	0	0
Hyperventilation	1 (0.1%)	0	0	0
Nervousness	1 (0.1%)	1 (0.1%)	1 (0.1%)	1 (0.1%)
Affect lability	0	1 (0.1%)	0	0
Disorientation	0	1 (0.1%)	0	0
Euphoric mood	0	1 (0.1%)	0	0
Vascular disorders	7 (0.9%)	14 (1.9%)	4 (0.5%)	3 (0.4%)
Flushing	4 (0.5%)	3 (0.4%)	1 (0.1%)	1 (0.1%)
Hot flush	1 (0.1%)	9 (1.2%)	1 (0.1%)	0
Hypertension	1 (0.1%)	0	0	0
Peripheral coldness	1 (0.1%)	1 (0.1%)	0	1 (0.1%)
Epistaxis	0	1 (0.1%)	1 (0.1%)	0
Hypotension	0	0	0	1 (0.1%)
Labile blood pressure	0	0	1 (0.1%)	0
Metabolism and nutrition disorders	6 (0.8%)	2 (0.3%)	0	1 (0.1%)
Thirst	2 (0.3%)	0	0	0
Anorexia	1 (0.1%)	0	0	0
Dehydration	1 (0.1%)	0	0	0
Fluid retention	1 (0.1%)	0	0	0
Polydipsia	1 (0.1%)	0	0	0
Alcohol intolerance	0	1 (0.1%)	0	0
Decreased appetite	0	1 (0.1%)	0	0
Increased appetite	0	0	0	1 (0.1%)
Eye disorders	3 (0.4%)	2 (0.3%)	1 (0.1%)	4 (0.5%)
Abnormal sensation in eye	1 (0.1%)	0	0	1 (0.1%)
Asthenopia	1 (0.1%)	0	0	0
Visual disturbance	1 (0.1%)	0	0	0
Eye disorder	0	0	0	1 (0.1%)
Eye pain	0	1 (0.1%)	0	1 (0.1%)
Eye pruritus	0	1 (0.1%)	0	1 (0.1%)
Lacrimation increased	0	0	1 (0.1%)	1 (0.1%)
Investigations	3 (0.4%)	2 (0.3%)	0	1 (0.1%)
Body temperature decreased	1 (0.1%)	0	0	0
Fundoscopy abnormal	1 (0.1%)	0	0	0
Heart rate increased	1 (0.1%)	1 (0.1%)	0	1 (0.1%)
Blood pressure increased	0	1 (0.1%)	0	0
Blood and lymphatic system disorders	2 (0.3%)	1 (0.1%)	1 (0.1%)	1 (0.1%)
Lymphadenopathy	2 (0.3%)	1 (0.1%)	1 (0.1%)	1 (0.1%)
Ear and labyrinth disorders	2 (0.3%)	1 (0.1%)	3 (0.4%)	0
Ear discomfort	1 (0.1%)	0	0	0
Tinnitus	1 (0.1%)	0	1 (0.1%)	0
Cerumen impaction	0	0	1 (0.1%)	0
Ear pain	0	1 (0.1%)	0	0
Sensation of block in ear	0	0	1 (0.1%)	0
Renal and urinary disorders	1 (0.1%)	1 (0.1%)	0	1 (0.1%)
Micturition urgency	1 (0.1%)	0	0	0
Nephrolithiasis	0	1 (0.1%)	0	0
Renal and urinary disorders (Cont.)	1 (0.1%)	1 (0.1%)	0	1 (0.1%)
Pollakiuria	0	0	0	1 (0.1%)
Reproductive system and breast disorders	1 (0.1%)	0	0	1 (0.1%)
Breast pain	1 (0.1%)	0	0	0
Erection increased	0	0	0	1 (0.1%)
Injury, poisoning, procedural complications	0	0	3 (0.4%)	0
Animal scratch	0	0	1 (0.1%)	0
Contusion	0	0	1 (0.1%)	0
Joint sprain	0	0	1 (0.1%)	0
Pregnancy, puerperium and perinatal conditions	0	1 (0.1%)	0	0
Ectopic pregnancy	0	1 (0.1%)	0	0

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Laboratory testing was carried out for subjects in the controlled trials, but these were essentially all single dose studies, such that drug exposure was very low, and it would be unlikely for most drug effects to be detected.

The open-label study of Trexima did not have a comparator group, greatly limiting power to identify anything but very rare events.

For all studies, laboratory testing was conducted at times remote from Trexima dosing (baseline and follow-up visits), increasing the difficulty of associating changes to drug effects.

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

All studies submitted were used for analysis of laboratory values.

7.1.7.3 Standard analyses and explorations of laboratory data

Primary Safety Population

Table 57 lists selected markedly abnormal laboratory values in study 301 and 302 (Table 58 shows cutoffs for defining values as markedly abnormal). There was no increase in abnormal values for Trexima versus the three other study arms.

I reviewed the individual hematology data for the subjects with markedly abnormal values and believe that none were serious.

Blood chemistry showed one Trexima-treated patient with hyperkalemia (baseline 5.4 mEq/L, increased to 6.6, then 1 day later decreased to 5.4) a known adverse effect of NSAIDs.

Modest elevations in certain enzymes (e.g. CPK, AST) were seen in a small number of subjects in all groups, but without apparent relationship to pre- or post-dosing, or treatment arm.

Table 57: Selected Markedly Abnormal Laboratory Abnormalities, Primary Safety Population

	Treatment Groups			
	Trexima N = 737	Sumatriptan N = 735	Naproxen Sodium N = 732	Placebo N = 752
	n	n	n	n
Hematology				
Any Abnormality ¹	20	28	23	38
Hemoglobin ²	3	3	2	7
Platelet Count ²	0	0	0	0
Blood Chemistry				
Any Abnormality ³	32	54	54	62
ALT ⁴	2	7	5	11
AST ⁴	3	4	2	3
Alk Phos ⁴	0	3	1	0
Bilirubin ⁴	2	0	1	1
Creatinine ⁴	0	0	1	1
CK ⁴	5	4	13	6

¹ Total number of subjects with at least one markedly abnormal hematology value
² Total number of subjects with at least one value below preset limit (Section 2.7.4.7.12)
³ Total number of subjects with at least one markedly abnormal blood chemistry value
⁴ Total number of subjects with at least one value above preset limit (Section 2.7.4.7.12)

Table 58: Cutoff Definition of Markedly Abnormal Laboratory Values

(Table 14.2.20, MT400-303_final)

PARAMETER	MINIMUM	MAXIMUM	UNITS
UREA (BUN)	N.A.	40.0	mg/dL
CHOLESTEROL, TOTAL	N.A.	300.0	mg/dL
TRIGLYCERIDES	N.A.	500.0	mg/dL
ALKALINE PHOSPHATASE	N.A.	180.0	U/L
AST	N.A.	75.0	U/L
ALT	N.A.	100.0	U/L
SODIUM	128.0	150.0	mEq/L
CHLORIDE	90.0	116.0	mEq/L
BICARBONATE	18.0	40.0	mEq/L
TOTAL PROTEIN	5.0	9.0	g/dL
ALBUMIN	3.0	5.8	g/dL
TOTAL BILIRUBIN	N.A.	2.5	mg/dL
CALCIUM	7.5	12.0	mg/dL
PHOSPHATE	2.0	6.0	mEq/L
POTASSIUM	3.1	5.8	mEq/L
MAGNESIUM	0.9	2.8	mEq/L
GLOBULIN	0.7	5.5	g/dL
WBC	2.8	16.0	$\times 10^3$ /mCL
NEUTROPHILS	10.0	80.0	%
LYMPHOCYTES	N.A.	80.0	%
EOSINOPHILS	N.A.	15.0	%
PLATELETS	100.0	500.0	$\times 10^3$ /mm ³
GLUCOSE, RANDOM, SERUM	45.0	280.0	mg/dL
CREATININE - FEMALES	N.A.	1.5	mg/dL
URIC ACID - FEMALES	N.A.	8.5	mg/dL
CK - FEMALES	N.A.	500.0	U/L
HGB - FEMALES	10.0	17.0	g/dL
HCT - FEMALES	30.0	50.0	%
CREATININE - MALES	N.A.	1.9	mg/dL
URIC ACID - MALES	N.A.	10.0	mg/dL
CK - MALES	N.A.	700.0	U/L
HGB - MALES	11.0	17.0	g/dL
HCT - MALES	35.0	53.0	%

MT400-303, Open Label Safety Study

This study included the collection of clinical laboratory test data at the time of the screening visit, at the 6 month visit, and at the 12 month visit. Routine hematology and chemistry tests were performed.

7.1.7.3.1 Analyses focused on measures of central tendency

Pozen reports, and I agree, that:

“There was no evidence of a relationship between episodic treatment with Trexima over the period of this study and the results of any specific clinical laboratory tests.”

“Because of the possible effects of NSAIDs on hepatic and renal function, hepatic enzymes (ALT and AST) and renal function parameters (creatinine and BUN) were examined specifically and no suggestion of a safety signal was present.”

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Little change occurred for most of the hematology and blood chemistry values in the long term study. For MCHC (mean corpuscular hemoglobin concentration)(Table 1), 23% of subjects shifted from 'high or normal to low.' However, MCHC was a highly volatile measure, with 12% of subjects showing 'change to normal,' while other hematology values showed 2-4% shift to normal. Also, decreased MCHC was not accompanied by other laboratory signs of anemia, suggesting it is not indicative of a true adverse effect.

Table 59: Hematology shift values, MT400-303

HCT	
Low or Normal -> High	11 (2%)
High or Normal -> Low	12 (2%)
No Change	477 (92%)
Change to Normal	21 (4%)
Total	521
HGB	
Low or Normal -> High	8 (2%)
High or Normal -> Low	15 (3%)
No Change	483 (93%)
Change to Normal	15 (3%)
Total	521
MCH	
Low or Normal -> High	7 (1%)
High or Normal -> Low	17 (3%)
No Change	484 (93%)
Change to Normal	13 (2%)
Total	521
MCHC	
Low or Normal -> High	1 (<1%)
High or Normal -> Low	119 (23%)
No Change	338 (65%)
Change to Normal	63 (12%)
Total	521
MCV	
Low or Normal -> High	2 (<1%)
High or Normal -> Low	5 (<1%)
No Change	504 (97%)
Change to Normal	10 (2%)
Total	521
RBC	
Low or Normal -> High	1 (<1%)
High or Normal -> Low	7 (1%)
No Change	504 (97%)
Change to Normal	9 (2%)
Total	521

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

There were two subjects with increased liver enzymes likely due to Trexima (see section 7.1.3, Dropouts and Other Significant Averse Events). Otherwise, only a small number of marked laboratory value outliers were identified, and no patterns of abnormalities were found.

7.1.7.4 Additional analyses and explorations

None

7.1.7.5 Special assessments

None

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Both sumatriptan and naproxen are known to increase blood pressure, but insufficient blood pressure data was collected in the Trexima studies. Clinical pharmacology studies did not record vital signs during medication administration. The controlled trials measured blood pressure only days before, or days after single doses. The safety study measured blood pressure only at baseline.

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

(see 7.1.8.1)

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

Table 60 lists vital signs change from the single-dose studies 301 and 302. Vital signs differences were calculated between screening and follow-up visits, distant from drug dosing. Vital signs, including blood pressure, showed no meaningful change.

Table 60: Vital Signs Change, Studies 301 and 302

POZEN, Inc. Study Number MT400-ISS

Table 2.7.4.7.14.3
 Vital Signs Change from Screening to Follow-up
 Safety Population from Studies 301 and 302

	Trexima (N=737)	Sumatriptan (N=735)	Naproxen (N=732)	Placebo (N=752)
Heart Rate (Beats per Minute):				
N	728	724	719	740
Mean (std)	2.3 (9.5)	3.0 (9.6)	2.0 (9.8)	2.2 (9.9)
Median	2.0	2.0	2.0	1.0
Min - Max	-24 - 40.0	-36 - 40.0	-48 - 41.0	-38 - 38.0
Blood Pressure (Systolic mmHg):				
N	728	724	717	741
Mean (std)	0.0 (11.3)	0.1 (12.1)	0.2 (11.0)	0.2 (11.6)
Median	0.0	0.0	0.0	0.0
Min - Max	-38 - 55.0	-38 - 46.0	-34 - 32.0	-38 - 36.0
Blood Pressure (Diastolic mmHg):				
N	728	724	717	741
Mean (std)	-0.0 (8.3)	0.0 (8.5)	-0.1 (8.2)	-0.2 (8.5)
Median	0.0	0.0	0.0	0.0
Min - Max	-26 - 30.0	-30 - 32.0	-28 - 35.0	-30 - 32.0

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

No patients on Trexima in the single dose trials MT400-301 and MT400-302 (combined N=737) experienced the adverse event of 'blood pressure increased' as determined by blood pressure measurement at follow-up visit.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

None

7.1.8.4 Additional analyses and explorations

None

7.1.9 Electrocardiograms (ECGs)

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

No ECG testing was conducted at the time of Trexima exposure in any study. Controlled trials and the safety trial examined ECGs only at baseline.

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

No data available (see Section 7.1.9.1)

7.1.9.3 Standard analyses and explorations of ECG data

No data available (see Section 7.1.9.1)

7.1.9.3.1 Analyses focused on measures of central tendency

Not data available (see Section 7.1.9.1)

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

No data available (see Section 7.1.9.1)

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

No data available (see Section 7.1.9.1)

7.1.9.4 Additional analyses and explorations

No data available (see Section 7.1.9.1)

7.1.10 Immunogenicity

The components of Trexima are not considered immunogenic.

7.1.11 Human Carcinogenicity

No carcinogenicity studies were conducted with the combination of sumatriptan and naproxen.

Neither sumatriptan alone, nor naproxen alone, were found to be carcinogenic after lifetime, oral administration studies in rodents (from prescribing information for Imitrex and Naprosyn).

7.1.12 Special Safety Studies

None

7.1.13 Withdrawal Phenomena and/or Abuse Potential

While triptans and NSAIDs are not subject to abuse in the classic sense, migraine headache medication is frequently overused. Overuse is defined by the IHS as intake more than 15 times a

month for a minimum of three months. Frequent use of sumatriptan or naproxen can cause 'medication overuse headache (MOH).' MOH is treated by medication withdrawal. Withdrawal of headache medication itself often causes a 'withdrawal headache' lasting about 5-10 days.

The Imitrex label states: "One clinical study with IMITREX (sumatriptan succinate) Injection enrolling 12 patients with a history of substance abuse failed to induce subjective behavior and/or physiologic response ordinarily associated with drugs that have an established potential for abuse."

7.1.14 Human Reproduction and Pregnancy Data

Sumatriptan:

Pregnancy category C

No evidence suggests that sumatriptan increases human fetal abnormalities. Weak and contradictory data suggests that sumatriptan might increase the rate of preterm delivery (reviewed in TERIS, The Teratogen Information System).

Distribution in breast milk (from Martindale)

"The distribution of sumatriptan into breast milk following a 6-mg subcutaneous dose has been studied in 5 lactating mothers. The mean total recovery of sumatriptan in breast milk was estimated to be 14.4 micrograms or 0.24% of the dose. It was calculated that on a weight adjusted basis an infant could receive a maximum of 3.5% of the maternal dose."

Naproxen:

Pregnancy category C

The risk of congenital anomalies from naproxen is not likely to be great. Persistent pulmonary hypertension and premature closure of the ductus arteriosus have been reported in infants whose mothers took naproxen just before delivery (from TERIS).

Distribution in breast milk (from Martindale)

"In a study of a breast-fed infant only 0.26% of the mother's dose was recovered from the infant

7.1.15 Assessment of Effect on Growth

Sumatriptan:

Safety and effectiveness of sumatriptan in pediatric patients has not been established. Sumatriptan increases the release of growth hormone

Naproxen:

Experience in juvenile arthritis and other use experience have established that single doses of 2.5 to 5 mg/kg, with total daily dose not exceeding 15 mg/kg/day, are well tolerated in pediatric patients over 2 years of age (from prescription naproxen label).

7.1.16 Overdose Experience

No cases of Trexima overdose are reported. Overdose experience with the individual drugs, as reflected in labeling, is presented below.

Sumatriptan overdose:

“Patients (n=670) have received single oral doses of 140 to 300 mg without significant adverse effects. Volunteers (n=174) have received single oral doses of 140 to 400 mg without serious adverse events.”

“It is unknown what effect hemodialysis or peritoneal dialysis has on the serum concentrations of sumatriptan.”

Naproxen overdose:

“Significant naproxen overdose may be characterized by lethargy, dizziness, drowsiness, epigastric pain, abdominal discomfort, heartburn, indigestion, nausea, transient alterations in liver function, hypoprothrombinemia, renal dysfunction, metabolic acidosis, apnea, disorientation or vomiting. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression, and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose. Because naproxen sodium may be rapidly absorbed, high and early blood levels should be anticipated. A few patients have experienced convulsions, but it is not clear whether or not these were drug-related. It is not known what dose of the drug would be life threatening.”

“Patients should be managed by symptomatic and supportive care following a NSAID overdose. There are no specific antidotes. Hemodialysis does not decrease the plasma concentration of naproxen because of the high degree of its protein binding. Emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) and/or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose. Forced diuresis, alkalinization of urine or hemoperfusion may not be useful due to high protein binding.”

7.1.17 Postmarketing Experience

Trexima is not marketed in any other country. No other combination of triptan/NSAID is marketed.

Extensive postmarketing experience exists for both sumatriptan and naproxen.

Naproxen:

Major recognized adverse effects of NSAIDs, including naproxen, are listed in Table 61.

Table 61: Major adverse effects of non-steroidal anti-inflammatory drugs (NSAIDs)

Serious side effects include:	Other side effects include:
<ul style="list-style-type: none">•heart attack•stroke•high blood pressure•heart failure from body swelling (fluid retention)•kidney problems including kidney failure•bleeding and ulcers in the stomach and intestine•low red blood cells (anemia)•life-threatening skin reactions•life-threatening allergic reactions•liver problems including liver failure•asthma attacks in people who have asthma	<ul style="list-style-type: none">•stomach pain•constipation•diarrhea•gas•heartburn•nausea•vomiting•dizziness

Sumatriptan:

The following adverse events are taken from the “Postmarketing Experience” for Imitrex:

Blood: Hemolytic anemia, pancytopenia, thrombocytopenia.

Cardiovascular: Atrial fibrillation, cardiomyopathy, colonic ischemia (see WARNINGS), Prinzmetal variant angina, pulmonary embolism, shock, thrombophlebitis.

Ear, Nose, and Throat: Deafness.

Eye: Ischemic optic neuropathy, retinal artery occlusion, retinal vein thrombosis.

Gastrointestinal: Ischemic colitis with rectal bleeding (see WARNINGS), xerostomia.

Hepatic: Elevated liver function tests.

Neurological: Central nervous system vasculitis, cerebrovascular accident, dysphasia, subarachnoid hemorrhage.

Non-Site Specific: Angioneurotic edema, cyanosis, death (see WARNINGS), temporal arteritis.

Psychiatry: Panic disorder.

Respiratory: Bronchospasm in patients with and without a history of asthma.

Skin: Exacerbation of sunburn, hypersensitivity reactions (allergic vasculitis, erythema, pruritus, rash, shortness of breath, urticaria; in addition, severe anaphylaxis/anaphylactoid reactions have been reported [see WARNINGS]), photosensitivity.

Urogenital: Acute renal failure.

7.2 Adequacy of Patient Exposure and Safety Assessments

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

(see also Section 4, Data Sources, Review Strategy, and Data Integrity)

7.2.1.1 Study type and design/patient enumeration

Tables enumerating all subjects and patients across phase 1 (Table 62), phase 2 (Table 63) and phase 3 (Table 64) are shown below.

Table 62: Phase I studies: objectives, design, patient enumeration

Study Reference Number and Report Location ¹	Study Objectives	Study Design	Treatments: Dose, Dosage Form	Subjects: Number, Sex (M/F), Mean Age, Type
Phase I Studies				
MT400-101 Module 5.3.1.1	Bioavailability of Trexima, each of its components and marketed versions of components	Open, 3-way crossover, incomplete block, single dose study	1) Trexima Tablets (sumatriptan 85 mg RT / naproxen sodium 500 mg) 2) Sumatriptan Tablets (85 mg non-RT) 3) Naproxen Sodium Tablets (500 mg) 4) Imitrex® Tablets (100 mg non-RT) 5) Anaprox® DS Tablets (550 mg)	40 (15M/25F) treated, all evaluable, 44 years, healthy volunteers
MT400-102 Module 5.3.1.1	Food effect on the bioavailability of Trexima and sumatriptan	Open, 3-way crossover, single dose study	1) Trexima Tablets (sumatriptan 85 mg RT / naproxen sodium 500 mg), fasted and fed 2) Sumatriptan Tablets (85 mg RT)	24 (12M/12F) treated, 21 completed, 50 years, healthy volunteers
MT400-103 Module 5.3.1.1	Bioavailability of co-administration of different dose combinations of sumatriptan and naproxen sodium	Open, 3-way crossover, incomplete block, single dose study	1) Trexima Tablets (sumatriptan 85 mg RT / naproxen sodium 500 mg) 2) Sumatriptan Tablets (85 mg RT) 3) Naproxen sodium Tablets (500 mg) 4) Sumatriptan Tablets (85 mg non-RT) 5) Imitrex® Tablets (50 mg non-RT)	31 (15M/16F) treated, 27 completed, 42 years, healthy volunteers
MT400-104 Module 5.3.3	Pharmacokinetics of Trexima administered during and outside a migraine	Open, 2- period, single dose study	1) Trexima Tablets (sumatriptan 85 mg RT / naproxen sodium 500 mg)	18 (5M/13F) treated, all evaluable, 43 years, subjects with migraine
MT400-105 Module 5.3.3	Pharmacokinetics of two single doses of Trexima administered 2 hours apart	Open, 2-way crossover, single dose two hours apart study	1) Trexima Tablets (sumatriptan 85 mg RT / naproxen sodium 500 mg)	24 (12M/12F) treated, all evaluable, 29 years, healthy volunteers

Table 63: Phase 2 studies: objectives, design, patient enumeration

Study Reference Number and Report Location ¹	Study Objectives	Study Design	Treatments: Dose, Dosage Form	Subjects: Number, Sex (M/F), Mean Age, Type
Phase 2 Study				
MT400-204 Module 5.3.5.1	Comparison of pain response rates in migraine subjects with migraine	Double-blind, parallel-group, single dose, multicenter study	1) MT400: Overencapsulated Imitrex® Tablets (50 mg non-RT) + Naproxen Sodium Tablets (500 mg) 2) Naproxen Sodium Tablets (500 mg) 3) Overencapsulated Imitrex® Tablets (50 mg non-RT) 4) Placebo tablets 5) Placebo capsules	972 treated: 251 MT400 (16M / 235F), 43 years; 229 sumatriptan (21M / 208F), 41 years; 249 naproxen sodium (27M / 223F), 42 years; 241 placebo (28M / 214F), 41 years moderate to severe migraine subjects

Table 64: Phase 3 studies: objectives, design, patient enumeration

Study Reference Number and Report Location	Study Objectives	Study Design	Treatments: Dose, Dosage Form	Subjects: Number, Sex (M/F), Mean Age, Type
Phase 3 Studies				
MT400-301 Module 5.3.5.1	Placebo controlled safety and efficacy of Trexima in migraine subjects	Double-blind, parallel-group, single dose, multicenter study	1) Trexima Tablets (sumatriptan 85 mg RT / naproxen sodium 500 mg) 2) Sumatriptan Tablets (85 mg RT) 3) Naproxen sodium Tablets (500 mg) 4) Placebo Tablet	1495 treated: 362 Trexima (47M/320F), 39 years; 362 sumatriptan (47M/323F), 40 years; 364 naproxen sodium (42M/329F), 40 years; 382 placebo (42M/345F), 41 years moderate to severe migraine subjects
MT400-302 Module 5.3.5.1	Placebo controlled safety and efficacy of Trexima in migraine subjects	Double-blind, parallel-group, single dose, multicenter study	1) Trexima Tablets (sumatriptan 85 mg RT / naproxen sodium 500 mg) 2) Sumatriptan Tablets (85 mg RT) 3) Naproxen sodium Tablets (500 mg) 4) Placebo Tablet	1461 treated: 364 Trexima (48M/322F), 40 years; 361 sumatriptan (52M/313F), 40 years; 356 naproxen sodium (50M/311F), 39 years; 360 placebo (57M/308F), 40 years moderate to severe migraine subjects
MT400-303 Module 5.3.5.2	Repeat dose safety of Trexima in multiple migraine episodes over 12 months	Open, multicenter, repeat dose study	1) Trexima tablets (sumatriptan 85 mg RT/ naproxen sodium 500 mg)	561 treated: 406 completed 6 months, (80M/481F), 44 years, moderate to severe migraine subjects

7.2.1.2 Demographics

The demographics of the expanded safety population (MT400-104; MT400-204; MT400-301; MT400-302; MT400-303) are summarized in Table 65. This population comprised primarily non-smoking Caucasian females with a median age of 41 years. These demographics are not different between treatment groups, and are not different between the individual studies and the pooled summary.

Table 65: Demographics, Expanded Safety Population

Parameter	Treatment groups				
	Trexima	Sumatriptan 50 mg (non-RT) + Naproxen Sodium 500 mg	Sumatriptan 85 mg (RT)	Naproxen Sodium 500 mg	Placebo
	N = 1160	N = 251	N = 735	N = 982	N = 994
Gender – n (%)					
Males	155 (13)	16 (6)	99 (13)	119 (12)	127 (13)
Females	1005 (87)	235 (94)	636 (87)	863 (88)	867 (87)
Age (years)					
Mean	40.7	42.5	40.2	40.5	40.6
Range	18 - 65	19 – 73	18 - 65	18 - 75	18 - 68
Race –n (%)					
Caucasian	1047 (90)	218 (87)	643 (87)	871 (89)	867 (87)
African-American	78 (7)	11 (4)	73 (10)	69 (7)	77 (8)
Asian	13 (1)	3 (1)	6 (<1)	5 (<1)	5 (<1)
American Indian / Alaska Native	4 (<1)	0	4 (<1)	2 (<1)	8 (<1)
Native Hawaiian/Pacific Islander	1 (<1)	0	2 (<1)	1 (<1)	0
Other	16 (1)	19 (7)	7 (<1)	34 (3)	36 (4)
Unknown	1 (<1)	0	0	0	1 (<1)
Weight (pounds)					
Mean	163.1	158.0	165.8	161.8	164.1
Range	89 - 320	94 – 280	95 - 361	96 - 452	90 - 333

† Studies MT400-104; MT400-204; MT400-301; MT400-302; MT400-303 (Data from subjects in which only a single dose of a Trexima tablet was taken for the first treated migraine)

7.2.1.3 Extent of exposure (dose/duration)

Study MT400-303, a one year open label study of Trexima, is the only study with exposure greater than one (efficacy studies) or a few (PK studies) doses of Trexima.

Table 66 shows extent of exposure by treatment arm.

Table 66: Extent of Exposure, by treatment arm
 (from Table 2.7.57)

Doses	Total Subjects Exposed						Total
	1	2	3-6	7-24	25-48	>48	
Trexima (sumatriptan 85 mg (RT) / naproxen sodium 500 mg)	796	53†	68‡	79	113	296	1405
Sumatriptan 50 mg (non-RT) + Naproxen Sodium 500 mg	251	0	0	0	0	0	251
Sumatriptan 85 mg (RT)	787	0	0	0	0	0	787
Sumatriptan 85 mg (non-RT)	24	0	0	0	0	0	24
Sumatriptan 50 mg (non-RT)	229	0	0	0	0	0	229
Imitrex 100 mg (non-RT)	24	0	0	0	0	0	24
Imitrex 50 mg (non-RT)	29	0	0	0	0	0	29
Naproxen Sodium 500 mg	1077	0	0	0	0	0	1077
Anaprox 550 mg	24	0	0	0	0	0	24

† Two doses distributed as follows: MT400-102 - 22 subjects; MT400 - 104 18 subjects; MT400-303 – 13 subjects

‡ Three doses distributed as follows: MT400-105 – 24 subjects; MT400-303 – 44 subjects

Nineteen subjects were identified who were possibly enrolled in two studies at some time during the Phase 3 program. An additional three such subjects were identified at individual study sites during monitoring activities.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

None

7.2.2.2 Postmarketing experience

See Section 7.1.17

7.2.2.3 Literature

See Section 8.6, Literature Review.

7.2.3 Adequacy of Overall Clinical Experience

As for most new drugs, the extent and duration of clinical experience documented for Trexima is limited. Clinical experience is adequate to identify common safety risks when used as intended in an otherwise healthy migraine population. However, rare adverse events would not likely have been identified due to limited overall exposure. Sumatriptan is known to cause cardiovascular adverse events, and naproxen is also suspected of increasing cardiovascular risk. The safety database is not adequate to address the cardiovascular risk of Trexima. The well-controlled efficacy trials of Trexima were single-dose studies with consequent very low patient exposure. The open-label safety study of Trexima demonstrated that serious cardiovascular adverse events do occur with use of the drug, but no true estimation of risk can be determined from this data.

The patient population for Trexima studies was largely female, Caucasian, and middle-aged. This study population reflects a large portion of the population expected to most commonly use Trexima. Significant use of Trexima would also be expected in other demographic groups less well represented in Trexima studies, such as men and older patients. The cardiovascular risk from Trexima in these other groups might be higher due to more underlying cardiovascular risk factors.

Gender

About 100-150 men were in each arm of the pivotal Trexima trials. In this small number of individuals and exposures, no increased risk for males was identified, including cardiovascular:

“Males treating a migraine attack generally reported adverse events less frequently than females (Sections 2.7.4.7.3.1 and 2.7.4.7.3.2). Sixteen percent of males taking Trexima reported adverse events, compared to 28% of females. Those males and females taking sumatriptan, naproxen sodium and placebo reported 21% and 27%, 12% and 14%, and 11% and 11%, respectively. Overall, males reported a slightly higher incidence of events in gastrointestinal disorders. System Organ Classifications where males reported fewer