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

Table 51: Adverse Events in ≥ 2% of subjects, MT400-204

	Treatment Groups			
Body System Adverse event (preferred term)	**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 Event[1]	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)
Resipratory, 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

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