

Table 29: Nausea Efficacy, Study 302, 0-4 hrs.

POZEN, Inc.

Study Number MT400-302

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
<b>Trexima (N=364)</b>					
Absent	188 ( 52%)	189 ( 52%)	260 ( 71%)	285 ( 78%)	295 ( 81%)
Present	176 ( 48%)	175 ( 48%)	104 ( 29%)	79 ( 22%)	69 ( 19%)
<b>Sumatriptan (N=361)</b>					
Absent	194 ( 54%)	185 ( 51%)	238 ( 66%)	260 ( 72%)	257 ( 71%)
Present	167 ( 46%)	176 ( 49%)	123 ( 34%)	101 ( 28%)	104 ( 29%)
<b>Naproxen (N=356)</b>					
Absent	182 ( 51%)	216 ( 61%)	248 ( 70%)	249 ( 70%)	240 ( 67%)
Present	174 ( 49%)	140 ( 39%)	108 ( 30%)	107 ( 30%)	116 ( 33%)
<b>Placebo (N=360)</b>					
Absent	211 ( 59%)	221 ( 61%)	233 ( 65%)	217 ( 60%)	199 ( 55%)
Present	149 ( 41%)	139 ( 39%)	127 ( 35%)	143 ( 40%)	161 ( 45%)
<b>P-Values<sup>1</sup></b>					
Trexima vs. Placebo			0.056		<0.001
Trexima vs. Sumatriptan			0.141		0.002
<b>P-Values<sup>2</sup></b>					
Trexima vs. Placebo			0.007		<0.001
Trexima vs. Sumatriptan			0.070		<0.001

<sup>1</sup> P-Values are from the Cochran-Mantel-Haenszel test, with pooled investigator site as the strata.

<sup>2</sup> P-Values are from Logistic Regression, with pooled investigator site and baseline nausea as covariables.

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Photophobia

Trexima was statistically superior to placebo for photophobia at 2 hours in both study 301 (50% photobia-free vs. 32% for placebo)(Table 30), and study 302 (58% photophobia-free, versus 36% for placebo)(Table 31).

Table 30: Photophobia, 0-4 hrs, study 301

Table 14.2.3.1  
 Photophobia 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	62 ( 17%)	91 ( 25%)	180 ( 50%)	230 ( 64%)	248 ( 69%)
Present	300 ( 83%)	271 ( 75%)	182 ( 50%)	132 ( 36%)	114 ( 31%)
Sumatriptan (N=362)					
Absent	60 ( 17%)	91 ( 25%)	166 ( 46%)	200 ( 55%)	213 ( 59%)
Present	302 ( 83%)	271 ( 75%)	196 ( 54%)	162 ( 45%)	149 ( 41%)
Naproxen (N=364)					
Absent	63 ( 17%)	87 ( 24%)	148 ( 41%)	172 ( 47%)	185 ( 51%)
Present	301 ( 83%)	277 ( 76%)	216 ( 59%)	192 ( 53%)	179 ( 49%)
Placebo (N=382)					
Absent	72 ( 19%)	83 ( 22%)	122 ( 32%)	140 ( 37%)	144 ( 38%)
Present	310 ( 81%)	299 ( 78%)	260 ( 68%)	242 ( 63%)	238 ( 62%)
P-Values <sup>1</sup>					
Trexima vs. Placebo			<.001		<.001
Trexima vs. Sumatriptan			0.220		0.004

<sup>1</sup> P-Values are from the Cochran-Mantel-Haenszel test, with pooled investigator site as the strata.

Table 31: Photophobia, 0-4 hrs, Study 302

POZEN, Inc. Study Number MT400-302

Table 14.2.3.1  
 Photophobia 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=364)					
Absent	76 ( 21%)	105 ( 29%)	211 ( 58%)	254 ( 70%)	271 ( 74%)
Present	288 ( 79%)	259 ( 71%)	153 ( 42%)	110 ( 30%)	93 ( 26%)
Sumatriptan (N=361)					
Absent	65 ( 18%)	102 ( 28%)	173 ( 48%)	210 ( 58%)	221 ( 61%)
Present	296 ( 82%)	259 ( 72%)	188 ( 52%)	151 ( 42%)	140 ( 39%)
Naproxen (N=356)					
Absent	69 ( 19%)	100 ( 28%)	166 ( 47%)	189 ( 53%)	202 ( 57%)
Present	287 ( 81%)	256 ( 72%)	190 ( 53%)	167 ( 47%)	154 ( 43%)
Placebo (N=360)					
Absent	74 ( 21%)	89 ( 25%)	131 ( 36%)	131 ( 36%)	137 ( 38%)
Present	286 ( 79%)	271 ( 75%)	229 ( 64%)	229 ( 64%)	223 ( 62%)
P-Values <sup>1</sup>					
Trexima vs. Placebo			<.001		<.001
Trexima vs. Sumatriptan			0.007		<.001

<sup>1</sup> P-Values are from the Cochran-Mantel-Haenszel test, with pooled investigator site as the strata.

- Phonophobia

Trexima was statistically superior to placebo for phonophobia in study 301 (56% phonophobia-free, vs. 34% for placebo)(Table 32), and in study 302 (61% phonophobia-free, vs. 38% for placebo)(Table 33).

Table 32: Phonophobia, 0-4 hrs, Study 301

Treatment Group Symptom	HOURS POST-DOSE				
	0.0	1.0	2.0	3.0	4.0
Table 14.2.4.1 Phonophobia by Time Post-Dose All Subjects in the Intent-to-Treat Population					
Trexima (N=362)					
Absent	69 ( 19%)	115 ( 32%)	204 ( 56%)	239 ( 66%)	259 ( 72%)
Present	293 ( 81%)	247 ( 68%)	158 ( 44%)	123 ( 34%)	103 ( 28%)
Sumatriptan (N=362)					
Absent	76 ( 21%)	111 ( 31%)	188 ( 52%)	219 ( 60%)	224 ( 62%)
Present	286 ( 79%)	251 ( 69%)	174 ( 48%)	143 ( 40%)	138 ( 38%)
Naproxen (N=364)					
Absent	68 ( 19%)	97 ( 27%)	159 ( 44%)	179 ( 49%)	193 ( 53%)
Present	296 ( 81%)	267 ( 73%)	205 ( 56%)	185 ( 51%)	171 ( 47%)
Placebo (N=382)					
Absent	66 ( 17%)	85 ( 22%)	128 ( 34%)	138 ( 36%)	146 ( 38%)
Present	316 ( 83%)	297 ( 78%)	254 ( 66%)	244 ( 64%)	236 ( 62%)
P-Values <sup>1</sup>					
Trexima vs. Placebo			<.001		<.001
Trexima vs. Sumatriptan			0.137		0.003

<sup>1</sup> P-Values are from the Cochran-Mantel-Haenszel test, with pooled investigator site as the strata.

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Table 33: Phonophobia, 0-4 hrs, Study 302

Treatment Group Symptom		HOURS POST-DOSE				
		0.0	1.0	2.0	3.0	4.0
POZEN, Inc. <span style="float: right;">Study Number MT400-302</span>						
Table 14.2.4.1 Phonophobia by Time Post-Dose All Subjects in the Intent-to-Treat Population						
Trexima (N=364)						
Absent		83 ( 23%)	127 ( 35%)	223 ( 61%)	261 ( 72%)	274 ( 75%)
Present		281 ( 77%)	237 ( 65%)	141 ( 39%)	103 ( 28%)	90 ( 25%)
Sumatriptan (N=361)						
Absent		75 ( 21%)	107 ( 30%)	180 ( 50%)	210 ( 58%)	226 ( 63%)
Present		286 ( 79%)	254 ( 70%)	181 ( 50%)	151 ( 42%)	135 ( 37%)
Naproxen (N=356)						
Absent		91 ( 26%)	117 ( 33%)	181 ( 51%)	196 ( 55%)	215 ( 60%)
Present		265 ( 74%)	239 ( 67%)	175 ( 49%)	160 ( 45%)	141 ( 40%)
Placebo (N=360)						
Absent		82 ( 23%)	99 ( 28%)	138 ( 38%)	145 ( 40%)	148 ( 41%)
Present		278 ( 77%)	261 ( 73%)	222 ( 62%)	215 ( 60%)	212 ( 59%)
P-Values <sup>1</sup>						
Trexima vs. Placebo				<.001		<.001
Trexima vs. Sumatriptan				0.002		<.001
<sup>1</sup> P-Values are from the Cochran-Mantel-Haenszel test, with pooled investigator site as the strata.						

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Primary endpoint, 24 hour time point

Trexima claims efficacy as a combination product of sumatriptan and naproxen, and was therefore required to show that the combination is statistically superior to the individual components for at least one clinically meaningful endpoint. The endpoint agreed to with the Division was sustained efficacy against migraine, termed ‘sustained pain-free 2-24 hours.’ (choice of endpoint discussed in section 6.1.2, *General Discussion of Endpoints*). Trexima was not required to show superiority versus its components for associated migraine symptoms, but was expected to be no worse.

- Sustained pain-free 2-24 hours

In both study 301 and 302, Trexima was statistically superior for this endpoint to its components, sumatriptan and naproxen, and to placebo (Table 34). The margin of superiority was clinically significant: patients taking Trexima who were pain free at 2 hours had a ≈25% chance of being pain free through 24 hours, while for sumatriptan (85 mg RT), Naproxen (500 mg), and placebo, this chance was, respectively, ≈15%, ≈10%, and ≈8% (average results from the two studies).

Note that the percentage of patients that were pain free at 24 hours is probably ‘artificially’ low because only those patients pain free at 2 hours were measured for the “pain free between 2 and 24 hour” time point. In actual clinical practice, many patients probably experience long-lasting relief, but with initial onset of relief later than 2 hours, or experience some residual pain, but relief appears adequate, at least insofar as rescue medication is not taken (presumably because it is not subjectively necessary)(see Figure 7: Percent Taking Rescue Medication, All Treatments).

Table 34: Sustained pain-free 2-24 hours, 301, 302

	Trexima	Sumatriptan 85 mg	Naproxen Sodium 500 mg	Placebo
<b>MT400-302</b>	25% <sup>†</sup> (90/364)	16% (59/361)	10% (37/356)	8% (30/360)
<b>MT400-301</b>	23% <sup>‡</sup> (83/362)	14% (51/362)	10% (37/364)	7% (25/382)

<sup>†</sup> p<0.001 versus placebo, sumatriptan and naproxen sodium

<sup>‡</sup> p<0.001 versus placebo and naproxen sodium; p=0.009 versus sumatriptan.

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- Photophobia, phonophobia, nausea-free

For the migraine-associated symptoms of photophobia and phonophobia, Trexima was statistically superior to its components in both study 301 (Table 35) and 302 (Table 36). For nausea, Trexima was statistically superior only in study 302, while in study 301, Trexima was numerically but not statistically superior (48% sustained nausea-free for Trexima, versus 44%, 41%, and 28% for sumatriptan, naproxen, and placebo, respectively).

Table 35: Associated symptoms, sustained-relief, Study 301

Treatment Group Symptom	Sustained Photophobia-Free	Sustained Phonophobia-Free	Sustained Nausea-Free
Trexima (N=362)			
No	228 ( 63%)	213 ( 59%)	188 ( 52%)
Yes	134 ( 37%)	149 ( 41%)	174 ( 48%)
Sumatriptan (N=362)			
No	252 ( 70%)	243 ( 67%)	203 ( 56%)
Yes	110 ( 30%)	119 ( 33%)	159 ( 44%)
Naproxen (N=364)			
No	265 ( 73%)	259 ( 71%)	214 ( 59%)
Yes	99 ( 27%)	105 ( 29%)	150 ( 41%)
Placebo (N=382)			
No	322 ( 84%)	314 ( 82%)	275 ( 72%)
Yes	60 ( 16%)	68 ( 18%)	107 ( 28%)
<b>P-Values<sup>1</sup></b>			
Trexima vs. Placebo	<.001	<.001	<.001
Trexima vs. Sumatriptan	0.050	0.014	0.203

<sup>1</sup> P-Values are from the Cochran-Mantel-Haenszel test, with pooled investigator site as the strata.

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Table 36: Associated symptoms, sustained -relief, Study 302

Table 14.2.8  
 Sustained Symptom-Free During 2-24 Hours Post-Dose  
 All Subjects in the Intent-to-Treat Population

Treatment Group Symptom	Sustained Photophobia-Free	Sustained Phonophobia-Free	Sustained Nausea-Free
Trexima (N=364)			
No	196 ( 54%)	184 ( 51%)	160 ( 44%)
Yes	168 ( 46%)	180 ( 49%)	204 ( 56%)
Sumatriptan (N=361)			
No	235 ( 65%)	232 ( 64%)	201 ( 56%)
Yes	126 ( 35%)	129 ( 36%)	160 ( 44%)
Naproxen (N=356)			
No	246 ( 69%)	228 ( 64%)	199 ( 56%)
Yes	110 ( 31%)	128 ( 36%)	157 ( 44%)
Placebo (N=360)			
No	285 ( 79%)	283 ( 79%)	243 ( 68%)
Yes	75 ( 21%)	77 ( 21%)	117 ( 33%)
P-Values <sup>1</sup>			
Trexima vs. Placebo	< .001	< .001	< .001
Trexima vs. Sumatriptan	0.002	< .001	0.002

<sup>1</sup> P-Values are from the Cochran-Mantel-Haenszel test, with pooled investigator site as the strata.

Other analysis supportive of efficacy

*Remaining pain free between 2-24 hours*

The endpoint 'sustained pain free at 24 hours' for this study was designed with the unintended effect that the number of patients counted at 24 hours is partially dependent on the percentage of patients with pain relief at 2 hours. In other words, the higher the number of subjects that are pain free at 2 hours, the higher the number that are likely to be pain free at 24 hours, since the number at 24 hours depends, in part, on the 'gate-keeping' function of 'pain relief at 2 hours.' A scenario could therefore be envisioned in which a) the combination drug is more effective than its components at 2 hours but, b) the chance of relapse between 2 and 24 is actually *higher* for the combined drugs than for the individual components, but that c) the combined drug still has a higher number of patients with pain relief at 24 hours. I therefore also examined the *proportion* of patients pain free at 2 hours who remain pain free at 24. For Trexima, I calculated the chance of remaining pain free at 24 hours, given pain relief at 2 hours: the proportion is higher for Trexima (38%) than for sumatriptan (28-29%) or naproxen (23%), indicating that symptom relief by Trexima is not weighted to early time points (Table 37).

Table 37: Probability of remaining pain-free at 24 hrs. given pain free at 2 hrs.

Study number	Trexima	Sumatriptan	Naproxen
301	23/57 = <b>38%</b>	14/50 = <b>28%</b>	10/43 = <b>23%</b>
302	25/65 = <b>38%</b>	16/55 = <b>29%</b>	10/44 = <b>23%</b>

Probability of remaining pain-free at 24 hrs. given pain free at 2 hrs is calculated from the percentage of patients positive for sustained pain free at 2-24 hours divided by percentage of patients with pain score of 0 or 1 at 2 hours

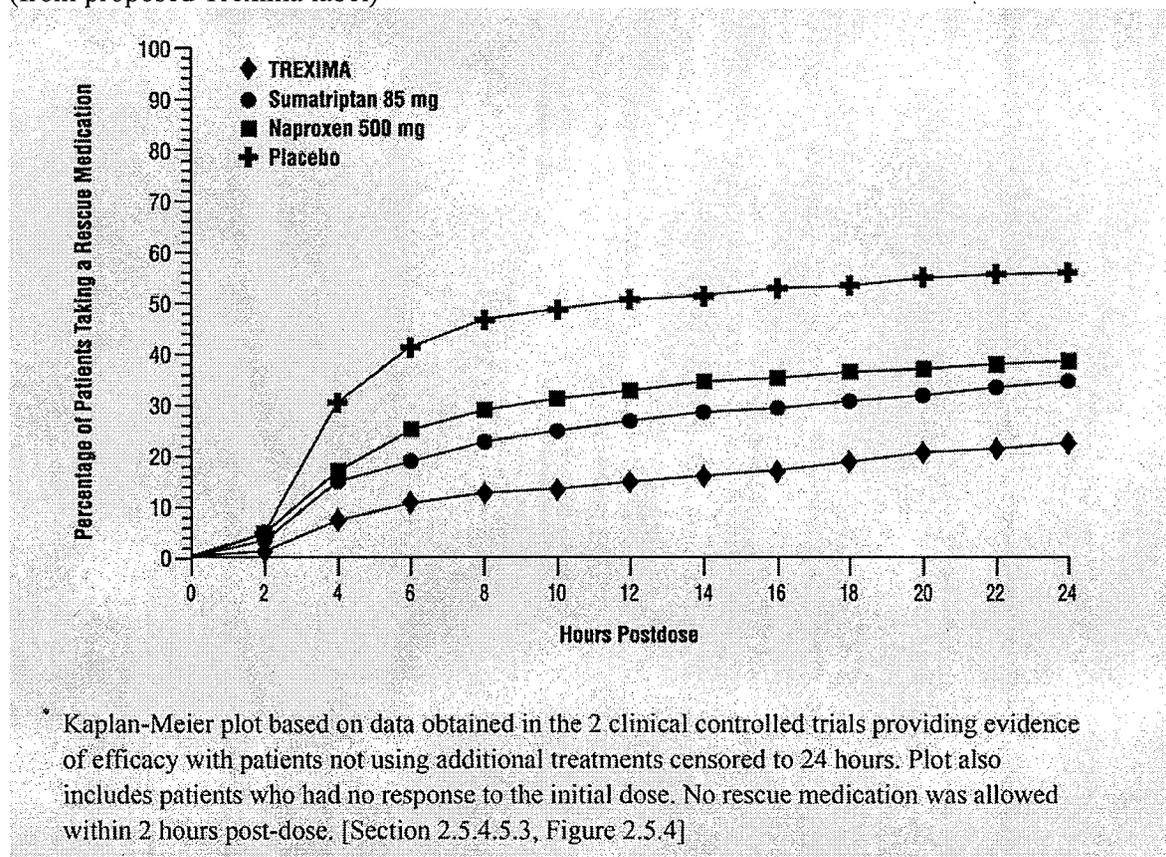
- Rescue medication use through 24 hours

The proposed label includes a figure showing percentage of study patients who used rescue medication for symptoms inadequately treated by the first dose of medication (Figure 7). This endpoint was included as a secondary outcome in the SAP, but did not reach statistical significance in the step-down procedure based on a preceding outcome that did not reach statistical significance. Despite this fact, I believe the figure can be included in labeling. The primary endpoint for approval of Trexima under the combination rule was “sustained pain free, 2-24 hours.” This outcome understates numerically the apparent efficacy of the medication, because only those patients who are pain free at 2 hours are counted at the later 24 hour time point. In fact, a higher percentage of patients are arguably treated adequately over 24 hours, as documented by the high percentage of patients who do not take rescue medication through 24 hours. This majority of patients is composed of those who either had complete pain relief but after the 2 hour cutoff point, or had incomplete but still clinically beneficial pain relief (so as not to take rescue medication) across time points. Thus, “sustained pain free, 2-24 hours,” while a useful and valid study endpoint, does not fully describe the clinical efficacy of the medication. Arguably, too, one of the most important characteristics of migraine therapy for patients is the likelihood of requiring rescue medication, such that it should be included in labeling despite the relative lack of statistical support.

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Figure 7: Percent Taking Rescue Medication, All Treatments

(from proposed Trexima label)



### Secondary endpoints

Secondary endpoints were analyzed based on a hierarchical stepdown procedure designed to preserve study type I error. Below, I examine each secondary endpoint both for statistical significance and for the degree of support it provides for the primary outcomes.

#### *1. Pain-free at 2 hours for Trexima vs. placebo*

This outcome was demonstrated statistically (Table 27). The Division required Trexima to be superior to placebo at 2 hours, so this endpoint is part of a primary outcome variable.

#### *2. Sustained pain relief for Trexima vs. placebo*

This outcome was demonstrated statistically (Table 34). The outcome differs only slightly from a component of the primary outcome variable, 'sustained pain-free 2-24 hrs' for Trexima vs. placebo. Pain relief is defined in this secondary endpoint as moderate or severe pain decreasing to mild or no pain.

*3. Sustained pain relief for Trexima vs. sumatriptan*

This was demonstrated in both pivotal studies (Table 38, Table 39). This secondary outcome is very similar to the primary outcome, sustained pain-free 2-24 hours versus Trexima's components (Table 34).

Table 38: Sustained Pain Relief at 24 hours, MT400-301

	<b>Trexima</b> N = 362	<b>Sumatriptan</b> N = 362	<b>Placebo</b> N = 382
Sustained Pain Relief – n (%)	158 (44)	121 (33)	64 (17)
p-value vs. Trexima	--	0.002	<0.001

Table 39: Sustained Pain Relief at 24 hours, MT400-302

	<b>Trexima</b> N = 364	<b>Sumatriptan</b> N = 361	<b>Placebo</b> N = 360
Sustained Pain Relief – n (%)	174 (48)	127 (35)	64 (18)
p-value vs. Trexima	--	<0.001	<0.001

*4. Sustained symptom-free (photophobia-free, phonophobia-free, or nausea-free) for Trexima vs. sumatriptan*

This was achieved in one, but not in two studies, and thus is a failed secondary endpoint. All 3 components (photophobia, phonophobia, and nausea) were achieved for study 302, but in study 301, sustained nausea-free was 48% for Trexima vs. 44% percent for sumatriptan (p=.203).

The secondary endpoints below I do not consider statistically significant based on failure of the preceding endpoint to reach significance at 'p = 0.05.' However, I have addressed them as individual endpoints, at p = 0.05 uncorrected for multiplicity.

*5. Use of rescue medication for Trexima vs. sumatriptan*

This was a statistically significant endpoint (uncorrected for multiplicity). I believe this outcome is important for communicating the effectiveness of Trexima to the public, as discussed above in this section under "Other analysis supportive of efficacy".

6. *Time to rescue for Trexima vs. sumatriptan*

Pozen claims this as a statistically significant result (Table 40, Table 41), but does not explain adequately how it was derived. It appears to be very similar to secondary endpoint #5, use of rescue medication for Trexima vs. sumatriptan. I find Figure 7 adequate to describe 'time to rescue.'

Table 40: Time to rescue medication use, MT400-301

POZEN, Inc.		Table 14.2.10 Use of Rescue Medication and Time to Rescue All Subjects in the Intent-to-Treat Population				Study Number MT400-301
	Trexima (N=362)	Sumatriptan (N=362)	Naproxen (N=364)	Placebo (N=362)	P-Value <sup>a</sup> (Trexima vs. Sumatriptan)	
<b>Used Rescue Medication</b>						
No	279 ( 77%)	225 ( 62%)	221 ( 61%)	159 ( 42%)	<0.001	
Yes	83 ( 23%)	137 ( 38%)	143 ( 39%)	223 ( 58%)		
<b>Time to Rescue - All Subjects</b>						
Median <sup>b</sup> (Hours)	N/A	N/A	N/A	10.0	<0.001	
95% C.I.				( 7.0, 19.0)		
<b>Time to Rescue - Subjects Who Rescued</b>						
N	83	137	143	223		
Mean (std)	9.4 ( 7.1)	8.2 ( 6.5)	7.0 ( 5.3)	6.2 ( 4.8)		
Median	6.0	5.0	5.0	4.0		
Min - Max	1.5 - 24.0	2.0 - 24.0	1.5 - 24.0	1.5 - 23.0		

<sup>a</sup> P-Value for Use of Rescue is from the Cochran-Mantel-Haenszel test, with pooled investigator site as the Strata. P-Value for Time to Rescue is from the Log-Rank Test.

<sup>b</sup> The estimated median rescue time and its Confidence Interval were from the Kaplan-Meier method. Subjects who did not take any rescue medication were censored at 24 hours.

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Table 41: Time to rescue medication use, MT400-302

POZEN, Inc.		Table 14.2.10 Use of Rescue Medication and Time to Rescue All Subjects in the Intent-to-Treat Population				Study Number MT400-302
	Trexima (N=364)	Sumatriptan (N=361)	Naproxen (N=356)	Placebo (N=360)	P-Value <sup>1</sup> (Trexima vs. Sumatriptan)	
<b>Used Rescue Medication</b>						
No	283 ( 78%)	246 ( 68%)	221 ( 62%)	168 ( 47%)	0.003	
Yes	81 ( 22%)	115 ( 32%)	135 ( 38%)	192 ( 53%)		
<b>Time to Rescue - All Subjects</b>						
Median <sup>2</sup> (Hours)	N/A	N/A	N/A	15.0	0.002	
95% C.I.				( 8.0, N/A )		
<b>Time to Rescue - Subjects Who Rescued</b>						
N	81	115	135	192		
Mean (std)	10.0 ( 6.6)	8.1 ( 6.2)	6.8 ( 5.0)	5.5 ( 4.0)		
Median	8.0	6.0	5.0	4.0		
Min - Max	2.0 - 23.0	1.0 - 24.0	2.0 - 23.0	2.0 - 21.0		
<sup>1</sup> P-Value for Use of Rescue is from the Cochran-Mantel-Haenszel test, with pooled investigator site as the Strata. P-Value for Time to Rescue is from the Log-Rank Test.						
<sup>2</sup> The estimated median rescue time and its Confidence Interval were from the Kaplan-Meier method. Subjects who did not take any rescue medication were censored at 24 hours.						

7. *Pain-relief at 4 hours for Trexima vs. sumatriptan*

This was statistically significant in both study MT400-301 and MT100-302 (uncorrected for multiplicity). Four hours is a later time point than acute migraine studies generally examine, and I do not believe it adds significantly to study findings given that at 2 hours Trexima was shown to be superior to sumatriptan alone for pain-free.

8. *Symptom-free (photophobia-free, phonophobia-free, or nausea-free) at 4 hours for Trexima vs. sumatriptan*

This was not a statistically significant result in two studies, based on failure to show 'nausea-free' at 4 hours in study MT400-301 (p-value 0.140) (Table 42). It was statistically significant in study MT400-302 (Table 43). I find this endpoint provides little additional information regarding efficacy.

Table 42: Symptom-free, 4 hrs, MT400-301 (ITT Population)

	Trexima N = 362	Sumatriptan N = 362	p-Value
<b>4 Hours</b>			
Pain Relief – n (%)	259 (72)	222 (61)	0.002
Photophobia-free – n (%)	248 (69)	213 (59)	0.004
Phonophobia-free – n (%)	259 (72)	224 (62)	0.003
Nausea-free – n (%)	266 (73)	250 (69)	<i>0.140</i>

Table 43: Symptom-free, 4 hrs, MT400-302 (ITT Population)

	Trexima N = 364	Sumatriptan N = 361	p-Value
<b>4 Hours</b>			
Pain Relief – n (%)	285 (78)	240 (66)	< 0.001
Photophobia-free – n (%)	271 (74)	221 (61)	< 0.001
Phonophobia-free – n (%)	274 (75)	226 (63)	< 0.001
Nausea-free – n (%)	295 (81)	257 (71)	0.002

9. *Pain relief at 2 hours Trexima vs. sumatriptan*

This was statistically significant in both study MT400-301 and MT100-302 (uncorrected for multiplicity). Endpoints using pain *relief* and pain *free* are closely correlated, such that there is little extra information contributed.

10. *Symptom-free (photophobia-free, phonophobia-free, or nausea-free) at 2 hours for Trexima vs. sumatriptan*

This was not shown in either study, due to multiple non-significant p-values (nausea in both studies, and additionally photophobia-free and phonophobia-free in study MT400-301).

**6.1.5 Clinical Microbiology**

Not applicable.

**6.1.6 Efficacy Conclusions**

Based on efficacy, Trexima is approvable under the Combination Drug Rule.

## 7 INTEGRATED REVIEW OF SAFETY

### 7.1 Methods and Findings

#### *Study Safety Monitoring*

Throughout Trexima development, critical cardiovascular safety data was not collected.

For the two initial Phase 1 studies (MT400-101 and MT400-103), the following assessments were performed at screening and following the final dose of study medication [Note: no assessments were performed proximate to dosing]:

- medical history review (screening only)
- physical examination
- ECG
- vital signs (heart rate and blood pressure)
- clinical laboratory tests (hematology and chemistry)
- urine pregnancy test
- adverse event assessment (assessed throughout all phases of the study).

The other three Phase 1 studies had these safety assessments performed at screening only, with adverse events assessed throughout the study.

In the proof of concept single-dose study (MT400-204) the subjects had the following at screening and follow up:

- review of medical history
- physical examination
- vital signs (heart rate and blood pressure)
- clinical laboratory tests (hematology and chemistry)
- urine pregnancy test
- Adverse events were assessed following administration of study medication through the follow-up visit.

In the two phase 3 pivotal studies (MT400-301 and MT400-302), the following assessments were performed at screening and, up to several days following a single dose of study medication, at the follow-up visit:

- Review of medical history (at screening only)
- Physical examination
- ECG (post-dosing only if chest symptoms suggestive of cardiac abnormality occurred post dosing).
- vital signs (heart rate and blood pressure)
- clinical laboratory tests (hematology and chemistry)
- urine pregnancy test
- adverse events were reported through the follow-up visit

During review of the application the sponsor was asked by the Agency:

“We are interested in the cardiovascular effects of Trexima near peak drug levels. Where in the NDA submission is this addressed? Can you summarize the data you have on this issue? Do you have any additional cardiovascular safety data collected while Trexima’s components were present in circulation?”

The sponsor responded:

“There are no additional data other than that presented in the original NDA and the 120-Day safety update submitted on December 5, 2005 (Amendment 005).

Five Phase 1 studies (MT400-101, MT400-102, MT400-103, MT400-104, and MT400-105) were conducted as pharmacokinetic studies and while these studies did not include direct evaluations of possible cardiovascular effects, subjects remained under observation in clinic for at least 24 hours after dosing. The respective study reports identified all adverse events with onset during these post-dosing periods. The data, from 140 subjects receiving doses of Trexima, did not suggest a risk of cardiovascular effects during the 24 hours after dosing corresponding to the times of peak levels of the components (for convenience, tables from the study reports are presented in Appendix 1). Further, there is no evidence of increased incidence of cardiovascular events in subjects who received Trexima when compared to subjects who received comparators.

The long-term safety study (MT400-303) included a presentation of all reported adverse events with onset within 24 hours of dosing with Trexima. This 24-hour period would include the times of the peak blood levels of both components of Trexima. The profile of adverse events in these subjects (Please see Tables 14.2.7.2.1, 14.2.7.2.2 and 14.2.7.2.3 from the final report of the long term safety study MT400-303 submitted December 5, 2005, Amendment #003, as part of the 120-Day Safety Update) was not remarkably different from subjects who received either Trexima or monotherapy with sumatriptan or naproxen in the controlled trials.

Trexima is a formulation containing two drugs that are approved for marketing and have established pharmacokinetic (PK) and safety profiles. The results of the PK studies within this NDA [filed under the provisions of 505(b)(2)] are consistent with the previously demonstrated pharmacokinetic and cardiovascular safety data for both sumatriptan and naproxen.”

The safety assessments for the long term, open label safety study (MT400-303) are listed in Table 44 and Table 45. Note that vital signs are measured only at screening.

Table 44: Safety Assessments, Long-term safety study (MT400-303)

	Screening	1-Month Follow-up	2-Month Follow-up	3-Month Follow-up	6-Month Follow-up	9-Month Follow-up	12-Month Follow-up
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Informed Consent	X						
Diagnosis Confirmation	X						
Medical History	X						
Physical Examination	X				X		X
12-Lead ECG <sup>1</sup>	X						
Vital Signs	X						
Clinical Lab Tests	X				X		X
Pregnancy test (females of childbearing potential)	X	X	X	X	X	X	X
Study Drug Dispensed /Drug Accountability	X	X	X	X <sup>2</sup>	X <sup>3</sup>	X	X <sup>4</sup>
Satisfaction & Quality of Life Questionnaires <sup>5</sup>	X			X			X
Adverse Event Assessment		X	X	X	X	X	X
Return Diary Card		X	X	X	X	X	X
Record Concurrent Medications	X	X	X	X	X	X	X

<sup>1</sup> If any chest symptoms suggestive of cardiac abnormality occurred, an ECG was to be performed at any time during the study.  
<sup>2</sup> Only subjects who had treated at least 6 migraines with study medication in the previous 3 months could continue participation in the study.  
<sup>3</sup> Only subjects who had treated at least 12 migraines with study medication in the previous 6 months could continue participation in the study.  
<sup>4</sup> Drug Accountability only.  
<sup>5</sup> If the subject withdrew from the study prior to 3 or 12 months, the questionnaires were to be completed at the final visit.

<sup>1</sup>An ECG was required only if “chest symptoms suggestive of cardiac abnormality occurred post-dosing.”

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Table 45: Laboratory Tests, Long-term Safety Study (MT400-303)

Hematology	Blood Chemistry
Hemoglobin	Sodium
Hematocrit	Potassium
Platelet Count	Calcium
Red Blood Cell (RBC) Count	Chloride
RBC Morphology	Phosphorous (inorganic)
Mean Corpuscular Volume (MCV)	Bicarbonate
Mean Corpuscular Hemoglobin (MCH)	Glucose
Mean Corpuscular Hemoglobin Concentration (MCHC)	Total Protein
White Blood Cell (WBC) Count	Albumin
Differential, including:	Creatine Kinase (CK)
Neutrophils	Magnesium
Lymphocytes	Triglycerides
Basophils	Globulin
Monocytes	Total Cholesterol
Eosinophils	Blood Urea Nitrogen (BUN)
Bands	Creatinine
	Uric Acid
	Total Bilirubin
	Alkaline Phosphatase
	Aspartate Aminotransferase (AST)
	Alanine Aminotransferase (ALT)

### 7.1.1 Deaths

#### *Deaths, Controlled Trials*

There was a single death due to a gunshot wound to the chest from an assault that occurred in a subject in the Trexima arm of the study.

- Subject 7235 / Site 351 / Fatal Gunshot Wound / Treatment Group: Trexima / ██████████

28-year old male

Following a domestic altercation, the subject received a gunshot wound to the chest from a passing automobile. He died on that date at a local hospital. Efforts to determine if he had administered study drug prior to his death were unsuccessful. I find this death unrelated to Trexima.

*Deaths, Open Label Safety Study*

None

### **7.1.2 Other Serious Adverse Events**

***Serious and severe adverse events, Controlled Trials***

I have examined both severe adverse events (immediately following) and serious adverse events. By separating severe adverse events from those of mild or moderate intensity, I believe specific attention can be given to those that are potentially 'close to' serious adverse events. Given that both pivotal studies involved only a single dose of study drug, few serious adverse events related to drug were, or could have been detected.

- **MT400-204 Severe Adverse Events**

There were 15 severe adverse events, and no serious adverse events in the phase II controlled trial MT400-204 (Table 46). This trial tested a combination of a lower dose of sumatriptan (50 mg non-RT) with sumatriptan than used in the final Trexima formulation (85 mg-RT). There was no discernable pattern of severe adverse events among treatment arms, but of note the single case of 'chest pain' was in the MT400/combination arm. This event was also associated with increased blood pressure (summarized below) (There was an additional adverse associated with increased blood pressure in a PK study, which is described under Section 7.13, *Dropouts and Other Serious Adverse Events*).

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Table 46: Severe Adverse Events, MT400-204

POZEN, Inc.		Study Number MT400-204			
Table 15 Severe Adverse Events By Body System and Preferred Term					
	MT400 (N=251)	Sumatriptan (N=229)	Naproxen Sodium (N=250)	Placebo (N=242)	
Subject Had at Least One Severe Adverse Event					
No	246 (98%)	226 (99%)	248 (99%)	237 (98%)	
Yes	5 (2%)	3 (1%)	2 (1%)	5 (2%)	
General disorders and admin. site conditions					
Chest pain	1 (<1%)	0	0	0	
Fatigue	1 (<1%)	0	0	0	
Feeling jittery	1 (<1%)	0	0	0	
Eye disorders					
Eye pain	1 (<1%)	0	0	0	
Photophobia	0	0	0	1 (<1%)	
Investigations					
Blood pressure increased	1 (<1%)	0	0	0	
Nervous system disorders					
Tension headaches	1 (<1%)	1 (<1%)	0	1 (<1%)	
Dizziness (excl vertigo)	0	0	0	1 (<1%)	
Somnolence	0	1 (<1%)	0	0	
Ear and labyrinth disorders					
Tinnitus	0	0	1 (<1%)	0	
Gastrointestinal disorders					
Diarrhoea NOS	0	2 (1%)	1 (<1%)	3 (1%)	
Dyspepsia	0	0	0	1 (<1%)	
Nausea	0	1 (<1%)	1 (<1%)	0	
Nausea aggravated	0	1 (<1%)	0	2 (1%)	
Vomiting aggravated	0	0	0	1 (<1%)	
TREATMENT GROUPS: MT400= 50 mg sumatriptan plus 500 mg naproxen sodium. Sumatriptan= 50 mg sumatriptan. Naproxen Sodium= 500 mg naproxen sodium.					
Note: Adverse Events that occurred before dosing date were excluded.					

*Severe Adverse Events of Interest, MT400-204*

Subject 179/1562 / Chest pain, blood pressure increased / Treatment group: MT-400

[Reviewer's assessment: likely drug-related adverse event.]

25-year old female

One hour after dosing of MTR-400, the subject experienced chest heaviness/pressure, for 55 minutes. Her blood pressure was measured at her workplace by ambulance service, and was elevated for 135 minutes post-dose, with maximum of 154/100. No treatment was given.

Significant medical history:

Hypertension treated with Lotrel (amlodipine/benazepril)

Screening blood pressure: 136/86

Concurrent medications included: Celexa, Lotrel

- **MT400-301 and MT400-302**

***Severe Adverse Events, studies 301 and 302***

For studies 301 and 302 combined, there was a small excess of severe adverse events in the Trexima arms compared to the other arms (2.6% for Trexima vs. 1.9%, 0.8%, and 1.3% for sumatriptan, naproxen, and placebo, respectively (

Table 47). Although the numbers are small, I think differences between groups are potentially informative, particularly for Trexima vs. sumatriptan. Close attention is especially warranted for differences in 'cardiac disorders' between arms, with 5 for Trexima and 1 for sumatriptan, of which 'chest pain/discomfort' accounted for 4 for Trexima and none for sumatriptan (in study MT400-204, 'chest pain' occurred once in the combination drug arm, and not in other arms).

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Table 47: Severe adverse events, combined MT400-301 and MT400-302

POZEN, Inc.		Study Number MT400-ISS			
Table 2.7.4.7.6.3 Severe 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	19 ( 2.6%)	14 ( 1.9%)	6 ( 0.8%)	10 ( 1.3%)	
Gastrointestinal disorders	9 ( 1.2%)	7 ( 1.0%)	3 ( 0.4%)	5 ( 0.7%)	
Nausea	4 ( 0.5%)	2 ( 0.3%)	2 ( 0.3%)	2 ( 0.3%)	
Dry mouth	2 ( 0.3%)	1 ( 0.1%)	0	0	
Diarrhoea	1 ( 0.1%)	0	0	0	
Dyspepsia	1 ( 0.1%)	2 ( 0.3%)	0	0	
Vomiting	1 ( 0.1%)	0	1 ( 0.1%)	3 ( 0.4%)	
Abdominal pain	0	1 ( 0.1%)	0	0	
Abdominal pain upper	0	1 ( 0.1%)	0	0	
Nervous system disorders	6 ( 0.8%)	2 ( 0.3%)	2 ( 0.3%)	1 ( 0.1%)	
Somnolence	2 ( 0.3%)	0	2 ( 0.3%)	0	
Burning sensation	1 ( 0.1%)	1 ( 0.1%)	0	0	
Dizziness	1 ( 0.1%)	1 ( 0.1%)	0	0	
Mental impairment	1 ( 0.1%)	0	0	0	
Migraine	1 ( 0.1%)	0	0	1 ( 0.1%)	
Cardiac disorders	5 ( 0.7%)	1 ( 0.1%)	0	1 ( 0.1%)	
Chest discomfort	3 ( 0.4%)	0	0	0	
Chest pain	1 ( 0.1%)	0	0	1 ( 0.1%)	
Palpitations	1 ( 0.1%)	1 ( 0.1%)	0	1 ( 0.1%)	
General disorders	4 ( 0.5%)	0	0	1 ( 0.1%)	
Feeling hot	2 ( 0.3%)	0	0	0	
Fatigue	1 ( 0.1%)	0	0	1 ( 0.1%)	
Lethargy	1 ( 0.1%)	0	0	0	
Musculoskeletal and connective tissue	2 ( 0.3%)	1 ( 0.1%)	0	0	
Musculoskeletal discomfort	1 ( 0.1%)	0	0	0	
Musculoskeletal stiffness	1 ( 0.1%)	0	0	0	
Sensation of heaviness	0	1 ( 0.1%)	0	0	
Psychiatric disorders	1 ( 0.1%)	0	0	0	
Hyperventilation	1 ( 0.1%)	0	0	0	
Eye disorders	0	0	0	2 ( 0.3%)	
Eye pain	0	0	0	1 ( 0.1%)	
Eye pruritus	0	0	0	1 ( 0.1%)	
Lacrimation increased	0	0	0	1 ( 0.1%)	
Infections and infestations	0	1 ( 0.1%)	0	0	
Sinusitis	0	1 ( 0.1%)	0	0	
Pregnancy, puerperium and perinatal conditions	0	1 ( 0.1%)	0	0	
Ectopic pregnancy	0	1 ( 0.1%)	0	0	
Respiratory, thoracic and mediastinal	0	1 ( 0.1%)	0	0	
Dyspnoea	0	1 ( 0.1%)	0	0	
Skin and subcutaneous tissue disorders	0	1 ( 0.1%)	0	0	
Pruritus generalised	0	1 ( 0.1%)	0	0	
Rash	0	1 ( 0.1%)	0	0	
Vascular disorders	0	0	1 ( 0.1%)	0	
Flushing	0	0	1 ( 0.1%)	0	

**Serious Adverse Events, studies 301 and 302**

Six serious adverse events occurred in studies 301 and 302 combined, 2 each in the Trexima, sumatriptan, and naproxen arms (Table 48). The only cardiovascular event was in the sumatriptan arm.

Table 48: Serious Adverse Events, MT400-301 and 302

	Trexima (N=857)	Sumatriptan (N=849)	Naproxen (N=853)	Placebo (N=856)
Subject Had at Least One Serious Adverse Event	2 ( 0.2%)	2 ( 0.2%)	2 ( 0.2%)	0
Injury, poisoning and procedural complications	2 ( 0.2%)	0	0	0
Ankle fracture	1 ( 0.1%)	0	0	0
Gun shot wound	1 ( 0.1%)	0	0	0
Cardiac disorders	0	1 ( 0.1%)	0	0
Palpitations	0	1 ( 0.1%)	0	0
Infections and infestations	0	0	1 ( 0.1%)	0
Viral infection	0	0	1 ( 0.1%)	0
Metabolism and nutrition disorders	0	0	1 ( 0.1%)	0
Dehydration	0	0	1 ( 0.1%)	0
Neoplasms benign, malignant and unspecified	0	0	1 ( 0.1%)	0
Lung neoplasm malignant	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
Renal and urinary disorders	0	0	1 ( 0.1%)	0
Renal insufficiency	0	0	1 ( 0.1%)	0

NOTE: Gun shot wound, Viral infection, Dehydration, Renal insufficiency, Lung neoplasm and Ankle fracture occurred prior to study drug dosing.

- Subject 6761 / Site 339 / Heart Palpitations resulting in hospitalization / Treatment Group: **Sumatriptan**

[Reviewer’s assessment: likely drug-related adverse event.]

58-year old female

After administration of study drug, the subject experienced heart palpitations and was seen at a hospital and admitted. She received treatment with Ativan, aspirin and nitroglycerin in the hospital. In the opinion of the Principal Investigator, the serious adverse event of heart palpitations was possibly related to study drug. The subject refused to allow access to hospital records to further investigate details of this event.

Significant medical history:

- Type 2 diabetes
- Smoking (three cigarettes per day since 1966)
- BMI 35.0
- Hypercholesterolemia (total cholesterol 302 mg/dL) and hypertriglyceridemia (triglycerides 406 mg/dL).

The screening ECG was interpreted as showing non-specific T-wave flattening anteriorly of no clinically significance.

Concurrent medications included Klonopin, Effexor, Darvocet, vitamins and Glucophage.

*Serious Adverse Events, Open Label Safety Study MT400-303*

Fourteen subjects (2.5% of total) reported a total of 20 separate serious adverse events in the long-term open label safety study of Trexima.

Table 49: Serious Adverse Events, MT400-303 (Open label safety study)

(From Table 2.7.64, Safety Update)

Type of Event	Overall Safety Population N = 565 n (%)	6-month Completers N = 414 n (%)	12-month Completers N = 362 n (%)
<b>Subjects With At Least One Serious Adverse Event</b>	14 (1.8)	6 (1.4)	4 (1.1)
<b>Infections and Infestations</b>			
Any Event	5 (0.9)	3 (0.7)	1 (0.3)
Kidney infection	2 (0.4)	2 (0.5)	1 (0.3)
Cellulitis <sup>1</sup>	1 (0.2)	0	0
Sepsis	1 (0.2)	1 (0.2)	0
Staphylococcal infection	1 (0.2)	0	0
Viral myocarditis	1 (0.2)	1 (0.2)	0
<b>Cardiac Disorders</b>			
Any Event	3 (0.5)	1 (0.2)	0
Acute coronary syndrome	2 (0.4)	0	0
Cardiac failure congestive	1 (0.2)	1 (0.2)	0
Chest pain	1 (0.2)	0	0
Right ventricular failure	1 (0.2)	1 (0.2)	0
<b>Injury, Poisoning and Procedure Complications</b>			
Any Event	2 (0.4)	1 (0.2)	1 (0.3)
Ankle fracture	1 (0.2)	0	1 (0.3)
Hip fracture	1 (0.2)	1 (0.2)	0
<b>Neoplasms benign, malignant and unspecified</b>			
Any Event	1 (0.2)	0	0
Breast cancer	1 (0.2)	0	0

Uterine leiomyoma	1 (0.2)	1 (0.2)	0
<b>Renal and urinary disorders</b>			
Any Event	2 (0.4)	1 (0.2)	1 (0.3)
Renal insufficiency	1 (0.2)	1 (0.2)	0
Urinary incontinence	1 (0.2)	0	1 (0.3)
<b>Hepatobiliary Disorders</b>			
Any Event	1 (0.2)	1 (0.2)	0
Biliary colic	1 (0.2)	1 (0.2)	0

<b>Reproductive system and breast disorder</b>			
Any event	1 (0.2)	0	1 (0.3)
Ovarian Cyst	1 (0.2)	0	1 (0.3)
<b>Respiratory, thoracic and mediastinal</b>			
Any Event	1 (0.2)	1 (0.2)	0
Pleurisy	1 (0.2)	1 (0.2)	0

Three of these subjects had serious cardiovascular adverse events. Two of these were judged by the investigator not related to treatment with Trexima (subject 296/2129, acute coronary syndrome; subject 100/2415, congestive heart failure, renal failure, right ventricular insufficiency, viral myocarditis, viral septicemia). The third subject (subject 030/2143) experienced acute coronary syndrome judged probably related to use of study drug by the principal investigator, due to the proximity of use of study drug. This 47 year-old premenopausal female was found on angiography to have significant single-vessel coronary artery disease, and had risk factors for coronary artery disease of obesity, family history of cardiovascular disease and hypercholesterolemia (cases discussed immediately below).

***SAE's possibly related to Trexima, safety study MT400-303:***

- ***Subject 2143 / Site 030 / acute coronary syndrome***

[Reviewer's assessment: Probably drug-related exacerbation of underlying cardiovascular disease. This case was judged by the investigator to be related to Trexima.]

47-year old female

During the course of her study participation, the subject treated 39 migraine headaches (54% with 2 tablets of study drug); an average of six headaches per month. Concurrently, she received, Excedrin migraine, ranitidine, Elavil, vitamins and a sleep-aid (OTC). Imitrex is listed as a concomitant medication in the ISS narrative, but in the CRF is noted as a medication the patient used for migraine before the study. During the study, Ultracet and Tylenol were used as

migraine rescue medications. The subject received the first dose of open-label study drug on August 2, 2004 and the last dose on [REDACTED]

Approximately two hours after taking study drug on [REDACTED] the subject experienced chest discomfort and some shortness of breath. She presented to the emergency department and was given nitroglycerin, which provided some relief. An electrocardiogram showed ST-T wave changes in the lateral precordium. Troponin and CK levels were normal in the emergency room. Based on the subject's age and family history, the subject was admitted to the hospital for further evaluation. A cardiac catheterization, performed [REDACTED] showed a moderate dilation of the left ventricle with moderate mitral regurgitation, severe hypokinesis of the antero-apical wall of the left ventricle and a calculated ejection fraction of 27 percent. The left anterior descending coronary artery had a concentric discrete 70% narrowing of the ostium as it arose from the left main coronary artery. There was a post-stenotic filling defect suggestive of a thrombus. No significant disease was present in either the left main coronary artery or the right coronary artery. On [REDACTED] the subject underwent coronary artery bypass grafting surgery including the left internal mammary artery to left anterior descending artery. The subject was discharged from the hospital on [REDACTED] and treated with carvedilol, furosemide, and lisinopril for hypertension, aspirin for cardiac prophylaxis, potassium, Zocor for hypercholesterolemia and Percocet for postoperative pain.

Medical History:

The subject was a nonsmoker and reported that her father died of a myocardial infarction in his 50s.

She had a history of tubal ligation, tension headaches, sinus headaches, seasonal allergies, obesity, mild rosacea, mild depression, insomnia, acid reflux, and two cesarean sections, BMI 35.7

Allergic to penicillin, codeine, erythromycin and clindamycin

At screening, her physical examination and electrocardiogram were normal. Screening laboratory results revealed cholesterol of 200mg/dL and triglycerides of 386 mg/dL.

• *Subject 2129 / Site 296 /acute coronary syndrome, hypertension*

[Reviewer's assessment: Possibly related to Trexima. The event was judged by the study investigator not to be related to Trexima.]

44 year old female

At screening she was found to have sitting blood pressure of 110/82. During the study she treated six migraine attacks with a total of seven doses of Trexima between July 13, 2004 and August 20, 2004. Her last dose of Trexima before onset of the adverse events was on August 20, 2004 at 2318 hours. She reported the onset of dull left-sided chest pain with dizziness on August 22, 2004 with radiation to the left arm and jaw. The pain was accompanied by some nausea. She was

seen in an emergency room on [REDACTED] at about 1700 hours. In the emergency room, the ECG showed normal sinus rhythm and her blood pressure was 182/95. She was treated with nitroglycerin, aspirin, Pepcid, Lovenox, morphine, Angemet, Lopressor and Ativan. By 1755 hours her chest pain had resolved. The creatine kinase-myocardial band was normal, as was troponin I. On discharge she received valdecoxib for musculoskeletal chest pain and Altace for hypertension.

Past medical history: Non-smoker, BMI 22.5

Concomitant medications: feverfew, vitamins, Buspar and fish oil

- *Subject 2709 / Site 296 / pleurisy chest wall pain syndrome*

[Reviewer's assessment: Possibly related to Trexima. Chest wall pain is a known adverse effect of sumatriptan.]

27 year old female

On [REDACTED], she went to an emergency room and gave history of chronic recurrent chest pain with radiation of pain to her left arm. She had treated five migraine attacks during November 2004 with Trexima and the last attack treated was on November 21, 2004 when she used doses of Trexima at 1830 hours and at 2030 hours.

Past medical history: knee arthroscopy, cesarean section, appendectomy, laparoscopy, left eardrum rupture, and toxemia of pregnancy. BMI 38.9

Concomitant medications: Singulair, Nasalcort, Advair, Allegra, hormonal contraceptive and Patanol.

*SAE's not likely related to Trexima:*

- Site 027 / Subject 2572 / left breast cancer
- Site 027 / Subject 2664 / kidney infection
  - Preceded by UTI and outpatient oral antibiotic treatment.
- Site 101 / Subject 2261 / right leg cellulitis
  - Past history of leg cellulites, borderline diabetes, obesity (BMI 50.3)
- Site 133 / Subject 2580 / biliary colic
  - Past history of gallstones
- Site 248 / Subject 2242 / broken hip
  - Fall, [REDACTED]
- Site 251 / Subject 2564 / kidney infection
  - Preceded by UTI and outpatient antibiotic treatment
- Site 279 / Subject 2184 / methicillin-resistant Staphylococcus aureus (infection)[of anterior abdominal wall]
  - Past history of recurrent inguinal cysts
- Site 346 / Subject 2309 / urinary incontinence

- Site 100/ Subject 2415 / Congestive heart failure, renal failure, right ventricular insufficiency, viral myocarditis, viral septicemia
  - Completely excluding drug-induced myocarditis is not possible. I did not identify a known association of myocarditis with sumatriptan or naproxen.
- Site 347/ Subject 2470 / benign ovarian cyst, uterine fibroids

### 7.1.3 Dropouts and Other Significant Adverse Events

#### 7.1.3.1 Overall profile of dropouts

##### Phase I studies

One dropout occurred in a Trexima PK study, MT400-102, due to consistently increased blood pressure. Little temporal relationship of blood pressure elevation to Trexima dosing is present.

##### *Narrative.*

Site 292 / Subject 1024

54 year old male

Prior to dosing, the subject's blood pressure was 134/88. About 3 hours after Trexima was administered the subject reported mild facial numbness and mild dizziness. In response, blood pressure was obtained. At 4 hours after dosing, blood pressure was 152/102, and at 6 hours (last measured), 139/92. No additional medications were given in the clinic during this visit.

One week later, *prior to dosing* the subject reported dizziness. His blood pressure was 153/110. Repeat blood pressure was 136/96. He was dosed with Trexima, and 4 hours later his blood pressure was 132/92. No further blood pressure measurements were reported.

One week later, the subject returned to the clinic for dosing, but was discontinued due to the previous elevated blood pressure. Blood pressure in the clinic at that time was 130/82.

Past medical history: No history of hypertension, non-smoker, BMI 27.4

##### Controlled trials

In the single-attack studies, by definition, there were no drop-outs or discontinuations.

##### Safety trial MT400-303

“A total of 43 of 565 subjects discontinued participation in the study due to either adverse events (41/565; 7%) or pregnancy (two subjects). Five of these 43 subjects reported adverse events that met the definition of serious adverse event (SAE).”

***Dropouts related to abnormal laboratory values***

Two patients in study 303 had treatment-emergent elevation of AST and ALT. Both patients took Trexima approximately 10 doses/month for 6 months.

Naproxen, and NSAIDs as a class, is known to cause borderline elevations of one or more liver tests in up to 15% of patients. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with naproxen and other NSAIDs.

Imitrex labeling lists “Disturbances of liver function tests” under ‘Other Events Observed.’

I find the liver enzyme elevations are possibly drug-related. The adverse events were not serious, and statistical power is inadequate to suggest a risk of liver toxicity greater than the individual active components of Trexima.

***Subject 2361/site 308/elevated liver function tests***

44 year old female

The adverse event was reported as “elevated liver function tests”. This subject had elevated ALT approximately 3 times baseline that resolved following discontinuation from the study.

Concurrent medications: estrogens, Synthroid, propranolol and azelastine nasal spray.

Between May 24, 2004 and November 13, 2004, the subject treated 42 migraine attacks with 51 doses of Trexima.

At the 6-month follow-up visit on November 15, 2004, abnormal liver function tests were noted (see below). The subject did not report any adverse events at this time. The last dose of Trexima was administered on November 13, 2004.

Type of Visit:	Screening	6 months	Unscheduled #1	Unscheduled #2
Date:	May 20, 2004	Nov.15, 2004	Dec.10, 2004	Jan.19, 2005
Analyte				
ALT (U/L)				
AST (U/L)				
Bilirubin (mg/dL)				
Alk Phos (U/L)				
Cholesterol (mg/dL)				

*Subject 2276/Site 334 / abnormal liver function tests*

33 year old female

This subject was found to have elevated liver function tests at the 6 month visit, after which she discontinued the medication.

Concurrent medications were Paxil and Xanax.

Between June 16 and to December 16 2004, the subject treated 48 migraine attacks with 49 doses of Trexima. No adverse events were reported during the study.

Type of Visit:	Screening	6 months	Unscheduled	Final visit
Date:	June 16, 2004	Dec 16 2004	January 3, 2005	March 7, 2005
<b>Analyte</b>				
ALT (U/L)				
AST (U/L)				
Bilirubin (mg/dL)				
Alk Phos (U/L)				
Triglycerides (mg/dL)				

7.1.3.2 Adverse events associated with dropouts

The only study to which this category applies is MT400-303, the 1-year open label extension study of Trexima.

Thirty-eight subjects discontinued due to non-serious adverse events (36 subjects) or pregnancy (2 subjects). Including the five subjects who discontinued due to serious adverse events, a total of 41 subjects (7%) discontinued due to any adverse event. In Table 50, I arrange withdrawals according to first-listed adverse event, although many subjects had multiple adverse events. The adverse events are similar to those expected from sumatriptan or naproxen alone, or with migraine in general.

Table 50: Discontinuations, Non-Serious Adverse Events, MT400-303

<u>Nausea/ abdominal pain</u>	Site 002 / Subject 2076/ nausea, vomiting Site 091 / Subject 2104/ nausea, stomach pain Site 142 / Subject 2160/ nausea, increased irritable bowel syndrome Site 173 / Subject 2694/ upset stomach Site 248 / Subject 2251/ nausea
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Site 254 / Subject 2049/ abdominal pain  
Site 251 / Subject 2562/ nausea, shakiness, sleepy, weak  
Site 027 / Subject 2727/ H. pylori lab test positive, heartburn, increase in abdominal gas  
Site 254 / Subject 2556/ flare up of ulcer disease, gastritis  
Site 338 / Subject 2234/ epigastric tenderness  
Site 362 / Subject 2032/ colitis  
Site 367 / Subject 2200/ nausea, tongue tingling numbness

Worse headache

Site 016 / Subject 2513/ status migraine  
Site 142 / Subject 2163/ increase in migraine frequency  
Site 251 / Subject 2432/ headache  
Site 335 / Subject 2205/ increased migraine frequency  
Site 367 / Subject 2201/ headache, heartburn, increased heart rate, light headedness, nausea, pain in jaw, pain in neck, pain in throat, pressure in jaw, pressure in neck, pressure in throat, shortness of breath, vertigo

Muscle/throat tightness

Site 002 / Subject 2083/ muscle ache, muscle tightness, sensitive to heat  
Site 002 / Subject 2084/ tightness in jaw, tightness in shoulders  
Site 308 / Subject 2368/ throat tightness  
Site 362 / Subject 2034/ shoulder discomfort, neck discomfort

Difficulty breathing

Site 279 / Subject 2183/ difficulty breathing, face pain, throat pain  
Site 279 / Subject 2605/ shortness of breath  
Site 367 / Subject 2195/ difficulty breathing, epigastric abdominal pain, nausea

Chest/heart

Site 335 / Subject 2210/ premature ventricular complexes  
In the opinion of the principal investigator, the reported event of premature ventricular contractions was unlikely related to the use of study drug.  
Site 346 / Subject 2302/ palpitations

Anxiety

Site 254 / Subject 2059/ anxiety, increased heart rate  
Site 254 / Subject 2554/ anxiety, chest tightness, cold sweats, increased heart rate, tension in back of neck,

Dizziness

Site 173 / Subject 2443/ dizziness  
Site 002 / Subject 2729/ cold chills, dizziness, spinning room, vomiting

Drowsy/fatigue

Site 248 / Subject 2246/ disoriented, extremely drowsy, feeling 'stupified'  
Site 254 / Subject 2054/ fatigued, increased sleepiness, tingling in hands, tingling over whole body, unable to process thoughts