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

[1] P-Values are from the Cochran-Mantel-Haenszel test, with pooled investigator site as the strata.
[2] 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[1]					
Trexima vs. Placebo			<.001		<.001
Trexima vs. Sumatriptan			0.220		0.004

[1] 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[1]					
Trexima vs. Placebo			<.001		<.001
Trexima vs. Sumatriptan			0.007		<.001

[1] 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

Table 14.2.4.1
Phonophobia 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	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[1]					
Trexima vs. Placebo			<.001		<.001
Trexima vs. Sumatriptan			0.137		0.003

[1] 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

POZEN, Inc. Study Number MT400-302

Table 14.2.4.1
Phonophobia 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	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[1]					
Trexima vs. Placebo			<.001		<.001
Trexima vs. Sumatriptan			0.002		<.001

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

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**
MT400-302	25%† (90/364)	16% (59/361)	10% (37/356)	8% (30/360)
MT400-301	23%‡ (83/362)	14% (51/362)	10% (37/364)	7% (25/382)

† p<0.001 versus placebo, sumatriptan and naproxen sodium
‡ p<0.001 versus placebo and naproxen sodium; p=0.009 versus sumatriptan.

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