

# **Analyses of POZEN MT100 Clinical Trials Data Conducted by Ken Kolodner Sc.D. and Richard Lipton M.D. (6-22-2005)**

## **Purpose**

The primary focus of this analysis has been to determine whether there is evidence of a differential response for MT100 for different levels of baseline nausea. In analysis conducted by Pozen, Pozen believed that they saw evidence that MT100 showed greater response for those with lower levels of baseline nausea relative to those with higher levels of baseline nausea.

A total of five trials are used in the analysis. However, because of various design differences, all the trials can not be combined. Instead, four different “pools” were created to answer a variety of questions.

## **Sample (“pools”)**

We defined four pools of studies: (1.) Pool #1: studies 301 and 304 to compare MT 100 one tablet group vs. naproxen (and to metoclopramide); (2.) Pool #2: studies 306, 308 and 402 to compare MT 100 one tablet group vs. placebo; (3.) Pool #3: studies 306 and 401A comparing two tablet MT100 vs. placebo; (4.) Pool #4: studies 306 and 308 to compare MT100 one tablet to Sumatriptan.

## **Overview of outcomes**

Most of the analysis has focused on four pain-related outcomes: (1.) 2 hour headache response (defined as none/mild at two hours if the subject did not rescue); (2.) 2 hour pain free response (defined as none at 2 hours if the subject did not rescue); (3.) 24 hour sustained pain response (none/mild at all time points with no rescuing); (4.) 24 hour sustained pain free response (none at all time points with no rescuing).

## **Statistical Analysis**

Two potentially important issues had to be addressed in the analysis: (1.) missing data; and (2.) the enrollment of some of the same subjects across studies.

### **Missing data.**

First, in general, last observation carried forward (LOCF) has been used where data are missing for 2 hours. The numbers of subjects for whom LOCF was used is noted as footnotes in the tables.

Second, in some instances, last observation carried backward (LOCB) has been used to fill in critical data points. The numbers of subjects for whom LOCB was used is noted as

footnotes in the tables. In general, the numbers of times LOCF and LOCB were used is quite small.

### **Duplicate subjects across trials.**

A relatively small number of subjects were used in more than one trial. For pool #1, there were seven subjects in both studies 301 and 304 (0.2% of a total of 3680 subjects). For pool #2, there were 21 subjects found to be in more than one of the studies 306, 308 and 402 (1.2% out of a total of 1795 subjects). For pool #3, there were 14 subjects were in both studies 306 and 401A (1.6% out of a total of 889 subjects). For pool #4, there were 14 subjects in both studies 306 and 308 (0.9% out of a total of 1559 subjects).

We chose to keep these in the analysis for the following reasons. First, the numbers of duplicates is relatively small. Re-analysis of the data omitting duplicates has shown minimal impact on the results. Second, by including the subjects we maintain consistency with the results reported from the individual trials. Third, an alternative strategy is to include the subjects but use analytic methods to account for the correlation in the data due to using the same subjects more than once. Analysis using general estimating equations (GEEs) (Zeger, SL, Liang, K-Y, Albert, P, 1988. Models for longitudinal data, a generalized estimating equation approach. *Biometrics*. 44, 1049-1060.) produced essentially identical results, no doubt because of the small numbers of duplicates. To retain simplicity in the presentation of the data, we present analysis with duplicates retained. Statistical testing is presented as if all subjects are unique.

### **Analysis of primary outcomes.**

In most of the analysis, we conducted one of the following comparisons: (1.) the four primary outcomes are compared across two or possibly three treatment groups; (2.) the four outcomes are compared by treatment group stratifying by baseline nausea (as a dichotomous variable collapsed as none/mild vs. moderate/severe); (3.) the four outcomes by baseline nausea stratifying within two or three treatment groups. This last comparison is really just an alternate way to view the second set of comparisons.

For all of the dichotomous outcomes (which represent all of the primary outcomes and most of the secondary outcomes), comparisons between treatment groups are made using contingency tables and presented using percentages and odds ratios with 95% confidence intervals. All of these comparisons are generally made for each study and for all studies combined within a pool. To combine studies, for dichotomous outcomes, we tested for heterogeneity using the Breslow-Day chi-square test for the heterogeneity of the odds ratios. Since there was generally little or no evidence of heterogeneity, the Mantel-Haenszel common odds ratios was used for a summary odds ratios as opposed to the more conservative random effects model (DerSimonian R, Laird NM (1986) "Meta-analysis in clinical trials" *Control Clinical Trials* 7:177-188.)

Since the comparisons listed above (#2 and #3) and the main purpose of these analyses are essentially tests of interaction, logistic regression was also used. Logistic regressions

were run where main effects included treatment group, baseline nausea (dichotomized), a study term, and an interaction term of baseline nausea X treatment group.

For the dichotomous co-primary outcomes, we used the same analytic approach. Again, since there are a small number of duplicates GEEs were also run but because the results are nearly identical, they are not presented in these tables.

## **Results**

Using “Pool #1” (studies 301 and 304 separately and combined), we compared the MT 100 one tablet group vs. naproxen sodium for four primary pain outcomes. These comparisons are repeated and stratified by baseline nausea. See Tables 1.1 through 1.12.

## Pool 1 Results

Study	Treatment Group	Response		No Response		p value	Crude Odds Ratio	(95% CI)
		#	%	#	%			
301 <sup>1</sup>	MT100	203	48.10	219	51.90	0.6646	1.061	(0.811 – 1.389)
	Naproxen	200	46.62	229	53.38			
304 <sup>2</sup>	MT100	513	49.76	518	50.24	0.1672	1.129	(0.950 – 1.340)
	Naproxen	494	46.74	563	53.26			
301+304	MT100	716	49.28	737	50.72	0.1624	1.109 <sup>3</sup>	(0.959 – 1.282)
	Naproxen	694	46.70	792	53.30			

Breslow-Day chi-square=0.143 p=0.7058

<sup>1</sup> For Study 301, last observation carried forward substitution was used for 14 patients with missing values of two hour headache response (9 patients in the MT100 group and 5 patients in the Naproxen group.)

<sup>2</sup> For Study 304, last observation carried forward substitution was used for 17 patients with missing values of two hour headache response (11 patients in the MT100 group and 6 patients in the Naproxen group.)

<sup>3</sup> Mantel-Haenszel common odds ratio used for pooled studies 301+304.

Study	Treatment Group	Response		No Response		p value	Crude Odds Ratio	(95% CI)
		#	%	#	%			
301 <sup>1</sup>	MT100	79	18.72	343	81.28	0.0618	1.416	(0.982 – 2.043)
	Naproxen	60	13.99	369	86.01			
304 <sup>2</sup>	MT100	173	16.78	858	83.22	0.6253	1.060	(0.840 – 1.336)
	Naproxen	169	15.99	888	84.01			
301+304	MT100	252	17.34	1201	82.66	0.1567	1.152 <sup>3</sup>	(0.947 – 1.400)
	Naproxen	229	15.41	1257	84.59			

Breslow-Day chi-square=1.726 p=0.1889

<sup>1</sup> For Study 301, last observation carried forward substitution was used for 14 patients with missing values of two hour headache response (9 patients in the MT100 group and 5 patients in the Naproxen group.)

<sup>2</sup> For Study 304, last observation carried forward substitution was used for 17 patients with missing values of two hour headache response (11 patients in the MT100 group and 6 patients in the Naproxen group.)

<sup>3</sup> Mantel-Haenszel common odds ratio used for pooled studies 301+304.

## Pool 1 Results

Study	Treatment Group	Response		No Response		p value	Crude Odds Ratio	(95% CI)
		#	%	#	%			
301	MT100	150	35.55	272	64.45	0.0759	1.297	(0.973 – 1.728)
	Naproxen	128	29.84	301	70.16			
304	MT100	328	31.81	703	68.19	0.0512	1.205	(0.999 – 1.454)
	Naproxen	295	27.91	762	72.09			
301+304	MT100	478	32.90	975	67.10	0.0092	1.232 <sup>1</sup>	(1.053 – 1.442)
	Naproxen	423	28.47	1063	71.53			

Breslow-Day chi-square=0.175 p=0.6755

<sup>1</sup> Mantel-Haenszel common odds ratio used for pooled studies 301+304.

Study	Treatment Group	Response		No Response		p value	Crude Odds Ratio	(95% CI)
		#	%	#	%			
301	MT100	64	15.17	358	84.83	0.0534	1.488	(0.992 – 2.232)
	Naproxen	46	10.72	383	89.28			
304	MT100	118	11.45	913	88.55	0.4469	1.113	(0.845 – 1.465)
	Naproxen	110	10.41	947	89.59			
301+304	MT100	182	12.53	1271	87.47	0.0849	1.220 <sup>1</sup>	(0.972 – 1.532)
	Naproxen	156	10.50	1330	89.50			

Breslow-Day chi-square=1.357 p=0.2440

<sup>1</sup> Mantel-Haenszel common odds ratio used for pooled studies 301+304.

## Pool 1 Results

Study	Treatment Group	Response		No Response		p value	Crude Odds Ratio	(95% CI)
		#	%	#	%			
301 <sup>1</sup>	MT100	116	50.66	113	49.34	0.2462	1.242	(0.861 – 1.790)
	Naproxen	105	45.26	127	54.74			
304 <sup>2</sup>	MT100	183	54.63	152	45.37	0.0507	1.347	(0.999 – 1.817)
	Naproxen	168	47.19	188	52.81			
301+304	MT100	299	53.01	265	46.99	0.0254	1.304 <sup>3</sup>	(1.034 – 1.644)
	Naproxen	273	46.43	315	53.57			

Breslow-Day chi-square=0.115 p=0.7350

<sup>1</sup> For Study 301, last observation carried forward substitution was used for 8 patients with missing values of two hour headache response (5 patients in the MT100 group and 3 patients in the Naproxen group.)

<sup>2</sup> For Study 304, last observation carried forward substitution was used for 5 patients with missing values of two hour headache response (all 5 of these patients were in the MT100 group.)

<sup>3</sup> Mantel-Haenszel common odds ratio used for pooled studies 301+304.

Study	Treatment Group	Response		No Response		p value	Crude Odds Ratio	(95% CI)
		#	%	#	%			
301 <sup>1</sup>	MT100	87	45.31	105	54.69	0.5651	0.890	(0.597 – 1.325)
	Naproxen	95	48.22	102	51.78			
304 <sup>2</sup>	MT100	330	47.62	363	52.38	0.6769	1.046	(0.847 – 1.291)
	Naproxen	326	46.50	375	53.50			
301+304	MT100	417	47.12	468	52.88	0.9202	1.010 <sup>3</sup>	(0.838 – 1.216)
	Naproxen	421	46.88	477	53.12			

Breslow-Day chi-square=0.495 p=0.4819

<sup>1</sup> For Study 301, last observation carried forward substitution was used for 6 patients with missing values of two hour headache response (4 patients in the MT100 group and 2 patients in the Naproxen group.)

<sup>2</sup> For Study 304, last observation carried forward substitution was used for 12 patients with missing values of two hour headache response (6 patients in the MT100 group and 6 patients in the Naproxen group.)

<sup>3</sup> Mantel-Haenszel common odds ratio used for pooled studies 301+304.

## Pool 1 Results

Study	Treatment Group	Response		No Response		p value	Crude Odds Ratio	(95% CI)
		#	%	#	%			
301 <sup>1</sup>	MT100	48	20.96	181	79.04	.0767	1.544	(0.952 – 2.504)
	Naproxen	34	14.66	198	85.34			
304 <sup>2</sup>	MT100	68	20.30	267	79.70	0.1729	1.309	(0.888 – 1.928)
	Naproxen	58	16.29	298	83.71			
301+304	MT100	116	20.57	448	79.43	0.0300	1.397 <sup>3</sup>	(1.032 – 1.889)
	Naproxen	92	15.65	496	84.35			

Breslow-Day chi-square=0.275 p=0.6000

<sup>1</sup> For Study 301, last observation carried forward substitution was used for 8 patients with missing values of two hour headache response (5 patients in the MT100 group and 3 patients in the Naproxen group.)

<sup>2</sup> For Study 304, last observation carried forward substitution was used for 5 patients with missing values of two hour headache response (all 5 of these patients were in the MT100 group.)

<sup>3</sup> Mantel-Haenszel common odds ratio used for pooled studies 301+304.

Study	Treatment Group	Response		No Response		p value	Crude Odds Ratio	(95% CI)
		#	%	#	%			
301 <sup>1</sup>	MT100	31	16.15	161	83.85	0.4111	1.266	(0.720 – 2.226)
	Naproxen	26	13.20	171	86.80			
304 <sup>2</sup>	MT100	105	15.15	588	84.85	0.7246	0.949	(0.710 – 1.269)
	Naproxen	111	15.83	590	84.17			
301+304	MT100	136	15.37	749	84.63	0.9481	1.008 <sup>3</sup>	(0.779 – 1.305)
	Naproxen	137	15.26	761	84.74			

Breslow-Day chi-square=0.796 p=0.3724

<sup>1</sup> For Study 301, last observation carried forward substitution was used for 6 patients with missing values of two hour headache response (4 patients in the MT100 group and 2 patients in the Naproxen group.)

<sup>2</sup> For Study 304, last observation carried forward substitution was used for 12 patients with missing values of two hour headache response (6 patients in the MT100 group and 6 patients in the Naproxen group.)

<sup>3</sup> Mantel-Haenszel common odds ratio used for pooled studies 301+304.

## Pool 1 Results

Study	Treatment Group	Response		No Response		p value	Crude Odds Ratio	(95% CI)
		#	%	#	%			
301	MT100	88	38.43	141	61.57	0.0231	1.570	(1.063 – 2.319)
	Naproxen	66	28.45	166	71.55			
304	MT100	123	36.72	212	63.28	0.0046	1.594	(1.154 – 2.202)
	Naproxen	95	26.69	261	73.31			
301+304	MT100	211	37.41	353	62.59	0.0003	1.584 <sup>1</sup>	(1.235 – 2.032)
	Naproxen	161	27.38	427	72.62			

Breslow-Day chi-square=0.035 p=0.9527

<sup>1</sup> Mantel-Haenszel common odds ratio used for pooled studies 301+304.

Study	Treatment Group	Response		No Response		p value	Crude Odds Ratio	(95% CI)
		#	%	#	%			
301	MT100	62	32.29	130	67.71	0.8623	1.038	(0.678 – 1.591)
	Naproxen	62	31.47	135	68.53			
304	MT100	205	29.58	488	70.42	0.6657	1.052	(0.835 – 1.326)
	Naproxen	200	28.53	501	71.47			
301+304	MT100	267	30.17	618	69.83	0.6461	1.049 <sup>1</sup>	(0.856 – 1.286)
	Naproxen	262	29.18	636	70.82			

Breslow-Day chi-square=0.0029 p=0.9573

<sup>1</sup> Mantel-Haenszel common odds ratio used for pooled studies 301+304.

## Pool 1 Results

Study	Treatment Group	Response		No Response		p value	Crude Odds Ratio	(95% CI)
		#	%	#	%			
301	MT100	40	17.47	189	82.53	0.0270	1.834	(1.066 – 3.157)
	Naproxen	24	10.34	208	89.66			
304	MT100	46	13.73	289	86.27	0.0860	1.507	(0.941 – 2.414)
	Naproxen	34	9.55	322	90.45			
301+304	MT100	86	15.25	478	84.75	0.0057	1.641 <sup>1</sup>	(1.150 – 2.341)
	Naproxen	58	9.86	530	90.14			

Breslow-Day chi-square=0.286 p=0.5925

<sup>1</sup> Mantel-Haenszel common odds ratio used for pooled studies 301+304.

Study	Treatment Group	Response		No Response		p value	Crude Odds Ratio	(95% CI)
		#	%	#	%			
301	MT100	24	12.50	168	87.50	0.6841	1.136	(0.614 – 2.104)
	Naproxen	22	11.17	175	88.83			
304	MT100	72	10.39	621	89.61	0.7841	0.954	(0.678 – 1.341)
	Naproxen	76	10.84	625	89.16			
301+304	MT100	96	10.85	789	89.15	0.9645	0.994 <sup>1</sup>	(0.737 – 1.339)
	Naproxen	98	10.91	800	89.09			

Breslow-Day chi-square=0.239 p=0.6251

<sup>1</sup> Mantel-Haenszel common odds ratio used for pooled studies 301+304.