



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**STATISTICAL REVIEW AND EVALUATION**  
Clinical Studies

NDA/Serial Number: 21-645/000  
Drug Name: MT100  
Indication: Migraine  
Applicant: Pozen  
Dates: Date of Document: July 31, 2003  
PDUFA Due Date: May 31, 2004  
Review Priority: Standard  
Biometrics Division: Biometrics I, HFD-710  
Statistical Reviewer: Yeh-Fong Chen, Ph.D.  
Concurring Reviewers: Kun Jin, Ph.D., Statistical Team Leader  
James Hung, Ph.D., Acting Deputy Director  
Medical Division: Division of Neuropharmacological Drug Products, HFD-120  
Clinical Team: Kevin Prohaska, D.O., Medical Reviewer  
Eric Bastings, M.D., Medical Team Leader  
Project Manager: Lana Yan Chen

# Table of Contents

1.1 CONCLUSIONS AND RECOMMENDATIONS.....	4
1.2 BRIEF OVERVIEW OF CLINICAL STUDIES.....	4
1.3 STATISTICAL ISSUES AND FINDINGS.....	5
1.3.1 For Factorial Studies: MT 100-301 and MT 100-304.....	5
1.3.2 For Other Placebo and/or Active Controlled Studies.....	5
<b>2. INTRODUCTION.....</b>	<b>6</b>
2.1 OVERVIEW.....	6
2.2 DATA SOURCES.....	7
<b>3. STATISTICAL EVALUATION.....</b>	<b>7</b>
3.1 EVALUATION OF EFFICACY.....	7
3.1.1 Description of Study MT 100-301.....	7
3.1.1.1 Study Objectives.....	7
3.1.1.2 Study Design.....	7
3.1.1.3 Efficacy Variables.....	8
3.1.1.4 Statistical Methods.....	8
3.1.1.4.1 Determination of Sample Size.....	8
3.1.1.4.2 Efficacy Analysis Plans.....	8
3.1.2 Analysis Results for Study MT 100-301.....	9
3.1.2.1 Disposition of Patients and Data Sets Analyzed.....	9
3.1.2.2 Demographic and Patient Characteristics.....	10
3.1.2.3 Sponsor’s Efficacy Analysis Results.....	11
3.1.2.3.1 Primary Efficacy Analysis Results.....	11
3.1.2.3.2 Secondary Efficacy Analysis Results.....	11
3.1.2.4 Sponsor’s Overall Conclusions.....	13
3.1.2.5 Statistical Reviewer’s Comments.....	14
3.1.3 Description of Study MT 100-304.....	15
3.1.3.1 Study Objectives.....	15
3.1.3.2 Study Design.....	15
3.1.3.3 Efficacy Variables.....	15
3.1.3.4 Statistical Methods.....	16
3.1.3.4.1 Determination of Sample Size.....	16
3.1.3.4.2 Efficacy Analysis Plan.....	16
3.1.4 Analysis Results for Study MT 100-304.....	17
3.1.4.1 Disposition of Patients and Data Sets Analyzed.....	17
3.1.4.2 Demographic and Patient Characteristics.....	17
3.1.4.3 Sponsor’s Efficacy Analysis Results.....	18
3.1.4.3.1 Primary Efficacy Analysis Results.....	18
3.1.4.3.2 Secondary Efficacy Analysis Results.....	19
3.1.4.4 Sponsor’s Overall Conclusions.....	22
3.1.4.5 Statistical Reviewer’s Comments.....	22
3.1.5 Description of Study MT 100-306.....	23
3.1.5.1 Study Objectives.....	23
3.1.5.2 Study Design.....	24
3.1.5.3 Efficacy Variables.....	24
3.1.5.4 Statistical Methods.....	25
3.1.5.4.1 Determination of Sample Size.....	25
3.1.5.4.2 Efficacy Analysis Plan.....	25
3.1.6 Analysis Results for Study MT 100-306.....	26
3.1.6.1 Disposition of Subjects and Data Sets Analyzed.....	26
3.1.6.2 Demographic and Patient Characteristics.....	26
3.1.6.3 Sponsor’s Efficacy Analysis Results.....	27
3.1.6.3.1 Primary Efficacy Analysis Results.....	27
3.1.6.3.2 Secondary Efficacy Analysis Results.....	27
3.1.6.4 Sponsor’s Overall Conclusions.....	30
3.1.6.5 Statistical Reviewer’s Comments.....	31

3.1.7 Description of Study MT 100-308.....	31
3.1.7.1 Study Objectives.....	31
3.1.7.2 Study Design.....	32
3.1.7.3 Efficacy Variables.....	33
3.1.7.4 Statistical Methods.....	33
3.1.7.4.1 Determination of Sample Size.....	33
3.1.7.4.2 Efficacy Analysis Plan.....	33
3.1.8 Analysis Results for Study MT 100-308.....	34
3.1.8.1 Disposition of Patients and Data Sets Analyzed.....	34
3.1.8.2 Demographic and Patient Characteristics.....	35
3.1.8.3 Sponsor’s Efficacy Analysis Results.....	36
3.1.8.3.1 Primary Efficacy Analysis Results.....	36
3.1.8.3.2 Secondary Efficacy Analysis Results.....	36
3.1.8.4 The Sponsor Overall Conclusions.....	40
3.1.8.5 The Statistical Reviewer’s Comments.....	40
3.1.9 Description of Study MT 100-303.....	41
3.1.9.1 Study Objective.....	41
3.1.9.2 Study Design.....	42
3.1.9.3 Efficacy Variables.....	42
3.1.9.4 Statistical Methods.....	42
3.1.9.4.1 Determination of Sample Size.....	42
3.1.9.4.2 Efficacy Analysis Plan.....	43
3.1.10 Analysis Results for Study MT 100-303.....	44
3.1.10.1 Disposition of Patients and Data Sets Analyzed.....	44
3.1.10.2 Demographic and Patient Characteristics.....	44
3.1.10.3 Sponsor’s Efficacy Analysis Results.....	45
3.1.10.3.1 Primary Efficacy Analysis Results.....	45
3.1.10.3.2 Secondary Efficacy Analysis Results.....	46
3.1.10.4 Sponsor’s Efficacy Conclusions.....	49
3.1.10.5 Statistical Reviewer’s Comments.....	49
3.2 EVALUATION OF SAFETY.....	50
<b>4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS.....</b>	<b>50</b>
4.1 GENDER, RACE AND AGE.....	50
4.1.1 Factorial Designed Studies (MT 100-301 and MT 100-304).....	50
4.1.2 Pivotal Placebo Controlled Studies (MT 100-306, MT 100-308 and MT 100-303).....	51
4.2 OTHER SPECIAL/SUBGROUP POPULATIONS.....	52
4.2.1 Factorial Designed Studies (MT 100-301 and MT 100-304).....	52
4.2.2 Pivotal Placebo Controlled Studies (MT 100-306, MT 100-308 and MT 100-303).....	53
<b>5. SUMMARY AND CONCLUSIONS.....</b>	<b>54</b>
5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE.....	54
5.2 CONCLUSIONS AND RECOMMENDATIONS.....	55
<b>6. APPENDICES.....</b>	<b>57</b>

# 1. EXECUTIVE SUMMARY

## *1.1 CONCLUSIONS AND RECOMMENDATIONS*

There were five studies statistically reviewed for efficacy in this submission. They were Studies MT 100-301, MT 100-304, MT 100-306, MT 100-308 and MT 100-303. The first two studies were factorial designed to compare the combination drug of MT 100 with both individual components to meet the rule of marketing a combination drug. The rest of three studies were either placebo and/or active controlled designed for mainly demonstrating the MT 100's efficacy comparing with the placebo and/or comparing with the other active comparator. The purpose of these three studies was for the sponsor's possible marketing claims, not for the approval of the MT100 itself. That is, the validity of these three studies is under the condition that two factorial studies showed positive results.

First of all, this reviewer found in both factorial studies that the MT 100 failed to show significant improvement on the primary endpoint of 2-hours to 24 hours sustained pain response rate for acute migraine patients, comparing with one of the individual components, Naproxen, according to the protocol specified statistical method although the MT 100 clearly showed significant results when comparing with the other component, Metoclopramide. For all three major migraine symptoms, the MT 100 also failed to show any significant improvement when comparing with the component, Naproxen in both studies. So, these two studies were determined as failed studies which therefore failed to meet the requirement of marketing a combination drug.

Secondly, for the other three studies, only one study, MT 100-306 showed significant results for its primary endpoint. In that study, none of MT 100 arms showed significant results on all three major migraine symptoms. Although, for the insignificant results of these secondary endpoints, p-values were close to 0.05, one should keep in mind that since the sponsor included two arms of MT100 in one study but did not provide any pre-specified statistical analysis method for dealing with the problem of multiple comparisons, how to assess the closeness of significance for these insignificant results of migraine symptoms is not clear.

In conclusion, the data did not support the MT 100's efficacy in treating acute migraine patients whether it was for comparing the MT 100 with its individual components, with the placebo or with the other approved drug, sumatriptan.

## *1.2 BRIEF OVERVIEW OF CLINICAL STUDIES*

The sponsor submitted this application for the approval of the combination drug MT 100. Their clinical drug development program consisted of 11 Phase 2 and Phase 3 studies. After discussing with the medical reviewer, it was agreed that 5 of 11 studies needed statistical efficacy review and evaluations. They were Studies MT 100-301, MT 100-304, MT 100-306, MT 100-308 and MT 100-303. The first two studies

were factorial designed to compare the MT 100 versus individual components to meet the rule of marketing a combination drug. The rest of three studies were designed as either placebo and/or an active controlled for mainly demonstrating the MT 100's efficacy comparing with the placebo and/or with the other comparator. Notice that the purpose of these three studies was for the sponsor's possible marketing claims, not for the approval of the MT100 itself. So, the validity of these three studies is under the condition that two factorial studies showed positive results.

### *1.3 STATISTICAL ISSUES AND FINDINGS*

#### 1.3.1 For Factorial Studies: MT 100-301 and MT 100-304

For both factorial studies MT 100-301 and MT 100-304, this reviewer found that the sponsor did not use the protocol specified statistical methods to analyze the data. For Study MT 100-301, the protocol specified method was the logistic regression with baseline pain as the covariate but the sponsor did not mention the baseline pain as the covariate in their study report. Their p-values for both MT 100 versus individual components comparisons were found to be obtained from the logistic regression model but without any covariates. This reviewer had a different p-value for the comparison between MT 100 and Naproxen by the logistic regression model with the baseline pain as the covariate although the difference was not big enough to affect the conclusions.

For Study MT 100-304, the protocol specified method was the extended Mantel Haenzel statistic with scores of 0, 1, and 2 for the three ordered categories and using a model that controls for center, baseline pain and gender. The sponsor, however, used the ordered logistic regression model with baseline pain and investigator site as covariates. When this application was reviewed, the sponsor was asked to perform the protocol specified statistical method for this study. They showed us the new p-value of 0.038 (it was 0.03 before) for the comparison between the MT 100 and Naproxen and concluded that the difference was too small to affect the final conclusions. After this reviewer performed the re-analysis, it was found that the p-value from the pre-specified method should be 0.063, not 0.038, which was obtained due to the sponsor's programming error.

#### 1.3.2 For Other Placebo and/or Active Controlled Studies

For Study MT 100-306, this reviewer confirmed the sponsor's analysis results for the primary endpoint and most of secondary endpoints. For the secondary endpoint of incidence of phonophobia at 2 hour post dose, this reviewer had different p-values for the comparisons between the 1 tablet of MT 100 and 2 tablets of MT 100 with the placebo, although the numbers of patients with phonophobia at 2 hours post dose for all treatment groups were the same. The differences between the sponsor's and the reviewer's p-values were, however, not big enough to affect the final conclusions. This reviewer also found that in the original protocol of MT 100-306, only 3 arms of single tablet of MT 100, the sumatriptan and the placebo were included in the study,

the sponsor later added the arm of 2 tablets of MT 100 into the study per the amendment, but did not propose any statistical method for dealing with multiple comparisons although the inconsistency due to a lack of this preplanned multiple comparison procedure did not occur in this data set.

For Study MT 100-308, the primary objective of the study was to compare the safety and efficacy of a single tablet dose of MT 100 with the over-encapsulated sumatriptan by non-inferiority test. Although the sponsor submitted this study and concluded the comparability of these two drugs, due to some major problems about the study design, in which the sponsor failed to reach the agreement with the agency, the non-inferiority study results are not appropriate for any efficacy claims. Beside that, in regarding to the sponsor's non-inferiority study results, this reviewer had different conclusions. By using the confidence interval approach for the non-inferiority test or the Blackwelder test for equivalence, the results clearly showed that the null hypothesis was not rejected. Therefore, the non-inferiority of MT 100 to the sumatriptan was not demonstrated.

For Study MT 100-303, it was also found that the sponsor's analysis results for the primary endpoint were different from the reviewer's by the protocol specified statistical method. According to the sponsor's protocol Amendment #2, it was stated that the 2-hour sustained response data will be analyzed by the ordered logistic regression controlling for center, baseline severity and gender, but the sponsor's study report only mentioned center and baseline severity into the model. The sponsor's results were, however, obtained by the ordered regression model without adding any covariates.

## **2. INTRODUCTION**

### **2.1 OVERVIEW**

The sponsor submitted this application for the approval of the combination drug MT 100. Their clinical development program consisted of 11 Phase 2 and Phase 3 studies. Given that the components of MT 100 are already approved products with established efficacy and safety profiles, the sponsor's clinical development program was designed to characterize the required pharmacokinetics of MT 100, to demonstrate that MT 100 satisfies the regulatory requirements for combination products, to demonstrate that MT 100 was an effective treatment for migraine versus placebo and an active comparator (sumatriptan) and to evaluate populations that either had an inadequate response to sumatriptan, had demonstrated intolerance to 5-HT agonists, or had cardiovascular risk factors.

After discussing with the medical reviewer, it was agreed that 5 of 11 studies needed statistical efficacy review and evaluations. They are Studies MT 100-301, MT 100-304, MT 100-306, MT 100-308 and MT 100-303. The first two studies were factorial designed to compare the MT 100 versus individual components. The last three studies were either placebo and/or active controlled for mainly demonstrating the MT 100's efficacy comparing with the placebo and the other active drug.

## 2.2 DATA SOURCES

The sponsor's original submission and data are stored in the EDR with the following directory: [\\CDSESUB1\N21645\N 000\2003-07-31](#). Some other NDA amendments are also stored in the EDR with same submission number but different dates.

## 3. STATISTICAL EVALUATION

### 3.1 EVALUATION OF EFFICACY

The following descriptions of studies are based on the sponsor's study reports. Some discrepancies found between the protocols and study reports will be addressed in the section of reviewer's comments by individual studies.

#### 3.1.1 Description of Study MT 100-301

This study was titled as "A Single Dose, Double-Blind, Safety and Efficacy Study of MT 100, Metoclopramide Hydrochloride and Naproxen Sodium in Subjects with Acute Migraine Attacks." There were 39 investigative centers in the US involved.

##### 3.1.1.1 Study Objectives

The primary objective of this study was to compare the safety and efficacy of single doses of MT 100 (naproxen sodium 500 mg / metoclopramide hydrochloride 16 mg) with single doses of metoclopramide hydrochloride (16 mg) and naproxen sodium (500 mg) in the acute treatment of migraine attacks in an outpatient setting.

##### 3.1.1.2 Study Design

This was a Phase III, randomized, double-blind, parallel group, multicenter study consisting of a screening visit, at home treatment of an acute migraine attack and a follow-up visit occurring 24-72 hours after the treated migraine attack.

At the end of the screening visit, subjects were randomly assigned to one of the following three treatments (See Table 3.1.1.1) for oral administration of blinded study medication.

Table 3.1.1.1 Summary of Treatments for Study MT 100-301

Treatment Arm	No. of Subjects Planned	Study Medication
A	400	MT 100 (naproxen sodium 500 mg/metoclopramide hydrochloride 16 mg)
B	400	Naproxen Sodium 500 mg
C	200	Metoclopramide hydrochloride 16 mg

Subjects were instructed to review the eligibility checklist to ascertain whether they continued to meet the eligibility criteria and had a headache of moderate (pain score 2) to severe (pain score 3) pain intensity when their next migraine attack occurred.

Subjects who remained eligible completed the assessments in a study diary just prior to taking study medication, and every 30 minutes for 2 hours and then hourly while awake for the next 22 hours after taking study medication (total evaluation period was 24 hours). If nausea was present at baseline, subjects started a stopwatch so that the time to nausea relief could be recorded. Rescue medication was permitted no sooner than 2 hours after dosing, if necessary, for those subjects who still had moderate or severe pain.

### 3.1.1.3 Efficacy Variables

The primary efficacy outcome measure was sustained pain response during 24 hours after dosing. Sustained pain response was defined as a pain score of 0-1 (no or mild pain) at 2 hours, which did not relapse (return to a pain score of 2 or 3) or require rescue medication within the succeeding 22 hours.

Secondary outcome measures included incidence of nausea relief, time to nausea relief, percentage of responders at 2 hours, percentage of subjects pain free at 2 hours, incidence of photophobia and phonophobia, time to use of rescue medication, total pain relief (TOTPAR), time to relapse for responders (pain intensity returning to level 2 or 3, or the use of rescue medication), pain intensity difference (PID), and 24-hour sum of pain intensity differences (SPID).

### 3.1.1.4 Statistical Methods

#### 3.1.1.4.1 Determination of Sample Size

Based on the assumptions of 56%, 46% and 33% of the proportion of subjects with sustained pain response during 24 hours after dosing with MT 100, naproxen and metoclopramide, respectively, 1000 subjects (400 MT 100 subjects, 400 naproxen subjects and 200 metoclopramide subjects) were required to achieve approximately 80% power to detect a difference of 10% between MT 100 and naproxen, and to detect a difference of 20% between MT 100 and metoclopramide in the sustained pain response measure at a 5.0% level of significance (chi-square test, two tailed).

#### 3.1.1.4.2 Efficacy Analysis Plans

Analysis of the efficacy data from the intent-to-treat population with LOCF algorithm was considered the primary analysis. Unless specified otherwise, all statistical tests were two-sided at  $\alpha = 0.05$ .

According to the sponsor's study report, the primary efficacy outcome measure was the proportion of subjects with sustained pain response during 24 hours after dosing using **logistic regression**. In addition to this, the sponsor also performed a post hoc analysis for the sustained pain response data by the ordered logistic regression with baseline pain and investigator site as the covariates. They defined the following three categories for the outcomes.

- 0) non-responders = subjects with a pain score of 2 or 3 at 2 hours, subjects with a pain score of 0 or 1 at 2 hours that either had a pain score of 2 or 3 after 2 hours or received rescue medication
- 1) sustained relief = subjects with a pain score of 0 or 1 at 2 hours, with pain scores no greater than 1 after 2 hours without the use of rescue medication
- 2) sustained pain free = subjects with a pain score of 0 at 2 hours and no greater than 0 after 2 hours without the use of rescue medication.

For secondary outcome measures, a Wilcoxon Rank Sum Test was used to compare the differences in the distribution of time to nausea relief between MT 100 and each of its components. The analysis of nausea relief was restricted to subjects with nausea at baseline. A Cox Proportional Hazards Model (with pooled site and baseline pain as covariates) was used to compare the differences in the distribution of time to relapse and time to rescue between MT 100 and each of its components.

The Cochran-Mantel-Haenszel test with site as strata was to be used to compare the proportion of responders at each time-point between MT 100 and each of its components.

ANOVA with treatment and center as fixed effects was used to test the differences in mean PID, mean SPID, and mean pain relief (TOTPAR) at 2 hours after dosing between MT 100 and each of its components.

Either Fisher's Exact Test or chi-square test was used on categorical variables, such as incidence of nausea, depending on number of observations in each cell of the contingency tables.

Subgroup analyses on the efficacy measures were performed within age group, gender group, and subject groups with and without nausea at baseline. In addition, efficacy analyses were performed on subject groups based on severity of migraine pain at baseline.

### *3.1.2 Analysis Results for Study MT 100-301*

#### *3.1.2.1 Disposition of Patients and Data Sets Analyzed*

A total of 1067 subjects were screened and subsequently entered the treatment phase of the study (423 in the MT 100 group, 430 in the naproxen group and 214 in the metoclopramide group). All but 3 subjects completed the study with evaluable efficacy data. One subject in each treatment group failed to return for final study assessments. No subject terminated early for lack of efficacy or adverse events. Thus, the ITT efficacy population consisted of 422 subjects in the MT 100 group, 429 subjects in the naproxen group and, 213 subjects in the metoclopramide group for a total of 1064 subjects.

### 3.1.2.2 Demographic and Patient Characteristics

Table 3.1.2.1 presents baseline demographic characteristics. As we can observe from the table, more than 80% of subjects, in all treatment groups, were Caucasian and females with a mean age of approximately 40 years. The sponsor also showed a table for patient' baseline migraine symptoms, like migraine history and migraine symptoms at baseline for the 1067 subjects. According to the table (see Table 6.1 in Appendice), subjects had suffered from migraine attacks for an average of 18 years and most reported the absence of aura symptoms at screening. there were no statistically significant differences among the three treatment groups for any parameter tested.

Table 3.1.2.1 Demographic Characteristics for Study MT 100-301

Parameter		MT 100 (N=423)		Naproxen (N=430)		Metoclopramide (N=214)		p-value
		N	(%)	N	(%)	N	(%)	
Gender	Male	59	(14)	48	(11)	28	(13)	0.463
	Female	364	(86)	382	(89)	186	(87)	
Race	Caucasian	350	(83)	365	(85)	185	(86)	0.681
	Black	50	(12)	36	(8)	18	(8)	
	Oriental	2	(<1)	3	(1)	1	(<1)	
	Hispanic	20	(5)	22	(5)	9	(4)	
	Other	1	(<1)	4	(1)	1	(<1)	
Age (years)	Mean	40.3		40.5		39.4		0.504
	SD	10.93		10.98		10.99		
Age range (years)	18-35	141	(33)	144	(33)	74	(35)	0.802
	36-55	247	(58)	251	(58)	128	(60)	
	>55	35	(8)	35	(8)	12	(6)	
Weight (pounds)	Mean	156.5		155.4		158.0		0.608
	SD	31.45		29.89		29.94		
Height (inches)	Mean	65.6		65.2		65.4		0.295
	SD	3.37		3.21		3.36		

### 3.1.2.3 Sponsor's Efficacy Analysis Results

#### 3.1.2.3.1 Primary Efficacy Analysis Results

According to the sponsor's study reports, the planned statistical analysis of sustained pain response was **logistic regression**. Using this analysis, MT 100 was statistically superior to metoclopramide ( $p < 0.001$ ), with a trend towards significance over naproxen sodium ( $p = 0.077$ ).

The sponsor also emphasized in their study report that because sustained pain response has 2 levels of positive outcomes (1=no or mild pain at 2 hours and no more than mild pain or use of rescue medication for 2 to 24 hours; 2=no pain at 2 hours and no pain at all or use of rescue medication for 2 to 24 hours postdose), a **post hoc analysis** was conducted using the method of ordered logistic regression. Using ordered logistic regression analysis, MT 100 was significantly better than both naproxen ( $p = 0.025$ ) and metoclopramide ( $p < 0.001$ ). Table 3.1.2.2 shows the sponsor's analysis results.

Table 3.1.2.2 The Sponsor's Primary Efficacy Analysis Results (LOCF) for Study MT100-301

Variable	MT100	Naproxen	Metoclopramide	p-value	
	N (%)	N (%)	N (%)	MT 100 vs. Naproxen	MT 100 vs. Metoclopramide
Total Subjects	422 (100)	429 (100)	213 (100)		
Sustained Pain Free	64 (15.17)	46 (10.72)	15 (7.04)		
Sustained Pain Response	86 (20.38)	82 (19.11)	27 (12.68)		
Total Sustained Pain Response	150 (35.55)	128 (29.84)	42 (19.72)		
Logistic Regression				0.077	<0.001
Ordered Logistic Regression (post hoc analysis)				0.025	<0.001

#### 3.1.2.3.2 Secondary Efficacy Analysis Results

##### Pain Response at 2 hours

Table 3.1.2.3 shows the sponsor's analysis results for pain response at 2 hour time point by the LOCF method. As we can observe from the table, MT100 produced a significantly greater 2-hour pain response ( $p < 0.001$ ) and 2-hour pain free rate ( $p = 0.002$ ) than metoclopramide. MT 100 was also marginally significantly better than naproxen for the 2 hour pain free ( $p = 0.053$ ).

Table 3.1.2.3 Pain Response at the 2-hour Time Point by LOCF for Study MT 100-301

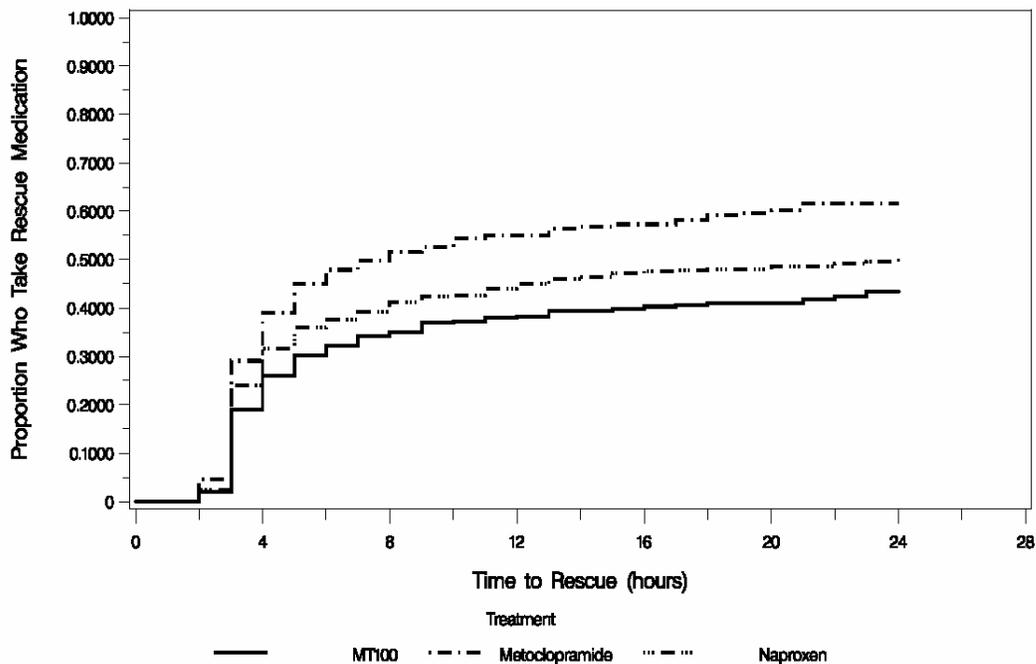
Variable	MT 100		Naproxen		Metoclopramide		p-value	
	N	(%)	N	(%)	N	(%)	MT 100 vs naproxen	MT 100 vs metoclopramide
Total subjects	422	(100)	429	(100)	213	(100)		
2-hour pain response	203	(48.10)	200	(46.62)	73	(34.27)	0.665	<0.001
2-hour pain free	79	(18.72)	60	(13.99)	20	(9.39)	0.053	0.002

Use of Rescue Medication and Incidence of Relapse

The number of subjects requiring rescue medication over the 24-hour period and the incidence of relapse in responders at 2 hours is displayed in Table 6.2 and 6.3 in the Appendices.

Fewer MT 100-treated subjects used rescue medication over the 24 hour period. The time to use of rescue medication was significantly later in the MT 100 group than in the naproxen (p=0.035) or metoclopramide (p<0.001) groups. Figure 3.1.2.1 shows the cumulative curves of proportions who take rescue medication for all treatment groups by Kaplan-Meier estimator.

Figure 3.1.2.1 Time to Use of Rescue Medication by Kaplan-Meier Estimator for Study MT100-301



### Mean Pain Intensity and Response Over Time

Mean values for the PID, SPID and TOTPAR variables over time are presented in Tables 6.4 to 6.6 of the Appendices. The 2-hour PID and SPID confirm the sustained pain response data. The 24-hour SPID and TOTPAR further confirm the lasting relief of pain.

### Nausea, Photophobia and Phonophobia at 2 hours post dose

The MT 100 group experienced significantly less photophobia at 2 hours after dosing compared to metoclopramide. Between treatment differences in nausea and phonophobia incidence were not significant at the 2-hour time point. Table 3.1.2.4 shows the detailed results.

Table 3.1.2.4 Incidence of Nausea, Photophobia and Phonophobia at 2 hours Post dose by LOCF for Study MT100-301

Variable	MT 100	Naproxen	Metoclopramide	p-value	
				MT 100 vs naproxen	MT 100 vs metoclopramide
N (%) w/ nausea at 2 hr postdose	100 (23.70)	114 (26.57)	54 (25.35)	0.333	0.646
N (%) w/ photophobia at 2 hr postdose	230 (54.50)	224 (52.21)	135 (63.38)	0.504	0.033
N (%) w/ phonophobia at 2 hr postdose	193 (45.73)	206 (48.02)	111 (52.11)	0.504	0.129

### Nausea Relief

Subjects with nausea at baseline in each of the three treatment groups had a mean nausea relief score of 0.6 at the 30 minute time point which improved by the 24 hour time point to 1.92 in the MT 100 group, 1.77 in the naproxen group and 1.48 in the metoclopramide group. There were no significant differences between treatments at any time point assessed.

### Vomiting

Too few subjects in any group experienced vomiting at the 24 hour time point to make a meaningful comparison among treatments.

### 3.1.2.4 Sponsor's Overall Conclusions

The planned statistical analysis of sustained pain response in study MT 100-301 was logistic regression. Using this analysis MT 100 was statistically superior to metoclopramide ( $p < 0.001$ ), and with a strong trend towards significance over naproxen sodium ( $p = 0.077$ ). A post hoc analysis was performed on sustained pain response

using the ordered logistic regression with subjects divided into a single negative outcome and 2 ordered positive outcomes. Using this refined analysis method, MT 100 was statistically superior to naproxen sodium and metoclopramide.

The sponsor concluded that MT 100 provides superior sustained pain response and is well tolerated. Therefore, the combination drug policy requirements have been met with the MT 100-301 study.

### 3.1.2.5 Statistical Reviewer's Comments

1. According to the sponsor's protocol, the primary efficacy endpoint of sustained pain relief was planned to be analyzed by the logistic regression with baseline pain as the covariate. In the sponsor's study report the sponsor, however only mentioned that the original analysis was "logistic regression". They did not address any covariate should be included into the logistic regression model. After this reviewer's evaluation, it was found that the sponsor's analysis results were indeed analyzed from the logistic regression model without including any covariate. After the reviewer analyzed the data by the logistic regression model but including the baseline as the covariate as prospectively specified in the protocol, the p-value for the comparison between the MT 100 and the Naproxen became 0.064 (it was 0.077 before) and the p-value for the comparison between the MT 100 and Metoclopramide was still less than 0.001. According to the reviewer's p-values, the difference between the MT100 and Naproxen was still not significant in the primary endpoint. Except the p-values changes, notice that the frequencies and percentages of the sustained pain relief in all treatment groups were the same as what were shown in Table 3.1.2.2.
2. This reviewer wants to make a point about the sponsor's significant results shown on the primary endpoint when the data was analyzed by the ordered logistic regression method with baseline pain and investigator site as the covariates. It is well known that the ordered logistic regression model can be applied only when the data hold the proportional odds assumption. Without having this assumption verified, the validity of the analysis results is questionable. That might be the reason why two analysis methods showed very different results. So, this analysis results are definitely unacceptable, let alone it is a post hoc analysis.
3. In conclusion, this study failed to show significant results on the comparison between the MT 100 and Naproxen for the primary endpoint nor for three major secondary endpoints for migraine symptoms, although for the comparison between the MT 100 and Metoclopramide, the sponsor showed significant results on some of these endpoints. So, it implies that the metoclopramide did not show significant contributions in treating patients with acute migraine attacks.

### 3.1.3 Description of Study MT 100-304

This study was titled as “A Single Dose, Double-Blind, Safety and Efficacy Study of MT 100, Metoclopramide Hydrochloride and Naproxen Sodium in Subjects with Acute Migraine Attacks”. There were 74 investigative centers in the US participated in the study.

#### 3.1.3.1 Study Objectives

The primary objective of this study was to compare the safety and efficacy of single doses of MT 100 (naproxen sodium 500 mg / metoclopramide hydrochloride 16 mg) with single doses of metoclopramide hydrochloride (16 mg) and naproxen sodium (500 mg) in the acute treatment of migraine attacks in an outpatient setting.

#### 3.1.3.2 Study Design

This was a Phase III, randomized, double-blind, parallel group, multicenter study consisting of a screening visit, at home treatment of an acute migraine attack, and a follow-up visit occurring 24-72 hours after the treated migraine attack. At the end of the screening visit, subjects were randomly assigned to one of the following three treatments (Table 3.1.3.1) for oral administration of blinded study medication.

Table 3.1.3.1 Summary of Treatments for Study MT 100-304

Treatment Arm	No. of Subjects Planned	Study Medication
A	1000	MT 100 (naproxen sodium 500 mg/metoclopramide hydrochloride 16 mg)
B	1000	Naproxen Sodium 500 mg
C	500	Metoclopramide hydrochloride 16 mg

Subjects were instructed to review the eligibility checklist to ascertain whether they continued to meet the eligibility criteria and had a headache of moderate (pain score 2) to severe (pain score 3) pain intensity when their next migraine attack occurred.

Subjects who remained eligible completed the assessments in a study diary just prior to taking study medication, and every 15 minutes for 2 hours, every 30 minutes until 4 hours and then hourly while awake for the next 20 hours after taking study medication (total evaluation period was 24 hours). Rescue medication was permitted no sooner than 2 hours after dosing, if necessary, for those subjects who still had moderate or severe pain.

#### 3.1.3.3 Efficacy Variables

The primary efficacy endpoint of sustained pain response was defined as a pain score of 0-1 (no or mild pain) at 2 hours, which did not relapse (return to a pain score of 2 or 3) or require rescue medication within the succeeding 22 hours.

Secondary outcome measures included the sustained pain free which is defined as a pain score of 0 (no pain) at 2 hours, which does not increase to a score of 1, 2, or 3 or require rescue medication within the succeeding 22 hours, the percentage of subjects with a severity of migraine pain score of 0 or 1 at 2 hours after dosing (responders) and the percentage of subjects with no pain 2 hours after dosing. Other secondary outcome measures included: time to relapse, time to rescue, incidence of nausea, photophobia and phonophobia, total pain relief (TOTPAR) using a 5-point scale over various intervals, pain intensity differences (PID) over various intervals, 24-hour sum of pain intensity differences (SPID), and nausea intensity using a 4-point scale.

### 3.1.3.4 Statistical Methods

#### 3.1.3.4.1 Determination of Sample Size

The sample size for this trial was calculated from the results of the MT 100-301 study. A difference in sustained pain response between MT 100 and naproxen sodium of 6% was projected. When analyzed by ordinal logistic regression, a sample size of 1000 subjects treated with MT 100 and 1000 subjects treated with naproxen sodium would provide approximately 90% power to detect the 6% difference at an alpha value of 0.05. A sample size of 500 subjects treated with metoclopramide provided more than 90% power to detect a 15% difference between MT 100 and metoclopramide at an alpha of 0.05 (two tailed Chi-square test).

#### 3.1.3.4.2 Efficacy Analysis Plan

Statistical analysis were performed on the primary and the secondary efficacy parameters in the “intent-to-treat” and the “per protocol” populations using data with the “last observation carried forward (LOCF)” algorithm. Unless specified, all statistical tests were two-sided at  $\alpha = 0.05$ . Analysis of the efficacy data from the intent-to-treat population with LOCF algorithm was considered the primary analysis. The primary efficacy endpoint of sustained pain response was evaluated in terms of 3 ordered categories:

- 0) non-responders = subjects with a pain score of 2 or 3 at 2 hours, subjects with a pain score of 0 or 1 at 2 hours who had a pain score return to 2 or 3 after 2 hours or who took rescue medication
- 1) sustained pain response = subjects with a pain score of 0 or 1 at 2 hours and pain scores no greater than 1 after 2 hours without the use of rescue medication
- 2) sustained pain free = subjects with a pain score of 0 at 2 hours and pain scores no greater than 0 after 2 hours without the use of rescue medication.

According to the sponsor’s study report, the ordered logistic regression, with baseline pain and investigator site as covariates, was used to test the following two contrasts:

1. MT 100 versus naproxen sodium, and
2. MT 100 versus metoclopramide hydrochloride.

**Note that,** this reviewer found that this ordered logistic regression method was not the sponsor's protocol specified primary method. The protocol specified method was the extended Mantel Haenzel statistic with score of 0, 1, and 2 for the three ordered categories and using a model that controls for center, baseline pain and gender.

For secondary outcome measures, a Cox Proportional Hazards Model (with pooled site and baseline pain as covariates) was used to compare the differences in the distribution of time to relapse and time to rescue between MT 100 and each of its components. The Cochran-Mantel-Haenszel test with center as strata was used to compare the proportion of responders between MT 100 and each of its components. The ANOVA with treatment and center as fixed effects was used to test the differences in mean PID, mean SPID, and mean pain relief (TOTPAR) at 2 hours after dosing between MT 100 and each of its components. Either Fisher's Exact Test or chi-square test was used on categorical variables, such as incidence of nausea, depending on cell size of the contingency tables.

#### *3.1.4 Analysis Results for Study MT 100-304*

##### *3.1.4.1 Disposition of Patients and Data Sets Analyzed*

The number of subjects screened for this study was 3141. Two thousand six hundred twenty-seven subjects subsequently entered the treatment phase of the study (1036 in the MT 100 group, 1062 in the naproxen group and 529 in the metoclopramide group). Eleven subjects (5 in the MT 100 group, 5 in the naproxen group and 1 in the metoclopramide group) failed to return for final study assessments and were excluded from all efficacy analyses. Additionally, one metoclopramide subject did not return for final assessments but did mail completed diary cards to the study site. Thus, the ITT efficacy population consisted of 1031 subjects in the MT 100 group, 1057 subjects in the naproxen group and 528 subjects in the metoclopramide group for a total of 2616 subjects.

##### *3.1.4.2 Demographic and Patient Characteristics*

Table 3.1.4.1 presents demographic characteristics for the 2627 subjects. There were no statistically significant differences among the three treatment groups for any parameter tested. The sponsor also performed the migraine history and migraine symptoms at baseline for the 2627 subjects. According to Table 6.7 of the Appendices, there was a statistically significant difference among the treatments for baseline pain severity ( $p=0.048$ ). A greater proportion of MT 100-treated subjects had severe pain at baseline compared to naproxen and metoclopramide-treated subjects.

Table 3.1.4.1 Demographic Characteristics for Study MT 100-304

Parameter		MT 100 (N=1036)		Naproxen (N=1062)		Metoclopramide (N=529)		p-value
		N	(%)	N	(%)	N	(%)	
Gender	Male	134	(13)	140	(13)	64	(12)	0.828
	Female	902	(87)	922	(87)	465	(88)	
Race	Caucasian	915	(88)	934	(88)	465	(88)	0.655
	Black	68	(7)	68	(6)	36	(7)	
	Oriental	8	(1)	11	(1)	5	(1)	
	Hispanic	37	(4)	41	(4)	14	(3)	
	Other	8	(1)	8	(1)	9	(2)	
Age (years)	Mean	41.6		41.3		41.1		0.646
	SD	10.65		11.11		10.99		
Age range (years)	18-35	302	(29)	314	(30)	163	(31)	0.937
	36-55	639	(62)	653	(61)	322	(61)	
	>55	95	(9)	95	(9)	43	(8)	
Weight (pounds)	Mean	154.7		155.3		155.2		0.881
	SD	30.44		30.41		29.25		
Height (inches)	Mean	65.4		65.6		65.4		0.579
	SD	3.40		3.37		3.36		

### 3.1.4.3 Sponsor's Efficacy Analysis Results

#### 3.1.4.3.1 Primary Efficacy Analysis Results

In the sponsor's study report, the primary endpoint, sustained pain response was analyzed by the ordered logistic regression method. It was stated that 'Analysis of the sustained pain response data demonstrated that MT 100 was significantly better than both naproxen (p=0.030) and metoclopramide (p<0.001)'. The detailed results are shown in Table 3.1.4.2.

Table 3.1.4.2 Primary Efficacy Results by LOCF for Study MT 100-304

Variable	MT 100		Naproxen		Metoclopramide		p-value*	
	N	(%)	N	(%)	N	(%)	MT 100 vs naproxen	MT 100 vs metoclopramide
Total subjects	1031	(100)	1057	(100)	528	(100)		
Sustained pain free	118	(11.45)	110	(10.41)	31	(5.87)		
Sustained pain response	210	(20.37)	185	(17.50)	68	(12.88)		
Ordered logistic regression							0.030	<0.001
<b>Total sustained pain responders</b>	<b>328</b>	<b>(31.81)</b>	<b>295</b>	<b>(27.91)</b>	<b>99</b>	<b>(18.75)</b>		

\* Ordered logistic regression w/ baseline pain and pooled site as covariates

**Notice that,** the agency later asked the sponsor to perform the reanalysis for the primary endpoint by the originally protocol specified method, i.e., the extended Mantel Haenzel statistic with score of 0, 1, and 2 for the three ordered categories and using a model with that controls for center, baseline pain and gender. Their reanalysis results showed a slightly higher p-value for comparison of MT 100 to Naproxen. The original p-value for the comparison between the MT 100 and Naproxen was 0.030 and the new p-value is 0.038. The p-value for the comparison of MT 100 to Metoclopramide was not changed. So, the sponsor concluded that the interpretation of the statistical significance of the results remains the same.

### 3.1.4.3.2 Secondary Efficacy Analysis Results

#### Pain Response at 2 hours

More subjects in the MT 100 group had a response to treatment at 2 hours or were pain free without the use of rescue medication at that time point compared to naproxen and metoclopramide, but the difference was statistically significant only for the comparison with the metoclopramide component. See Table 3.1.4.3 for the detailed result.

Table 3.1.4.3 Pain Response at the 2-Hour Time Point by LOCF for Study MT100-304

Variable	MT 100		Naproxen		Metoclopramide		p-value	
	N	(%)	N	(%)	N	(%)	MT 100 vs naproxen	MT 100 vs metoclopramide
Total subjects	1031	(100)	1057	(100)	528	(100)		
2-hour pain response	513	(49.76)	494	(46.74)	193	(36.55)	0.143	<0.001
2-hour pain free	173	(16.78)	169	(15.99)	48	(9.09)	0.604	<0.001

### Sustained Pain Free

As we can observe from Table 3.1.4.4 for the analysis results of sustained pain free endpoint, significantly more subjects were pain free at 2 hours and through 24 hours postdose in the MT 100 group compared to the metoclopramide group.

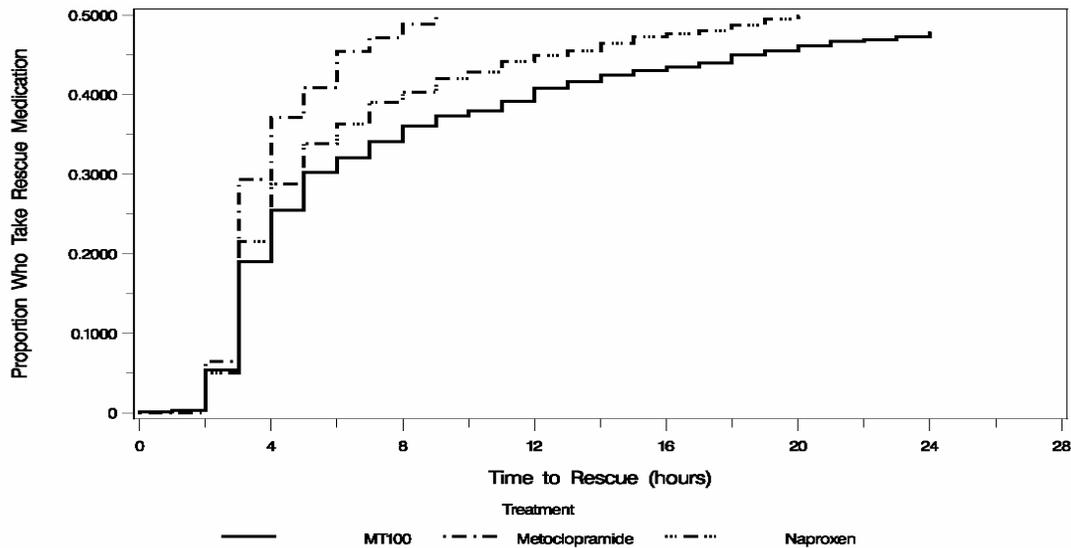
Table 3.1.4.4 Sustained Pain Free Results by LOCF for Study MT100-304

Variable	MT 100		Naproxen		Metoclopramide		p-value	
	N	(%)	N	(%)	N	(%)	MT 100 vs naproxen	MT 100 vs metoclopramide
Total subjects	1031	(100)	1057	(100)	528	(100)		
Sustained pain free	118	(11.45)	110	(10.41)	31	(5.87)	0.442	<0.001

### Use of Rescue Medication and Incidence of Relapse

The number of subjects requiring rescue medication over the 24-hour period and the incidence of relapse in both responders at 2 hours and in subjects with pain free at 2 hours are shown in Table 6.8 and 6.10 of the Appendices. As we can observe from Table 6.7, a lower proportion of subjects in the MT 100 group required the use of rescue medication after dosing compared to subjects in the naproxen and metoclopramide groups. MT 100-treated subjects used rescue medication significantly later than subjects in the metoclopramide group ( $p < 0.001$ ). Figure 3.1.4.1 shows the cumulative curves of proportions who take rescue medication for all treatment groups by Kaplan-Meier estimator.

Figure 3.1.4.1 Time to Use of Rescue Medication (Kaplan-Meier) for Study MT 100-304



Mean Pain Intensity and Response Over Time

Mean values for the PID, SPID and TOTPAR variables over time are presented in Tables 6.8 to 6.10 of the Appendices. The 2, 12 and 24-hour PID and SPID confirm the sustained pain response data. Additionally, the MT 100 12- and 24-hour TOTPAR is significantly better than naproxen and metoclopramide.

Nausea, Photophobia and Phonophobia at 2 Hours Post Dose

The MT 100 group experienced significantly less nausea at 2 hours after dosing compared to metoclopramide. The incidence of photophobia was significantly different between MT 100 (55%) and metoclopramide (62%) at the 2 hour post-dose assessment. The difference in phonophobia incidence between MT 100 and metoclopramide approached significance at the 2 hour post-dose assessment and was significantly different at all subsequent time points. The detailed 2 hour postdose results are shown in Table 3.1.4.5.

Table 3.1.4.5 Incidence of Nausea, Photophobia and Phonophobia at 2 Hours Post-dose by LOCF for Study MT 100-304

Variable	MT 100	Naproxen	Metoclopramide	p-value	
				MT 100 vs naproxen	MT 100 vs metoclopramide
N (%) w/ nausea at 2 hr postdose	346 (33.56)	387 (36.61)	219 (41.48)	0.138	0.003
N (%) w/ photophobia at 2 hr postdose	565 (54.80)	570 (53.93)	328 (62.12)	0.721	0.007
N (%) w/ phonophobia at 2 hr postdose	495 (48.01)	508 (48.06)	279 (52.84)	1.00	0.080

### Nausea Intensity

Nausea intensity was significantly lower in the MT 100 group compared to metoclopramide from 45 minutes through 24 hours post dose. Mean nausea intensity was significantly different from naproxen in the MT 100 group from 3 hours through 24 hours post dose; no significant differences were noted at any other time points. The detailed analysis results are shown in Table 6.13 of the Appendices.

### Vomiting

Too few subjects in any group experienced vomiting at the 24 hour time point to make a meaningful comparison among treatments.

#### 3.1.4.4 Sponsor's Overall Conclusions

The sponsor summarized that the results of this study indicate that MT 100:

- is significantly more effective than both naproxen sodium and metoclopramide hydrochloride on the identified primary outcome measure of sustained pain response,
- is an effective treatment of migraine pain (significantly better than metoclopramide in 2-hour pain response,  $p < 0.001$ ),
- is an effective treatment for the secondary symptoms of migraine (nausea and photophobia at 2 hours and phonophobia at 2.5 hours) as shown by the superiority of MT 100 compared to metoclopramide, and
- produces a similar incidence of adverse events to its components.

Finally, the sponsor concluded that the results from this adequate and well-controlled trial, combined with the results from MT 100-301, provided convincing evidence of the superiority of MT 100 over its individual components.

#### 3.1.4.5 Statistical Reviewer's Comments

1. This reviewer found that the sponsor's analysis method for the primary endpoint shown in the study reports was different from what was originally planned in the protocol. The method that the sponsor used in the submission was the ordered logistic regression, with baseline pain and investigator site as covariates, but the method that they prospectively specified in the protocol was the extended Mantel Haenzel statistic with scores of 0, 1, and 2 for the three ordered categories and using a model that controls for center, baseline pain and gender.

The sponsor was later asked to perform the reanalysis by the pre-stated method in the protocol. They showed that the p-value for the comparisons between MT 100 and Naproxen was 0.038 (instead of 0.03 before) and for the comparisons between MT 100 and Metoclopramide was still  $< 0.001$ . The sponsor emphasized that they

performed this analysis by using the SAS Macro written by Koch<sup>\*</sup>. The reason why they did not analyze the data directly by using the SAS procedure was because of zero cells existing when stratifying factors of center, baseline pain and gender.

This reviewer requested the sponsor submitted their program and the SAS Macro by Koch and then evaluated their analysis results. It was found that by using the SAS Macro written by Koch the p-value for the comparisons between MT 100 and Naproxen should be 0.063 not 0.038. The sponsor mistakenly used equal weight for all stratum instead of a weight that is comparable to the strata's proportion of patients in the trial, where used in the extended Mantel-Haenszel statistics.

To further evaluate the robustness of the analysis results by the originally protocol specified method, this reviewer also analyzed the data by stratifying the center factor only, which is the only factor that we normally stratified. The p-value was shown as 0.0865, regardless of whether it was obtained by using the Koch's SAS Macro or simply by this reviewer's SAS program. Therefore, the insignificant findings about this data set was further confirmed and moreover, the reliability of the Koch's SAS macro was also somewhat verified.

2. In summary, this study failed to show that the MT 100 is statistically significantly more effective than both individual components in treating migraine patients' pain and three major symptoms. For the comparisons between the MT 100 and Naproxen, especially, the data did not show any significant efficacy improvement on treating patients' migraine pain and any of three symptoms.

### *3.1.5 Description of Study MT 100-306*

This study was titled as "A Double-Blind, Placebo-Controlled, Pilot Study to Evaluate the Safety and Efficacy of MT 100 versus Sumatriptan in Subjects with Acute Migraine Attacks" and there were twenty investigative centers in the US participated in the study.

#### *3.1.5.1 Study Objectives*

The objective of this study was to compare the safety and efficacy of one or two tablets of MT 100 with placebo and sumatriptan 50 mg for the acute treatment of a migraine attack in an outpatient setting.

---

\* The method was referred in the following paper:  
Koch, Gary G., Catherine M Tangen, Jin-Whan Jung and Ingrid A. Amara, (1998). Issues for covariance analysis of dichotomous and ordered categorical data from randomized clinical trials and non-parametric strategies for addressing them. *Statistics in Medicine*, Vol 17. pp1863-1892.

### 3.1.5.2 Study Design

This was a Phase III, randomized, double-blind, double-dummy, parallel group, multicenter study consisting of a screening visit, at home treatment of an acute migraine attack, and a follow-up visit occurring 24-72 hours after the treated migraine attack. At the end of the screening visit, subjects were randomly assigned to one of four treatments, which were shown on Table 3.1.5.1.

Table 3.1.5.1 Summary of Treatments for Study MT100-306

<b>Treatment Assignment</b>	<b>Study Medication</b>
A	MT 100 (Single Tablet) + Placebo Tablet + Placebo Capsule
B	Overencapsulated Sumatriptan 50 mg Capsule + 2 Placebo Tablets
C	2 Placebo Tablets + Placebo Capsule
D	MT 100 (Two Tablets) + Placebo Capsule

Subjects were instructed to review the eligibility checklist to ascertain whether they continued to meet the eligibility criteria and had a headache of moderate (pain score 2) to severe (pain score 3) pain intensity when their next migraine attack occurred. Subjects who remained eligible completed the assessments in a study diary just prior to taking study medication, and every 15 minutes for 2 hours, every 30 minutes until 4 hours and then hourly while awake for the next 20 hours after taking study medication (total evaluation period was 24 hours). Rescue medication was permitted no sooner than 4 hours after dosing, if necessary, for those subjects who still had moderate or severe pain.

### 3.1.5.3 Efficacy Variables

The primary efficacy variable was the percent of subjects with a pain response at 2 hours (defined as a pain score of 0 or 1 at 2 hours after dosing).

Secondary outcome measures compared both doses of MT 100, placebo and sumatriptan and were to include: the percentage of subjects with a severity of migraine pain score of 0 or 1 at 4 hour after dosing, percentage of subjects with no pain 2 and 4 hours after dosing, total pain relief (TOTPAR) using a 5-point scale over various intervals, and nausea intensity using a 4-point scale. Other secondary outcome measures would include time to relapse, PID (Pain Intensity Difference), SPID (Sum of Pain Intensity Differences), time to meaningful relief, sustained pain response, complete sustained response and time to rescue.

### 3.1.5.4 Statistical Methods

#### 3.1.5.4.1 Determination of Sample Size

Based on the assumptions of 48% and 30% of the proportion of subjects achieving 2 hour pain response with MT 100 and with placebo, respectively, 125 subjects per treatment group would be required to achieve approximately 80% power to detect a between treatment difference of 18% (Chi-square test, two sided).

#### 3.1.5.4.2 Efficacy Analysis Plan

Analysis of the efficacy data from the intent-to-treat population with LOCF algorithm was considered the primary analysis. Unless specified otherwise, all statistical tests were two-sided at  $\alpha = 0.05$ .

The primary efficacy outcome measure was the proportion of subjects with a pain response at 2 hours (pain score of 0 or 1 at 2 hours after dosing). The Cochran-Mantel-Haenszel test with center as strata was used to test the following pairwise comparisons:

1. MT 100 1 tablet versus placebo
2. MT 100 2 tablets versus placebo
3. Sumatriptan versus placebo
4. MT 100 2 tablets versus sumatriptan

About the secondary efficacy outcome measure, the Cochran-Mantel-Haenszel test with center as strata was to be used to compare the percentage of responders, subjects pain free, and subjects with phonophobia, photophobia and nausea. A post hoc analysis of ordered logistic regression was to be used to compare sustained pain response rates at 2 hours for all active treatments with placebo. Additionally, 2 tablets of MT 100 would be compared with 1 tablet of MT 100 and sumatriptan.

A post hoc analysis of ANOVA with treatment and center as fixed effects was used to test the differences in mean pain relief at 2 hours after dosing, nausea relief (5-point scale), PID, SPID and TOTPAR. Either Fisher's Exact Test or Chi-square test was used on categorical variables, such as incidence of nausea.

A Cox Proportional Hazards Model (with baseline pain and pooled site as covariates) was used to test the differences in the distribution of time to relapse, the distribution of time to rescue, and time to meaningful relief between MT 100 and sumatriptan.

Subgroup analyses on the efficacy measures were performed within age group, gender group, and subject groups based on severity of migraine pain and the presence of nausea at baseline.

### 3.1.6 Analysis Results for Study MT 100-306

#### 3.1.6.1 Disposition of Subjects and Data Sets Analyzed

Six hundred thirty-five subjects were screened and 546 subsequently entered the treatment phase of the study. All 546 treated subjects completed the study. Thus, the ITT efficacy population consisted of 138 subjects in the group of MT 100 single tablet, 142 subjects in the group of MT 100 2-tablet, 129 subjects in the sumatriptan group, and 137 subjects in the placebo group for a total of 546 subjects.

#### 3.1.6.2 Demographic and Patient Characteristics

A summary of the demographic characteristics is presented in Table 3.1.6.1. As we can observe from the table, there were no statistically significant differences among the four treatment groups for any demographic parameter tested. The majority of subjects in all treatment groups were female Caucasians with a mean age of approximately 40 years.

Table 3.1.6.1 Demographic Characteristics for Study MT 100-306

Parameter		MT 100 1 tablet (N=138)		MT 100 2 tablets (N=142)		Sumatriptan (N=129)		Placebo (N=137)		p-value
		N	(%)	N	(%)	N	(%)	N	(%)	
Gender	Male	14	(10)	26	(18)	12	(9)	19	(14)	0.103
	Female	124	(90)	116	(82)	117	(91)	118	(86)	
Race	Caucasian	115	(83)	98	(69)	95	(74)	108	(79)	0.167
	Black	12	(9)	21	(15)	17	(13)	14	(10)	
	Oriental	0	(0)	0	(0)	2	(2)	1	(1)	
	Hispanic	11	(8)	19	(13)	14	(11)	13	(9)	
	Other	0	(0)	4	(3)	1	(1)	1	(1)	
	Age (years)	Mean	40.4		39.2		40.4		40.5	
	SD	10.75		10.42		10.40		11.06		
Age range (years)	18-35	48	(35)	55	(39)	46	(36)	45	(33)	0.685
	36-55	78	(57)	80	(56)	73	(57)	77	(56)	
	>55	12	(9)	7	(5)	10	(8)	15	(11)	
Weight (pounds)	Mean	158.5		160.2		152.8		154.7		0.175
	SD	29.08		34.37		28.63		29.83		
Height (inches)	Mean	65.4		65.9		65.4		65.6		0.543
	SD	3.18		3.72		3.30		3.19		

The sponsor also showed a summary of the migraine history and migraine symptoms at baseline for the 546 randomized subjects (See Table 6.14 of the Appendix). As we can observe from the table, there was a slight imbalance in the distribution of subjects with severe baseline migraine pain and with nausea. Only 34% of the sumatriptan group had severe pain at baseline compared with 44% of the MT 100 single tablet group. Similarly, only 59% of the sumatriptan group had nausea at baseline compared with 69% of the MT 100 single tablet group. Subjects had experienced migraine attacks for an average of 18 years and also the majority of subjects had migraine without aura.

### 3.1.6.3 Sponsor’s Efficacy Analysis Results

#### 3.1.6.3.1 Primary Efficacy Analysis Results

The primary efficacy measure was 2-hour pain response, defined as a change in headache pain from moderate or severe at baseline to mild or no pain at 2 hours without the use of rescue medication. The sponsor’s analysis of the pain response (0-1 score) data at 2 hours indicated that each of the active treatment groups was significantly better than placebo. It was shown in Table 3.1.6.2.

Table 3.1.6.2 Primary Efficacy Results by LOCF for Study MT 100-306

<b>Variable</b>	<b>Number of responders (%)</b>
<b>Pain response at 2 hours</b>	
MT 100 1 tablet (N=138)	73 (52.90)
MT 100 2 tablets (N=142)	83 (58.45)
Sumatriptan (N=129)	69 (53.49)
Placebo (N=137)	40 (29.20)
p-value MT 100 1 tablet vs. placebo	<0.001
p-value MT 100 2 tablets vs. placebo	<0.001
p-value MT 100 1 tablet vs. MT 100 2 tablets	0.320
p-value sumatriptan vs. placebo	<0.001
p-value MT 100 2 tablets vs. sumatriptan	0.454

#### 3.1.6.3.2 Secondary Efficacy Analysis Results

##### Sustained Pain Response

Sustained pain response is presented in Table 3.1.6.3. The sustained pain response was significantly better in both MT 100 groups compared to placebo (p=0.029 for the MT 100 single tablet group; p<0.001 for the MT 100 2-tablet group). Sumatriptan was different from placebo but just failed to reach the level of statistical significance (p=0.055). Sustained pain response was significantly better in the MT 100 2-tablet group compared to sumatriptan (p=0.032). Additionally, the MT 100 2-tablet dose was significantly greater than the MT 100 1-tablet dose (p=0.047).

Table 3.1.6.3 Sustained Pain Response during 24 Hours After dosing by LOCF for Study MT 100-306

Variable	MT 100 1 tablet (n=138)	MT 100 2 tablets (n=142)	Suma (n=128)	Pbo (n=137)	p-value*				
					MT 100 1 tab vs. Pbo	MT 100 2 tabs vs. Pbo	MT 100 1 tab vs. 2 tabs	Suma vs. Pbo	MT 100 2 tabs vs. Suma
N(%) Sustained pain free	20 (14.49)	27 (19.01)	22 (17.05)	13 (9.49)					
N(%) Sustained pain response	27 (19.57)	39 (27.46)	20 (15.50)	17 (12.41)					
Ordered logistic regression					0.029	<0.001	0.047	0.055	0.032
<b>N (%) Total sustained pain responders</b>	<b>47 (34.06)</b>	<b>66 (46.48)</b>	<b>42 (32.56)</b>	<b>30 (21.90)</b>					

Ordered logistic regression w/ baseline pain and pooled site as covariates.

Note: Pbo=placebo; Suma=Sumatriptan

### Sustained Pain Free

Significantly more subjects were pain free at 2 hours and through 24 hours post dose in the MT 100 2-tablet group compared to placebo. Neither the single tablet dose of MT 100 nor sumatriptan were significantly different from placebo. The detailed results are shown in Table 3.1.6.4.

Table 3.1.6.4 Sustained Pain Free Results by LOCF for Study MT 100-306

Variable	MT 100 1 tablet		MT 100 2 tablets		Suma		Pbo		p-value			
	N	(%)	N	(%)	N	(%)	N	(%)	MT 100 1 tab vs. Pbo	MT 100 2 tabs vs. Pbo	Suma vs. Pbo	MT 100 2 tabs vs. Suma
Total subjects	138	(100)	142	(100)	129	(100)	137	(100)				
Sustained pain free	20	(14.49)	27	(19.01)	22	(17.05)	13	(9.49)	0.201	0.022	0.080	0.610

### Time to Onset of Pain Response

The percentage of subjects with pain response was significantly greater in each of the active treatment groups compared to placebo beginning at 0.75 hours post dose. Mean pain response at selected time points was assessed using the PID, SPID and TOTPAR variables. All active treatments had significantly more rapid onset of activity compared to placebo for all three measures by 1.5 hours postdose ( $p < 0.05$ ). The PID and SPID scores for the MT 100 single tablet group and the sumatriptan group were nearly identical at all time points. The numerically greater pain relief scores on sumatriptan may reflect the lower percentage of subjects with severe pain at baseline in this group.

The response rate in subjects with moderate pain at baseline was greater than in subjects with severe baseline pain. Table 6.15 of the Appendices shows the results.

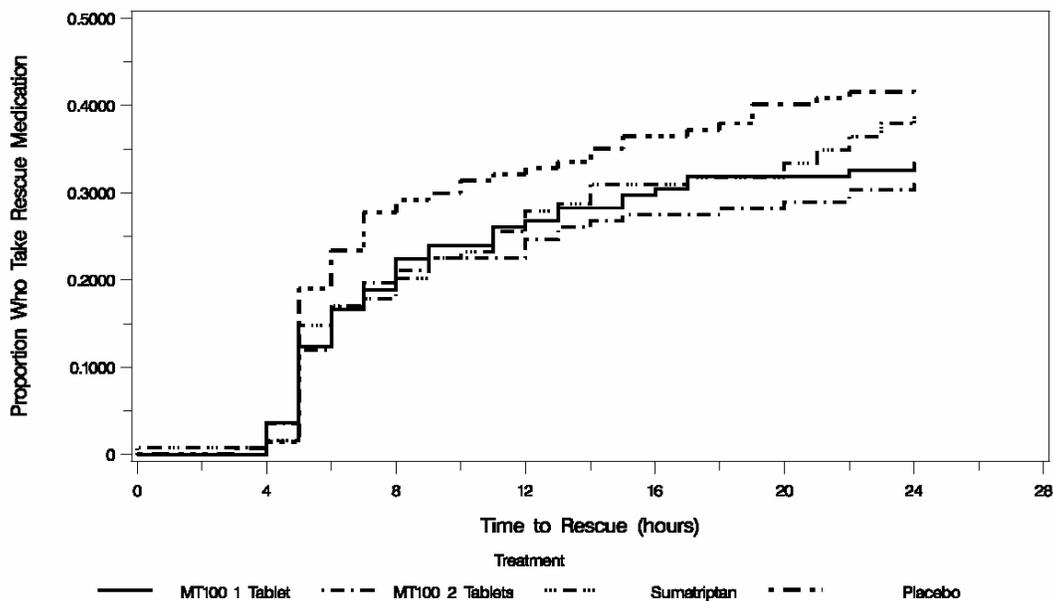
### Meaningful Pain Relief

Significantly more subjects in the MT 100 2-tablet ( $p<0.001$ ) and sumatriptan ( $p=0.011$ ) groups experienced meaningful pain relief within the first 4 hours after dosing compared to placebo. No significant differences were noted between the MT 100 single tablet group and placebo. The detailed results are shown in Table 6.16 of the Appendices.

### Use of Rescue Medication and Incidence of Relapse

The number of subjects requiring rescue medication over the 24-hour period and the incidence of relapse in both responders at 2 hours are displayed in Table 6.17 and Table 6.18 of the Appendices. A lower proportion of subjects in the MT 100 groups required the use of rescue medication after dosing compared to subjects in the sumatriptan and placebo groups. Subjects in the MT 100 2-tablet group used rescue medication significantly later than subjects in the placebo group (see Figure 3.1.6.1).

Figure 3.1.6.1 Time to Use of Rescue Medication Analysis by Kaplan-Meier for Study MT 100-306



### Nausea, Photophobia and Phonophobia at 2 Hours Post Dose

There was significantly less nausea at 2 hours after dosing in the MT 100 single tablet group compared to placebo, with the 2 tablet dose just failing to reach statistical significance ( $p=0.054$ ). No significant differences were noted between the sumatriptan group and placebo at this time point.

The percentage of subjects with photophobia was significantly less in each of the active treatment groups than in the placebo group. Between treatment differences

compared to placebo for phonophobia were significant at the 2 hour time point for the MT 100 2-tablet and sumatriptan groups. The single tablet dose of MT 100 indicated a strong trend towards significance for the 2 hour assessment of phonophobia. The detailed analysis results by the sponsor are shown in Table 3.1.6.5 below.

Table 3.1.6.5 Incidence of Nausea, Photophobia and Phonophobia at 2 Hours Post Dose by LOCF for Study MT 100-306.

Variable	MT 100 1 tablet (n=138)	MT 100 2 tablets (n=142)	Suma (n=128)	Pbo (n=137)	p-value			
					MT 100 1 tab vs. Pbo	MT 100 2 tabs vs. Pbo	Suma vs. Pbo	MT 100 2 tabs vs. Suma
N (%) w/ nausea at 2 hr postdose	38 (27.54)	39 (27.46)	51 (39.53)	53 (38.69)	0.049	0.054	0.880	0.033
N (%) w/ photophobia at 2 hr postdose	65 (47.10)	64 (45.07)	50 (38.76)	91 (66.42)	0.002	<0.001	<0.001	0.354
N (%) w/ phonophobia at 2 hr postdose	60 (43.48)	59 (41.55)	41 (31.78)	76 (55.47)	0.062	0.027	<0.001	0.124

### Nausea Intensity

Mean nausea intensity at 2 hours post-dose was 0.39 in the MT 100 single tablet group, 0.38 in the MT 100 2-tablet group and 0.77 in the sumatriptan and placebo groups. Mean nausea intensity was not significantly different from placebo in any treatment group at this time point.

### Vomiting

Too few subjects in any group experienced vomiting over the 24 hour period to make a meaningful treatment comparison.

### 3.1.6.4 Sponsor's Overall Conclusions

The results of this trial in subjects with moderate or severe migraine pain demonstrate that:

1. the single tablet dose of MT 100 is more effective than placebo for the relief of migraine pain and associated symptoms of photophobia, phonophobia and nausea.
2. the efficacy of a single tablet of MT 100 is generally similar to that provided by sumatriptan 50 mg, with the notable difference of providing better nausea relief at 2 hours, and
3. the dose of two tablets of MT 100 provides similar 2-hour pain relief but superior sustained pain response compared to the single tablet dose of MT 100 and sumatriptan 50 mg.

### 3.1.6.5 Statistical Reviewer's Comments

1. This reviewer confirmed the sponsor's analysis results for the primary endpoint and most of secondary endpoints. For the secondary endpoint of incidence of phonophobia at 2 hours post dose, this reviewer had different p-values from the sponsor's for the comparisons between the 1 tablet of MT 100 and 2 tablets of MT 100 versus the placebo, respectively, although this reviewer had the same numbers of patients with phonophobia at 2 hours post dose for all treatment groups as the sponsor had. The reviewer's p-values for the comparisons between 1 tablet of MT 100 and placebo, and 2 tablets of MT 100 and placebo are 0.053 and 0.0201, respectively, but the sponsor's p-values for them were 0.062 and 0.027, respectively.
2. This reviewer noticed that in the sponsor's original protocol, there did not exist the arm of 2 tablets of MT 100 in the study. That treatment arm was later added per the amendment No. 1. With the action of adding this extra arm, the sponsor, however, did not provide any study analysis plan for dealing with multiple comparisons for 1 tablet of MT 100 and 2 tablets of MT 100 versus the placebo, respectively. Nevertheless, according to the analysis results from this study, it does not seem to have any inconsistent conclusions by different multiple comparison procedures. It is clear that the data showed the evidence of MT 100's efficacy on pain relief at 2 hours but not on all of three major migraine symptoms.
3. Although the sponsor showed the MT 100's efficacy on pain relief and two of three major migraine symptoms versus the placebo in this study, this reviewer wants to emphasize that since this study did not provide any information on the contribution from the individual components to the effect of MT 100, and also the sponsor failed on both factorial designed trials for showing the contribution of both individual components statistically significantly, one can not claim any significant findings based on this type of placebo comparison trials.

### 3.1.7 Description of Study MT 100-308

This study was titled as 'A Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of MT 100 Versus Over-Encapsulated Sumatriptan in Subjects with Acute Migraine Attacks.' There were forty-one investigative centers in the US participated in the study.

#### 3.1.7.1 Study Objectives

The objectives of this study are:

- To compare the safety and efficacy of a single tablet dose of MT 100 with over-encapsulated sumatriptan in the acute treatment of migraine attacks in an outpatient setting

- To compare the safety and efficacy of a single tablet dose of MT 100 with placebo in the acute treatment of migraine attacks in an outpatient setting
- To compare the safety and efficacy of a single tablet dose of over-encapsulated sumatriptan with placebo in the acute treatment of migraine attacks in an outpatient setting

### 3.1.7.2 Study Design

This was a Phase III, randomized, double-blind, double-dummy, placebo controlled, parallel group, multicenter study consisting of a screening visit, the at-home treatment of an acute migraine attack, and a follow-up visit occurring 24-72 hours after the treated migraine attack.

At the end of the screening visit, subjects were randomly assigned in a 1:1:1 ratio to one of the following three treatments (Table 3.1.7.1) for oral administration of blinded study medication.

Table 3.1.7.1 Summary of Treatments for Study MT100-308

<b>Treatment Assignment</b>	<b>Study Medication</b>
A	1 MT 100 Tablet & 1 Placebo Capsule
B	1 Placebo Tablet & 1 Over-encapsulated Sumatriptan 50 mg Capsule
C	1 Placebo Tablet & 1 Placebo Capsule

Three hundred twenty-five subjects per treatment group were targeted for completion (revised from 250 per group by Amendment 2).

When the next migraine attack occurred, the subjects were instructed to review the eligibility checklist to ascertain whether they continued to meet the eligibility criteria for use of study drug and verify that they had a headache of moderate (pain score 2) or severe (pain score 3) intensity.

Subjects who remained eligible completed the assessments in a study diary just prior to taking study medication. After taking the medication they completed the same assessments every 15 minutes for 2 hours, every 30 minutes for the next 2 hours and then every hour while awake for the next 20 hours. Rescue medication was permitted no sooner than 2 hours (changed from 4 hours by Amendment 1) after dosing, if necessary, for those subjects who had either moderate or severe pain at that time.

### 3.1.7.3 Efficacy Variables

The primary efficacy variable was the proportion of subjects who achieved a 2-hour pain response, defined as a pain score of 0 or 1 (no or mild pain), at 2 hours.

Secondary outcome measures included percentage of subjects with a sustained pain response; percentage sustained pain free; pain intensity difference from baseline (PID); 24-hour sum of pain intensity differences (SPID); time to use of rescue medication; time to relapse; incidence of nausea, photophobia, phonophobia and vomiting; nausea intensity, and clinical disability at various time points.

### 3.1.7.4 Statistical Methods

#### 3.1.7.4.1 Determination of Sample Size

Based on the assumptions of 54%, 53% and 29% of the proportion of subjects achieving pain response at 2 hours in the sumatriptan group, the MT 100 group and the placebo, respectively, 323 subjects per group are required to achieve approximately 80% power to conclude there is no treatment difference (within 10%) between MT 100 and sumatriptan.

When the sample size in each group is 323 subjects, there is more than 99% power, with a two-sided 0.050 significance level, to detect a difference between MT 100 and placebo in the proportion of subjects exhibiting pain response at 2 hours. Similarly, 323 subjects provide more than 99% power to detect the difference between sumatriptan and placebo.

#### 3.1.7.4.2 Efficacy Analysis Plan

Statistical analysis was to be performed on the primary and secondary efficacy parameters in the ITT and PP populations using data subjected to the last observation carried forward (LOCF) algorithm. Specifically, missing values were to be replaced with the last prior non-missing value. Additionally, for subjects who rescued, their baseline pain scores were to replace all post-rescue measurements. The worst possible photophobia, phonophobia, nausea and clinical disability were to replace all post-rescue measurements.

In general, the MT 100 versus sumatriptan equivalence comparisons were primary, while the comparisons to examine differences between active and placebo were performed to validate the study design and patient population.

For comparison of proportions of 2 hour pain responders between the two active treatments, the two-group Chi-square test for equivalence (Blackwelder, 1982) was employed. Ninety-five percent confidence intervals of the difference in proportion of responders receiving MT 100 and sumatriptan were calculated. Comparisons were to consider the two active treatments to be equivalent if the proportions were within a

margin of 0.10, using the following hypothesis structure:

$$H_0: P_1 > P_2 + 0.10 \quad H_A: P_1 \leq P_2 + 0.10$$

Where  $P_1$  denotes the proportion in the sumatriptan group and  $P_2$  denotes the proportion in the MT 100 group.

To test for differences between each active treatment and placebo, the Cochran Mantel Haenszel test was used, with a two-sided 0.050 level of significance.

Secondary efficacy outcome measures were of two types: proportions (of subjects) and numeric values. Analyses of secondary efficacy outcome measures were to compare the two active treatments and to examine each active treatment for difference from placebo. For data expressed as numeric values, analyses were to perform comparisons for treatment differences.

Analyses to detect proportional treatment differences between active and placebo were performed with the Cochran Mantel Haenszel test described in the same section.

Nausea intensity and pain intensity treatment comparisons were performed using the analysis of variance (ANOVA), with treatment and center as fixed effects, and including pair-wise treatment comparisons.

For examination of “time to” analyses, such as time to rescue and time to relapse, Kaplan Meier survival methodology was used to examine treatment differences in the distributions.

Subgroup analyses of pain response were performed for subjects with moderate pain at baseline, subjects with severe pain at baseline, subjects with nausea at baseline, and subjects without nausea at baseline. These analyses were to be performed if the subgroups contained at least 50 subjects in one or more treatment groups.

### *3.1.8 Analysis Results for Study MT 100-308*

#### 3.1.8.1 Disposition of Patients and Data Sets Analyzed

A total of 1272 subjects were screened at 40 study centers, and 1027 subsequently entered the treatment phase of the study (337 in the MT 100 treatment group, 343 in the sumatriptan group, and 347 in the placebo group). Fourteen subjects were excluded from the ITT efficacy analyses. The subjects who were excluded had no efficacy data showing moderate or severe pain at baseline. Thus, the ITT efficacy population consisted of 1013 subjects: 332 in the MT 100 group, 340 in the sumatriptan group, and 341 in the placebo group. The PP population consisted of 1004 subjects: 328 in the MT 100 group, 337 in the sumatriptan group, and 339 in the placebo group.

### 3.1.8.2 Demographic and Patient Characteristics

Table 3.1.8.1 summarizes demographic characteristics for the 1027 treated subjects. As we observe from the table, the majority of subjects in all treatment groups were female Caucasians with a mean age of approximately 40 years. Subjects had suffered from migraine attacks for an average of 19 years.

Table 3.1.8.1 Demographic Characteristics for Study MT 100-308

Parameter	MT 100		Sumatriptan		Placebo		p-value	
	N	(%)	N	(%)	N	(%)		
<b>Screening</b>								
<b>Total</b>	<b>337</b>		<b>343</b>		<b>347</b>			
Gender	Male	55	16	44	13	39	11	0.180
	Female	282	84	299	87	308	89	
Age group (years)	18-35	124	37	106	31	123	35	0.083
	36-55	191	57	200	58	185	53	
	>55	22	7	37	11	39	11	
Race	Caucasian	286	85	291	85	295	85	0.845
	African American	27	8	26	8	21	6	
	Oriental/Asian	3	1	4	1	8	2	
	Hispanic	18	5	20	6	19	5	
	Other	3	1	2	1	4	1	
Age (years)	Mean	39.9	NA	40.9	NA	40.5	NA	0.494
	SD	11.12	NA	11.38	NA	11.76	NA	
Height *(inches)	Mean	66.2	NA	65.6	NA	65.8	NA	0.076
	SD	3.37	NA	3.25	NA	3.27	NA	

The sponsor also showed migraine history at screening and baseline symptoms of the treated migraine for those treated subjects (See Table 6.19 of the Appendices). According to the table, approximately 56% to 62% of subjects across treatment groups had moderate pain and 38% to 43% had severe pain at baseline with the treated

migraine. The majority of subjects had migraines with nausea and without aura. Additionally, 82% to 84% of the subjects had baseline photophobia and 78% to 82% had baseline phonophobia.

### 3.1.8.3 Sponsor’s Efficacy Analysis Results

#### 3.1.8.3.1 Primary Efficacy Analysis Results

The difference in pain response between MT 100 and 50 mg sumatriptan at 2 hours was 3.4% with a 95% confidence interval between –4.2% and 10.9%. Both of the active treatments were superior to placebo. Table 3.1.8.2 shows the detailed analysis results. It also includes pain response data at various time points up to 2 hours.

Table 3.1.8.2 Primary Efficacy Results – Pain Response over Time Post-Dose for Study MT 100-308

Variable		Time post-dose (hours)						
		0.5	0.75	1	1.25	1.5	1.75	2
<b>Pain Response</b>								
MT 100 (N = 332)	N of responders	18	43	74	102	122	128	<b>146</b>
	% of responders	5.4	13.0	22.3	30.7	36.8*	38.6	<b>44.0*</b>
Sumatriptan (N = 340)	N of responders	16	38	70	84	110	134	<b>161</b>
	% of responders	4.7	11.2	20.6	24.7	32.4	39.4	<b>47.4*</b>
<b>p-value<sup>†</sup></b>		<0.001	<0.001	<0.001	<0.001	<0.001	0.008	0.042
<b>Difference</b>								3.4
<b>95% CI</b>								(-4.2, 10.9)

† p-values from Blackwelder test of equivalence

#### 3.1.8.3.2 Secondary Efficacy Analysis Results

##### Sustained Pain Response and Sustained Pain Free

As shown in Table 3.1.8.3 there were higher percentages of subjects in both active treatment groups with sustained pain response and sustained pain free than in the placebo group.

The post-hoc analysis of equivalence, between the two active treatments, indicated comparability between MT 100 and sumatriptan with respect to the proportions of sustained pain responders (p=0.023) and the proportion of sustained pain free subjects (p<0.001). The difference in sustained pain response between MT 100 and 50 mg sumatriptan was 2.8% with a 95% confidence interval between -4.2% and 9.8%. The difference in sustained pain free response between MT 100 and 50 mg sumatriptan was 0.9% with a 95% confidence interval between -6.1% and 4.2%.

Table 3.1.8.3 Sustained Pain Response and Sustained Pain Free During 24 Hours After Dosing by LOCF for Study MT 100-308

Variable	MT 100		Sumatriptan		Placebo		p-values*		
	N	%	N	%	N	%	MT 100 vs Placebo	Sumatriptan vs Placebo	Equivalence MT100 vs Sumatriptan
Total subjects	332	100.0	340	100.0	341	100.0			
Sustained pain response	98	29.52	110	32.35	60	17.60	<0.001	<0.001	0.023 Difference: 2.8% (-4.2%, 9.8%)
Sustained pain free	46	13.86	44	12.94	27	7.92	0.012	0.031	0.001 Difference: -0.9% (-6.1%, 4.2%)

Protocol MT100-308

\* p-values for comparisons to Placebo were obtained from ordered logistic regression with baseline pain and investigative site as covariates. p-values for comparison of MT 100 to Sumatriptan were obtained from two group Chi-square test for equivalence (Blackwelder, 1982).

### Pain Free Over Time

The number and percentage of pain free subjects at each time point by treatment group are presented in Table 6.20 of the Appendices. The 2-hour pain free rates were similar for MT 100 and sumatriptan, 19% and 20%, respectively. Both were significantly better than placebo (13%).

### Pain Intensity Differences (PID) and Sum of Pain Intensity Differences (SPID)

Mean pain response at selected time points was assessed using the PID and SPID Variables and are shown in Table 3.1.8.4. PID scores in subjects treated with MT 100 were significantly different from placebo by 1.25 hours post dose. In contrast the PID scores in subjects treated with sumatriptan were not statistically different from placebo until 1.75 hours post dose. As we can observe from the table, the SPID data show a slightly delayed effect compared to the PID data.

Table 3.1.8.4 PID and SPID Analysis Results for Study MT 100-308

Variable	Time post-dose (hours)						
	1	1.25	1.5	1.75	2	3	4
<b>MT 100 (N = 332)</b>							
PID	0.35	0.50*	0.61*	0.70*	0.81*	0.96*	0.97*
SPID	0.14	0.27	0.42	0.60	0.80*	1.72*	2.70*
<b>Sumatriptan (N = 340)</b>							
PID	0.29	0.43	0.58	0.70*	0.88*	1.06*	1.16*
SPID	0.10	0.21	0.36	0.53	0.75	1.77*	2.91*
<b>Placebo (N = 341)</b>							
PID	0.27	0.35	0.45	0.48	0.54	0.65	0.68
SPID	0.12	0.21	0.32	0.44	0.57	1.21	1.89

#### Use of Rescue Medication and Relapse

The number of subjects requiring rescue medication over the 24-hour period and the incidence of relapse among responders at 2 hours are displayed in Table 6.21 and Table 6.22 of the Appendices, respectively. According to the tables, the percentage of subjects requiring medication was similar for the MT 100 treatment group (50%) and the sumatriptan group (48%). Both active treatment groups were significantly better than placebo in the time to rescue comparison.

The MT 100 treatment group relapse rate (33%) was similar to the rate of relapse in the sumatriptan treatment group (32%). Only the sumatriptan group was statistically significantly greater with time to relapse than the placebo group (p=0.011).

#### Incidence of Nausea, Photophobia and phonophobia at 2 hours post-dose

The incidences of nausea, photophobia and phonophobia were significantly lower in the active treatment groups than in the placebo group two to three hours post dosing. Symptoms of phonophobia and photophobia appeared to respond to both MT 100 and sumatriptan earlier than nausea. Table 3.1.8.5 shows the detailed results.

Table 3.1.8.5 Incidence of Nausea, Photophobia and Phonophobia at 2 Hours Post dose by LOCF for MT 100-308

Variable	Time post-dose (hours)				
	2	2.5	3	3.5	4
<b>Nausea (%)</b>					
MT 100 (N = 332)	42.5	44.9	43.1	45.2	44.6
p-value vs. placebo	0.980	0.517	0.012	0.006	<0.001
Sumatriptan (N = 340)	45.0	44.4	42.7	42.7	42.1
p-value vs. placebo	0.489	0.498	0.010	<0.001	<0.001
Placebo (N = 341)	42.5	47.5	52.8	55.7	58.1
<b>Photophobia (%)</b>					
MT 100 (N = 332)	54.8	54.5	52.1	50.9	50.0
p-value vs. placebo	0.044	0.019	<0.001	<0.001	<0.001
Sumatriptan (N = 340)	55.9	53.2	50.0	49.7	48.5
p-value vs. placebo	0.087	0.009	<0.001	<0.001	<0.001
Placebo (N = 341)	62.8	63.6	65.1	65.4	67.2
<b>Phonophobia (%)</b>					
MT 100 (N = 332)	50.9	51.5	49.7	48.5	49.7
p-value vs. placebo	0.079	0.036	0.002	<0.001	<0.001
Sumatriptan (N = 340)	50.9	49.4	48.5	49.1	47.4
p-value vs. placebo	0.099	0.011	0.001	0.002	<0.001
Placebo (N = 341)	57.8	59.8	61.6	62.2	63.3

### Nausea Intensity

In subjects with nausea at baseline, mean nausea intensity at 2 hours after dosing was similar in the MT 100 and sumatriptan groups (0.70 and 0.75, respectively) Mean nausea intensity in both active treatment groups was significantly different from placebo by 3 hours post dosing.

### Vomiting

Too few subjects in any group experienced vomiting over the 24-hour period to make a meaningful treatment comparison.

### Clinical Disability

In subjects who reported clinical disability due to their migraines, those with any clinical disability over the 24 hours after dosing were similar in the MT 100 and sumatriptan groups at most time points. The percentage of subjects with any clinical disability was significantly less in the MT 100 and the sumatriptan groups starting at 2.5 hours through the 24 hours post dosing compared to the placebo group.

#### 3.1.8.4 The Sponsor Overall Conclusions

The results of this study are consistent with those obtained in study MT100-306. Both studies demonstrated that the onset of pain relief, the percentage of subjects with pain relief at 2 hours, and the sustained pain response rate with MT 100 are comparable to that obtained with 50 mg sumatriptan. In contrast to MT100-306, resolution of the secondary symptoms of migraine did not occur until 2 to 3 hours post dosing. This outcome, combined with the overall pain responses observed with MT 100 and sumatriptan in MT100-308 compared with MT100-306, suggests that the populations were different. There are no demographic differences that would account for the different responses. Nevertheless, these data confirm the benefit of MT 100 in the acute treatment of migraine and the comparable efficacy obtained with MT 100 compared to sumatriptan.

The results of this study suggest that MT 100 is an acceptable alternative to sumatriptan 50 mg for the acute treatment of migraine, with an efficacy and safety profile similar to sumatriptan. Additionally, the results of this study demonstrate that:

- MT 100 and sumatriptan are of comparable effectiveness in relieving migraine pain,
- MT 100 and sumatriptan are more effective than placebo for the relief of migraine pain and associated symptoms,
- the incidence of adverse events was similar across all treatment groups.

#### 3.1.8.5 The Statistical Reviewer's Comments

1. When the sponsor submitted the original protocol to the agency, the DNDP sent the comments to the sponsor about the problems of the whole study design. The major problems were, first of all, this kind of non-inferiority trial was not acceptable since the sponsor did not plan to compare the efficacy results of MT 100 with the entire approved therapeutic range for Imitrex. Secondly, the analysis plan to compare proportions of 2-hour responders taking MT 100 and sumatriptan using chi-square test for equivalence fails to define what margin of difference would be acceptable to determine equivalence. Finally, since an effective anti-migraine agent has beneficial effects not just on pain, but also on nausea, photophobia, and phonophobia, comparison of a new drug to an approved migraine drug should also assess the comparative effects on these important associated symptoms. The sponsor, however,

did not provide any detailed discussion about these issues although they specified a margin, which we did not agree to. Therefore, this non-inferiority study result is not appropriate for any efficacy claim.

2. Regarding the sponsor's non-inferiority test results, this reviewer disagreed with the sponsor's final conclusion about the efficacy comparability of MT 100 and sumatriptan. In addition to what was mentioned in Comment #1, first of all, the sponsor did not address how they reached this conclusion. Secondly, since the upper limit of confidence interval of responder proportion difference between the sumatriptan and the MT 100 is greater than 0.1, the margin specified for the largest difference that is clinically acceptable (and/or also the p-value from the one sided Blackwelder test,  $0.042 > 0.025$ ), the study failed on showing the comparability of MT 100 and sumatriptan in terms of 2-hour pain relief.
3. This reviewer also disagreed with the sponsor's final conclusion about the MT 100's efficacy on relieving migraine pain and associated symptoms comparing with the placebo. As data showed for three major migraine related symptoms: nausea, photophobia and phonophobia, the MT 100 only had significant results on photophobia. Moreover, as it was mentioned for the previous study MT 100 -306, without positive factorial designed studies to demonstrate the contribution of both individual components, any significant results shown from this type of placebo comparison studies can not be claimed. On top of that, since this study was not mainly designed for the comparison between MT 100 and the placebo, due to the possible overpower concern, making conclusions about the results of the comparison between the MT 100 and the placebo by this study data may not be appropriate.

### *3.1.9 Description of Study MT 100-303*

This study was titled as "A Randomized, Double Blind, and Placebo Controlled Evaluation of One or Two Doses of MT 100 in Subjects with Acute Migraine Attacks." There were 15 investigative centers in the US participated in the study.

#### *3.1.9.1 Study Objective*

The primary objective of this study was to compare the safety and efficacy of a single dose of MT 100 (naproxen sodium 500 mg/ metoclopramide hydrochloride 16 mg) with a single dose of placebo in the acute treatment of migraine attacks in an outpatient setting.

The secondary objective of this study was to compare the safety and efficacy of a second dose of MT 100 with placebo in subjects with acute migraine attacks who have not responded to an initial dose of MT 100 within 2 hours.

### 3.1.9.2 Study Design

This was a Phase III randomized, double-blind, placebo controlled, parallel group, multi-center study consisting of a screening visit, at home treatment of a single migraine attack, and a follow-up visit occurring 24-72 hours after the treated migraine attack.

At the end of the screening visit, subjects were randomly assigned to either MT 100 (naproxen sodium 500 mg and metoclopramide hydrochloride 16 mg) or placebo for oral administration of blinded study medication.

Subjects were instructed to review the eligibility checklist to ascertain whether they continued to meet the entry criteria and had a headache of moderate (pain score 2) to severe (pain score 3) pain intensity when their next migraine attack occurred. Subjects who remained eligible completed the assessments in a study diary just prior to taking study medication, every 15 minutes for the first 2 hours, every 30 minutes for hours 2-4, and then hourly while awake for the next 20 hours after taking study medication (total evaluation period was 24 hours).

If a subject had pain of moderate or severe intensity at the 2-hour time point, a second dose of study medication was taken. Subjects initially randomized to MT 100 were randomized to a second dose of either MT 100 or placebo; subjects initially randomized to placebo received MT 100. Additional rescue medication was permitted no sooner than 4 hours after dosing, if necessary, for those subjects who still had moderate or severe pain.

### 3.1.9.3 Efficacy Variables

The primary efficacy outcome measure was the proportion of subjects with sustained pain response during 24 hours after dosing. Secondary outcome measures included: the percentage of pain responders at 4 hours in subjects taking a second dose of study medication, the percentage of subjects with no pain 2 and 4 hours after dosing, total pain relief (TOTPAR) using a 5-point scale over various intervals, and nausea relief using a 5-point scale. Other secondary outcome measures included time to relapse, 24-hour SPID, time to rescue, incidence of photophobia and phonophobia.

### 3.1.9.4 Statistical Methods

#### 3.1.9.4.1 Determination of Sample Size

The sample size for this study was driven by the requirement for an adequate number of subjects to assess the value of the second dose of MT 100. A sample size of 450 subjects randomized 3:1 to MT 100 and placebo provided approximately 90% power to detect a difference in 2-hour pain response of 18% (48% vs. 30%). The projected 50% non-response rate at 2-hours in subjects initially randomized to MT 100 provided approximately 170 subjects for the second dose randomization. With a balanced

second randomization (1:1) to MT 100 (85 subjects) or placebo (85 subjects) at 2-hours, the study would have 80% power to detect a 20% difference in 4-hour response if the responses are 35% and 15% for MT 100 and placebo, respectively, and 63% power to detect a 20% difference between response rates of 55% and 35%.

#### 3.1.9.4.2 Efficacy Analysis Plan

Statistical analyses were to be performed on the primary and secondary efficacy parameters in the intent-to-treat and the per protocol populations using data with the observed case algorithm and the last observation carried forward (LOCF) algorithm. The intent-to-treat population (ITT) consisted of randomized subjects who took study medication, had a baseline efficacy evaluation and at least one post-baseline efficacy evaluation. The per protocol population consisted of subjects in the ITT population minus those subjects who violated the study protocol. Subjects taking the second dose of study medication 2 hours  $\pm$  30 minutes from the first dose of study medication would be included in the analysis. Analysis of the efficacy data from the intent-to-treat population with LOCF algorithm was considered the primary analysis. Unless specified otherwise, all statistical tests were two-sided at  $\alpha = 0.05$ .

The primary efficacy outcome measure was the proportion of subjects with sustained pain response during 24 hours after dosing using ordered logistic regression. The outcomes were ordered into the following categories:

0) non-responders = subjects with a pain score of 2 or 3 at 2 hours, subjects with a pain score of 0 or 1 at 2 hours that either had a pain score of 2 or 3 after 2 hours or received rescue medication

1) sustained relief = subjects with a pain score of 0 or 1 at 2 hours, with pain scores no greater than 1 after 2 hours without the use of rescue medication

2) sustained pain free = subjects with a pain score of 0 at 2 hours and no greater than 0 after 2 hours without the use of rescue medication.

Ordered logistic regression with baseline pain and investigator site as the covariates was used to test differences between: MT 100 versus placebo (1st dose) and MT 100 versus placebo (2nd dose in non-responders; based on the 4-hour time point)

For secondary outcome measures, the Cochran-Mantel-Haenszel test with center as strata was used to compare the proportion of responders between MT 100 and placebo. ANOVA with treatment and center as fixed effects was used to test the differences in mean total pain relief at 2 hours after dosing between MT 100 and placebo.

Cox Proportional Hazards Model approach was used to test the differences in the distribution of time to relapse and the distribution of time to rescue between MT 100 and placebo.

Baseline pain and investigator site were used as covariates in the analysis of the primary and secondary endpoints. Subgroup analyses on the primary efficacy measure were performed within gender group and subject groups based on severity of migraine pain at baseline (pain response for the 24 hours) and nausea status.

### *3.1.10 Analysis Results for Study MT 100-303*

#### 3.1.10.1 Disposition of Patients and Data Sets Analyzed

A total of 427 subjects were screened and subsequently entered the treatment phase of the study (318 in the MT 100 group and 109 in the placebo group). Two subjects reported treating a migraine but failed to return to the study center for follow-up. These subjects were excluded from the efficacy analyses. So, there were total four hundred twenty-five subjects (317 initially randomized to MT 100 and 108 initially randomized to placebo) included in the efficacy analyses.

A total of 184 subjects (58%) initially randomized to MT 100 treatment received a second dose of study medication (90 subjects received a second dose of MT 100; 94 received placebo). Seventy-four subjects (68%) initially randomized to placebo received MT 100 as a second dose of study medication. No subject terminated early because of lack of efficacy or adverse events.

#### 3.1.10.2 Demographic and Patient Characteristics

Table 3.1.10.1 presents baseline demographic characteristics for the 425 subjects receiving one dose of MT 100 or placebo as well as subjects receiving 2 doses of MT 100. There were no statistically significant differences between the groups for any parameter tested except for race. As we can observe from the table, more than 60% of subjects in all treatment groups were Caucasian and more than 79% were female. The mean age was approximately 40 years. Subjects had experienced migraine attacks an average of 16 to 19.5 years and most reported the absence of aura symptoms at screening.

Table 6.20 of the Appendices presents migraine symptomatology at baseline for the 425 subjects receiving one dose of MT 100 or placebo as well as subjects receiving 2 doses of MT 100. At baseline, 53%-58% of all subjects experienced a moderate level of migraine pain and 42%-47% experienced severe pain. Subjects were fairly evenly divided between the presence and absence of nausea. Most subjects also reported photophobia (79%-87%) and phonophobia (76%-81%) at baseline.

The sponsor also performed and showed summary tables for baseline medical conditions, vital signs, physical examinations and concurrent medications in their study reports. They mentioned that none of the medical conditions noted were considered to preclude subjects from entering the study. There were no apparent differences among the treatment groups for these baseline parameters.

Table 3.1.10.1 Demographic Characteristics for Study MT 100-303

Parameter		Screening						p-value
		MT 100 (N=303)		MT 100/MT 100 (N=90)		Placebo (N=34)		
		N	%	N	%	N	%	
Gender	Male	51	17	16	18	7	21	0.109
	Female	252	83	74	82	27	79	
Race	Caucasian	236	78	75	83	21	62	<0.001
	African/ American	59	19	14	16	11	32	
	Oriental	2	1	0	0	2	6	
	Hispanic	6	2	1	1	0	0	
Age (years)	Mean	40.2		40.2		38.1		0.074
	SD	10.45		10.39		11.22		
Age range (years)	18-35	99	33	30	33	14	41	0.298
	36-55	185	61	53	59	20	59	
	>55	19	6	7	8	0	0	
Weight (pounds)	Mean	161.2		160.4		170.7		0.228
	SD	30.76		32.96		29.42		
Height (inches)	Mean	65.8		66.1		65.9		0.430
	SD	3.32		3.34		3.09		

### 3.1.10.3 Sponsor's Efficacy Analysis Results

#### 3.1.10.3.1 Primary Efficacy Analysis Results

According to the sponsor's study report, ordered logistic regression analysis of the sustained pain response data demonstrated that an initial dose of MT 100 was significantly better than placebo (p=0.048). Approximately 34% of subjects in the MT 100 group had a sustained pain response to treatment compared to 24% of placebo subjects. Table 3.1.10.2 shows the detailed results.

Table 3.1.10.2 Primary Efficacy Results by LOCF After the Initial Dose

Variable	MT 100		Placebo		p-value* MT 100 vs. placebo
	N	(%)	N	(%)	
Total subjects	317	(100)	108	(100)	
Sustained pain free	57	(17.98)	11	(10.19)	
Sustained pain response	50	(15.77)	15	(13.89)	
Ordered logistic regression					0.048
<b>Total sustained pain responders</b>	<b>107</b>	<b>(33.75)</b>	<b>26</b>	<b>(24.07)</b>	

### 3.1.10.3.2 Secondary Efficacy Analysis Results

#### Pain Response at 2 Hours and Over Time

More subjects in the MT 100 group responded to treatment at 2 hours or were pain free without use of rescue medication at that time point than in the placebo group. MT 100 produced a significantly greater 2- hour pain response (p=0.021) than placebo. Table 3.1.10.3 shows the detailed results.

Table 3.1.10.3 Pain Response at the 2-Hour Time Point (LOCF) After the Initial Dose for Study MT 100-303

Variable	MT 100		Placebo		p-value MT 100 vs. placebo
	N	(%)	N	(%)	
Total subjects	317	(100)	108	(100)	
2-hour pain response	132	(41.64)	31	(28.70)	0.021
2-hour pain free	67	(21.14)	15	(13.89)	0.138

Table 3.1.10.4 displays the number and percentage of subjects with a pain score of 0 or 1 (i.e., responders) over the first 2 hours post-dose. The percentage of responders was significantly greater on MT 100 versus placebo at each time point from 1.25 through 2 hours.

Table 3.1.10.4 Responders After the First Dose by LOCF for Study MT 100-303

Variable		Assessment time (hours post dose)							
		0.25	0.5	0.75	1	1.25	1.5	1.75	2
<b>Pain response</b>									
MT 100	Total number	317	317	317	317	317	317	317	317
	Number (%) of responders	5	20	43	66	93	110	125	132
	% of responders	1.58	6.31	13.56	20.82	29.34	34.70	39.43	41.64
Placebo	Total number	108	108	108	108	108	108	108	108
	Number of responders	0	4	12	15	21	25	29	31
	% of responders	0	3.70	11.11	13.89	19.44	23.15	26.85	28.70
	p-value	0.188	0.292	0.522	0.107	0.050	0.030	0.020	0.021

### Sustained Pain Free

More subjects were pain free at 2 hours and through 24 hours post-dose (sustained pain free) in the MT 100 group (18%) compared to the placebo (10%) group.

### Mean Pain Intensity and Response Over Time

Mean values for the PID, SPID and TOTPAR variables over time are presented in Tables 6.21 to 6.23 of the Appendices. These results confirm the sustained pain response data.

### Use of Rescue Medication and Relapse

A higher percentage of subjects who responded at 2 hours relapsed in the MT 100 group compared to placebo (19.20% versus 11.54%). Time to relapse was not significantly different ( $p=0.250$ ) between treatment groups in subjects who initially responded at the 2-hour time point.

A higher percentage of subjects required rescue medication in the placebo group compared to MT 100 (73.15% versus 47.00%). The time to use of rescue medication was significantly later in the MT 100 group than in the placebo ( $p<0.001$ ) group.

### Nausea, Photophobia and Phonophobia at 2 Hours Post Dose

MT 100 was significantly better than placebo for relief of photophobia and phonophobia at the 2-hour time point. For relief of nausea, MT 100 was not significantly better than placebo at 2 hour time point, although it was significantly better than placebo at the 1.75 hour and 3.5 hour time points. Table 3.1.10.5 shows the sponsor's analysis results at 2-hour time point.

Table 3.1.10.5 Incidence of Nausea, Photophobia and Phonophobia at 2 Hours Post Dose by LOCF for Study MT 100-303

Variable	MT 100	Placebo	p-value
			MT 100 vs placebo
N (%) w/ nausea	92 (29.02)	41 (37.96)	0.070
N (%) w/ photophobia	153 (48.26)	68 (62.96)	0.010
N (%) w/ phonophobia	152 (47.95)	65 (60.19)	0.030

### Vomiting

Too few subjects in any group experienced vomiting at the 24 hour time point to allow for a meaningful comparison.

### Response in 2 Hour Non-responders for MT 100 Subjects

Subjects initially randomized to MT 100, with a pain score of 2 or 3 (moderate or severe pain) at 2 hours, were randomized to either a second dose of MT 100 or placebo. A total of 184 of the 317 subjects initially randomized to MT 100 received a second dose of double-blind study medication 2 hours after the first dose; 90 subjects received a second dose of MT 100 and 94 subjects received placebo. As displayed in Table 3.1.10.6, there was no advantage of a second dose of MT 100 compared to placebo in the sustained pain response.

Table 3.1.10.6 Response to 2<sup>nd</sup> Dose Administered at 2 Hours to MT 100 Non-Responders by LOCF for Study MT 100-303

Variable	MT 100 - MT 100		MT 100 - Placebo		p-value *
	N	(%)	N	(%)	MT 100 - MT 100 vs MT 100 - placebo
Total subjects	90	(100)	94	(100)	0.198
Sustained pain free	13	(14.44)	8	(8.51)	
Sustained pain response	19	(21.11)	20	(21.28)	
Ordered logistic regression					
<b>Total sustained pain responders</b>	32	(35.56)	28	(29.79)	

Likewise, there was no difference in the 4-hour pain response rate (2 hours after the repeat dose in non-responders) between the MT 100/MT 100 and MT 100/placebo treatment groups.

#### Response in 2-Hour Non-Responders for Placebo Subjects

The response rate for the 74 subjects who took placebo followed by MT 100 was 29.73%, which was similar to that observed in subjects who received MT 100 followed by placebo.

#### 3.1.10.4 Sponsor's Efficacy Conclusions

The results of this study demonstrate that an initial dose of MT 100 is effective for the relief of migraine pain and associated symptoms. However, a second dose of MT 100 was no more effective than placebo in subjects that failed to respond by 2 hours after an initial dose.

#### 3.1.10.5 Statistical Reviewer's Comments

1. For the primary endpoint, the proportion of subjects with sustained pain response during 24 hours after dosing, the sponsor reported the p-value from the ordered logistic regression 0.048 but this reviewer found the p-value should be 0.062. According to the sponsor's protocol Amendment # 2, it was stated that the 2-hour sustained response data will be analyzed by the ordered logistic regression controlling for center, baseline severity and gender. This reviewer found that the sponsor's p-value of 0.048 was actually obtained from the ordered logistic regression model without including any covariates although the study reports mentioned the baseline pain and investigator site as covariates, which was also inconsistent.
2. According to the sponsor's protocol amendment No. 2, the last amendment, the study was amended to have two primary endpoints. One is the 2-hour sustained response for subjects initially randomized to MT 100 or placebo and the other is the 4-hour sustained response for MT 100 non-responders randomized to a second dose of MT 100 or placebo. The sponsor, however, did not mention that the 4-hour sustained response was the second primary endpoint in their study report and there was nowhere mentioning any pre-planned multiple comparison method to deal with co-primary endpoints for preserving the type I error rate.

Now that the sponsor failed to show any significant results on either primary endpoint. The aforementioned missing multiple comparison procedure does not change the conclusion.

3. In conclusion, this is a failed study since the data did not show any significant results on either 2-hour sustained response for subjects initially randomized to MT 100 or placebo, or the 4-hour sustained response for MT 100 non-responders randomized to a second dose of MT 100 or placebo.

### 3.2 EVALUATION OF SAFETY

The safety evaluation was not performed in this review.

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

In this section, most of reported results were abstracted from the sponsor’s submission. There were few results performed by this reviewer because the sponsor did not provide their analysis results for those cases. Basically, this reviewer confirmed all of the sponsor’s subgroup analysis results. There was only very small differences between this reviewer’s and the sponsor’s results found in the placebo group of data for Study MT 100-308. The differences were too small to affect any conclusions.

### 4.1 GENDER, RACE AND AGE

#### 4.1.1 Factorial Designed Studies (MT 100-301 and MT 100-304)

The sponsor’s comparison of the sustained pain response results for studies MT100-301 and MT100-304 by gender was shown in Table 4.1.1. The sponsor explains in the Integrated Summary of Efficacy (ISE) of the submission that due to the large proportion of females in these studies (>85%), as expected, analyses by gender yielded results similar to the overall analyses. Moreover, results for males lack sufficient sample size (11-14% of the total population) for meaningful interpretation.

Table 4.1.1 Sponsor’s Sustained Pain Response Data by Gender

Group	MT 100-301			MT 100-304		
	MT 100	NAP	MC	MT 100	NAP	MC
All Subjects (%)	35.6 (N=422)	29.8 (N=429)	19.7 (N=213)	31.8 (N=1031)	27.9 (N=1057)	18.8 (N=528)
Females (%)	34.6 (N=364)	30.7 (N=381)	20.5 (N=185)	32.4 (N=900)	27.2 (N=917)	18.3 (N=464)
Males (%)	41.4 (N=58)	22.9 (N=48)	14.3 (N=28)	27.5 (N=131)	32.9 (N=140)	21.9 (N=64)

Note: the test p-values were not reported here due to the issue of changing analysis methods.

The sponsor did not provide the subgroup analysis for race and age for these two studies, so this reviewer performed the analyses and showed results in Tables 4.1.2 and 4.1.3.

Table 4.1.2 Reviewer’s Sustained Pain Response Data by Age

Group	MT 100-301			MT 100-304		
	MT 100	NAP	MC	MT 100	NAP	MC
Age ≤ 40 (%)	42.9 (N=219)	35.1 (N=208)	23.4 (N=107)	38.2 (N=456)	30.2 (N=496)	22.6 (N=248)
Age >40 (%)	27.6 (N=203)	24.9 (N=221)	16.0 (N=106)	26.8 (N=575)	25.9 (N=561)	15.4 (N=280)

Table 4.1.3 Reviewer’s Sustained Pain Response Data by Race

Group	MT 100-301			MT 100-304		
	MT 100	NAP	MC	MT 100	NAP	MC
White (%)	35.5 (N=349)	26.9 (N=364)	19.5 (N=185)	30.1 (N=910)	26.1 (N=930)	17.5 (N=464)
Non-White (%)	35.6 (N=73)	46.2 (N=65)	21.4 (N=28)	44.6 (N=121)	40.9 (N=127)	28.1 (N=64)

4.1.2 Pivotal Placebo Controlled Studies (MT 100-306, MT 100-308 and MT 100-303)

For all these studies, the sponsor did not provide the subgroup analysis for gender. So, this reviewer performed the analyses and showed results in Tables 4.1.4 and 4.1.5.

Table 4.1.4 Pain Responses at 2 Hours by Gender for Studies 306 and 308

Group	MT 100-306				MT 100-308		
	MT 100 × 1	MT100 × 2	Suma	Placebo	MT 100	Suma	Placebo
Male (%)	50 (N=14)	61.5 (N=26)	58.3 (N=12)	47.4 (N=19)	32.1 (N=53)	51.2 (N=43)	32.4 (N=37)
Female (%)	58.2 (N=124)	57.8 (N=116)	53 (N=117)	26.3 (N=118)	46.2 (N=279)	46.8 (N=297)	32.1 (N=302)

Table 4.1.5 Sustained Pain Response by Gender for Study 303

Group	MT 100-303	
	MT 100	Placebo
Male (%)	42.4 (N=59)	28.6 (N=14)
Female (%)	31.8 (N=258)	23.4 (N=94)

Table 4.1.6 summarizes the sponsor’s results for race and age subgroups for the primary endpoint for studies MT 100-306 and MT 100-308. According to the sponsor, responses appeared to be similar between these demographic groups. The 2-hour pain responses among non-Caucasians receiving active treatments showed the least difference from placebo, however, the numbers of such subjects were extremely small.

Table 4.1.6 Pain Response at 2 Hours Analyses for Race and Age Subgroups

Outcome Measure	MT 100 × 1	MT 100 × 2	Sumatriptan	Placebo
2-hour Pain Response (%) – Caucasian				
MT 100-306	54.8	59.2	56.8	24.1
MT 100-308	44.9		47.9	31.1
2-hour Pain Response (%) – Non-Caucasian				
MT 100-306	43.5	56.8	44.1	48.3
MT 100-308	38.8		44.0	36.5
2-hour Pain Response (%) - < 45 Years				
MT 100-306	52.9	57.7	45.7	37.7
MT 100-308	47.9		45.4	32.7
2-hour Pain Response (%) ≥ 45 Years				
MT 100-306	52.9	60.0	66.7	15.4
MT 100-308	37.2		50.8	30.7

This reviewer performed the race and age subgroup analyses for the primary endpoint for Study MT 100-303. The results are shown in Table 4.1.7.

Table 4.1.7 Sustained Pain Response Analyses for Race and Age for Study MT 100-303

Group	MT 100-303	
	MT 100	Placebo
Age ≤ 40 (%)	34.1 (N=167)	26.8 (N=41)
Age > 40 (%)	33.3 (N=150)	22.4 (N=67)
White (%)	28.6 (N=245)	17.7 (N=85)
Non-White (%)	51.4 (N=72)	47.8 (N=23)

#### 4.2 OTHER SPECIAL/SUBGROUP POPULATIONS

The sponsor performed the analysis by baseline pain severity and nausea status for the primary endpoint for all studies.

##### 4.2.1 Factorial Designed Studies (MT 100-301 and MT 100-304)

Table 4.2.1 shows the sponsor’s analysis results by baseline pain severity and nausea status for the primary endpoint. According to the sponsor’s study reports, for Study MT 100-301, the difference in sustained pain response rate between MT 100 and naproxen indicated a stronger trend toward significance in the moderate pain group. In subjects with nausea at baseline, the sustained pain response rates were similar for MT 100 and naproxen, and both were approximately 10% greater than metoclopramide. In subjects without nausea, the sustained pain response rate was nearly 10% greater on MT 100 compared with naproxen alone.

For Study MT 100-304, the difference in sustained pain response rate between MT 100 (36%) and naproxen (30%) was significantly greater in the moderate pain group. There was no difference between MT 100 and naproxen in subjects with severe baseline pain. Significant differences between MT 100 and metoclopramide were present in subjects with moderate baseline pain as well as in subjects with severe baseline pain. In subjects with nausea at baseline the sustained pain response rates were similar for MT 100 and naproxen however, in subjects without nausea the sustained pain response rate was greater for MT 100 compared with naproxen alone. In subjects with and without nausea at baseline MT 100 was significantly better than metoclopramide.

Table 4.2.1 Sustained Pain Response Analysis Results for Baseline Pain Severity and Nausea Status for Studies 301 and 304

Group	MT 100-301			MT 100-304		
	MT 100	NAP	MC	MT 100	NAP	MC
Baseline Pain: Moderate (%)	39.84 (N=251)	33.08 (N=266)	23.19 (N=138)	36.14 (N=581)	29.92 (N=635)	20.48 (N=332)
Baseline Pain: Severe (%)	28.82 (N=170)	24.07 (N=162)	13.33 (N=75)	26.52 (N=445)	24.57 (N=411)	15.98 (N=194)
With Nausea at Baseline (%)	32.29 (N=192)	31.47 (N=197)	20.39 (N=103)	29.58 (N=693)	28.53 (N=701)	19.95 (N=366)
Without Nausea at Baseline (%)	38.43 (N=229)	28.45 (N=232)	19.09 (N=110)	36.72 (N=335)	26.69 (N=356)	26.05 (N=162)

#### 4.2.2 Pivotal Placebo Controlled Studies (MT 100-306, MT 100-308 and MT 100-303)

For Study MT 100-306, the sponsor showed that in each of the active treatment groups, the 2-hour pain response rate was greater in subjects with moderate baseline pain than in those with severe baseline pain. In subjects with severe baseline pain, only the MT 100 2-tablet dose was significantly more effective than placebo. Moreover, for nausea status at baseline, the 2-hour pain response was similar in subjects treated with a single tablet of MT 100 or sumatriptan regardless of the presence or absence of nausea. In the MT 100 2-tablet group, however, a larger percentage of subjects with nausea responded to treatment by 2 hours (64.6%) compared to subjects without nausea (50.0%). For Study MT 100-308, In both active treatment groups, the 2-hour pain response rate was greater in subjects with moderate baseline pain than in those with severe baseline pain. Treatment with MT 100 and sumatriptan was more effective than placebo for subjects with moderate pain at baseline. In subjects without nausea, both active treatments were superior to placebo. In subjects with nausea, only the sumatriptan group was superior to placebo at 2 hours. Table 4.2.2 shows the detailed results for these baseline pain severity and nausea status subgroup analyses.

Table 4.2.2 Pain Response at 2 Hours Analysis Results by Baseline Pain Severity and Nausea Status for Studies 306 and 308

Group	MT 100-306				MT 100-308		
	1 Tablet of MT 100	2 Tablets of MT 100	Suma	Placebo	MT 100	Suma	Placebo
Moderate (%)	63.16 (N=76)	65.06 (N=83)	64.71 (N=85)	27.54 (N=69)	49.76 (N=205)	52.60 (N=192)	35.58 (N=208)*
Severe (%)	39.34 (N=61)	50.88 (N=57)	31.82 (N=44)	30.88 (N=68)	34.65 (N=127)	40.54 (N=148)	26.32 (N=133)*
With Nausea (%)	53.68 (N=95)	64.63 (N=82)	55.26 (N=76)	32.14 (N=84)	39.17 (N=217)	45.33 (N=214)	31.58 (N=209)
Without Nausea (%)	50 (N=42)	50 (N=60)	51.92 (N=52)	24.53 (N=53)	53.51 (N=114)	50.79 (N=126)	33.33 (N=129)

\*Note: This reviewer's analysis results showed N=207 and N=133 instead.

For Study MT 100-303, the sponsor's analyses results by baseline pain and nausea status for the primary efficacy endpoint are shown in Table 4.2.3.

Table 4.2.3 Sustained Pain Response Analysis Results by Baseline Pain Severity and Nausea Status

Group	MT 100-303	
	MT 100	Placebo
Baseline Pain: Moderate (%)	38.59 (N=184)	27.59 (N=58)
Baseline Pain: Severe (%)	26.52 (N=132)	20.00 (N=50)
With Nausea (%)	30.13 (N=156)	23.08 (N=52)
Without Nausea (%)	37.27 (N=161)	25.00 (N=56)

According to the sponsor, for subjects with moderate pain at baseline, the sustained pain response rate was significantly superior ( $p=0.028$ ) with MT 100 compared to placebo. For subjects with severe pain at baseline, although not statistically significant, the sustained pain response rate was 6% higher in the MT 100 treatment group compared to placebo. For subjects with nausea at baseline the sustained pain response rates for MT 100 were approximately 7% greater than placebo. For subjects without nausea the sustained pain response rate was 12% greater on MT 100 compared with placebo. Both comparisons did not show significant results.

## **5. SUMMARY AND CONCLUSIONS**

### *5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE*

For both factorial studies MT 100-301 and MT 100-304, this reviewer found that the sponsor did not use the protocol specified statistical methods to analyze their data. For Study MT 100-301, the protocol specified method was the logistic regression with baseline pain as the covariate but the sponsor did not mention the baseline pain as the covariate in their study report. Their p-values for both MT 100 versus individual components comparisons were found to be obtained from the logistic regression model but without any covariates. This reviewer had a different p-value for the comparison between MT 100 and Naproxen by the logistic regression model with the baseline pain as the covariate although the difference was not big enough to affect the conclusions.

For Study MT 100-304, the protocol specified method was the extended Mantel Haenzel statistic with scores of 0, 1, and 2 for the three ordered categories and using a model that controls for center, baseline pain and gender. The sponsor, however, used the ordered logistic regression model with baseline pain and investigator site as covariates. When this application was reviewed, the sponsor was asked to perform the protocol specified statistical method for this study. They showed us a new p-value of 0.038 (than 0.03) for the comparison between the MT 100 and Naproxen and they concluded that the difference was too small to affect the final conclusions. After this reviewer performed the analysis, it was found the p-value for the prospectively specified method should be 0.063, not 0.038, which was obtained due to the sponsor's programming error.

For Study MT 100-306, this reviewer confirmed the sponsor's analysis results for the primary endpoint and most of secondary endpoints. For the secondary endpoint of incidence of phonophobia at 2 hour post dose, this reviewer had different p-values for the comparisons between the 1 tablet of MT 100 and 2 tablets of MT 100 with the placebo, although the number of patients with phonophobia at 2 hours post dose for all treatment groups were the same. The differences between the sponsor's and the reviewer's p-values were, however, not big enough to affect the final conclusions. Moreover, this reviewer also found that the arm of 2 tablets of MT 100 was later added per the amendment but the sponsor did not propose any method for dealing with multiple comparisons although the inconsistency did not occur in this data set due to a lack of this preplanned multiple comparison procedure.

For Study MT 100-308, the primary objective of the study was to compare the safety and efficacy of a single tablet dose of MT 100 with the over-encapsulated sumatriptan by non-inferiority test. Although the sponsor submitted this study and concluded the comparability of these two drugs, due to some major problems about the study design, in which the sponsor failed to reach the agreement with the agency, the non-inferiority study results are not appropriate for any efficacy claims. Beside that, about the sponsor's non-inferiority study results, this reviewer had different conclusions. By using the confidence interval approach for the non-inferiority test or the Blackwelder test for equivalence, the results clearly showed that the null hypothesis was not rejected. Therefore, the non-inferiority of MT 100 to the sumatriptan was not demonstrated.

For Study MT 100-303, it was also found that the sponsor's analysis results for the primary endpoint was different from the reviewer's by the protocol specified statistical method. According to the sponsor's protocol Amendment #2, it was stated that the 2-hour sustained response data will be analyzed by the ordered logistic regression controlling for center, baseline severity and gender but the sponsor's study report only mentioning center and baseline severity into the model and the results were, however, obtained by the ordered regression model without adding any covariates.

## *5.2 CONCLUSIONS AND RECOMMENDATIONS*

There were five studies statistically reviewed for efficacy in this submission. They were Studies MT 100-301, MT 100-304, MT 100-306, MT 100-308 and MT 100-303. The first two studies were factorial designed to compare the combination drug of MT 100 with both individual components to meet the rule of marketing a combination drug. The rest of three studies were either placebo and/or active controlled designed for mainly demonstrating the MT 100's efficacy comparing with the placebo and/or comparing with the other active comparator. The purpose of these three studies was for the sponsor's possible marketing claims, not for the approval of the MT100 itself. That is, the validity of these three studies is under the condition that two factorial studies showed positive results.

First of all, this reviewer found in both factorial studies that the MT 100 failed to show significant improvement on the primary endpoint of 2-hours to 24 hours sustained pain response rate for acute migraine patients, comparing with one of the individual components, Naproxen, according to the protocol specified statistical method although the MT 100 clearly showed significant results when comparing with the other component, Metoclopramide. For all three major migraine symptoms, the MT 100 also failed to show any significant improvement when comparing with the component, Naproxen in both studies. So, these two studies were determined as failed studies which therefore failed to meet the requirement of marketing a combination drug.

Secondly, for the other three studies, only one study, MT 100-306 showed significant results for its primary endpoint. In that study, none of MT 100 arms showed significant results on all three major migraine symptoms. Although, for the insignificant results of

these secondary endpoints, p-values were close to 0.05, one should keep in mind that since the sponsor included two arms of MT100 in one study but did not provide any pre-specified statistical analysis method for dealing with the problem of multiple comparisons, how to assess the closeness of significance for these insignificant results of migraine symptoms is not clear.

In conclusion, the data did not support the MT 100's efficacy in treating acute migraine patients whether it was for comparing the MT 100 with its individual components, with the placebo or with the other approved drug, sumatriptan.

---

Yeh-Fong Chen, Ph.D.  
Mathematical Statistician

cc: NDA 21-645  
HFD-120/Dr. Katz  
HFD-120/Dr. Bastings  
HFD-120/Dr. Prohaska  
HFD-120/Ms. Chen  
HFD-700/Dr. Anello  
HFD-710/Dr. Mahjoob  
HFD-710/Dr. Hung  
HFD-710/Dr. Jin  
HFD-710/Dr. Chen  
This review consists of 69 pages. MS Word: C:/yfchen/NDA21645/review.doc

## 6. APPENDICES

Table 6.1 Baseline Migraine Symptoms for Study MT100-301

Parameter		MT 100 (N=423)		Naproxen (N=430)		Metoclopramide (N=214)		p-value
		N	(%)	N	(%)	N	(%)	
Time since first migraine attack (years)	Mean	18.6		18.5		18.1		NA
	SE	0.59		0.57		0.82		
Migraine type at screening	Without aura	299	(71)	326	(76)	160	(75)	NA
	With aura	52	(12)	35	(8)	26	(12)	
	With and without aura	71	(17)	69	(16)	28	(13)	
Pain intensity at baseline	Moderate	251	(59)	266	(62)	138	(65)	0.705
	Severe	170	(40)	162	(38)	75	(35)	
Nausea at baseline		192	(46)	197	(46)	103	(48)	0.781
Photophobia at baseline		359	(85)	355	(83)	179	(84)	0.597
Phonophobia at baseline		328	(78)	341	(80)	160	(75)	0.479

Table 6.2 Time to Rescue Analysis Results for Study MT100-301

	Treatments		
	MT100	Naproxen	Metoclopramide HCL
Total Number Treated	422	429	213
Number Who Rescue <sup>2</sup>	183	216	132
Percent Who Rescue	43.36	50.35	61.97
Mean Time (hours) to Rescue	9.56	8.52	6.88
Std Err Time (hours) to Rescue	0.97	0.71	0.90
Treatment Comparisons with MT100 (P-Value)		0.035	<0.001

<sup>1</sup> Kaplan Meier techniques were used to model time to rescue; comparisons were done with log likelihood methods.

<sup>2</sup> Mean time to rescue was defined as the time from dosing to the time rescue medication was administered, only for subjects who did rescue.

Table 6.3 Time to Relapse in Responders at 2 Hours for Study MT100-301

	Treatments		
	MT100	Naproxen	Metoclopramide HCL
Number of Responders	203	200	73
Number Who Relapse <sup>2</sup>	53	72	31
Percent Who Relapse	26.11	36.00	42.47
Mean Time (hours) to Relapse	9.41	7.74	6.06
Std Err Time (hours) to Relapse	0.95	0.67	0.84
Treatment Comparisons with MT100 (P-Value)		0.069	0.003

<sup>1</sup> Kaplan Meier techniques were used to model time to relapse; comparisons were done with log likelihood methods.

<sup>2</sup> Relapse was defined as a pain score of 2 (moderate pain) or 3 (severe pain) or use of rescue, in responders (subjects who had achieved a score of 0 (no pain) or 1 (mild pain) at 2 hours post-dose). Mean time to relapse did not include non-responders who did not relapse.

Table 6.4 Pain Intensity Difference (PID)[2] by LOCF for Study MT100-301

		Assessment Time (Hours Post Dose)					
		0.5	1	2	3	4	
MT100 (N=422)	Mean	0.05	0.37	0.93	1.05	1.08	
	Std	0.39	0.66	0.97	1.02	1.05	
Naproxen Sodium (N=429)	Mean	0.06	0.30	0.78	0.88	0.90	
	Std	0.42	0.70	0.96	1.00	1.03	
Metoclopramide HCL (N=213)	Mean	0.03	0.20	0.56	0.65	0.67	
	Std	0.38	0.64	0.91	0.94	0.99	
P-value [1]	MT100 vs. Naprox.	0.695	0.120	0.016	0.014	0.012	
	MT100 vs. Meto.	0.524	0.003	<0.001	<0.001	<0.001	
		Assessment Time (Hours Post Dose)					
		8	10	12	16	20	24
MT100 (N=422)	Mean	1.14	1.16	1.19	1.23	1.27	1.24
	Std	1.14	1.16	1.16	1.18	1.20	1.21
Naproxen Sodium (N=429)	Mean	0.97	1.00	1.05	1.09	1.11	1.09
	Std	1.09	1.11	1.15	1.18	1.19	1.22
Metoclopramide HCL (N=213)	Mean	0.73	0.76	0.79	0.82	0.84	0.86
	Std	1.06	1.08	1.11	1.13	1.14	1.15
P-value [1]	MT100 vs. Naprox.	0.048	0.060	0.084	0.109	0.065	0.108
	MT100 vs. Meto.	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

[1] ANOVA with treatment and center as fixed effects was used to test the differences in mean 24-hour post dosing PID among the three treatments. This is a two-sided test at a 0.05 significance level.

[2] PID was defined as pain score at a given time point subtracted from the pain score at baseline.

Table 6.5 Sum of Pain Intensity Difference (SPID) [2] by LOCF for Study MT 100-301

		Assessment Time (Hours Post Dose)				
		0.5	1	2	3	4
MT100 (N=422)	Mean	0.03	0.21	1.03	2.08	3.16
	Std	0.19	0.47	1.21	2.08	3.02
Naproxen Sodium (N=429)	Mean	0.03	0.18	0.85	1.73	2.63
	Std	0.21	0.52	1.28	2.16	3.09
Metoclopramide HCL (N=213)	Mean	0.02	0.12	0.60	1.25	1.92
	Std	0.19	0.46	1.22	2.01	2.87
P-value [1]	MT100 vs. Naprox.	0.695	0.360	0.044	0.018	0.012
	MT100 vs. Meto.	0.524	0.021	<0.001	<0.001	<0.001

		Assessment Time (Hours Post Dose)					
		8	10	12	16	20	24
MT100 (N=422)	Mean	7.64	9.94	12.32	17.17	22.18	27.16
	Std	7.15	9.32	11.45	15.75	20.10	24.49
Naproxen Sodium (N=429)	Mean	6.44	8.43	10.53	14.83	19.25	23.68
	Std	7.01	9.06	11.11	15.37	19.76	24.16
Metoclopramide HCL (N=213)	Mean	4.77	6.27	7.85	11.10	14.40	17.81
	Std	6.73	8.75	10.79	14.93	19.09	23.25
P-value [1]	MT100 vs. Naprox.	0.015	0.021	0.025	0.036	0.041	0.046
	MT100 vs. Meto.	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

[1] ANOVA with treatment and center as fixed effects was used to test the differences in mean 24-Hour post-dosing PID among the three treatments. This is a two-sided test at a 0.050 significance level.

[2] SPID was defined as the sum of the pain intensity score differences at time T $\times$  (hour elapsed since previous observation) plus all previous time points.

Table 6.6 Total Pain Relief (TOTPAR) [2] by LOCF for Study MT 100-301

		Assessment Time (Hours Post Dose)				
		0.5	1	2	3	4
MT100 (N=422)	Mean	0.12	0.47	1.93	3.77	5.62
	Std	0.27	0.63	1.70	3.08	4.59
Naproxen Sodium (N=429)	Mean	0.12	0.46	1.74	3.29	4.89
	Std	0.28	0.68	1.78	3.16	4.65
Metoclopramide HCL (N=213)	Mean	0.11	0.38	1.37	2.56	3.78
	Std	0.27	0.64	1.62	2.82	4.15
P-value [1]	MT100 vs. Naprox.	0.769	0.803	0.102	0.020	0.019
	MT100 vs. Meto.	0.761	0.107	<0.001	<0.001	<0.001

		Assessment Time (Hours Post Dose)					
		8	10	12	16	20	24
MT100 (N=422)	Mean	13.24	17.11	21.11	29.26	37.63	45.93
	Std	11.01	14.39	17.75	24.61	31.65	38.65
Naproxen Sodium (N=429)	Mean	11.45	14.82	18.33	25.49	32.85	40.31
	Std	10.97	14.26	17.58	24.50	31.67	38.81
Metoclopramide HCL (N=213)	Mean	8.74	11.31	13.97	19.50	25.06	30.70
	Std	10.08	13.23	16.43	23.02	29.70	36.60
P-value [1]	MT100 vs. Naprox.	0.018	0.023	0.025	0.031	0.034	0.042
	MT100 vs. Meto.	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

[1] ANOVA with treatment and center as fixed effects was used to test the differences in mean pain relief (TOTPAR) at each time point after dosing between MT 100 and Naproxen Sodium and Metoclopramide HCL. This is a two-sided test at the 0.05 significance level.

[2] TOTPAR = sum of pain relief score at time T $\times$  (hours elapsed since previous observation) plus all previous time points.

Table 6.7 Baseline Migraine Symptoms for Study MT 100-304

Parameter		MT 100 (N=1036)		Naproxen (N=1062)		Metoclopramide (N=529)		p-value
		N	(%)	N	(%)	N	(%)	
Time since first migraine attack (years)	Mean	19.8		19.5		18.9		NA
	SE	0.40		0.39		0.53		
Migraine type at screening	Without aura	770	(74)	828	(78)	399	(75)	NA
	With aura	139	(13)	128	(12)	70	(13)	
	With and without aura	127	(12)	106	(10)	60	(11)	
Pain intensity at baseline	Moderate	581	(56)	635	(60)	332	(63)	0.048
	Severe	446	(43)	411	(39)	194	(37)	
Nausea at baseline		694	(67)	701	(66)	366	(69)	0.791
Photophobia at baseline		843	(82)	864	(82)	434	(82)	0.975
Phonophobia at baseline		781	(76)	801	(76)	384	(73)	0.335

Table 6.8 Time to Relapse<sup>1</sup> in Responders at 2 Hours by for Study MT 100-304

	Treatments		
	MT100	Naproxen	Metoclopramide HCL
Number of Responders	513	494	193
Number Who Relapse	185	199	94
Percent Who Relapse	36.06	40.28	48.70
Mean Time (hours) to Relapse	8.37	7.33	7.15
Std Err Time (hours) to Relapse	0.42	0.38	0.51
Treatment Comparisons with MT100 (P-Value <sup>2</sup> )		0.121	<0.001

<sup>1</sup> Time to Relapse was calculated in subjects with a pain score of 0 (no pain) or 1 (mild pain) at 2 hours post-dose.

Time to Relapse was defined as the time interval from 2 hours post-dose to the time of a pain score of 2 (moderate pain) or 3 (severe pain), or use of rescue medication.

<sup>2</sup> Kaplan-Meier techniques were used to model time to relapse; comparisons were done with log likelihood methods.

Table 6.9 Time to Rescue<sup>1</sup> Analysis Results for Study MT 100-304

	Treatments		
	MT100	Naproxen	Metoclopramide HCL
Total Number Treated	1031	1057	528
Number Who Rescue <sup>2</sup>	493	544	321
Percent Who Rescue	47.82	51.47	60.80
Mean Time (hours) to Rescue	8.95	8.18	7.94
Std Err Time (hours) to Rescue	0.47	0.42	0.59
Treatment Comparisons with MT100 (P-Value <sup>2</sup> )		0.074	<0.001

<sup>1</sup> Time to Rescue was defined as the time from baseline to the overall time rescue medication was administered.

<sup>2</sup> Kaplan-Meier techniques were used to model time to rescue; comparisons were done with log likelihood methods.

Table 6.10 Pain Intensity Difference (PID)[2] by LOCF for Study MT100-304

		Assessment Time (Hours Post Dose)					
		0.5	1	2	3	4	
MT100 (N=1031)	Mean	0.10	0.44	0.93	1.07	1.13	
	Std	0.47	0.75	0.95	1.00	1.07	
Naproxen Sodium (N=1057)	Mean	0.08	0.39	0.81	0.94	0.98	
	Std	0.50	0.79	0.99	1.03	1.08	
Metoclopramide HCL (N=528)	Mean	0.06	0.25	0.61	0.70	0.73	
	Std	0.46	0.68	0.89	0.96	1.02	
P-value [1]	MT100 vs. Naprox.	0.603	0.112	0.004	0.002	0.001	
	MT100 vs. Meto.	0.212	<0.001	<0.001	<0.001	<0.001	
		Assessment Time (Hours Post Dose)					
		8	10	12	16	20	24
MT100 (N=1031)	Mean	1.13	1.15	1.14	1.16	1.14	1.14
	Std	1.11	1.12	1.15	1.18	1.20	1.21
Naproxen Sodium (N=1057)	Mean	0.99	0.98	0.98	1.01	1.03	1.04
	Std	1.12	1.12	1.13	1.16	1.18	1.20
Metoclopramide HCL (N=528)	Mean	0.74	0.72	0.74	0.76	0.79	0.83
	Std	1.05	1.05	1.08	1.10	1.13	1.17
P-value [1]	MT100 vs. Naprox.	0.005	<0.001	0.001	0.004	0.025	0.046
	MT100 vs. Meto.	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

[1] ANOVA with treatment and center as fixed effects was used to test the differences in mean 24-Hour post-dosing PID among the three treatments. This is a two-sided test at a 0.050 significance level.

[2] PID was defined as pain score at a given time point subtracted from the pain score at baseline.

Table 6.11 Sum of Pain Intensity Difference (SPID)[2] by LOCF for Study MT100-304

		Assessment Time (Hours Post Dose)				
		0.5	1	2	3	4
MT100 (N=1031)	Mean	0.02	0.20	0.98	2.02	3.14
	Std	1.17	0.45	1.23	2.09	3.01
Naproxen Sodium (N=1057)	Mean	0.02	0.18	0.84	1.75	2.72
	Std	1.17	0.47	1.27	2.14	3.07
Metoclopramide HCL (N=528)	Mean	0.01	0.11	0.60	1.28	2.00
	Std	0.16	0.42	1.11	1.89	2.77
P-value [1]	MT100 vs. Naprox.	0.999	0.257	0.012	0.004	0.002
	MT100 vs. Meto.	0.204	<0.001	<0.001	<0.001	<0.001

		Assessment Time (Hours Post Dose)					
		8	10	12	16	20	24
MT100 (N=1031)	Mean	7.68	9.96	12.24	16.82	21.43	26.01
	Std	6.95	9.01	11.10	15.31	19.61	23.96
Naproxen Sodium (N=1057)	Mean	6.71	8.68	10.63	14.66	18.75	22.87
	Std	7.04	9.08	11.16	15.32	19.56	23.90
Metoclopramide HCL (N=528)	Mean	4.96	6.42	7.88	10.90	14.03	17.34
	Std	6.53	8.46	10.37	14.17	18.14	22.31
P-value [1]	MT100 vs. Naprox.	0.001	<0.001	<0.001	0.001	0.001	0.002
	MT100 vs. Meto.	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

[1] ANOVA with treatment and center as fixed effects was used to test the differences in mean 24-Hour post-dosing SPID among the three treatments. This is a two-sided test at a 0.05 significance level.

[2] SPID was defined as the sum of the pain intensity score differences over the observation period, weighted for the time between observations.

Table 6.12 Total Pain Relief (TOTPAR)[2] by LOCF for Study MT100-304

		Assessment Time (Hours Post Dose)				
		0.5	1	2	3	4
MT100 (N=1031)	Mean	0.09	0.45	1.79	3.49	5.30
	Std	0.21	0.59	1.72	3.05	4.49
Naproxen Sodium (N=1057)	Mean	0.10	0.44	1.68	3.27	4.97
	Std	0.22	0.58	1.65	2.95	4.38
Metoclopramide HCL (N=528)	Mean	0.08	0.35	1.32	2.49	3.73
	Std	0.19	0.52	1.47	2.64	3.95
P-value [1]	MT100 vs. Naprox.	0.628	0.682	0.125	0.083	0.078
	MT100 vs. Meto.	0.497	0.002	<0.001	<0.001	<0.001

		Assessment Time (Hours Post Dose)					
		8	10	12	16	20	24
MT100 (N=1031)	Mean	12.54	16.16	19.76	27.01	34.36	41.62
	Std	10.70	13.97	17.29	23.97	30.72	37.55
Naproxen Sodium (N=1057)	Mean	11.58	14.82	18.02	24.67	31.44	38.26
	Std	10.55	13.72	16.94	23.56	30.35	37.32
Metoclopramide HCL (N=528)	Mean	8.67	11.11	13.53	18.50	23.68	29.08
	Std	9.74	12.74	15.73	21.75	28.09	34.72
P-value [1]	MT100 vs. Naprox.	0.033	0.022	0.017	0.019	0.023	0.033
	MT100 vs. Meto.	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

[1] ANOVA with treatment and center as fixed effects was used to test the differences in mean pain relief (TOTPAR) at each time point after dosing between MT100 and Naproxen Sodium and Metoclopramide HCL. This is a two-sided test at the 0.05 significance level. Analysis was based on data with pooled sites.

[2] TOTPAR= sum of pain relief score at time T × (hours elapsed since previous observation).

Table 6.13 Nausea Intensity Score [2] by LOCF for Study MT 100-304

		Assessment Time (Hours Post Dose)					
		0.5	0.75	1	1.25	1.5	1.75
MT100 (N=1031)	Mean	0.91	0.78	0.67	0.58	0.52	0.48
	Std	0.83	0.81	0.80	0.77	0.76	0.75
Naproxen Sodium (N=1057)	Mean	0.89	0.78	0.69	0.62	0.57	0.53
	Std	0.86	0.85	0.84	0.83	0.83	0.80
Metoclopramide HCL (N=528)	Mean	0.94	0.87	0.79	0.72	0.65	0.62
	Std	0.88	0.88	0.85	0.85	0.86	0.86
P-value [1]	MT100 vs. Naprox.	0.696	0.834	0.570	0.246	0.256	0.145
	MT100 vs. Meto.	0.477	0.051	0.011	0.002	0.004	<0.001

		Assessment Time (Hours Post Dose)					
		2	2.5	3	3.5	4	24
MT100 (N=1031)	Mean	0.54	0.72	0.80	0.86	0.92	1.51
	Std	0.90	1.10	1.20	1.25	1.30	1.46
Naproxen Sodium (N=1057)	Mean	0.60	0.79	0.90	0.99	1.06	1.63
	Std	0.92	1.13	1.23	1.28	1.33	1.45
Metoclopramide HCL (N=528)	Mean	0.71	1.01	1.20	1.22	1.34	1.91
	Std	1.01	1.24	1.34	1.36	1.40	1.41
P-value [1]	MT100 vs. Naprox.	0.160	0.206	0.040	0.020	0.017	0.050
	MT100 vs. Meto.	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

[1] ANOVA with treatment and center as fixed effects was used to test the difference among treatments in mean nausea relief at each assessment time after dosing. This was a two-sided test at 0.050 significance level.

[2] Nausea rated on a four point scale (0 = No Nausea, 1 = Mild Nausea, 2 = Moderate Nausea, 3 = Severe Nausea). If rescue medication was administered at any time, the nausea rating was set to 3 for that time point and forward.

Table 6.14 Baseline Migraine Symptoms for Study MT 100-306

Parameter		MT 100 1 tablet (N=138)		MT 100 2 tablets (N=142)		Sumatriptan (N=129)		Placebo (N=137)		p-value
		N	(%)	N	(%)	N	(%)	N	(%)	
Time since first migraine attack (years)	Mean	19.3		18.1		18.0		18.1		NA
	SE	1.07		1.06		0.99		1.02		
Migraine type at screening	Without aura	90	(65)	101	(71)	89	(69)	97	(71)	NA
	With aura	25	(18)	21	(15)	21	(16)	21	(15)	
	With and without aura	23	(17)	20	(14)	19	(15)	19	(14)	
Pain intensity at baseline	Mild	1	(1)	2	(1)	0	(0)	0	(0)	0.106
	Moderate	76	(55)	83	(58)	85	(66)	69	(50)	
	Severe	61	(44)	57	(40)	44	(34)	68	(50)	
Nausea at baseline		95	(69)	82	(58)	76	(59)	84	(61)	0.471
Photophobia at baseline		111	(80)	117	(82)	107	(83)	122	(89)	0.242
Phonophobia at baseline		102	(74)	118	(83)	100	(78)	114	(83)	0.155

Table 6.15 Pain Response over Time with LOCF for Study MT 100 -306

		Assessment Time (Hours Post Dose)				
		0.25	0.5	0.75	1	1.25
MT 100 1 Tablet (N=138)	No. of Responders	1	5	24	40	51
	% of Responders	0.72	3.62	17.39	28.99	36.96
MT 100 2 Tablets (N=142)	No. of Responders	4	12	25	37	49
	% of Responders	2.82	8.45	17.61	26.06	34.51
Sumatriptan (N=129)	No. of Responders	2	7	23	44	54
	% of Responders	1.55	5.43	17.83	34.11	41.86
Placebo (N=137)	No. of Responders	2	7	12	16	25
	% of Responders	1.46	5.11	8.76	11.68	18.25
		Assessment Time (Hours Post Dose)				
		1.5	1.75	2	2.5	
MT 100 1 Tablet (N=138)	No. of Responders	61	65	73	82	
	% of Responders	44.20	47.10	52.90	59.42	
MT 100 2 Tablets (N=142)	No. of Responders	64	76	83	90	
	% of Responders	45.07	53.52	58.45	63.38	
Sumatriptan (N=129)	No. of Responders	65	68	69	73	
	% of Responders	50.39	52.71	53.49	56.59	
Placebo (N=137)	No. of Responders	32	39	40	49	
	% of Responders	23.36	28.47	29.20	35.77	

Table 6.16 Time to Meaningful Relief Analysis for Study MT 100-306

	Treatments			
	MT 100 1 Tablet	MT 100 2 Tablets	Sumatriptan	Placebo
Number of Subjects	138	142	129	137
Number with Meaningful Relief	72	91	74	57
% with Meaningful Relief [1]	52.17	64.08	57.36	41.61
P-value vs. Placebo	0.111	<0.001	0.011	
Mean (minutes)	120.6	127.4	119.4	123.2
Standard Deviation	57.71	53.50	63.32	57.31
Median	120.00	120.00	105.00	105.00
Max	240.0	240.0	240.0	240.0
Min	30.0	30.0	30.0	30.0
P-values for Time to Meaningful Relief [2]	0.890	0.549	0.481	

[1] Cochran-Mantel-Haenszel test with pooled site as strata was used for a two-sided test at a 0.05 significance level.

[2] A Wilcoxon Rank Sum Test approach was used to compare the differences in the distribution of Time to Meaningful Pain Relief.

Table 6.17 Time to Rescue [1] Analysis by Kaplan-Meier Methodology for Study MT 100-306

	Treatments			
	MT 100 1 Tablet	MT 100 2 Tablets	Sumatriptan	Placebo
Total Number Treated	138	142	129	137
Number Who Rescue	46	44	50	58
Percent Who Rescue	33.33	30.99	38.76	42.34
Mean Time (Hours) to Rescue	8.52	8.66	10.24	8.67
Standard Error Time (Hours) to Rescue	0.72	0.82	0.91	0.71
Treatment Comparisons vs. Placebo [2]	0.172	0.022	0.290	

[1] Time to Rescue was defined as the time from baseline to the overall time rescue medication was administered.

[2] Kaplan-Meier techniques were used to model time to rescue; comparisons were done with log likelihood methods.

Table 6.18 Time to Relapse [1] in Responders at 2 Hours Analysis by Kaplan-Meier Methodology for Study MT 100-306

	Treatments			
	MT 100 1 Tablet	MT 100 2 Tablets	Sumatriptan	Placebo
Total Number Treated	73	83	69	40
Number Who Rescue	26	17	27	10
Percent Who Rescue	35.62	20.48	39.13	25.00
Mean Time (Hours) to Rescue	8.72	12.29	11.81	10.40
Standard Error Time (Hours) to Rescue	1.09	1.85	1.30	2.21
Treatment Comparisons vs. Placebo [2]	0.281	0.407	0.662	

[1] Time to Relapse was calculated in subjects with a pain score of 0 (no pain) or 1 (mild pain) at 2 hours post-dose.

Time to Relapse was defined as the time interval from 2 hours post-dose to the time of a pain score of 2 (moderate pain) or 3 (severe pain), or use of rescue medication.

[2] Kaplan-Meier techniques were used to model time to relapse; comparisons were done with log likelihood methods.

Table 6.19 Pain Free Over Time with LOCF for Study MT 100-308

		Assessment Time (Hours Post Dose)			
		0.25	0.5	0.75	1
MT 100 (N=332)	Number of Responders	0	1	4	12
	% of Responders	0.00	0.30	1.20	3.61
Imitrex (N=340)	Number of Responders	1	4	5	14
	% of Responders	0.29	1.18	1.47	4.12
Placebo (N=341)	Number of Responders	0	0	2	7
	% of Responders	0.00	0.00	0.59	2.05
P-Values	MT 100 vs. Imitrex	0.386	0.206	0.807	0.729
	MT 100 vs. Placebo	NC	0.298	0.416	0.275
	% of Responders	0.35	0.038	0.273	0.169
		Assessment Time (Hours Post Dose)			
		1.25	1.5	1.75	2
MT 100 (N=332)	Number of Responders	22	36	49	63
	% of Responders	6.63	10.84	14.76	18.98
Imitrex (N=340)	Number of Responders	24	37	49	67
	% of Responders	7.06	10.88	14.41	19.71
Placebo (N=341)	Number of Responders	15	24	35	45
	% of Responders	4.40	7.04	10.26	13.20
P-Values	MT 100 vs. Imitrex	0.836	0.927	0.820	0.938
	MT 100 vs. Placebo	0.230	0.093	0.089	0.047
	% of Responders	0.164	0.101	0.126	0.033

Table 6.19 Migraine History at Screening and Baseline Characteristics of Treated Migraine for Study MT 100-308

Parameter		MT 100		Sumatriptan		Placebo		p-value
		N	(%)	N	(%)	N	(%)	
<b>Screening</b>								
Weight (pounds)	Mean	156.7	NA	153.2	NA	153.7	NA	0.255
	SD	32.84	NA	29.19	NA	29.75	NA	
Smoking status	Current smoker	54	16	53	15	41	12	0.231
	Not current smoker	283	84	290	85	306	88	
Migraine characteristics at screening	Without aura	244	72	242	71	245	71	ND
	With aura	38	11	33	10	49	14	ND
	With and without aura	55	16	67	20	53	15	ND
Time from first migraine attack (years)	Mean	18.3	NA	19.4	NA	18.8	NA	ND
	SD	0.63	NA	0.66	NA	0.67	NA	ND
<b>Baseline</b>								
Photophobia	Absent	60	18	53	16	64	19	0.547
	Present	272	82	288	84	279	81	
	Missing	5	<1	2	<1	4	<1	

Parameter		MT 100		Sumatriptan		Placebo		p-value
		N	(%)	N	(%)	N	(%)	
<b>Baseline</b>								
Phonophobia	Absent	66	20	61	18	77	22	0.324
	Present	266	80	280	82	266	78	
	Missing	5	<1	2	<1	4	<1	
Nausea	None	115	35	127	37	131	38	0.894
	Mild	128	59	126	59	129	61	
	Moderate	74	34	72	34	64	30	
	Severe	15	7	16	7	18	9	
	Missing	5	<1	2	<1	5	<1	
Pain at baseline	Moderate	205	62	192	56	207	60	0.379
	Severe	127	38	148	43	132	38	
	Missing	4	<1	2	<1	4	<1	

Table 6.20 Baseline Migraine Symptomatology for Study MT 100-303

Screening								
Parameter		MT 100 (N=303)		MT 100/MT 100 (N=90)		Placebo (N=34)		p-value
		N	%	N	%	N	%	
Time since first migraine attack (years)	Mean		19.5		17.3		16.1	NA
	SE		0.66		1.11		1.46	
Migraine type at screening	Without aura	220	73	70	78	19	56	NA
	With aura	21	7	5	6	3	9	
	With and without aura	62	20	15	17	12	35	
Baseline								
Parameter		MT 100 (N=301)*		MT 100/MT 100 (N=90)		Placebo (N=34)		p-value
		N	%	N	%	N	%	
Pain intensity at baseline	Moderate	175	58	49	54	18	53	0.894
	Severe	125	42	41	46	16	47	
Nausea at baseline	Present	141	47	49	54	18	53	0.399
Photophobia at baseline	Present	243	81	78	87	27	79	0.430
Phonophobia at baseline	Present	240	80	73	81	26	76	0.847

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Yeh-Fong Chen  
5/10/04 11:51:10 AM  
BIOMETRICS

Kun Jin  
5/10/04 01:27:24 PM  
BIOMETRICS

James Hung  
5/10/04 02:21:24 PM  
BIOMETRICS