

# Clinical Review Cover Sheet

<b>NDA:</b>	<b>21-645</b>
<b>Sponsor:</b>	<b>Pozen Inc.</b>
<b>Drug:</b>	<b>Myzan; previously MT100 (naproxen sodium 500 mg and metoclopramide 16 mg)</b>
<b>Proposed Indication:</b>	<b>Migraine</b>
<b>Correspondence Date:</b>	<b>July 31, 2003</b>
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<b>Division:</b>	<b>HFD-120 DNDP</b>
<b>Reviewer:</b>	<b>Kevin Prohaska, D.O.</b>

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## Clinical Review for NDA 21-645

### Executive Summary

#### 1. Recommendations

##### 1.1 Recommendation on Approvability

In my clinical opinion I do not believe MT100 should be approved for the treatment of migraine in adults.

Overall I do not believe the risk benefit assessment favors the approval of MT100 for the treatment of migraine in adults. To begin with the 2 factorial studies (MT100-301 and MT100-304) have not adequately demonstrated significant clinical benefit of MT100 over naproxen, although both studies demonstrated clear benefit of MT100 over metoclopramide. While the results for sustained pain response (primary endpoint in both studies) of MT100 compared to naproxen strongly trended toward significance ( $p=0.064$  trial 301,  $p=0.063$  trial 304) I believe the small therapeutic benefit of MT100 over naproxen is too small (5.8% trial 301, 3.9% trial 304) to justify the added risks of metoclopramide (ex. tardive dyskinesia). Likewise neither study demonstrated a significant benefit of MT100 over naproxen as measured by the traditional endpoint of headache pain response at 2 hours ( $p=0.665$  trial 301,  $p=0.143$  trial 304) or pain freedom at 2 hours ( $p=0.053$  trial 301,  $p=0.604$  trial 304). Despite the problems with the factorial studies the 3 efficacy studies (MT100-306, MT100-308 and MT100-303) did demonstrate evidence that MT100 is superior to placebo for pain however the 3 studies demonstrated inconclusive results for the various associated symptoms (see 6.3.3.1 and 6.3.4). Finally, given the added concerns about the findings from the 2-year carcinogenicity study (increased prolactin related tumorigenicity/carcinogenicity) I do not believe MT100 should be approved.

In conclusion I do not believe the two factorial studies adequately demonstrate the benefit of MT100 over naproxen. Although the results of the primary endpoint analysis in the 2 factorial studies strongly trended towards significance, the small therapeutic benefit of MT100 over naproxen is outweighed by the added risks associated with metoclopramide in my opinion. The three pivotal efficacy studies collectively demonstrate significant benefit of MT100 over placebo for the treatment of headache pain associated with migraine and inconclusive results for the treatment of nausea and phonophobia associated with migraine.

I briefly discuss the efficacy findings below and in further detail in section 6 of this review. I briefly discuss the safety findings below and in further details in section 7 of this review.

##### 1.2 Recommendation on Phase 4 Studies and/or Risk Management Steps

If approved, Phase IV commitments should include a clinical development program to evaluate the safety and effectiveness of MT100 in adolescent migraineurs (12 to 17 years of age). The sponsor does not provide a pediatric development program for my evaluation but does request a waiver on pediatric studies until after approval. If MT100 is approved for marketing within the United States, I recommend a deferral be given for the adolescent migraineur population until

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after approval and a full waiver be given for children under 12 years of age since migraine is not thought to occur in this age group to any great extent.

**2. Background**

Pozen Inc. has submitted a new drug application (NDA) for the use of MYZAN™ (previously MT100) for the intermittent treatment of acute migraine with and without an aura in adults (up to 6 times per month). MYZAN is a combination product consisting of a metoclopramide hydrochloride monohydrate (16 mg/tablet) shell, and naproxen sodium (500 mg/tablet) central core. Additional details about the chemistry of the combination product can be found in section 2.1 of this review.

The NDA is formatted according to the International Conference on Harmonization (ICH) Common Technical Document and has been submitted electronically at:

[\\CDSESUB1\N21645\N\\_000\2003-07-31](\\CDSESUB1\N21645\N_000\2003-07-31). Thirteen amendments have been submitted to the NDA as of April 13, 2004. MT100 is not approved in any foreign country however both individual components are approved in the United States and most countries world wide for a variety of conditions.

Metoclopramide is a dopamine receptor antagonist approved since 1980 (original NDA 017854, Reglan Tablets) for the following indications; gastroesophageal reflux disease (up to 15 mg QID up to 12 weeks), diabetic gastric stasis (10 mg q AC for 2 to 8 weeks), prevention of nausea and vomiting associated with cancer chemotherapy (initially 2 mg/kg IV, may be repeated 5 times over 13 hours), prevention of postoperative nausea and vomiting (up to 20 mg IM), to facilitate small bowel intubation (10 mg), and to aid in radiological examinations (10 mg).

Naproxen sodium is a non-steroidal anti-inflammatory drug (non-specific COX inhibitor, NSAID) that has been previously shown to be effective in migraine syndrome (Advil Migraine, NDA 020402, approved 4/20/1995) and is also approved for the treatment of rheumatoid arthritis, osteoarthritis, and Ankylosing Spondylitis (generally up to 500 mg BID occasionally more), juvenile arthritis (5 mg/kg BID), the treatment of pain, primary dysmenorrhea, tendonitis and bursitis (up to 500 mg BID), and gout (750 mg initially followed by 250 mg TID).

MT100 is formulated to provide coordinated and sequential release of metoclopramide followed by naproxen. The sponsor asserts naproxen and metoclopramide act synergistically through complementary pharmacologic mechanisms to alleviate the pathophysiologic processes thought to be responsible for migraine pain and secondary symptoms. Additionally the sponsor asserts the activity of naproxen is facilitated by the gastrointestinal prokinetic activity of metoclopramide, which appears to speed the absorption of naproxen during a migraine attack.

A discussion about the present available treatments for acute migraine can be found in section 1.2 of this review. Briefly, the most common treatment for acute migraine prescribed in the United States are a group of medications collectively known as triptans (ex. sumatriptan). All triptan products are associated with cardiovascular adverse events including myocardial infarction and should be given with great care to subjects with multiple risk factors for cardiovascular disease. It is believed that approximately 40% of all migraine patients in the

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United States treat their migraines with non-steroidal anti-inflammatory drugs such as naproxen. Naproxen is generally believed to not have any clinically significant effects on the heart although it has been shown to slightly increase blood pressure in controlled studies. Naproxen (and recently rofecoxib) has been shown to be effective in migraine. Metoclopramide has also been shown to be effective in the treatment of migraine in several published studies although it does not carry this indication.

### 3. Summary of Clinical Findings

#### 3.1 Brief Overview of Clinical Program

The following table briefly summarizes the clinical development program for MT100 in the treatment of migraine.

**Table 1** Overall Clinical Development Program for MT100

Trial #	Dose (mg)	Type of Trial	N	Duration	Notes
<b>Phase I Clinical Pharmacology Trials</b>					
MT100-101	NAP 500 mg/Met 8	PK	11	Single and double doses	Open label, bioavailability study
MT100-102	MT100 vs. components	PK	24	Single and double dose	Open label, 4-period, crossover, comparative PK study
MT100-103	MT100	PK	16	Single dose	Open label, hepatic insufficiency safety study
MT100-105	sumatriptan 50 mg	PK	28	Single dose	Open label bioequivalence study between sumatriptan and over-encapsulated sumatriptan
MT100-106	MT100	PK	13	Single dose	Open label, two period (during and outside migraine) PK study.
MT100-107	MT100	PK	24	Single dose	Food effect study
<b>Phase II Dose Ranging Studies</b>					
MT100-201	Variable (see below)	Efficacy	514	Single attack	Double blind, placebo controlled dose finding efficacy study
MT100-201	Variable (see below)	Efficacy	182	Single attack	Double blind, placebo controlled
<b>Phase III Trials</b>					
MT100-301	MT100 vs. components	Efficacy	1067	Single attack	Double blind, uncontrolled, randomized trial
MT100-304	MT100 vs. components	Efficacy	2627	Single attack	Double blind, uncontrolled, randomized trial
MT100-306	MT100 vs. sumatriptan	Efficacy	635	Single attack	Double blind, placebo and active controlled trial.
MT100-308	MT100 vs. sumatriptan	Efficacy	1272	Single attack	Double blind, placebo and active controlled trial
MT100-303	1 or 2 tablets of MT100	Efficacy	427	Single attack	Double blind, placebo controlled, study to evaluate the efficacy of a 2 <sup>nd</sup> dose of MT100 given as rescue.
MT100-401A	2 Tablets of MT100	Efficacy	343	Single attack	Double blind, placebo controlled trial
MT100-402	MT100	Efficacy	238	Single attack	Double blind, placebo controlled trial to evaluate the efficacy of MT100 in subjects intolerant of triptans.
MT100-307	MT100	Efficacy	142	Multiple attacks	Double blind, placebo controlled trial to evaluate the efficacy of MT100 in the treatment of multiple migraines during the prodrome stage.
MT100-302	MT100	Safety-Long term	1123	Multiple attacks	Open label, repeat dose, long term safety study

For the purposes of my efficacy review I focused on trial MT100-301, MT100-304, MT100-306, MT100-308 and MT100-303. Trial MT100-301 and MT100-304 are the two key factorial studies and trials MT100-303, MT100-306 and MT100-308 are the key placebo controlled efficacy

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studies. A description of the design of each trial can be found in section 4.2 of this review. Briefly the two factorial studies evaluated the safety and efficacy of MT100 compared to its components using 2 hour sustained headache response as the primary endpoint. As per our agreement the studies did not include a placebo. Trial MT100-306 and MT100-308 were double blind, placebo and active controlled (sumatriptan 50 mg) trials. In trial MT100-306 subjects were randomized to 1 tablet of MT100, 2 tablets of MT100, sumatriptan 50 mg or placebo in a double dummy manner. The primary endpoint was 2-hour pain relief. In trial MT100-308 subjects were randomized to MT100, sumatriptan 50 mg or placebo; the primary endpoint was also 2 hour pain relief. Trial MT100-303 was a double blind placebo controlled parallel study in which a second dose of MT100 was used in 2-hour non-responders. In trial MT100-303 all subjects were initially randomized to MT100 or placebo however subjects not responding to MT100 at 2 hours were then re-randomized to placebo or a second dose of MT100. Placebo subjects not responding at 2 hours were all given MT100. The primary endpoints for trial MT100-303 were sustained pain response at 2 hours in all subjects and sustained pain response at 4 hours in MT100 first dose non-responders. For the purposes of my review I focused on the findings at 2 hours in trial MT100-303.

The following table briefly summarizes the amount of exposure from these single attack studies. Overall 2252 subjects received a single dose of MT100 in the primary single attack studies, additional short term exposure was seen in other studies described in the review. The amount of short-term exposure is adequate.

**Table 2** Exposure from Primary Single Attack Studies

Trial	MT100 X 1	MT100 X 2	NAP	MET	SUMA	Placebo
MT100-301	423		430	214		
MT100-304	1036		1062	529		
MT100-306	138	142			129	137
MT100-308	337				343	347
MT100-303*	318					109

\* Initial Randomization

For the purposes of my safety review I reviewed the safety findings from all studies conducted in support of this NDA. The primary trial for long-term safety was trial MT100-302. In this trial approximately 621 subjects treated on average 3 migraine attacks per month for 6 months and 329 subjects treated on average 3 attacks per month for 12 months. The amount of long-term exposure is sufficient to meet the minimum requirements of 300 subjects for 6 months and 100 subjects for 1 year, treating at least 2 attacks per month on average. A complete discussion of patient exposure can be found in section 7.2 of this review.

### 3.2 Efficacy

The primary endpoint for the 2 factorial studies (MT100-301 and MT100-304) was **sustained headache response** defined as moderate to severe headache pain at baseline going to no or mild pain at 2 hours and did not relapse or require rescue medication up to hour 24. Secondary endpoints included incidence of associated symptoms at various timepoints. As agreed neither study included a placebo. At the time of the original review the sponsor successfully argued that since a recently completed phase 2 study demonstrated metoclopramide had no significant effect on sustained response and since there is no published literature to suggest oral metoclopramide is

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effective for migraine then it would be unethical to expose additional patients to ineffective treatment.

As is typical of migraine studies, screened adult subjects ( $\geq 18$  years) meeting the International Headache Society's definition of migraine with and without aura (1.1 and 1.2) were enrolled if they were otherwise healthy. Migraine frequency had to be  $\geq 2$  attacks per month but no more than 6 attacks per month (8 in trial MT100-303) or 20 migraine days in any given month. All other headache types could not be greater than 15 days per month. Subjects with an initial diagnosis of migraine at greater than 50 years of age were excluded. All subjects on migraine prophylaxis had to be on stable doses (generally 2 weeks prior to entry). Studies with sumatriptan (MT100-306 and MT100-308) also included appropriate exclusions such as significant cardiovascular risk factors and a diagnosis of hemiplegic migraine. All successfully screened subjects were instructed to treat their next migraine attack of moderate to severe intensity with randomized medication. Subjects were followed with a typical 24-hour migraine diary.

In trial MT100-301 assessment were done at baseline, then every 30 minutes for 2 hours, then hourly while awake until 24 hours. If nausea was present at baseline subjects assessed time to relief of nausea using a stopwatch. In trial MT100-304 assessment were done at baseline, then every 15 minutes for 2 hours, then every 30 minutes until hour 4, then hourly while awake until 24 hours. In both studies rescue medication was prohibited for the first 2 hours and subjects were instructed to return to the clinic for post treatment evaluation within 72 hours of treatment.

The analysis of trials MT100-301 and MT100-304 was done on the Intent-to-Treat population defined as all subjects who received study medication and had both a baseline efficacy evaluation and at least one post-treatment efficacy evaluation. Missing values were handled using a last observation carried forward algorithm. Subjects taking rescue medication at any time had their subsequent efficacy values set to their baseline values or in the case of associated symptoms (nausea, photophobia, phonophobia) was set to the worst possible outcome (i.e., present). In trial MT100-301 the pre-stated analysis plan was to analyze the proportion of patient reporting sustained response using logistic regression with baseline pain as the only covariate. In trial MT100-304 the pre-stated analysis plan for sustained pain response included a plan to categorize response into 3 ordered categories (non-responders, sustained pain relief, and sustained pain free). The pre-stated plan was to analyze the results "*by methods for 3 ordered categories such as extended Mantel Haenzel statistics with a score of 0, 1, and 2 for the three ordered categories*" using a model that controls for center, baseline pain and gender. In both study reports, the integrated summary of efficacy, and the overall summary the sponsor presents a post hoc analysis using ordered logistical regression for both studies. For the purposes of my review I relied primarily on the results obtained using the pre-stated analysis plan.

The following table summarizes the results of the primary endpoint for trials MT100-301 and MT100-304. As demonstrated in the table the combination product MT100 was significantly superior to metoclopramide in both studies irrespective of which analysis method is used ( $p < 0.001$ ). The issue of superiority of MT100 compared to metoclopramide is clear and not in dispute however the benefit of MT100 over naproxen is not so clear. In trial MT100-301 the

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comparison of MT100 to naproxen for sustained response was not significant using the prestated analysis plan ( $p=0.077$ ). The sponsor is aware we consider this a failed study. The critical issue that needs to be decided is whether we consider the comparison of MT100 to naproxen in trial MT100-304 to be significant. In trial MT100-304 the sponsor reports this comparison was nominally significant ( $p=0.038$ ) using the prestated analysis method. However the Agency statistician reports 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, were used in the extended Mantel-Haenszel statistics.”* The statistician assures me variable weight, based on the strata’s proportion in the trial, is standard methodology and should have been followed. Using the method suggested by the Agency statistician the comparison of subjects with sustained response taking MT100 and subjects taking naproxen is 0.063 not 0.038. Hence trial MT100-304 failed to demonstrate a statistically significant benefit of MT100 over naproxen for the prestated primary endpoint using the prestated analysis plan and the weighting method suggested by the Agency statistician. Regardless of which analysis one chooses to rely on for trial MT100-304, I do not believe the treatment effect of 3.9% for 2 hour sustained pain response is clinically relevant especially given the potential dangers of metoclopramide (discussed below). The overall therapeutic effect for MT100 over metoclopramide was 15.9% in trial MT100-301 and 13.0% in trial MT100-304. Both results are clinically relevant in my opinion.

**Table 3** Sustained Pain Response (any response) in MT100-301 and MT100-304

Trial	MT100 n(%)	Naproxen 500 mg n(%)	Metoclopramide 16 mg n(%)
<b>MT100-301</b> N=1067	150 (35.6%)	128 (29.8%) $p=0.077^{*\ddagger}$	42 (19.7%) $p<0.001^{*\ddagger}$
<b>MT100-304</b> N=2627	328 (31.8%)	295 (27.9%) $p=0.038^{*\#}$ <b>(<math>p=0.063</math>)<math>^{\Omega}</math></b>	99 (18.8%) $p<0.001^{*\#}$

Adapted from sponsor table 23 study report MT100-301 and amended table 27 study report MT100-304 (paper submission 1/14/04).

\*p-values for comparison to MT100 versus individual component alone using prestated analysis plan from both studies, Trial 301 logistic regression, trial 304 CMH.

$\ddagger$  using post hoc ordered logistical regression, MT100 vs. naproxen  $p=0.025$  and MT100 vs. metoclopramide  $p<0.001$ . Source sponsor table 5, study report 301.

$\#$  using post hoc ordered logistical regression, MT100 vs naproxen  $p=0.030$  and MT100 vs. metoclopramide  $p<0.001$ . Source sponsor table 5 and 27 (original report), study report 304.

$\Omega$  p-value from Agency Statistician’s analysis who reports sponsor’s analysis had a programmatic error.

The lack of benefit of MT100 over naproxen is further supported by many of the secondary endpoints as demonstrated in the following table. In trial MT100-304 there was no significant difference between subjects taking MT100 and subjects taking naproxen for 2 hour pain response ( $p=0.143$ ), 2 hour pain free ( $p=0.604$ ), 2 hour nausea ( $p=0.138$ ), 2 hour photophobia ( $p=0.0721$ ), 2 hour phonophobia ( $p=0.983$ ), sustained nausea free ( $p=0.083$ ), sustained photophobia free ( $p=0.584$ ), and sustained phonophobia free ( $p=0.135$ ). All of these findings support my belief that the sponsor has failed to demonstrate a clear clinical benefit of MT100 over naproxen in trial MT100-304.

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**Table 4** Selected Secondary Endpoint Results from Trials MT100-301 and MT100-304

Parameter	MT100-301			MT100-304		
	MT100	NAP	MET	MT100	NAP	MET
2-hr pain response (%)	48.1	46.6 p=0.665	34.3 <b>p&lt;0.001</b>	49.8	46.7 p=0.143	36.6 <b>p&lt;0.001</b>
2-hr pain free (%)	18.7	14.0 p=0.053	9.4 <b>p=0.002</b>	16.8	16.0 p=0.604	9.1 <b>p&lt;0.001</b>
2-hr Nausea <sup>€</sup> (%)	23.7	26.6 p=0.333	25.4 p=0.646	33.7	36.7 p=0.138	41.5 <b>p=0.003</b>
2-hr Photophobia <sup>€</sup> (%)	54.5	52.2 p=0.504	63.4 <b>p=0.033</b>	54.8	53.9 p=0.721	62.1 <b>p=0.007</b>
2-hr Phonophobia <sup>€</sup> (%)	45.7	48.0 p=0.504	52.1 p=0.129	48.0	48.1 p=0.983	52.8 p=0.080
Sustained Nausea Free (%)†	45.3	39.4 p=0.100	30.5 <b>p&lt;0.001</b>	37.0	33.5 p=0.083	26.7 <b>p&lt;0.001</b>
Sustained Photophobia Free (%)†	32.2	29.8 p=0.409	19.7 <b>p&lt;0.001</b>	27.9	27.0 p=0.584	21.0 <b>p&lt;0.003</b>
Sustained Phonophobia Free (%)†	35.3	30.3 p=0.174	22.5 <b>p&lt;0.001</b>	32.3	29.3 p=0.135	21.4 <b>p&lt;0.001</b>

Source: Adapted from sponsor tables 6, 7, and 8 study report MT100-301, table 6, 7, and 8 study report MT100-304 and table 12 ISE.pdf.

All p-values are for comparison to MT100

† Sustained responses for associated symptoms are not included in the original study reports and come from ise.pdf tables 19.1 through 19.6.

€ represents the number and proportions of subjects reporting the associated symptoms at 2 hours

In conclusion I believe both factorial studies fail to demonstrate any statistically and clinically significant benefit of MT100 over naproxen. Although the sponsor's analysis of the primary endpoint in trial MT100-304 demonstrated a statistically significant benefit of MT100 over naproxen for sustained response the findings were not very robust and disappear under the scrutiny of review. Additionally trials MT100-301 and MT100-304 failed to demonstrate any significant benefit of MT100 over naproxen for nausea, photophobia and phonophobia (2 hour incidence and sustained response) as well as 2 hour pain response and pain freedom. I discuss the results from trial MT100-301 and MT100-304 in further detail in section 6.3.2 of this review.

The following table briefly summarizes the primary endpoints and selected secondary endpoints from the 3 pivotal efficacy trials (MT100-306, MT100-308, and MT100-303). Trials MT100-306 and MT100-308 were blinded, placebo and active controlled, multicenter, parallel design studies in which subjects treated a single migraine of moderate to severe intensity with randomized drug. In trial MT100-306 subjects were randomized to either 1 tablet of MT100 (n= 138), 2 tablets of MT100 (n=142), 1 tablet of over-encapsulated sumatriptan 50 mg (n=129) or placebo (n=137) in a double dummy fashion. In trial MT100-308 subjects were randomized to either 1 tablet of MT100 (n=337), 1 tablet of over-encapsulated sumatriptan 50 mg (n=343) or placebo (n=347). Otherwise both studies were of nearly identical design. The primary endpoint for both trials was 2-hour pain response defined as a change in headache pain severity from moderate to severe at baseline to mild or none at 2 hours without the use of rescue. Trial MT100-303 was a double blind, placebo controlled study in which subjects were initially randomized to MT100 (n=318) or placebo (n=109). Subjects initially receiving MT100 and not responding at 2 hours were then rerandomized to either a second dose of MT100 or placebo. Subjects initially randomized to placebo and not responding at 2 hours were all given MT100 (placebo non-responders). The primary endpoint for subjects initially randomized to MT100 or placebo was 2-hour sustained

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pain response. The primary endpoint for MT100 1<sup>st</sup> dose non-responders was 4-hour sustained pain response. For the purposes of my review I focused primarily on the 2-hour endpoint. In all 3 studies subjects meeting the International Headache Society’s definition of migraine with and without an aura were enrolled if they were otherwise healthy. All subjects used a standard 24-hour migraine diary. Final follow-up visits occurred generally between 1 to 3 days after treatment.

**Table 5 Overall Summary of Efficacy, Trial MT100-306, MT100-308 and MT100-303**

Efficacy Studies					
		MT100 X 1	Sumatriptan 50 mg	Placebo	Comment
<b>MT100-306</b>	2-hour Pain Response† p-value	73 (52.9%) p<0.001	69 (53.9%) p<0.001	40 (29.2%)	Won compared to placebo*.
	2 hour Nausea p-value	38 (27.5%) p=0.049	51 (39.5%) p=0.880	53 (38.7%)	Won on nausea
	2-hour Photophobia p-value	65 (47.1%) p=0.002	50 (38.8%) p<0.001	91 (66.4%)	Won on photophobia
	2-hour Phonophobia p-value	60 (43.5%) p=0.062	41 (31.8%) p=0.027	76 (55.5%)	Lost on phonophobia <sup>1</sup>
<b>MT100-308</b>	2-hour Pain Response† p-value vs. placebo p-value vs. sumatriptan	146 (44.0%) p=0.001 p=0.042	161 (47.4%) p<0.001 NA	109 (32.0%)	Lost compared to sumatriptan (primary comparison of interest)
	2 hour Nausea p-value	141 (42.5%) p=0.980	153 (45.0%) p=0.489	145 (42.5%)	Lost on nausea
	2-hour Photophobia p-value	182 (54.8%) p=0.044	190 (55.9%) p=0.087	214 (62.8%)	Won on photophobia
	2-hour Phonophobia p-value	169 (50.9%) p=0.079	173 (50.9%) p=0.099	197 (57.8%)	Lost on phonophobia
<b>MT100-303</b>	Sustain Pain Response 2 hr† p-value	107 (33.8%) p=0.048 (Sponsor) p=0.062 (Agency)		26 (24.1%)	Lost on both primary endpoints using Agency results.
	Sustain Pain Response 4 hr p-value	32 (35.6%) p=0.198		28 (29.8%)	
	2-hour Pain Response p-value	132 (41.6%) p=0.021		31 (28.7%)	Won compared to placebo
	2 hour Nausea p-value	92 (29.0%) p=0.070		41 (38.0%)	Lost at 2 hrs, won at 1.75 hrs (p=0.046).
	2-hour Photophobia p-value	153 (48.3%) p=0.010		68 (63.0%)	Won compared to placebo
	2-hour Phonophobia p-value	152 (48.0%) p=0.030		65 (60.2%)	Won compared to placebo

† Primary endpoint for study (In trial MT100-308 comparison to sumatriptan was primary.)

\*Not shown but MT100 X 2 tablets lost against sumatriptan 50 mg (58.5% vs. 53.5% respectively, p=0.454)

<sup>1</sup> MT100 won on phonophobia at 30 and 60 minutes but not 1.5 and 2.0 hours.

In trial MT100-306 and MT100-308 the sponsor included a sumatriptan arm in order to determine whether MT100 offers any benefit over sumatriptan. The primary endpoint for both trials was 2 hour pain response defined in the usual manner. In trial MT100-306 the comparison of primary interest was MT100 vs. placebo. In trial MT100-308 the comparison of primary interest was between MT100 and sumatriptan 50 mg using an equivalence/non-inferiority analysis plan while the comparisons of MT100 to placebo was performed to “validate the study design and patient population”. In trial MT100-308 the comparison between the two active treatments was to be considered equivalent if the proportions were within a margin of 10% (the delta). In a letter dated October 24, 2001 we informed the sponsor the proposed equivalence (MT100-308) analysis plan using a 10% margin was unacceptable since a comparison directly to placebo was possible from the proposed trial and a 10% delta was too high. Therefore for the

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purposes of this review I focused primarily on the comparison of MT100 to placebo for both trials.

As demonstrated in my summary table above a significantly higher proportion of subjects randomized to MT100 reported 2 hour pain relief than subjects randomized to placebo in trial MT100-306 ( $p < 0.001$ ), MT100-308 ( $p < 0.001$ ) and MT100-303 ( $p = 0.021$ ). However pain response at 2 hours compared to placebo was the pre-stated primary endpoint for trial MT100-306 only. In trial MT100-308 the comparison of MT100 1 tablet vs. sumatriptan for 2 hour pain response was significant ( $p = 0.042$ ), favoring sumatriptan (44.0% MT100 vs. 47.4% sumatriptan 50 mg), although the treatment effect difference between the two active products (3.4%, 95% CI -4.2, 10.9) is probably of little clinical significance. The sponsor asserts these findings support their argument that the two products are equivalent however the Agency statistician reports the sponsor is incorrect in their interpretation of the study. Specifically she states in her review *“since the upper limit of confidence interval of responder proportion differences between sumatriptan and MT100 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 MT100 and sumatriptan in terms of 2 hour pain relief.”* Regardless of the interpretation of the Blackwelder test the results of the comparison of MT100 versus placebo for 2-hour pain response is supportive of efficacy relative to the pain of migraine, although the Agency statistician argues study MT100-308 was overpowered for this endpoint.

Trial MT100-303 had two pre-stated primary endpoints (sustained pain response at 2 hours and sustained pain response at 4 hours). As demonstrated in the summary table, the sponsor's analysis demonstrated a significant difference between MT100 and placebo for 2 hour sustained pain response ( $p = 0.048$ ) but not for 4 hour sustained pain response ( $p = 0.198$ ). However using the Agency statistician's results there was no statistical difference between MT100 and placebo for 2 hour sustained pain response ( $p = 0.062$ ). The Agency statistician reports the sponsor's analysis did not include all the pre-stated covariates in their calculations.

Despite the conflicting results from the various pain endpoints for trial MT100-306, MT100-308 and MT100-303 I believe there is ample evidence that MT100 is effective, compared to placebo, in the treatment of headache pain associated with migraine. If MT100 is approved I believe no statement relative to efficacy of MT100 compared to sumatriptan should be permitted since the sponsor did not evaluate the full dosing regimen of sumatriptan, the Blackwelder equivalence analysis in trial MT100-308 used an unacceptable delta of 10%, and the Agency statistician's interpretation of the Blackwelder test result is consistent with non-equivalence.

As demonstrated in my summary table the three efficacy studies demonstrated mixed results relative to efficacy for the associated symptoms of nausea, photophobia, and photophobia. In trial MT100-306 there was a nominally significant difference between MT100 and placebo in the proportion of subjects reporting nausea at 2 hours ( $p = 0.049$ ) and in trial MT100-303 there was a nominally significant difference between MT100 and placebo for the proportion of subjects reporting nausea at 1.75 hours ( $p = 0.046$ ) but not at 2 hours ( $p = 0.070$ ). This may be enough evidence of efficacy relative to nausea however in trial MT100-308 there was no difference

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between MT100 and placebo in the proportion of subjects reporting nausea at 2 hours ( $p=0.980$ ) or any time earlier ( $p\geq 0.273$ ). Similarly there were mixed results for phonophobia, with trial MT100-306 and MT100-308 both failing to demonstrate significant efficacy at 2 hours ( $p=0.062$  and  $0.079$  respectively), and trial MT100-303 demonstrating significant efficacy at 2 hours ( $p=0.030$ ). In all three trials there was a significant difference between subjects receiving MT100 compared to placebo for the proportion of subjects reporting photophobia at 2 hours ( $p\leq 0.044$ ).

In conclusion the three efficacy studies (MT100-306, MT100-308 and MT100-303) collectively demonstrate significant benefit of MT100 over placebo for the treatment of headache pain associated with migraine and mixed results for the treatment of nausea and phonophobia associated with migraine. If approved, despite the lack of benefit over naproxen seen in the factorial studies, I would recommend that MT100 be approved for the headache pain of migraine and not the migraine syndrome since the pivotal studies demonstrated conflicting results relative to nausea and phonophobia. I discuss the results from trial MT100-306, MT100-308 and MT100-303 in further detail in section 6.3.3 and 6.3.4 of this review.

### 3.3 Safety

The safety database for this NDA contains the safety information from 6 phase I pharmacokinetics studies (MT100-101, MT100-102, MT100-103, MT100-105, MT100-106 and MT100-107), 2 phase II dose ranging studies (MT100-201 and MT100-202), 8 phase III efficacy studies (MT100-301, MT100-304, MT100-306, MT100-308, MT100-303, MT100-401A, MT100-402, and MT100-307) and a single long term safety study (MT100-302). A description of the trial designs for each study can be found in section 4.2 of this review and are briefly summarized in table 1 above. Each of the phase III studies included assessments of adverse events, physical examinations including vitals and basic laboratory studies done at baseline and follow up visits (generally 1 to 3 days in single attack studies).

The following table briefly summarizes the total extent of exposure to MT100 during the single attack phase II and phase III studies. In total, 2725 subjects received a single dose of MT100 (1 tablet and 2 tablets) within the combined phase II and phase III program. Additionally in trial MT100-307, 69 subjects received multiple one tablet doses of MT100 during the treatment of multiple migraine prodromes. The amount of acute exposure is satisfactory. In addition to the exposure to MT100 outlined above, there were 88 subjects who participated in 5 different phase I PK studies that included various combinations of metoclopramide (8, 16, or 32 mg) and naproxen (500 or 1000 mg).

**Table 6** Total Single Dose Exposure to MT100

	MT100 x 1	MT100 x 2	Naproxen	Metoclopramide	Sumatriptan	Placebo
Total subjects exposed	2412	313	1549	800	474	867

Source: Adapted from Sponsor table 18.2, iss.pdf, page 58. Includes subjects from trials 201, 301, 303, 304, 306, 308, 401A and 402.

The following table summarizes the amount of long-term (up to 1 year) exposure to MT100 during trial MT100-302. In all, a total of 1006 subjects treated 23,195 migraine attacks during the course of the study (average of 23 attacks per person). As demonstrated in the table 621 subjects completed at least 6 months of the study and treated over 2 migraines per month on

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average. Likewise 329 subjects completed 1 year (defined as 355 days by sponsor) of the study and also treated well over 2 migraines per month on average. The amount of long term exposure exceeds the ICH requirements of at least 300 subjects treated for 6 month and 100 subjects treated for 1 year with each treating at least 2 attacks per month.

**Table 7** Six Month and 1 Year Long Term Exposure, Study MT100-302

	All subjects	6-Month Completers	1-year Completers
<b>Total number of subjects</b>	1006	621	329
<b>Mean (SD) number of attacks per subject</b>	23.1 (15.11)	19.3 (5.62)	38.6 (9.68)
<b>Minimum and maximum number of attacks treated</b>	1.0, 78.0	12.0, 43.0	24.0, 78.0
<b>Total number of attacks treated</b>	23,195	11,959	12,711
<b>Average per month</b>		3.2	3.2

Source: Adapted from Sponsor table 8, study report 302.pdf, page 102.

The following table briefly summarizes the demographics of all subjects in the safety database. Over the entire safety database the mean age for all participants was 41 years of age, 85% were Caucasian, 87% were female, and the mean weight was 71.04 kilograms. The majority of subjects had a history of migraine without and aura (73%), 12% had migraine with aura and 14% reported a combination of both. Cohorts for each study were fairly well balanced for each of these parameters. These demographic characteristics are typical for migraine NDAs I have reviewed. A further discussion of patient demographics by study can be found in section 4.3 of this review.

**Table 8** Combined\* Exposure and Demographics for All Single Dose Randomized Studies.

Study	MT 100	MT 100 2 tablets	Naproxen	Metoclopramide	Sumatriptan <sup>1</sup>	Placebo	Total
<b>Number of Subjects</b>	2412	313	1549	800	472	867	6413
<b>Gender</b>							
Male, N (%)	337 (14)	39 (12)	198 (13)	104 (13)	56 (12)	109 (13)	843 (13)
Female, N (%)	2075 (86)	274 (88)	1351(87)	696 (87)	416 (88)	758 (87)	5570 (87)
<b>Age, years</b>							
Mean (range)	41.0 (18- 78)	41.2 (19-72)	41.1 (18-75)	40.6 (18-77)	40.8 (18-72)	41.8 (18-78)	41.1 (18-78)
18-40, N (%)	1139 (47)	148 (47)	729 (47)	384 (48)	230 (49)	385 (44)	3015 (47)
> 40, N (%)	1273 (53)	165 (53)	820 (53)	416 (52)	242 (51)	482 (56)	3398 (53)
<b>Race, N (%)</b>							
Caucasian	2041 (85)	255 (81)	1350 (87)	699 (87)	386 (82)	723 (83)	5454 (85)
Black	244 (10)	30 (10)	109 (7)	61 (8)	43 (9)	86 (10)	573 (9)
Oriental/Asian	16 (<1)	1 (<1)	14 (<1)	6 (<1)	6 (1)	12 (1)	55 (<1)
Hispanic	98 (4)	22 (7)	63 (4)	24 (3)	34 (7)	39 (4)	280 (4)
Other	13 (<1)	5 (2)	13 (<1)	10 (1)	3 (<1)	7 (<1)	51 (<1)
<b>Weight (kg)</b>							
Mean (Range)	71.31 (39.0-182.0)	70.95 (41.4-117.9)	70.78 (36.3-151)	70.90 (40.4-121.1)	69.45 (37.2-139.3)	71.80 (41.5-146.1)	71.04 (36.3-182.0)
<b>Migraine history, N (%)</b>							
With aura	299 (12)	31 (10)	178 (11)	113 (14)	54 (11)	126 (15)	801 (12)
Without aura	1755 (73)	221 (71)	1196 (77)	599 (75)	331 (70)	594 (69)	4696 (73)
Mixed	357 (15)	61 (19)	175 (11)	88 (11)	86 (18)	147 (17)	914 (14)
Missing	1	0	0	0	1	0	2

\*Combined database includes: MT100-201, MT100-301, MT100-303, MT100-304, MT100-306, MT100-308, MT100-401A and MT100-402

<sup>1</sup>Sumatriptan = over-encapsulated Imitrex 50mg tablets

Source: Sponsor table 3, ISS page 16.

The primary source of data for this safety review include the Integrated Summary of Safety (ISS), the individual study reports, and the SAS transport files for each study submitted electronically by the sponsor on July 31, 2003. For the purposes of my safety review I give added emphasis to the 2 phase III pivotal trials (MT100-306 and MT100-308) and the long-term

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safety trial MT100-302. Additionally since the sponsor is not seeking approval of a 2 tablet dosing regimen for MT100 I will focus primarily on subjects that treated their migraines with a single dose of MT100. I reviewed the sponsor's translation of verbatim terms to COSTART and MedDRA terms in each study and there appears to be no significant errors or omissions.

There were no deaths in any trial during the entire clinical development program for MT100. In section 7.4.2 of this review I discuss the serious adverse events reported during the entire clinical development program for MT100. Of the subjects taking MT100, 27 serious adverse events were reported. Most of these occurred during the long-term safety trial MT100-302. I reviewed the case report forms for each patient with a serious adverse event and in my opinion none of the serious adverse events could reasonably be attributed to MT100. Similarly, there were no withdrawal due to an adverse event in the single attack acute studies but several occurred during the long-term study. Overall, 82 subjects (8%) withdrew from trial MT100-302 due to an adverse event. Common adverse events leading to early withdrawal included somnolence (10%), restlessness (9%), diarrhea (9%), anxiety (11%), and tremor, dyspepsia, nausea and fatigue (all less than 5%). All events were generally mild and transient. Overall the number of early withdrawals due to an adverse event for the entire clinical development plan for MT100 was low. There does not appear to be any particular pattern to the nature of adverse events leading to withdrawal.

The following table summarizes the combined incidence of common adverse events ( $\geq 1\%$ ) in all single-dose, randomized, phase III studies comparing MT100 to placebo. Adverse events were reported by 22% of those subjects receiving a single one-tablet dose of MT100 and by 15% of subjects treated with placebo. As demonstrated the most common adverse events with a single dose of MT100 was somnolence (4%), diarrhea (3%), dizziness (exclude vertigo, 2%), dry mouth (2%), and fatigue (2%). As would be expected the adverse events commonly reported for MT100 were those typically associated with the use of either metoclopramide or naproxen alone.

A single two-tablet dose of MT100 was evaluated in trials MT100-102, MT100-306, and MT100-401A. Additionally subjects in MT100-303 received a second dose of MT100 two hours after the initial dose if required. As demonstrated in the table a single two-tablet dose of MT100 was associated with a higher rate of adverse events compared to the single one tablet dose of MT100. More common in the 2 tablet cohorts were restlessness, somnolence, dizziness and some GI complaints (primarily dyspepsia). A rescue dose of MT100 was generally well tolerated in trial MT100-303 although there was a slight increase in the common adverse events. The sponsor does not intend to market the double dose of MT100 as the recommended initial first dose.

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**Table 9** Incidence of AE ( $\geq 1\%$ ) in All Phase III Trials with MT100 and Placebo, n (%)

	MT100 N=2355	MT100 X 2 N=313	Placebo N=810
Any adverse event	513 (22)	111 (35)	121 (15)
Nervous System			
Somnolence	100 (4)	32 (10)	10 (1)
Dizziness (exclude vertigo)	55 (2)	20 (6)	22 (3)
Restlessness	13 (<1)	12 (4)	4 (<1)
Paresthesia	14 (<1)	4 (1)	3 (<1)
Gastrointestinal	209 (9)	39 (12)	40 (5)
Diarrhea	76 (3)	16 (5)	7 (<1)
Dry Mouth	37 (2)	3 (<1)	12 (1)
Dyspepsia	28 (1)	3 (<1)	6 (<1)
Abdominal Pain (upper)	27 (1)	4 (1)	3 (<1)
Abdominal pain NOS	15 (<1)	5 (2)	7 (<1)
General disorders	81 (3)	20 (6)	27 (3)
Fatigue	38 (2)	6 (2)	6 (<1)
Feeling Jittery	13 (<1)	4 (1)	1 (<1)
Psychiatric Disorders	31 (1)	14 (4)	6 (<1)
Anxiety	9 (<1)	7 (2)	2 (<1)
Skin/subcutaneous tissue*	27 (1)	5 (2)	7 (<1)
Ear and Labyrinth disorders*	16 (<1)	3 (<1)	10 (1)
Musculoskeletal and Connective tissues*	14 (<1)	4 (1)	9 (1)
Infections and infestations*	18 (<1)	2 (<1)	6 (<1)
Respiratory, thoracic and mediastinal*	19 (<1)	2 (<1)	3 (<1)
Vascular disorders*	15 (<1)	3 (<1)	1 (<1)
Eye disorders*	7 (<1)	2 (<1)	7 (<1)
Investigations*	10 (<1)	0	3 (<1)
Injury, poisoning and procedural complications*	9 (<1)	1 (<1)	1 (<1)
Renal and urinary disorders*	4 (<1)	2 (<1)	2 (<1)
Cardiac disorders*	3 (<1)	0	2 (<1)
Blood and lymphatic system disorders*	5 (<1)	0	0
Reproductive system and breast disorders*	4 (<1)	0	1 (<1)
Metabolic and nutrition disorders*	2 (<1)	1 (<1)	1 (<1)
Endocrine disorders*	1 (<1)	0	2 (<1)
Immune system disorders*	1 (<1)	0	2 (<1)
Pregnancy, puerperium and perinatal conditions*	2 (<1)	0	0

\*System contained no adverse event occurring  $\geq 1\%$  in any actively treated cohort.

Source: Adapted from sponsor table 18.4.1.11, ISS.pdf

Trial MT100-306 and MT100-308 included a sumatriptan arm as an active comparator. A comparison of adverse events in each cohort in these trials demonstrates both active products to be well tolerated. The overall incidence of adverse events between MT100 and sumatriptan were comparable (23% for MT100 vs. 24% for sumatriptan). As would be expected there were less complaints of chest tightness with MT100 (1% MT100 vs. 2% sumatriptan) whereas subjects randomized to MT100 reported more diarrhea, dyspepsia and abdominal pain than subjects randomized to sumatriptan. In trial MT100-306 adverse events occurring in more than 2% of subjects receiving a single dose of MT100 were somnolence (4%), diarrhea (4%), dizziness (4%), restlessness (2%), upper abdominal pain (2%) and dyspepsia (2%). This compares to the following incidence rates in subjects taking sumatriptan; somnolence (2%), diarrhea (0%), dizziness (6%), restlessness (<1%), upper abdominal pain (0%) and dyspepsia (<1%). Common

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adverse events reported in the sumatriptan cohort included fatigue (4%), chest tightness (4%) and throat tightness (3%). In trial MT100-308 the MT100 and sumatriptan cohorts were similar in the nature and incidence of adverse events. The sponsor does not provide any discussion whether any of these findings are statistically significant however given the small numbers it is unlikely

The following table summarizes the breakdown of adverse events reported in the single dose studies by severity reported for each cohort. Overall AEs were reported by 22% of subjects receiving a single one-tablet dose of MT100, 35% of subjects treated with two-tablets dose of MT100, 15% of subjects treated with placebo, 18% of subjects receiving naproxen 500 mg, 24% of subjects receiving metoclopramide and 24% of subject receiving sumatriptan. As demonstrated in the table 87% of all adverse events reported by subjects administering a single dose of MT100 were reported as mild to moderate intensity compared to 91% for subjects taking placebo. Overall the various cohorts were remarkably similar for the percentage of subjects rating their adverse events as mild, moderate and severe with the exception of subjects taking metoclopramide where 21% of subjects reporting an adverse event rated it as severe. Among the 65 subjects who reported severe adverse events following administration of one-tablet of MT100, the majority (n=51) reported events in the nervous system (n=24) or gastrointestinal system (n=27). Somnolence was the most prevalent severe adverse event (n=17) in the nervous system and diarrhea accounted for the majority of the severe events reported in the gastrointestinal system (n=8).

**Table 10** Adverse Event Severity by Dose and Drug Product

	<b>MT100 x 1</b>	<b>MT100 x 2</b>	<b>Naproxen</b>	<b>Metoclopramide</b>	<b>Sumatriptan</b>	<b>Placebo</b>
Total Subjects	2412	313	1549	800	474	867
Total AEs	519 (22%)	111 (35%)	275 (18%)	189 (24%)	114 (24%)	127 (15%)
Mild (%)	260 (50%)	45 (41%)	151 (55%)	89 (47%)	64 (56%)	66 (52%)
Moderate (%)	194 (37%)	49 (44%)	108 (39%)	61 (32%)	40 (35%)	50 (39%)
Severe (%)	65 (13%)	17 (15%)	16 (6%)	39 (21%)	10 (9%)	11 (9%)

Source: Adapted from sponsor table 18.4.3, iss.pdf, page 164

Adverse events described during the early phase I PK studies and trial MT100-307 (prodrome study) were similar in nature and severity as to those reported in the controlled clinical trials described above. The incidence of adverse events with a single dose of MT100 was no greater than with the individual components. Of particular interest was trial MT100-102 where the incidence of adverse events in the 2 tablet MT100 cohort was generally 2 to 3 times the incidence rate seen in the single tablet cohort (see Table 67). In trial MT100-103 (hepatic impairment PK study) MT100 was well tolerated with only a single patient reporting an adverse event (diarrhea).

In the long term trial MT100-302, screened subjects were followed for 1 year. All subjects took a single tablet of MT100 at the onset of a migraine attack (any grade). Unlike most triptan studies subjects were not permitted to re-administer MT100 at any time during the 24-hour period of the attack. Safety follow up was done every 3 months. Diary assessments were done for 24 hours for each attack treated. The overall reporting rate for subjects reporting at least one adverse event was 78%. As would be expected for an acute intermittent therapy the reporting rate for any adverse events reduced with the duration of therapy. Reported rates for the 0 to 3 month period were 65%, compared to 44% for the 3 to 6 month period, 35% for the 6 to 9 month period and 32% for the 9 to 12 month period. The most common adverse events reported are summarized in

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the following table. The majority of the adverse events were graded mild or moderate in severity. Somnolence was the only adverse event reported as severe by more than 1% of subjects [n=19 (2%)]. Overall the nature of the adverse events seen during the long-term study is similar to the nature of the adverse events seen during the short-term, single attack migraine studies described earlier.

**Table 11** Common Adverse Events ( $\geq 2\%$ ), Trial MT100-307, n (%)

System Organ Class/Preferred Term	Number of Subjects (%) (N = 1006)	
	All Events	Events within 24 Hours of Exposure
<b>Subjects with at Least One Adverse Event</b>	<b>785 (78%)</b>	<b>563 (56%)</b>
<b>Gastrointestinal Disorder</b>		
Diarrhea NOS	147 (15)	109 (11)
Dyspepsia	74 (7)	54 (5)
Nausea	65 (6)	53 (5)
Abdominal Pain Upper	48 (5)	27 (3)
Dry Mouth	38 (4)	36 (4)
Pharyngolaryngeal Pain	52 (5)	22 (2)
Abdominal Pain NOS	26 (3)	19 (2)
Vomiting NOS	24 (2)	15 (1)
Constipation	24 (2)	12 (1)
Toothache	21 (2)	9 (<1)
<b>Infections and Infestations</b>		
Nasopharyngitis	170 (17)	53 (5)
Sinusitis NOS	103 (10)	26 (3)
Upper Respiratory Tract	68 (7)	18 (2)
Bronchitis	45 (4)	11 (1)
<b>Nervous System Disorders</b>		
Somnolence	108 (11)	101 (10)
Dizziness (Excluding Vertigo)	67 (7)	59 (6)
Insomnia	33 (3)	28 (3)
Restlessness	18 (2)	16 (2)
Headache NOS	17 (2)	11 (1)
<b>General Disorders/Administrative Site Condition</b>		
Fatigue	73 (7)	65 (6)
Influenza Like Illness	29 (3)	10 (<1)
Feeling Jittery	17 (2)	16 (2)
Pain NOS	17 (2)	11 (1)
Pyrexia	16 (2)	9 (<1)
<b>Musculoskeletal and Connective Tissue Disorders</b>		
Back Pain	38 (4)	13 (1)
Myalgia	26 (3)	17 (2)
Arthralgia	29 (3)	12 (1)
Neck pain	16 (2)	8 (<1)
Pain in Limb	16 (2)	5 (<1)
<b>Respiratory, Thoracic and Mediastinal Disorders</b>		
Cough	34 (3)	13 (1)
Nasal Congestion	29 (3)	9 (<1)
Sinus Congestion	19 (2)	7 (<1)
Rhinorrhea	17 (2)	7 (<1)
<b>Psychiatric Disorders</b>		
Anxiety NEC	19 (2)	4 (<1)
<b>Skin and Subcutaneous Tissue Disorders</b>		
Rash NOS	20 (2)	10 (<1)
<b>Reproductive System and Breast Disorders</b>		
Dysmenorrhea	20 (2)	8 (<1)

Source: Adapted from Sponsor table 12\*, ISS.pdf.

The safety laboratory database for MT100 demonstrates no clinically significant changes in clinical chemistries or hematology. A few patients (<1.0%) experienced transient elevation in liver enzymes or increases in their creatinine kinase levels. Despite the lack of any serious adverse events relative to laboratory findings the label for MT100 (if approved) should reflect

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the safety concerns summarized in the labels of its components. For example naproxen use has been associated with prolonged bleeding times, anemia, renal toxicity, and hepatic toxicity; metoclopramide use has been associated with hepatic toxicity.

In each phase II and phase III controlled clinical trial vital signs and a physical evaluation were done at baseline and follow up visit. In the open label, long term study MT100-302, vital signs and physical examination were evaluated at baseline then every 3 months up to 1 year. Overall in all phase II and phase III studies there was no clinically meaningful changes between baseline and follow up for systolic blood pressure, diastolic blood pressure, pulse, or any physical finding.

In trial MT100-101 serial 12-lead ECGs were conducted at screening, baseline, and days 1, 3, 4, and 5. A review of these ECGs fails to find any clinically significant changes. No other study included ECGs.

No formal drug-drug interaction studies were conducted during the clinical development program for MT100. No formal drug-demographic or drug disease interactions (other than hepatic impairment trial MT100-103) studies were conducted during the clinical development program for MT100. In trial MT100-103 eight subjects with mild hepatic impairment (Grade B or score of 7-9 points on the Child-Pugh Classification<sup>1</sup>) were given a single tablet of MT100. Overall MT100 was well tolerated with only a single patient reporting an adverse event (diarrhea).

In conclusion the 17 clinical trials conducted in support of this NDA demonstrate MT100 to be generally well tolerated. Common adverse events seen during the trials were consistent with the common adverse events seen with the use of naproxen and metoclopramide individually. As with most NDA safety databases there was inadequate exposure to fully address uncommon and rare adverse events. Both naproxen and metoclopramide have been approved in the United States for many years and both have been associated with serious adverse events on rare occasions. Of particular concern to this reviewer is the extrapyramidal side effects seen on rare occasions (0.2% to 2% depending on dose and route of administration) with the use of metoclopramide. I discuss this concern in greater detail in section 7.4.14 of this review.

### 3.4 Dosing

The proposed dosing regimen for MT100 is 1 tablet of MT100 at the onset of a migraine attack. A second dose or double dose of MT100 is not recommended although the proposed label does not explicitly state this. The proposed dosage and administration statement reads:

*“The recommended dose is one tablet of MYZAN. Taking a second dose of MYZAN (i.e., if relief is not provided within two hours of the first dose) has not been shown to have a beneficial effect, although the incidence or severity of side effects was not increased.”*

A single two-tablet dose of MT100 was evaluated in trials MT100-102, MT100-306, and MT100-401A. Additionally subjects in MT100-303 received a second dose of MT100 two hours after the initial dose if required. As discussed earlier a single two-tablet dose of MT100 was

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<sup>1</sup> Child-Pugh Grading based on presence of encephalopathy, ascites and the level of serum bilirubin, albumin and prothrombin time each using a 3 point scale.

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associated with a higher rate of adverse events compared to the single one tablet dose of MT100 (35% vs. 22%). A rescue dose of MT100 was generally well tolerated in trial MT100-303 although there was a slight increase in the common adverse events. As described in the label for Reglan, metoclopramide is associated with serious extrapyramidal adverse events, especially at high and or prolonged doses. Therefore it would be prudent to avoid multiple and prolonged doses of MT100. If MT100 is approved I would recommend the dosage and administration section be changed to reflect clearly that a rescue dose (and double dose) of MT100 is not recommended.

The final formulation for MT100 was determined by the results of trials MT100-201 and MT100-202. In both trials several different combinations of naproxen and metoclopramide were evaluated for safety and efficacy. MT100-201 was a single dose, double blind, dose-ranging, placebo controlled, nine cell study of four different formulations of naproxen/metoclopramide combination in the treatment of an acute migraine. Cohorts included the following: placebo, MET 8 mg, MET 16 mg, NAP 500 mg, NAP 1000 mg, MET 8 mg + NAP 500 mg, MET 16 mg + NAP 500 mg (MT100), MET 8 mg + NAP 1000 mg, and MET 16 mg + NAP 1000 mg. The primary endpoint for this study was 2 hour Sum of Pain Intensity Differences (SPID)<sup>2</sup> and 2 hour nausea relief. I describe the results of trial MT100-201 in section 6.3.1 however only the naproxen 500 mg plus metoclopramide 16 mg cohort demonstrated a strong trend towards statistical significance for both SPID and the proportion of subject reporting no nausea at 2 hours (p=0.064 and 0.054 respectively). Interestingly in trial MT100-201 the addition of metoclopramide (16 mg) to 500 mg of naproxen did not improve the SPID scores compared to naproxen alone, in fact naproxen 500 mg alone was numerically better than naproxen 500 mg plus metoclopramide 16 mg (SPID 1.57 vs. 1.45 respectively). However the addition of 16 mg of metoclopramide to naproxen 500 mg did result in a numerical benefit for the proportion of subjects reporting no nausea at 2 hours compared to naproxen alone (89% vs. 81% respectively) suggesting some benefit. Of the formulations evaluated in study MT100-201 the combination of naproxen 500 mg and metoclopramide 16 mg appeared to offer the best evidence of effectiveness.

Trial MT100-202 was a single dose, double blind, placebo controlled, multicenter trial comparing naproxen 500 mg/metoclopramide 8 mg, naproxen 1000 mg/metoclopramide 16 mg and placebo. The primary endpoint of this study is 2-hour headache response defined as moderate to severe intensity at baseline going to mild or no pain at 2 hours, without the use of rescue medication. The study demonstrated that significantly more patients receiving naproxen 1000 mg/metoclopramide 16 mg reported headache relief at 2 hours compared to placebo (p<0.001). Likewise the naproxen 1000 mg/metoclopramide 16 mg cohort of subjects reported significantly less nausea, photophobia and phonophobia at 2 hours compared to placebo (p<0.001, 0.002, 0.015 respectively). The lower dose cohort (500/8) was not significantly different from placebo for pain response at 2 hours. The study did not include a cohort of subjects receiving naproxen 500 mg and metoclopramide 16 mg (i.e., MT100). The sponsor concludes that naproxen 1000 mg/metoclopramide 16 mg is the minimally effective dose for relief of migraine pain and associated symptoms at 2 hours.

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<sup>2</sup> SPID =  $\sum \text{PID}_i \times [\text{time (hours) elapsed since previous observation}]$

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Overall, between the two trials the combination of naproxen 1000 mg plus metoclopramide 16 mg appeared to offer the best evidence of effectiveness in my opinion however the sponsor chose to further develop the combination naproxen 500 mg plus metoclopramide 16 mg as the final formulation for MT100. The choice of this formulation is reasonable given the results of trial MT100-201. The sponsor does not discuss why they did not chose to pursue the combination product naproxen 1000 mg/metoclopramide 16 mg which appears effective. At the conclusion of trial MT100-201 and MT100-202 we had an end-of-phase II meeting with the sponsor (3/31/99). At that time we agreed that the combination of metoclopramide 16 mg and naproxen 500 mg was a rational combination for the treatment of migraine.

Specific studies to assess overdosage and/or the abuse potential of MT100 have not been conducted by the sponsor. However neither naproxen or metoclopramide have been shown to be addictive or result in withdrawal phenomena after years of marketing within the United States and abroad. Additionally, no adverse events of drug abuse or overdose with MT100 were reported in any clinical trial conducted for this NDA.

Despite the lack of demonstrated addiction potential for MT100, migraineurs have been shown in several studies (Diener 1993, Kaube 1994, Limmroth 1999) to be prone to overuse of migraine treatments. Analgesic overuse is a known cause of withdrawal headaches. Overuse of MT100 could potentially be dangerous since repeated and/or high doses of metoclopramide have been shown to produce clinically significant adverse events such as Tardive Dyskinesia. For this reason the total monthly doses of MT100 (if approved) should be limited to what is adequately supported by the safety data supplied in this NDA. Patients should be instructed to not exceed the recommended daily and monthly dose described in labeling. The sponsor proposes that no more than 6 tablets of MT100 should be used in any single month and no more than a single dose of MT100 should be used in a single migraine event. This seems reasonable to this reviewer. The professional labeling for MT100 (if approved) should contain language similar to the language seen in the warning and contraindications sections of the Naproxen and Reglan labels relative to overdosages.

### **3.5 Special Populations**

The clinical development program for MT100 contains few males, non-Caucasians or elderly subjects. Overall 85% of all participants were Caucasian, less than 10% were African American, 87% were female, and there were no subjects less than 18 years of age. These demographic findings are common in migraine NDAs that I have reviewed. In addition to these demographic subset analyses the sponsor also conducted a separate trial to evaluate the safety of a single dose of MT100 in subjects with mild hepatic insufficiency (MT100-103).

The sponsor's post hoc subset analysis of efficacy from trials MT100-301 and MT100-304 (factorial studies) by gender demonstrated mixed results between the 2 studies. In trial MT100-301 34.6% of all women reported a sustained response, which was numerically superior to the naproxen female-only cohort (30.7%) and statistically superior to the metoclopramide female-only cohort (20.5%). Whereas in trial MT100-301 a statistically higher percentage of males subjects using MT100 reported sustained response than males using naproxen or

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metoclopramide (41.4% vs. 22.9% and 14.3% respectively). Opposite findings were seen in trial MT100-304 where MT100 seems to work better in women than it does in men (see Table 77). However since few men participated in the factorial studies it is difficult to make firm conclusions from this data. Relative to safety there was minimal difference between males and females for the incidence and nature of adverse events reported in all trials. Overall 20% of males reported at least one adverse event; the most frequently reported events were diarrhea (4%) and somnolence (3%). This compares to 22% of female subjects reporting at least one adverse event; the most frequently reported events were also somnolence (4%) and diarrhea (3%).

Overall approximately 15% of all subjects in the clinical development program are non-Caucasian. The sponsor's subset analysis of efficacy from trial MT100-306 and MT100-308 (placebo and active controlled studies) by race demonstrates conflicting results between Caucasians and non-Caucasians for 2 hour pain response. In trial MT100-306 and MT100-308 Caucasian subjects taking a single dose of MT100 consistently reported more response at 2 hours than Caucasian subjects taking placebo (54.8% and 44.9% vs. 24.1% and 31.1%). Whereas in trial MT100-306 non-Caucasian subjects taking placebo more often reported response at 2 hours than non-Caucasian subjects taking a single tablet of MT100 (48.3% vs. 43.5%). The reason for this difference is not immediately clear but may be due to the low number of non-Caucasians in trial MT100-306 and MT100-308. Relative to safety 22% of Caucasians reported at least one adverse event compared to 18% of non-Caucasians. The incidence of diarrhea was the same (3%), somnolence was similar (5% non-Caucasian vs. 4% Caucasian) and dizziness was similar (3% non-Caucasian vs. 4% Caucasian).

The sponsor subset analysis of trials MT100-306 and MT100-308 by age (<45 and  $\geq$ 45 years) demonstrated a good response in both age categories although older subjects tended to respond less often than younger subjects. Subjects less than 45 years of age reported a response rate of 52.9% in trial MT100-306 and 47.9% in trial MT100-308. Subjects  $\geq$  45 years of age reported a response rate of 47.9% in trial MT100-306 and 37.2% in trial MT100-308. These results compare to placebo response rates of 37.7% and 32.7% in trial MT100-306 and MT100-308 respectively in subjects less than 45 years of age and 15.4% and 30.7% in subjects  $\geq$  45 years of age. The sponsor does not describe the findings in the elderly ( $\geq$ 65 years of age) however in all studies there were very few subjects age 65 years or older. In trial MT100-306 there were 3 subjects  $\geq$ 65 years of age and in trial MT100-308 there were 18 subjects  $\geq$ 65 years of age. There was minimal difference between age groups relative to safety. Twenty-one percent (21%) of 18-40 year olds reported at least one adverse event compared to 22% of subjects > 40 years. The incidence of diarrhea (3% in young, 3% in >40 year olds) and somnolence (5% in young and 4% in >40 year olds) was similar. I reviewed the adverse events for the few elderly subjects from each trial and did not see any unique events or concerns.

As discussed earlier the sponsor has not evaluated the safety and efficacy of MT100 in adolescent migraineurs. The sponsor has not proposed a pediatric program and requests a waiver. If this NDA is approved the sponsor should evaluate the safety and efficacy of MT100 in the treatment of migraine in adolescent patients.

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In trial MT100-103 eight subjects with mild hepatic impairment (Grade B or score of 7-9 points on the Child-Pugh Classification<sup>3</sup>) were given a single tablet of MT100 in order to evaluate safety and the pharmacokinetics of metoclopramide and naproxen. Efficacy was not assessed. Overall MT100 was well tolerated with only a single patient reporting an adverse event (diarrhea). Overall moderate hepatic insufficiency had no effect on the pharmacokinetics of metoclopramide. However the total naproxen AUC<sub>inf</sub> was approximately 1.3 fold higher and the unbound naproxen AUC<sub>inf</sub> was approximately 2.7 fold higher in subjects with moderate hepatic failure compared to normal subjects. The sponsor states since MT100 is intended for intermittent use then no adjustment in patients with hepatic impairment is recommended. I don't agree with this recommendation. Although the label for Reglan states it is safe to use even in the setting of advanced liver disease, the label for Anaprox states a lower dose should be considered in patients with hepatic impairment. Given the altered pharmacokinetics of naproxen seen in study MT100-103 in the setting of moderate hepatic insufficiency, I recommend a statement in the MT100 labeling (if approved) consistent with the Anaprox label. A reasonable statement might state that MT100 should be used with caution in subjects with moderate hepatic insufficiency.

The use of MT100 in renally impaired subjects has not been evaluated by the sponsor. The sponsor states that the presence of renal impairment has no effect on naproxen half-life however they provide no reference for this statement. The Reglan package insert recommends a 50% reduction in dose in patients with creatinine clearance below 40 ml/min. The label for Anaprox warns that naproxen and its metabolites may accumulate in the presence of renal insufficiency and states a lower dose should be considered. I believe MT100 should be used with caution in patients with renal impairment. If approved, the label for MT100 should reflect the concerns about renal impairment found in the labels for metoclopramide and naproxen.

No new Human reproductive studies were performed in support of this NDA. In total there were nine pregnancies during the clinical development program for MT100. Three of these subjects were randomized to naproxen during the early factorial studies and 6 of these subjects were randomized to MT100. Of the women taking MT100, three were exposed to a single dose of study medication (PID 6434, 4985, and 4724) and 3 were exposed to multiple intermittent single doses of MT100 during the open label long-term study MT100-302 (PID 2002, 1065, and 2020). My review of the pregnancy outcomes did not find any particular signals for concern. None-the-less, the use of MT100 during pregnancy should be discouraged since there are no adequate and well controlled studies that demonstrate safety during pregnancy. The label for MT100 (if approved) should include warnings relative to pregnancy similar to those found in the naproxen and metoclopramide labels.

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<sup>3</sup> Child-Pugh Grading based on presence of encephalopathy, ascites and the level of serum bilirubin, albumin and prothrombin time each using a 3 point scale.

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#### 1. Introduction and Background

##### 1.1 Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

MT100<sup>TM</sup> Tablets is a combination product consisting of 16 mg of metoclopramide hydrochloride and 500 mg of naproxen sodium. MT100 is formulated to provide coordinated and sequential release of metoclopramide followed by naproxen. The sponsor seeks Agency approval for the intermittent use (up to 6 times per month) of MT100 in the treatment of acute migraine with and without an aura in adults. The proposed marketing name is Myzan.

Metoclopramide is a dopamine receptor antagonist approved since 1980 (original NDA 017854, Reglan Tablets) for the following indications; gastroesophageal reflux disease (up to 15 mg QID up to 12 weeks), diabetic gastric stasis (10 mg q AC for 2 to 8 weeks), prevention of nausea and vomiting associated with cancer chemotherapy (initially 2 mg/kg IV, may be repeated 5 times over 13 hours), prevention of postoperative nausea and vomiting (up to 20 mg IM), to facilitate small bowel intubation (10 mg), and to aid in radiological examinations (10 mg). The sponsor asserts that the prokinetic effects of metoclopramide may help in the treatment of migraine by improving absorption of naproxen sodium. Additionally the sponsor assert that metoclopramide may have direct analgesic benefit for migraine sufferers via dopamine receptor antagonism. In support of this theory Del Bene (Headache 1994) demonstrated that the administration of low-dose apomorphine (dopamine agonist) can induce migraine in migraineurs. Additionally the sponsor asserts that several dopamine antagonist (haloperidol, prochlorperazine, chlorpromazine, and metoclopramide) have all been shown to be effective against migraine with efficacy rates between 46% to 100%.

Naproxen sodium is a non-steroidal anti-inflammatory drug (non-specific COX inhibitor) that has been previously shown to be effective in migraine syndrome (Advil Migraine, NDA 020402, approved 4/20/1995) and is also approved for the treatment of rheumatoid arthritis, osteoarthritis, and Ankylosing Spondylitis (generally up to 500 mg BID occasionally more), juvenile arthritis (5 mg/kg BID), the treatment of pain, primary dysmenorrhea, tendonitis and bursitis (up to 500 mg BID), and gout (750 mg initially followed by 250 mg TID).

##### 1.2 State of Armamentarium for Indication(s)

Migraine is a common neurological disorder usually characterized by attacks of moderate to severe pulsating, unilateral, headache often associated with nausea, photophobia, and phonophobia. In approximately 10 to 20% of migraineurs there is a preceding aura. Each attack can generally last from 4 to 72 hours. The prevalence of migraine has been estimated to be between 3 to 8% of all men and 11 to 18% of all women. In general migraine is more common in women during their reproductive years. It estimated that one-third of all migraine attacks are disabling enough to require bed rest.

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The exact etiology of migraine is not known however it is believed that dilation of cranial blood vessels is a major contributor, possibly in combination with sensitization of trigeminal sensory nerve fibers and/or neurogenic inflammation. Several biochemical pathways are thought to be involved with the manifestations of migraine. Many substances, including serotonin and prostaglandins are believed to play a role in migraine. It is believed prostaglandins may contribute to migraine by their pro-inflammatory and nociceptive action. Recently, hyperactivity or hypersensitivity of the dopaminergic system has been suggested as a key pathophysiologic component of migraine, especially as it might relate to nausea, vomiting and gastroparesis (Lai 1997, Mascia 1998, Fancuillacci 2000, Peroutka 1997).

There are currently 16 approved drug products for treatment of acute migraine. The majority of the prescription products fall within the 5-hydroxytryptamine<sub>1B/1D</sub> (5HT<sub>1B/1D</sub>) receptor agonist family often referred to as “triptans”. These include Amerge (naratriptan), Axert (almotriptan), Frova (frovatriptan), Imitrex (sumatriptan), Maxalt (rizatriptan), Relpax (elatriptan) and Zomig (zolmitriptan). Many of these triptan products are available in several formulations (see table below). Additionally Advil Migraine Liquidgels (ibuprofen), Motrin Migraine Pain Caplets (ibuprofen) and Excedrin Migraine Caplets/Gelcaps/Tablets (acetaminophen, aspirin and caffeine) are also approved as over-the-counter treatments for the indication of acute migraine. In addition to these products, there are a wide variety of approved treatment options for acute migraine including Bayer Aspirin (OTC-pain of migraine approval only), dihydroergotamines, and isometheptene (Midrin, labeled as “possibly effective in migraine”). Many general analgesics are used off label in the treatment of migraine.

**Table 12** Prescription Treatment for Migraine

Drug Product	NDA	Sponsor	FDA Approval	Approved Strengths
Imitrex Injection	20-080	Glaxo Wellcome	12/28/1992	6 mg
Imitrex Tablets	20-132	Glaxo Wellcome	6/1/1995	25 and 50 mg
Imitrex Nasal Spray	20-626	Glaxo Wellcome	8/26/1997	5, 10, and 20 mg/spray
Zomig Tablets	20-768	IPR	11/25/1997	2.5 and 5.0 mg
Zomig-ZMT	21-231	Astra Zeneca	2/13/2001	2.5 mg
Zomig Nasal Spray	21-450	Astra Zeneca	9/30/03	5.0 mg
Amerge Tablets	20-763	Glaxo Wellcome	2/10/1998	1 and 2.5 mg
Maxalt Tablet	20-864	Merck	6/29/1998	5 and 10 mg
Maxalt-MLT Tablets	20-865	Merck	6/29/1998	5 and 10 mg
Axert Tablets	21-001	Pharmacia and Upjohn	5/7/2001	6.25 and 12.5 mg
Relpax Tablets	21-016	Pfizer	12/26/2002	20 and 40 mg
Vioxx	21-647	Merck & Co.	3/26/2004	25 and 50 mg

Since all triptan products are associated with cardiovascular adverse events the sponsor has developed MT100 as an alternative treatment option to these products. Approximately 40% of all patients in the United States treat their migraines with non-steroidal anti-inflammatory drugs. The sponsor asserts that MT100 is formulated to provide a synergistic effect of metoclopramide and naproxen in the treatment of migraine. The initial release of metoclopramide is designed to improve the absorption of naproxen by its prokinetic effects on gastric motility. Additionally metoclopramide has been shown to be effective in the treatment of migraine (Ellis 1993, Coppola 1995, Jones 1996). Metoclopramide is believed to be effective in migraine due to its antagonism of central and peripheral dopamine receptors (Lai 1997, Mascia 1998 Peroutka 1997). Naproxen is expected to provide migraine relief through inhibition of cyclooxygenase

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(COX inhibition). Naproxen has been shown to be effective in migraine syndrome and is approved by this Agency for migraine (Advil Migraine).

### 1.3 Important Milestones in Product Development

The following milestones occurred during the clinical development program for MT100 Tablets in the treatment of acute migraine:

- June 11, 1997 Pre-IND meeting with sponsor.
- September 5, 1997 IND submitted containing protocol MT100-201 (dose finding study). The safety review resulted in a HOLD (see below for details).
- October 8, 1997 HOLD letter issued.
- February 5, 1998 HOLD lifted.
- March 31, 1999 End of Phase II meeting occurred (see below for details).
- June 2, 1999 Protocol MT100-301 submitted (factorial study).
- July 7, 1999 Teleconference with sponsor to discuss proposed PK program. We suggested the sponsor evaluate the metabolism of MT100 and its pharmacokinetics in renal and hepatic insufficiency.
- July 20, 1999 Protocol MT100-102 submitted (PK study).
- September 10, 1999 Protocol MT100-302 submitted (long term safety study).
- February 14, 2000 Protocol MT100-303 submitted (MT100 1 tablet vs. 2 tablets vs. placebo).
- February 25, 2000 Protocol MT100-306 submitted (MT100 vs. sumatriptan)
- March 27, 2000 Teleconference with sponsor to discuss results of trial 301. The sponsor was reminded that a carcinogenicity study was required for registration.
- April 13, 2000 Protocol MT100-103 submitted (hepatic impairment study).
- May 3, 2000 Protocol MT100-304 submitted (2<sup>nd</sup> factorial study).
- May 9, 2000 Protocol MT100-106 submitted (absorption study).
- May 15, 2000 Sponsor requests a waiver of the requirements for a 2 year carcinogenicity study.
- May 19, 2000 Protocol MT100-105 submitted (sumatriptan bioequivalence study).
- July 21, 2000 Teleconference with sponsor to discuss 2-year carcinogenicity waiver request.
- October 6, 2000 Pre-NDA meeting held.
- May 15, 2001 Protocol MT100-307 submitted (Prodrome study).
- June 18, 2001 Protocol MT100-308 submitted (Non-inferiority study with sumatriptan).
- July 30, 2001 Agency letter issued denying Fast Track request.
- September 6, 2001 Agency letter issued stating that the 2-year carcinogenicity study can not be submitted as a Phase IV commitment.
- September 17, 2001 Protocol MT100-402 submitted (MT100 efficacy study in subjects intolerant to triptans).
- November 8, 2001 Protocol MT100-401A submitted (sumatriptan non-responder study).

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- December 20, 2001 Regulatory briefing meeting to discuss issues relative to the 2-year carcinogenicity study.
- February 14, 2002 Meeting with sponsor to discuss timing for the submission of 2 year carcinogenicity study (see below for details).
- December 18, 2002 Protocol MT100-107 submitted (bioavailability study).
- January 15, 2003 Protocol MT100-403 submitted (early treatment of migraine).
- May 19, 2003 Agency letter issues denying the sponsor's request for a waiver of the user fees.
- June 4, 2002 Pre-NDA meeting (see below for details).
- July 31, 2003 NDA for MT100 submitted.

The IND was initially placed on HOLD due to unexpected dose dependent anemia in rats and dogs. A HOLD letter was issued on October 8, 1997. After several submissions (October 8, 1997, October 24, 1997 and November 17, 1997) the sponsor provided a complete response to the HOLD and the HOLD was lifted on February 5, 1998. See the pharmacotoxicology reviews for additional details.

On March 31, 1999 we had an end-of phase II meeting with the sponsor. At that time we informed the sponsor that their planned Phase III studies (MT100-301 and MT100-304) should include separate arms for naproxen and metoclopramide. We discussed the possibility of leaving out the placebo arm but suggested they keep it in (per Dr. Oliva's note), however in a later teleconference (May 19, 1999) we agreed that no placebo arm was required. We agreed their primary endpoint of 2 hour sustained response was reasonable. We stated a sustained response to nausea should also be used in order to strengthen the case for a sustained response of the formulation. We agreed that the proposed studies could be single attack studies of identical design. Finally we informed them that Stage 2 reproductive studies would be required and depending upon the results, carcinogenicity studies may be required. The timing of the carcinogenicity studies was not discussed.

On March 27, 2000 we had a teleconference with the sponsor to discuss the results of trial MT100-301 (factorial trial). At issues was whether we believed the study demonstrated efficacy. The *a priori* primary efficacy parameter was sustained response analyzed using logistical regression. Using the protocol specified analysis plan the comparison of MT100 to naproxen was not significant ( $p=0.077$ ) and we informed the sponsor we do not believe trial MT100-301 demonstrated significance. This fact is clearly stated in Dr. Oliva's notes (see review of serial 042, dated 2/9/00). Despite the negative results using the pre-stated analysis plan we agreed that an "almost positive" study (MT100-301) and a positive second factorial study (MT100-304) and the 2 proposed efficacy trial (presumably MT100-306 and MT100-308) would be acceptable to demonstrate efficacy over placebo. We reminded the sponsor we will be looking for improvement in associated symptoms in order to assess migraine efficacy.

On February 14, 2002 we had a meeting with the sponsor to discuss the timing for submitting the 2 year carcinogenicity study. At that time we stated that the study should be submitted prior to approval unless the clinical studies would support the continued marketing of the drug in the presence of a positive carcinogenicity study. We discussed several clinical trial design options that might support this approach including studying the safety and efficacy of MT100 in a

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population of patients who have severely disabling migraines and who have few approved treatment options. Additionally we agreed to accept the 2-year carcinogenicity study during the review process, however we would need at least 3 to 4 months to properly review the complete final study report.

On June 4, 2002 we had a pre-NDA meeting with the sponsor. At that time we informed them it was unacceptable to submit the 2-year carcinogenicity study as a response to an "Approvable letter". Additionally we stated that if they intend to pursue approval of a double dose of MT100 then long term studies will be needed to support the safe use of a double dose of MT100.

#### 1.4 Other Relevant Information

MT100 is not approved in any foreign country however both metoclopramide and naproxen have been approved in the United States for many years. I discuss the known safety profile of both components in section 7.4.14 of this review. The sponsor does not provide a discussion whether either component has been withdrawn from any country.

### 2. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, and Biopharmaceutics

#### 2.1 Chemistry, Manufacturing and Control Summary

MT100 is formulated to provide the sequential release of metoclopramide followed by naproxen. The tablets are pink, oval, and film coated with black print on one side. Both active compounds are USP products.

The sponsor refers to the Drug Master File No (b) (4) for details regarding (b) (4). A letter of authorization has been provided by the (b) (4) (b) (4). The sponsor refers to the Drug Master File No (b) (4) for details regarding (b) (4). A letter of authorization is provided by (b) (4) (b) (4) following table summarizes the formula for MT100. Metoclopramide hydrochloride monohydrate (16 mg/tablet) (b) (4). The amount of metoclopramide corresponds to 13.5 mg of metoclopramide free base.

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**Table 13** Composition of MT100

Ingredient	mg/tablet
<b>Quantitative Formula for MT100 Core Tablets</b>	
Naproxen sodium, USP	500.0
Povidone, USP	(b) (4)
Microcrystalline Cellulose, NF	
Croscarmellose Sodium, NF	
Talc, USP	
Magnesium Stearate, NF	
Purified Water	
<b>Quantitative Formula for MT100 Tablet</b>	
Tablet Core	MT100 core Tablet (500 mg Naproxen) (b) (4)
Barrier Film coat	
Active Film coat	16.0 (b) (4)
Pink Film coat	
Clear Film coat	
Waxing	
Printing	
<b>Total Tablet Weight</b>	

Adapted from sponsor table 3 and 4, page 40 and 41 of "Overall Summary, volume 1.

The sponsor states that stability tests demonstrate MT100 is stable for up to 36 months at 25°C/60% RH and up to 6 months at 40°C/75% RH when packaged in 250 cc bottles or in unit-dose foil laminated pouches. Additional stability studies are ongoing. An expiration date of 48 months is proposed for MT100 tablets when stored at 25°C; excursions permitted to 15 to 30°C in either HDPE 250-cc bottles or in unit dose foil pouches. I defer to the Chemistry reviewer as to the acceptability of this request.

On March 31, 2004 the chemistry reviewer (Josephine Jee) informs me she has no significant concerns with the chemistry data submitted in support of this NDA. Her final review is pending however she states she has several minor issues such as "tightening the specifications" which will be discussed in detail in her review.

## 2.2 Animal Pharmacokinetics and Pharmacodynamics

The sponsor has not conducted any animal pharmacology studies using MT100 to support this NDA. Instead the sponsor provides a summary of available literature for each component of MT100. What follows is a brief summary of the sponsor's discussion. Additional details for each component of MT100 can be found in the product label for each individual component.

Hyperactivity of the dopaminergic system has been demonstrated to be involved with migraine development, especially nausea, vomiting and gastroparesis (Peroutka et al., Headache 1998). Metoclopramide is a central and peripheral dopamine receptor antagonist hence the sponsor believes it may be effective in the treatment of migraine. Metoclopramide is a chemical

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derivative of procainamide, a local anesthetic, and is chemically similar to cisapride, granisetron (Kytril<sup>®</sup>), and ondansetron (Zofran<sup>®</sup>). Granisetron and Ondansetron are approved anti-emetic agents used primarily in oncology. Cisapride (Propulsid<sup>®</sup>) is an anti-emetic, prokinetic drug that was withdrawn from the U.S. market in 2000 due to serious cardiac arrhythmias possibly due to prolonged QT intervals (270 cases reported from 1993 to 1999). Unlike metoclopramide, cisapride does not have dopamine blocking activity and is largely devoid of central depressant effects (Micromedex, DrugDex Website). To my knowledge QT prolongation with metoclopramide has not been reported. I performed a PubMed search using metoclopramide and QT prolongation and did not find any relevant articles.

Metoclopramide has been shown to be a 5-HT<sub>4</sub> partial agonist, a 5-HT<sub>3</sub> antagonist, and a dopamine D<sub>2</sub>/D<sub>3</sub> antagonist (Rizzi et al., *Neuropharmacology*, 1997, Borne, *Drug Topics*, 1994, Peroutka, *Neurology*, 1998). The sponsor attributes the anti-migraine effect of metoclopramide primarily to D<sub>2</sub>/D<sub>3</sub> antagonism. The sponsor attributes the anti-emetic effects of metoclopramide primarily to D<sub>2</sub> antagonism. The following table briefly summarizes several analgesic models for metoclopramide.

**Table 14** Animal Models of Analgesic Activity of Metoclopramide

Model	Reference
Acetic acid-induced writhing in mice	Ramaswamy, 1986
Antagonism of the development of tolerance to morphine induced analgesia, suppression of morphine withdrawal signs	Ramaswamy, 1987
Hot plate assay in mice, mechanism of analgesia	Ghelardi et al., 1992

Adapted from Sponsor table 29, page 77 of "Overall Summary, Volume 1"

Naproxen is a non-steroidal anti-inflammatory agent (NSAID). Naproxen is a well known analgesic already approved for the treatment of migraine and other painful conditions. Naproxen is a non-specific cyclooxygenase (COX) inhibitor that has been shown to have anti-inflammatory, anti-pyretic and anti-platelet properties. Cyclooxygenase converts arachidonic acid to prostaglandin (PG) H<sub>2</sub>, which is then metabolized to various PGs, prostacyclin, and thromboxanes (Thiemermann, Eicosanoids 1991). Increased prostaglandins and thromboxanes have been demonstrated in a variety of pain conditions including migraine. Naproxen has been shown by a number of investigators to result in a reduction in prostaglandins and thromboxanes in multiple animal models (Abdel-Halim et al 1978, Blackham et al 1985, Ferrari et al 1990 and others). Naproxen has also been shown to have a number of pharmacological properties that may affect inflammation and pain by mechanism other than inhibition of PG synthesis as demonstrated in the following table.

**Table 15** Alternative Pharmacological Properties of Naproxen (Non-PG Inhibition)

Pharmacological Property	Reference
Inhibition of PG transport across cell membranes	Bito et al., 1976
Stabilization of lysosomal membranes	Smith et al., 1976
Inhibit response to neutrophils to chemotactic stimuli, in-vivo	Parente et al., 1979
Inhibition of lysosomal enzymes in inflamed rat tissue, in-vivo	Suzaki et al., 1976
Relaxation of guinea pig tracheal ring preparations, in-vitro	Diamantis et al., 1979
Relaxation of vanadate-induced uterine contractions in rat, in-vivo	Cantabrana et al., 1995
Inhibition of adolase reductase in rat, dog, goat, human eye lens	Gupta et al., 1991
Selective activation of peroxisome proliferator-activated receptors	Gilroy et al., 2000

Adapted from Sponsor table 19, page 68 of "Overall Summary, Volume 1"

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Naproxen has been shown to cause gastric mucosal damage and ulceration in several animal models. This effect is believed to be primarily caused by inhibition of COX-1 leading to a decrease in cytoprotective prostaglandins (Fosslien, 1998). Naproxen has been shown to cause decrease renal function in several animal models (Cox 1990, Chan 1988, Zambraski 1984, Pedrera 1991). Naproxen has been shown to reduce platelet aggregation in several animal models (McIntyre 1977, Bolli 1981). The sponsor states that animal safety cardiovascular studies found a tendency for naproxen to reduce blood flow and increase peripheral vascular resistance in tissue preparations however there was no alteration in blood pressure in rabbit or changes in cardiac output and total peripheral resistance in normovolemic rats. The effects of naproxen on the central nervous system has not been systematically reported. Naproxen has been shown to cross the placenta in rats (MT100-109) and rabbits (MT100-T20). Naproxen has been shown to be excreted in rat breast milk (MT100-T27).

Metoclopramide inhibits the D<sub>2</sub> receptors in the mesolimbic and extrapyramidal systems of the central nervous system (Jenner 1979, Suarez-Roca 1987). The following table briefly outlines the multiple animal models that have demonstrated the central dopamine antagonist effects of metoclopramide. Central D<sub>2</sub> receptors CNS effects reported in animals exposed to metoclopramide include catalepsy, dyskinesia, dystonic reactions, and increase in behavioral sensitivity to apomorphine (Lautin 1980). Other central nervous system effects reported in animals exposed to metoclopramide include inhibition of spontaneous locomotion, exploratory behavior and food intake in rodents (Chandler 1990, Blackburn 1989, Alphin 1972).

**Table 16** Models of Central Dopamine Antagonist-like Profile of Metoclopramide in Rodent

Models	Reference
Inhibition of Apomorphine-Induced Behaviors	
Climbing (mouse)	Worms (1982)
Hypothermia (mouse)	
Hypermotility (mouse)	
Stereotypy (rat)	
Hypermotility (mouse)	Vaccheri (1986)
Yawning	Heaton (1991)
Inhibition of Conditioned Avoidance Responses	
Sidman avoidance (rat and squirrel monkey)	Hori (1983)
Inhibition of intracranial self-stimulation (rat)	
Inhibition of food-reinforced operant response (rat)	Beninger (1987)
Induction of catalepsy (rat)	Worms 1982

Source: Adapted from Sponsor table 35, page 83 of "Overall Summary, volume 1"

Metoclopramide has no effect on gastric acid secretions in dog or rat (Jacoby 1967, Takeuchi 1997). Metoclopramide has been reported to cause increased prolactin secretion from pituitary glands in several animal models (Carlson 1977, Fitzgerald 1982, Durant 1995 and Sowers 1982). This finding may be relevant to the findings demonstrated in the 2 year carcinogenicity study, Metoclopramide has been shown to stimulate aldosterone release from isolated perfused rat zona glomerulosa cells (Braley 1983). The sponsor states that relevant changes in prolactin, aldosterone, renin and angiotensin are not expected for MT100 since exposure to metoclopramide is low and the frequency of exposure is intermittent. I concur that the clinical intermittent use of metoclopramide has failed to demonstrate safety concerns for these systems however these animal findings suggest that daily use of MT100 should be restricted.

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The cardiovascular effects of metoclopramide vary depending upon the animal model used and route of administration. Gupta (1985) demonstrated that metoclopramide (IV) produced a dose dependent reduction in blood pressure and heart rate however higher oral doses had no effect in rats. Whereas in dogs, IV metoclopramide had no effect on blood pressure, pulse, renal blood flow or renal vascular resistance (Hahn 1980).

A complete review of the pharmacotoxicology studies for this NDA is being conducted by Dr. Kathleen Haberny.

### 2.3 Animal Toxicology Studies using MT100

The sponsor conducted multiple preclinical safety toxicology studies using MT100 and other combinations of naproxen/metoclopramide. The sponsor states the results from these trials indicate that the toxicity of the combination products is characterized by the known toxicity of naproxen. Additionally they state that there is no evidence that the toxicity of naproxen was enhanced by the co-administration of metoclopramide. Many studies used a 62.5:1 ratio of naproxen to metoclopramide however the pivotal studies all used the clinical ratio of 31.25:1 NAP/MC. A few studies were conducted using a ratio consistent with the maximally tolerated doses of each product. These studies included the rat and mouse carcinogenicity studies and an in-vitro mouse lymphoma study.

The single dose studies demonstrated safety findings typical of naproxen and included gastrointestinal ulceration/hemorrhage and renal interstitial nephritis and tubular dilation. The LD<sub>50</sub> in rat was approximately 500 NAP/8 MC mg/kg. The cause of death was generally gastrointestinal in nature. The oral LD<sub>50</sub> reported in the literature for naproxen is 500 mg/kg in rats and 1000 mg/kg in dog. The sponsor states the acute toxicity studies did not demonstrate any synergist effects of naproxen and metoclopramide relative to toxicity.

The sponsor asserts that the repeat dose toxicity studies (28 day and 3 month) in mice, rat and minipigs also demonstrated findings typical of naproxen without synergistic effects from metoclopramide. Toxicities were generally gastrointestinal (erosions, ulcers, perforation, peritonitis) or renal (degeneration and/or edema of renal papilla, tubular basophilia, and tubular hyaline casts) in nature. Anemia (regenerative, macrocytic, hypochromic) due to blood loss was also seen. The sponsor states an in-vitro toxicity study using rat, dog and human whole blood samples, MT100 and its components did not cause hemolysis. The NOAEL for toxicity from the 3 month studies is demonstrated in the following table.

**Table 17** NOAELs for NAP/MC from Repeat-Dose Studies

Species	Test Article	G.I. NOAEL (NAP/MC mg/kg)	Renal NOAEL (NAP/MC mg/kg)	Anemia NOAEL (NAP/MC mg/kg)
Rat	NAP/MC	5/0.08 <sup>a</sup>	<5/0.08 <sup>a</sup>	5/0.08 <sup>a</sup>
		>8/0.256 <sup>b</sup>	2/0.064 <sup>b</sup>	>8/0.256 <sup>b</sup>
Minipig	NAP/MC	10/0.32 <sup>c</sup>	>70/2.24 <sup>c</sup>	>70/2.24 <sup>c</sup>

a. MT100-T13 (28 day study) NAP alone was not tested in this study.

b. MT100-T14 (3-month study)

c. MT100-T22 (3 month study)

Source: Sponsor table 37, page 96 of Overall summary, volume 1.

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Lethargy, prostration, and decreased activity were observed in mice at doses  $\geq 15$  mg/kg/day MC with and without NAP. This is consistent with the toxicity of metoclopramide alone reported in the literature. The sponsor states that metoclopramide-induced behavioral changes were not observed in any study using the clinical ratio of NAP/MC.

A 26 week genotoxic carcinogenicity study in p53 transgenic mice showed no evidence of carcinogenic activity when the combination was given in the clinical ratio (50/1.6 mg/kg) or in the maximally tolerated ratio (50/50 mg/kg). The doses were based on the results of two 28-day dose range-finding studies, and the protocol received Agency Carcinogenicity Advisory Committee (CAC) concurrence (letter dated April 11, 2001, IND 54,039). The results of the 26-week carcinogenicity study in mice showed no effects of MT100 on survival food consumption and gross pathology. Body weights and body weight gains were reduced in the mid-dose and high dose males, and prostration was observed in the mid-dose and high dose males and females. The non-neoplastic findings were dose-related hypertrophy in the pituitary gland pars intermedia, and hyperplasia in the glandular stomach chief cells and fore-stomach epithelial cells in males and females, and in the adrenal gland subcapsular spindle cells in the males. Also, treatment-related ectopic thymus in the thyroid glands, hepatic necrosis, fibrous osteodystrophy and necrosis in the costochondral junction were observed in females. MT100 was negative for genotoxic carcinogenicity in the male and female mice in this study. This study was reviewed by the CAC on March 30, 2004 and it was agreed the study was adequately designed and they concurred with the study was negative. Additional details of this study can be found in the review done by Dr. Haberny.

At the request of the Agency the sponsor conducted a 2-year carcinogenicity study in rats. Doses of 5/8, 10/8, and 20/8 mg/kg/day metoclopramide and naproxen were used (60/sex/group). Additional groups received a negative control (distilled water), metoclopramide alone at 20 mg/kg/day, and naproxen alone at 8 mg/kg/day. The doses were based on the results of a 3-month oral range-finding study. The protocol received concurrence by the CAC on December 11, 2001 (see minutes, IND 54,039).

The sponsor summarizes the findings as follows:

*“The administration of metoclopramide/naproxen to rats induced dose-related increases in prolactin levels in both sexes at all doses. The increases in prolactin levels reflected the effect of metoclopramide since they did not occur in the group administered naproxen alone.*

*Increased incidences of adrenal cortical adenomas (both sexes) and carcinomas (females only), adrenal pheochromocytomas (males only), mammary gland adenomas (both sexes) and adenocarcinomas (females only) and fibroadenomas (males only) and pancreatic islet cell carcinomas (males only) were seen in the naproxen/metoclopramide combination groups as well as in the metoclopramide only group. The neoplastic lesions were statistically significantly different from the control group for adrenal cortical adenomas (mid-dose combination males), adrenal cortical carcinomas (high-dose combination females), adrenal benign pheochromocytomas (high-dose combination males), mammary gland adenomas and adenocarcinomas (high-dose combination females), mammary gland fibroadenomas (high-dose combination males) and pancreatic*

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*islet cell carcinomas (high-dose combination males and metoclopramide only males). The high-dose combination group was also significantly increased from the naproxen-only group for adrenal cortical adenomas (high-dose combination females), benign adrenal pheochromocytomas (high-dose combination males), pancreatic islet cell carcinomas (high-dose combination males) and mammary gland adenocarcinomas (high-dose combination females). There were no statistically significant differences between the high-dose combination group and the metoclopramide only group. The increased incidence of neoplastic findings in the adrenal glands, mammary glands and endocrine pancreas are considered secondary to the chronic hyperprolactinemia experienced by the affected animals; they were not considered direct test article-related effects. The presence of naproxen did not significantly alter the tumorigenic activity associated with metoclopramide induced chronic hyperprolactinemia. There was no evidence of a synergistic adverse effect when metoclopramide and naproxen were combined.*

*Nonneoplastic lesions associated with metoclopramide administration included adrenal cortical hyperplasia, ovarian cysts, hyperplasia of pars distalis of the pituitary, and mammary galactoceles (males only) All these changes were considered secondary to hyperprolactinemia. Nonneoplastic lesions associated with naproxen administration included renal papillary necrosis and alterations to the glandular stomach (erosions, ulcers, glandular epithelial hyperplasia, and subacute inflammation).*

*All the test article related neoplastic lesions that occurred in this study are considered to be related to the chronic hyperprolactinemia associated with metoclopramide administration. There does not appear to be an increased risk of carcinogenicity of the combination of metoclopramide and naproxen administered on a chronic intermittent basis to humans for the acute treatment of migraine.”*

Additionally the sponsor submits an expert opinion from Hugh E. Black D.V.M., Ph.D. to support their position. Dr. Black writes “*None of the neoplastic findings observed in this study were considered to be secondary to metoclopramide or naproxen; all were considered to be secondary to metoclopramide-induced chronic hyperprolactinemia in the affected animals*”.

According to Dr. Haberny the results of the 2-year study showed slightly increased survival in the treated rats compared to controls, treatment-related clinical signs (e.g., decreased activity, prostration), and reduced body weights and food consumption in the males. Gross pathologic effects included naproxen-related erosions, ulcers, inflammation, hyperplasia, and fibrosis in the glandular stomach in the males, naproxen-related thickened glandular stomach in the males and females, and metoclopramide-related enlarged adrenal glands, subcutaneous skin masses, and ovarian cysts in the females. The non-neoplastic histopathologic observations in the males were adrenal gland focal cortical hyperplasia in all treated groups, naproxen-related retinal atrophy, kidney papillary necrosis, and glandular stomach erosions, ulcers, fibrosis, hyperplasia, and inflammation, and metoclopramide-related mammary gland galactoceles and diffuse pituitary (pars distalis) hyperplasia. In the females, there was increased metoclopramide-related adrenal gland focal cortical hyperplasia, pituitary hyperplasia (focal and diffuse, pars distalis), and ovarian cyst, and naproxen-related increased kidney papillary necrosis and glandular stomach erosions, ulcers, fibrosis, epithelial glandular hyperplasia, and inflammation.

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The CAC met on March 30, 2004 to discuss the above findings and agreed that the study was positive for the following tumors: adrenal gland cortical adenomas in males (10/8 and 20/8 mg/kg/day) and females (20/8 mg/kg/day), benign pheochromocytomas in males at 20/8 mg/kg/day, mammary adenomas and adenocarcinomas in females at 20/8 mg/kg/day (although results were equivocal when these tumors were combined with fibroadenomas), and combined mammary neoplasms (adenoma/fibroadenoma/adenocarcinoma) in males at 20/8 mg/kg/day. Although the incidence of pancreatic islet cell carcinomas was increased in the 20/8 and 20/0 male groups, the Committee concluded that there was no clear effect in the pancreas since the incidence of islet cell adenomas and carcinomas combined was not statistically significantly increased. The CAC did not discuss the sponsor's argument that the tumors seen were related to hyperprolactinemia.

In a personal communication with Dr Haberny she states *“an association between increased prolactin and mammary gland tumors in rodents is well known. Also, there are prolactin receptors on the adrenal cortex and pancreatic islet cells. The sponsor rationalizes that the neoplasms in the rat study were increased significantly only at metoclopramide exposures (AUCs) 23X-27X the AUCs at the MRHD (highest metoclopramide dose tested of 20 mg/kg/day), and that other approved and marketed drugs that antagonize dopamine receptors also cause these tumors in rodents, but not in humans according to the sponsor. Prolactin was increased 9X-11X over control levels in the high dose rats. The sponsor did not give a rationale why increased prolactin is a problem in the rats, but would not be in humans. Also, the sponsor rationalizes that MT100 use would be intermittent, so not as likely to be a risk for carcinogenicity in people.”* Dr Haberny states the sponsor's argument that the tumors are caused by increased prolactin may have some merit (particularly for mammary tumors), but she argues that prolactin is also increased by dopamine receptor antagonists, including metoclopramide in humans. The sponsor does not discuss whether there may be a difference in response to increased prolactin with regard to tumorigenicity between humans and animals. Prolactin levels were not collected during any of the clinical trials conducted in support of this NDA. Overall I don't fully agree with the sponsor that the intermittent use of MT100 should not cause a problem. First of all I don't believe this has been demonstrated in animals or humans. Secondly it is well known that many migraineurs overuse prescription medication to treat their migraines. Finally it is uncertain what the cumulative effect of intermittent use of MT100 would be over several decades of migraine therapy. Please see the review of this study done by Dr. Kathleen Haberny for additional details. These findings should be considered when evaluating the risk benefit ratio for MT100.

The sponsor states the reproductive and developmental toxicity studies using MT100 were the same as those seen for naproxen alone. There was no effect on rat fertility, and no selective effects on the embryo or fetus in rats or rabbits. Increased pregnancy lengths in rats and dystocia occurred, leading to prenatal offspring mortality. Withholding treatment during late pregnancy ameliorated the effects on parturition and perinatal survival, but there were still effects on the offspring in the lactation period (decreased weight, delayed maturation).

MT100 underwent a series of genotoxicity tests including in-vitro assays (Ames, chromosomal aberration in CHO cells, mouse micronucleus) and in-vivo assays (chromosomal aberration in rat

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bone marrow, mouse micronucleus). The sponsor states all studies were negative except a moderately positive results in the in-vitro mouse lymphoma TK± assay in the presence of S9 metabolic activation. The sponsor asserts the naproxen component of MT100 caused the abnormal test result and there was no synergy with metoclopramide.

A complete review of the pharmacotoxicology studies for this NDA is being conducted by Dr. Kathleen Haberny.

### 3. Human Pharmacokinetics and Pharmacodynamics

#### 3.1 Pharmacokinetics

The sponsor conducted 6 phase I PK studies (MT100-101, MT100-102, MT100-103, MT100-105, MT100-106 and MT100-107) to evaluate the pharmacokinetics of several combinations of metoclopramide and naproxen. A description of each trial design is discussed in section 4.2.1 of this review.

The following table summarizes the pharmacokinetics of MT100 (single and double dose), naproxen 500 mg alone and metoclopramide 16 mg alone as determined in trial MT100-102. As demonstrated in the table the C<sub>max</sub> or AUC of naproxen are similar whether given as MT100 or given alone. However the addition of metoclopramide does appear to result in an earlier t<sub>max</sub> for naproxen compared to naproxen alone (0.7 hours vs. 1.2 hours). This is consistent with what was predicted by the sponsor. Overall the naproxen in MT100 is relatively quickly absorbed with a mean T<sub>max</sub> of 0.73 hours. In trial MT100-102 the t<sub>1/2</sub> of naproxen 500 mg was 18.0 (±2.7) hours and the clearance (CL/F) was 0.0051 (±0.0012) L/hr/kg following naproxen 500 mg. The pharmacokinetics of metoclopramide were relatively unchanged whether it was given as MT100 or alone. The volume of distribution for naproxen in trial MT100-102 was 0.16 L/kg. The terminal half-life following a 1.1-1.4 mg/kg dose was 13.9±2.6 hours.

**Table 18** Mean PK Results MT100 1 tablet vs. 2 Tablet and its Components, MT100-102

	T <sub>MAX</sub> (hr)	C <sub>max</sub> (mcg/ml)	AUC <sub>0-∞</sub> mcg hr /ml	t <sub>1/2</sub> (hr)
<b>Comparison of naproxen PK results</b>				
NAP 500 mg	1.20±1.0	84.1±13.2	1324.3±289.5	18.00±2.7
1 Tablet MT100	0.73±0.3	96.8±13.6	1288.6±243.8	17.93±2.8
2 tablets MT100	0.80±0.3	151.6±27.4	1939.0±311.0	18.01±3.1
<b>Comparison of metoclopramide PK results</b>				
MC 16 mg	1.42±0.4	59.5±19.8	605.8±332.5	7.2±2.2
1 Tablet MT100	1.31±0.4	58.4±22.3	642.3±338.3	7.6±2.2
2 tablets MT100	1.36±0.5	116.7±38.8	1280.9±655.1	9.3±7.1

Source: Adapted from Sponsor table 14.2.4.1 through 14.2.4.3 and 14.2.12.1 through 14.2.12.3, Study report 102.pdf

In trial MT100-107 the absorption of metoclopramide was minimally affected when MT100 was administered within 30 minutes after a high fat meal (C<sub>max</sub>: fed 52.9 vs. fasted 57.3 ng/ml; AUC fed 433.0 vs. fasted 453.9 ng•hr/ml). The t<sub>max</sub> of naproxen from MT100 was increased by approximately 78 minutes (fed 2 hours vs. fasted 0.67 hours) and the C<sub>max</sub> was decreased by approximately 24% (fasted 71.1 vs. fed 54.2 mcg/ml) when the tablet was administered within 30 minutes after a high fat meal. However overall there was no change in the total AUC of naproxen with or without a meal (fasted 903.8 vs. fed 907.4 mcg•h/ml).

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In trial MT100-106, the pharmacokinetics of MT100 were evaluated in 11 subjects during a migraine attack and between a migraine attack. The presence of an acute migraine attack had no significant effects on the pharmacokinetics of metoclopramide. However during an attack the  $t_{max}$  of naproxen was slightly delayed (68 vs. 49 minutes) and both the mean  $AUC_{0-4}$  and the  $C_{max}$  were slightly lower ( $AUC$ : 154.3 vs. 171.6 mcg•hr/ml;  $C_{max}$  59.2 vs. 69.4 mcg/ml).

From published literature the sponsor provides the following details regarding the pharmacokinetics of naproxen alone. The bioavailability of naproxen was demonstrated by Runkel (1972) to be greater than 90% in healthy subjects. The label for Anaprox states that naproxen is greater than 99% bound to albumin at therapeutic doses. Studies in human and other animals (Runkel 1972, Thompson 1973) demonstrated that naproxen is primarily excreted in the urine (>80%) with minor amounts recovered in the feces. In human approximately 1% was excreted in the urine as unchanged naproxen following oral administration. Naproxen is extensively metabolized by the liver to naproxen acyl glucuronide (51%), 6-O-desmethyl naproxen (14.3%), and the isomeric form of each compound (6.5% and 5.5% respectively, Vree 1993). The cytochrome P450s responsible for the formation of 6-O-desmethylnaproxen in man include CYP2C9 and CYP1A2 (Rodrigues 1996, Tracy 1997). CYP2C9 is the primary isoform responsible for normal metabolism under in-vivo conditions.

From published literature the sponsor provides the following details regarding the pharmacokinetics of metoclopramide alone. The bioavailability of metoclopramide in three different human studies ranged between 61% to 90% (Batemen 1980, Ross-Lee 1981, Vergin 2002). Metoclopramide at concentration of 60 ng/ml (approximate level reached by 16 mg) was approximately 40% bound to albumin (Webb 1986). The estimated volume of distribution ( $V_{d_z}$ ) after intravenous administration in humans ranged from 2.2 to 3.4 L/kg (Teng 1977, Graffner 1977, Ross-Lee 1981). The sponsor states tissue distribution data for metoclopramide is not available however since it is lipid soluble it is likely to freely distribute to all compartments/tissues including the central nervous system. Metoclopramide is extensively metabolized by sulfation to the N-4 sulfate and to a de-ethylated metabolite by CYP2D6 (Desa 2002). In a study done by Teng (1977) the urine of healthy subjects given 20 mg of metoclopramide contained approximately 20% unchanged metoclopramide and 60% metabolized metoclopramide. Other studies confirmed that conjugation reactions are the most important metabolic pathway in humans with sulfation accounting for 20 to 30% of the total dose administered (Batemen 1980, Speg 1987).

In study MT100-103 the sponsor evaluated the pharmacokinetics of MT100 in the setting of moderate hepatic insufficiency (Grade B or score of 7-9 points on the Child-Pugh Classification<sup>4</sup>). Overall moderate hepatic insufficiency had no effect on the pharmacokinetics of metoclopramide. However the total naproxen  $AUC_{inf}$  was approximately 1.3 fold higher and the unbound naproxen  $AUC_{inf}$  was approximately 2.7 fold higher in subjects with moderate hepatic failure compared to normal subjects. The sponsor states since MT100 is intended for intermittent use then no adjustment in patients with hepatic impairment is recommended. I don't fully agree with this recommendation. Although the label for Reglan states it is safe to use even in the

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<sup>4</sup> Child-Pugh Grading based on presence of encephalopathy, ascites and the level of serum bilirubin, albumin and prothrombin time each using a 3 point scale.

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setting of advanced liver disease, the label for Anaprox states a lower dose should be considered in patients with hepatic impairment. Given the altered pharmacokinetics of naproxen seen in study MT100-103 in the setting of moderate hepatic insufficiency I recommend a statement in labeling consistent with the Anaprox label. A reasonable statement might state that MT100 should be used with caution in subjects with moderate hepatic insufficiency.

The sponsor has not conducted any studies to evaluate the effects of renal impairment on the elimination of MT100. The Reglan package insert recommends a 50% reduction in dose in patients with creatinine clearance below 40 ml/min. The label for Anaprox warns that naproxen and its metabolites may accumulate in the presence of renal insufficiency and states a lower dose should be considered. The sponsor states that the presence of renal impairment has no effect on naproxen half-life however they provide no reference for this statement. I believe MT100 should be used with caution in patients with renal impairment.

The sponsor has not evaluated the pharmacokinetics of MT100 in geriatric or pediatric patients. There were no clinically significant differences in the pharmacokinetics of MT100 by gender. The sponsor asserts in general women in trial MT100-102 had slightly greater values than men however the differences can be explained by plasma albumin concentrations, weight, and by renal function and do not require dosage adjustments based on gender.

A complete review of the biopharmacology studies for this NDA is being conducted by Dr. Kofi Kumi. On March 31, 2004 Dr. Komi informs me he has no significant concerns with the PK/PD data submitted in support of this NDA. His final review is pending at this time.

### **3.2 Pharmacodynamics**

The sponsor conducted 2 phase II dose ranging studies (MT100-201 and MT100-202) to evaluate the efficacy of several different combinations of naproxen sodium and metoclopramide. A description of each trial design is discussed in section 4.2.2 of this review. A description of the results from each trial is summarized in section 6.3.1 of this review.

## **4. Description of Clinical Data and Sources**

### **4.1 Overall Data source and Tabular Listing of Trials**

The data used in this review are exclusively from the 17 clinical trials conducted by the sponsor in support of this NDA. The following table briefly summarizes the trials conducted by the sponsor. A further description of each trial design follows. Data from each trial was submitted electronically and can be found at [CDSESUB1\N21645\N\\_000\2003-07-31](#).

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**Table 19** Overall Clinical Development Program for MT100

Trial #	Dose (mg)	Type of Trial	N	Duration	Notes
<b>Phase I Clinical Pharmacology Trials</b>					
MT100-101	NAP 500 mg/Met 8	PK	11	Single and double doses	Open label, bioavailability study
MT100-102	MT100 vs. components	PK	24	Single and double dose	Open label, 4-period, crossover, comparative PK study
MT100-103	MT100	PK	16	Single dose	Open label, hepatic insufficiency safety study
MT100-105	sumatriptan 50 mg	PK	28	Single dose	Open label bioequivalence study between sumatriptan and over-encapsulated sumatriptan
MT100-106	MT100	PK	13	Single dose	Open label, two period (during and outside migraine) PK study.
MT100-107	MT100	PK	24	Single dose	Food effect study
<b>Phase II Dose Ranging Studies</b>					
MT100-201	Variable (see below)	Efficacy	514	Single attack	Double blind, placebo controlled dose finding efficacy study
MT100-201	Variable (see below)	Efficacy	182	Single attack	Double blind, placebo controlled
<b>Phase III Trials</b>					
MT100-301	MT100 vs. components	Efficacy	1067	Single attack	Double blind, uncontrolled, randomized trial
MT100-304	MT100 vs. components	Efficacy	2627	Single attack	Double blind, uncontrolled, randomized trial
MT100-306	MT100 vs. sumatriptan	Efficacy	635	Single attack	Double blind, placebo and active controlled trial.
MT100-308	MT100 vs. sumatriptan	Efficacy	1272	Single attack	Double blind, placebo and active controlled trial
MT100-303	1 or 2 tablets of MT100	Efficacy	427	Single attack	Double blind, placebo controlled, study to evaluate the efficacy of a 2 <sup>nd</sup> dose of MT100 given as rescue.
MT100-401A	2 Tablets of MT100	Efficacy	343	Single attack	Double blind, placebo controlled trial
MT100-402	MT100	Efficacy	238	Single attack	Double blind, placebo controlled trial to evaluate the efficacy of MT100 in subjects intolerant of triptans.
MT100-307	MT100	Efficacy	142	Multiple attacks	Double blind, placebo controlled trial to evaluate the efficacy of MT100 in the treatment of multiple migraines during the prodrome stage.
MT100-302	MT100	Safety-Long term	1123	Multiple attacks	Open label, repeat dose, long term safety study

The following amendments were submitted during the review of this NDA:

- September 23, 2003      Amendment 1 (updated/corrected datasets for study 301)
- November 3, 2003      Amendment 2 (re-analysis of study 304)
- November 26, 2003     Amendment 3 (safety update report with study 403)
- January 14, 2004      Amendment 4 (re-analysis of study 304)
- January 27, 2004      Amendment 5 (2-year carcinogenicity study results)
- January 29, 2004      Amendment 6 (requested SAS macro)
- February 3, 2004      Amendment 7 (name change to Myzan<sup>TM</sup>)
- February 13, 2004     Amendment 8 (updated 2 yr carcinogenicity study report)
- February 20, 2004     Amendment 9 (new .xpt data table labeled “tumor”)
- March 2, 2003         Amendment 10 (correction to datasets for trial 301)
- March 3, 2004         Amendment 11 (updated draft labeling)
- March 10, 2004        Amendment 12 (reanalysis of 304)
- March 12, 2004        Amendment 13 (updated labeling, usable word document)

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### 4.2 Design of Clinical Trials

The following clinical studies were conducted in support of this NDA. All studies included adult subjects with a history of acute migraine attacks meeting the International Headache Society definitions for acute migraine with and without an aura (IHS 1.1 and 1.2). Women who were pregnant or breast feeding was excluded from participation in all studies. All subjects had to have a history of migraine onset prior to the age of 50 and could not have any active medical or psychiatric conditions at screening. Subjects experiencing greater than 6 migraines attacks per month or 20 migraines days per month were excluded hence subjects with frequent and generally more severe migraine condition were excluded from study. Subjects with hemiplegic migraines, basilar migraines, significant cardiovascular conditions, or significant cardiovascular risk factors were excluded from the pivotal trials (MT100-306 and MT100-308). The entry criteria for each of these studies is typical for what I have seen for other migraine NDAs.

#### 4.2.1 Phase I Pharmacokinetic Studies

The sponsor conducted six Phase I clinical pharmacokinetic studies involving 116 subjects during the development of MT100. The first study (MT100-101) used a formulation that is no longer in development (naproxen 500 mg/metoclopramide 8 mg). A second study (MT100-105) compared the bioequivalence of marketed sumatriptan 50 mg to over-encapsulated sumatriptan 50 mg in preparation for phase III trials. The remaining four studies involved 77 subjects receiving at least 1 dose of MT100. The following is a brief description of each trial design. A detailed review of each PK trial has been conducted by the biopharmacology reviewer. A brief summary of pertinent findings can be found in section 3.

##### 1. MT100-101

This was an open label, non-randomized, single dose bioavailability study of a combination of naproxen 500 mg and metoclopramide 8 mg in 11 healthy volunteers. Each subjects received 1 and 2 doses of the combination product separated by 4 days. This formulation is no longer in development.

##### 2. MT100-102

This was an open label, randomized, four-period, cross-over phase I comparative PK study involving 24 subjects (14 females, 10 males). The goal of the study was to compare the PK of a single and double dose of MT100 to the PK of each component alone. Each treatment period was separated by a 5 day washout period. This study provides the best insight into the standard pharmacokinetic parameters required for labeling in my opinion.

##### 3. MT100-103

This was an open label, parallel group study to compare the PK, safety and tolerability of a single dose of MT100 between 8 subjects with moderate hepatic impairment and 8 subject with normal hepatic function. Subjects were matched for age, weight, gender and smoking history.

##### 4. MT100-105

This was a randomized, cross-over study to evaluate the bioequivalence of sumatriptan 50 mg tablet compared to over-encapsulated sumatriptan 50 mg tablet in 28 subjects. No subjects received MT100. This study was conducted to confirm that the 2 products were bioequivalent in preparation for study MT100-306 and MT100-308 (sumatriptan vs. MT100 clinical efficacy study).

##### 5. MT100-106

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This was an open label, single site, two-period crossover study to investigate the effects of migraine attacks on the pharmacokinetics of a single dose of MT100 administered during and outside an attack in 13 subjects.

#### 6. MT100-107

This was an open label, single center, two-period crossover study to evaluate the effects of food on the bioavailability of MT100 in 24 healthy volunteers. Periods were separated by a 7 day washout period. Subjects were given a high fat meal.

#### 4.2.2 Phase II Dose Ranging, Placebo Controlled Studies

The Phase II clinical development plan consisted of two dose ranging studies. One conducted in the United States (MT100-201) and the other conducted in Europe (MT100-202). In both studies screened subjects returned to the clinical site at the onset of a migraine of moderate to severe intensity for randomized treatment. Subjects remained in the clinical center for the first 2 hours after study drug administration, thereafter subjects followed their migraine using a typical migraine diary for the next 22 hours. A detailed description of pertinent efficacy findings are described in section 6.3.1 of this review. Additional details about the design of each trial follows:

##### 1. MT100-201:

This was a randomized, single dose, double blind, dose ranging, placebo controlled, safety and efficacy study of various combinations of naproxen and metoclopramide in 514 subjects with acute migraine. The following table summarizes the various treatments and size of each cohort. Each subject treated a migraine of moderate to severe intensity using test product in a double-dummy fashion. Each migraine were initially treated in clinic for 2 hours then followed as an outpatient using a standard migraine diary for 24 hours. Rescue medication was not permitted for 2 hours. The primary endpoint for this study was 2 hour Sum of Pain Intensity Differences and 2 hour nausea relief. Pain intensity difference is defined as the difference in pain scores between baseline and at post treatment timepoints ( $PID = P_0 - P_t$ ).

Cohorts E and H (8/500 and 8/1000) produced 2 hour SPID scores that were significantly greater than placebo with a strong trend seen in Cohort F (16/500, MT100, see Table 27). None of the treatment combinations were statistically superior to placebo in providing improvement in nausea at 2 hours. However MT100 (cohort F) demonstrated a strong trend towards significance ( $p=0.054$ ) hence the sponsor decided to develop the naproxen 500 mg and metoclopramide 16 mg combination product as MT100. The choice of cohort F for further development seems reasonable to this reviewer. I describe the results from this trial in further detail in section 6.3.1 of this review.

**Table 20** Cohorts, Trial MT100-201

Cohort	MC (mg)/NAP (mg)	N	Cohort	MC (mg)/NAP (mg)	N
A	0/0	57	F	16/500 (MT100)	57
B	8/0	58	G	0/1000	61
C	16/0	57	H	8/1000	52
D	0/500	57	I	16/1000	58
E	8/500	57			

##### 2. MT100-202

This was a randomized, single dose, double blind, parallel group, multicenter trial comparing the effects of two different combinations of naproxen and metoclopramide with placebo in

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182 subjects with an acute migraine. Each subject treated a migraine of moderate to severe intensity. Each migraine was initially treated in clinic for 2 hours then followed as an outpatient using a standard migraine diary for 24 hours. Rescue medication was not permitted for 2 hours. The following table summarizes the various treatment cohorts. No patient received naproxen and metoclopramide in the doses used in the final formulation of MT100. The primary endpoint of this study is 2 hour headache response defined as moderate to severe intensity at baseline going to mild or no pain at 2 hours. The study demonstrated that significantly more subjects taking MC 16 mg/NAP 1000 mg reported headache relief at 2 hours compared to placebo (76% vs. 42%,  $p < 0.001$ ). Whereas there was no statistical difference between subjects taking MC 8 mg/NAP 500 mg compared to placebo for headache relief at 2 hours (50% vs. 42%,  $p = 0.428$ ). I describe the results from this trial in further detail in section 6.3.1 of this review.

**Table 21** Cohorts, Trial MT100-202

Cohort	MC (mg)/NAP (mg)	N
A	8/500	60
B	16/1000	59
C	0/0	60

#### 4.2.3 Phase III Clinical Development Program

In this section I describe the designs of the Phase III studies submitted in support of this NDA. The Phase III clinical development program consists of 9 studies. Two studies (MT100-301 and MT100-304) were factorial type studies similarly designed to meet the Agency regulatory requirements for combination products (21 CFR 300.50). Two studies (MT100-306 and MT100-308) were conducted to compare the efficacy of MT100 to over-encapsulated sumatriptan 50 mg. Two studies were conducted to compare MT100 with placebo in subjects that either had a history of an inadequate response to sumatriptan 50 mg (MT100-401A), or had a history of intolerance to 5-HT agonist, or had cardiovascular risk factors (MT100-402). Study (MT100-303) evaluated the efficacy of MT100 relative to a second dose in MT100 non-responders. Study MT100-307 was conducted to evaluate the efficacy of MT100 when administered during a prodrome period of multiple migraines. Finally the sponsor conducted a single long term study (MT100-302) to assess the safety of MT100 over a 1 year period. No efficacy data was collected during trial MT100-302. Only the phase III studies are included in the sponsor's Integrated Summary of Efficacy. Although many of the studies are capable of demonstrating efficacy the sponsor relies on trial MT100-306 and MT100-308 as their pivotal trials they describe in labeling. Hence during my efficacy review I will primarily focus on trial MT100-306 and MT100-308 during my discussion of efficacy. All studies will be included in my safety discussion.

##### 4.2.3.1 Phase III, MT100 Factorial Studies

###### 1. MT100-301

This was a single dose, double blind, safety and efficacy study of MT100, metoclopramide, or naproxen in 1067 subjects with an acute migraine of moderate to severe intensity. Each subject was randomized to either 1 tablet of MT100 ( $n = 423$ ), naproxen 500 mg ( $n = 430$ ) or metoclopramide 16 mg ( $n = 214$ ). No placebo was included as per an agreement with the Agency. At the time of the original review the sponsor successfully argued that since a recently completed phase 2 study demonstrated metoclopramide had no significant effect on sustained response and since there is no published literature to suggest oral metoclopramide

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is effective for migraine then it would be unethical to expose additional patients to ineffective treatment. Hence it was agreed that metoclopramide could function as placebo (see teleconference memo May 19, 1999 and Dr. Oliva's review of serial 042). Since that time the sponsor has provided supporting evidence that in fact metoclopramide has been shown to be effective in the treatment of migraine (Ellis 1993, Coppola 1995 and Jones 1996). The sponsor does not discuss why they changed their opinion regarding the potential efficacy of metoclopramide in the treatment of migraine. The lack of a placebo in this study could potentially be problematic and may make the study difficult to interpret however since the studies were designed to demonstrate superiority I don't believe the lack of a true placebo is much of a problem.

At the screening visit subjects were randomized and instructed to treat their next migraine of moderate to severe intensity with randomized treatment so long as they satisfy the eligibility checklist for treatment (review of medication prohibitions, assessment of pain intensity etc). In trial MT100-301 subjects were followed using a typical migraine diary for 24 hours. Assessment were done at baseline, then every 30 minutes for 2 hours, then hourly while awake until 24 hours. If nausea was present at baseline subjects assessed time to relief of nausea using a stopwatch. Rescue medication was prohibited for the first 2 hours. Subjects were instructed to return to the clinic for post treatment evaluation within 72 hours of treatment.

The primary endpoint was **sustained headache response** defined as moderate to severe headache pain at baseline going to no or mild pain at 2 hours and did not relapse or require rescue medication up to hour 24. Secondary endpoints included incidence of associated symptoms at various timepoints. This protocol was submitted to the Agency in on May 10, 1999. A review at that time stated the trial design was acceptable as long as it is understood that, "in order to demonstrate efficacy and superiority to its components, MT100 will have to beat both components on its primary efficacy variable, namely sustained pain response". Since the time of the submission the Division has come to realize the use of a sustained headache response as a sole primary endpoint may not be clinically appropriate. We have come to appreciate that a drug product may demonstrate significance for sustained pain response starting at 2 hours but not be any better than placebo for pain response at 2 hours. Given such a situation it was felt sustained response may not be clinically relevant.

The sponsor calculates 1000 subjects (400 MT100 subject, 400 naproxen subjects and 200 metoclopramide subjects) will provide 80% power to detect a 10% difference between MT100 and naproxen and a 20% difference between MT100 and metoclopramide for sustained pain response. I describe the results from this trial in section 6.3.2 of this review.

#### 2. **MT100-304**

This was a single dose, double blind, safety and efficacy study of MT100, metoclopramide, or naproxen in 2627 subjects with an acute migraine of moderate to severe intensity. Each subject was randomized to either MT100 (n=1036), naproxen 500 mg (n=1062) or metoclopramide (n=529). As in trial MT100-301 there was no placebo. Prior to treatment with randomized medications subjects were instructed to review the eligibility checklist. Subjects were followed using a typical migraine diary for 24 hours and rescue medication was not permitted for 2 hours. Assessment were done at baseline, then every 15 minutes for 2

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hours, then every 30 minutes until hour 4, then hourly while awake until 24 hours. Follow up visits were to occur within 72 hours of treatment. The primary endpoint was **sustained headache response** defined as moderate to severe headache pain at baseline going to no or mild pain at 2 hours and did not relapse or require rescue medication up to hour 24. Secondary endpoints included incidence of associated symptoms at various timepoints.

The sponsor calculates a sample size of 2500 subjects (1000 MT100, 1000 naproxen and 500 metoclopramide) would provide 90% power to detect a 6% difference between MT100 and naproxen, and a 15% difference between MT100 and metoclopramide for sustained headache response. This protocol was submitted to the Agency on May 2, 2000. A review at that time expressed concern about the clinical significance of an expected 6% treatment effect between MT100 and naproxen 500 mg in such a large study otherwise there were no other significant concerns. In the end the treatment effect between MT100 and naproxen was only 3.9%. I describe the results from this trial in section 6.3.2 of this review.

#### 4.2.3.1 Phase III Placebo and Active Controlled Studies

##### 1. MT100-306 (Pivotal)

This was a randomized, double blind, placebo and active controlled study to evaluate the safety and efficacy of MT100 versus sumatriptan in 635 subjects with an acute migraine of moderate to severe intensity. Each subject was randomized to 1 tablet of MT100 (n= 138), 2 tablets of MT100 (n=142), 1 tablet of over-encapsulated sumatriptan 50 mg (n=129) or placebo (n=137). Over-encapsulated sumatriptan 50 mg was shown to be bioequivalent to commercial Imitrex 50 mg in trial MT100-105. The sponsor calculates 125 subjects per treatment arm would provide 80% power to detect an 18% treatment difference between MT100 and placebo for pain response at 2 hours. This assumes a 48% response rate for MT100 and a 30% response rate for placebo. Subjects were followed using a typical 24 hours migraine diary. Assessments were done at baseline, then every 15 minutes for 2 hours, then every 30 minutes until hour 4, then hourly while awake until hour 24. Prior to treatment with randomized medications subjects were instructed to review the eligibility checklist. Rescue medication was not permitted for 4 hours. Follow up was to occur within 72 hours of treatment.

The primary endpoint was 2 hour pain relief defined as moderate to severe pain at baseline going to mild or no pain at 2 hours without the use of rescue. The Cochran-Mantel-Haenszel test with center as strata was used to test the following pairwise comparisons; (1) MT100 1 tablet vs. placebo, (2) MT100 2 tablets vs. placebo, (3) sumatriptan vs. placebo, and (4) MT100 2 tablets vs. sumatriptan. Secondary endpoints included the incidence of associated symptoms at various timepoints. This protocol was submitted to the Agency on February 25, 2000. A review at that time stated no claims relative to sumatriptan are possible from this design because (1) the comparison between MT100 and sumatriptan is not the designated primary endpoint, (2) sumatriptan is encapsulated and the sponsor would have to demonstrate that the native and encapsulated forms are equivalent, and (3) the sponsor would need to study the entire therapeutic sumatriptan range including 100 mg. The second condition was met since trial MT100-105 demonstrated the bioequivalence of sumatriptan 50 mg with over encapsulated sumatriptan 50 mg under fasting conditions. I describe the results from this trial in section 6.3.3 of this review.

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#### 2. **MT100-308 (Pivotal)**

This was a double blind, placebo controlled study to evaluate the safety and efficacy of MT100 versus over encapsulated sumatriptan in 1272 subjects with an acute migraine attack of moderate to severe intensity. Each subject was randomized to either 1 tablet of MT100 (n=337), over-encapsulated sumatriptan tablet 50 mg (n=343) or placebo (n=347). The sponsor calculates a sample size of 323 subjects per cohort would provide 80% power to conclude there is no treatment difference (within 10%) between MT100 and sumatriptan. Subjects were followed using a typical migraine diary for 24 hours and rescue medication was not permitted for 2 hours. Assessments were done at baseline then every 15 minutes for 2 hours, then every 30 minutes until hour 4, then hourly until hour 24. Patients were instructed to follow up within 72 hours of treatment.

The primary endpoint was **2 hour pain relief** defined as moderate to severe pain at baseline going to mild or no pain at 2 hours. Secondary endpoints included the incidence of associated symptoms at various timepoints. The prestated analysis plan for the primary endpoint used the two-group Chi-Square test for equivalence (Blackwelder) to test the proportions of 2-hour responders between the two active treatments and the CMH test was used to test each active treatment for differences from placebo. This protocol was submitted to the Agency on June 15, 2001 and amended July 19, 2001. In a letter dated 10/24/01 we informed the sponsor that comparability statements relative to sumatriptan could not be made due to multiple design (primarily lack of sumatriptan 100 mg arm) and statistical concerns (primarily difficulty in determining appropriate delta in non-inferiority trials). I describe the results from this trial in section 6.3.3 of this review.

#### 4.2.3.1 Phase III Placebo Controlled Study with a Rescue Dose of MT100.

##### 1. **MT100-303**

This was a randomized, double blind, placebo controlled study to evaluate a single or a second dose (as rescue) of MT100 in 427 subjects with an acute migraine attack of moderate to severe intensity. Each subject was initially randomized to either MT100 (n=318), or placebo (n=109). Subjects initially receiving MT100 and not responding at 2 hours were then rerandomized to either MT100 or placebo. Subject initially randomized to placebo and not responding at 2 hours were all given MT100. The final cohort groups were as follows (1) MT100 single dose (n=133), (2) MT100 followed by placebo at 2 hours (n=94), (3) MT100 followed by MT100 at 2 hours (n=90), (4) placebo followed by MT100 at 2 hours (n=74), and (5) placebo single dose (n=34). Two subjects reported treating a migraine but failed to return to the center for follow up (PID 080 randomized to MT100/placebo, PID 355 randomized to placebo/MT100). Subjects were followed using a typical migraine diary for 24 hours and rescue medication was not permitted for 4 hours. Assessments were done at baseline, then every 15 minutes for the first 2 hours, then every 30 minutes for 2 hours, then hourly until hour 24. Subjects were instructed to follow up within 72 hours of treatment.

The primary endpoint was **sustained pain response** defined as headache pain intensity of mild to none at 2 hours after the initial dose which did not relapse or require rescue medication up to hour 24. A 4-hour sustained pain response was evaluated in subjects requiring a second dose of study medication. The primary endpoint for subjects initially randomized to MT100 or placebo was 2 hour sustained pain response. The primary endpoint

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for subjects initially randomized to MT100 with a pain score of 2 or 3 at 2 hours and receiving a second dose of either MT100 or placebo was 4-hour sustained pain response. Analysis of sustained pain response was performed using ordered logistic regression by ordering the data into the following three categories:

- (0) non-responders = subjects with a pain score of 2 or 3 at 2 hours, or 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 relief = 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.

Ordered logistic regression was used to test differences between: (1) MT100 vs. placebo (1<sup>st</sup> dose) and (2) MT100 vs. placebo (2<sup>nd</sup> dose in MT100 non-responders; based on the 4 hour timepoint). This protocol was submitted to the Agency on February 11, 2000. A review at that time resulted in relatively minor comments to be forward to the sponsor (request for an analysis of time to response using Kaplan-Meier method and improvements in patient diary).

The sample size for this study was driven by the requirement for an adequate number of subjects to assess the results of the second dose of MT100 in 1<sup>st</sup> dose MT100 non-responders. Specifically the sponsor calculated a sample size of 450 subjects randomized 3:1 to MT100 and placebo would provide approximately 90% power to detect an 18% difference in the 2 hour response rate between MT100 and placebo. Assuming a 50% non-response rate at 2 hours in MT100 subjects would provide approximately 170 subjects for the second dose randomization. A balanced randomization of 85 subjects per cohort (MT100-MT100 vs. MT100-Placebo) would provide 80% power to detect a 20% difference in the 4 hour response rate. I describe the results from this trial in section 6.3.4 of this review.

#### 4.2.3.1 Other studies

##### 1. MT100-401A

This was a double blind, randomized, placebo controlled study to evaluate the safety and efficacy of a two tablet dose of MT100 for the treatment of an acute migraine of moderate to severe intensity in 343 sumatriptan nonresponders. Sumatriptan non-response was determined historically as any subject who had an inadequate response to sumatriptan tablets (failure to reduce headache pain, return of headache pain within 24 hours, or requires additional medication) in more than half of at least three treated attacks. Each subject was randomized to either 2 tablets of MT100 (n=171) or placebo (n=172). Subjects were followed using a typical migraine diary for 24 hours and rescue medication was not permitted for 2 hours. The primary endpoint was the percent of subjects with **sustained response** defined as no or mild pain at 2 hours, without return of moderate to severe pain or the use of rescue medication within 24 hours. Secondary endpoint included the proportion of subjects reporting an associated symptom at various timepoints. This protocol was submitted to the Agency on November 8, 2001. A review at that time recommended the sponsor consider a prospective evaluation of sumatriptan to determine non-response. Additionally the sponsor was informed this study could not be used to support any comparative claims in labeling with respect to sumatriptan. I describe the results from this trial in section 6.3.5 of this review.

##### 2. MT100-402

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This was double blind, randomized, placebo controlled study to evaluate the safety and efficacy of MT100 for treatment of an acute migraine of moderate to severe intensity in 238 subjects who are intolerant to 5-HT agonists or have cardiovascular risk factors. Each subject was randomized to 1 tablet of MT100 (n=118) or placebo (n=120). Originally 470 subjects were planned for enrollment however the sponsor states they had difficulties with enrollment. Intolerance to triptans and cardiovascular risk factors were determined historically. Subjects were followed using a typical migraine diary for 24 hours and rescue medication was not permitted for 2 hours. The primary endpoint was **2 hour sustained pain response** defined as no or mild pain at 2 hour, no use of rescue medication through hour 24 and no return of moderate to severe pain. This protocol was submitted to the Agency on September 17, 2001. A review at that time did not result in any significant comments to the sponsor. I describe the results from this trial in section 6.3.5 of this review.

#### 3. MT100-307

This was a double blind, randomized, placebo controlled study to evaluate the safety and efficacy of MT100 in the treatment of migraine prodrome in 142 subjects. Each subject was randomized to either MT100 (n=70) or placebo (n=72). The study consisted of a 4 week baseline period during which migraine symptoms (including prodrome) and frequency were established. This was followed by a 4 week treatment period during which eligible subjects treated migraine prodrome syndrome with randomized drug. In order to be eligible for entry into the treatment period subjects had to experience 2 to 6 migraines during their baseline period, were able to predict at least 50% of these migraines from their prodrome symptoms, and all migraines had to be preceded by a prodrome. Eligible subjects then treated up to six prodrome events with study medication. Each event was followed using a typical migraine diary for 48 hours. Rescue medication (generally rizatriptan 10 mg) was prohibited for 2 hours. The primary endpoint was the **number of prodromes treated with study medication that resulted in an absence of moderate to severe pain** and no use of rescue medication within 24 hours of study drug administration. This protocol was submitted to the Agency on May 15, 2001. A review at that time resulted in several significant comments being forwarded to the sponsor. We informed the sponsor that we were not convinced that the prodrome phase of a migraine is a well-defined, well-accepted, and easily identifiable entity. We advised the sponsor that if they intend to seek labeling for a prodrome indication they would need to submit additional information to support the notion that the prodrome phase of a migraine is a well defined condition and accepted by experts in the field, and is easily identifiable in the clinical setting. Additionally we recommended the sponsor use as their primary endpoint the number of prodromes treated with MT100 vs. placebo that resulted in an absence of any migraine pain within 48 hours of study drug administration in order to take into account the potential that treatment in prodrome phase may merely delay the onset of migraine. Other comments sent were primarily statistical in nature. The sponsor responded (serial 084) by stating this trial was exploratory in nature and agrees the concept of a prodrome is “nebulous”. The endpoint was not changed. I describe the results from this trial in section 6.3.5 of this review.

#### 4. MT100-302

This was an open label repeat dose, long term safety study of MT100 in subjects with acute migraine attacks. The primary objective of this study was to assess the safety of MT100 in the treatment of migraine attacks occurring approximately twice a month for a period of 1 year. A total of 1123 subjects were enrolled and 1006 subjects received at least 1 dose of

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study medication. The sponsor categorizes subjects in this trial as either 6 month completers or 12 month completers. A 6-month completer (n=621) was defined as a subject who participated in the study for at least 182 days and took at least 12 doses of MT100. A 12-month completer (n=329) was a subject who was a 6-month completer and who participated in the study for at least 355 days and took at least 24 doses of MT100. Subjects who did not average at least 2 migraines per month for the first 6 months were discontinued from the study at the 6 month visit. The subjects who completed 12 months treated a total of 12,711 migraine attacks. As can be seen the sponsor has enough long term exposure to meet the ICH guidelines for minimum long term exposure (i.e., 300 to 600 for six month, 100 for 1 year all treating at least 2 migraines/month on average). Safety visits occurred every 3 months. This study did not include any efficacy endpoints. This study was submitted to the Agency on February 4, 2000. A review at that time did not result in any significant comments. I describe the results from this trial in section 6.3.5 of this review.

#### 4.3 Overall Data, Demographics and Patient Disposition

The following table briefly summarizes the total number of patients exposed to MT100 in the Phase II and Phase III acute studies. Additionally, in study MT100-303, 90 subjects received a second dose of MT100 2 hours after receiving a first dose of MT100 (non-responders) and in the phase II studies, 286 subjects received combinations of naproxen and metoclopramide that differed from MT100, and 119 subjects received one of individual components at doses other than those seen in the final formulation for MT100.

**Table 22** Total Number of Subjects in Controlled Clinical Trials

Study	MT100		Metoclopramide	Naproxen	Sumatriptan	Placebo
	1 tablet	2 tablet	16 mg	500 mg	50 mg	0 mg
201	57		57	57		57
301	423		214	430		
303	318					109
304	1036		529	1062		
306	138	142			129	137
308	337				343	347
401a		171				172
402	118					120
<b>Total</b>	<b>2427</b>	<b>313</b>	<b>800</b>	<b>1549</b>	<b>472</b>	<b>942</b>

Source: Adapted from sponsor table 50, Overall summary Volume 1, page 148.

Of the 7795 subjects that participated in the clinical development program for MT100, 1076 subjects participated in 2 or more clinical trials. A complete listing of these subjects and the trials in which they participated in can be found in Appendix 1 of the ise.pdf. The following table lists the 19 subjects that participated in both pivotal trials (MT100-306 and MT100-308) and their reporting of pain intensity at 2 hours (0=no pain, 3=severe pain). As can be seen there does not appear to be any pattern to the randomization or the response to treatment for subjects enrolled in both studies hence I do not believe this affected the trial results in any appreciable manner.

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**Table 23** Subjects Enrolled in Both MT100-306 and MT100-308 and 2 hr Pain Response

Unique ID Sex-Birth Day- Initials	MT100-306 Site/PID/Treatment	Pain Intensity at 2 hours	MT100-308 Site/PID/Treatment	Response at 2 hours
F (b) (6)	Site 081/6069/Placebo	0	Site 152/4413/Placebo	0
F	Site 111/6257/MT100x2	2	Site 133/4173/MT100	2
F	Site 111/6263/MT100x2	0	Site 133/4164/Placebo	0
F	Site 111/6266/MT100	2	Site 133/4176/MT100	2
F	Site 111/6691/MT100x2	3	Site 133/4166/Imitrex	3
F	Site 116/6285/MT100x2	2	Site 141/5053/Imitrex	0
F	Site 138/6588/Placebo	0	Site 138/5338/MT100	1
F	Site 138/6562/MT100	1	Site 138/5340/Placebo	1
F	Site 138/6577/Imitrex	1	Site 138/5333/Imitrex	0
F	Site 138/6569/Imitrex	2	Site 138/5334/Imitrex	3
F	Site 138/6576/MT100	2	Site 138/5332/Imitrex	2
F	Site 138/6578/Placebo	1	Site 138/5317/Imitrex	2
F	Site 116/6283/MT100x2	2	Site 141/4884/Placebo	2
M	Site 116/6290/Imitrex	2	Site 141/4885/Imitrex	1
F	Site 122/6301/MT100	2	Site 141/4887/Placebo	3
F	Site 116/6284/Placebo	1	Site 141/4110/Imitrex	1
F	Site 110/6114/MT100	0	Site 203/4595/MT100	1
F	Site 111/6258/Imitrex	3	Site 133/4177/Imitrex	2
F	Site 111/6260/MT100	0	Site 133/5141/Imitrex	0

Source: Appendix 1, ise.pdf

The following table summarizes the demographics of subjects that participated in the controlled clinical trials. Overall the percentage of females in these studies was 87% and the mean age was 41 years of age (range 18 to 87 years of age), both of which are typical of migraine studies I have reviewed and consistent with gender and age distribution of migraineurs in the general public. The overall ethnic breakdown in the controlled clinical trials was as follows: Caucasian 85%, Black 9%, Hispanic 4% and other 2%. In the two pivotal trials (MT100-306 and 308) there was good balance between cohorts for mean age, gender, race and the presence of aura. In the 2 pivotal trials there was a total of 21 subjects (1.3%) 65 years or older (range 65 to 78). Hence there is little experience in the geriatric population.

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**Table 24** Demographic of Participants in Controlled Clinical Trials

	Placebo	MT100 x 1	MT100 x 2	Naproxen	Metoclopramide	Sumatriptan
<b>Mean Age (yrs)</b>						
MT100-301		40.3		40.5	39.4	
MT100-303	38.1	40.2				
MT100-304		41.6		41.3	41.1	
MT100-306	40.5	40.4	39.2			40.4
MT100-308	40.5	39.9				40.9
MT100-401A	41.0		42.8			
MT100-402	49.1	44.1				
<b>Gender: Female (%)</b>						
MT100-301		86%		89%	87%	
MT100-303	79%	83%				
MT100-304		87%		87%	88%	
MT100-306	86%	90%	82%			91%
MT100-308	89%	84%				87%
MT100-401A	88%		92%			
MT100-402	86%	88%				
<b>Race: Caucasian (%)</b>						
MT100-301		83%		85%	86%	
MT100-303	62%	78%				
MT100-304		88%		88%	88%	
MT100-306	79%	83%	69%			74%
MT100-308	85%	85%				85%
MT100-401A	90%		92%			
MT100-402	79%	75%				
<b>Migraine Characteristics at Screening; With Aura (%)</b>						
MT100-301		12%		8%	12%	
MT100-303	9%	7%				
MT100-304		13%		12%	13%	
MT100-306	15%	18%	15%			16%
MT100-308	14%	11%				10%
MT100-401A	9%		6%			
MT100-402	13%	5%				

Source: Adapted from Sponsor Table 51, Overall Summary Volume 1, page 150.

The following table briefly summarizes the baseline migraine characteristics of subjects participating in the controlled clinical trials for MT100. Overall, cohorts in each trial were balanced for pain severity and the presence of each associated symptom at baseline. Approximately 50% to 60% of the subjects presented with moderate pain and nausea at baseline. Phonophobia and photophobia were present at baseline in approximately 70% to 90% of subjects. In trial MT100-306 there was fair balance between placebo and MT100 (single dose) for the percentage of subjects reporting severe headache pain at baseline (50% vs. 44%) however the sumatriptan 50 mg cohort had appreciably fewer subjects complaining of severe headache pain at baseline (34%). Since the primary comparison of interest for trial MT100-306 is between MT100 and placebo this difference should have minimal significance. Otherwise trial MT100-306 had good balance between cohorts for the proportion of subjects reporting each of the baseline associated symptoms. In trial MT100-308 there was good balance between all cohorts for the proportion of patients reporting severe headache pain at baseline as well as the proportion of subjects reporting each associated symptom.

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**Table 25** Baseline Migraine Characteristics of Subjects in Controlled Clinical Trials.

	Placebo	MT100 x 1	MT100 x 2	Naproxen	Metoclopramide	Sumatriptan
<b>Pain Severity; Severe (%)</b>						
MT100-301		40%		38%	35%	
MT100-303	47%	42%				
MT100-304		43%		39%	37%	
MT100-306	50%	44%	40%			34%
MT100-308	38%	38%				43%
MT100-401A	33%		34%			
MT100-402	49%	36%				
<b>Nausea Present (%)</b>						
MT100-301		45%		46%	49%	
MT100-303	53%	47%				
MT100-304		67%		66%	69%	
MT100-306	61%	69%	58%			59%
MT100-308	62%	65%				63%
MT100-401A	64%		68%			
MT100-402	63%	62%				
<b>Photophobia Present (%)</b>						
MT100-301		85%		83%	84%	
MT100-303	79%	81%				
MT100-304		82%		82%	82%	
MT100-306	89%	80%	82%			83%
MT100-308	81%	82%				84%
MT100-401A	88%		80%			
MT100-402	85%	83%				
<b>Phonophobia Present (%)</b>						
MT100-301		78%		80%	75%	
MT100-303	76%	80%				
MT100-304		76%		76%	73%	
MT100-306	83%	74%	83%			78%
MT100-308	78%	80%				82%
MT100-401A	87%		75%			
MT100-402	82%	79%				

Source: Adapted from Sponsor table 52, Overall Summary, volume 1, page 151.

All subjects participating in controlled clinical trials for MT100 were diagnosed with an acute migraine meeting the International Headache Society's definition for acute migraine with and without an aura (1.1 and 1.2). Subjects were enrolled if they were at least 18 years of age, in general good health, and experienced their first migraine prior to 50 years of age. Subjects were required to have a migraine frequency between 2 to 6 attacks per month and no more than 15 migraine days per month. Hence subjects with complicated medical histories and prolonged and frequent migraine attacks were generally excluded. Women not using some form of effective birth control were excluded. These inclusion/exclusion criteria are typical for most migraine studies I have reviewed.

#### 4.4 Postmarketing Experience

MT100 is not marketed in any country. Naproxen sodium and metoclopramide individually have been marketed for many years in the United States and most other countries.

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### 4.5 Literature Review

I conducted several focused PubMed searches while reviewing this NDA. Most of these searches were related to safety concerns and in general did not find any new information.

### 5. Clinical Review Methods

#### 5.1 How the Review was Conducted

The materials reviewed for this NDA include the original electronic NDA submission dated July 31, 2003, updated datasets received September 23, 2003 and an updated study report for Trial MT100-304. Additionally I reviewed every submission received under IND 54039, all amendments to the NDA (12 as of March 22, 2004), and all Medical Officer reviews and Agency Letters in DFS.

The emphasis of this review with respect to efficacy will be trials MT100-306 and MT100-308 both of which compared the safety and efficacy of MT100 to placebo and sumatriptan 50 mg. For reasons previously outlined we have informed the sponsor that comparative claims against sumatriptan would not be permitted in labeling hence I will focus on the results of the comparison between MT100 and placebo. In addition to these two trials I will also focus a fair amount of attention to trials MT100-301 and MT100-304 which evaluated the safety and efficacy of MT100 compared to its components but not placebo. All efficacy data presented comes from the intent to treat populations only unless otherwise stated. In addition to my review of these trials I have blended in the findings provided by the Agency statistician (Yeh-Fong Chen) in her review.

My safety review consists of safety findings from all clinical trials conducted in support of this NDA. Additionally I will discuss the known safety issues for naproxen and metoclopramide as they are summarized in the labels for Naproxen and Reglan respectively. Since the pharmacokinetic and bioavailability studies include close monitoring they provide useful safety data despite their limited size. The majority of my review of adverse events will be derived from trials MT100-301, MT100-304, MT100-306 and MT100-308 plus the long term (1 year) safety trial MT100-302. The long term trial MT100-302 is complete and no safety update is expected.

The pharmacokinetic data from the early studies is reviewed in detail by the biopharmacology reviewer however I briefly summarize the results in section 3 of this review.

#### 5.2 Overview of Methods Used to Evaluate Data Quality and Integrity

The Division of Scientific Inquiry investigated the following sites for audit:

- Site 012 Trial MT100-306 (b) (4)
- Site 115 Trial MT100-306
- Site 116 Trial MT100-306
- Site 191 Trial MT100-304

(b) (4) enrolled 57 subjects into trial MT100-306. A review of all completed migraine diaries (52) was done. Violations noted included the following:

1. Nine subjects were seen 6 to 28 days outside the protocol stated timeframe for follow up visit.

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2. Seven subjects did not have a completed physical at the final follow up visit.
3. A single subject was enrolled despite elevated liver function tests at baseline.
4. Six subjects took prohibited medication within 24 hours of treatment.

(b) (4) enrolled 40 subjects into trial MT100-306. An audit of all source records found the following violations:

1. A single subject was enrolled despite not meeting the weight requirements stated in the inclusion criteria.
2. A single subject was enrolled despite prior use of MT100 in another trial (MT100-302).
3. A pregnancy was not correctly reported to the IRB or entered into the electronic case report form.

Additionally it was noted that 34 out of 35 subjects had incorrect transcription of a secondary endpoint (pain relief) from the source document to the materials provided to the Agency investigator. Upon closer examination it was found that the mistake was due to a programmatic error and was limited to the materials given the inspector only. This explanation was deemed acceptable by the Agency in teleconference with the sponsor on March 24, 2004.

(b) (4) center participated in study MT100-306 and enrolled 44 subjects. Twenty subjects were selected for audit by the Agency inspector. All subjects signed the informed consent and no Form FDA0483's were issued. The inspection did not find any underreporting of adverse events and he concludes the data appear acceptable.

(b) (4) enrolled 51 subjects into trial MT100-304. Thirty-five subjects completed the study. An investigation by the sponsor (conducted in 2000) noted multiple date changes to the patient diaries in order to make it appear subjects returned for their final follow up visit within the 3 day window allotted. The study site was terminated by the sponsor and the event was reported to the Agency (11/22/00). An audit of source documents by DSI found the following violations:

1. No records were available for review in regards to receipt of the drug from the sponsor, storage of the drug on the site and return of the investigational drug to the supplier.
2. Four subjects were seen on final follow up 60 days outside the allotted timeframe.
3. Seven subjects were enrolled and treated prior to a review of their baseline laboratories.
4. Four subjects had their date of treatment over-written in order to make it appear they follow up within the allotted period.
5. A single subject's clinic chart was not available for review.

Overall multiple protocol violations were noted by the Agency auditors. The most common violation found was that many subjects were seen outside the allotted 72 hours for their post treatment follow up visit. This violation has minimal implications relative to the assessment of efficacy and does not alter my findings. Likewise I don't believe this violation has much of an impact on my assessment of safety. As I note in my safety review post treatment laboratory results done generally 1 to 3 days after treatment (or later) have limited usefulness in assessing acute changes resulting from a single dose of study medication. In my review of efficacy from

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trial MT100-304 I reviewed the results with and without the data obtained from (b) (4) site and found no difference.

#### 5.3 Were Trials Conducted in Accordance with Accepted Ethical Standards

The Sponsor states that their clinical trials provided in support of this NDA comply with the ethical principals of Good Clinical Practice (GCP) as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki.

My own review of previously submitted protocols and monitoring of the clinical development program during the past several years has not resulted in any ethical concerns.

#### 5.4 Evaluation of Financial Disclosure

As required the sponsor submits a completed FDA Form 3454, "Certification: Financial Interests and Arrangements of Clinical Investigators". Relative to all investigators the sponsor certifies that for all clinical studies submitted in support of this application they have not entered into any financial arrangement with any investigators whereby the value of compensation could be affected by the outcome of this study as defined in 21 CFR 54.2(a). Additionally the sponsor certifies that no listed clinical investigators, except the three investigators discussed below, reported any proprietary interest in this product or a significant equity in the sponsor. Finally the sponsor certifies that no Investigator was the recipient of significant payments of other sorts as defined in 21CFR.2(f).

The following three investigator hold equity positions in Pozen Inc.

- Participated in study MT100 301 and MT100-303
- Participated in study MT100 301 and MT100-306
- Participated in study MT100-306

Each of these investigators were awarded approximately 10,000 shares of Pozen stock options as part of their participation in the company's (b) (4) (b) (4) enrolled 44 out of 1,067 patients in study MT100-301 and 34 out of 427 patients in study MT100-303. Dr. (b) (4) enrolled 51 out of 1,067 patients in study MT100-301 and 52 out of 546 subjects in study MT100-306. Finally (b) (4) enrolled 17 out of 546 subjects in study MT100-306. Given the small number of patients enrolled by these investigators relative to the total number of patients participating in each trial I do not believe this has had any significant effect on the results of the trials.

### 6. Integrated Review of Efficacy

#### 6.1 Brief Statement of Conclusions

In section 6.4 of this review I summarize the findings and my opinion of the 5 randomized control studies (2 factorial studies, 3 efficacy studies) conducted by the sponsor in support of this NDA. Overall I do not believe the sponsor has adequately demonstrated the benefit of MT100 over naproxen in the two factorial studies provided. Although the results strongly trended towards significance I believe the small therapeutic benefit of MT100 over naproxen is outweighed by the added risks of metoclopramide (ex. tardive dyskinesia). The 3 efficacy studies conducted by the sponsor supports the argument that MT100 is beneficial compared to placebo

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for the treatment of pain associated with migraine however the results were mixed relative to nausea and phonophobia. Additional details are discussed below.

### 6.2 General Approach to Review of the Efficacy of the Drug

The sponsor conducted two phase II trials to assess the safety and efficacy of multiple different combinations of naproxen and metoclopramide (MT100-201 and MT100-202). There are five phase III clinical studies involving MT100 that the sponsor relies on to demonstrate efficacy: MT100-301, MT100-303, MT100-304, MT100-306 and MT100-308. Trial MT100-306 and MT100-308 are described in labeling and serve as the primary pivotal trials hence I will discuss these two trials in considerable details. The other trials I will primarily focus on their primary endpoint and relevant secondary endpoints. A detailed description of each trial design can be found in section 4 of this review.

### 6.3 Detailed Review of Trials

In this section I describe the efficacy results from the two dose finding trial (MT100-201 and MT100-202), the two factorial design studies (MT100-301 and MT100-304) and finally the two primary pivotal trials (MT100-306 and 308). This will be followed by a brief description of the efficacy results from trial MT100-303 (MT100 as rescue medication) and other controlled clinical trials. My review of these trials incorporates the findings from the Agency statistician, which in many areas differed considerably from the findings presented by the sponsor. The design of each study is described in section 4.2 of this review. The following table briefly summarizes the design of the single dose efficacy studies.

**Table 26** Summary of Single Dose Efficacy Studies

Study	Design*	Active Cohorts (NAP/MET)#: N	Control: N	Primary Endpoints	Goal
MT100-201	R, DB, PC, MC	500/16: 57 500/8: 57 1000/8: 52 100/16: 58 0/8: 58 0/16: 57 500/0: 57 1000/0: 61	Placebo: 57	2 hour SPID; 2 hour nausea	Evaluate safety and efficacy of various combinations.
MT100-202	R, DB, PC, MC	500/8: 60 1000/16: 59	Placebo 62	2 hour pain response	Evaluate safety and efficacy of various combinations
MT100-301	R, DB, PC, MC	500/16: 423	NAP 500: 430 MET 16: 214	Sustained pain response	Fulfill requirements of 21 CFR 300.50
MT100-303	R, DB, PC, MC	500/16: 303 500/16 + 500/16: 90	Placebo (1 <sup>st</sup> dose): 34 Placebo (2 <sup>nd</sup> dose): 94	Sustained pain response	Efficacy single tablet and rescue treatment.
MT100-304	R, DB, MC	500/16: 1036	NAP: 1062 MET: 529	Sustained pain response	Fulfill requirements of 21 CFR 300.50
MT100-306	R, DB, DD, PC, MC	500/16: 138 2 X 500/16: 142	Placebo: 137 Sumatriptan: 129	2 hour pain response	Efficacy –single tablet and comparison to sumatriptan
MT100-308	R, DB, PC, MC	500/16: 337	Placebo: 347 sumatriptan: 343	2 hour pain response	Efficacy –single tablet and comparison to sumatriptan
MT100-401A	R, DB, PC, MC	2 X 500/16: 171	Placebo: 172	Sustained pain response	Efficacy in subjects with prior history of inadequate response to sumatriptan
MT100-402	R, DB, PC, MC	500/16: 118	Placebo: 120	Sustained pain response	Efficacy in subjects with intolerance to triptans or CV risk factors

\*R = randomized, DB = double-blind, DD = double dummy, PC = placebo controlled, MC = multicenter, # NAP = naproxen (dose in mg); MET = metoclopramide (dose in mg); Source: Sponsor Table 1, ISE.pdf

All efficacy studies enrolled subjects meeting the International Headache Society criteria for migraine with and without and aura (1.1 and 1.2). A review of the baseline migraine

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characteristics for each study showed good compliance in meeting the IHS criteria. Subjects enrolled were generally between 18 to 65 years of age with few subjects in the geriatric age range. Subjects were required to have between 2 to 6 migraine attacks per month on average and no more than 15 migraine days per month hence the more severe migraineur was excluded. Women who were pregnant or breast feeding were excluded. In general these entry criteria are typical for migraine studies.

All phase III efficacy studies involved self administration of study drug with at least 24 hours of self observation using a standard migraine diary. Placebo and active comparators were physically indistinguishable from MT100. Statistical analyses were performed on the primary and secondary endpoints using an LOCF algorithm for missing data. The primary analyses for all studies used the Intent to Treat population defined as all subjects treating with test medication and providing at least a single post treatment observation.

#### **6.3.1 Dose selection trials: MT100-201 and MT100-202**

Trial MT100-201 and MT100-202 were designed to facilitate in dose selection. In both trials several different combinations of naproxen and metoclopramide were evaluated for safety and efficacy. Only trial MT100-201 had a cohort of subjects receiving naproxen 500 mg/metoclopramide 16 mg (MT100 combination). In both studies prescreened subjects returned to the clinic site at the onset of a migraine event of moderate to severe intensity in order to receive randomized treatment. A detailed review of the trial design for each study can be found in section 4.2.2

MT100-201 was a single dose, double blind, dose-ranging, placebo controlled, nine cell study of four different formulations of naproxen/metoclopramide combination in the treatment of an acute migraine (placebo, NAP 500 mg/MC 8 mg, NAP 500 mg/MC 16 mg, NAP 1000 mg/ MC 8 mg, NAP 1000 mg/MC 16 mg, MC 8 mg alone, MC 16 mg alone, NAP 500 mg alone, and NAP 1000 mg alone). The primary endpoint for this study was 2 hour Sum of Pain Intensity Differences (SPID)<sup>5</sup> and 2 hour nausea relief. Pain intensity difference is defined as the difference in pain scores between baseline and at post treatment timepoints ( $PID = P_0 - P_t$ ). Nausea “relief” is actually a comparison of the proportion of subjects reporting no nausea at 2 hours. The demographics of subjects in this trial are outlined in Table 24 however in general the various cohorts are well balanced and are typical of migraine studies I have reviewed in the past.

The following table briefly summarizes the major efficacy results of trial MT100-201. As demonstrated in the table only the naproxen 500 mg plus metoclopramide 16 mg cohort demonstrated a strong trend towards statistical significance for both SPID and the proportion of subject reporting no nausea at 2 hours ( $p=0.064$  and  $0.054$  respectively). Paradoxically, the highest dose group (1000/16) did less well than the other active treatments for SPID and nausea at 2 hours. The sponsor speculates this finding may be due to chance since they could not determine any randomization or packaging errors. Clinically it make some sense that subjects taking naproxen 1000 mg may report more nausea at 2 hours than in other cohorts since NSAIDs are known to cause gastrointestinal upset. It does not appear that the addition of metoclopramide (16 mg) to 500 mg of naproxen added any significant improvement in SPID scores and in fact

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<sup>5</sup> SPID =  $\sum PID_t \times$  [time (hours) elapsed since previous observation]

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naproxen 500 mg alone was numerically better than naproxen 500 mg plus metoclopramide 16 mg (SPID 1.57 vs. 1.45 respectively). However the addition of 16 mg of metoclopramide to naproxen 500 mg did result in a numerical benefit for the proportion of subjects reporting no nausea at 2 hours compared to naproxen alone (89% vs. 81% respectively) suggesting some benefit.

Interestingly, none of the naproxen/metoclopramide combination products were significantly better than placebo for pain response at 2 hours (traditional migraine primary endpoint). The reason for this finding is not immediately clear however it may be due to the high response rate seen for placebo (67%). In most studies of migraine I have reviewed the 2 hour placebo response rates were generally between 20 to 40%. Additionally it must be remembered this study was not designed or powered for 2 hour headache response. The sponsor concludes that the naproxen 500 mg/metoclopramide 16 mg combination provided the best clinical benefit in acute migraine of all combinations tested and was chosen for further phase III development.

The 2 hour SPID for metoclopramide 16 mg (n=57) alone was 1.39. The 2 hour SPID for naproxen 500 mg alone (n=57) was 1.57. A pairwise comparison of MT100 vs. its components was not significant for SPID (MT100 vs. MC 16mg p=0.764; MT100 vs. NAP 500 mg p=0.656)<sup>6</sup>. The proportion of patients reporting no nausea at 2 hours for metoclopramide 16 mg alone was 77% and for naproxen 500 mg alone was 81%. A pairwise comparison of MT100 vs. its components was not significant for nausea relief at 2 hours (MT100 vs. MC 16 mg p=0.123; MT100 vs. Nap 500 mg p=0.131)<sup>7</sup>. The sponsor did not analyze SPID results for the comparison of metoclopramide 16 mg alone vs. placebo and naproxen 500 mg alone vs. placebo. An overall comparison of the results for 2 hour SPID suggests the metoclopramide alone vs. placebo would not be significant since the results were less favorable than those seen for MT100 (1.39 vs. 1.45) and the sample sizes were identical. Likewise the comparison of metoclopramide 16 mg vs. placebo for nausea at 2 hours would most likely also not be significant since each cohort had a 77% no nausea reporting rate at 2 hours. Similarly naproxen 500 mg alone compared to placebo would most likely be significant since its 2 hour SPID was 1.57, which is numerically higher than the SPID seen for MT100 (1.45). Whereas the comparison of naproxen 500 mg alone vs. placebo for nausea at 2 hours would most likely not be significant since the reporting rate for no nausea at 2 hours for naproxen alone was 81% which was numerically worse than MT100 (89%) which barely missed significance (p=0.054).

For completeness I also included in the following table the results of the sponsor's analysis for photophobia and phonophobia relief at two hours (traditional essential secondary migraine endpoints). As demonstrated in the table the MT100 combination did not demonstrate benefit for pain relief or photophobia at 2 hours compared to placebo. The sponsor did not analyze the comparison of results for the naproxen alone or metoclopramide alone compared to placebo however a review of the numbers suggests neither individual component alone demonstrated any benefit for pain relief at 2 hours, or photophobia at 2 hours. In the past naproxen has been shown to be effective for these endpoints and is approved for the treatment of migraine. The reason for this unexpected finding is not immediately clear.

<sup>6</sup> Source: Sponsor table 13.4.1, 201.pdf

<sup>7</sup> Source: Sponsor table 18.1, 201.pdf.

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**Table 27** Major Efficacy Results from Trial MT100-201, ITT Population, LOCF

Parameter	Placebo N=57	Naproxen/metoclopramide regimen							
		500/8 N=57	500/16 N=57	1000/8 N=52	1000/16 N=58	0/8 N=58	0/16 N=57	500/0 N=57	1000/0 N=61
Mean SPID <sub>0-2 hours</sub> *	1.01	1.55	1.45	1.75	1.27	1.15	1.39	1.57	1.76
p-value		0.042	0.064	0.003	0.276				
No Nausea at 2 hrs, n(%)*	44 (77)	49 (86)	51 (89)	44 (85)	49 (84)	47 (81)	44 (77)	46 (81)	55 (90)
p-value		0.145	0.054	0.331	0.252				
No Photophobia at 2 hr, n(%)	30 (53)	34 (60)	35 (61)	33 (64)	31 (53)	27 (47)	30 (53)	34 (60)	40 (66)
p-value		0.443	0.357	0.315	0.996				
No Phonophobia at 2 hrs, n(%)	35 (61)	44 (77)	43 (75)	36 (69)	40 (69)	35 (60)	39 (68)	44 (77)	51 (84)
p-value		0.061	0.054	0.604	0.610				
Pain response at 2 hours, n(%)	38 (67)	39 (68)	44 (77)	40 (77)	36 (62)	35 (60)	38 (67)	39 (68)	45 (74)
p-value		0.884	0.145	0.420	0.549				

\*Co-Primary endpoints, SPID p-values based on two-sample t-test using LOCF, Associated Symptoms p-values based on CMH  
Source: Adapted from Sponsor table 7.1, 13.4.1, 18.1, 24, and 22, study report MT100-201.pdf

The following table briefly summarizes the major efficacy results of trial MT100-202. This was a single dose, double blind, placebo controlled, multicenter trial comparing naproxen 500 mg/metoclopramide 8 mg, naproxen 1000 mg/metoclopramide 16 mg and placebo. As previously stated this trial did not include MT100 in the formulation used during the phase III trials and planned for marketing. The primary endpoint of this study is 2 hour headache response defined as moderate to severe intensity at baseline going to mild or no pain at 2 hours, without the use of rescue medication. As demonstrated in the table, significantly more patients receiving naproxen 1000 mg/metoclopramide 16 mg reported headache relief at 2 hours compared to placebo ( $p < 0.001$ ). Likewise the naproxen 1000 mg/metoclopramide 16 mg cohort of subjects reported significantly less nausea, photophobia and phonophobia at 2 hours compared to placebo ( $p < 0.001$ , 0.002, 0.015 respectively). The lower dose cohort (500/8) was not significantly different from placebo for pain response at 2 hours. The sponsor concludes that naproxen 1000 mg/metoclopramide 16 mg is the minimally effective dose for relief of migraine pain and associated symptoms at 2 hours. Overall trial MT100-202 adds little information to the dose selection for MT100 and is presented here only for completeness. The sponsor does not discuss why they did not chose to pursue the combination product naproxen 1000 mg/metoclopramide 16 mg which appears effective.

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**Table 28** Major Efficacy Results from Trial MT100-202, ITT Population, LOCF

Parameter	Placebo N=62	Naproxen/metoclopramide	
		500/8 N=60	1000/16 N=59
Pain Response at 2 hrs, n(%)	26 (42)	30 (50)	45 (76)
p-value*		0.428	<0.001
No nausea at 2 hrs, n(%)	40 (65)	46 (78)	55 (93)
p-value*		0.052	<0.001
No photophobia at 2 hrs, n(%)	21 (34)	32 (53)	37 (63)
p-value*		0.039	0.002
No phonophobia at 2 hrs, n(%)	30 (48)	33 (55)	42 (71)
p-value*		0.432	0.015

\*comparison to placebo using CMH test, ITT population and LOCF

Adapted from Sponsor tables 2.1.1, 2.6.1, 2.8.1 and 2.9.1 study report 202.pdf

At the conclusion of trial MT100-201 and MT100-202 we had an end-of-phase II meeting with the sponsor (3/31/99). At that time we agreed that the combination of metoclopramide and naproxen was a rational combination for the treatment of migraine. However we stated we were not convinced that the combination is better than either component alone and we required appropriately designed single attack factorial studies. At the meeting we suggested that these factorial studies include a placebo however we later agreed no placebo was required. Additionally we agreed 2 hour sustained pain response was a reasonable choice for a primary endpoint although we encouraged the sponsor to use pain free at 2 hours and no rescue within 24 hours. Finally we informed the sponsor their factorial studies would need to show “*that MT100 beats metoclopramide alone on pain and beats naproxen alone on nausea*” and “*each component should be better than placebo (i.e., naproxen is better than placebo in pain, and metoclopramide is better than placebo on nausea)*”.<sup>8</sup>

### 6.3.2 Factorial studies; MT100-301 and MT100-304

In order to meet the regulatory requirements for combination products contained in 21 CFR 300.50 the sponsor conducted two clinical trials (MT100-301 and MT100-304) to evaluate the safety and efficacy of MT100 compared to its components in 3694 subjects. The demographics of these subjects are discussed in section 4.3. The design of these trials are discussed in section 4.2.3.1. Briefly, these studies were single dose, double blind, parallel design studies in which subjects treated a single migraine of moderate to severe intensity with either MT100, naproxen 500 mg or metoclopramide 16 mg. As agreed neither trial included a placebo cohort. Ideally it would have been better in my opinion if trial MT100-301 and MT100-304 had a true placebo arm especially since there is some evidence that metoclopramide is beneficial in the treatment of migraine<sup>9</sup>. In a teleconference on May 19, 1999 the trial design of MT100-301 was determined to be acceptable however we stated in order to win “MT100 needs to prove its superiority to both components on sustained pain response” (see Teleconference Memo May 19, 1999).

The primary endpoint for both trials was sustained pain response defined as a pain score of 0 or 1 (none or mild) at 2 hours post dosing which did not relapse (return to pain score 2 or 3) or require rescue medication within the succeeding 22 hours. The analysis of both trials was done

<sup>8</sup> Source: Dr. Oliva’s notes from the EOP2 meeting, review of meeting package located in Division File.

<sup>9</sup> Ellis GL et al., Annals of Emergency Medicine 1993; Coppola M et al., Annals of Emergency Medicine 1995 and Jones J. et al., American Journal of Emergency Medicine 1996 and others.

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on the Intent-to-Treat population defined as all subjects who received study medication and had both a baseline evaluation and at least one post-baseline efficacy evaluation. Missing values were handled using a last observation carried forward algorithm. Subjects taking rescue medication at any time had their subsequent efficacy values set to their baseline values or in the case of associated symptoms (nausea, photophobia, phonophobia) was set to the worst possible outcome (i.e., present).

In trial MT100-301 the prestated analysis plan was to analyze the proportion of patient reporting sustained response using logistic regression with baseline pain as the only covariate to test the following hypothesis:  $H_0: P_1 \leq P_2$  or  $P_1 \leq P_3$ ;  $H_A: P_1 > P_2$  and  $P_1 > P_3$ . Where  $P_1$  denotes the proportion of subjects with sustained response after dosing with MT100,  $P_2$  denotes the proportion of subjects with sustained response after dosing with naproxen, and  $P_3$  denotes the proportion of subjects with sustained response after dosing with metoclopramide. The original protocol was submitted on June 2, 1999 and amended twice (July 2, 1999 and August 10, 1999). Neither amendment changed the analysis plan for the primary endpoint. However in the final study report the primary endpoint was analyzed by ordered logistical regression using 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 have a pain score of 2 or 3 after 2 hours or receive rescue medication.
- 1) sustained pain 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 logistical regression with baseline pain and investigator site as covariates was used to test the following two contrasts; MT100 versus naproxen and MT100 versus metoclopramide. As justification for presenting a post hoc analysis the sponsor states in the study report:

*“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 more appropriate method, ordered logistic regression.”*

In the ISE the sponsor presents only the post hoc analysis results, (which are minimally significant), and does not clearly designate the results as a post hoc analysis. Whereas in the “overall summary” (page 147) the sponsor is a little more clear about the difference between the prestated analysis results and the post hoc analysis results. In the summary document the sponsor states:

*“Upon further examination of the data it became clear that the sustained pain response parameter could be logistically ordered into 2 subgroups, patients with no pain from 2 to 24 hours without use of rescue medication (in one subgroup) and patients with no more than mild pain from 2 to 24 hours without use of rescue medication (in a second subgroup). Therefore, a refined analysis using ordered logistic regression was performed with the MT100-301 data.”*

In a teleconference with the sponsor on March 27, 2002 we informed the sponsor that the use of post hoc analysis as evidence of efficacy for a pivotal trial was unacceptable and we consider the prestated analysis plan as the primary analysis for the study. For this reason I will focus

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primarily on the results using the prestated analysis plan for trial MT100-301. The sponsor's "refined analysis" will be briefly presented for completeness.

In trial MT100-304 the prestated analysis plan for sustained pain response included a plan to categorize response into 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 that either have a pain score of 2 or 3 after 2 hours or receive rescue medication.
- 1) sustained pain 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.

The pre-stated plan was to analyze this variable "by methods for 3 ordered categories such as extended Mantel Haenzel statistics with a score of 0, 1, and 2 for the three ordered categories" using a model that controls for center, baseline pain and gender. However in the study report and the ISE the sponsor only presents a post hoc analysis of sustained response analyzed using ordered logistic regression with baseline pain and investigator site as covariates to test MT100 versus naproxen and MT100 versus metoclopramide ("refined" analysis plan used for the post hoc analysis of study 301). The sponsor does not state the analysis presented in either the ISE or the study report is a post hoc analysis however in the "overall summary" (page 147) the sponsor states we agreed to this analysis plan during a teleconference (March 27, 2000). The sponsor states:

*"It was agreed that if MT100-304 was conducted and the data analyzed using ordered logistic regression specified a priori as the method of analysis of the sustained pain response data, and if the results were consistent with MT100-301, then the results of MT100-301 would be accepted as the second adequate and well controlled trial to satisfy the combination drug rule (21CFR300.25)."*

However according to the medical reviewer's minutes and the sponsor's supplied minutes there was no documented agreement about how the primary endpoint would be analyzed. Additionally, according to the sponsor supplied minutes we required that the second study "demonstrate that MT100 is superior to the components on sustained pain response at the  $p \leq 0.05$  level in one (1) additional study". It does not appear to this reviewer we agreed that the second study had to be consistent (i.e. almost positive) with the first study. Considering what the sponsor states above then they failed to designate this "refined analysis" *a-priori* in the protocol which was submitted on May 2, 2000 (serial 051) and amended twice (May 30, 2000 and July 11, 2000). I spoke with the Agency statistician and she states the CMH method designated in the original protocol is reasonable. For this reason I requested the sponsor to analyze and submit the results of trial MT100-304 using the pre-specified analysis plan stated in the original protocol (see e-mail October 23, 2003 and November 25, 2003). On January 14, 2004 the sponsor submitted in paper format the results of their analysis of trial MT100-304 using the prestated analysis plan. As I did with study 301 I will briefly summarize the sponsor's post hoc analysis using ordered logistic regression however I will give primary emphasis to the results using the prestated analysis plan.

The following table summarizes the results of the primary endpoint for trials MT100-301 and MT100-304. As demonstrated in the table, using the sponsor's analysis, the combination product MT100 was significantly superior to both naproxen 500 mg alone ( $p \leq 0.038$ ) and metoclopramide

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16 mg alone ( $p < 0.001$ ) for sustained headache relief in trial MT100-304 using the prestated analysis plan. The results were similar using the sponsor's post hoc refined analysis of ordered logistic regression ( $p \leq 0.030$ ). Although the results were statistically significant, the comparison of MT100 to naproxen for sustained response was not very robust ( $p = 0.038$ ) and in my opinion the treatment effect of 3.9% is of questionable clinical significance. In trial MT100-301 the comparison of MT100 to naproxen for sustained response trended towards significance when analyzed by the sponsor using the prestated logistical regression method ( $p = 0.077$ ) and was significant when analyzed by the sponsor using the ordered logistical regression method used in trial MT100-304 ( $p = 0.025$ , post-hoc analysis). As in trial MT100-304 the treatment effect compared to naproxen was small (5.8%) and is of questionable clinical significance in my opinion. We are on record as having told the sponsor we believe trial MT100-301 was negative because it did not "win" on the primary endpoint using the prestated analysis method. I concur with that assessment.

The overall therapeutic effect for MT100 over metoclopramide was 15.9% in trial MT100-301 and 13.0% in trial MT100-304. Both results are clinically relevant in my opinion. Relative to the low therapeutic effect between MT100 and naproxen for sustained response the sponsor argues a therapeutic effect of 5.8% and 3.9% represents a "relative therapeutic gain" of 57% and 43% respectively for MT100 over naproxen in comparison to metoclopramide [5.8%/10.1% ( derived by 15.9% metoclopramide minus 5.8% naproxen) in trial MT100-301 and 3.9%/9.1% (derived by 13.0% minus 3.9%) in trial MT100-304]. I don't know if I fully follow their argument and would counter that 3.9% difference is still only 3.9% difference no matter how you look at it.

In the process of trying to replicate the sponsor's analysis of the primary endpoint from trial MT100-301 the Agency statistical reviewer notes the sponsor did not include baseline pain as the covariate as originally planned in the data analysis plan. In so doing the Agency statistician was able to replicate the same incidences as reported by the sponsor but had a p-value of 0.0637 instead of 0.077. This minor difference does not affect our final conclusion that the study failed to demonstrate efficacy of MT100 over naproxen for the prestated primary endpoint using the prestated analysis plan.

In the process of trying to replicate the sponsor's analysis of the primary endpoint (using the prestated plan, SAS macro by Koch provided by sponsor) from trial MT100-304 the Agency statistical reviewer notes 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, were used in the extended Mantel-Haenszel statistics.*" The statistician assures me variable weight, based on the strata's proportion in the trial, is standard methodology and should have been followed. Using the method suggested by the Agency statistician the comparison of subjects with sustained response taking MT100 and subjects taking naproxen is 0.063 not 0.038. Hence the sponsor failed to demonstrate a statistically significant benefit of MT100 over naproxen for the prestated primary endpoint using the prestated analysis plan and the weighting method suggested by the Agency statistician.

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**Table 29** Sustained Pain Response (any response) in MT100-301 and MT100-304

Trial	MT100 n(%)	Naproxen 500 mg n(%)	Metoclopramide 16 mg n(%)
<b>MT100-301</b> N=1067	150 (35.6%)	128 (29.8%) p=0.077*‡	42 (19.7%) p<0.001*‡
<b>MT100-304</b> N=2627	328 (31.8%)	295 (27.9%) p=0.038*¥ (p=0.063) <sup>Ω</sup>	99 (18.8%) p<0.001*¥

Adapted from sponsor table 23 study report MT100-301 and amended table 27 study report MT100-304 (paper submission 1/14/04).

\*p-values for comparison to MT100 versus individual component alone using prestated analysis plan for both studies, Trial 301 logistic regression, trial 304 CMH.

‡ using post hoc ordered logistical regression, MT100 vs. naproxen p=0.025 and MT100 vs. metoclopramide p<0.001. Source sponsor table 5, study report 301.

¥ using post hoc ordered logistical regression, MT100 vs naproxen p=0.030 and MT100 vs. metoclopramide p<0.001. Source sponsor table 5 and 27 (original report), study report 304.

Ω p-value from Agency Statistician's analysis

The following table summarizes the sponsor's analysis of sustained pain response in subjects reporting baseline pain of moderate and severe intensity separately analyzed using ordered logistic regression. As demonstrated in the table the combination product MT100 was consistently numerically, but not statistically, better than naproxen alone in treating subjects with baseline migraine pain of severe in both studies (p=0.329 and 0.627). For subjects reporting moderate pain at baseline, MT100 was significantly better than naproxen alone in trial MT100-304 (p=0.020) and trended strongly for this comparison in trial MT100-301 (p=0.063). The comparison of MT100 to metoclopramide demonstrated significance for both subpopulations in both trials (p≤0.008). In summary MT100 is not statistically superior to naproxen alone in subjects reporting severe migraine pain although it is superior to metoclopramide in subjects reporting severe pain at baseline. In trial MT100-301 MT100 appears statistically superior to both component for subjects reporting moderate pain at baseline. Therefore the win (as per the sponsor's analysis) seen for the comparison of MT100 to naproxen for sustained response in trial MT100-304 was driven mostly by subjects reporting moderate pain intensity at baseline.

**Table 30** Sustained Pain Response (any response) by Baseline Pain Severity, Trial MT100-301 and MT100-304

Subgroup	MT100-301			MT100-304		
	MT100 (N=422)	NAP (N=429)	MET (N=213)	MT100 (N=1031)	NAP (N=1057)	MET (N=528)
<b>Moderate Pain n(%)</b>	251(59.5)	266 (62.0)	138 (64.9)	581 (56.4)	635 (60.1)	332 (62.9)
Sustained Pain Response n(%)	100 (39.8)	88 (33.1)	32 (23.2)	210 (36.1)	190 (29.9)	68 (20.5)
p-value		0.063	<0.001		0.020	<0.001
<b>Severe Pain n(%)</b>	170 (40.1)	162 (37.8)	75 (35.2)	445 (43.2)	411 (38.9)	194 (36.7)
Sustained Pain Response n(%)	49 (28.8)	39 (24.1)	10 (13.3)	118 (26.5)	101 (24.6)	31 (16.0)
p-value		0.329	0.008		0.627	0.002

Source: Sponsor tables 26 and 27, 301.pdf and tables 30 and 31 report 304.pdf

Analyzed using ordered logistic regression with baseline pain as covariate (post hoc analysis).

The following table summarizes several (not all) of the secondary endpoints from trial MT100-301 and MT100-304. As can be seen MT100 was superior to metoclopramide for every secondary endpoint except 2 hour nausea in trial MT100-301 (p=0.646) and 2 hour phonophobia in trials MT100-301 and MT100-304 (p=0.129 and 0.080 respectively). Despite this lack of superiority MT100 was numerically better than metoclopramide for the proportion of subjects reporting nausea at 2 hours in trial MT100-301 (23.7% vs. 25.4%) and the proportion reporting phonophobia at 2 hours in trials MT100-301 (45.7% vs. 52.1%) and MT100-304 (48.0% vs.

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52.8%). Especially important amongst these endpoints was 2 hour pain response which demonstrated superior efficacy for MT100 over metoclopramide in both studies ( $p < 0.001$  both studies). This endpoint is important because it assures us that MT100 compared to metoclopramide is effective at 2 hours (traditional endpoint) and the pain benefit is sustained (study endpoint). Despite the lack of significance for phonophobia and inconsistent findings for nausea I would conclude that MT100 is superior to metoclopramide in the treatment of the pain of migraine.

Unfortunately the comparison of MT100 to naproxen is not as favorable for most of the secondary endpoints. As the following table demonstrates the comparison of MT100 to naproxen was not significantly different for several important secondary endpoints. Key amongst these endpoints is 2 hour pain response which failed to demonstrate a significant difference between MT100 and naproxen in trials MT100-301 and MT100-304 ( $p = 0.665$  and  $0.143$  respectively). This would suggest relative to pain, MT100 offers no additional benefit over naproxen at 2 hours. Other important secondary endpoints to consider is the efficacy of MT100 over its component for nausea, photophobia and phonophobia. However as demonstrated in the table MT100 failed to demonstrate any statistical benefit compared to naproxen for any of these associated symptoms in both trials as assessed by the proportion of subjects reporting each symptom ( $p \geq 0.138$ ) and the proportion of subjects with sustained response for each symptoms (post hoc analysis,  $p \geq 0.083$ ). Although MT100 consistently demonstrated statistical significance over naproxen for mean PID at 2 hours and mean SPID at 2 hours it is difficult to understand the clinical relevance of these endpoints and in my opinion do not override the lack of efficacy seen in the comparison of pain response at 2 hours (traditional migraine primary endpoint). Overall I would conclude that MT100 offers little to no benefit over naproxen for the migraine syndrome.

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**Table 31** Secondary Endpoint Results from Trials MT100-301 and MT100-304

Parameter	MT100-301			MT100-304		
	MT100	NAP	MET	MT100	NAP	MET
2-hr pain response (%)	48.1	46.6 p=0.665	34.3 p<0.001	49.8	46.7 p=0.143	36.6 p<0.001
2-hr pain free (%)	18.7	14.0 p=0.053	9.4 p=0.002	16.8	16.0 p=0.604	9.1 p<0.001
Sustained pain free (%)‡	15.2	10.7 p=0.046	7.0 p=0.002	11.5	10.4 p=0.442	5.9 p<0.001
Mean PID 2 hours	0.93	0.78 p=0.016	0.56 p<0.001	0.93	0.81 p<0.001	0.61 p<0.001
Mean SPID 2 hours	1.03	0.85 p=0.044	0.60 p<0.001	0.98	0.84 p=0.012	0.60 p<0.001
2-hr Nausea <sup>ε</sup> (%)	23.7	26.6 p=0.333	25.4 p=0.646	33.7	36.7 p=0.138	41.5 p=0.003
2-hr Photophobia <sup>ε</sup> (%)	54.5	52.2 p=0.504	63.4 p=0.033	54.8	53.9 p=0.721	62.1 p=0.007
2-hr Phonophobia <sup>ε</sup> (%)	45.7	48.0 p=0.504	52.1 p=0.129	48.0	48.1 p=0.983	52.8 p=0.080
Sustained Nausea Free (%)†	45.3	39.4 p=0.100	30.5 p<0.001	37.0	33.5 p=0.083	26.7 p<0.001
Sustained Photophobia Free (%)†	32.2	29.8 p=0.409	19.7 p<0.001	27.9	27.0 p=0.584	21.0 p<0.003
Sustained Phonophobia Free (%)†	35.3	30.3 p=0.174	22.5 p<0.001	32.3	29.3 p=0.135	21.4 p<0.001

Source: Adapted from sponsor tables 6, 7, and 8 study report MT100-301. table 6, 7, and 8 study report MT100-304 and table 12 ISE.pdf.

All p-values are for comparison to MT100

† Sustained responses for associated symptoms are not included in the original study reports and come from ise.pdf tables 19.1 through 19.6.

‡ Sustained pain free was a post hoc endpoint in trial MT100-301

<sup>ε</sup> represents the number and proportions of subjects reporting the associated symptoms at 2 hours

In judging the validity of these studies, one point to consider is whether we consider sustained headache response to be a clinically relevant endpoint. This issue was discussed with the sponsor early in the development program and it was agreed that sustained response was an acceptable primary endpoint. However recently the division has had the experience where a drug product being developed for migraine won on sustained response but was inferior to placebo for 2 hour headache response (and earlier). This unusual situation has made some reviewers re-question whether sustained response is clinically relevant. From this experience the Division has decided, relative to migraine studies, that a win on sustained response that fails to demonstrate a significant difference from placebo at some clinically relevant timepoint (traditionally 2 hours) is not clinically relevant. In trial MT100-301 and MT100-304 metoclopramide is acting as placebo (debatable if appropriate) and the comparison of MT100 to metoclopramide did win on sustained response and pain relief at 2 hours in both trials. Hence it is clear that MT100 offers significant benefit over metoclopramide for migraine. However this is not the case for the comparison with naproxen. In trial MT100-301 the sponsor clearly did not demonstrate benefit of MT100 over naproxen for the sustained response (p=0.077) or 2 hour pain response (p=0.665). The sponsor is aware we consider trial MT100-301 a failed study. In trial MT100-304 the sponsor also did not demonstrate efficacy for MT100 over naproxen for sustained response (p=0.063, Agency statistician results) and 2 hour pain relief (p=0.143, sponsor results). Hence it could be argued that the combination product does not offer any significant benefit over each component (specifically naproxen) as required by the Combination Rule.

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However if we were to consider the sponsor's analysis of trial MT100-304 by extended Mantel-Haenszel statistics using equally weighted stratum, the comparison of MT100 to naproxen for the proportion of subjects with sustained response was nominally statistically significant ( $p=0.038$ ). Thus it could be argued that the combination product over naproxen adds additional benefit relative to sustained response (but not pain response at 2 hours). Whether this benefit is clinically relevant is debatable. However the overall therapeutic benefit of MT100 over naproxen for sustained pain relief was only 3.9% in trial MT100-304. I would not consider this difference to be clinically relevant despite the sponsor's argument that this represents a relative therapeutic benefit 43%. Additionally I would argue that the small benefit of adding metoclopramide to naproxen is outweighed by the additional serious risks associated with metoclopramide (i.e., acute dystonic reactions).

In conclusion I believe both studies fail to demonstrate any statistically and clinically significant benefit of MT100 over naproxen. Although the sponsor's analysis of the primary endpoint in trial MT100-304 demonstrated a statistically significant benefit of MT100 over naproxen for sustained response the findings were not very robust and disappear under the scrutiny of review. Additionally trials MT100-301 and MT100-304 failed to demonstrate any benefit of MT100 over naproxen for nausea, photophobia and phonophobia (2 hour incidence and sustained response).

### **6.3.3 Pivotal Trials; MT100-306 and MT100-308**

A total of 1573 subjects participated in trials MT100-306 and MT100-308. A description of each trial design can be found in section 4.2.3.1 of this review. Briefly, these were placebo controlled, multicenter, parallel design studies in which subjects treated a single migraine of moderate to severe intensity with randomized drug. In trial MT100-306 subjects were randomized to either 1 tablet of MT100 ( $n=138$ ), 2 tablets of MT100 ( $n=142$ ), 1 tablet of over-encapsulated sumatriptan 50 mg ( $n=129$ ) or placebo ( $n=137$ ) in a double dummy fashion. In trial MT100-308 subjects were randomized to either 1 tablet of MT100 ( $n=337$ ), 1 tablet of over-encapsulated sumatriptan 50 mg ( $n=343$ ) or placebo ( $n=347$ ). Otherwise both studies were of identical design hence I will combine my discussion of the efficacy results from these trials. Although both trials contain sumatriptan 50 mg as an active comparator we informed the sponsor on several occasions that marketing claims against sumatriptan could not be supported by these studies for a number of reasons; primarily since the full spectrum of sumatriptan doses were not being evaluated and the planned delta for the non-inferiority comparison was too large (see Agency letter 10/24/01, and 6/8/01). For this reason I will focus my comments on how MT100 compares to placebo. Additionally since the sponsor seeks approval of only a single tablet regimen for MT100 I will give added emphasis to the efficacy data seen in that cohort.

The primary endpoint for both trials was 2 hour pain response defined in the traditional manner for migraine studies. The analysis of both trials was done on the Intent-to-Treat population defined as all subjects who received study medication and had both a baseline evaluation and at least one post-baseline efficacy evaluation. Missing values were handled using a last observation carried forward algorithm. Subjects taking rescue medication at any time had their subsequent efficacy values set to their baseline values or in the case of associated symptoms (nausea, photophobia, phonophobia) was set to the worst possible outcome (i.e., present).

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In trials MT100-306 and MT100-308 screened subjects took randomized treatment at the onset of their next migraine of moderate to severe intensity if they continued to meet entry criteria (i.e., no prohibited medications or change in medical status). Subjects recorded assessments of their symptoms in a typical migraine diary at the onset of treatment, every 15 minutes for the first 2 hours, every 30 minutes between 2 to 4 hours then hourly for the next 20 hours while awake. Subjects were instructed to stay awake for the first 4 hours in order to record “meaningful relief”. Subjects were instructed to return to the clinic within 72 hours of their treated migraine event. Rescue medication was not permitted for 2 hours in trial MT100-308 and 4 hours in trial MT100-306.

Subject demographics and disposition in trials MT100-306 and MT100-308 are discussed in section 4.3 of this review. Overall there was good balance between all cohorts in both trials for baseline demographics and migraine characteristics.

#### **6.3.3.1 Primary Endpoint, Trial MT100-306 and MT100-308**

The primary endpoint for both trials was 2 hour pain response defined as a change in headache pain severity from moderate to severe at baseline to mild or none at 2 hours without the use of rescue. This endpoint is commonly used in migraine NDAs and has been well accepted within the Division although recently we have been suggesting sponsors use pain freedom as the primary endpoint of choice as recommended by the International Headache Society. In trial MT100-306 the comparison of primary interest was MT100 vs. placebo. In trial MT100-308 the comparison of primary interest was between MT100 and sumatriptan 50 mg using an equivalence/non-inferiority analysis plan while the comparisons of MT100 to placebo was performed to “validate the study design and patient population”. In trial MT100-306 the Cochran-Mantel-Haenszel test with center as strata was used to test the following pairwise comparisons; (1) MT100 1 tablet vs. placebo, (2) MT100 2 tablets vs. placebo, (3) sumatriptan vs. placebo, and (4) MT100 2 tablets vs. sumatriptan. The sponsor did not specify any correction for multiple primary endpoints in trial MT100-306. In trial MT100-308 the two-group Chi-Square test for equivalence (Blackwelder) with an alpha of 0.05 was used to test the proportions of 2-hour responders between the two active treatments (MT100 vs. sumatriptan) and the CMH test was used to test each active treatment for differences from placebo.

In trial MT100-308 the comparison between the two active treatments (MT100 and sumatriptan) was to be considered equivalent if the proportions were within a margin of 10% (the delta). In a letter dated October 24, 2001 we informed the sponsor the proposed equivalence (MT100-308) analysis plan using a 10% margin (delta) was unacceptable since a comparison directly to placebo was possible from the proposed trial and a 10% delta was too high. Therefore for the purposes of this review I will focus primarily on the comparison of MT100 to placebo for both trials. However the Agency statistician points out that study MT100-308 is overpowered for the comparison of MT100 to placebo. The sponsor calculated that 323 subjects per treatment arm would be required to achieve approximately 80% power to conclude there is no treatment difference between MT100 and sumatriptan. The Agency statistician calculates 323 subjects per treatment provides more than 99% power to detect a difference between MT100 and placebo in the proportion of subjects reporting pain relief at 2 hours.

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All analyses were done on the Intent-to-Treat population and used an LOCF algorithm for missing data. Rescue medication was not permitted for the first 2 hours in both trials.

The following table summarizes the sponsor’s analysis of the primary endpoint. As can be seen a single dose and a double dose of MT100 was clearly superior to placebo for the percentage of patients reporting headache pain relief at 2 hours in trials MT100-306 and MT100-308 ( $p \leq 0.001$ ). In trial MT100-306 there was no statistical difference between response rates for the comparisons MT100 1 tablet vs. MT100 2 tablets ( $p=0.320$ ) and MT100 2 tablets vs. sumatriptan ( $p=0.454$ ). The sponsor did not analyze MT100 1 tablet vs. sumatriptan in trial MT100-306 however there is very little relative treatment effect between the two products (0.6%). Whereas in trial MT100-308 the comparison of MT100 1 tablet vs. sumatriptan was significant ( $p=0.042$ ), favoring sumatriptan (44.0% vs. 47.4%), although the treatment effect difference between the two active products (3.4%, 95% CI -4.2, 10.9) is probably of little clinical significance.

The sponsor asserts the Blackwelder test of equivalence/non-equivalence demonstrates the two products have comparable efficacy and are equivalent. Although the Blackwelder equivalence/non-inferiority analysis of MT100 vs. sumatriptan in trial MT100-308 is not crucial to the possible approval of MT100 (in my opinion) I discussed the interpretation of the results with the Agency statistician and she informs me that in fact the sponsor actually lost on this comparison because they should have used an alpha of 0.025 hence the two products are not equivalent. In her review she states “*since the upper limit of confidence interval of responder proportion differences between sumatriptan and MT100 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 MT100 and sumatriptan in terms of 2 hour pain relief.*” Otherwise the Agency statistician replicated and confirmed the sponsor’s analysis of the primary endpoints from trials MT100-306 and MT100-308.

**Table 32** Percentages of Headache Responders in Trial MT100-306 and MT100-308

	MT100-306				MT100-308		
	MT100 1 Tablet N=138	MT100 2 Tablets N=142	Sumatriptan 50 mg N=129	Placebo N=137	MT100 1 Tablet N=332	Sumatriptan 50 mg N=340	Placebo N=341
2 hr Pain Response n(%)	73 (52.9%)	83 (58.5%)	69 (53.5%)	40 (29.2%)	146 (44.0%)	161 (47.4%)	109 (32.0%)
p-value vs. placebo*	<0.001	<0.001	<0.001	NA	0.001	<0.001	NA
p-value vs. sumatriptan†		0.454			0.042		

\*Compared to placebo, CMH analysis

Source: Sponsor Table 31 and Table 5 study report 306.pdf; Table 35 and Table 35a study report 308.pdf

† Blackwelder 2-Group Chi Squared test for equivalence for a one-sided test at a 0.025 significance level

In summary, these results support the statement MT100 is superior to placebo in the treatment of acute headache pain associated with migraine syndrome as evaluated by 2 hour headache response in trial MT100-306 and MT100-308 (may have been over powered). No statement relative to efficacy of MT100 compared to sumatriptan can be made since the sponsor did not evaluate the full dosing regimen of sumatriptan, the Blackwelder equivalence analysis in trial

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MT100-308 used an unacceptable delta of 10 %, and the Agency statistician's interpretation of the Blackwelder test result is consistent with non-equivalence.

#### 6.3.3.1 Secondary Endpoints Trial MT100-306 and MT100-308

##### Pain Response

The following table briefly summarizes the results from the sponsor's analysis of 2 hour pain freedom, sustained pain response and sustained pain freedom. Two-hour pain freedom is defined as moderate to severe pain at baseline going to no pain at two hours and without the use of rescue medication for the first 2 hours. Sustained pain response is defined as mild or no pain at 2 hours with no relapse of pain up to hour 24 and no use of rescue for the entire 24 hour period. Sustained pain freedom is defined as no pain at 2 hours with no return of any level of pain through hour 24 and no use of rescue throughout the entire 24 hour period. Sustained pain freedom is a subset of sustained pain response. The sponsor analyzed pain freedom at various times using CMH test with center as strata. The sponsor analyzed sustained pain-free and sustained pain response using ordered logistical regression with baseline pain and site as covariates.

As demonstrated in the table, MT100 (single and double dose) was superior to placebo for the proportion of patients reporting pain freedom at 2 hours in trial MT100-306 ( $p \leq 0.031$ ) and trial MT100-308 ( $p \leq 0.047$ ). This particular endpoint has recently been suggested by the International Headache Society as the preferred primary endpoint for migraine studies. As demonstrated in the table sumatriptan was also significantly better than placebo for this endpoint in both trials ( $p \leq 0.033$ ). The treatment effect of 1 tablet of MT100 compared to placebo for pain freedom at 2 hours was 5.8% in trial MT100-308 and 10.1% in trial MT100-306. A slightly larger treatment effect for sumatriptan compared to placebo was seen in both trials (6.5% trial MT100-308; 16.3% trial MT100-306) for 2 hour pain freedom. In both trials the proportion of patients reporting complete pain freedom at 2 hours was numerically higher for patients randomized to sumatriptan than patients randomized to a single or double dose of MT100. In trial MT100-306 there was no statistical difference between MT100 2 tablets and sumatriptan for pain freedom at 2 hours ( $p = 0.357$ )<sup>10</sup>. In trial MT100-308 there was no statistical difference between 1 tablet of MT100 and sumatriptan 50 mg for 2 hour pain freedom ( $p = 0.938$ ).<sup>11</sup> In trial MT100-306 there was a very slight numerical advantage of 2 tablets of MT100 compared to 1 tablet of MT100 for pain freedom at 2 hours. In summary a single tablet of MT100 was superior to placebo in providing complete pain relief at 2 hours and sumatriptan was numerically superior to a single and double dose of MT100 in providing complete pain relief at 2 hours in both trials.

As demonstrated in the table below MT100 (1 and 2 tablets) and sumatriptan all did well compared to placebo relative to sustained pain response however the results of the sponsor's analysis of sustained pain freedom across studies were inconsistent. In trial MT100-306 a single tablet of MT100 was not significantly better than placebo for sustained pain freedom ( $p = 0.201$ ) however in trial MT100-308 a single tablet of MT100 was superior to placebo for sustained pain freedom ( $p = 0.012$ ). A similar mixed result was also seen for sumatriptan. A two tablet dose of MT100 in trial MT100-306 was superior to placebo for the proportion of subjects reporting

<sup>10</sup> Source: Sponsor Table 36, study report 306.pdf, page 9053.

<sup>11</sup> Source: Sponsor Table 45, study report 308.pdf, page 178.

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sustained pain freedom (p=0.022). In summary, all actively treated patients in both trials demonstrated superiority to placebo treated patients for sustained pain response. There was inconsistent results for a single tablet of MT100 compared to placebo for sustained pain freedom with trial MT100-306 not demonstrating superiority (p=0.201) and trial MT100-308 demonstrating superiority (p=0.012).

**Table 33** 2-hour Pain Freedom and Sustained Response, Trial MT100-306 and MT100-308.

	MT100-306				MT100-308		
	MT100 1 Tablet N=138	MT100 2 Tablets N=142	Sumatriptan 50 mg N=129	Placebo N=137	MT100 1 Tablet N=332	Sumatriptan 50 mg N=340	Placebo N=341
<b>2 hr Pain Free n(%)</b>	31 (22.5%)	34 (23.9%)	37 (28.7%)	17 (12.4%)	63 (19.0%)	67 (19.7%)	45 (13.2%)
<b>p-value*</b>	0.031	0.014	0.001	NA	0.047	0.033	NA
<b>Sustained Pain Response n(%)</b>	47 (34.1%)	66 (46.5%)	42 (32.6%)	30 (21.9%)	98 (29.5%)	110 (32.4%)	60 (17.6%)
<b>p-value*</b>	0.029	<0.001	0.055	NA	<0.001	<0.001	NA
<b>Sustained Pain Free n(%)</b>	20 (14.5%)	27 (19.0%)	22 (17.1%)	13 (9.5%)	46 (13.9%)	44 (12.9%)	27 (7.9%)
<b>p-value*</b>	0.201	0.022	0.080	NA	0.012	0.031	NA

Source: Sponsor table 29, 34, and 45 study report 308.pdf; Sponsor table 62 Overall summary Volume 1, and Sponsor tables 6, 23, 30, and 36 study report 306.pdf.

\*p-value for comparison to placebo

The following table summarizes the sponsor's analysis of pain response at various time points through hour 4 in trials MT100-306 and MT100-308. As demonstrated in the table a single tablet of MT100 provided significant pain relief starting as early as 1 hour in trial MT100-306 and 1.5 hours in trial MT100-308.

**Table 34** Pain Response Over Time

	N		0.5 hrs	1.0 hrs	1.5 hrs	2 hrs	2.5 hr	3 hrs	4 hrs
<b>MT100-306</b>									
MT100 x 1	138	n (%)	5 (3.6)	40 (29.0)	61 (44.2)	73 (53.0)	82 (59.4)	85 (61.6)	92 (66.7)
MT100 x 2	142	n (%)	12 (8.5)	37 (26.1)	64 (45.1)	83 (58.5)	90 (63.4)	92 (64.8)	96 (67.6)
Sumatriptan	129	n (%)	7 (5.4)	44 (34.1)	65 (50.4)	69 (53.5)	73 (56.6)	80 (62.0)	87 (67.4)
Placebo	137	n (%)	7 (5.1)	16 (11.7)	32 (23.4)	40 (29.2)	49 (35.8)	53 (38.7)	63 (46.0)
<b>p-value</b>									
1 MT100 vs. placebo			0.632	<0.001	<0.001	<b>&lt;0.001</b>	<0.001	<0.001	<0.001
2 MT100 vs. placebo			0.209	0.002	<0.001	<b>&lt;0.001</b>	<0.001	<0.001	<0.001
Sumatriptan vs. placebo			0.886	<0.001	<0.001	<b>&lt;0.001</b>	<0.001	<0.001	<0.001
2 MT100 vs. sumatriptan			0.393	0.134	0.197	<b>0.454</b>	0.248	0.609	0.958
<b>MT100-308</b>									
MT100 x 1	332	n (%)	18 (5.4)	74 (22.3)	122 (36.8)	146 (44.0)	157 (47.3)	164 (49.4)	164 (49.4)
Sumatriptan	340	n (%)	16 (4.7)	70 (20.6)	110 (32.4)	161 (47.4)	173 (50.9)	178 (52.4)	186 (54.7)
Placebo	341	n (%)	9 (2.6)	63 (18.5)	97 (28.5)	109 (32.0)	111 (32.55)	109 (32.0)	119 (34.9)
<b>p-value</b>									
1 MT100 vs. placebo			0.082	0.226	0.021	<b>0.001</b>	<0.001	<0.001	<0.001
Sumatriptan vs. placebo			0.098	0.526	0.302	<b>&lt;0.001</b>	<0.001	<0.001	<0.001

Source: Adapted from Sponsor table 35 308.pdf and table 31, 306.pdf.  
p-value compared to placebo, analyzed using CMH test with site as strata

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### Associated Symptoms

#### *Nausea*

The following table summarizes the sponsor's analysis of the proportion of subjects reporting nausea at various times. As is customary in the Division I give added emphasis to the 2 hour timepoint since this is the timepoint for the primary endpoint and the results after 2 hours may be confounded by the use of rescue medication (rescue restricted until 4 hours in trial MT100-306). As demonstrated in the table a single tablet of MT100 was nominally superior to placebo in the proportion of patients reporting nausea at 2 hours (27.5% MT100 vs. 38.7% placebo,  $p \leq 0.049$ ) in trial MT100-306. No apparent dose effect for this outcome was apparent in trial MT100-306 where a two-tablet dose of MT100 was not any better than a single tablet dose of MT100 (both 27.5%). Oddly sumatriptan was not superior to placebo in trial MT100-306 for the proportion of patients reporting nausea at 2 hours or any time prior through 4 hours even though sumatriptan has been shown effective for this endpoint in previous trials. However in trial MT100-308 a single dose of MT100 was not superior to placebo in the relief of nausea at 2 hours ( $p=0.980$ ). This comparison reaches significance starting at 3 hours ( $p=0.012$ ) however this may be confounded by the use of rescue medication. In summary, a single tablet of MT100 demonstrated inconsistent efficacy for nausea at 2 hours as assessed by the proportion of subjects reporting nausea at 2 hours in trial MT100-306 and trial MT100-308. The reason for the failure of sumatriptan to demonstrate efficacy for this endpoint at 2 hours in both trials is not apparent to this reviewer.

**Table 35** Proportion of Subjects Reporting Nausea at Various Timepoints: n(%)

	N	0 hrs	0.5 hrs	1.0 hrs	1.5 hrs	2 hrs	2.5 hr	3 hrs	4 hrs
<b>MT100-306</b>									
MT100 x 1	138	95 (68.8)	89 (64.5)	62 (44.9)	46 (33.3)	38 (27.5)	32 (23.2)	31 (22.5)	27 (19.6)
MT100 x 2	142	82 (57.7)	81 (57.0)	61 (43.0)	49 (34.5)	39 (27.5)	30 (21.1)	25 (17.6)	23 (16.2)
Sumatriptan	129	76 (58.9)	81 (62.8)	66 (51.2)	53 (41.1)	51 (39.5)	46 (35.7)	42 (32.6)	36 (27.9)
Placebo	137	84 (61.3)	86 (62.8)	84 (61.3)	64 (46.7)	53 (38.7)	48 (35.0)	39 (28.5)	39 (28.5)
p-value									
1 MT100 vs. placebo			0.710	0.007	0.026	<b>0.049</b>	0.035	0.274	0.120
2 MT100 vs. placebo			0.334	0.003	0.048	<b>0.054</b>	0.010	0.024	0.012
Sumatriptan vs. placebo			0.974	0.105	0.363	<b>0.880</b>	0.899	0.466	0.932
2 MT100 vs. sumatriptan			0.299	0.180	0.247	<b>0.033</b>	0.006	0.003	0.012
<b>MT100-308</b>									
MT100 x 1	332	217 (65.4)	216 (65.1)	172 (51.8)	148 (44.6)	141 (42.5)	149 (44.9)	143 (43.1)	148 (44.6)
Sumatriptan	340	214 (62.9)	208 (61.2)	191 (56.2)	172 (50.6)	153 (45.0)	151 (44.4)	145 (42.7)	143 (42.1)
Placebo	341	211 (61.9)	208 (61.0)	180 (52.8)	147 (43.1)	145 (42.5)	162 (47.5)	180 (52.7)	198 (58.1)
p-value									
1 MT100 vs. placebo			0.273	0.811	0.663	<b>0.980</b>	0.517	0.012	<0.001
Sumatriptan vs. placebo			0.946	0.313	0.045	<b>0.489</b>	0.498	0.010	<0.001
1 MT100 vs. sumatriptan			0.257	0.271	0.133	<b>0.524</b>	0.878	0.857	0.478

Source: Adapted from Sponsor table 49 study report 308.pdf, and Sponsor table 42 study report 306.pdf  
Analysis done by CMH test with site as strata.

In addition to analyzing the proportion of patients reporting nausea at various timepoints the sponsor also prospectively planned to analyze the difference in mean nausea intensity using a 4-point scale at various times in trial MT100-306 and trial MT100-308. The results of this analysis are not presented in the ISE however the study report for trial MT100-306 states mean nausea intensity was not significantly different from placebo in any treatment group at 2 hours. The study report for trial MT100-308 does not discuss the results of this analysis in text however sponsor table 41 of the study report demonstrates no significant difference between actively

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treated subjects and placebo at 2 hours. The mean nausea intensity at 2 hours for each group is presented in the following table. In summary both trials failed to demonstrate a significant difference between MT100 and placebo for mean nausea intensity at 2 hours.

**Table 36** Mean Nausea Intensity at 2 hours, Trial MT100-306 and MT100-308

	MT100-306				MT100-308		
	MT100 1 Tablet N=138	MT100 2 Tablets N=142	Sumatriptan 50 mg N=129	Placebo N=137	MT100 1 Tablet N=332	Sumatriptan 50 mg N=340	Placebo N=341
Mean score (SD)	0.39 (0.74)	0.38 (0.71)	0.55 (0.77)	0.52 (0.77)	0.70 (0.98)	0.75 (0.97)	0.76 (1.05)
p-value	0.177	0.122	0.716		0.595	0.427	

Adapted from sponsor table 41 study report 306.pdf; table 48 study report 308.pdf.  
Analyzed using ANOVA with treatment and center as fixed effects

The following table summarizes the sponsor’s post-hoc analysis of sustained nausea free. Sustained nausea freedom is defined as “subjects with a nausea intensity score of 0 at 2 hours and no intensity score greater than 0 after 2 hours without the use of rescue medication”. As demonstrated in the table, significantly more patients experienced sustained nausea free compared to placebo in trial MT100-306 (p=0.049) and in trial MT100-308 (p<0.001). From the sponsor’s definition it does not appear the status of nausea at baseline was considered. This is important because there is a slight imbalance between cohorts for subjects reporting nausea at baseline (range 58% to 69%, see Table 25). Since this analysis was done post hoc and since baseline nausea may not have been considered I do not believe this analysis is valid for our consideration.

**Table 37** Sustained Nausea Free, Trial MT100-306 and Trial MT100-308

	MT100-306				MT100-308		
	MT100 1 Tablet N=138	MT100 2 Tablets N=142	Sumatriptan 50 mg N=129	Placebo N=137	MT100 1 Tablet N=332	Sumatriptan 50 mg N=340	Placebo N=341
Sustained Nausea Free n(%)	64 (46.4)	72 (50.7)	52 (40.3)	50 (36.5)	105 (31.6)	108 (31.8)	72 (21.1)
p-value	0.048	0.019	0.581		<0.001	<0.001	

Adapted from sponsor tables 19.7, 19.8 ISE.pdf  
Analyzed using logistical regression with baseline nausea and site as covariates

In summary, I do not believe the sponsor has shown convincing evidence of efficacy for MT100 in the treatment of nausea associated with migraine in trials MT100-306 and MT100-308. Although the comparison of the proportion of patient reporting nausea at 2 hours in trial MT100-306 did demonstrate statistical significance between MT100 and placebo the results were not very robust (p=0.049) and the comparison of mean nausea intensity at 2 hours was not statistically different between cohorts (p≥0.122). Similarly in trial MT100-308 the comparison of the proportion of subjects reporting nausea at 2 hours was not statistically different between MT100 and placebo (p=0.980) nor was the comparison of mean nausea intensity at 2 hours (p=0.595). This lack of consistent evidence of efficacy for this very important associated symptom in my opinion should at best result in granting a limited claim of efficacy for migraine. Language such as “for the pain of migraine” should be considered, assuming we consider the factorial studies as demonstrating efficacy.

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### ***Photophobia***

The following table summarizes the sponsor's analysis of the proportion of subjects reporting photophobia at various times. As is customary in the Division I give added emphasis to the 2 hour timepoint since this is the timepoint for the primary endpoint and the results after 2 hours may be confounded by the use of rescue medication (rescue restricted until 4 hours in trial MT100-306). As demonstrated in the table a single tablet of MT100 was superior to placebo in the proportion of patients reporting photophobia at 2 hours in trials MT100-306 (p=0.002) and MT100-308 (p=0.044). In trial MT100-306 two tablets of MT100 was numerically better than a single tablet of MT100 (45.1% vs. 47.1%) and superior to placebo (p<0.001) in the proportion of patients reporting photophobia at 2 hours. In both trials there were no statistical differences between MT100 and sumatriptan for the proportion of subjects reporting photophobia at 2 hours. These findings support the statement that MT100 is effective in the treatment of photophobia associated with migraine.

**Table 38** Proportion of Subjects Reporting Photophobia at Various Timepoints

	N	0 hrs	0.5 hrs	1.0 hrs	1.5 hrs	2 hrs	2.5 hr	3 hrs	4 hrs
<b>MT100-306</b>									
MT100 x 1	138	111 (80.4)	106 (76.8)	98 (71.0)	76 (55.1)	65 (47.1)	55 (39.9)	47 (34.1)	45 (32.6)
MT100 x 2	142	117 (82.4)	114 (80.3)	102 (71.8)	78 (54.9)	64 (45.1)	52 (36.6)	45 (31.7)	41 (28.9)
Sumatriptan	129	107 (82.9)	101 (78.3)	86 (66.7)	63 (48.8)	50 (38.8)	47 (36.4)	41 (31.8)	34 (26.4)
Placebo	137	122 (89.1)	125 (91.2)	114 (83.2)	98 (71.5)	91 (66.4)	83 (60.6)	79 (57.7)	70 (51.1)
p-value									
1 MT100 vs. placebo			0.002	0.024	0.007	<b>0.002</b>	<0.001	<0.001	0.003
2 MT100 vs. placebo			0.015	0.033	0.006	<b>&lt;0.001</b>	<0.001	<0.001	<0.001
Sumatriptan vs. placebo			0.005	0.003	<0.001	<b>&lt;0.001</b>	<0.001	<0.001	<0.001
2 MT100 vs. sumatriptan			0.800	0.430	0.378	<b>0.354</b>	1.000	1.000	0.744
<b>MT100-308</b>									
MT100 x 1	332	272 (81.9)	275 (82.8)	240 (72.3)	205 (61.8)	182 (54.8)	181 (54.5)	173 (52.1)	166 (50.0)
Sumatriptan	340	288 (84.7)	289 (85.0)	270 (79.4)	232 (68.2)	190 (55.9)	181 (53.2)	170 (50.0)	165 (48.5)
Placebo	341	279 (81.8)	274 (80.4)	256 (75.1)	233 (68.3)	214 (62.8)	217 (63.6)	222 (65.1)	229 (67.2)
p-value									
1 MT100 vs. placebo			0.345	0.510	0.105	<b>0.044</b>	0.019	0.600	0.706
Sumatriptan vs. placebo			0.109	0.138	0.869	<b>0.087</b>	0.009	<0.001	<0.001
1 MT100 vs. sumatriptan			0.503	0.038	0.077	<b>0.783</b>	0.727	<0.001	<0.001

Source: Adapted from Sponsor tablet 52 and 28 study report 308.pdf, and Sponsor table 45 study report 306.pdf  
Analysis done by CMH test with site as strata.

### ***Phonophobia***

The following table summarizes the sponsor's analysis of the proportion of subjects reporting phonophobia at various times. As is customary in the Division I give added emphasis to the 2 hour timepoint since this is the timepoint for the primary endpoint and the results after 2 hours may be confounded by the use of rescue medication (rescue restricted until 4 hours in trial MT100-306). As demonstrated in the table a single tablet of MT100 was numerically but not statistically superior to placebo in both studies for the proportion of patients reporting phonophobia at 2 hours (p=0.062 trial MT100-306; p=0.079 trial MT100-308). However in both trials this comparison reached the threshold for significance from 2.5 hours onward although results after hour 2 may be confounded by use of rescue medication. In trial MT100-306 two tablets of MT100 was superior to placebo in the proportion of patients reporting phonophobia at 2 hours (p=0.027).

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**Table 39** Proportion of Subjects Reporting Phonophobia at Various Timepoints

	N	0 hrs	0.5 hrs	1.0 hrs	1.5 hrs	2 hrs	2.5 hr	3 hrs	4 hrs
<b>MT100-306</b>									
MT100 x 1	138	102 (73.9)	99 (71.7)	84 (60.9)	72 (52.2)	60 (43.5)	47 (34.7)	39 (28.3)	36 (26.1)
MT100 x 2	142	118 (83.1)	114 (80.3)	94 (66.2)	71 (50.0)	59 (41.6)	51 (35.9)	46 (32.4)	42 (29.6)
Sumatriptan	129	100 (77.5)	95 (73.6)	78 (60.5)	57 (44.2)	41 (31.8)	37 (28.7)	34 (26.4)	31 (24.0)
Placebo	137	114 (83.2)	114 (83.2)	100 (73.0)	85 (62.0)	76 (55.5)	67 (48.9)	66 (48.2)	61 (44.5)
p-value									
1 MT100 vs. placebo			0.033	0.045	0.126	<b>0.062*</b>	0.017	0.001	0.002
2 MT100 vs. placebo			0.633	0.270	0.057	<b>0.027*</b>	0.038	0.010	0.014
Sumatriptan vs. placebo			0.080	0.041	0.005	<b>&lt;0.001</b>	0.001	<0.001	<0.001
2 MT100 vs. sumatriptan			0.248	0.394	0.403	<b>0.124</b>	0.254	0.340	0.373
<b>MT100-308</b>									
MT100 x 1	332	266 (80.1)	262 (78.9)	220 (66.3)	191 (57.5)	169 (50.9)	171 (51.5)	165 (49.7)	165 (48.5)
Sumatriptan	340	280 (82.4)	281 (82.7)	250 (73.5)	211 (62.1)	173 (50.9)	168 (49.4)	165 (48.5)	161 (47.4)
Placebo	341	266 (78.0)	262 (76.8)	240 (70.4)	218 (63.9)	197 (57.8)	204 (59.8)	210 (61.6)	216 (63.3)
p-value									
1 MT100 vs. placebo			0.472	0.277	0.198	<b>0.079</b>	0.036	0.002	<0.001
Sumatriptan vs. placebo			0.055	0.319	0.098	<b>0.099</b>	0.011	0.001	<0.001
1 MT100 vs. sumatriptan			0.202	0.037	0.729	<b>0.975</b>	0.606	0.798	0.863

Source: Adapted from Sponsor tablet 53 and 28 study report 308.pdf, and Sponsor table 46 study report 306.pdf

Analysis done by CMH test with site as strata.

\*The Agency's statistician calculates p=0.053 for phonophobia at 2 hours (MT100 vs. placebo) and p=0.0201 (MT100 X 2 vs. placebo). This does not alter my conclusions.

Since phonophobia responses were collected as a dichotomous variable the sponsor did not analyze phonophobia intensity. However as with nausea the sponsor conducted a post hoc analysis of sustained phonophobia free (see following table). As demonstrated in the table the proportion of subjects with sustained phonophobia free was not significantly different from placebo in trial MT100-306 (p=0.145) although in trial MT100-308 this comparison was significant (p<0.004). I believe sustained responses that demonstrate no difference from placebo at 2 hours is of questionable clinical relevance. Overall I do not believe these studies support the statement that MT100 is effective in the treatment of phonophobia associated with migraine.

**Table 40** Sustained Phonophobia Free, Trial MT100-306 and Trial MT100-308

	<b>MT100-306</b>				<b>MT100-308</b>		
	MT100 1 Tablet N=138	MT100 2 Tablets N=142	Sumatriptan 50 mg N=129	Placebo N=137	MT100 1 Tablet N=332	Sumatriptan 50 mg N=340	Placebo N=341
Sustained Phonophobia Free n(%)	50 (36.2)	69 (48.6)	58 (45.0)	36 (26.3)	97 (29.2)	106 (31.2)	69 (20.2)
p-value	0.145	<0.001	0.002		0.004	<0.001	

Source: Adapted from sponsor tables 19.11, 19.12 ISE.pdf

Analyzed using logistical regression with baseline nausea and site as covariates

### ***Vomiting***

Too few subjects in trial MT100-306 and MT100-308 experienced vomiting over the 24 hour period to make meaningful treatment comparisons.

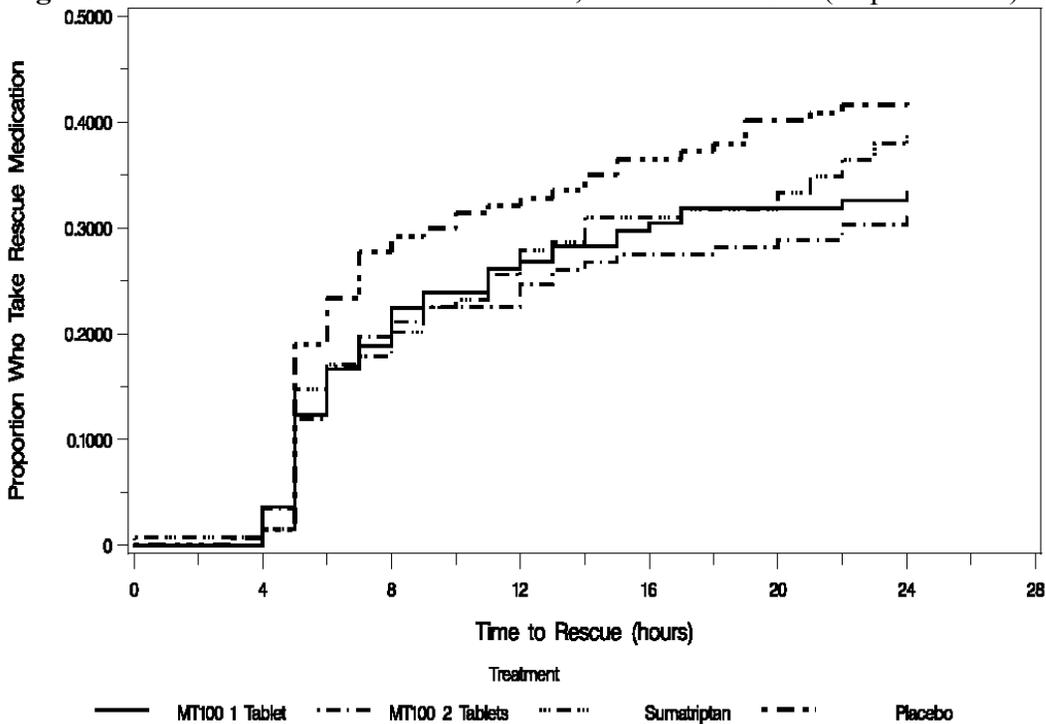
### **Time to Use of Rescue Medication**

The estimated proportion of subjects requiring rescue medication over the 24-hour period is displayed in the following 2 figures.

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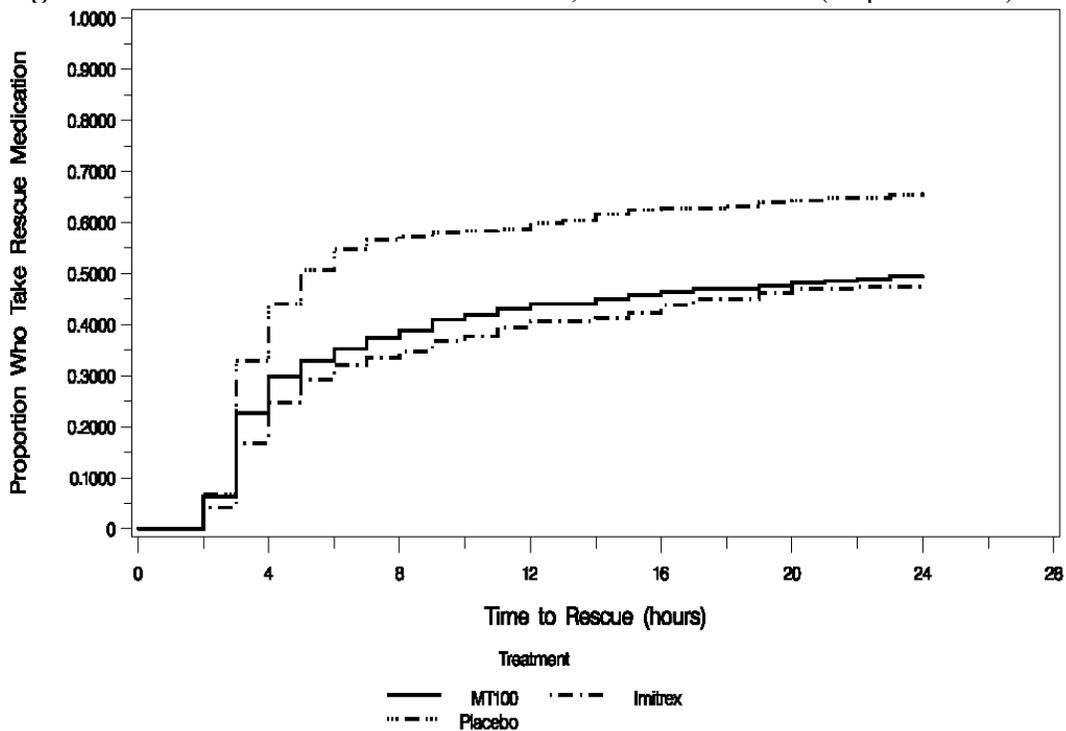
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**Figure 1** Time to Use of Rescue Medication; Trial MT100-306 (Kaplan Meier)



Source: 1 Sponsor figure 4, ise.pdf, page 49

**Figure 2** Time to Use of Rescue Medication; Trial MT100-308 (Kaplan Meier)



Source: 2 Sponsor figure 5, ise.pdf, page 50.

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The sponsor states in the ISE that in study MT100-306, subjects who had received either MT100 (single tablet) or sumatriptan used rescue medication later than did those who had been treated with placebo. However as demonstrated in the following table the mean time to the use of rescue medication was dramatically earlier for subjects using MT100 (1 tablet 9.39 hours, 2 tablets 11.07 hours) and sumatriptan (13.57 hours) than subjects using placebo (15.71 hours). Likewise in the ISE the sponsor states that in study MT100-308, both active treatment groups demonstrated significantly longer time to use of rescue medication than placebo ( $p < 0.001$ ). However as demonstrated in the following table the mean time to rescue medication for all treatment groups was tightly clustered between 8.16 to 8.86 hours.

As demonstrated in the table a smaller proportion of subjects taking a single tablet of MT100 required the use of rescue medication compared to placebo in trial MT100-306 (33.3% vs. 42.3% respectively) and MT100-308 (49.7% vs. 65.7% respectively).

**Table 41** Time to Rescue using Kaplan Meier Method, ITT Population

	MT100-306				MT100-308		
	MT100 1 Tablet N=138	MT100 2 Tablets N=142	Sumatriptan 50 mg N=129	Placebo N=137	MT100 1 Tablet N=332	Sumatriptan 50 mg N=340	Placebo N=341
Number who used rescue (%)	46 (33.3)	44 (31.0)	50 (38.8)	58 (42.3)	165 (49.7)	163 (47.9)	224 (65.7)
Mean time to rescue (SD) hrs.	9.39 (1.20)	11.07 (1.59)	13.57 (1.39)	15.71 (1.87)	8.48 (0.81)	8.86 (0.86)	8.16 (0.98)
p-value*	0.172	0.022	0.290		<0.001	<0.001	

\*compared to placebo, comparisons were done with log-likelihood methods  
Source: Adapted from Sponsor table 49, 306.pdf and table 56, 308.pdf.

### **Time to Relapse in Responders**

The following table summarizes the proportion of subjects relapsing after initial response at 2 hours and the comparisons of mean time to relapse in trial MT100-306 and MT100-308. Time to relapse is defined as the time interval from 2 hours post dose in responders to the time of pain score of 2 or 3 or the use of rescue medication. As demonstrated in the table more subjects on a single dose of MT100 relapsed after responding at 2 hours than subjects taking placebo (35.6% vs. 25.0%) in trial MT100-306. Opposite findings was seen in trial MT100-308 where 32.9% of subjects on MT100 (single dose) relapsed compared to 45.0% of subjects on placebo. In trial MT100-308 actively treated subjects had a slightly later mean time to relapse then subjects on placebo (8.13 hours MT100, 9.14 hours sumatriptan vs. 7.48 hours placebo). Results in trial MT100-306 were quit variable for the comparison of mean time to relapse (MT100 single dose 8.72 hours, MT100 double dose 12.29 hours, sumatriptan 11.81 hours vs. placebo 10.40 hours).

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**Table 42** Time to Relapse in 2 Hour Responders using Kaplan Meier Method, ITT Population

	MT100-306				MT100-308		
	MT100 1 Tablet N=138	MT100 2 Tablets N=142	Sumatriptan 50 mg N=129	Placebo N=137	MT100 1 Tablet N=332	Sumatriptan 50 mg N=340	Placebo N=341
Responders (%)	73	83	69	40	146	161	109
Relapse (%)	26 (35.6)	17 (20.5)	27 (39.1)	10 (25.0)	48 (32.9)	51 (31.7)	49 (45.0)
Mean Time (hrs) to relapse (SD)	8.72 (1.09)	12.29 (1.85)	11.81 (1.30)	10.40 (2.21)	8.13 (0.78)	9.14 (0.84)	7.48 (0.90)
p-value	0.281	0.407	0.662		0.064	0.011	

\*compared to placebo, comparisons were done with log-likelihood methods  
Source: Adapted from Sponsor table 48, 306.pdf and table 55, 308.pdf.

In summary there was no consistent evidence of benefit for a single tablet of MT100 compared to placebo as assessed by the comparison of mean time to relapse in 2 hour responders and the proportion of responders reporting a relapse.

### **Meaningful pain relief**

In trial MT100-306 the sponsor evaluated the time to meaningful relief. Meaningful relief is defined as the time interval from baseline to the time subjects reported meaningful pain relief within the first 4 hours. Meaningful relief was not assessed in trial MT100-308. As demonstrated in the following table a numerically higher proportion of subjects randomized to a single tablet of MT100 reported meaningful relief compared to placebo in trial MT100-306 (52.2% vs. 41.6%) however this did not reach the level of statistical significance (p=0.111). Likewise a comparison of the distribution of time to meaningful relief for the subjects randomized to a single tablet of MT100 and placebo also failed to reach the level of statistical significance (p=0.890).

**Table 43** Time to Meaningful Relief within 4 Hours

	MT100-306			
	MT100 1 Tablet N=138	MT100 2 Tablets N=142	Sumatriptan 50 mg N=129	Placebo N=137
Number with meaningful relief (%)	72 (52.2)	91 (64.1)	74 (57.4)	57 (41.6)
p-value*	0.111	<0.001	0.011	
Mean time (SD) in min.	120.6 (57.71)	127 (53.50)	119.4 (63.32)	123.2 (57.31)
Median	120.0	120.0	105.0	105.0
p-value#	0.890	0.549	0.481	

\*compared to placebo, Proportions analyzed using CMH test with pooled site as strata  
#compared to placebo, Distribution of time compared using Wilcoxon Rank Sum Test  
Source: Adapted from Sponsor table 40, 306.pdf and table

In summary there was no significant difference between subjects randomized to a single tablet of MT100 or placebo for the proportion of subjects reporting meaningful relief within 4 hours and the time to meaningful relief in trial MT100-306.

### **Pain Intensity Difference**

In trial MT100-306 pain response at selected time points was assessed using Pain Intensity Difference (PID), Sum of Pain Intensity Differences (SPID) and Total Pain Relief (TOTPAR). In

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trial MT100-308 pain response at selected time points was assessed by PID and SPID. Pain Intensity Difference (PID) is defined as the difference from baseline in pain score at any timepoint. Sum of Pain Intensity Differences (SPID) is defined as the sum of the pain intensity score difference over different periods from baseline. Total Pain Relief (TOTPAR) is defined as the sum of pain relief scores at each timepoint, adjusted for the interval between assessments. The sponsor conducted a post hoc analysis using ANOVA with treatment and center as fixed effects to test the differences in mean pain relief at 2 hours after dosing.

The following table summarizes the sponsor's results of PID, SPID and TOTPAR for selected time points up to 4 hours. Additional time points up to 24 hours can be found in the original study reports. As demonstrated in the table there was a significant difference, compared to placebo, favoring a single tablet of MT100 for mean PID starting as early a 1 hour (p=0.007) in trial MT100-306 and 2 hours (p=0.001) in trial MT100-308. Likewise there was a significant difference favoring a single tablet of MT100 for mean SPID starting at 1 hours in trial MT100-306 (p=0.045) and 2 hours in trial MT100-308 (p=0.026). Finally, subjects randomized to a single tablet of MT100 had a significantly higher TOTPAR compared to placebo in trial MT100-306 starting at 2 hours (p=0.013).

**Table 44** Pain Intensity Difference, Trial MT100-306 and MT100-308

		Trial MT100-306				Trial MT100-308			
		1.0 hrs	2 hrs	3 hrs	4 hrs	1.0 hrs	2 hrs	3 hrs	4 hrs
Mean PID	MT100 x 1	0.54	1.04	1.25	1.36	0.35	0.81	0.96	0.97
	MT100 x 2	0.46	1.07	1.32	1.43				
	Sumatriptan	0.52	1.02	1.20	1.39	0.29	0.88	1.06	1.16
	Placebo	0.29	0.65	0.82	0.95	0.27	0.54	0.65	0.68
<b>p-value MT100 x 1 vs. placebo*</b>		<b>0.007</b>	<b>0.001</b>	<b>0.001</b>	<b>0.002</b>	<b>0.212</b>	<b>0.001</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>
Mean SPID	MT100 x 1	0.24	1.10	2.30	3.64	0.14	0.80	1.72	2.70
	MT100 x 2	0.19	1.07	2.31	3.73				
	Sumatriptan	0.19	1.04	2.20	3.57	0.10	0.75	1.77	2.91
	Placebo	0.13	0.67	1.47	2.42	0.12	0.57	1.21	1.89
<b>p-value MT100 x 1 vs. placebo*</b>		<b>0.045</b>	<b>0.005</b>	<b>0.002</b>	<b>0.001</b>	<b>0.466</b>	<b>0.026</b>	<b>0.003</b>	<b>0.001</b>
Mean TOTPAR	MT100 x 1	0.40	1.76	3.66	5.81	Not evaluated			
	MT100 x 2	0.40	1.82	3.90	6.27				
	Sumatriptan	0.44	1.99	4.12	6.53				
	Placebo	0.28	1.24	2.58	4.14				
<b>p-value MT100 x 1 vs. placebo*</b>		<b>0.059</b>	<b>0.013</b>	<b>0.003</b>	<b>0.002</b>				

\*Analyzed using ANOVA with treatment and center as fixed effects (post hoc analysis)

Source: Adapted from Sponsor tables 38, 39, and 37 study report 306.pdf; tables 46 and 47 study report 308.pdf

In summary, a single dose of MT100 demonstrated significant benefit over placebo as assessed by PID, SPID and TOTPAR. Although it may be conceptually difficult to understand the clinical relevance of these calculated scores of pain their relevance lies in the fact that they support the sponsor's contention that a single dose of MT100 is effective in the treatment of pain associated with migraine.

### **Clinical disability**

In trial MT100-308 subjects assessed clinical disability through hour 24 using a 4 point scale with 0 equal to functioning normally to 3 equal to requiring bed rest. Trial MT100-306 did not

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assess this endpoint. The following table summarizes the proportion of subjects reporting any clinical disability at selected time points. As demonstrated in the table a significantly smaller proportion of subject randomized to MT100 reported any clinical disability starting at 2.5 hours after study drug administration ( $p=0.015$ ). There was no statistical difference between MT100 and placebo in the proportion of subjects reporting any clinical disability at 2 hours ( $p=0.118$ ).

**Table 45** Proportion of Subjects Reporting any Disability, Trial MT100-308.

	N	1.0 hrs	2 hrs	2.5 hrs	3 hrs	4 hrs
MT100 x 1 n(%)	332	136 (41.0)	119 (35.8)	119 (35.8)	130 (39.2)	140 (42.2)
Sumatriptan n(%)	340	173 (50.9)	124 (36.5)	126 (37.1)	122 (35.9)	128 (37.7)
Placebo n(%)	341	153 (44.9)	144 (42.2)	155 (45.5)	172 (50.4)	190 (55.7)
p-value (1 MT100 vs. placebo)		0.354	0.118	0.015	0.004	<0.001

Source: Adapted from sponsor table 57, study report 308.pdf  
Analyzed using CMH test with site as strata

### **Subpopulation Efficacy Analysis**

Due to the small number of male subjects enrolled in trials MT100-306 and MT100-308 the sponsor did not conduct a by-gender analysis on the primary endpoint results. Likewise due to the small number of participants greater than 55 years of age (<10%) the sponsor did not conduct a by-age analysis of the primary endpoint results.

The following table summarizes the sponsor's analysis of the primary efficacy endpoint, pain response at 2 hours, by baseline pain severity. As demonstrated a single tablet of MT100 and a single tablet of sumatriptan 50 mg produced significant relief in subjects reporting moderate pain at baseline in both trials ( $p<0.001$  trial MT100-306;  $p\leq 0.002$  trial MT100-308). However in trial MT100-308 a higher percentage subjects with moderate pain at baseline and receiving sumatriptan reported pain relief at 2 hours compared to subjects receiving MT100 (52.6% vs. 49.8%). This comparison was nearly statistically significant ( $p=0.07$ ). In trial MT100-306 there was very little difference in treatment effects between any of the actively treated cohorts. For subjects with severe pain at baseline, a single tablet of MT100 did not show any improvement over placebo in subjects reporting relief at 2 hours in both trials ( $p=0.313$  trial MT100-306;  $p=0.129$  trial MT100-308). Whereas a double dose of MT100 did demonstrate significance over placebo in trial MT100-306. The results for sumatriptan were mixed in subjects reporting severe pain at baseline with trial MT100-306 failing to demonstrate superiority ( $p=0.975$ ) and trial MT100-308 demonstrating superiority ( $p=0.025$ ) over placebo. Trial MT100-308 did not demonstrate any significant difference between a single dose of MT100 compared to placebo for 2 hour relief in subjects with severe pain at baseline.

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**Table 46** 2-Hour Pain Response by Baseline Pain Severity, Trial MT100-306 and MT100-308

	MT100-306				MT100-308		
	MT100 1 Tablet N=138	MT100 2 Tablets N=142	Sumatriptan 50 mg N=129	Placebo N=137	MT100 1 Tablet N=332	Sumatriptan 50 mg N=340	Placebo N=341
<b>Moderate Pain at Baseline</b>							
Total subjects	76	83	85	69	205	192	208
<b>2 hr Pain Response n(%)</b>	48 (63.2)	54 (65.1)	55 (64.7)	19 (27.5)	102 (49.8)	101 (52.6)	74 (35.6)
<b>p-value vs. placebo</b>	<0.001	<0.001	<0.001		0.002	0.001	
<b>p-value vs. sumatriptan</b>		0.927			0.077		
<b>Severe Pain at Baseline</b>							
Total subjects	61	57	44	68	127	148	133
<b>2 hr Pain Response n(%)</b>	24 (39.3)	29 (50.9)	14 (31.8)	21 (30.9)	44 (34.7)	60 (40.5)	35 (26.3)
<b>p-value vs. placebo</b>	0.313	0.021	0.975		0.129	0.025	
<b>p-value vs. sumatriptan</b>		0.045			0.241		

Source: Adapted from sponsor tables 34 and 35 study report 306.pdf; tables 39, 39a, 40, 40a study report 308.pdf.

In summary, a single tablet of MT100 appears to be very effective in subjects reporting moderate pain at baseline but not in subjects reporting severe pain at baseline. In both trials a single tablet of sumatriptan was numerically superior to a single tablet of MT100 for pain relief at 2 hours in subjects reporting moderate pain at baseline. A single tablet of MT100 did not provide significant relief compared to placebo in subjects reporting severe pain at baseline in both studies.

#### 6.3.3.1 Overall summary of trials MT100-306 and MT100-308

The following table briefly summarizes the results of the analyses of the essential and pre-stated endpoints discussed above from trials MT100-306 and MT100-308. For the purposes of this summary I focus solely on the results of the comparison of MT100 to placebo. As demonstrated in the table MT100 was shown to be effective in the treatment of headache pain associated with migraine in trial MT100-306 and MT100-308 as demonstrated by the positive results for the primary endpoint (2 hour pain response) and most secondary pain endpoints (2 hour pain freedom, sustained pain response). Trial MT100-308 may have been over powered for the endpoint of 2 hour headache response. Unfortunately the results of the analyses for the proportion of patients reporting an associated symptom at 2 hours was not as consistent or robust. In trial MT100-306 a single tablet of MT100 demonstrated significant efficacy for nausea as determined by the proportion of subjects reporting nausea at 2 hours however this was not replicated in trial MT100-308. Additionally the analysis of mean nausea intensity at two hours failed to demonstrate significance in both trials. In trial MT100-306 and MT100-308 a single tablet of MT100 demonstrated significant efficacy for the endpoint photophobia at 2 hours. Finally in trial MT100-306 and MT100-308 a single tablet of MT100 failed to provide significant benefit for the proportion of subjects reporting phonophobia at 2 hours. As previously discussed many other secondary endpoints were not supportive of efficacy.

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**Table 47** Brief Summary of Results from Trial MT100-306 and MT100-308\*#.

	MT100-306			MT100-308	
	MT100 1 Tablet N=138	MT100 2 Tablets N=142	Sumatriptan 50 mg N=129	MT100 1 Tablet N=332	Sumatriptan 50 mg N=340
<b>2 hr Pain Response (primary endpoint)</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>0.001</b>	<b>&lt;0.001</b>
2 hr Pain Free	<b>0.031</b>	<b>0.014</b>	<b>0.001</b>	<b>0.047</b>	<b>0.033</b>
Sustained Pain Response	<b>0.029</b>	<b>&lt;0.001</b>	0.055	<b>&lt;0.001</b>	<b>&lt;0.001</b>
Sustained Pain Freedom	0.201	<b>0.022</b>	0.080	<b>0.012</b>	<b>0.031</b>
Nausea at 2 hours	<b>0.049</b>	0.054	0.880	0.980	0.489
Mean Nausea at 2 hours	0.177	0.122	0.716	0.595	0.437
Photophobia at 2 hours	<b>0.002</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>0.044</b>	0.087
Phonophobia at 2 hours	0.062	<b>0.027</b>	<b>&lt;0.001</b>	0.079	0.099
Mean Time to Rescue	0.172	<b>0.022</b>	0.290	<b>&lt;0.001</b>	<b>&lt;0.001</b>
Mean Time to Relapse	0.281	0.407	0.662	0.064	<b>0.011</b>
Proportion with meaningful relief	0.111	<b>&lt;0.001</b>	<b>0.011</b>	NA	NA
Mean time to meaningful relief	0.890	0.549	0.481	NA	NA
Mean PID at 2 hours	<b>0.001</b>	NC	NC	<b>0.001</b>	NC
Mean SPID at 2 hours	<b>0.005</b>	NC	NC	<b>0.026</b>	NC
Mean TOTPAR at 2 hours	<b>0.013</b>	NC	NC	NA	NA
Disability at 2 hours	NA	NA	NA	0.118	NC

NA= not assessed, NC= not calculated,

\*All values are in comparison to placebo.

# Bolding denotes statistical significance

In summary Trials MT100-306 and MT100-308 clearly demonstrate benefit for the pain of migraine however there was inconsistent evidence for effectiveness for the associated symptoms of migraine. As discussed earlier the sponsor failed to adequately demonstrate equivalence/non-inferiority for a single tablet of MT100 and sumatriptan 50 mg. If we were to rely strictly on these two studies alone for the approval of MT100 in the treatment of migraine, at the most I would recommend the approval of MT100 only for the pain of migraine and not the migraine syndrome.

#### 6.3.4 Trial MT100-303: MT100 as Rescue Medication

A total of 427 subjects participated in trial MT100-303. A description of the trial design can be found in section 4.2.3.1 of this review. In summary MT100-303 was a randomized, double blind, placebo controlled study. The primary objective of the study was to evaluate the efficacy of MT100 for acute migraine. A secondary objective was to evaluate the benefit of a second dose of MT100 at 2 hours in subjects that did not respond to an initial dose of MT100 (MT100 1<sup>st</sup> dose non-responders). Each subject was initially randomized to either MT100 (n=318), or placebo (n=109). Subjects initially receiving MT100 and not responding at 2 hours were then rerandomized to either a second dose of MT100 or placebo. Subjects initially randomized to placebo and not responding at 2 hours were all given MT100 (placebo non-responders). The final cohorts were as follows (1) MT100 single dose (n=133), (2) MT100 followed by placebo at 2 hours (n=94), (3) MT100 followed by MT100 at 2 hours (n=90), (4) placebo followed by MT100 at 2 hours (n=74), placebo single dose (n=34). Amendment 2 of the protocol stipulates separate primary endpoints for 2 different populations (all randomized subjects and re-randomized MT100 1<sup>st</sup> dose non-responders). The primary endpoint for subjects initially randomized to MT100 or placebo was 2-hour sustained pain response. The primary endpoint for MT100 1<sup>st</sup> dose non-responders was 4-hour sustained pain response (i.e., 2 primary endpoints). The study was powered primarily to

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provide enough subjects to detect a significant difference in the second primary endpoint. The problem with sustained response endpoints was previously discussed in this review.

The following table summarizes the analysis (Sponsor's and Agency statistician's) of the first primary endpoint (sustained pain response starting at 2 hours) for the initial randomization (MT100 or placebo). The sponsor's analysis demonstrates a nominally significant higher proportion of subjects treated with an initial dose of MT100 reported sustained pain response than subjects treated with placebo, 33.8% vs. 24.1% respectively (p=0.048). However the Agency statistician's results are not consistent with the sponsors. The Agency statistician reports that she derived a p-value of 0.0619 for this comparison. The Agency statistician states the sponsor's analysis failed to include all the covariates (center, baseline severity and gender) described in the prestated analysis plan (amendment 2 of protocol). Likewise the Agency statistician points out the data analysis plan does not include a correction factor for the multiple primary endpoints. It should be noted that both the study report and the ISE presents the results of the analysis of 4-hour sustained pain response in MT100 1<sup>st</sup> dose non-responders as a secondary endpoint. For my review I have elevated this endpoint back to the position of co-primary.

**Table 48** Sustained Pain Response Starting at 2 hour, Trial MT100-303\*.

	<b>Placebo N= 108</b>	<b>MT100 N= 317</b>	<b>p-value</b>
<b>Sustained Pain Response (excluding pain free)</b>	15 (13.9%)	50 (15.8%)	
<b>Sustained Pain Free</b>	11 (10.2%)	57 (18.0%)	
<b>Total Sustained pain response starting at 2 hours (any response).</b>	26 (24.1%)	107 (33.8%)	0.048 <b>(0.0619)<sup>†</sup></b>

\* Analyzed using ordered logistic regression, ITT, LOCF

<sup>†</sup>: Agency Statistician's results using ordered logistical regression controlling for center, baseline severity and gender.

Source: Sponsor table 5, study report 303.pdf

The following table summarizes the sponsor's subset analysis of the first primary endpoint by baseline nausea and pain severity. As demonstrated in the table a single tablet of MT100 appears to work best in subjects with moderate pain and no nausea at baseline (i.e., less severe migraineurs). The study had too few male subjects or non-Caucasians to make a by-gender or by-race subset analysis meaningful.

**Table 49** Sustained Pain Response by Baseline Nausea/Pain Intensity

	<b>Placebo N= 108</b>	<b>MT100 N= 317</b>	<b>p-value</b>
<b>Total Sustained Pain Response</b>			
<b>With baseline nausea</b>	12 (23.1%)	47 (30.1%)	0.551
<b>Without baseline nausea</b>	14 (25.0%)	60 (37.3%)	0.051
<b>Moderate pain at baseline</b>	16 (27.6%)	71 (38.6%)	0.028
<b>Severe pain at baseline</b>	10 (20.0%)	35 (26.5%)	0.848

Source: Sponsor tables 6 and 7 study report 303.pdf

The following table summarizes the sponsor's analysis of the second primary endpoint for trial MT100-303. As demonstrated, among the MT100 1<sup>st</sup> dose non-responders (n=184), there was no statistical difference between subjects randomized to a second dose of MT100 (n=90) or placebo (n=94) for sustained response starting at 4 hours (2 hours after 2<sup>nd</sup> dose of

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study medication). The proportion of subjects reporting sustained response after receiving a second dose of MT100 or placebo was 35.6% and 29.8% respectively (p=0.198). Likewise a second dose of MT100 (MT100-MT100) did not provide significant benefit in MT100 1<sup>st</sup> dose non-responders compared to placebo (MT100-placebo) for the proportion of patient reporting pain relief at 4 hours (46.7% vs. 46.8% respectively, p=0.821). Similar findings were seen in subjects who initially did not respond to placebo.

**Table 50** Response at 4 hrs in MT100 1<sup>st</sup> Dose Non-Responders, Trial MT100-303

	<b>MT100-Placebo N=94</b>	<b>MT100-MT100 N=90</b>	<b>p-value</b>
<b>Sustained response at 4 hours</b>	28 (29.8%)	32 (35.6%)	0.198
<b>Pain Relief at 4 hours</b>	44 (46.8%)	42 (46.7%)	0.821

Source: Sponsor tables 41 and 45, study report 303.pdf

In summary the analysis of the two co-primaries fails to demonstrate any statistically significant benefit of MT100 over placebo for sustained response at 2 hours in all randomized subjects and sustained response at 4 hours in the subset of subjects not responding to MT100 at 2 hours.

The following table summarizes relevant secondary endpoints analyses for the first treatment period of trial MT100-303 (initial 2 hours). As demonstrated subjects initially randomized to MT100 had significantly more patients reporting pain relief at 2 hours (traditional primary endpoint) compared to placebo (p=0.021). This piece of information is consistent with other studies that have shown benefit of MT100 for pain response at 2 hours. The comparison of cohorts for pain relief reached the threshold for statistical significance as early as 1.25 hours. However a higher percentage of subjects who responded at 2 hours relapsed in the MT100 group compared to placebo (19.2% vs. 11.5%). Yet a higher percentage of placebo subjects required rescue medication compared to MT100 subjects (73.2% vs. 47.0%). Subjects randomized to MT100 were numerically but not statistically less likely to report nausea at 2 hours compared to placebo (p=0.07). However the comparison of cohorts for the incidence of nausea reached statistical significance at 1.75 hours (p=0.046), favoring MT100, thus showing benefit of MT100 for nausea at 1.75 hours but not 2.0 hours (traditional timepoint of interest). Subjects randomized to MT100 were statistically less likely to report photophobia at 2 hours compared to placebo (p=0.010). This comparison reached statistical threshold favoring MT100 as early as 1.75 hours (p=0.027). Subjects randomized to MT100 were less likely to report phonophobia at 2 hours compared to placebo (p=0.030). This comparison reached statistical threshold favoring MT100 as early as 1.5 hours (p≤0.027). Although this is not one of the pivotal trials these findings support the argument that MT100 is effective in the treatment of symptoms (nausea, photophobia, and phonophobia) associated with migraine.

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**Table 51** Selected Secondary Endpoints, Trial MT100-303; n(%)

	Placebo N=108	MT100 N=317	p-value
<b>Proportion of subjects reporting Pain Response</b>			
1.25 hour pain response	21 (19.4%)	93 (29.3%)	0.050
1.5 hour pain response	25 (23.2%)	110 (34.7%)	0.030
1.75 hour pain response	29 (26.9%)	125 (39.4%)	0.020
2.0 hour pain response	31 (28.7%)	132 (41.6%)	0.021
<b>Proportion of subjects reporting Pain Freedom</b>			
1.5 hour pain freedom	9 (8.3%)	29 (9.2%)	0.942
2.0 hour pain freedom	15 (13.9%)	67 (21.1%)	0.138
2.5 hour pain freedom*	19 (17.6%)	84 (26.5%)	0.091
3.0 hour pain freedom*	23 (21.3%)	107 (33.8%)	0.021
<b>Proportion of subjects reporting Nausea</b>			
1.5 hour nausea	45 (41.7%)	101 (31.9%)	0.052
1.75 hour nausea	42 (38.9%)	92 (29.0%)	0.046
2 hour nausea	41 (38.0%)	92 (29.0%)	0.070
<b>Proportion of subjects reporting Phonophobia</b>			
1.5 hour phonophobia	72 (66.7%)	173 (54.6%)	0.027
1.75 hour phonophobia	69 (63.9%)	162 (51.1%)	0.023
2.0 hour phonophobia	65 (60.2%)	152 (48.0%)	0.030
<b>Proportion of subjects reporting Photophobia</b>			
1.75 hour photophobia	72 (66.7%)	170 (53.6%)	0.021
2.0 hour photophobia	68 (63.0%)	153 (48.3%)	0.010
<b>Time to rescue (after initial dose)</b>			
Number who rescued (%)	79 (73.2%)	149 (47.0%)	
Mean time to rescue (hrs)	5.71	8.43	<0.001
<b>Time to Relapse in Responders at 2 Hours</b>			
Number who Relapse (%)	3 (11.5%)	24 (19.2%)	
Mean time to relapse (hrs)	7.00	7.35	0.250

Source: Sponsor table 29, 38, 39, 40, 48 and 47 study report 303.pdf.

Pain response/Associated Symptoms analyzed using CMH test with pooled study site as strata.

\* times after 2 hours may have been confounded by repeat rerandomized dosing.

In summary this study failed to demonstrate a significant difference between MT100 and placebo for sustained pain response at 2 hours in all randomized subjects, and sustained pain response at 4 hours in the subset of subjects not responding to the 1<sup>st</sup> dose of MT100. However this study does support the assertion MT100 (single tablet) is effective in the treatment of the associated symptoms of migraine (nausea, phonophobia, and photophobia). The efficacy of MT100 for the associated symptoms of migraine was demonstrated by the finding that a statistically smaller proportion of subjects reported these complaints following treatment with MT100 than in placebo starting as early as 1.5 hours for nausea, 1.5 hours for phonophobia and 1.75 hours for photophobia.

### 6.3.5 Other Controlled Trials

#### **MT100-401A**

A description of the trial design for MT100-401A can be found in section 4.2.3.1 of this review. Briefly MT100-401A was a double blind, randomized, placebo controlled study designed to evaluate the safety and efficacy of a two tablet dose of MT100 for the treatment of a single migraine in 343 subjects with a history of non-response to oral sumatriptan. Sumatriptan non-

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response was determined retrospectively as any subject who had an inadequate response (failure to reduce headache pain, return of headache pain within 24 hours, or requires additional medication) to sumatriptan tablets (dose not specified) in more than half of at least three treated attacks. Each subject was randomized to either 2 tablets of MT100 (n=171) or placebo (n=172).

The primary endpoint was the percent of subjects with sustained response starting at 2 hours. The problem with sustained response as a primary endpoint was previously discussed in this review. The following table summarizes the efficacy results from trial MT100-401A. As demonstrated a significantly higher proportion of subjects taking MT100 2 tablets reported sustained pain response starting at 2 hours compared to placebo (21.6% vs. 9.3%, p<0.001).

**Table 52** Sustained Pain Response, Trial MT100-401A

	<b>MT100 2 tablet N=171</b>	<b>Placebo N=172</b>	<b>p-value</b>
<b>Sustained Pain Free</b>	14 (8.2%)	9 (5.2%)	
<b>Sustained Pain Response</b>	37 (21.6%)	16 (9.3%)	
<b>Sustained Non-Responders</b>	120 (70.2%)	147 (85.5%)	
<b>Ordered Logistic Regression</b>			<0.001

Sustained pain response was analyzed using ordered logistic regression with baseline pain and site as covariates. Sustained pain response does not include sustained pain free.

Source: Adapted from Sponsor Table 28, study report 401A.pdf, page 101.

The following table briefly summarizes the sponsor's analysis of relevant secondary endpoints. As demonstrated a statistically greater percentage of subjects randomized to 2 tablets of MT100 reported pain relief at 2 hours compared to placebo (p<0.001). As previously stated this is a standard endpoint frequently designated as primary in most migraine studies and has clinical validity. A statistically smaller proportion of patients randomized to MT100 (2 tablets) reported photophobia and phonophobia at 2 hours compared to placebo (p=0.003 and 0.009 respectively). The proportion of subjects reporting nausea at 2 hours was not statistically different between cohorts although there was a strong numerical trend favoring MT100 (44.4% vs. 61.6%, p=0.062). At 3 hours this comparison did reach threshold for statistical significance however the results may have been confounded by rescue medication use. As shown in previous studies there appears to be a great deal of variability in the evidence of efficacy for MT100 in the treatment of nausea associated with migraine.

**Table 53** Secondary Endpoints, Trial MT100-401A

	<b>MT100 2 tablet N=171</b>	<b>Placebo N=172</b>	<b>p-value</b>
<b>2-hour pain response</b>	80 (46.8%)	48 (27.9%)	<0.001
<b>Proportion of subjects reporting nausea at 2 hours</b>	77 (45.0%)	95 (55.2%)	0.062
<b>Proportion of subjects reporting nausea at 3 hours*</b>	76 (44.4%)	106 (61.6%)	0.001
<b>Proportion of subjects reporting phonophobia at 2 hours</b>	88 (51.5%)	112 (65.1%)	0.009
<b>Proportion of subjects reporting photophobia at 2 hours</b>	94 (55.0%)	121 (70.4%)	0.003

Source: Sponsor tables 36, 44, 48, and 49 study report 401A.pdf

Pain response and associated symptoms analyzed using CMH test with site as strata.

\*May have been confounded by rescue medication

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In summary this trial demonstrates that 2 tablets of MT100 is effective in the treatment of migraine pain and the associated symptoms of phonophobia and photophobia. There was a strong trend towards significance for the treatment of nausea at 2 hours. In my opinion the trial has limited usefulness relative to making claims against sumatriptan since it did not prospectively determine sumatriptan nonresponsiveness, did not include a single tablet MT100 cohort, and did not specify what dose of sumatriptan was historically not satisfactory to the subject. The results of this study also suggest patients will have a high preponderance to use rescue medication since the sustained response rate was only 21.6% and the pain response was only 46.8% for two tablets of MT100. Although it is difficult to compare across studies, controlled clinical trials described in the Imitrex label, using Imitrex Tablets 100 mg had a 2 hour response rate between 56 to 62% and controlled studies using Imitrex Injection 6 mg had a 2-hour response rate between 81 to 82%. These results suggest that sumatriptan (and probably other triptans) is a better first choice for migraine subjects without any contraindications to triptans.

### **MT100-402**

A description of the trial design for MT100-402 can be found in section 4.2.3.1 of this review. Briefly this was double blind, randomized, placebo controlled study to evaluate the safety and efficacy of MT100 for treatment of an acute migraine in 238 subjects who are intolerant to 5-HT agonists or have significant cardiovascular risk factors. Each subject was randomized to 1 tablet of MT100 (n=118) or placebo (n=120). Originally 470 subjects were planned for enrollment however the sponsor states they had difficulties with enrollment. Intolerance to triptans and cardiovascular risk factors were determined retrospectively. Documented intolerance to triptans included conditions such as chest pain or throat tightness with triptan use or one of the following contraindications: cardiovascular disease, cerebrovascular accidents, transient ischemia attacks, peripheral vascular disease or ischemic bowel syndrome. Excluding cardiovascular risk factors included age over 45 years with 2 or more known cardiac risk factors (hypertension, hypercholesterolemia, diabetes, smoking, postmenopausal, and/or strong family history of CAD).

The primary endpoint was 2 hour sustained pain response defined as no or mild pain at 2 hour, no use of rescue medication through hour 24 and no return of moderate to severe pain. The problem with sustained response as a primary endpoint was previously discussed in this review. The following table summarizes the primary endpoint efficacy results from trial MT100-402. As demonstrated a significantly higher proportion of subjects reported sustained pain response starting at 2 hours compared to placebo (p=0.002).

**Table 54** Sustained Pain Response, Trial MT100-402

	<b>MT100 1 tablet N=116</b>	<b>Placebo N=120</b>	<b>p-value</b>
<b>Sustained Pain Free</b>	22 (19.0%)	14 (11.7%)	
<b>Sustained Pain Response</b>	25 (21.6%)	10 (8.3%)	
<b>Sustained Non-Responders</b>	69 (59.5%)	96 (80.0%)	
<b>Ordered Logistic Regression</b>			0.002

Sustained pain response was analyzed using ordered logistic regression with baseline pain and site as covariates. Sustained pain response does not include sustained pain free.

Source: Adapted from Sponsor Table 28, study report 402.pdf, page 101.

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The following table briefly summarizes the sponsor's analysis of relevant secondary endpoints. As demonstrated a statistically greater percentage of subject randomized to a single tablet of MT100 reported pain relief at 2 hours compared to placebo ( $p < 0.001$ ). As previously stated this is a standard endpoint frequently designated as primary in most migraine studies and has clinical validity. At 2 hours there was no statistical difference between MT100 and placebo for the proportion of subjects reporting nausea ( $p = 0.141$ ), phonophobia ( $p = 0.070$ ), or photophobia ( $p = 0.446$ ). None of these comparisons reached the threshold for significance prior to 2 hours for any of the associated symptoms ( $p \geq 0.119$ ). At three hours these comparisons demonstrated improved efficacy and met or nearly met the threshold for significance however these results may have been confounded by the use of rescue. As previously discussed the efficacy of MT100 in the treatment of associated symptoms has been quite variable in the studies conducted for this NDA.

**Table 55** Secondary Endpoints, Trial MT100-402

	<b>MT100 1 tablet N=116</b>	<b>Placebo N=120</b>	<b>p-value</b>
<b>2-hour pain response</b>	63 (54.3%)	39 (32.5%)	<0.001
<b>2-hour pain freedom</b>	24 (20.7%)	16 (13.3%)	0.126
<b>Proportion of subjects reporting nausea at 2 hours</b>	40 (34.5%)	53 (44.2%)	0.141
<b>Proportion of subjects reporting nausea at 3 hours*</b>	38 (32.8%)	63 (52.5%)	0.003
<b>Proportion of subjects reporting phonophobia at 2 hours</b>	56 (48.3%)	72 (60.0%)	0.070
<b>Proportion of subjects reporting phonophobia at 3 hours*</b>	46 (39.7%)	75 (62.5%)	<0.001
<b>Proportion of subjects reporting photophobia at 2 hours</b>	70 (60.3%)	79 (65.8%)	0.446
<b>Proportion of subjects reporting photophobia at 3 hours*</b>	61 (52.6%)	78 (65.0%)	0.060
<b>Mean time to rescue (hrs)</b>	10.80	7.57	<0.001

Source: Sponsor tables 35, 40, 43, 47, 48 and 51 study report 402.pdf

Pain response and associated symptoms analyzed using CMH test with site as strata.

\*May have been confounded by rescue medication

In summary this study support the assertion MT100 (single tablet) is effective in the treatment of pain of migraine but not the associated symptoms of migraine (nausea, phonophobia, and photophobia) in subjects unable to take triptan medications. The efficacy of MT100 for pain relief was demonstrated by a greater proportion of patients reporting sustained pain response starting at 2 hours (primary endpoint,  $p = 0.002$ ) as well as the more traditional endpoint of pain response at 2 hours ( $p < 0.001$ ). However the efficacy of MT100 for associated symptoms of migraine was not demonstrated at any time prior to the use of rescue medication (2 hours).

### **MT100-307**

A description of the trial design for MT100-307 can be found in section 4.2.3.1 of this review. Briefly this was a double blind, randomized, placebo controlled study to evaluate the safety and efficacy of MT100 in the treatment of migraine prodrome in 142 subjects. Each subject was randomized to either MT100 ( $n = 70$ ) or placebo ( $n = 72$ ). The study consisted of a 4 week baseline period during which migraine symptoms (including prodrome) and frequency were established. This was followed by a 4 week treatment period during which eligible subjects treated migraine

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prodrome syndrome with randomized drug. In order to be eligible for treatment subjects had to experience 2 to 6 migraines during their baseline period, were able to predict at least 50% of these migraines from their prodrome symptoms, and all migraines had to be preceded by a prodrome. The primary endpoint was the number of prodromes treated with study medication that resulted in an absence of moderate to severe pain and no use of rescue medication within 24 hours of study drug administration. As previously stated the sponsor intended this study to be exploratory and agrees with our assertion that migraine prodrome is a poorly defined entity. As demonstrated in the following table there was no significant difference between subjects on MT100 and subjects on placebo for the proportion of treated prodromes progressing to a migraine of moderate to severe pain intensity.

**Table 56** 1st Prodrome Treated Progressing to Migraine Within 24 hours

MT100 N=70	Placebo N=72	p-value
31 (44%)	32 (44%)	0.863

Source: sponsor table 7, study report 307.pdf, page 48  
Analyzed using CMH for the first prodrome event

Multiple secondary endpoints were included in the study however they are non-contributory to the approval of MT100 in the treatment of acute migraine and will not be discussed in this review.

#### 6.4 Efficacy Conclusions

The sponsor provides the following efficacy conclusions:

1. *The MT100 500/16 dose was a reasonable choice for development.*
2. *MT100 is an effective migraine treatment and is more effective than its components, metoclopramide hydrochloride and naproxen sodium.*
3. *The relative therapeutic gain of MT100 over naproxen alone is approximately 50%.*
4. *In subjects without nausea at baseline, the relative therapeutic gain over naproxen alone is approximately 100%.*
5. *A single one-tablet of MT100 is significantly superior to placebo and similar in efficacy to sumatriptan 50 mg.*
6. *The efficacy of MT100 appears to be dose-related with the two-tablet dose providing greater benefits over a one-tablet dose of MT100 or sumatriptan 50 mg.*

The following statements will address each of the final conclusions provided by the sponsor. This will be followed by additional comments.

1. As discussed in my review, trial MT100-201 supports the development of a fixed combination of naproxen 500 mg and metoclopramide 16 mg (MT100) for the treatment of acute migraine. Additionally trial MT100-202 demonstrated that a fixed combination of naproxen 1000 mg plus metoclopramide 8 mg was also beneficial however the sponsor has chosen not to pursue this combination at this time. I concur that MT100 (500/16) dose is a reasonable choice for development.
2. The two factorial studies (MT100-301 and MT100-304) clearly demonstrated that a single dose of MT100 is statistically superior to metoclopramide 16 mg as assessed by sustained pain response (primary endpoint,  $p < 0.001$ ) and 2 hour pain response ( $p < 0.001$ ). However trial MT100-301 and MT100-304 failed to demonstrate a significant difference between MT100 compared to naproxen for sustained pain response (primary endpoint,  $p = 0.077$  in trial

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MT100-301,  $p=0.063$  in trial MT100-304) and 2 hour pain response ( $p=0.665$  in trial MT100-301,  $p=0.143$  in trial MT100-304). The sponsor has previously been informed we consider trial MT100-301 to be a failed study. It should be noted the sponsor's analysis of trial MT100-304 demonstrated a nominally significant difference between MT100 and naproxen for sustained response ( $p=0.038$ ) however the Agency statistician reports the sponsor erroneously used equal weight for all stratum in their analysis using CMH statistics. Both the sponsor and the Agency statistician agree that MT100 failed to demonstrate significant benefit over naproxen as assessed by 2-hour pain response ( $p=0.143$ ). In a previous discussion with the sponsor we agreed that an almost positive factorial study (MT100-301) and a second positive factorial study (MT100-304) plus two positive pivotal trials would be acceptable evidence of efficacy. In my opinion the sponsor has failed to meet the requirements of the combination rule, which requires the demonstration of significant benefit from each component to the overall effect of the combination product. In this case the combination does not appear to provide any additional benefit of MT100 over naproxen relative to efficacy (sustained response or 2 hour pain response) and as discussed in my safety review MT100 does not appear to offer any additional safety benefit over either product alone.

3. The sponsor's comment about relative therapeutic benefit of MT100 over naproxen appears to come from their commentary about trial MT100-301 and MT100-304 (factorial studies). Although I agree with the sponsor's calculations of 50% relative therapeutic gain of MT100 over naproxen, as I discussed in my review I have doubts whether the actual therapeutic gain of MT100 over naproxen is clinically relevant. The therapeutic effect of MT100 over naproxen 500 mg was only 5.8% in trial MT100-301 (a clearly failed study) and 3.9% in trial MT100-304. Relative to the potential significant adverse events from the addition of metoclopramide (see safety review) and the findings from the 2 year carcinogenicity study (increased prolactin related tumors/cancers) it could be argued that the small benefit of MT100 over naproxen do not outweigh the added risks from metoclopramide. Likewise as discussed above, the analysis of the primary endpoints from both studies failed to demonstrate a significant difference between MT100 and naproxen.
4. I am uncertain from which study the sponsor has determined that the relative therapeutic gain of MT100 over naproxen for subjects without nausea at baseline is 100%. Presumably it is one of the 2 factorial studies. Regardless of where it is derived I have previously discussed why I think relative therapeutic gain is not a valid way of looking at the results. If one does consider it valid then it could be argued that trial MT100-308 demonstrated that sumatriptan 50 mg provide a relative therapeutic gain over MT100 of 28% despite the actual difference being only 3.4%. Likewise this statement seems promotional in nature and is not derived from the analysis of a primary endpoint of any study conducted with MT100 and is not consistently seen in multiple studies.
5. The sponsor's comment about the benefits of MT100 over sumatriptan are derived from their experience in trials MT100-306 and MT100-308. As previously discussed we have informed the sponsor on several occasions that promotional statements comparing MT100 to sumatriptan would not be permitted due to the design and analysis plan of these studies. Additionally the sponsor was told that statements about comparability between 2 products would also have to be supported by findings of similarity between other endpoints such as safety and associated symptoms. That aside, trial MT100-308 (equivalence/non-equivalence study) failed to reject the null hypothesis using the confidence intervals set by the sponsor.

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That is, the non-inferiority of MT100 to sumatriptan was not demonstrated. Additionally the data does not support the non-inferiority of MT100 to sumatriptan for the associated symptoms of migraine. Specifically there were inconsistent evidence of efficacy for nausea as demonstrated by the comparison of the proportion of subjects reporting nausea at 2 hours (trial MT100-306  $p=0.049$ , trial MT100-308  $p=0.980$ ). The lack of efficacy towards nausea is further cast in doubt by the sponsor's analysis of change in nausea intensity at 2 hours which failed to demonstrate benefit in both studies (MT100-306  $p=0.177$ , MT100-308  $p=0.595$ ). Overall I do not concur with the sponsor's argument that MT100 and sumatriptan have similar efficacy profiles. The Blackwelder equivalence/non-inferiority analysis done in trial MT100-308 demonstrated a significant difference between MT100 and sumatriptan ( $p=0.042$ ) favoring sumatriptan for 2 hour pain response (47.4% vs. 44.0%). Although the difference is less than 10% (chosen delta) the sponsor was told early that this delta was unacceptable.

6. The sponsor's statement about the dose effect of MT100 appears to be derived from their experience in trial MT100-306, which is the only trial to include a single and double dose of MT100. I partially concur with the sponsor's statement that the efficacy of MT100 appears to be *dose-related with the two-tablet dose providing [numerically] greater benefits over a one-tablet dose of MT 100*. This was true for pain response at 2 hours and for the proportion of subjects reporting phonophobia and photophobia at 2 hours however there was no numerical difference between 1 and 2 tablets of MT100 in the proportion of subjects reporting nausea at 2 hours (both 27.5%). Additionally the comparison of a 2 tablet dose of MT100 to a single tablet of sumatriptan 50 mg is not appropriate since 50 mg is not the maximum dose of sumatriptan approved for use and a double dose of MT100 exceeds the projected recommended dosage of MT100 sought by the sponsor.

The following table summarizes the results from the analysis of the essential endpoints from the 2 factorial studies (MT100-301 and MT100-304), the 2 pivotal trials (MT100-306, MT100-308) and trial MT100-303. For simplicity I do not show the findings from the MT100 X 2 cohort in trial MT100-306 since this dosing regimen is not being considered for approval.

As demonstrated in the table subjects taking a single tablet of MT100 statistically more often experienced sustained pain relief than subjects taking metoclopramide in both factorial studies ( $p<0.0001$ ). This finding of superiority against metoclopramide is supported by the finding that significantly more subjects taking MT100 reported pain relief at 2 hours than subjects taking metoclopramide ( $p<0.001$ ) in both factorial studies. The findings relative to metoclopramide are robust and not in doubt. However the findings relative to naproxen are not as clear. Over the course of this review, and during Dr. Oliva's early review of trial MT100-301, there has been a considerable amount of confusion and discussion about the pre-stated analysis plan for trials MT100-301 and MT100-304. After several clarifications and much in depth review the results presented in the table below are only from the pre-stated analysis plans for both studies. As demonstrated in the table, trial MT100-301 failed to demonstrate a significant difference between MT100 and naproxen for sustained pain response ( $p=0.077$  Sponsor, 0.064 Agency). The clinical validity of this findings is supported by the lack of difference between MT100 and naproxen for pain response at 2 hours ( $p=0.665$ ) in trial MT100-301. Likewise in trial MT100-304, using the pre-stated analysis plan, there was no significant difference between MT100 and naproxen for the proportion of subjects experiencing sustained pain response ( $p=0.063$ ). The

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sponsor calculated a p-value of 0.038 for this comparison however the Agency statistician informs me the SAS macro employed by the sponsor had a programmatic error resulting in an erroneous finding. She states 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, were used in the extended Mantel-Haenszel statistics.*” The clinical validity of this finding is supported by the finding that there was no statistical difference between MT100 and naproxen in the proportion of subjects reporting pain relief at 2 hours in trial MT100-304 ( $p=0.143$ ). Certainly it could be argued that there was a numerical difference between MT100 and naproxen for sustained response, favoring MT100, however the actual therapeutic difference was only 3.9%. A very small difference in my opinion that may be outweighed by the added dangers of metoclopramide (see safety section). A similar small difference was also seen for pain response at 2 hours (1.5%). Finally as demonstrated in the table below, MT100 failed to demonstrate benefit over naproxen for nausea, photophobia and phonophobia at 2 hours in the factorial studies. In summary I do not believe the sponsor has sufficiently demonstrated benefit of MT100 over naproxen in the treatment of migraine. If we were to accept the sponsor’s results of trial MT100-304 I would still argue that the small benefit of MT100 over naproxen is outweighed by the potential adverse effects of metoclopramide.

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**Table 57 Overall Summary of Efficacy**

<b>Factorial Studies</b>					
		MT100	Naproxen	Metoclopramide	Comment
<b>MT100-301</b>	Sustained Pain Response† p-value	150 (35.6%)	128 (29.8%) p=0.077 (Sponsor) p=0.064 (Agency)	42 (19.7%) p<0.001	Failed compared to NAP
	2-hour Pain Response p-value	203 (48.1%)	200 (46.6%) p=0.665	73 (34.3%) p<0.001	Failed compared to NAP
	2 hour Nausea p-value	100 (23.7%)	114 (26.6%) p=0.333	54 (25.4%) p=0.646	Failed compared to NAP and MET
	2-hour Photophobia p-value	230 (54.5%)	224 (52.2%) p=0.504	135 (63.4%) p=0.033	Failed compared to NAP
	2-hour Phonophobia p-value	193 (45.7%)	206 (48.0%) p=0.504	111 (52.1%) p=0.129	Failed compared to NAP and MET
<b>MT100-304</b>	Sustained Pain Response† p-value	328 (31.8%)	295 (27.9%) p=0.038 (Sponsor) p=0.063 (Agency)	99 (18.8%) p<0.001	Failed compared to NAP using agency results.
	2-hour Pain Response p-value	513 (49.8%)	494 (46.7%) p=0.143	193 (36.6%) p<0.001	Failed compared to NAP
	2 hour Nausea p-value	347 (33.7%)	388 (36.7%) p=0.138	219 (41.5%) p=0.003	Failed compared to NAP
	2-hour Photophobia p-value	565 (54.8%)	570 (53.9%) p=0.721	328 (62.1%) p=0.007	Failed compared to NAP
	2-hour Phonophobia p-value	495 (48.0%)	509 (48.2%) p=0.983	279 (52.8%) p=0.080	Failed compared to NAP and MET
<b>Efficacy Studies</b>					
		MT100 X 1	Sumatriptan 50 mg	Placebo	Comment
<b>MT100-306</b>	2-hour Pain Response† p-value	73 (52.9%) p<0.001	69 (53.9%) p<0.001	40 (29.2%)	Won compared to placebo*.
	2 hour Nausea p-value	38 (27.5%) p=0.049	51 (39.5%) p=0.880	53 (38.7%)	Won on nausea
	2-hour Photophobia p-value	65 (47.1%) p=0.002	50 (38.8%) p<0.001	91 (66.4%)	Won on photophobia
	2-hour Phonophobia p-value	60 (43.5%) p=0.062	41 (31.8%) p=0.027	76 (55.5%)	Lost on phonophobia <sup>1</sup>
<b>MT100-308</b>	2-hour Pain Response† p-value vs. placebo p-value vs. sumatriptan	146 (44.0%) p=0.001 p=0.042	161 (47.4%) p<0.001 NA	109 (32.0%)	Lost compared to sumatriptan (primary comparison of interest)
	2 hour Nausea p-value	141 (42.5%) p=0.980	153 (45.0%) p=0.489	145 (42.5%)	Lost on nausea
	2-hour Photophobia p-value	182 (54.8%) p=0.044	190 (55.9%) p=0.087	214 (62.8%)	Won on photophobia
	2-hour Phonophobia p-value	169 (50.9%) p=0.079	173 (50.9%) p=0.099	197 (57.8%)	Lost on phonophobia
<b>MT100-303</b>	Sustain Pain Response 2 hr† p-value	107 (33.8%) p=0.048 (Sponsor) p=0.062 (Agency)		26 (24.1%)	Lost on both primary endpoints using Agency results.
	Sustain Pain Response 4 hr p-value	32 (35.6%) p=0.198		28 (29.8%)	
	2-hour Pain Response p-value	132 (41.6%) p=0.021		31 (28.7%)	Won compared to placebo
	2 hour Nausea p-value	92 (29.0%) p=0.070		41 (38.0%)	Lost at 2 hrs, won at 1.75 hrs (p=0.046).
	2-hour Photophobia p-value	153 (48.3%) p=0.010		68 (63.0%)	Won compared to placebo
	2-hour Phonophobia p-value	152 (48.0%) p=0.030		65 (60.2%)	Won compared to placebo

† Primary endpoint for study (In trial MT100-308 comparison to sumatriptan was primary.)

\*Not shown but MT100 X 2 tablets lost against sumatriptan 50 mg (58.5% vs. 53.5% respectively, p=0.454)

<sup>1</sup> MT100 won on phonophobia at 30 and 60 minutes but not 1.5 and 2.0 hours.

As demonstrated in my summary table, the sponsor conducted 3 efficacy trials. The first two trials (MT100-306, and MT100-308) included a sumatriptan arm in order to determine whether MT100 offers any benefit over sumatriptan. The primary endpoint for both trials was 2 hour pain response defined in the usual manner. In trial MT100-306 the comparison of primary interest

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was MT100 vs. placebo. In trial MT100-308 the comparison of primary interest was between MT100 and sumatriptan 50 mg using an equivalence/non-inferiority analysis plan while the comparisons of MT100 to placebo was performed to “validate the study design and patient population”. In trial MT100-308 the comparison between the two active treatments was to be considered equivalent if the proportions were within a margin of 10% (the delta). In a letter dated October 24, 2001 we informed the sponsor the proposed equivalence (MT100-308) analysis plan using a 10% margin was unacceptable since a comparison directly to placebo was possible from the proposed trial and a 10% delta was too high. Therefore for the purposes of this review I focused primarily on the comparison of MT100 to placebo for both trials. The third trial (MT100-303) was a somewhat unique design in which all subjects were initially randomized to MT100 or placebo, then MT100 subjects not responding to treatment at 2 hours were rerandomized to placebo or a second dose of MT100. The study had two primary endpoints; sustained pain response at 2 hours (all randomized subjects) and sustained pain response at 4 hour (only MT100 1<sup>st</sup> dose non-responders).

As demonstrated in my summary table a significantly higher proportion of subjects randomized to MT100 reported 2 hour pain relief than subjects randomized to placebo in trial MT100-306, MT100-308 and MT100-303. However pain response at 2 hours compared to placebo was the pre-stated primary endpoint for trial MT100-306 only. In trial MT100-308 the comparison of MT100 1 tablet vs. sumatriptan was significant ( $p=0.042$ ), favoring sumatriptan (44.0% vs. 47.4%), although the treatment effect difference between the two active products (3.4%, 95% CI -4.2, 10.9) is probably of little clinical significance. The sponsor asserts these findings support their argument that the two products are equivalent however the Agency statistician reports the sponsor is incorrect. Specifically she states in her review “*since the upper limit of confidence interval of responder proportion differences between sumatriptan and MT100 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 MT100 and sumatriptan in terms of 2 hour pain relief.*” Regardless of the interpretation of the Blackwelder test the results of the comparison of MT100 versus placebo for 2-hour pain response is supportive of efficacy relative to the pain of migraine, although the Agency statistician argues study MT100-308 was overpowered for this endpoint.

Trial MT100-303 had two pre-stated primary endpoints (sustained pain response at 2 hours and sustained pain response at 4 hours). As demonstrated in the summary table, there was no significant difference between MT100 and placebo for either endpoint (using the Agency results). As noted the sponsor obtained a p-value of 0.048 for the comparison of MT100 to placebo for 2 hour response rate however the Agency statistician reports the sponsor’s analysis did not include all the pre-stated covariates in their calculations.

Despite the conflicting results from the various primary endpoints for trial MT100-306, MT100-308 and MT100-303 I believe there is ample evidence that MT100 is effective, compared to placebo, in the treatment of headache pain associated with migraine. If MT100 is approved I believe no statement relative to efficacy of MT100 compared to sumatriptan should be permitted since the sponsor did not evaluate the full dosing regimen of sumatriptan, the Blackwelder equivalence analysis in trial MT100-308 used an unacceptable delta of 10%, and the Agency statistician’s interpretation of the Blackwelder test result is consistent with non-equivalence.

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As demonstrated in my summary table the three efficacy studies demonstrated mixed results relative to efficacy for the associated symptoms of nausea, photophobia, and photophobia. In trial MT100-306 there was a nominally significant difference between MT100 and placebo in the proportion of subjects reporting nausea at 2 hours ( $p=0.049$ ) and in trial MT100-303 there was a nominally significant difference between MT100 and placebo for the proportion of subjects reporting nausea at 1.75 hours ( $p=0.046$ ) but not at 2 hours ( $p=0.070$ ). However in trial MT100-308 there was no difference between MT100 and placebo in the proportion of subjects reporting nausea at 2 hours ( $p=0.980$ ) or any time earlier ( $p\geq 0.273$ ). Similarly there were mixed results for phonophobia, with trial MT100-306 and MT100-308 both failing to demonstrate significant efficacy at 2 hours ( $p=0.062$  and  $0.079$  respectively), and trial MT100-303 demonstrating significant efficacy at 2 hours ( $p=0.030$ ). In all three trials there was a significant difference between subjects receiving MT100 compared to placebo for the proportion of subjects reporting photophobia at 2 hours ( $p\leq 0.044$ ).

In conclusion I do not believe the two factorial studies (MT100-301 and MT100-304) adequately demonstrate the benefit of MT100 over naproxen. Although in the results of the primary endpoint analysis strongly trended towards significance, the small therapeutic benefit of MT100 over naproxen is outweighed by the added risks associated with metoclopramide in my opinion. The three efficacy studies (MT100-306, MT100-308 and MT100-303) collectively demonstrate significant benefit of MT100 over placebo for the treatment of headache pain associated with migraine and mixed results for the treatment of nausea and phonophobia associated with migraine.

#### **7. Integrated Review of Safety**

The safety database for this NDA contains the safety information from 6 phase I pharmacokinetics studies (MT100-101, MT100-102, MT100-103, MT100-105, MT100-106 and MT100-107), 2 phase II dose ranging studies (MT100-201 and MT100-202), 8 phase III efficacy studies (MT100-301, MT100-304, MT100-306, MT100-308, MT100-303, MT100-401A, MT100-402, and MT100-307) and a single long term safety study (MT100-302). A description of the trial designs for each study can be found in section 4 of this review. Each of the phase III studies included assessments of adverse events, physical examinations including vitals and basic laboratory studies done at baseline and follow up visits (generally 1 to 3 days in single attack studies).

For the purposes of the integrated review the sponsor combines the safety data from studies MT100-201, MT100-301, MT100-303, MT100-304, MT100-306, MT100-308, MT100-401A, and MT100-402 since they all used the final MT100 formulation (naproxen 500 mg/metoclopramide 16 mg) and were all controlled, single migraine attack studies. The sponsor presents the safety findings from the following studies separately: the 5 phase I PK studies (all healthy subjects and open label), trial MT100-302 (open label long-term study), trial MT100-202 (did not use MT100 final formulation), trial MT100-307 (single dose, multiple prodrome study), and trial MT100-303 (MT100 administered as rescue medication if required). For simplicity my discussion of safety will parallel the sponsor's organization however I will primarily focus on the single attack controlled clinical studies that used the final MT100 formulation and the single long term study.

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### 7.1 Brief Statement of Conclusions

Overall the total amount of short term and long term exposure to MT100 is adequate for a migraine NDA. In general the 17 clinical trials conducted in support of this NDA did not demonstrate any clinically significant serious adverse events. Common adverse events seen during the trials were consistent with the common adverse events seen with the use of naproxen and metoclopramide individually. As with most NDA safety databases there was inadequate exposure to fully address uncommon and rare adverse events. Both naproxen and metoclopramide have been approved in the United States for many years and both have been associated with serious adverse events on rare occasions. Of particular concern to this reviewer is the extrapyramidal side effects seen on rare occasions (0.2% to 2% depending on dose and route of administration) with the use of metoclopramide. I discuss this concern in greater detail in section 7.4.14 of this review.

### 7.2 Description of Patient Exposure

The database evaluated in the safety review includes all patients who received trial medication. The following table briefly summarizes the total extent of exposure to MT100 (naproxen 500 mg and metoclopramide 16 mg) during the acute phase II and phase III studies. In total, 2725 subjects received a single dose of MT100 (1 tablet and 2 tablets) within the combined phase II and phase III program. Additionally in trial MT100-307, 69 subjects received multiple one tablet doses of MT100 during the treatment of multiple migraine prodromes. The amount of acute exposure is satisfactory.

**Table 58** Total Single Dose Exposure to MT100

	MT100 x 1	MT100 x 2	Naproxen	Metoclopramide	Sumatriptan	Placebo
<b>Total subjects exposed</b>	2412	313	1549	800	474	867

Source: Adapted from sponsor table 18.2, iss.pdf, page 58. Includes subjects from trials 201, 301, 303, 304, 306, 308, 401A and 402.

In addition to the exposure to MT100 outlined above, there were 88 subjects who participated in 5 different phase I PK studies that included various combinations of metoclopramide (8, 16, or 32 mg) and naproxen (500 or 1000 mg). The design of each of these studies is outlined earlier in this review.

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**Table 59** Phase I PK Studies, Dosage, Exposure, and Demographics

Study	Treatment Groups Naproxen mg / Metoclopramide mg	Number of Subjects	Mean Age Years (Range)	Male / Female (% Caucasian / Other)
MT100-101	500/8	11	37 (26-57)	6/5 (Not Reported)
MT100-102	500/16 500/0 0/16 1000/32 (2 MT 100 tablets)	24	35 (20-55)	10/14 (75/25)
MT100-103	500/16	16	55 (40-67)	8/8 (50/50)
MT100-106	500/16	13	35 (20-53)	1/12 (77/23)
MT100-107	500/16	24	27 (20-35)	12/12 (9/15)

Source: MT100-101; MT100-102; MT100-103; MT100-106; MT100-107

Source: Sponsor table 16, ISS.pdf

The following table summarizes the amount of long-term (up to 1 year) exposure to MT100 during trial MT100-302. In all, a total of 1006 subjects treated 23,195 migraine attacks during the course of the study (average of 23 attacks per person). As demonstrated in the table 621 subjects completed at least 6 months of the study and treated well over 2 migraines per month on average. Likewise 329 subjects completed 1 year (defined as 355 days by sponsor) of the study and also treated well over 2 migraines per month on average. The amount of long term exposure exceeds the ICH requirements of at least 300 subjects treated for 6 month and 100 subjects treated for 1 year with each treating at least 2 attacks per month.

**Table 60** Six Month and 1 year Long Term Exposure in Study MT100-302

	All subjects	6-Month Completers	1-year Completers
<b>Total number of subjects</b>	1006	621	329
<b>Mean (SD) number of attacks per subject</b>	23.1 (15.11)	19.3 (5.62)	38.6 (9.68)
<b>Minimum and maximum number of attacks treated</b>	1.0, 78.0	12.0, 43.0	24.0, 78.0
<b>Total number of attacks treated</b>	23,195	11,959	12,711
<b>Average per month</b>		3.2	3.2

Source: Adapted from Sponsor table 8, study report 302.pdf, page 102.

The following table briefly summarizes the baseline characteristics of all subjects in the safety database. Over the entire safety database the mean age for all participants was 41 years of age, 85% were Caucasian, 87% were female, and the mean weight was 71.04 kilograms. The majority of subjects had a history of migraine without and aura (73%), while 12% had migraine with aura and 14% reported a combination of both. Cohorts for each study were well balanced for each of these parameters. These demographic characteristics are typical for migraine NDAs I have reviewed. A further discussion of patient demographics by study can be found in section 4.3 of this review.

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**Table 61** Combined\* Exposure and Demographics for all Single Dose Randomized Studies.

Study	MT 100	MT 100 2 tablets	Naproxen	Metoclopramide	Sumatriptan <sup>1</sup>	Placebo	Total
Number of Subjects	2412	313	1549	800	472	867	6413
Gender							
Male, N (%)	337 (14)	39 (12)	198 (13)	104 (13)	56 (12)	109 (13)	843 (13)
Female, N (%)	2075 (86)	274 (88)	1351(87)	696 (87)	416 (88)	758 (87)	5570 (87)
Age, years							
Mean (range)	41.0 (18-78)	41.2 (19-72)	41.1 (18-75)	40.6 (18-77)	40.8 (18-72)	41.8 (18-78)	41.1 (18-78)
18-40, N (%)	1139 (47)	148 (47)	729 (47)	384 (48)	230 (49)	385 (44)	3015 (47)
> 40, N (%)	1273 (53)	165 (53)	820 (53)	416 (52)	242 (51)	482 (56)	3398 (53)
Race, N (%)							
Caucasian	2041 (85)	255 (81)	1350 (87)	699 (87)	386 (82)	723 (83)	5454 (85)
Black	244 (10)	30 (10)	109 (7)	61 (8)	43 (9)	86 (10)	573 (9)
Oriental/Asian	16 (<1)	1 (<1)	14 (<1)	6 (<1)	6 (1)	12 (1)	55 (<1)
Hispanic	98 (4)	22 (7)	63 (4)	24 (3)	34 (7)	39 (4)	280 (4)
Other	13 (<1)	5 (2)	13 (<1)	10 (1)	3 (<1)	7 (<1)	51 (<1)
Weight (kg)							
Mean (Range)	71.31 (39.0-182.0)	70.95 (41.4-117.9)	70.78 (36.3-151)	70.90 (40.4-121.1)	69.45 (37.2-139.3)	71.80 (41.5-146.1)	71.04 (36.3-182.0)
Migraine history, N (%)							
With aura	299 (12)	31 (10)	178 (11)	113 (14)	54 (11)	126 (15)	801 (12)
Without aura	1755 (73)	221 (71)	1196 (77)	599 (75)	331 (70)	594 (69)	4696 (73)
Mixed	357 (15)	61 (19)	175 (11)	88 (11)	86 (18)	147 (17)	914 (14)
Missing	1	0	0	0	1	0	2

\*Combined database includes: MT100-201, MT100-301, MT100-303, MT100-304, MT100-306, MT100-308, MT100-401A and MT100-402

<sup>1</sup>Sumatriptan = over-encapsulated Imitrex 50mg tablets

Source: Sponsor table 3, ISS page 16.

### 7.3 Methods Safety Review

The primary source of data for this safety review include the Integrated Summary of Safety (ISS), the individual study reports, and the SAS transport files for each study submitted electronically by the sponsor on July 31, 2003. Case report forms (CRFs) and individual narrative summaries for adverse events were consulted as needed. All documents in support of this NDA are available in the Electronic Document Room at [\\CDSESUB1\N21645\N\\_000\2003-07-31](\\CDSESUB1\N21645\N_000\2003-07-31). As of April 1, 2004 there have been 13 amendments to this NDA. For the purposes of my safety review I give added emphasis to the 2 phase III pivotal trials (MT100-306 and MT100-308) and the long term safety trial MT100-302. Additionally since the sponsor is not seeking approval of a 2 tablet dosing regimen for MT100 I will focus primarily on subjects that treated their migraines with a single dose of MT100.

### 7.4 Safety Review Findings

Adverse events were coded by the sponsor using COSTART Adverse Events Dictionary during the phase I studies and the MedDRA Dictionary during the phase II and phase III studies. All adverse events from the start of study medication until any follow up visit were recorded. I reviewed the sponsor's translation of verbatim terms to COSTART and MedDRA terms in each study and there appears to be no significant errors or omissions.

#### 7.4.1 Deaths

There were no deaths in any trial during the entire clinical development program for MT100.

#### 7.4.2 Serious Adverse Events

The following table summarizes the serious adverse events reported during the clinical development program for MT100. No serious adverse events were reported during any of the

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following studies: all pharmacokinetic studies (MT100-101, MT100-102, MT100-103, MT100-105, MT100-106, and MT100-107), MT100-202, MT100-304, MT100-306, MT100-303, MT100-307, MT100-401A, and MT100-402. As demonstrated, no subject randomized to MT100 during the single dose studies reported a serious adverse event. Of all the events listed below only the chest pain experienced by patient MT100-301/028/545 (placebo) and the congenital anomaly seen in the newborn of patient MT100-301/097/434 (naproxen) were considered by the investigator to be “possible related” to the use of study medication. All other events were considered unrelated.

**Table 62** Listing of Serious Adverse Events During MT100 Clinical Development Program

Study/Site/PID	Treatment	Severity	Event within 24 hrs of treatment	Event
MT100-201/011/227	MET	Moderate	No	Asthma attack
MT100-301/097/434	NAP	Moderate	No	Congenital Anomaly
MT100-301/028/545	MET	Severe	No	Strained heart/Kidney Infection/Pyelonephritis/Trichomoniasis/Anemia
MT100-308/222/5129	Placebo	Moderate	No	Chest Pain
MT100-302/013/2011	MT100	Severe	No	Rotator Cuff Syndrome
MT100-302/013/2008	MT100	Severe	No	Limb Fracture/MVA
MT100-302/025/1315	MT100	Severe	No	Kidney Stones
MT100-302/027/0014	MT100	Severe	Yes	Abdominal Pain/Diarrhea/Vomiting/Pyrexia
MT100-302/028/2005	MT100	Severe	No	Sciatica
MT100-302/069/2025	MT100	Severe	No	Rectal Cancer
MT100-302/074/1387	MT100	Severe	No	Chronic Cholecystitis
MT100-302/094/0262	MT100	Severe	No	Cholecystitis
MT100-302/094/0266	MT100	Severe	No	Menorrhagia
MT100-302/094/2007	MT100	Severe	No	Surgery for Obstructive Sleep Apnea
MT100-302/095/590	MT100	Severe	No	Unstable Angina
MT100-302/096/0084	MT100	Moderate	No	Pneumonia
MT100-302/097/432	MT100	Moderate	No	Concussion/MVA
MT100-302/101/2002	MT100	Severe	Yes	Pneumonia/Bronchitis/Asthma Attack
		Moderate	No	Cellulitis
		Severe	No	Pulmonary Embolism
MT100-302/101/2005	MT100	Severe	Yes	Pneumonia
MT100-302/104/0885	MT100	Severe	No	Ovarian Cystectomy
MT100-302/106/0552	MT100	Severe	No	Intervertebral Disc Herniation
MT100-302/115/1242	MT100	Severe	No	Endometriosis
MT100-302/116/0924	MT100	Severe	No	Appendicitis
MT100-302/118/2020	MT100	Unrated	No	Pregnancy/Premature Rupture of membranes
MT100-302/119/2003	MT100	Severe	No	Diarrhea
MT100-302/119/2025	MT100			Acute bronchitis
MT100-302/124/2011	MT100	Severe	No	Intervertebral Disc Herniation
MT100-302/125/2004	MT100	Severe	No	Vaginal Prolapse
MT100-302/130/2014	MT100	Severe	Yes	Cellulitis
MT100-302/133/2005	MT100	Severe	No	Limb Fracture

Source: Adapted from Sponsor table 8, iss.pdf, page 25 and sponsor table 15, iss.pdf, page 38 through 41

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I reviewed the narratives for each event and concur with the investigator's assessment of relationship to study medication. Of the narratives I reviewed the following events stood out as remarkable since they either occurred within 24 hours of study drug administration or could possibly have been related to study drug use.

- In trial MT100-201 a 42 year old female (MT100-201/011/227) developed progressive shortness of breath and chest pain soon after taking study medication (metoclopramide) for an acute migraine (timing not clear). Two days later she was hospitalized for acute exacerbation of asthma. In my opinion it is unlikely this event was related to study medication. The patient has a significant past medical history for asthma and allergic rhinitis and was experiencing a sinus infection at the time of hospitalization.
- In trial MT100-301 a 34 year old female (MT100-301/097/434) delivered a 38 week old infant noted to have syndactyly of the 3<sup>rd</sup> and 4<sup>th</sup> digit of the hand, prominence of the left cardiac ventricle, and development delays associated with chromosome 2 abnormalities. The patient had taken a single dose of study medication (naproxen) on (b) (6) and had a negative pregnancy test on follow up visit on (b) (6). However on (b) (6) she was noted to be pregnant and an ultrasound at that time dated the pregnancy approximately 13.1 weeks hence the patient was most likely in the early first trimester at the time she took study medication. The label for naproxen warns against the use of naproxen during the late third trimester due to an increased risk of neonatal complications such as necrotizing enterocolitis, patent ductus arteriosus and intracranial hemorrhage. The label does not discuss problems seen when naproxen is given in the first trimester and is rated category B (use only if clearly needed). In my opinion the event is probably not related although it is not possible to state this with 100% certainty.
- In trial MT100-302 a 45 year old female (MT100-302/101/2002) was hospitalized on day 79 of the study for pneumonia, exacerbation of asthma and bronchitis within 24 hours of taking MT100 for a migraine attack. The patient had been seen by her primary care physician approximately 1 week before hospitalization for "cold symptoms" and was given oral antibiotics. In my opinion the event is probably not related to the use of MT100. The patient has multiple pre-existing conditions such as asthma, morbid obesity, and diabetes which may have contributed to the development of pneumonia. This patient also experienced cellulitis (day 285) and a pulmonary embolism/deep vein thrombosis (day 307) both requiring hospitalization. Neither of these events were temporally related to the use of MT100 and in my opinion unrelated since MT100 had been discontinued several weeks (approximately 3 weeks) prior to the events. Predisposing risk factors for both events include morbid obesity, diabetes, and a previous history of "leg cellulitis and varicose veins". Chronic concomitant medications include albuterol, lorabid, glyburide, and fluticasone.
- In trial MT100-302 a 53 year old male (MT100-302/130/2014) developed periorbital rash within 24 hours of taking MT100. Approximately 1 week later the rash worsened and he was hospitalized on day 75 of the study for periorbital cellulitis. The event resolved without incidence and in my opinion is probably not related to MT100. The patient does not have any significant past medical history. The patient discontinued MT100 at the onset of the event.
- In trial MT100-302 a 36 year old female (MT100-302/101/2005) was hospitalized on day 159 of the study for pneumonia within 24 hours of taking MT100 for migraine. In my opinion the event is probably unrelated to the use of MT100. The patient has a significant

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past medical history of morbid obesity, and asthma which may have contributed to the development of pneumonia. The patient continued in the study without problems.

- In trial MT100-302 a 36 year old female (MT100-302/027/0014) was hospitalized on day 317 of the study due to severe abdominal cramps and diarrhea within 24 hours of taking MT100. An evaluation at that time was consistent with a diagnosis of diverticulitis. The patient has a past medical history of migraine, insomnia, sinusitis, peptic ulcer disease, renal stones, appendectomy, and tonsillectomy. The patient was treated with intravenous antibiotics with good results. In my opinion the event is probably unrelated to study medication. The patient completed the study without further problems.

In summary there does to appear to have been any significant serious adverse events during the clinical development of MT100 that could reasonably be attributed to MT100 or its components.

### 7.4.3 Withdrawals Due to Adverse Events

As seen in most single attack migraine studies there were no withdrawals due to adverse events during the single dose, single attack clinical studies using MT100. During the early Phase 1 studies a single subject withdrew consent early due to an adverse event. This subject (PID #102, 30 year old female) was participating in trial MT100-102 (4 period PK trial) when she experienced nausea, restlessness, tremors, abdominal pain, diarrhea, chest pain, epigastric pain, lightheadedness and paresthesia soon after receiving metoclopramide and later 2 tablets of MT100. All events resolved within 24 hours of onset and were considered mild in severity except for abdominal pain which was graded as moderate. In trial MT100-307 (single dose, multiple prodromes study) 2 subjects withdrew due to an adverse event. Subject 227/04 withdrew due to the development of sciatica greater than 24 hours after dosing with placebo and subject 100/004 withdrew due to severe somnolence, fatigue and restlessness soon after a single dose of MT100. The events in subject 100/004 resolved and were considered related to study medication. None of these events were rated as serious.

As would be expected the number of withdrawals in the long term study MT100-302 were significantly higher than during the acute single dose studies. The following table summarizes the various reasons for early withdrawal from the long-term study. As demonstrated in the table few subjects withdrew due to an adverse event [82 (8%)]. Common adverse events leading to early withdrawal included somnolence (10%), restlessness (9%), diarrhea (9%), anxiety (11%), and tremor, dyspepsia, nausea and fatigue (all less than 5%).

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**Table 63** Cited Reasons for Early Withdrawal, Trial 302

Reason for Discontinuation in First 6 Months	Subjects Who Discontinued (%)
Lack of Efficacy	13
Adverse Event	6
Less than Two Migraines Per Month	8
Failed to Return	4
Protocol Violation	4
Sponsor Terminated Study	1
Other	2
Reason for Discontinuation after 6 Months	
Sponsor Terminated Study	10
Other	7
Lack of Efficacy	3
Protocol Violation	3
Adverse Event	2
Less than Two Migraines per Month	1
Failed to Return	1

Source: Sponsor table 13, study report ISS.pdf

Overall the number of early withdrawals due to an adverse event for the entire clinical development plan for MT100 was low. There does not appear to be any particular pattern to the nature of adverse events leading to withdrawal.

#### 7.4.4 Common Adverse Events, Short Term Controlled Studies

The following sponsor table briefly summarizes the more common adverse events seen during the controlled, single attack trials for MT100. Adverse events were reported by 22% of those subjects receiving a single one-tablet dose of MT100 and by 15% of subjects treated with placebo. As demonstrated the most common adverse events with a single dose of MT100 was somnolence (4%), diarrhea (3%), dizziness (exclude vertigo, 2%), dry mouth (2%), and fatigue (2%). As would be expected the adverse events commonly reported for MT100 were those typically associated with the use of either metoclopramide or naproxen alone.

A single two-tablet dose of MT100 was evaluated in trials MT100-102, MT100-306, and MT100-401A. Additionally subjects in MT100-303 received a second dose of MT100 two hours after the initial dose if required. As demonstrated in the table a single two tablet dose of MT100 was associated with a higher rate of adverse events (35%) compared to the single one tablet dose of MT100 (22%). More common in the 2 tablet cohorts were restlessness, somnolence, dizziness and some GI complaints (primarily dyspepsia). The sponsor reports the onset of somnolence was generally within 1 hour after a two tablet dose of MT100 and had a mean duration of 5.7 hours. The onset of restlessness was within 2 hours of dosing and the duration averaged approximately 9 hours. A rescue dose of MT100 was generally well tolerated in trial MT100-303 although there was a slight increase in common adverse events. The sponsor does not intend to market the double dose of MT100 as the recommended initial first dose.

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**Table 64** Common ( $\geq 1\%$ ) AEs, Combined Controlled Single-Attack Studies

System Organ Class/ Preferred Term	MT 100 (N = 2412)	MT 100 2 Tablets (N = 313)	NAP (N = 1549)	MC (N = 800)	Suma (N = 472)	Placebo (N = 867)
<b>Nervous System Disorders</b>						
Somnolence	102 (4)	32 (10)	25 (2)	33 (4)	13 (3)	11 (1)
Dizziness (Excluding Vertigo)	56 (2)	20 (6)	31 (2)	21 (3)	25 (5)	22 (3)
Paraesthesia	14 (<1)	4 (1)	11 (<1)	9 (1)	4 (<1)	3 (<1)
Restlessness	13 (<1)	12 (4)	5 (<1)	4 (<1)	1 (<1)	5 (<1)
Insomnia	6 (<1)	3 (<1)	8 (<1)	1 (<1)	6 (1)	2 (<1)
<b>Gastrointestinal Disorders</b>						
Diarrhoea NOS	77 (3)	16 (5)	19 (1)	30 (4)	4 (<1)	7 (<1)
Dry Mouth	38 (2)	3 (<1)	26 (2)	7 (<1)	14 (3)	14 (2)
Dyspepsia	30 (1)	3 (<1)	20 (1)	6 (<1)	8 (2)	6 (<1)
Abdominal Pain, Upper	27 (1)	4 (1)	12 (<1)	8 (1)	1 (<1)	3 (<1)
Abdominal Pain, NOS	15 (<1)	5 (2)	10 (<1)	2 (<1)	4 (<1)	7 (<1)
Nausea	19 (<1)	3 (<1)	7 (<1)	2 (<1)	7 (1)	4 (<1)
<b>General Disorders and Administration Site Conditions</b>						
Fatigue	39 (2)	6 (2)	8 (<1)	5 (<1)	10 (2)	6 (<1)
Chest Tightness	8 (<1)	1 (<1)	4 (<1)	2 (<1)	11 (2)	10 (1)
Feeling Jittery	13 (<1)	4 (1)	3 (<1)	3 (<1)	2 (<1)	1 (<1)
<b>Psychiatric Disorders</b>						
Anxiety NEC	9 (<1)	7 (2)	5 (<1)	5 (<1)	0	2 (<1)
<b>Skin and Subcutaneous Tissue Disorders</b>						
Sweating Increased	3 (<1)	1 (<1)	5 (<1)	1 (<1)	6 (1)	1 (<1)
<b>Ear and Labyrinth Disorders</b>						
Tinnitus	10 (<1)	2 (<1)	5 (<1)	0	7 (1)	8 (<1)

NAP = Naproxen sodium; MC = Metoclopramide Hydrochloride; Suma = over-encapsulated Imitrex 50 mg tablet

Source: Sponsor Table 71, Overall summary volume 1, page 168

The following table summarizes the breakdown of adverse events reported in the single dose studies by severity reported for each cohort. Overall AEs were reported by 22% of subjects receiving a single one-tablet dose of MT100, 35% of subjects treated with two-tablets dose of MT100, 15% of subjects treated with placebo, 18% of subjects receiving naproxen 500 mg, 24% of subjects receiving metoclopramide and 24% of subject receiving sumatriptan. As demonstrated in the table 87% of all adverse events reported by subjects administering a single dose of MT100 were reported as mild to moderate compared to 91% for subjects taking placebo. Overall the various cohorts were remarkably similar for the percentage of subjects rating their adverse events as mild, moderate and severe with the exception of subjects taking metoclopramide where 21% of subjects reported a severe adverse event. Among the 65 subjects who reported severe adverse events following administration of one-tablet of MT 100, the majority (n=51) reported events in the nervous system (n=24) or gastrointestinal system (n=27). Somnolence was the most prevalent severe adverse event (n=17) in the nervous system and

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diarrhea accounted for the majority of the severe adverse events reported in the gastrointestinal system (n=8).

**Table 65** Adverse Event Severity by Dose and Drug Product

	<b>MT100 x 1</b>	<b>MT100 x 2</b>	<b>Naproxen</b>	<b>Metoclopramide</b>	<b>Sumatriptan</b>	<b>Placebo</b>
Total Subjects	2412	313	1549	800	474	867
Total AEs	519 (22%)	111 (35%)	275 (18%)	189 (24%)	114 (24%)	127 (15%)
Mild (%)	260 (50%)	45 (41%)	151 (55%)	89 (47%)	64 (56%)	66 (52%)
Moderate (%)	194 (37%)	49 (44%)	108 (39%)	61 (32%)	40 (35%)	50 (39%)
Severe (%)	65 (13%)	17 (15%)	16 (6%)	39 (21%)	10 (9%)	11 (9%)

Source: Adapted from sponsor table 18.4.3, iss.pdf, page 164

The following table summarizes the common adverse events seen during trial MT100-307. Trial MT100-307 was a multiple attack, placebo controlled study to evaluate the safety and efficacy of MT100 when administered to migraineurs during the prodrome stage of a migraine. Each prodrome was treated with a single dose of MT100. Subjects were permitted to treat up to 6 prodromes in a 4 week period. Safety follow ups occurred within 1 to 3 days of the end of the treatment period. As noted in the table the majority of adverse events were gastrointestinal in nature. The most common adverse events were diarrhea (4%), somnolence (3%), upper respiratory infection (3%), and fatigue (3%).

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**Table 66** Adverse Event Reported in Trial MT100-307

System Organ Class/Preferred Term	Number of Subjects (%)	
	MT 100 (N = 70)	Placebo (N = 72)
<b>Gastrointestinal Disorder</b>		
Diarrhea	3 (4)	0
Abdominal Pain	0	1 (1)
Dyspepsia	1 (1)	0
Nausea	1 (1)	0
Dry mouth	1 (1)	0
Vomiting NOS	1 (1)	0
Vomiting Aggravated	1 (1)	0
Tooth Disorder	1 (1)	0
<b>Nervous System Disorders</b>		
Somnolence	2 (3)	0
Dizziness (Excluding Vertigo)	0	1 (1)
Entrapment Neuropathy	0	1 (1)
Restlessness	1 (1)	0
<b>Infections and Infestations</b>		
Upper Respiratory Tract Infection NOS	2 (3)	0
Nasopharyngitis	0	1 (1)
Bronchitis	0	1 (1)
Urinary Tract Infection NOS	0	1 (1)
<b>General Disorders and Administrative Site Conditions</b>		
Fatigue	2 (3)	1 (1)
Influenza Like Illness	1 (1)	0
Pyrexia	0	1 (1)
<b>Psychiatric Disorders</b>		
Confusion	0	1 (1)
Depression NOS	0	1 (1)
Depression Aggravated	0	1 (1)
<b>Skin and Subcutaneous Disorders</b>		
Eczema NOS	0	1 (1)
Pruritus NOS	1 (1)	0
Rash NOS	0	1 (1)
<b>Reproductive System and Breast Disorders</b>		
Vaginal Hemorrhage	0	1 (1)

Source: Sponsor table 10, ISS.pdf

Adverse events described during the early phase I PK studies were similar in nature and severity as to those reported in the controlled clinical trials. The incidence of adverse events with a single dose of MT100 was no greater than with the individual components. Of particular interest was trial MT100-102 where the incidence of adverse events in the 2 tablet MT100 cohort was generally 2 to 3 times the incidence rate seen in the single tablet cohort as demonstrated in the following table.

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**Table 67** Summary of Adverse Events in Trial MT100-102 by System

COSTART Preferred Term	Treatment Group			
	MT 100: 1 Tablet (N = 24)	MT 100: 2 Tablets (N = 24)	Metoclopramide 16 mg (N = 24)	Naproxen 500 mg (N = 24)
	N (%)	N (%)	N (%)	N (%)
<b>Number of Subjects with at Least One Adverse Event</b>	3 (13)	12 (50)	5 (21)	5 (21)
<b>Body as a Whole</b>				
Pain Abdominal	1 (4)	2 (8)	1 (4)	0 (0)
Headache	1 (4)	3 (13)	2 (8)	0 (0)
Injury Accident	0 (0)	1 (4)	1 (4)	1 (4)
Pain	0 (0)	0 (0)	1 (4)	1 (4)
Pain Chest	0 (0)	1 (4)	0 (0)	0 (0)
Pain Neck	0 (0)	0 (0)	0 (0)	1 (4)
Tremor	0 (0)	1 (4)	0 (0)	0 (0)
<b>Nervous System</b>				
Dizziness	1 (4)	2 (8)	1 (4)	0 (0)
Nervousness	0 (0)	3 (13)	1 (4)	0 (0)
Somnolence	0 (0)	3 (13)	0 (0)	0 (0)
Paresthesia	0 (0)	1 (4)	0 (0)	0 (0)
<b>Skin and Appendages</b>				
Application Site Reaction	1 (4)	3 (13)	2 (8)	2 (8)
Nodule Subcutaneous	0 (0)	1 (4)	0 (0)	0 (0)
<b>Digestive</b>				
Constipation	1 (4)	0 (0)	0 (0)	1 (4)
Diarrhea	0 (0)	1 (4)	0 (0)	0 (0)
Dry Mouth	1 (4)	0 (0)	0 (0)	0 (0)
Dyspepsia	0 (0)	1 (4)	0 (0)	0 (0)
Nausea	0 (0)	0 (0)	1 (4)	0 (0)
Ulcer Mouth	1 (4)	0 (0)	0 (0)	0 (0)

Source: MT100-102, Section 14.3.1

Source: Sponsor table 17, ISS.pdf

In trial MT100-103 (hepatic impairment PK study) MT100 was well tolerated with only a single patient reporting an adverse event (diarrhea).

The following table briefly summarizes the common adverse events reported in trial MT100-306 and MT100-308. Trial MT100-306 and MT100-308 included a sumatriptan arm as an active comparator. During our discussions with the sponsor we informed them that marketing claims and labeling claims relative to sumatriptan would not be possible due to the design of the studies and the analysis plan. However a comparison of adverse events in each cohort in these trials demonstrates both active products to be well tolerated. The overall incidence of adverse events between MT100 and sumatriptan were comparable (23% for MT100 vs. 24% for sumatriptan). As would be expected there was less complaints of chest tightness with MT100 (1% MT100 vs. 2% sumatriptan) whereas subjects randomized to MT100 reported more diarrhea, dyspepsia and abdominal pain than subjects randomized to sumatriptan. In trial MT100-306 adverse events occurring in more than 2% of subjects receiving a single dose of MT100 were somnolence (4%), diarrhea (4%), dizziness (4%), restlessness (2%), upper abdominal pain (2%) and dyspepsia (2%) this compares to the following incidence rates in subjects taking sumatriptan; somnolence (2%), diarrhea (0%), dizziness (6%), restlessness (<1%), upper abdominal pain (0%) and dyspepsia (<1%). Common adverse events reported in the sumatriptan cohort included fatigue (4%), chest

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tightness (4%) and throat tightness (3%). In trial MT100-308 the MT100 and sumatriptan cohorts were similar in the nature and incidence of adverse events. The sponsor does not provide any discussion whether any of these findings are statistically significant however given the small numbers it is unlikely.

**Table 68** Adverse Events ( $\geq 2\%$ ), Trial MT100-306 and MT100-308.

<b>Trial MT100-306</b>				
	<b>MT100 X 1 N=138</b>	<b>MT100 X 2 N=142</b>	<b>Sumatriptan N=129</b>	<b>Placebo N=137</b>
At least 1 AE	32 (23%)	66 (46%)	38 (29%)	26 (19%)
Dizziness	5 (4%)	13 (9%)	8 (6%)	7 (5%)
Somnolence	5 (4%)	22 (15%)	2 (2%)	3 (2%)
Restlessness	3 (2%)	10 (7%)	1 (<1%)	1 (<1%)
Dysgeusia	1 (<1%)	3 (2%)	0 (0%)	1 (<1%)
Hypoaesthesia	1 (<1%)	0 (0%)	3 (2%)	0 (0%)
Diarrhea	5 (4%)	7 (5%)	0 (0%)	4 (3%)
Dry mouth	2 (1%)	1 (<1%)	2 (2%)	5 (4%)
Upper Abdominal pain	3 (2%)	4 (3%)	0 (0)	0 (0%)
Dyspepsia	3 (2%)	2 (1%)	1 (<1%)	1 (<1%)
Abdominal pain NOS	0 (0%)	3 (2%)	0 (0%)	1 (<1%)
Nausea	0 (0%)	1 (<1%)	2 (2%)	0 (0%)
Throat Irritation	0 (0%)	0 (0%)	2 (2%)	0 (0%)
Fatigue	2 (1%)	3 (2%)	5 (4%)	3 (2%)
Chest tightness	0 (0%)	1 (<1%)	5 (4%)	4 (3%)
Chest Pain	0 (0%)	0 (0%)	3 (2%)	0 (0%)
Increased Sweating	1 (<1%)	1 (<1%)	3 (2%)	1 (<1%)
Muscle tightness	0 (0%)	0 (0%)	3 (2%)	1 (<1%)
Anxiety	0 (0%)	6 (4%)	0 (0%)	0 (0%)
Throat tightness	0 (0%)	0 (0%)	4 (3%)	0 (0%)
Tinnitus	1 (<1%)	1 (<1%)	2 (2%)	3 (2%)
Increased heart rate	0 (0%)	0 (0%)	2 (2%)	1 (<1%)
Urine Frequency	0 (0%)	1 (<1%)	2 (2%)	0 (0%)
<b>Trial MT100-308</b>				
	<b>MT100 N=337</b>		<b>Sumatriptan N=343</b>	<b>Placebo N=347</b>
At least 1 AE	75 (22%)		76 (22%)	66 (19%)
Dizziness	13 (4%)		17 (5%)	12 (3%)
Somnolence	12 (4%)		11 (3%)	4 (1%)
Insomnia	0 (0%)		6 (2%)	1 (<1%)
Diarrhea	14 (4%)		4 (1%)	3 (<1%)
Dry mouth	3 (<1%)		12 (3%)	5 (1%)
Dyspepsia	4 (1%)		7 (2%)	1 (<1%)
Chest tightness	6 (2%)		6 (2%)	5 (1%)
Fatigue	8 (2%)		5 (1%)	1 (<1%)

Source: Adapted from sponsor tables 9, trial report MT100-308 and table 9 study report MT100-306.

### 7.4.5 Common Adverse Events, Long-Term Safety Trial MT100-302

In trial MT100-302 screened subjects were followed for 1 year. All subject took a single tablet of MT100 at the onset of a migraine attack (any grade). Unlike most triptan studies subjects were not permitted to re-administer MT100 at any time during the 24 hour period of the attack. Safety follow up was done every 3 months. Diary assessments were done for 24 hours for each attack treated. The overall reporting rate for subjects reporting at least one adverse event was 78%. As would be expected for an acute intermittent therapy the reporting rate for any adverse events reduced with the duration of therapy. Reported rates for the 0 to 3 month period were 65%, compared to 44% for the 3 to 6 month period, 35% for the 6 to 9 month period and 32% for the 9

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to 12 month period. The most common adverse events reported are summarized in the following table. The majority of the adverse events were graded mild or moderate in severity. Somnolence was the only adverse event reported as severe by more than 1% of subjects [n=19 (2%)]. Overall the nature of the adverse events seen during the long term study is similar to the nature of the adverse events seen during the short-term, single attack migraine studies described earlier.

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**Table 69** Common Adverse Events ( $\geq 1\%$ ), Trial MT100-307, n (%)

System Organ Class/Preferred Term	Number of Subjects (%) (N = 1006)	
	All Events	Events within 24 Hours of Exposure
<b>Subjects with at Least One Adverse Event</b>	<b>785 (78%)</b>	<b>563 (56%)</b>
<b>Gastrointestinal Disorder</b>		
Diarrhea NOS	147 (15)	109 (11)
Dyspepsia	74 (7)	54 (5)
Nausea	65 (6)	53 (5)
Abdominal Pain Upper	48 (5)	27 (3)
Dry Mouth	38 (4)	36 (4)
Pharyngolaryngeal Pain	52 (5)	22 (2)
Abdominal Pain NOS	26 (3)	19 (2)
Vomiting NOS	24 (2)	15 (1)
Constipation	24 (2)	12 (1)
Toothache	21 (2)	9 (<1)
Flatulence	12 (1)	10 (<1)
Gastro-esophageal Reflux Disease	11 (1)	3 (<1)
<b>Infections and Infestations</b>		
Nasopharyngitis	170 (17)	53 (5)
Sinusitis NOS	103 (10)	26 (3)
Upper Respiratory Tract	68 (7)	18 (2)
Bronchitis	45 (4)	11 (1)
Ear Infection NOS	14 (1)	2 (<1)
Fungal Infection (NOS)	13 (1)	3 (<1)
<b>Nervous System Disorders</b>		
Somnolence	108 (11)	101 (10)
Dizziness (Excluding Vertigo)	67 (7)	59 (6)
Insomnia	33 (3)	28 (3)
Restlessness	18 (2)	16 (2)
Headache NOS	17 (2)	11 (1)
Paresthesia	13 (1)	12 (1)
Tremor	12 (1)	10 (<1)
Sinus Headache	14 (1)	7 (<1)
<b>General Disorders/Administrative Site Condition</b>		
Fatigue	73 (7)	65 (6)
Influenza Like Illness	29 (3)	10 (<1)
Feeling Jittery	17 (2)	16 (2)
Pain NOS	17 (2)	11 (1)
Pyrexia	16 (2)	9 (<1)
<b>Musculoskeletal and Connective Tissue Disorders</b>		
Back Pain	38 (4)	13 (1)
Myalgia	26 (3)	17 (2)
Arthralgia	29 (3)	12 (1)
Neck pain	16 (2)	8 (<1)
Pain in Limb	16 (2)	5 (<1)
Muscle Cramps	11 (1)	6 (<1)
<b>Respiratory, Thoracic and Mediastinal Disorders</b>		
Cough	34 (3)	13 (1)
Nasal Congestion	29 (3)	9 (<1)
Sinus Congestion	19 (2)	7 (<1)
Rhinorrhea	17 (2)	7 (<1)
Dyspnea NOS	11 (1)	8 (<1)
Sinus Pain	11 (1)	8 (<1)
<b>Psychiatric Disorders</b>		
Anxiety NEC	19 (2)	4 (<1)
Nervousness	12 (1)	3 (<1)
Depression NOS	12 (1)	2 (<1)
<b>Skin and Subcutaneous Tissue Disorders</b>		
Rash NOS	20 (2)	10 (<1)
<b>Ear and Labyrinth Disorders</b>		
Tinnitus	13 (1)	8 (<1)
Vertigo	12 (1)	9 (<1)
<b>Reproductive System and Breast Disorders</b>		
Dysmenorrhea	20 (2)	8 (<1)

Source: Adapted from Sponsor table 12\*, ISS.pdf. Seasonal allergy, dysmenorrhea, viral infection, influenza and UTI excluded.

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### 7.4.6 Adverse Events Incidence Table

The following table summarizes the combined incidence of common adverse events ( $\geq 1\%$ ) in all single dose, randomized, phase III studies comparing MT100 to placebo.

**Table 70** Incidence of AE ( $\geq 1\%$ ) in all Phase III Trials with MT100 and Placebo, n (%)

	MT100 N=2355	MT100 X 2 N=313	Placebo N=810
Any adverse event	513 (22)	111 (35)	121 (15)
Nervous System			
Somnolence	100 (4)	32 (10)	10 (1)
Dizziness (exclude vertigo)	55 (2)	20 (6)	22 (3)
Restlessness	13 (<1)	12 (4)	4 (<1)
Paresthesia	14 (<1)	4 (1)	3 (<1)
Gastrointestinal	209 (9)	39 (12)	40 (5)
Diarrhea	76 (3)	16 (5)	7 (<1)
Dry Mouth	37 (2)	3 (<1)	12 (1)
Dyspepsia	28 (1)	3 (<1)	6 (<1)
Abdominal Pain (upper)	27 (1)	4 (1)	3 (<1)
Abdominal pain NOS	15 (<1)	5 (2)	7 (<1)
General disorders	81 (3)	20 (6)	27 (3)
Fatigue	38 (2)	6 (2)	6 (<1)
Feeling Jittery	13 (<1)	4 (1)	1 (<1)
Psychiatric Disorders	31 (1)	14 (4)	6 (<1)
Anxiety	9 (<1)	7 (2)	2 (<1)
Skin/subcutaneous tissue*	27 (1)	5 (2)	7 (<1)
Ear and Labyrinth disorders*	16 (<1)	3 (<1)	10 (1)
Musculoskeletal and Connective tissues*	14 (<1)	4 (1)	9 (1)
Infections and infestations*	18 (<1)	2 (<1)	6 (<1)
Respiratory, thoracic and mediastinal*	19 (<1)	2 (<1)	3 (<1)
Vascular disorders*	15 (<1)	3 (<1)	1 (<1)
Eye disorders*	7 (<1)	2 (<1)	7 (<1)
Investigations*	10 (<1)	0	3 (<1)
Injury, poisoning and procedural complications*	9 (<1)	1 (<1)	1 (<1)
Renal and urinary disorders*	4 (<1)	2 (<1)	2 (<1)
Cardiac disorders*	3 (<1)	0	2 (<1)
Blood and lymphatic system disorders*	5 (<1)	0	0
Reproductive system and breast disorders*	4 (<1)	0	1 (<1)
Metabolic and nutrition disorders*	2 (<1)	1 (<1)	1 (<1)
Endocrine disorders*	1 (<1)	0	2 (<1)
Immune system disorders*	1 (<1)	0	2 (<1)
Pregnancy, puerperium and perinatal conditions*	2 (<1)	0	0

\*System contained no adverse event occurring  $\geq 1\%$  in any actively treated cohort.

Source: Adapted from Sponsor table 18.4.1.11, ISS.pdf

### 7.4.7 Laboratory Findings

The timing of safety laboratories during the phase I trials are outlined in the following table. Overall during the early phase I trials for MT100 no clinically significant abnormalities was detected in hematology, or blood chemistry assessments.

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**Table 71** Frequency of Routine Laboratory Examinations, Phase I

Protocol	Frequency and Timing of Lab Collection
MT100-101	Screening, baseline, 1, 3 and 5 days
MT100-102	Screening, follow-up
MT100-103	Screening, baseline, end of study
MT100-106	Screening, end of both treatment periods (4 hours post-dose)
MT100-107	Screening

Source: Sponsor table 18, ISS.pdf

The timing of safety laboratories collected during the phase II and phase III trials are summarized in the following table. As is typical for migraine studies the follow up laboratories were often done days to weeks after study drug administration hence very little useful information can be determined about the acute changes that can occur with intermittent MT100 use. For the single attack studies follow-up visits generally occurred between 1 to 3 days after treatment. For the single long term study follow-up visits occurred every 3 months irrespective of when a migraine was treatment.

**Table 72** Frequency of Routine Laboratory Examinations, Phase II and Phase III

Protocol	Frequency and Timing of Lab Collection
<b>Controlled Clinical Trials</b>	
MT100-201	Screening, prior to treatment and follow-up
MT100-202	Screening, prior to treatment and follow-up
MT100-301	Screening and follow-up
MT100-303	Screening and follow-up
MT100-304	Screening and follow-up
MT100-306	Screening and follow-up
MT100-308	Screening and follow-up
MT100-401A	Screening
MT100-402	Screening
Open Label Safety (Multiple Dose)	
MT100-302	Screening, 3, 6, 9 and 12 months
<b>Controlled; Multiple Dose in Migraine Prodrome</b>	
MT100-307	Screening, end of baseline and follow-up

Source: Sponsor table 4, iss.pdf, page 19

The following table summarizes the mean values for each chemistry laboratory assessment done at baseline and follow up during the acute single dose studies. A review of changes in mean laboratory values comparing baseline to follow up assessments showed no clinically meaningful changes within any treatment group.

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**Table 73** Mean Chemistries Values, Baseline and Follow-up

	MT100 x 1 N=2412		MT100 x 2 N=313		Placebo N=867	
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
Albumin	4.10	4.07	4.05	4.05	4.13	4.13
Alk Phos	69.0	68.3	71.1	70.6	71.6	69.8
ALT	20.4	20.8	21.5	21.9	21.6	20.0
AST	20.8	21.0	21.4	21.1	20.8	20.1
BUN	13.1	13.3	13.4	13.4	13.3	13.3
Calcium	9.33	9.31	9.3	9.28	9.39	9.33
Chloride	104.3	104.6	103.5	105.0	103.2	103.7
Cholesterol	198.3	195.5	195.2	191.2	201.3	197.4
CO <sub>2</sub>	25.98	25.87	25.02	24.32	25.37	25.44
Creatine Kinase	105.9	110.4	115.9	117.7	106.8	97.9
Creatinine	0.75	0.75	0.78	0.77	0.77	0.76
Globulin	3.14	3.10	3.09	3.12	3.06	3.05
Glucose	91.5	93.6	89.9	94.9	93.3	94.4
Magnesium	1.75	1.72	1.73	1.81	1.69	1.70
Phosphorus	3.57	3.56	3.55	3.58	3.63	3.62
Potassium	4.24	4.18	4.26	4.22	4.26	4.21
Sodium	140.4	140.5	140.3	140.9	140.3	140.5
T. Bilirubin	0.41	0.42	0.40	0.40	0.45	0.45
Protein	7.24	7.17	7.14	7.17	7.19	7.18
Triglyceride	153.6	153.0	142.2	148.8	147.1	145.0
Uric Acid	4.51	4.44	4.42	4.66	4.52	4.53

Source: Adapted from Sponsor table 18.6.1, iss.pdf

Includes subjects from trial MT100-201, 301, 303, 304, 306, 308, 401A, and 402.

A review of individual patient shifts from low/normal to high or high/normal to low for each chemistry parameter did not show any clinically significant trends or unusual outliers in most situations. The only parameter with any significant number of outliers at follow up was creatine kinase however many of these subjects in each cohort had elevated CK levels at baseline (see following table). The sponsor argues that elevations in creatine kinase can occur in migraine attacks and cites an article by Bell (1978). My own experience has shown that creatine kinase can be elevated with traumatic blood sampling, hemolysis of blood samples and in very muscular individuals who may have exercised prior to sampling. It does not appear samples with elevated CK levels were fractionated (MB, MM) hence I am unable to determine whether the increases reflect a muscular or cardiac origin. None of the subjects with elevated CK levels complained of unusual chest pain or muscular aches hence I do not believe these findings are clinically significant. Repeat follow up levels returned to normal in most cases. The label for Reglan and Anaprox do not describe elevations in creatinine kinase.

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**Table 74** Prevalence of Markedly Elevated CK Levels

	MT100 x 1 N=2412	MT100 x 2 N=313	Naproxen N=1549	Metoclopramide N=800	Sumatriptan N=474	Placebo N=867
Subjects with ↑* CK levels at follow up	53 (2.2%)	5 (1.6%)	26 (1.7%)	17 (2.1%)	10 (2.1%)	8 (0.9%)
Percent with ↑* CK levels at baseline	24 (45%)	3 (60%)	6 (23%)	7 (41%)	4 (40%)	4 (50%)

\*Levels  $\geq$  350 IU/L

Adapted from Sponsor table 18.6.3, iss.pdf

In the entire safety database 3 subjects had clinically significant elevations in their liver function tests. In trial MT100-301, a 51 year old female (PID 301-114-0808) developed a 14 fold increase in her ALT and an 8 fold increase in her AST 24 hours after taking MT100. The case is confounded by concomitant use of sumatriptan (3 doses), Lasix, vitamins, Alka-Selzer and thyroid medication. Repeat liver function tests 5 days later demonstrated a marked reduction in liver function tests towards normal. The patient was referred to her primary care doctor for additional evaluations. In trial MT100-304 two subjects had clinically significant elevations in their liver enzymes. A 40 year old male (PID 304-164-2245) developed a 5 to 6 fold increase in ALT and AST noted 4 days after treatment with naproxen. All laboratories returned to normal 4 days later. In the second case a 24 year old male (PID 304-186-1490) developed a 9 fold increase in his AST level noted 4 days after treatment with metoclopramide. No follow up laboratories are noted in the study report for this patient. His case is confounded by the concomitant use of Maxalt, Midrin and ibuprofen. The label for Reglan (metoclopramide) states that *rare cases of hepatotoxicity have been reported when metoclopramide was administered with other drugs with known hepatotoxic potential*. The label for Anaprox (naproxen sodium) states that *borderline elevations of one or more liver tests may occur in up to 15% of patients and meaningful (3 times the upper limit of normal) elevations of ALT and AST occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with naproxen as with other nonsteroidal anti-inflammatory drugs. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (eg, eosinophilia, rash, etc.), naproxen should be discontinued*. In my opinion a similar warning should be included in the label for MT100 if approved.

The following table summarizes the mean values for each hematology assessment done at baseline and follow up in the acute single dose studies. A review of changes in mean laboratory values comparing baseline to follow up assessments showed no clinically meaningful changes within any treatment group. A review of individual patient shifts from low/normal to high or high/normal to low for each hematology parameter did not show any clinically significant trends or unusual outliers.

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**Table 75** Mean Hematology Values, Baseline and Follow-Up

	MT100 x 1 N=2412		MT100 x 2 N=313		Placebo N=867	
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
Hemoglobin	13.57	13.45	13.61	13.62	13.46	13.35
Hematocrit	40.7	40.1	40.9	40.1	41.0	40.4
RBC	4.52	4.48	4.51	4.48	4.48	4.45
Platelets	268.2	268.4	288.3	266.3	283.3	276.0
WBC	6.870	6.792	7.144	7.026	6.717	6.566
Bands	0.01	0.01	NA	NA	0.25	0.18
Basophils	0.69	0.69	0.71	0.65	0.76	0.76
Eosinophils	1.97	2.02	2.01	1.78	2.04	1.96
Lymphocytes	31.52	31.82	30.70	32.60	32.03	32.38
MCH	30.1	30.1	30.2	30.0	30.2	30.1
MCHC	33.4	33.6	33.3	33.7	32.9	33.1
MCV	90.4	89.7	90.9	89.0	91.9	91.0
Monocytes	5.57	5.54	5.48	5.46	5.31	5.39
Neutrophils	60.29	59.95	61.09	59.47	59.90	59.61

Source: Adapted from Sponsor table 18.7.1 iss.pdf

Includes subjects from trial MT100-201, 301, 303, 304, 306, 308, 401A, and 402.

I reviewed the laboratory changes reported for trial MT100-302 and noted no significant trends or serious outliers. There was no appreciable change in the mean values for any hematology or chemistry parameter from the screening assessment through any follow up assessment. As would be expected for a long term study there were several patients who developed clinically significant abnormal values however few of them were deemed to be treatment related and none required specific clinical intervention. The following cases were considered possibly related to study medication according to the sponsor.

- A 46 year old female (subject 096/0092) had a low WBC count at the 9 month follow up visit (1.94, baseline 5.02). There did not appear to be any contributing factors. The WBC count returned to normal on follow up evaluation.
- A 61 year old female (subject 107/2020) had elevated liver enzymes after 7 months of treatment (ALT 274, AST 110, Alkaline Phosphatase 202). However the AST, ALT and alkaline phosphatase were elevated throughout the study (generally 1 to 2 times normal). Past medical history included hysterectomy, uterine cancer, and lower extremity lymphedema. Concomitant medications included Premarin, multivitamins, Echinacea, Fioricet, and intermittent H<sub>2</sub> blockers (Zantac, Tagamet etc.).
- A 46 year old female (subject 125/2006) was noted to have microcytic anemia at the 3 month visit (HGB 8.8, baseline 13.2). Repeat studies one week later were normal which suggest the earlier low value was in error. Past medical history included a hysterectomy, allergies and multiple knee surgeries. The subject discontinued from the study at 6 months after taking 36 doses of MT100 because the sponsor terminated the study.
- A 43 year old female (subject 133/2007) was noted to have microcytic anemia at the 3 month visit (HGB 9.2, baseline 9.9). Her past medical history included iron deficiency anemia (microcytic). The subject discontinued from the study after 3 months due to lack of efficacy.

Additionally there was a small number of subjects (n=8) who had elevated eosinophils however almost all cases were attributed to seasonal allergies or hives and a few subjects (n=4) were found to have elevated glucose levels (>300). Three of the subjects with post treatment elevated glucose levels had clinically significant elevations in their baseline glucose levels (range 178 to

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266). Additionally a few subjects had transient changes in their electrolytes however there were no consistent trends in these findings. Finally approximately 4.3% of subjects enrolled in trial MT100-302 had post-baseline creatine kinase values that met the criteria for markedly elevated (>350 U/L). Similar rates were seen in earlier single dose studies. The sponsor states no clear relationship between elevated CK levels and treatment were noted.

In summary the safety laboratory data base for MT100 demonstrates no unusual changes in clinical chemistries or hematology. A few patients (<1.0%) experienced transient elevation in liver enzymes or increases in their creatinine kinase levels. Despite the lack of any serious adverse events relative to laboratory findings the label for MT100 should reflect the safety concerns summarized in the labels of its components. For example naproxen use has been associated with prolonged bleeding times, anemia, renal toxicity, and hepatic toxicity; metoclopramide use has been associated with hepatic toxicity.

#### **7.4.8 Vital Signs and Physical Findings**

In most of the early phase I PK trials vital signs and physical evaluations were done at screening, baseline and follow up (MT100-107 had screening values only). Overall there were no clinically significant changes in vital signs or physical findings in each study.

In each phase II and phase III controlled clinical trial vital signs and a physical evaluation were done at baseline and follow up. In the open label, long term study MT100-302, vital signs and physical examination were evaluated at baseline then every 3 months up to 1 year. Overall in all phase II and phase III studies there was no clinically meaningful changes between baseline and follow up for systolic blood pressure, diastolic blood pressure, pulse, or any physical finding.

#### **7.4.9 Electrocardiogram Findings**

In trial MT100-101 serial 12-lead ECGs were conducted at screening, baseline, and days 1, 3, 4, and 5. A review of these ECGs fails to find any clinically significant changes. No other study included ECGs.

#### **7.4.10 Drug-Drug Interaction**

No formal drug-drug interactions studies were conducted during the clinical development program for MT100.

#### **7.4.11 Drug-Disease, Drug-Demographic Interactions, Special Populations**

No formal drug-demographic or drug disease interactions (other than hepatic impairment trial MT100-103) studies were conducted during the clinical development program for MT100. In trial MT100-103 eight subjects with mild hepatic impairment (Grade B or score of 7-9 points on the Child-Pugh Classification<sup>12</sup>) were given a single tablet of MT100. Overall MT100 was well tolerated with only a single patient reporting an adverse event (diarrhea).

There was no significant difference between Caucasian and non-Caucasians for the incidence and nature of adverse events during the clinical program for MT100. There was no significant difference between subjects less than 40 years of age and subjects greater than 40 years of age

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<sup>12</sup> Child-Pugh Grading based on presence of encephalopathy, ascites and the level of serum bilirubin, albumin and prothrombin time each using a 3 point scale.

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for the incidence and nature of adverse events during the clinical program for MT100. There was no significant difference between males and females for the incidence and nature of adverse events during the clinical program for MT100.

#### **7.4.12 Withdrawal Phenomena, Abuse Potential, and Overdose**

Specific studies to assess overdosage and/or the abuse potential of MT100 have not been conducted by the sponsor. However neither naproxen or metoclopramide have been shown to be addictive or result in withdrawal phenomena after years of marketing within the United States and abroad. Additionally, no adverse events of drug abuse or overdose with MT100 were reported in any clinical trial conducted for this NDA.

Despite the lack of demonstrated addiction potential for MT100, migraineurs have been shown in several studies (Diener 1993, Kaube 1994, Limmroth 1999) to be prone to overuse of migraine treatments. Analgesic overuse is a known cause of withdrawal headaches. Overuse of MT100 could potentially be dangerous since repeated and/or high doses of metoclopramide have been shown to produce clinically significant adverse events such as Tardive Dyskinesia (see section 7.4.14 for additional details). For this reason the total monthly doses of MT100 should be limited to what is adequately supported by the safety data supplied in this NDA. Patients should be instructed to not exceed the recommended daily and monthly dose described in labeling. The sponsor proposes that no more than 6 tablets of MT100 should be used in any single month and no more than a single dose of MT100 should be used in a single migraine event. This seems reasonable to this reviewer.

The professional labeling for MT100 should contain language similar to the language seen in the warning and contraindications sections of the Naproxen and Reglan labels relative to overdosages. The label for metoclopramide (Reglan) states overdosage with metoclopramide may result in drowsiness, disorientation and extrapyramidal reactions. Symptoms are self-limiting and usually disappear within 24 hours however anticholinergic drugs, anti-Parkinson drugs, or antihistamines with anticholinergic properties may be helpful in controlling the extrapyramidal reactions. Hemodialysis is of limited benefit. In children accidental overdoses have resulted in seizures, extrapyramidal reactions, and lethargy. Methemoglobinemia has occurred in neonates who were given overdosages of metoclopramide (1-4 mg/kg/day orally, intramuscularly or intravenously for 1 to 3 or more days).

The label for naproxen (Anaprox) states overdose with naproxen may result in drowsiness, heartburn, indigestion, nausea and vomiting. A few patients have experienced seizures, but it is not clear whether or not these were drug-related. It is not known what dose of the drug would be life-threatening. In the setting of naproxen overdose gastric lavage and supportive measures are suggested. Hemodialysis has not been shown to be effective.

The sponsor provides the following information from the published literature relative to the known overdosages of metoclopramide and/or naproxen:

- Beno (1991) reports a fatality (completed suicide) in a 25 year old female after ingesting a large quantity of metoclopramide and diltiazem (calcium channel blocker). The patient had a history of alcoholism and cocaine abuse. On admission the patient had a 3<sup>rd</sup> degree heart block and severe hypotension which progressed to asystole. She was initially resuscitated but

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died 4 days later. One hour after admission plasma levels for metoclopramide was 4.4 mg/L and diltiazem was 8.49 mg/L. Although it is not possible to state with complete certainty in my opinion the cardiac event was most likely caused by the diltiazem.

- Kearns (1988) reports a case of methemoglobinemia in a 3 week old male after receiving metoclopramide (1.0 mg/kg every 6 hours) for 36 hours for the treatment of suspected gastroesophageal reflux. Other symptoms included cyanosis, lethargy, irritability, decreased feeding, diarrhea and respiratory distress. The patient responded well to a single dose of methylene blue.
- Batts (1998) reports a 6 month old infant accidentally overdosed with metoclopramide (24 mg, 3 mg/kg). The patient developed toxic extrapyramidal effects within 9 hours.
- Kulling (1995) reports two cases of transient acute renal dysfunction after an overdose of naproxen. In the first case a 22 year old male presented 3 days after ingested 5 grams of naproxen. The patient experienced repeated emesis and epigastric and lumbar pain. His serum creatinine reached a peak of 227  $\mu\text{mol/L}$  (2.6 mg/L) on day 4 but returned to normal by day 14. The second case was a 19 year old male who was admitted to hospital 2 days after ingesting 3.75 grams of naproxen. He was complaining of malaise, vomiting and lumbar pain. His peak serum creatinine was 330  $\mu\text{mol/L}$  (3.8 mg/L) and returned to normal by 2 months.
- Martinez (1989) reports the development of metabolic acidosis and seizures in a 15 year old female after intentional overdose with naproxen (approximately 14 grams). Soon after the overdose the patient complained of abdominal pain, nausea and dizziness. Within 30 minutes of ingestion the patient became disoriented, combative and vomited. While in the emergency department the patient had a generalized seizure. The patient responded well to supportive therapy and was released without any long term effects.
- Bortone (1998) reports the development of acute encephalopathy in a 36 year old male after intentional overdose with naproxen (90 grams).
- Waugh (1983) reports the development of transient hypofibrinemia in a 16 year old female after intentional overdose with naproxen (10 grams). Several hours after the overdose the patient's prothrombin time increased and remained so for several days. The patient responded well to supportive care and vitamin K supplementation.

In summary, since MT100 is intended for intermittent single dose administration withdrawal effects or abuse potential is not expected. However accidental and/or intentional overdose of MT100 may be associated with serious adverse events.

#### 7.4.13 Human Reproductive Data

The following table summarizes the reported pregnancies that occurred during the clinical development program for MT100. Each study excluded women who were pregnant at screening. In total there were nine pregnancies during the clinical development program for MT100. Three of these subjects were randomized to naproxen during the early factorial studies and 6 of these subjects were randomized to MT100. Of the women taking MT100, three were exposed to a single dose of study medication (PID 6434, 4985, and 4724) and 3 were exposed to multiple intermittent single doses of MT100 during the open label long term study MT100-302 (PID 2002, 1065, and 2020). The outcomes of these pregnancies is summarized in the table below.

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**Table 76** Pregnancy Outcomes

Protocol	Site #	Subject #	Treatment	Outcome
MT100-301	16	637	Naproxen 500 mg	Pregnancy terminated
MT100-301	97	434	Naproxen 500 mg	Infant born with chromosome 2 abnormality and syndactyly of fingers
MT100-304	144	1447	Naproxen 500 mg	Lost to follow-up
MT100-306	115	6434	MT 100	Lost to follow-up
MT100-308	207	4895	MT 100	Delivered normal infant
MT100-308	252	4724	MT 100	Delivered normal infant
MT100-302	13	2002	MT 100	Miscarriage
MT100-302	91	1065	MT 100	Lost to follow-up
MT100-302	118	2020	MT 100	Delivered normal infant

Source: Sponsor table 19, iss.pdf., page 47

In trial MT100-301 a 37 year old female (MT100-301/097/434) delivered a 38 week old infant noted to have syndactyly of the 3<sup>rd</sup> and 4<sup>th</sup> digit of the hand, prominence of the left cardiac ventricle, and development delays associated with chromosome 2 abnormalities. The patient had taken a single dose of study medication (naproxen) on (b) (6) and had a negative pregnancy test on the follow up visit on (b) (6). However on (b) (6) she was noted to be pregnant and an ultrasound at that time dated the pregnancy approximately 13.1 weeks hence the patient was probably early in her first trimester during the time she took study medication. The patient had no concurrent medications or significant past medical history that may have been contributory. The patient preferred method of birth control was condoms. The label for naproxen warns against the use of naproxen during the late third trimester due to an increased risk of neonatal complications such as necrotizing enterocolitis, patent ductus arteriosus and intracranial hemorrhage. The label does not discuss problems seen when naproxen is given in the first trimester and is rated category B (use only if clearly needed). In my opinion the event is probably not related although it is not possible to state this with 100% certainty.

In trial MT100-302 a 42 year old female (MT100-302/013/2002) experienced a miscarriage on (b) (6). The patient had a positive home pregnancy test on (b) (6) and apparently did not see a doctor until she was diagnosed with a miscarriage in early (b) (6). The narrative provided by the sponsor states the patient took MT100 eight times between (b) (6) for recurrent migraines. The patient withdrew from the study on (b) (6) due to lack of efficacy. Concomitant medications included Co-enzyme Q<sub>10</sub>, fish oil, vitamin B complex, calcium, vitamin E, glucosamine sulfate and magnesium all for general health maintenance. The narrative provided by the sponsor does not state how many weeks was the pregnancy but presumably it was very early in the first trimester. As with the earlier case I doubt the event is related to the use of MT100.

In summary the use of MT100 during pregnancy does not appear to result in any untoward effects. None-the-less, the use of MT100 during pregnancy should be discouraged since there are no adequate and well controlled studies that demonstrate safety during pregnancy. Likewise the label for MT100 should include warnings relative to pregnancy similar to those found in the naproxen and metoclopramide labels.

#### 7.4.14 Special Safety Issues/Class Effects

The label for metoclopramide (Reglan) states extrapyramidal symptoms, mainly acute dystonic reactions, occur in approximately 0.2% of patients receiving oral metoclopramide at doses

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between 30 to 40 mg per day and 2% of patients receiving intravenous metoclopramide. Symptoms include involuntary movement of limbs, facial grimacing, torticollis, oculogyric crises, rhythmic protrusion of tongue, bulbar type speech, trismus, opisthotonus and rarely, stridor and dyspnea possibly due to laryngospasm. Motor restlessness (akathisia) may consist of feeling of anxiety, agitation, jitteriness, and insomnia as well as an inability to sit still, pacing, and foot tapping.

During the clinical development program for MT100 there were two subjects reporting acute dystonic reactions. In trial MT100-303 (single attack migraine study) a 30 year old female (PID MT100-303/100/285) developed acute dystonic reaction (verbatim term; Dystonia) of moderate intensity, approximately 65 minutes after using MT100. The investigator treated the event with diphenhydramine and the complaint resolved within 19 hours. The subject's past medical history included migraine without aura, rhinitis, tension headaches, penicillin allergy and hypertension. Her medications included verapamil, nortriptyline, Zocor and oral contraceptives. Given her medication list I assume the patient also had hypercholesterolemia and possibly depression. In trial MT100-302 (long term safety study) a 32 year old male (PID 302/109/2007) reported an acute dystonic reactions following the first dose of MT100 and the subsequent 7 doses of medication. He reported the events as severe following the 3<sup>rd</sup> and 4<sup>th</sup> dose. Oddly he continued in the study and received an additional 17 doses of MT100 without any other reports of dystonic reactions. The subject voluntarily withdrew from the study after 9 months. I reviewed the adverse events database for each trial and could not find any other cases suggestive of an extrapyramidal reaction although there were a few cases of jitteriness and of course other non-specific complaints (anxiety, insomnia etc). The labeling for MT100 should include language similar to that described in the Reglan label for this concern.

Other significant adverse events or safety concerns described in the label for Reglan include the following<sup>13</sup>:

- Drowsiness and sedation occur in approximately 10% of all patients treated with Reglan.
- Metoclopramide is contraindicated in patients with pheochromocytoma (may cause a hypertensive crises), epilepsy or patients receiving other drugs that may cause extrapyramidal reactions (possible increase risk of extrapyramidal reactions), and in patients where the stimulation of gastric motility may be dangerous (i.e., gastrointestinal obstruction, gastrointestinal hemorrhage etc).
- The label for Reglan warns against the use of metoclopramide in patients with mental depression (due to a possible increase risk of suicide) and Parkinson's disease (Parkinsonian-like symptoms can occur with metoclopramide).
- The label for Reglan states Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with metoclopramide. The label warns that the risk appears highest in elderly women and increases with prolonged and cumulative use. Less frequently this syndrome can develop after a relatively brief treatment period with low doses however in these individual the condition is generally reversible.

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<sup>13</sup> The following items are derived from the Reglan professional package insert.

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- Metoclopramide has been shown to cause an increase in circulating catecholamines and aldosterone hence the labels states it should be used with caution in subjects with hypertension, cirrhosis, or congestive heart failure.
- There are isolated reports of convulsive seizures without a clear-cut relationship to metoclopramide.
- Rarely, hallucination have been reported.

The above partial listing of contraindications, warnings, precautions and adverse events clearly demonstrates that metoclopramide should be used with caution and for a limited period of time. Unfortunately the label for Reglan does not describe the primary clinical trials used for approval and does not describe adverse events seen after a single dose. These labeled concerns should be considered when evaluating the proposed label for MT100.

The following significant safety information is from the approved EC-Naprosyn (Roche) label.

- Naproxen is contraindicated in patients in whom aspirin or other nonsteroidal anti-inflammatory/analgesic drugs induce the syndrome of asthma, rhinitis, and nasal polyps due to a possible fatal reaction.
- Serious gastrointestinal toxicity such as bleeding, ulceration and perforation can occur at any time, with or without warning symptoms, in patients treated with NSAIDs.
- Because of adverse findings in animal studies with drugs of this class, it is recommended that ophthalmic studies be carried out if any change or disturbances in vision occurs.
- In humans there have been reports of acute interstitial nephritis, hematuria, proteinuria and occasionally nephrotic syndrome associated with naproxen containing products. Overt renal failure can occur in subjects with pre-renal conditions leading to a reduction in renal blood flow or blood volume. Patients at greatest risk are those with impaired renal function, heart failure, liver dysfunction, the elderly and those taking diuretics.
- Caution should be used in subjects with a creatinine clearance of less than 20 mL/min.
- Borderline elevations of one or more liver tests may occur in up to 15% of patients taking naproxen. Severe hepatic reactions have been reported.
- Peripheral edema has been seen in subjects taking naproxen.
- The label for EC-Naproxen describes a relatively long list of drug-drug interactions (ex aspirin, ACE inhibitors, lasix, lithium etc.) which should be considered when reviewing the label for MT100.
- The label for EC-Naproxen describes a few drug-laboratory interactions (ex. bleeding time, platelets etc.) that should be considered when reviewing the label for MT100.

The above partial list of contraindications, warnings, precautions and adverse events clearly demonstrate that MT100 should be used with caution and for a limited period of time in non-critical self-limiting conditions such as migraine. All labeled safety concerns from metoclopramide and naproxen should be considered when evaluating the final label for MT100.

### 7.5 Safety Update

The only ongoing study using MT100 at this time is trial MT100-403 which is evaluating the safety and efficacy of MT100 in the early treatment of migraine. To date no serious adverse events or unusual adverse events have been reported.

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#### **8. Dosing, Regimen, and Administration Issues**

The recommended dose of MT100 is 1 tablet at the start of a migraine attack. A second dose of MT100 as rescue medication for partial relief or recurrence within 24 hours is not recommended. Additionally the proposed label recommends treating no more than an average of six “headaches” in a 30 day period. Specific labeling comments (ex changing “headache” to migraine attacks) will be provided in a separate document however in general the proposed dosing recommendation is consistent with the safety and efficacy data provided in this NDA.

The sponsor chose the specific formulation of MT100 (metoclopramide 16 mg/naproxen 500 mg) based primarily on their experience from trial MT100-201. Details about this trial are discussed in section 3.2 of this review however in general the safety and efficacy experience from that trial support the choice of metoclopramide 16 mg and naproxen 500 mg. Other combinations evaluated in the trial included placebo, metoclopramide 8 mg/naproxen 500 mg, metoclopramide 8 mg/naproxen 1000 mg and metoclopramide 16 mg/naproxen 1000 mg. Although the metoclopramide 8 mg/naproxen 1000 mg showed the most efficacy relative to pain it did not demonstrate any benefit for nausea (an essential secondary endpoint). Oddly the highest dose group (metoclopramide 16 mg/naproxen 1000 mg) failed to demonstrate efficacy for both pain and nausea. The lowest dose group (metoclopramide 8 mg/naproxen 500 mg) demonstrated efficacy for pain but not nausea. The study was well designed and placebo controlled hence the choice of metoclopramide 16 mg/naproxen 500 mg seems appropriate.

The effects of food on the absorption of MT100 were evaluated in trial MT100-107. The results of the trial are briefly describe in section 3.1 of this review. In general the absorption of metoclopramide was minimally affected when MT100 was administered within 30 minutes after a high fat meal. The absorption of naproxen decreased by approximately 24% although there was no change in the total AUC of naproxen with or without a meal.

#### **9. Use in Special Populations**

The clinical development program for MT100 contains few males, non-Caucasians or elderly subjects. Overall 85% of all participants were Caucasian, less than 10% were African American, 87% were female, and there were no subjects less than 18 years of age. The sponsor does not provide a discussion about subjects greater than 65 years of age in their ISS. In addition to these demographic subset analyses the sponsor also conducted a separate trial to evaluate the safety of a single dose of MT100 in subjects with mild hepatic insufficiency (MT100-103).

##### **9.1 Safety and Efficacy by Gender**

Eighty-seven percent of all participants in the clinical development program were female. This is fairly common in migraine trials since migraine is more frequent in females. The following table summarizes the sponsor’s analysis of the primary endpoint (sustained response) by gender from trials MT100-304 and MT100-301 (factorial studies). The analysis presented uses the post hoc analysis (refined method) used by the sponsor in their original study reports for both trials. As demonstrated in the table the by gender analysis gave mixed results between the 2 studies. In trial MT100-301 34.6% of all women reported sustained response; this was numerically superior to the naproxen cohort (30.7%) and statistically superior to the metoclopramide cohort (20.5%). Whereas in trial MT100-301 a statistically higher percentage of males subjects using MT100 reported sustained response than males using naproxen or metoclopramide (41.4% vs. 22.9% and

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14.3% respectively). Opposite findings were seen in trial MT100-304 where MT100 seems to work better in women than it does in men. However since few men participated in the factorial studies it is difficult to make firm conclusions from this data.

**Table 77 Sustained Pain Response by Gender**

Group	MT100-301			MT100-304		
	MT 100	NAP	MC	MT 100	NAP	MC
All Subjects (%)	35.6 (N=422)	28.8* (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)

NAP = Naproxen sodium; MC = Metoclopramide hydrochloride

\*p<0.05 for MT 100 vs. individual components

Source: sponsor Table 22, ISE.pdf

Relative to safety there was minimal difference between males and females for the incidence and nature of adverse events reported in all trials. Overall 20% of males reported at least one adverse event; the most frequently reported events were diarrhea (4%) and somnolence (3%). This compares to 22% of female subjects reporting at least one adverse event; the most frequently reported events were also somnolence (4%) and diarrhea (3%).

## 9.2 Safety and Efficacy by Age and Race

The following table summarizes the sponsor's analysis of the primary endpoint (2 hour pain response) from trial MT100-306 and MT100-308 by age and race. The sponsor asserts the responses appear to be similar between these demographic groups with non-Caucasians showing the least difference from placebo. Overall approximately 15% of all subjects in the clinical development program are non-Caucasian. In trial MT100-306 and MT100-308 Caucasian subjects taking a single dose of MT100 consistently reported more response at 2 hours than Caucasian subjects taking placebo. Whereas in trial MT100-306 non-Caucasian subjects taking placebo more often reported response at 2 hours than non-Caucasian subjects taking a single tablet of MT100. The reason for this difference is not immediately clear but may be due to the low number of non-Caucasians in trial MT100-306 and MT100-308.

Relative to the sponsor's analysis of response by age both trials demonstrated a good response in both age categories (<45 and ≥45 years). The sponsor does not describe the findings in the elderly (≥65 years of age) however in all studies there were very few subjects age 65 years or older. In trial MT100-306 there were 3 subjects ≥65 years of age and in trial MT100-308 there were 18 subjects ≥65 years of age.

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**Table 78** 2-Hour Pain Response by Age and Race.

Outcome measure	MT 100 x 1	MT 100 x 2	Sumatriptan	Placebo
<b>2-hour Pain Response (%) – Caucasian</b>				
MT100-306	54.8	59.2	56.8	24.1
MT100-308	44.9	NA	47.9	31.1
<b>2-hr Pain Response (%) – Non-caucasian</b>				
MT100-306	43.5	56.8	44.1	48.3
MT100-308	38.8	NA	44.0	36.5
<b>2-hr Pain Response (%) - &lt; 45 Years</b>				
MT100-306	52.9	57.7	45.7	37.7
MT100-308	47.9	NA	45.4	32.7
<b>2-hr Pain Response (%) – ≥45 Years</b>				
MT100-306	52.9	60.0	66.7	15.4
MT100-308	37.2	NA	50.8	30.7

NA = Not applicable  
Source: Sponsor table 23, ISE.pdf

Relative to safety 22% of Caucasians reported at least one adverse event compared to 18% of non-Caucasians. The incidence of diarrhea was the same (3%), somnolence was similar (5% non-Caucasian vs. 4% Caucasian) and dizziness was similar (3% non-Caucasian vs. 4% Caucasian). Twenty-one percent (21%) of 18-40 year olds reported at least one adverse event compared to 22% of subjects > 40 years. The incidence of diarrhea (3% in young, 3% in >40 year olds) and somnolence (5% in young and 4% in >40 year olds) was similar. I reviewed the adverse events for the elderly subjects from each trial and did not see any unique events or concerns.

### 9.3 Evaluation of Hepatic Insufficiency on Safety of MT100

In trial MT100-103 eight subjects with mild hepatic impairment (Grade B or score of 7-9 points on the Child-Pugh Classification<sup>14</sup>) were given a single tablet of MT100. Overall MT100 was well tolerated with only a single patient reporting an adverse event (diarrhea).

### 9.4 Evaluation of Pediatric Program

The sponsor has not proposed a pediatric program. If this NDA is approved the sponsor should evaluate the safety and efficacy of MT100 in the treatment of migraine in adolescent patients.

<sup>14</sup> Child-Pugh Grading based on presence of encephalopathy, ascites and the level of serum bilirubin, albumin and prothrombin time each using a 3 point scale.

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#### 9.5 Comments on Data Available or Needed in Other Populations

The amount of adult safety and efficacy data is acceptable. As with most if not all NDA clinical development programs the amount of safety data is insufficient to adequately assess rare adverse events however both components of MT100 have been approved in the United States for many years. In general naproxen and metoclopramide are considered safe when used as instructed however both products are associated with serious adverse events on rare occasions (previously discussed). The use of MT100 in pregnancy has not been evaluated in a controlled clinical trial and should not be used unless absolutely required. The use of MT100 in renally impaired and hepatically impaired subjects should be consistent with what is labeled in the naproxen and metoclopramide labels.

#### 10. Conclusions and Recommendations

##### 10.1 Conclusions

In section 6.4 I summarize the efficacy findings from the 2 factorial (MT100-301 and MT100-304) and 3 efficacy studies (MT100-306, MT100-308 and MT100-303) done in support of this NDA. In section 7.1 I briefly summarized the safety findings from the clinical development program for MT100.

Overall I do not believe the risk benefit assessment favors the approval of MT100 for the treatment of migraine in adults. First of all I do not believe the 2 factorial studies have adequately demonstrated clinical benefit of MT100 over naproxen although both studies demonstrated clear benefit of MT100 over metoclopramide. While the results for sustained pain response (primary endpoint) of MT100 compared to naproxen strongly trended toward significance ( $p=0.064$  trial 301,  $p=0.063$  trial 304) I believe the small therapeutic benefit of MT100 over naproxen is too small (5.8% trial 301, 3.9% trial 304) to justify the added risks of metoclopramide (ex. tardive dyskinesia). Likewise neither study demonstrated a significant benefit of MT100 over naproxen as measured by the traditional endpoint of headache pain response at 2 hours ( $p=0.665$  trial 301,  $p=0.143$  trial 304). It is my understanding the demonstration of benefit of MT100 over each component is essential to the approval of an NDA. The findings from trial MT100-301 and MT100-304 do not support the approval of this NDA. Despite the problems with the factorial studies the 3 efficacy studies did demonstrate evidence that MT100 is superior to placebo for pain however the 3 studies demonstrated mixed results for the various associated symptoms (see Table 57). Additionally given the added concerns about the findings from the 2-year carcinogenicity study (increased prolactin related tumors/cancers) I do not believe MT100 should be approved.

In conclusion I do not believe the two factorial studies adequately demonstrate the benefit of MT100 over naproxen. Although the results of the primary endpoint analysis strongly trended towards significance, the small therapeutic benefit of MT100 over naproxen is outweighed by the added risks associated with metoclopramide in my opinion. The three efficacy studies collectively demonstrate significant benefit of MT100 over placebo for the treatment of headache pain associated with migraine and mixed results for the treatment of nausea and phonophobia associated with migraine.

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#### **10.2 Recommendations**

In my clinical opinion I do not believe MT100 should be approved for the treatment of migraine in adults.

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/s/

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Eric Bastings  
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I concur with Dr. Prohaska conclusions and recommendations.