AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

MT 100 (naproxen sodium and metoclopramide hydrochloride) Tablets

NDA 21-645

Briefing Document

For

Peripheral and Central Nervous System Drugs

Advisory Committee Meeting

4 August 2005

Sponsor

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1. BACKGROUND INFORMATION

POZEN began the development of MT 100 in 1997. A pre-investigational new drug application (IND) meeting was held with the Division of Neuropharmacological Drug Products (Division) on June 11, 1997. The IND for MT 100 (IND No. 54,039) was submitted on September 5, 1997. An end-of-phase 2 meeting was held on March 31, 1999 and a teleconference, during which endpoints for Phase 3 studies were discussed, was held on March 27, 2000. A pre-NDA meeting was held on June 4, 2002 and NDA 21-645 for MT 100 was submitted on July 31, 2003 and accepted for filing on September 29, 2003.

Throughout the development program for MT 100, frequent and constructive interactions occurred between the Division and POZEN, with numerous discussions of non-clinical and clinical development issues prior to submission of the NDA for MT 100. NDA 21-645 includes the results of six Phase 3 studies intended to provide substantial evidence of the safety and effectiveness of a single dose of MT 100 in the acute treatment of migraine, including a long term safety study. Two of these studies were also intended to provide data to satisfy the requirements of the combination drug policy (21 C.F.R. § 300.50).

On May 28, 2004 POZEN received a Not Approvable Letter (NAL) from the Division.

The NAL describes two efficacy deficiencies: (1) failure to demonstrate efficacy of MT 100 versus placebo in each of two adequate and well-controlled studies, and (2) failure to provide evidence of a contribution of metoclopramide to the claimed effect of MT 100.

The NAL also describes two concerns regarding the safety of MT 100: (1) the potential risk of tardive dyskinesia (TD), and (2) the potential risk to humans of carcinogenicity (secondary to metoclopramide). POZEN also understood from the end-of-review teleconference (June 21, 2004) that the Division's primary concern was the extent of the demonstration of a contribution of metoclopramide to the claimed effect of MT 100.

On October 28, 2004, at POZEN's request, a Type A meeting was held with the Division and POZEN during which the basis for the NAL was further discussed and data and analyses within the NDA were reviewed, including reference to data demonstrating the effect of MT 100 in treatment of migraine attacks without nausea. At that meeting the Division stated that the risk of TD (but not carcinogenicity) remained an approvability issue with respect to MT 100. In a subsequent teleconference on November 10, 2004, the Division advised POZEN that a new study would be needed to support efficacy of MT 100 and advised that such a study could be done in the subgroup of migraine attacks without nausea. The Division also said that it would plan to convene an Advisory

Committee to consider the risk of TD from the metoclopramide component of MT 100. POZEN believes that an Advisory Committee meeting should be held prior to further discussions of the need for additional clinical efficacy studies.

In a subsequent teleconference held on April 28, 2005, the Division advised POZEN that the question of the risk of TD was the primary reason for the Advisory Committee and that the FDA did not anticipate asking the Advisory Committee to consider the overall approvability of MT 100. The Division, however, agreed that POZEN could present efficacy data to allow the Advisory Committee to form an opinion of the possible benefits of MT 100, and also agreed to include the data demonstrating the effect of MT 100 in the acute treatment of migraine attacks without nausea.

In summary, this Briefing Document will present and review:

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B. TARDIVE DYSKINESIA

1. METOCLOPRAMIDE-ASSOCIATED TARDIVE DYSKINESIA

1.1 Introduction

As a potential acute treatment for migraine, the use of MT 100 -- a combination of two marketed products -- would be expected to involve certain risks of side effects known to be associated with each of the two pharmacologically active components- naproxen and metoclopramide.

Within this document, a full discussion of all of the adverse events associated with exposure to either naproxen or metoclopramide will not be undertaken since POZEN understands that a risk of TD has been identified by the FDA as the only remaining safety issue preventing approval of MT 100 for marketing in the United States.

The following statement was contained in the Not Approvable Letter issued by the FDA on May 28, 2004:

> "Further, chronic use of metoclopramide is known to be associated with a finite risk of tardive dyskinesia (TD), a devastating and often irreversible complication. Although you argue that the intermittent chronic use you would propose in product labeling would not be associated with TD, we do not have evidence that this is true. Indeed, given the number of patients exposed to MT 100 for at least one year in your database (about 300), the absence of any detected cases is consistent with a true rate of TD of about 1%, an unacceptably high risk in the absence of any demonstrated advantage of the product."

Subsequently, the Division's Memorandum of Meeting Minutes for the June 21, 2004 end-of-review teleconference states:

> "Tardive dyskinesia (TD) (and carcinogenicity findings) is not significant enough for the Agency to not approve the product if there was conclusive evidence of efficacy. Assuming the sponsor is able to meet the requirements of the Combination Rule and demonstrate efficacy we could describe the TD potential and carcinogenicity findings in labeling."

Following the Type A meeting between the FDA and POZEN on October 28, 2004, the Division's Memorandum of Meeting Minutes (issued on November 10, 2004) states:

> "The Agency told the sponsor that when they submit their NDA package[1], they plan to have an Advisory Committee (AC) meeting because of the risk of tardive dyskinesia (TD) from the metoclopramide. The Agency went on to state that even if an effect could be demonstrated in the non-nauseated group, it was not clear that the benefits of the drug would outweigh the risk, especially of TD.
>
> The Agency told the sponsor that another possibility would be to have the AC meeting before they begin the second study".

These minutes also stated:

> "…the sponsor would then be able to find out if the risk of TD would be considered too high to make the drug approvable."

Following this communication with the FDA, POZEN determined that if the FDA concerns regarding TD were of sufficient magnitude to prohibit the approval of MT 100 in any instance, further clinical studies of MT 100 were not appropriate until a final FDA decision had been reached on the issue of TD.

The designs of the Phase 3 studies which POZEN conducted to evaluate MT 100 were extensively discussed before initiation with the FDA, including the requirement that a long-term (one year) repeat dose safety trial be conducted for MT 100. The stated requirement of the FDA was for a long-term safety study that evaluated at least 300 subjects during 6 months of treatment and 100 subjects treated for one year, in keeping with ICH guidelines. POZEN's study MT100-302 exceeded these enrollment requirements by enrolling a total of 1006 subjects and data submitted in the NDA described 621 subjects treated for 6 months and 329 subjects treated for one year.

Because no cases of TD were seen in any POZEN studies, and therefore no incidence rate could be calculated, it is statistically correct for FDA, in the NAL, to state that a side effect with a true incidence of 1% cannot be ruled out with a database of 300 subjects. This is purely a statistical consideration. However, any implication that TD could occur at that rate (1%) would be unwarranted since other sources of information about metoclopramide and TD are available and will be discussed below.

Based on published data from peer reviewed journals, POZEN believes that the incidence of TD associated with exposure to metoclopramide is, in fact, much lower than 1%. Importantly, there are also data suggesting that the episodic use of metoclopramide (combined with analgesics) in the acute treatment of migraine has not been associated with even a single postmarketing report of TD despite extensive use of this type of treatment in the UK over at least two decades.

[1] The Division informed POZEN during this meeting that a "new study would be needed to support efficacy [of MT 100] in that sub-group, and that ideally it would be done in patients with and without baseline nausea associated with the migraine headache."

1.2 Tardive Dyskinesia

TD is a syndrome involving late onset symptoms of involuntary, often rapid, and abnormal movements. The mouth and tongue are the parts of the body most commonly affected. Common are choreoathetoid movements in the face (tongue protrusions, chewing movements, lip smacking and facial grimacing) as well as writhing or ticlike movements of the limbs and trunk.

The pathogenesis of TD has been explained by dopaminergic supersensitivity resulting from nigral cell damage by long-term neuroleptic use with various degrees of ensuing denervation supersensitivity in the striatal regions of the brain controlling oral and other motions (Seeman 1988)

Standard clinical definitions of TD require that a person be exposed to one or more neuroleptics on a daily basis (continually) for at least 3 months (1 month if older than 60 years), and have documented dyskinetic movements of at least moderate intensity while taking the neuroleptic or within 4-8 weeks of discontinuing the neuroleptic (Jeste 1982, Schooler 1982). Some case reviews have included patients as meeting criteria for TD if they had taken the suspect drug daily for a minimum of 1 month because a minimum of 1 month is necessary to avoid including acute and subacute dyskinesias that are clearly not "tardive" or "late-onset" (Sewell 1992).

The lack of a uniform definition of TD should be taken into account when considering data from databases containing spontaneously reported adverse events, such as the FDA's AERS database, wherein a wide range of health professionals and consumers may submit adverse event reports with unstandardized terminology without requirement for medical confirmation. Lastly, with regard to metoclopramide-associated cases of TD, several reviews in the literature include cumulative reviews of all prior case reports of TD associated with metoclopramide, resulting in some degree of double-counting of cases described in the available literature.

In contrast to TD, acute dystonic reactions usually occur within 24 to 72 hours following administration of a dopamine antagonist drug, are self-limiting, and are reversible upon drug discontinuation. An attack begins suddenly, often building to full intensity within a minute or two of onset. Unlike TD, acute dystonia is more common in younger patients and is rare after the age of 40 years.

1.3 Relative Affinity of Metoclopramide for the Dopamine Receptor

The relative affinity of metoclopramide for the dopamine receptor can be described as within the range of a number of 'looser binding' dopamine antagonists due to its K_i value (P. Seeman, personal communication, 2004), which is higher than the value for dopamine (K_i value of 2.1 nM) and much higher than the K_i values for the typical antipsychotics

having a higher risk of induction of TD (Seeman 1998). The newer atypical psychotics have dissociation constants significantly above that of dopamine.

Endogenous dopamine cannot easily displace typical antipsychotics from dopamine receptors in the brain. Antipsychotic drugs which are more likely to elicit drug-induced Parkinsonism (and perhaps TD) such as chlorpromazine and haloperidol bind more tightly than dopamine to the dopamine D2 receptor, while the antipsychotic drugs are less likely to cause these events (e.g. clozapine, olanzapine) bind more loosely than dopamine to the D2 receptors (Seeman 1998). From the K_i value data we can infer that endogenous dopamine should readily displace metoclopramide from dopamine receptors, because the dissociation constant for dopamine is roughly 8-fold lower than that of metoclopramide.

Peak plasma concentrations of metoclopramide after a single dose of MT 100 are approximately 60 ng/mL (MT100-102 study), or about 200 nM. Although metoclopramide is generally understood to cross the blood-brain barrier, quantitative evidence in humans is lacking in the medical literature. Metoclopramide was found to be nearly 30 times more potent when administered directly into the brains of rats via the cerebral ventricles than when injected intraperitoneally (Herberg 1980). From these observations it may be inferred that about 3% of metoclopramide crosses the blood-brain barrier, and that concentrations of metoclopramide in cerebrospinal fluid should be expected to approximate 3% of the plasma concentrations. Thus, in humans peak brain concentrations of metoclopramide would be expected to be less than 7 nM based on total plasma concentrations, and less than 5 nM based on the percentage of metoclopramide unbound to protein (70%).

At brain concentrations of 5-7 nM of metoclopramide, endogenous dopamine should rapidly displace metoclopramide bound to the dopamine receptor. Because this is a maximal concentration, the average occupancy of dopamine receptors in the brain by metoclopramide is expected to be very low under the conditions of a single dose of MT 100. Because the half-life of metoclopramide is approximately 7 hours after oral administration of MT 100, there should be essentially no metoclopramide remaining bound to dopamine receptors in the brain after 24 hours.

Based on the pharmacodynamic data summarized above, it could be theorized that the episodic use of MT 100 in the acute treatment of migraine would be unlikely to lead to tardive dyskinesia.

1.4 Safety Results from MT 100 Clinical Development Program

In the NDA for MT 100, POZEN submitted results from a total of nine (9) Phase 3 studies evaluating the safety and efficacy of MT 100. Eight of these studies evaluated MT 100 for the acute treatment of migraine headache of moderate or severe intensity. One study (MT100-307) evaluated the efficacy of MT 100 when used during migraine prodrome. A total of 3744 subjects received MT 100 in these studies and a total of 25,830

single tablet doses of MT 100 were administered. POZEN believes that this database is the largest prospectively assembled database to evaluate any dose of metoclopramide for any current indication for this drug. Included are safety data for the 1006 subjects who took part in the 12 month repeat dose study of MT 100 (MT100-302) in the acute treatment of multiple episodes of migraine.

In the overall safety database, the most commonly reported neurologic events were somnolence, dizziness, paresthesia, restlessness and insomnia.

Study MT100-302 was an open-label, long-term study to assess the safety and tolerability of multiple single doses of MT 100 administered for up to one year in the acute treatment of migraine. A total of 1006 subjects were enrolled in this study; 621 subjects participated for 6 months (182 days) and 329 subjects completed 12 months (355 days). Among individual subjects, exposure to MT 100 ranged from 1 to 78 single one-tablet doses and 467 subjects (49%) administered more than 24 doses. Overall, subjects treated a total of 23,195 migraine attacks in this study. The 329 subjects who completed one year of the study treated a total of 12,711 migraine attacks (mean of 39 attacks treated per subject) with a mean interval of 9.7 days between administration of each dose of MT 100.

No cases of TD were reported from study MT100-302. The use of MT 100 for repeated episodes of migraine during this study simulates the expected pattern of clinical use of MT 100 for the acute treatment of migraine. The most common nervous system events reported by subjects enrolled in MT100-302 were somnolence, dizziness, insomnia, restlessness, and headache. One subject in MT100-302 experienced an acute, self-limited dystonic reaction after his first use of MT 100 and after several additional administrations of MT 100. One other subject enrolled in a single attack study of MT100 reported an acute dystonic reaction.

1.5 Current FDA-Approved Indications For Metoclopramide And Safety Information Contained In Product Information

1.5.1 Current Indications for Metoclopramide

In the United States, metoclopramide was first approved for marketing in 1979 and is currently indicated for treatment of adults with symptomatic gastroesophageal reflux disease (GERD) and for the relief of symptoms associated with acute and recurrent diabetic gastric stasis. The approved labeling for Reglan® is included in this document at Appendix 1.

1.5.2 Metoclopramide Dosage and Administration

The recommended dosage of oral metoclopramide for treatment of GERD is 10-15 mg up to four times daily for up to 12 weeks. The recommended dosage for treatment of diabetic gastric stasis is 10mg up to 4 times daily for up to 8 weeks.

Therefore, adults treated for these indications may, under current labeling, receive a cumulative dose of metoclopramide of up to 5040 mg over a period of up to 84 days.

In contrast, the dosage of metoclopramide hydrochloride in MT 100 is 16 mg (13.5 mg of metoclopramide base) and exposure would occur episodically over time in the acute treatment of migraine attacks. In the case of a typical migraineur who might treat a maximum of 6 single migraine episodes per month, the total monthly exposure to metoclopramide hydrochloride might approach 100mg and the yearly exposure to metoclopramide hydrochloride might total 1200mg. This level of exposure is clearly lower than that which is recommended in the treatment of GERD and diabetic gastroparesis administered over a much shorter period of time.

1.5.3 Precautions and Warnings in Current Metoclopramide Labeling

Prescribing information for Reglan® identifies the incidence of acute dystonic reactions as approximately 0.2% (1/500). The prescribing information contains no estimate of the risk of TD with the indicated uses of metoclopramide.

The prescribing information also contains four separate CONTRAINDICATIONS—one of which states that "metoclopramide should not be used in epileptics or patients receiving other drugs which are likely to cause extrapyramidal reactions, since the frequency and severity of seizures or extrapyramidal reactions may be increased."

TD is discussed within the WARNINGS section of the Reglan® prescribing information as follows:

> "Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with metoclopramide. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients are likely to develop the syndrome. Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase with the duration of treatment and the total cumulative dose. Less commonly, the syndrome can develop after relatively brief treatment periods at low doses; in these cases, symptoms appear more likely to be reversible. There is no known treatment for established cases of tardive dyskinesia although the syndrome may remit, partially or completely, within several weeks-to-months after metoclopramide is withdrawn."

The current labeling for metoclopramide warns that TD may occur more commonly in elderly women--a readily identifiable risk group. Recent data also suggests that patients with diabetes - another easily identifiable risk group-- are at increased risk of TD.

The metoclopramide labeling also notes that cases of TD that may occur after "relatively brief treatment periods at low doses" are more likely to be reversible. The proposed use of MT 100 for the episodic treatment of migraine would entail a total monthly exposure to metoclopramide on the order of 64 to 96 mg (if 4 to 6 doses are taken). This dosage might arguably be included in the "low dose" treatment described in metoclopramide labeling, although non-continuous dosing is not presently addressed in metoclopramide labeling.

POZEN believes that if the risk of TD presented by higher daily doses of metoclopramide given for considerably longer periods of continuous treatment is acceptable for patients with gastroesophageal reflux disease (GERD) and diabetic gastric stasis, the risk of TD associated with the episodic use of the low dose of metoclopramide contained in MT 100 should be acceptable for patients with migraine in light of the benefits of MT 100.

1.6 Case-Control Studies

No case-control studies are available that would have direct bearing on estimations of the risk of TD with the episodic use of MT 100 for the acute treatment of migraine. Studies available describe patients with TD associated with chronic daily therapy with metoclopramide and, as such, provide a conservative view of the risk of TD with episodic use. The available studies employed varying methodology of case ascertainment and are reviewed below for completeness.

Although both of the studies reviewed (Ganzini 1993, Sewell 1994) failed to demonstrate a statistically significantly higher incidence of TD in metoclopramide treated elderly patients with chronic disease compared to matched controls, both studies may have been underpowered. Therefore, a link between metoclopramide use and occurrence of TD cannot be excluded by these relatively small studies.

1.6.1 Ganzini L, Casey DE, Hoffman WF, et al.

A case-control study (Ganzini 1993) was conducted which included 51 metoclopramide-treated elderly patients in a Veterans Administration Hospital setting. A total of 51 controls matched for age, gender, and presence of diabetes were utilized. Any patients who were prescribed <20mg / day of metoclopramide, or who received metoclopramide on an as-needed basis, or received less than 3 months' of the drug were excluded. Subjects and controls were evaluated by means of the Abnormal Involuntary Movement Scale (AIMS) and were diagnosed as having TD if a score of moderate or severe was assigned to any of seven body parts or a rating of mild was present in two or more body parts.

Twenty-nine percent (n=15) of metoclopramide users met the case definition of TD compared with 17.6% (n=9) of non-users (P=0.08; McNemar's test). The relative risk of TD was 1.67 (95% CI; 0.93-2.97) and the average daily dose of metoclopramide was 31 ± 11mg and the average duration of use was 2.6 ± 2.0 years.

1.6.2 Sewell DD, Kodsi AB, Caligiuri, MP, Jeste DV

A case control study was reported by Sewell et al (Sewell 1994). These authors evaluated elderly males from a Veterans Administration Hospital, 51 of who were treated with metoclopramide and 35 were "matched" (age, race, gender, diabetes) control subjects. TD was identified in 27% of metoclopramide-treated patients and in 12% of control subjects (p=0.08, two tailed Fisher's Exact test).

1.7 Case Series

Several relatively large case series describing patients with TD thought to be associated with metoclopramide have been published. These provide information on the characteristics of these patients and risk factors that may be associated with occurrence of TD following exposure to metoclopramide.

1.7.1 Sewell DD and Jeste DV

Sewell and Jeste (1992) published an extensive review of metoclopramide associated TD case reports. In their review, the authors included data from 21 separate articles describing 67 cases of TD. Of the 67 cases reviewed, 52 met the criteria for evaluation which included standard diagnostic criteria for TD and a minimum of 30 days exposure to metoclopramide.

Although the authors cautioned that their survey did not prove a causal relationship between metoclopramide treatment and TD, they believed that the information provides "highly suggestive indirect evidence" of an association. In addition, they identified a number of characteristics that can be useful in identifying risk factors or diagnosis.

The average age of the patients was 70 ± 10 years. The female:male ratio was 3:1 and 18 patients had co-existent Parkinsonian symptoms. TD developed during therapy in 81% of the cases, and after discontinuation of therapy in 19% of cases. The mean (± SD) length of treatment with metoclopramide before the onset of symptoms was 20 ± 15 months, and the average dose was 32 ± 7mg. The topographic location of the dyskinetic movements was the face (n=28), tongue (n=21), lips (n=19), jaw (n=19), trunk (n=9) and limbs (n=3). Overall, in 47% of the cases that were analyzed the TD symptoms persisted for at least 6 months. In 14 of the 21 case reports with follow-up information at 6 months or more, TD had not resolved.

Sewell and Jeste concluded by suggesting:

- Metoclopramide should be used with caution in patients who are at high risk of developing TD (e.g., elderly or diabetic patients).
- Patients who require metoclopramide should be monitored at regular intervals for signs of TD.
- If signs of TD appear, even if they are very mild, metoclopramide should be discontinued, if feasible.

1.7.2 Grimes JD, Hassan MN, Preston DN

Grimes et al (1982) described 18 patients with neurologic disorders induced by metoclopramide including acute dystonic reactions (4 patients), Parkinsonism (12 patients), and TD (7 patients). The patients with TD were aged 65 to 76 years and had been taking metoclopramide 20 to 40 mg daily for periods of 14 months to 4 years. In 3 of the 7 patients, dyskinetic facial and tongue movements persisted 15 months after the drug was discontinued.

1.7.3 Miller LG and Jankovic J

Miller and Jankovic (1989) described 16 patients with various movement disorders linked to the use of metoclopramide. Ten of the 16 patients had TD, five patients had drug-induced Parkinsonism and one patient had akathisia. The duration of exposure of patients with TD ranged from 2.5 months to 48 months. These authors included results of an extensive review of the literature on metoclopramide-induced movement disorders (20 references). Although they did not comment on the dose of metoclopramide used in these patients, the review noted that the total daily dose was usually 30mg or higher.

1.7.4 Mejia NI and Jankovic J

Prompted by a case of TD in a 1 year old female that developed following a 17-day treatment with high doses of metoclopramide, Mejia and Jankovic (2005) reviewed cases of TD reported in children since 1972. A total of 63 cases were identified. The authors noted two variables as risk factors for the development of TD; high dose and long exposure to the dopamine receptor blocking drug. Including the report by the authors, a total of 2 cases of TD in children linked to metoclopramide were found.

1.7.5 Wiholm B-E, Mortimer O, Boethius G, Haggstrom JE

Wiholm et al studied TD associated with metoclopramide in Sweden, based on cases reported to the Swedish Adverse Drug Reactions Advisory Committee from 1977 to 1981 (Wiholm 1984). All 11 cases were women, with median duration of treatment with metoclopramide before onset of symptoms of 14 months (range 4 to 44 months). All of the women were aged 69 years or older. The prescribed daily doses ranged from 10 to 60

mg and were often variable, but all cases had taken at least 30 mg a day during parts of their treatment. For all prescriptions of metoclopramide, the average daily dose prescribed was 30 mg, and the duration of treatment was 42 days for each prescription. Thirty percent of prescriptions were issued to patients aged 70 years or more, and 63% were issued to women.

1.8 Prospective Surveillance for Tardive Dyskinesia (UK)

A prospective study by Bateman and colleagues (Bateman 1989) examined the incidence and type of adverse reactions in patients in the UK receiving 'first time' prescriptions for metoclopramide over a 6-month period. Data were reviewed for 2557 patients receiving first prescriptions for metoclopramide "from general practitioners in the Northern Region of Great Britain using community pharmacists to identify prescriptions." It was determined that 50 of these 2557 patients (1.9%) took metoclopramide in conjunction with treatment of migraine. Among the 2557 patients, there were no cases of TD. There were 25 instances of "adverse extrapyramidal events", of which 12 were classified as dystonia-dyskinesia, eight as akathisia, and five as drug-induced Parkinsonism.

1.9 Postmarketing Surveillance for Tardive Dyskinesia

Systems that utilize passive reporting of events (spontaneous reporting) are subject to various strengths and limitations in interpretation of the data collected. Among the strengths of such systems is the fact that a large number of patient exposures should facilitate detection of extremely rare events and provide an indication of the type of events which are expected to occur during actual clinical use.

Limitations of such systems include the inability to calculate a precise incidence of a given adverse event due to: (a) lack of accurate information on total number of exposures to a drug and (b) incomplete reporting (underreporting) of the actual number of patients who experience a given reaction. A further limitation is that the ability to establish the cause of the adverse event is less than desired due to incomplete reporting of relevant clinical data.

TD associated with the use of metoclopramide for any clinical indication appears to be an extremely rare event, given the extensive clinical use of this drug over the past 30 to 40 years and the relative infrequency of reports submitted to passive surveillance systems maintained by regulatory agencies. Data from two governmental agency surveillance systems are reviewed below.

1.9.1 Postmarketing Surveillance for Tardive Dyskinesia (UK)

Metoclopramide was first approved for marketing in the UK in 1967 and the current indications are 1) the relief of symptoms of gastro-duodenal dysfunction, 2) relief of nausea and vomiting, 3) restoration of normal gastric emptying and motility in post-

operative conditions, and 4) as an adjunctive (facilitative) treatment in diagnostic procedures such as radiological examinations and duodenal intubation. An intravenous formulation of metoclopramide is marketed for the treatment of nausea and vomiting associated with chemotherapy.

In the UK, oral metoclopramide (as a single agent) is also indicated for the relief of symptoms of nausea and vomiting and gastric stasis associated with attacks of migraine.

Important for this discussion, is the fact that two fixed-combination drug products containing metoclopramide with an analgesic are marketed in the UK for the acute treatment of migraine. As such, these two combination products are very similar in composition to MT 100 and the indication—acute treatment of migraine—is identical. Thus, the postmarketing adverse event reports for these two products should reflect the potential postmarketing experience with MT 100 in the acute treatment of migraine in the United States. It should be noted, however, that the allowable daily exposure to metoclopramide with use of either of these products for migraine in the UK is approximately twice the dosage of metoclopramide contained in MT 100.

Paramax tablets consist of metoclopramide 5mg and paracetamol 500mg. The adult dosage is two tablets at the start of a migraine attack, then two additional tablets every 4 hours when necessary, to a maximum of six tablets in a 24-hour period (a total of 30mg metoclopramide/24hours). MigraMax sachets contain metoclopramide 10mg and the equivalent of aspirin 900mg. Adult dosage is one sachet in water at the start of a migraine attack and an additional sachet after 2 hours, if necessary, to a maximum of three sachets in a 24-hour period (a total of 30mg metoclopramide/24 hours). Paramax was marketed in 1988 and MigraMax was marketed in 2000. Prior to 2000, a product containing metoclopramide and aspirin (MigraVess) was available in the UK, containing the same dose of metoclopramide.

Spontaneous adverse event data are submitted to the UK Medicines and Health Regulatory Agency (MHRA) ADROIT database through the 'Yellow Card System'. These data can be used to identify the event reports for products containing metoclopramide as a component of the fixed combinations for treatment of migraine as well as reports associated with the use of single-agent metoclopramide products.

For the period of July 1, 1963 to February 11, 2005 a total of 2935 adverse drug reactions identifying metoclopramide as the suspect drug were reported to the MCA (Appendix 2). For 2779 of these reports (95%), the report noted that metoclopramide as a single agent was used. For 156 reports, a combination preparation for migraine containing metoclopramide was named as the suspect drug and 69 events categorized as nervous system disorders were listed. Table 1 below lists the 69 neurologic reactions reported in association with use of metoclopramide-containing combination products for migraine and, for comparison, lists the numbers of each respective reaction reported in association with the use of metoclopramide as a single agent.

Table 1: Adverse Reactions Classified as Neurologic Disorders Reported to the MHRA ADROIT Database (UK) by Metoclopramide Product Type; 1963-2005

Event Reported	Use in migraine product	Use as single agent
Tardive Dyskinesia	0	21
Dizziness	1	33
Parkinsonism	1	6
Opisthotonus	1	30
Torticollis	1	13
Akathisia	1	24
Psychomotor hyperactivity	1	1
Restless leg syndrome	1	0
Speech disorder	1	14
Cerebral hemorrhage	1	0
Cranial Nerve III paralysis	1	0
Headache	1	31
Somnolence	2	61
Trismus	2	7
Balance/Coordination impaired	2	14
Dysphasia	2	3
Dysarthria	3	9
Hypoaesthesia or paraesthesia	3	18
Dyskinesia	3	52
Tremor	7	49
Extrapyramidal Disorder NOS	8	404
Oculogyric Crisis	9	203
Dystonia	17	275
TOTAL REACTIONS	69	---

As shown in Table 1, no cases of TD have been reported in association with the use of any metoclopramide-containing product licensed for use in the UK for the treatment of migraine over the past 42 years. The occurrence of TD in a patient with migraine—typically a young woman—could certainly be characterized as extremely unexpected and, therefore, would be much more likely to be reported through a postmarketing surveillance system such as the one present in the UK.

The three individual reports of ‘dyskinesia’ were examined and found to involve patients with events after the use of MigraVess (aspirin and metoclopramide) and were reported prior to 2000. Each of the reports noted recovery of the patient after withdrawal of the drug and it is likely that these events were acute dystonic/dyskinetic reactions.

1.9.2 Postmarketing Surveillance for Tardive Dyskinesia (USA)

The FDA Adverse Event Reporting System (AERS) Database provides useful information relative to spontaneous reports of specific adverse events, possible attribution to potentially causative drugs, and demographic and other characteristics of patients that might indicate increased risks for certain adverse drug reactions.

A concise and detailed review of the case reports of TD within the FDA AERS database was conducted and recently published (Shaffer 2004). An objective of the authors of this review, several of whom are FDA medical officers, was to assess risk factors for TD as could be determined by review of spontaneous reports of TD associated with metoclopramide use.

The AERS database, containing over 3 million reports collected between 1968 through June 2003, was searched for reports of 'tardive dyskinesia' reported in association with the use of metoclopramide. In an attempt to standardize the data, the authors evaluated each case report to determine if it met the criteria for a TD case definition based on national guidelines as follows:

- Metoclopramide duration of exposure of 30 days or longer
- Documented abnormal involuntary movements (e.g., orofacial, extremity) or symptoms (e.g. akathisia).

The authors also estimated the number of outpatient prescriptions of metoclopramide using IMS HEALTH's National Prescription Audit Plus over a 12 year period from 1992 to 2003.

Their search of the AERS database yielded 98 metoclopramide-associated TD reports, but after the elimination of duplicate reports, 87 patients were included in the analysis. Of these, 40 patients met both study criteria for TD based on duration of exposure and involuntary movements.

Risk factors identified by the authors include the following:

- Increasing duration of use (mean 753 days, +/- 951 (SD) days, range not given)
- Increasing age (average 60 years; range 11 weeks-95 years)
- Female gender (67% of cases)
- Concomitant drug use with neuropsychiatric or CNS drugs (37%)
- Concomitant diseases such as neuropsychiatric illness and diabetes (18%).

The indications for use of metoclopramide were gastroesophageal reflux disease (30% of cases), gastroparesis (14% of cases) and nausea and vomiting (12% of cases).

Of the 87 patients included in the analysis, only 26% reported some disability associated with the disorder. There was no mention of the number of cases of TD that were determined to be irreversible.

In discussing the results of this review, the authors noted that risk factors linked to TD in the case series were increasing duration of use, increasing age, female gender, and certain concomitant drug and disease states.

1.9.3 Other Published Summaries of Regulatory Agency Postmarketing Data

In a report authored by Bateman and colleagues (Bateman 1985), extrapyramidal reactions reported to the Adverse Reactions Register of the Committee on the Safety of Medicines (CSM) in the United Kingdom (UK) were reviewed and compared with data on the prescribing of metoclopramide by general practitioners in the UK. During the 15 year period from 1967-1982, there were an estimated 15.9 million prescriptions for metoclopramide in the UK. The CSM received four (4) reports of TD associated with use of metoclopramide during this period.

1.10 Estimates of Clinical Exposure to Metoclopramide

1.10.1 Introduction

The total number of spontaneous reports submitted to the US and UK regulatory agencies purporting to describe TD cases associated with metoclopramide use is small – a total of less than 150 reports over nearly four decades of marketing in these two countries. In an effort to provide a context for that number of cases, this section will detail information available on the extent of clinical use of metoclopramide in the US and in the UK.

1.10.2 Clinical Exposure to Metoclopramide in the US

Data presented by Shaffer et al summarized the number of prescriptions for metoclopramide for the 12 year period of 1992 through 2003 from IMS HEALTH's National Prescription Audit Plus (Shaffer 2004). An average of approximately 4 million outpatient prescriptions per year were written for metoclopramide. In more recent years, the total number of prescriptions was estimated at between 5 and 6 million, following the market withdrawal of cisapride in 2000. Assuming that an average of 3 to 5 million prescriptions per year have been filled since the initial marketing of oral metoclopramide in the US in the early 1980s, approximately 60 to 100 million prescriptions for oral metoclopramide have been issued since the introduction of this product in the United States.

1.10.3 Clinical Exposure to Metoclopramide in the UK

As noted earlier, there are five approved indications for the use of single-agent metoclopramide in the UK are: (1) the relief of symptoms of gastro-duodenal dysfunction, (2) relief of nausea and vomiting, (3) restoration of normal gastric emptying and motility in post-operative conditions, (4) as an adjunctive (facilitative) treatment in diagnostic procedures such as radiological examinations and duodenal intubation. Metoclopramide was approved for use in the UK in 1967, over 10 years earlier than the first approval in the US. (5) As a single agent oral metoclopramide is also indicated in the UK for the relief of symptoms of nausea and vomiting and gastric stasis associated with attacks of migraine.

As noted earlier, two fixed-combination drug products containing metoclopramide with an analgesic are currently marketed in the UK for the acute treatment of migraine. Paramax tablets consist of metoclopramide 5mg and paracetamol 500mg. The adult dosage is two tablets at the start of a migraine attack, then two additional tablets every 4 hours when necessary, to a maximum of six tablets in a 24-hour period (a total of 30mg metoclopramide/24hours). MigraMax sachets contain metoclopramide 10mg and the equivalent of aspirin 900mg. Adult dosage is one sachet in water at the start of a migraine attack and an additional sachet after 2 hours, if necessary, to a maximum of three sachets in a 24-hour period (a total of 30mg metoclopramide/24 hours). Paramax was initially marketed in 1988 and MigraMax in 2000. Prior to 2000, a product containing metoclopramide and aspirin (MigraVess) was available in the UK, containing the same dosage of metoclopramide.

In January 2004, POZEN commissioned CompuFile Ltd. (UK) to perform a quantitative assessment of the prescribing patterns of UK general practitioners (GP) who treated patients with migraine. Each of the 10 UK Health Authorities was represented by 20 to 55 GPs, and from the actual numbers of patients with migraine treated, projections were made for the entire UK population. The prescribing data for migraine over a 5-year period ending in November 2003 were obtained. A summary of this report is contained in Appendix 3. The survey indicated that of every 10 patients with migraine treated by a GP in the UK, four were prescribed a non-narcotic analgesic, three were prescribed a triptan, two were prescribed an NSAID, and one was treated with a combination preparation containing metoclopramide and either paracetamol (acetaminophen) or aspirin.

The average yearly number of patients with migraine who were prescribed a combination of metoclopramide and either acetaminophen or aspirin each year between 1999 and 2003 was estimated at approximately 95,000. Sales data for this period indicate that an average of 8.1 million individual doses of Paramax or MigraMax were distributed per year in the UK. CompuFile reported that for patients who received Paramax, the most common dosage prescribed was two tablets (or sachets) three times per day, providing a total daily dose of metoclopramide of 30mg.

Data to estimate patient exposure to Paramax or to MigraMax prior to 1999 (or to MigraVess prior to 2000) are not available, and therefore the total patient exposure to available metoclopramide-containing migraine treatments corresponding to the entire period of postmarketing surveillance during which reports have been submitted to the MHRA ADROIT database cannot be estimated. However, the data that are available suggest that as many as 8.1 million doses of metoclopramide have been used by nearly 100,000 patients in the UK each over the past 5 years for the acute treatment of migraine and no cases of TD have been reported.

1.11 Tabular Summary--Evidence for Metoclopramide-Associated Tardive Dyskinesia

Source	TD Cases Identified	Estimated Exposures	Link between metoclopramide and TD	Possible Risk Factors Identified
Prospective Studies				
POZEN Clinical Trial Database	0	25,830 exposures in 3744 subjects	None	None
Post-Marketing Surveillance Studies				
Bateman Prospective	0	2557 patients	None	None
Bateman Retrospective	4	15.9 million prescriptions	Possible	Elderly
FDA AERS Database	87	Approximately 60-100 million prescriptions	Possible	Elderly; increasing duration of use; female gender; concomitant neuropsychiatric or CNS drug use; concomitant illness such as neuropsychiatric or diabetes
MCA "Yellow Card System"-Single component products containing metoclopramide	21	Approximately 40 million prescriptions (1967-2004)	Possible	Elderly

MCA "Yellow Card System"- Multi-component products containing metoclopramide	0	Approximately 40 million prescriptions (1999-2004)	None	None
Case Control Studies				
Ganzini et al	15 (9 cases in placebo group)	51	Possible	Elderly; diabetes; increasing duration of MC use; daily dosage
Sewell et al	14 (4 cases in 34 placebo subjects)	51	Possible	Diabetes; increasing duration of MC use; daily dosage; neuroleptic induced Parkinsonism
Published Case Reports				
Sewell and Jeste[2]	67	1967-1991 (approximate exposures equals total exposure since first marketing)	Possible	Elderly; females; co-existent parkinson's symptoms; increasing duration of exposure; increasing dose.
Grimes et al	7		Possible	Elderly; daily dosage 20-40mg for 14 months to 4 years; dyskinesia persisted in 3/7 patients
Miller and Jankovic	10		Possible	Daily dosage >30mg and duration of exposure 2.5 months to 48 months

[2] This is the largest and most comprehensive collection of published case reports; Some case reports are also included in spontaneous reports.

Mejia and Jankovic	63 cases in children		Possible	Of 63 cases, 2 occurred with metoclopramide exposure; high dosage and long exposure identified as risk factors
Wiholm et al	11	Reports to Swedish ADR Advisory Committee-1977-1981	Possible	Female; median duration of exposure to metoclopramide of 14 months; at least 30mg per day;

1.12 Overall Summary and Estimates of Yearly Risk of TD

Because both naproxen and metoclopramide have been approved for marketing by FDA for indications at doses in excess of those in the proposed MT 100 formulation and labeling, NDA 21-645 was submitted as a 505(b)(2) NDA and relied, in part, on the FDA's previous findings of safety for these component drugs contained within MT 100. The FDA-approved prescribing information for metoclopramide, and information in the FDA AERS database and in the medical literature should be taken into account when considering any risk of TD that might be associated with use of MT 100.

When all such information is fully considered, POZEN believes that the risk of TD that would be associated with the episodic administration of MT 100 is extremely low. This conclusion is based on an assessment of the totality of the information concerning reports of TD associated with metoclopramide exposure and takes into account the extensive use of metoclopramide in both the US and the UK for both non-migraine and migraine indications.

Table 2: Estimated Yearly Risks of TD Based on Cited Sources

Daily Use of Metoclopramide					
Source	**TD Cases**	**Patients Exposed**	**Exposure Estimate**	**Duration**	**Risk/Yr Estimate**
Bateman (1989)	0	2557	-	6 months	0
Bateman (1985)	4	-	15.9 million prescriptions	16 yr	* 0.0002%
Wiholm (1984)	11	-	11 million doses	5 yr	0.001%
Shaffer (2004	87	-	36-60 million prescriptions	12 yr	* 0.001-0.002%
Metoclopramide Use for Acute Treatment of Migraine					
POZEN	0	329	12,711 doses**	12 mo	0
UK	0	-	40 million doses	5 yr	0

* Risk/Yr estimate assumes 1% reporting of incident cases and one course of treatment per patient per prescription; rates are adjusted for number of years cited in study
** Mean number of doses of MT 100 was 39 administered during 12 months in Study MT100-302

Relative to the current risk of TD from the daily use of metoclopramide in the US, the risk of TD from the use of MT 100 for migraine should be put into perspective. If MT 100 is established as an effective migraine therapy, a theoretical risk of TD, which is necessarily lower than the risk of TD with metoclopramide as currently used in the US, should not prohibit the availability of this product for patients with migraine.

2. CLINICIAN ADVISORY PANEL TO CONSIDER THE RISK OF TARDIVE DYSKINESIA WITH USE OF MT 100 IN MIGRAINE

To further assess the risk of TD with the proposed use of MT 100, POZEN convened an advisory panel of clinicians with experience in the assessment and/or management of patients with drug-induced TD. The meeting of these clinicians was held in conjunction with the 9th International Congress of Parkinson's Disease & Movement Disorders on March 6, 2005. Each clinician had been provided with the following information: data describing results of the MT 100 clinical development program for migraine, Phase 3 efficacy data showing the effects of MT 100 versus naproxen sodium in acute treatment of migraine, Phase 3 safety data, including adverse events reported from POZEN Study MT100-302, and data summarized from the literature and from regulatory adverse event registries (FDA and MHRA) providing information describing cases of tardive dyskinesia from post-marketing experience with metoclopramide formulations. These clinicians were aware that the FDA did not conclude that MT 100 was an effective migraine agent and were shown the statement related to risk of TD from the NAL. The consensus statements of these clinicians are attached as Appendix 4.

The advisory panel reached a consensus that the risk of TD with use of MT 100 in the episodic acute treatment of migraine is small (and should not approximate the 1% suggested in the NAL). The risk present can be mitigated and managed through incorporation of the suggested limitations on use, and clear guidance on discontinuation of treatment if there is any evidence of acute dystonia, TD, or any other movement disorder.

The clinician advisory panel agreed on the following recommendations for consideration for inclusion in labeling for MT 100 for use in the acute treatment of migraine.

Contraindications:

- Patients less than 18 years of age and over 65 years of age
- Patients with a history of episodic or persistent dystonia or other involuntary movement disorder
- Patients with Parkinson's disease
- Patients using any dopamine-receptor blocking drug on a chronic basis for any indication.

Warnings:

A patient who experiences a documented acute dystonic reaction, evidence of tardive dyskinesia or other movement disorder following use of MT 100 should not be rechallenged and should not administer any other metoclopramide-containing preparation.

Precautions:

MT 100 should be used with caution in patients with risk factors for TD, including females over 60 years of age, and patients with concomitant diabetes or with concurrent affective disorder requiring drug treatment.

3. RISK ASSESSMENT SUMMARY

POZEN acknowledges that a risk of TD is possible after exposure to any dopamine antagonist drug such as metoclopramide. The need to definitively estimate the potential risk of TD associated with MT 100 was not considered by POZEN or raised by the Division until the NAL. As such, the agreed-upon extent of exposure to MT 100 in the development program was insufficient to exclude a risk as high as 1% for TD, as it would be for any rare event. Despite the long-term marketing and chronic use of Reglan® there are no well-controlled studies of sufficient size which address this issue.

Available case-control studies addressing this issue are quite limited and are not helpful in estimating the risk of TD with the episodic use of metoclopramide. The clinical experience with the use of metoclopramide over nearly four decades of marketing, and a number of published case reports, have resulted in recognition of a fairly well-defined

profile of the patient who is at higher risk for TD as a result of exposure to metoclopramide. This patient profile is generally not applicable to patients with migraine, who are most typically women aged 20-45 years.

POZEN believes that TD associated with chronic daily use of metoclopramide is a relatively rare adverse event, based on an appreciation of the small number of reported cases compared with the extensive use of metoclopramide in the US.

In summary, the extensive use of metoclopramide and the relative infrequency of reports of TD together with the absence of any reported cases of TD associated with the use of metoclopramide in the acute episodic treatment of migraine suggest that TD should not be a significant risk with the use of MT 100 as directed in labeling. Any risk of TD that is present should be lower than for the current uses of metoclopramide in clinical practice.

C. EFFICACY OF MT 100 IN ACUTE TREATMENT OF MIGRAINE

1. CONCEPTS UNDERLYING THE DEVELOPMENT OF MT 100

Within the past decade, a new class of drugs termed the 'triptans' has become a mainstay of migraine therapy and most clinicians believe that triptans are more effective than other migraine products (Lipton 2004). In the United States triptans are often used after over-the-counter (OTC) medications fail. However, triptans are expensive, often costing over $10 per dose (Adelman 2004), and may produce sustained pain-free migraine relief in only about 20% of patients after one dose (Ferrari 2001). There are also concerns about cardiovascular side effects associated with triptans, which have resulted in extensive warnings in the prescribing information for these drugs and in the information made available to patients (Dodick 2004). In one recent large survey, just over a third of patients indicated that concerns about side effects led them to delay or avoid use of some migraine treatments (Foley 2005).

Perhaps owing to their low cost, wide availability, and perceived safety, OTC analgesics are used as initial therapy by the majority of migraine patients for many of their attacks. Drugs such as ibuprofen, aspirin, acetaminophen, or combination products may provide symptom relief for up to 6 hours after a single dose (Wenzel 2003) and several preparations containing these drugs have been approved by FDA for this use.

However, OTC agents have rarely been demonstrated to be effective for patients whose attacks routinely require prescription migraine therapy (Lipton 1998). As reported by both Wenzel and Lipton, the studies evaluating these products usually only included patients who were known responders to OTC medicines, excluded patients who were typically more disabled during migraine attacks and collected headache response data for only 6 to 8 hours. The largest trial that evaluated ibuprofen failed to demonstrate significant relief of nausea, photophobia or phonophobia at two hours after dosing (Codispoti 2001).

MT 100 was designed in 1997 to provide effective and sustained relief of migraine symptoms without the risks of adverse events associated with the use of narcotics, barbiturates, or the vasoactive drugs used in migraine therapy, including the triptans, ergots, Midrin®, and caffeine-containing products that are available over the counter.

Since a number of individual patients with migraine are unhappy with their current therapy and would readily try a new product (Gallagher 2003), a combination tablet containing the long-acting NSAID naproxen and the dopamine-antagonist metoclopramide is thought to be a potentially useful addition to the array of drugs used to treat migraine. Although not indicated for migraine in the US, naproxen had been demonstrated in clinical practice to be effective in migraine. The anticipated effects of metoclopramide in the MT 100 combination were in two areas – to relieve nausea and/or vomiting present in severe attacks and to overcome the gastric stasis that often accompanies migraine and which may be responsible for the delay in the absorption, resulting in poor efficacy of oral drugs used in migraine (Goadsby 2002).

In Phase 1 studies conducted by POZEN, metoclopramide 16mg was shown to accelerate the time to maximum plasma concentrations of naproxen and to increase the maximum plasma concentration of this NSAID. These data are consistent with previous data describing similar effects on the pharmacokinetics of aspirin (Ross-Lee 1982) and acetaminophen (Crome 1980) when these analgesics were administered concurrently with metoclopramide to volunteers as well as to patients during migraine attacks. It was unclear whether the relatively low oral dose of metoclopramide (16mg) would have a positive effect on nausea occurring during a migraine attack.

Because of its non-vascular mode of action, MT 100 was intended to provide an alternative treatment especially useful for patients with cardiovascular disease or contraindications to the use of triptans, ergots, or other vasoactive migraine therapy. MT 100 could also be useful in patients in whom OTC medications fail as primary treatment and/or do not produce adequate sustained pain responses. The inclusion of naproxen, with its long duration of action, within MT 100 was intended to offer the benefit of less relapse after therapy, a problem common to the triptans (Ferrari 2001).

The convenience of having both active agents in the same tablet is important for patients and reassuring to physicians. Unlike the situation with use of individual tablets, administration of a dose of MT 100 ensures accurate and timely delivery of the appropriate doses of each component with every dosing. MT 100 represents a potentially safer, easier, and more effective way for physicians to prescribe this combination for their patients.

In this section of the Briefing Document, the clinical benefits of the inclusion of metoclopramide in MT 100 and the overall efficacy of this unique and rationally designed combination product in the acute treatment of migraine will be discussed. Also highlighted are data demonstrating the greater efficacy of MT 100 in acute treatment of

migraine attacks without nausea, which POZEN believes may be based on the findings from its pharmacokinetic studies.

2. PHARMACOKINETICS OF MT 100

2.1 Pharmacokinetic Studies in Volunteers

Accelerated gastric emptying produced by metoclopramide speeds the movement of naproxen sodium to its absorption site(s) in the small intestine, resulting in faster absorption of the drug than if metoclopramide were not present. To determine the lowest dose of metoclopramide that would improve naproxen absorption, POZEN conducted two studies (Studies 101[3] and 102[4]) to evaluate and identify a dose-response for oral metoclopramide with respect to the onset and rate of absorption of naproxen. Table 3 summarizes plasma concentrations of naproxen administered alone or with increasing doses of metoclopramide of 8 mg, 16 mg, and 32 mg. For direct comparison, plasma concentrations of the doses containing naproxen sodium 1000 mg were dose-adjusted to 500 mg.

Table 3: Plasma Concentrations of Naproxen (C_{max} and T_{max}) with Various Doses of Metoclopramide From Studies MT 100-101[5] and MT 100-102[6]

Doses Administered	C_{max}* (mcg/ml)	T_{max}* (minutes)
500mg naproxen + 0mg metoclopramide	84 (13.2)	72 (57.6)
500mg naproxen + 8mg metoclopramide	83 (13.6)	57 (22.5)
500mg naproxen + 16mg metoclopramide	97 (13.6)	44 (16.8)
1000mg naproxen + 16mg metoclopramide	92 (7.2)	50 (21.8)
1000mg naproxen + 32mg metoclopramide	102 (18.4)	48 (16.4)

* arithmetic mean (STD)

Doses of 16 mg and 32 mg of metoclopramide were similarly effective in shortening T_{max} for naproxen. The average T_{max} ranged from 44 minutes to 50 minutes for these two metoclopramide doses, while the T_{max} for naproxen alone was 72 minutes. The T_{max} for naproxen administered with metoclopramide 8 mg was shorter than with naproxen

[3] Study MT 100-101: "Single Dose Bioavailability Study of Two Doses of MT 100 in Healthy Volunteers."

[4] Study MT 100-102: "A Study to Compare the Pharmacokinetics of MT 100, Naproxen Sodium and Metoclopramide Hydrochloride in Healthy Volunteers."

sodium alone, but not as short as with 16 mg or 32 mg metoclopramide, confirming a dose-response for the metoclopramide acceleration of naproxen absorption. Maximum concentration (C_{max}) of naproxen also increased with 16 mg and 32 mg of metoclopramide, but not with 8 mg. Co-administration with metoclopramide did not affect total exposure (AUC) to naproxen.

In summary, in a Phase 1 studies in volunteers, it was found that the addition of metoclopramide 16 mg to naproxen sodium 500mg shortened the time to the naproxen Tmax from 72 minutes to 44 minutes (arithmetic means) - an improvement of nearly 30 minutes. In addition, the Cmax of naproxen was increased from 84 mcg/mL to 97 mcg/mL (a 15% increase in Cmax) when metoclopramide 16mg was administered with naproxen sodium.

2.2 Pharmacokinetic Studies in Subjects with Migraine

The Phase 1 observations summarized in 2.1 are supported by data from a subsequent pharmacokinetic evaluation of single doses of MT 100 in subjects with migraine who were administered the drug first during a migraine attack and later outside of a migraine attack (Study MT100-106[7]). Although the number of subjects studied was small (n=11), the data suggest that the presence of baseline nausea may be a marker of the severity of gastric stasis that may result in a delay in the absorption of naproxen. The median T_{max} for naproxen in these 11 subjects was 30 minutes (outside of a migraine attack). If the migraine attack was not accompanied by nausea, the median T_{max} increased to 45 minutes, indicating some degree of gastric stasis in migraine without nausea. However, if the migraine attack was accompanied by nausea at the time of administration of MT 100, the median T_{max} for naproxen increased by 126% to 68 minutes indicating a further degree of gastric stasis interfering with the absorption of naproxen.

[7] Study MT100-106: "An Open-Label Study to Investigate the Effect of Migraine Attacks on the Pharmacokinetics of a Single Dose of MT100 (metoclopramide hydrochloride and naproxen sodium) Administration both During and Outside of Migraine Attacks."

Table 4: Naproxen T_{max} in Subjects Administered MT 100 Outside of and During a Migraine Attack by Presence of Baseline Nausea

Population	T_{max} Median (minutes) (SD)	Absolute increase in median T_{max}	Percent increase in median T_{max}
Outside of Migraine Attack, n=11	30 (27)	NA	NA
During Migraine without Nausea, n=5	45 (48)	15 minutes	+ 50 %
During Migraine with Nausea, n=6	68 (28)	37 minutes	+ 126 %

3. STUDY DESIGNS AND EFFICACY RESULTS IN NDA 21-645

The pharmacokinetic data reviewed in Section 2 confirm that metoclopramide present within MT 100 accelerates the absorption of naproxen in volunteers. The data also suggest that nausea accompanying a migraine attack may delay absorption of naproxen, presumably indicating a higher degree of gastric stasis when nausea is present.

In this section of the document, POZEN will: (1) review the data demonstrating that the contribution of metoclopramide is clinically relevant to the anti-migraine efficacy of MT 100, (2) highlight data submitted in NDA 21-645 that confirm the even more substantial contribution of metoclopramide to the efficacy of MT 100 in a significant population of subjects with migraine (e.g., migraine attacks without nausea), and (3) present data showing that MT 100 is an effective drug for the acute treatment of migraine.

Presented below is a discussion of the results of the six Phase 3 clinical studies intended to provide substantial evidence of the efficacy of a single dose of MT 100 in the acute treatment of migraine (Studies 301, 303, 304, 306, 308, and 402). Two of these studies (301 and 304) were also designed to evaluate the contribution of each component to the claimed effect of MT 100 in migraine (Table 5).

Table 5: Study Designs For Six MT 100 Phase 3 Studies

Study	Study Design*	Number of Subjects	Primary Efficacy Variable	Goal of Study
MT100-301	R, DB, MC	MT 100: 423 Nap: 430 Meto: 214	Sustained pain response	Fulfill requirements of combination drug policy
MT100-303	R, DB, P, MC	MT 100: 303 MT 100 (2 tablets): 90 Placebo 1st dose: 34 Placebo 2nd dose: 94	Sustained pain response	Efficacy - single tablet; Efficacy - second single tablet for those who needed rescue
MT100-304	R, DB, MC	MT 100: 1036 Nap: 1062 Meto: 529	Sustained pain response	Fulfill requirements of combination drug policy
MT100-306	R, DB, DD, P, MC, AC	MT 100: 138 MT 100 (2 tablets): 142 Placebo: 137 Suma: 129	2 hour pain response	Efficacy - single tablet; Efficacy - two-tablets; Compare to sumatriptan and placebo
MT100-308	R, DB, DD, P, MC, AC	MT 100: 337 Suma: 343 Placebo: 347	2 hour pain response	Efficacy - single tablet; Compare to sumatriptan and placebo
MT100-402	R, DB, P, MC	MT 100: 118 Placebo: 120	Sustained pain response	Efficacy in subjects with intolerance to triptans or cardiovascular risk factors

*R = randomized, DB = double-blind, DD = double dummy, P = placebo controlled, MC = multicenter, AC = active controlled
Nap = naproxen sodium (500 mg); Meto = metoclopramide hydrochloride (16 mg); Suma = sumatriptan succinate (50 mg)

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In each of the Phase 3 studies, each subject was screened and determined to be eligible to participate. He/she was then dispensed study medication and instructed on how to determine his/her continued eligibility at the time of treatment and how to complete the paper diary. All subjects self-administered study drug in an outpatient setting and recorded their migraine symptoms on a diary at specified intervals (at least hourly while awake) through 24 hours post dose. Rescue medication was allowed 2 hours after study drug dosing, if necessary.

The initial two Phase 3 studies (Studies 301[8] and 304[9]) were identical in design and were conducted to meet the FDA's regulatory requirements for combination products (21 C.F.R. § 300.50). Subjects were randomized to receive a single tablet of MT 100, naproxen sodium 500 mg, or metoclopramide hydrochloride 16 mg and instructed to treat a moderate or severe migraine attack. Metoclopramide was considered a pseudo-placebo to allow evaluations of overall efficacy in these studies. There was no true placebo in these two studies per agreement with the FDA.

POZEN further evaluated the efficacy of MT 100 in the relief of pain and the associated symptoms of migraine in three placebo-controlled studies. The first of these studies, Study 303[10], also evaluated the utility of a second dose of MT 100 in non-responders. Initially, subjects received either MT 100 or placebo. In non-responders, as the second dose, placebo-treated subjects received MT 100, and subjects who received an initial dose of MT 100 were re-randomized to receive either MT 100 or placebo as the second dose. Two additional studies, Studies 306[11] and 308[12], compared MT 100 with over-encapsulated sumatriptan 50 mg and placebo. A two-tablet dose of MT 100 was also evaluated in Study 306.

An additional Phase 3 study was conducted comparing MT 100 with placebo in populations that had either demonstrated intolerance to 5-HT agonists, or had cardiovascular risk factors (Study 402[13]). Study 402 compared a single tablet of MT 100 with placebo.

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8 Study MT100-301: "A Single Dose, Double-blind, Safety and Efficacy Study of MT 100, Metoclopramide Hydrochloride and Naproxen Sodium in Subjects with Acute Migraine Headaches."

9 Study MT100-304: "A Single Dose, Double-blind, Safety and Efficacy Study of MT 100, Metoclopramide Hydrochloride and Naproxen Sodium in Subjects with Acute Migraine Attacks."

10 Study MT100-303: "A Randomized, Double blind, Placebo Controlled Evaluation of One or Two Doses of MT 100 in Subjects with Acute Migraine Attacks."

11 Study MT100-306: "A Double-blind, Placebo-Controlled, (Pilot) Study to Evaluate the Safety and Efficacy of MT 100 versus Sumatriptan in Subjects with Acute Migraine Attacks."

12 Study MT100-308: "A Double-blind, Placebo-Controlled, Study to Evaluate the Safety and Efficacy of MT 100 versus Over-Encapsulated Sumatriptan in Subjects with Acute Migraine Attacks."

13 Study MT100-402: "A Double-blind, Randomized, Placebo-Controlled Study to Evaluate the Safety and Efficacy of MT 100 for Treatment of Migraine in Subjects who are Intolerant to 5-HT Agonists or Have Cardiovascular Risk Factors."

Three additional Phase 3 studies were conducted and reported in NDA 21-645, but are not summarized here because they do not relate to evaluation of the efficacy of a single dose of MT 100 in the acute treatment of migraine: Study 302 (long-term safety) [this study is discussed in Section B.1.4.], Study 307 (prophylaxis study), and Study 401A (two-tablet dose study).

3.1. Component Studies

The NAL stated that the NDA for MT 100:

> "has not established that both active drug components make a contribution to the claimed effects of the product . . . both studies [301 and 304] fail to demonstrate a benefit of the combination over naproxen."

POZEN understood from this statement and from the June 21, 2004 end-of-review teleconference that the Division did not agree that the contribution of metoclopramide in MT 100 had been conclusively shown. However, the NAL also stated:

> "We acknowledge that the MT 100-naproxen comparisons do closely approach statistical significance, and that, therefore, one could argue that, for all intents and purposes, the contribution of the metoclopramide component can be considered to have been demonstrated. In such circumstances, were there an extremely compelling reason to suspend the typical standard for declaring statistical significance, we might be persuaded that these analyses sufficiently document the contribution of metoclopramide."

The Division's conclusion that metoclopramide was not adequately shown to contribute to the overall efficacy of MT 100 appears to rest on two points: (1) the lack of a statistically significant ($p \leq 0.05$) difference in the pre-specified, primary comparisons of MT 100 versus naproxen for Studies 301 and 304, and (2) the opinion that a 4% to 6% increase in treatment effect over naproxen sodium is not clinically relevant.

Regarding the first point, the Division and POZEN have had a number of discussions concerning the methods of statistical analyses of the primary endpoints in Studies 301 and 304. FDA believes that neither study achieved a p-value <0.05 using the protocol-specified analyses. POZEN disagrees. Different methods of analysis were used to obtain different p-values—0.06 in both studies by FDA and 0.03 in both studies by POZEN. A complete review of these discussions and of POZEN's position in support of the analyses submitted with the original NDA are presented in Appendix 5.

The NAL also stated:

> "In addition to the lack of a statistically significant difference between MT 100 and naproxen in the factorial studies, the treatment effect size (for sustained relief) of MT 100 over naproxen is clinically marginal (4-6%)."

POZEN submits that treatment differences on the order of 4-6% between active treatments can be clinically relevant, especially in a disease which involves an estimated several hundred million of attacks per year in the US. Furthermore, the difference in sustained pain response at 24 hours, the primary endpoint in these studies and which represents a composite measure of efficacy, is clinically meaningful.

Expressed another way, if ten percent of the estimated 28 million migraineurs in the US (Lipton 2001) treated an average of three migraine attacks per month with MT 100 instead of treating with naproxen sodium 500mg, a five percent improvement in sustained pain response among the 2.8 million patients would equate to an additional 5 million migraine attacks that did not relapse over 24 hours after treatment and for which additional drug exposure (rescue treatment) was not necessary. POZEN believes that this degree of improvement with the use of MT 100 should be considered clinically significant.

3.1.1 Analyses of the Primary Endpoint for the Component Studies as Submitted Within NDA 21-645

POZEN initially hypothesized that the metoclopramide present in MT 100 might have a beneficial effect on the associated symptom of nausea present during a migraine attack. For this reason, the prospective analysis plans for each of the pivotal Phase 3 studies specified the examination of treatment responses in subgroups of subjects who treated migraine attacks with and without nausea. These secondary analyses were reported in the NDA, and show an unambiguous and statistically significant benefit of MT 100 over naproxen sodium (alone) on the primary endpoint in Study MT100-301 and in Study MT100-304. A possible pharmacologic explanation for the better pain responses with MT 100 treatment in migraine attacks without nausea (e.g., the gastrokinetic effect of metoclopramide) was independently established by previous investigations and confirmed by the POZEN Phase 1 studies. However, it is also possible that another mechanism, i.e. a direct effect of metoclopramide on migraine, could partially explain or contribute to these results (Colman 2004). Whatever the explanation may be, POZEN believes that these data clearly show that the presence of nausea is a discriminator for pain responses in subjects with migraine and that metoclopramide contributes to the efficacy of MT 100.

The Tables below show data for the primary endpoint (sustained pain response) in Study MT100-301 and in Study MT100-304. Table 6 presents the comparisons of responses with each of the three treatment arms in the two studies in the ITT population. The difference in sustained pain response at 24 hours for the MT 100 treatment versus naproxen sodium alone is 6% in Study 301 and 4% in Study 304. The methods of statistical analysis used by POZEN are discussed in Appendix 5.

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Table 6: Sustained Pain Response at 24 Hours - All Migraine Attacks

Study	MT 100 (1)	Naproxen sodium (2)	Metoclopramide	p -value* (1) vs. (2)	p- value** (1) vs. (2)
MT100-301	35.6 % (n=422)	29.8 % (n=429)	19.7 % (n=213)	0.03	0.06
MT100-304	31.8 % (n=1031)	27.9 % (n=1057)	18.8 % (n=528)	0.03	0.06

* POZEN analyses - ordered logistic regression with baseline pain and investigation site as covariates
** FDA analyses

In Table 7, the data from these same two component studies show that, when used in the acute treatment of migraine attacks with nausea, MT 100 produces no significant improvement over naproxen sodium alone for the primary endpoint.

Table 7: Sustained Pain Response at 24 Hours - Migraine Attacks With Nausea

Study	MT 100 (1)	Naproxen sodium (2)	Metoclopramide (3)	p- value * (1) vs. (2)	p- value * (1) vs. (3)
MT100-301	32.2 % (n=192)	31.5 % (n=197)	20.4 % (n=103)	0.78	0.03
MT100-304	29.6 % (n=693)	28.5 % (n=701)	20.0 % (n=366)	0.66	<0.001

* ordered logistic regression with baseline pain and investigation site as covariates

In Table 8, the data from these same two component studies show that, when used in the acute treatment of migraine attacks without nausea, MT 100 produces highly significant improvements over naproxen sodium alone for the primary endpoint. These differences indicate a significant treatment effect of metoclopramide as a component of MT 100.

Table 8: Sustained Pain Response at 24 Hours-Migraine Attacks Without Nausea

Study	MT 100 (1)	Naproxen sodium (2)	Metoclopramide (3)	p -value * (1) vs. (2)	p- value * (1) vs. (3)
MT100-301	38.4 % (n=229)	28.5 % (n=232)	19.1 % (n=110)	0.009	<0.001
MT100-304	36.7 % (n=335)	26.7 % (n=356)	16.1 % (n=162)	0.004	<0.001

* ordered logistic regression with baseline pain and investigation site as covariates

3.1.2. Independent Analyses of the Primary Endpoint Data

POZEN asked Richard B. Lipton, MD, Professor of Neurology, Epidemiology, and Population Health, and Director, Montefiore Headache Unit at the Albert Einstein College of Medicine, New York, NY, to design and conduct independent analyses of the data from the POZEN Phase 3 trials of MT 100 in order to evaluate the strength of the efficacy data observed in subjects without nausea across these Phase 3 trials. In particular, POZEN was interested in whether independent analyses would provide support to the hypothesis that MT 100 was superior to naproxen sodium alone in the acute treatment of migraine in the overall population evaluated in studies MT 100-301 and MT 100-304, and within the subgroup of subjects with migraine without nausea.

Drs. Lipton and Ken Kolodner, Sc.D., (biostatistian) chose to employ methods of analysis that would evaluate dichotomous variables for the comparative evaluations – e.g., MT 100 versus naproxen sodium. A complete description of methods employed is included in Appendix 6. POZEN will provide the full results of the Lipton/Kolodner analyses to FDA in a future submission, but in this section of the document we present three tables showing results of these analyses.

The data from Studies MT100-301 and MT100-304 were independently examined by individual study and in a pooled fashion for the subjects who treated all migraine attacks (Table 9), migraine attacks with nausea (Table 10), and migraine attacks without nausea (Table 11).

Table 9 presents the comparisons of responses to treatment with MT 100 and naproxen sodium in the two studies within the ITT population. By this method of analysis, the p-values for the two studies are 0.08 and 0.05. When the data from the two studies are pooled, the p-value for this comparison is 0.01.

Table 9: Sustained Pain Response at 24 Hours- All Migraine Attacks

Study	MT 100	Naproxen sodium	Crude Odds Ratio	95% C.I.	p- value
MT100-301	35.6 % (n=422)	29.8 % (n=429)	1.297	0.973-1.728	0.08
MT100-304	31.8 % (n=1031)	27.9 % (n=1057)	1.205	0.999-1.454	0.05
Pooled	32.9 % (n=1453)	28.5 % (n=1486)	1.232	1.053-1.442	0.01

Mantel-Haenszel common odds ratio used for pooled studies

In Table 10, as was shown for the individual studies in the analyses submitted within NDA 21-645, the data from the two studies (individually or pooled) show that, when used in the acute treatment of migraine attacks with nausea, MT 100 produces no significant improvement over naproxen sodium alone for the primary endpoint.

Table 10: Sustained Pain Response at 24 Hours- Migraine Attacks With Nausea

Study	MT 100	Naproxen sodium	Crude Odds Ratio	95% C.I.	p- value
MT100-301	32.3 % (n=192)	31.5% (n=197)	1.038	0.687-1.591	0.86
MT100-304	29.6 % (n=693)	28.5 % (n=701)	1.052	0.835-1.326	0.66
Pooled	30.2% (n=885)	29.2 % (n=898)	1.049	0.856-1.286	0.65

Mantel-Haenszel common odds ratio used for pooled studies

In Table 11, as was shown for the two individual studies in the analyses submitted within NDA 21-645, the data show that, when used in the acute treatment of migraine attacks without nausea, MT 100 produces highly significant improvements over naproxen sodium alone for the primary endpoint in both studies individually as well as when the data from the two studies are pooled.

Table 11: Sustained Pain Response at 24 Hours- Migraine Attacks Without Nausea

Study	MT 100	Naproxen sodium	Crude Odds Ratio	95% C.I.	p- value
MT100-301	38.4 % (n=229)	28.5 % (n=232)	1.570	1.063-2.319	0.02
MT100-304	36.7 % (n=335)	26.7 % (n=356)	1.594	1.154-2.202	0.005
Pooled	37.4% (n=564)	27.4 % (n=588)	1.584	1.235-2.032	0.0003

Mantel-Haenszel common odds ratio used for pooled studies

In summary, these independent analyses confirm the results for the primary efficacy endpoint in Studies MT100-301 and MT100-304 as submitted in the MT 100 NDA showing the superior efficacy of MT 100 when compared to naproxen sodium alone in subjects treating migraine attacks without nausea.

3.3 Placebo-Controlled Studies

The NAL stated:

> "In order for the effectiveness of MT 100 to be established as an acute treatment for migraine, you would need to submit at least two adequate and well-controlled trials that demonstrate unambiguous statistically significant superiority of the treatment compared to an appropriate control on a valid measure of pain as well

as on the three associated symptoms of nausea, photophobia, and phonophobia. We acknowledge that Study 306 has met these criteria."

In the following section POZEN will: (1) review the data that the Division agreed provided evidence of efficacy from Study MT100-306, (2) review data showing that Studies MT100-304 and MT100-303 are also adequate and well-controlled studies that provide substantial evidence of efficacy of MT 100 for acute treatment of migraine, (3) review the totality of data from the six well-controlled Phase 3 studies showing the efficacy of single doses of MT 100 in the acute treatment of migraine, and (4) propose that pain is the generally-accepted sole primary endpoint for determining efficacy in migraine studies-- reviewing evidence across all measures of pain response showing that MT 100 is consistently superior to placebo (or the pseudo-placebo metoclopramide).

The data contained in Table 12 shows that in Study MT100-306 at 2 hours, MT 100 was significantly better than placebo for pain response ($p<0.001$) as well as for the incidences of nausea ($p=0.049$) and photophobia ($p=0.002$). The treatment difference in the incidence of phonophobia, though not statistically significant at 2 hours ($p=0.062$), was significant at 1.75 hours ($p=0.034$) and 2.5 hours after dosing ($p=0.017$). Therefore POZEN agrees with the Division that Study MT100-306 is an adequate and well controlled trial demonstrating the efficacy of MT 100.

Table 12: Key Results of Study 306

Study ID	N	MT 100 vs Placebo				
		Sustained Pain Response (2 – 24 hrs)	Comparisons at 2 hours After Treatment			
			Pain Response	Incidence of Nausea	Incidence of Photophobia	Incidence of Phonophobia
MT100 -306	MT 100=138 Placebo=137	34% vs. 22% (p=0.029)	53% vs. 29% (p<0.001)*	28% vs. 39% (p=0.049)	47% vs. 66% (p=0.002)	43% vs. 55% (p=0.062)

* prespecified primary endpoint

POZEN respectfully submits that Study MT100-304 and Study MT100-303 would each meet the Division's current criteria for approval of a drug for migraine, as stated in the NAL. Data to support this view are discussed below in 3.3.1 and 3.3.2.

3.3.1. Study MT100-304

Study MT100-304, along with Study MT100-301, is one of the two studies designed primarily to fulfill the requirements of the combination drug policy by comparing the efficacy of MT 100 with that of each individual component (naproxen sodium and metoclopramide hydrochloride). The metoclopramide component arm was used as a pseudo-placebo arm because in a Phase 2 clinical trial a 16 mg dose of metoclopramide

did not separate from placebo in relief of migraine pain at 2 hours. This design was agreed to by the Division.[14]

Consistent with this agreement, the NAL states:

> "We acknowledge that in the factorial studies (Studies 301 and 304) clear statistically significant between-treatment differences between MT 100 and a single component on all relevant outcome measures would qualify such a study as one providing evidence of effectiveness. Although this did not occur in Study 301, in Study 304 almost all of the MT 100-metoclopramide comparisons yielded statistically significant differences, save for the proportion of patients experiencing Phonophobia."

Although the primary objective of Study MT100-304, as agreed with the Division, was to compare sustained pain response of MT 100 to that of each of its components, secondary measures of pain response, and the incidences of nausea, photophobia and phonophobia at 2 hours were also assessed. In Study MT100-304, MT 100 was significantly better than metoclopramide (the pseudo-placebo) for the primary endpoint of sustained pain response ($p<0.001$) and for pain response at 2 hours ($p<0.001$), nausea incidence at 2 hours ($p=0.003$) and photophobia incidence at 2 hours ($p=0.007$). The MT 100 versus metoclopramide difference for phonophobia incidence was not significant at 2 hours after dosing ($p=0.08$) but was significant at 2.5 hours after dosing ($p=0.005$).

The NAL dismisses the positive results of Study MT100-304 by stating:

> "it is likely that between-treatment contrasts on the other major outcomes reached statistical significance because of the extremely large sample size enrolled."

While the sample size might be considered large for a standard placebo-controlled trial, the sample size for Study MT100-304 was appropriate for the primary objective of this study which was to compare the sustained pain response at 24 hours with MT 100 treatment to that of one of its components -- naproxen sodium -- a drug with known analgesic properties. Moreover, as regards the null hypothesis, the probability of a statistically significant difference is 0.05, no matter how large the sample size. One of the advantages of having a large study is the ability to estimate the magnitude of the treatment effect among all the components with increased precision.

Table 13 shows results from Study MT100-304 in conjunction with the results from Study MT100-306. This side-by-side comparison demonstrates that Study MT100-304 provides evidence of the efficacy of MT 100 which appears equally as valid as the evidence from Study MT100-306.

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[14] Teleconference between the Division and POZEN on May 19, 1999 to discuss the Phase 3 Development Plan for MT 100 filed to IND 54,039 May 10, 1999: serial #026. POZEN minutes of the teleconference filed June 1, 1999: serial #027.

Table 13: Key Results of Studies MT100-306 and MT100-304

Study ID	N	MT 100 vs Placebo				
		Sustained Pain Response (2 – 24 hrs)	Comparisons at 2 hours After Treatment			
			Pain Response	Incidence of Nausea	Incidence of Photophobia	Incidence of Phonophobia
306	MT 100=138 Placebo=137	34% vs. 22% (p=0.029)	53% vs. 29% (p<0.001)*	28% vs. 39% (p=0.049)	47% vs. 66% (p=0.002)	43% vs. 55% (p=0.062)
304	MT 100=1036 Meto[a]=529	32% vs. 19% (p<0.001)*	50% vs. 37% (p<0.001)	34% vs. 41% (p=0.003)	55% vs. 62% (p=0.007)	48% vs. 53% (p=0.08)

* prespecified primary endpoint

[a] The metoclopramide arm served as a pseudo-placebo control in this study.

3.3.2. Study MT100-303

The objective of Study MT100-303 was to evaluate the effect of a second dose of MT 100 for treatment of a single migraine attack of moderate to severe intensity. The primary endpoint for subjects initially randomized to MT 100 or placebo was sustained pain response evaluated from 2 to 24 hours after the initial dose. The protocol-specified primary analysis of sustained pain response called for ordered logistic regression with pooled site, baseline pain and gender as covariates. The resulting p-value for sustained pain response was slightly larger (p=0.054) than $p \leq 0.05$.[15] At the end-of-review meeting, the Division advised POZEN that it did not consider other data from this study because of the p=0.054 on the primary endpoint. POZEN believes this result does not preclude evaluation of the prespecified secondary endpoints of pain response and incidences of nausea, photophobia and phonophobia up at 2 hours when those results are used to evaluate the efficacy of MT 100 versus placebo. Differences after two hours could not be evaluated because use of a second dose of study medication after two hours was an option. However, this design does not diminish the validity of the data obtained at two hours, which are presented below in comparison with data from Studies MT100-306 and MT100-304 (Table 14).

Analyses of the secondary efficacy endpoints of pain, photophobia, and phonophobia at 2 hours after the initial dose of MT 100 demonstrated statistically significant benefit versus placebo with $p \leq 0.05$. The incidence of nausea was not statistically different between treatment groups at 2 hours (p=0.07). However, at 1.75 hours after dosing, the incidence of nausea in the MT 100 and placebo groups was 29% and 39%, respectively (p=0.046). These findings are consistent with results observed in Study MT100-306 and in Study MT100-304 and provide evidence from a third study that MT 100 is an effective agent in migraine versus placebo.

[15] N.B. The NDA originally reported a p-value of 0.048 for this endpoint because gender was not used as a covariate in performing the analysis.

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Table 14: Key Results of Studies MT100-306, MT100-304 and MT100-303

Study ID	N	MT 100 vs Placebo				
		Sustained Pain Response (2 – 24 hrs)	Comparisons at 2 hours After Treatment			
			Pain Response	Incidence of Nausea	Incidence of Photophobia	Incidence of Phonophobia
306	MT 100=138 Placebo=137	34% vs. 22% (p=0.029)	53% vs. 29% (p<0.001)*	28% vs. 39% (p=0.049)	47% vs. 66% (p=0.002)	43% vs. 55% (p=0.062)
304	MT 100=1036 Meto[a]=529	32% vs. 19% (p<0.001)*	50% vs. 37% (p<0.001)	34% vs. 41% (p=0.003)	55% vs. 62% (p=0.007)	48% vs. 53% (p=0.08)
303	MT 100=317 Placebo=108	34% vs. 24% (p=0.054)*	42% vs. 29% (p=0.021)	29% vs. 38% (p=0.07)	48% vs. 63% (p=0.01)	48% vs. 60% (p=0.03)

* prespecified primary endpoint

[a] The metoclopramide arm served as a pseudo-placebo control in this study.

In summary, any two of Studies MT100-306, MT100-304 and MT100-303 would meet the criteria of two adequate and well-controlled studies demonstrating "unambiguous statistically significant superiority of the treatment [MT 100] compared to an appropriate control on a valid measure of pain as well as on the three associated symptoms of nausea, photophobia, and phonophobia."

3.4 Results of Six Well-Controlled Studies of MT 100

Results from Studies MT100-306, MT100-304, and MT100-303, when coupled with those from three other well-controlled studies of the efficacy of a single dose of MT 100 (Studies MT100-301, MT100-308, and MT100-402), provide a totality of evidence that very clearly meets the statutory definition of "substantial evidence" of effectiveness.

The statutory requirement of "substantial evidence" of effectiveness for drug marketing approval in § 505(d) of the FDC Act does not exclusively require data from two adequate and well controlled clinical studies, each one demonstrating statistically significant superiority over a control. Instead, the FDC Act defines substantial evidence as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."[16] The FDA has apparently interpreted this approval standard, in most cases, to require demonstration of a statistically significant ($p \leq 0.05$) effect of the drug in each of at least two pivotal studies. FDA has explained that independent substantiation of a positive outcome protects against unconscious or

[16] FDC Act § 505(d).

conscious bias, a chance finding, lack of generalizability, or scientific fraud.[17] POZEN agrees. However, other independent evidence, such as consistent results in a series of well-controlled studies, even if all results do not reach $p \leq 0.05$ on a pre-specified primary endpoint, can also provide such substantiation. Studies MT100-301, MT100-303, MT100-304, MT100-308, and MT100-402 provide independent substantiation of the results of Study MT100-306. The totality of evidence from these five additional well-controlled studies, and the consistency of results across studies, precludes any reasonable possibility that bias, chance, fraud, or investigator/site-specific factors influenced the outcome of Study 306. Thus, the demonstration of efficacy in Study 306 is confirmed by the five other well-controlled studies and leads to the proper conclusion that MT 100 is effective in the treatment of migraine.

A finding of substantial evidence based on the totality of data from a series of clinical studies is fully consistent with, and arguably more robust than, a finding based on two pivotal studies. That is, a totality of the evidence from multiple studies, for which each of several comparisons, each for a different efficacy measure, shows significant or very nearly significant superiority for the test treatment, provides experts qualified by scientific training and experience a similar basis for fairly and responsibly concluding that the drug is effective. Consistent results showing benefit in six studies certainly constitutes "substantial evidence." A conclusion that independent substantiation can only consist of two adequate and well-controlled studies showing significant benefit in each of four prespecified primary endpoints ignores the fact that data have consistently demonstrated the efficacy of MT 100.

Because Studies MT100-306, MT100-304, and MT100-303 have been previously discussed, this section will focus on the results of Studies MT100-301, MT100-308, and MT100-402. Study MT100-301, like Study MT100-304, was designed to compare the efficacy of MT 100 with that of each individual component (naproxen sodium and metoclopramide hydrochloride). The metoclopramide arm was used as a pseudo-placebo arm for determination of the overall efficacy of MT 100. In Study MT100-301, MT 100 was significantly superior to metoclopramide for its primary outcome of sustained pain response at 24 hours ($p<0.001$) as well as for pain response at 2 hours ($p<0.001$), and for incidence of photophobia at 2 hours ($p=0.033$). The incidence of phonophobia for MT 100 subjects was, however, not statistically different from metoclopramide until 3 hours after dosing ($p=0.006$). The incidence of nausea did not differ significantly between the subjects who received MT 100 and those who received metoclopramide alone through the first 4 hours after dosing in this study, although rates of nausea were always numerically lower at 2 hours and after in the subjects receiving MT 100.

Study MT100-308 was designed primarily to compare the efficacy of MT 100 and sumatriptan (50 mg) using pain response at 2 hours as the primary outcome measure. Secondary analyses included comparison of MT 100 to placebo with respect to percent of

[17] FDA Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, 4-5 (May 1998).

subjects with sustained pain response from 2 to 24 hours after treatment, percent of subjects with pain response at 2 hours, and incidence rates of nausea, photophobia and phonophobia at 2 hours. Study MT100-308 failed to demonstrate statistical equivalence of MT 100 to sumatriptan 50 mg. However, MT 100 was significantly superior to placebo for sustained pain response over 24 hours ($p<0.001$), for pain response at 2 hours ($p=0.001$) and for the incidence of photophobia at 2 hours ($p=0.044$). The difference in incidence of phonophobia was not statistically significant at 2 hours ($p=0.079$), but was significant at 1.75 hours ($p=0.047$) and 2.5 hours ($p=0.036$) after treatment. The incidence of nausea was similar in both groups at 2 hours ($p=0.98$), but MT 100 showed benefit 3 hours after dosing ($p=0.012$).

Study MT100-402 was designed to compare a single dose of MT 100 with placebo with respect to safety and efficacy for acute treatment of migraine attacks in subjects intolerant to 5-HT agonists or with cardiovascular risk factors contraindicating the use of triptans. The protocol-specified primary endpoint was sustained pain response from 2 to 24 hours after treatment. Secondary endpoints included pain response at 2 hours, nausea severity over time (including 2 hours after treatment), and incidence of photophobia and phonophobia at 2 hours. Study MT100-402 called for 470 subjects to be enrolled and treated with study medication. The study was terminated early after 238 subjects had been treated (118 in the MT 100 treatment group and 120 in the placebo treatment group) due to slow enrollment. Despite the small sample size in Study 402, MT 100 was significantly better than placebo for the primary efficacy measure of sustained pain response ($p=0.002$) and for pain response at 2 hours ($p<0.001$). There were no significant differences for associated symptoms until 3 hours or more after dosing in this study. Treatment differences were 12% for phonophobia, 10% for nausea and 6% for photophobia at 2 hours, each in favor of MT 100. Results for Study MT100-402 are included in Table 15 below.

When taken as a whole, the data demonstrate the efficacy of a single dose of MT 100 for the acute treatment of migraine, including effects on pain and the associated symptoms of nausea, photophobia and phonophobia. While treatment group (MT 100 vs. placebo) differences for 2 hour incidence of associated symptoms (nausea, photophobia, and phonophobia) were not all significant, the magnitudes and directions of these differences are consistent, and consistently in favor of MT 100 in all six studies.

Statistically significant effects were observed with MT 100 versus placebo or pseudo-placebo:

- On pain response in all six studies at 2 hours after treatment
- On photophobia incidence at 2 hours in five of six studies
- On phonophobia incidence
  - Up to or at 2 hours in three studies
  - At 2.5 hours in one study (data not shown in Table 15)
  - At 4 hours in two studies (data not shown in Table 15)

- On nausea incidence
  - Up to or at 2 hours in three studies
  - At 3 hours in two studies (data not shown in Table 15)

The data for the associated symptom of nausea are notable considering that statistical significance was achieved in three studies up to or at 2 hours even though only approximately 60% of subjects studied had nausea at the time of treatment.

Table 15: Results of Six Well-Controlled Studies of MT 100

Study ID	N	MT 100 vs Placebo				
		Sustained Pain Response (2 – 24 hrs)	Comparisons 2 hours After Treatment (vs. Placebo)			
			Pain Response	Incidence of Nausea	Incidence of Photophobia	Incidence of Phonophobia
MT100-306	MT 100=138 Placebo=137	34% vs. 22% (p=0.029)	53% vs. 29% (p<0.001)*	28% vs. 39% (p=0.049)	47% vs. 66% (p=0.002)	43% vs. 55% (p=0.062)
MT100-304	MT 100=1036 Meto[a]=529	32% vs. 19% (p<0.001)*	50% vs. 37% (p<0.001)	34% vs. 41% (p=0.003)	55% vs. 62% (p=0.007)	48% vs. 53% (p=0.08)
MT100-303	MT 100=317 Placebo=108	34% vs. 24% (p=0.054)*	42% vs. 29% (p=0.021)	29% vs. 38% (p=0.07)	48% vs. 63% (p=0.01)	48% vs. 60% (p=0.03)
MT100-301	MT 100=423 Meto[a]=214	36% vs. 20% (p<0.001)*	48% vs. 34% (p<0.001)	24% vs. 25% (p=0.646)	54% vs. 63% (p=0.033)	46% vs. 52% (p=0.129)
MT100-308	MT 100=337 Placebo=347	30% vs. 18% (p<0.001)	44% vs. 32% (p=0.001)	42% vs. 43% (p=0.98)	55% vs. 63% (p=0.044)	51% vs. 58% (p=0.079)
MT100-402	MT 100=118 Placebo=120	40% vs. 20% (p=0.002)*	54% vs. 33% (p<0.001)	34% vs. 44% (p=0.141)	60% vs. 66% (p=0.446)	48% vs. 60% (p=0.07)

* prespecified primary endpoint

[a] The metoclopramide arm served as a pseudo-placebo control in these studies.

Shown below in Tables 16 and 17 are the data for sustained pain response and pain response at 2 hours following treatment with MT 100 or placebo (or metoclopramide as a pseudo-placebo) in the subgroups of subjects with migraine attacks with or without nausea. These data were included in NDA 21-645.

As shown in Table 16, in three of the four studies in which sustained pain response was the primary endpoint, MT 100 was statistically superior to placebo or pseudo-placebo for this endpoint in migraine attacks with nausea. Pain response at 2 hours was numerically greater with MT 100 treatment and significantly greater in three of six studies.

Table 16: Pain Responses in Migraine Attacks With Nausea

Study ID	N	Sustained Pain Response (2-24 hrs)	2 hr Pain Response
MT100-306	MT 100=95 Placebo=84	36% vs. 25% (p=0.148)	54% vs. 32% (p=0.009)
MT100-304	MT 100=693 Meto[a]=366	30% vs. 20% (p<0.001)*	48% vs. 36% (p<0.001)
MT100-303	MT 100=156 Placebo=52	30% vs. 23% (p=0.551)*	36% vs. 29% (p=0.490)
MT100-301	MT 100=192 Meto[a]=103	32% vs. 20% (p=0.032)*	45% vs. 35% (p=0.079)
MT100-308	MT 100=217 Placebo=209	25% vs. 16% (p=0.015)	39% vs. 32% (p=0.103)
MT100-402	MT 100=73 Placebo=76	41% vs. 21% (p=0.012)*	55% vs. 36% (p=0.024)

* prespecified primary endpoint

As shown in Table 17, in three of the four studies in which sustained pain response was the primary endpoint, MT 100 was statistically superior to placebo or pseudo-placebo for this endpoint in migraine attacks without nausea-in the fourth study the p-value was 0.06. In five of six studies, MT 100 was significantly superior to placebo (or metoclopramide as a pseudo-placebo) for pain response at 2 hours.

Table 17: Pain Responses in Migraine Attacks Without Nausea

Study ID	N	Sustained Pain Response (2-24 hrs)	2 hr Pain Response
MT100-306	MT 100=42 Placebo=53	31% vs. 17% (p=0.118)	50% vs. 25% (p=0.096)*
MT100-304	MT 100=335 Meto[a]=162	37% vs. 16% (p<0.001)*	55% vs. 37% (p<0.001)
MT100-303	MT 100=161 Placebo=56	37% vs. 25% (p=0.051)*	47% vs. 29% (p=0.034)
MT100-301	MT 100=229 Meto[a]=110	38% vs. 19% (p<0.001)*	51% vs. 34% (p=0.006)
MT100-308	MT 100=114 Placebo=129	39% vs. 20% (p=0.002)	54% vs. 33% (p=0.001)
MT100-402	MT 100=43 Placebo=44	40% vs. 18% (p=0.060)*	53% vs. 27% (p=0.023)

* prespecified primary endpoint

4. BENEFIT ASSESSMENT SUMMARY

The efficacy of MT 100 was demonstrated for pain responses at 2 hours versus placebo in six of six trials and MT 100 demonstrated significant benefit over placebo in producing sustained pain response at 24 hours in all migraine attacks. The most clinically relevant measures of the efficacy of a migraine treatment arguably include the sustained pain response at 24 hours and/or the sustained pain-free response at 24 hours.

The evaluation of the efficacy of MT 100 for the associated symptoms of migraine was not a primary focus of the MT 100 development program, as initially discussed with the Division. Thus, the Phase 3 studies were intentionally not powered to rigorously assess efficacy of MT 100 for the associated symptoms. Nevertheless, the data indicate that MT 100 has meaningful treatment effects for each of the associated symptoms of migraine.

The significantly better efficacy of MT 100 in the treatment of the headache pain in migraine attacks without nausea, a clinical finding present in 50% or more of individual attacks, was not fully discussed within the NDA for MT 100. Although the data demonstrating better efficacy of MT 100 versus naproxen sodium alone (and versus placebo) in migraine attacks without nausea were submitted for FDA review, the importance of these findings in this large subgroup was not emphasized by POZEN in that submission. This was because POZEN was confident that the analyses of Studies MT100-301 and MT100-304 in the overall population which demonstrated significant differences ($p=0.03$ in both studies) between the sustained pain response endpoint for MT 100 versus naproxen sodium would satisfy the requirements of the combination drug policy (21 C.F.R. § 300.50). The combination drug policy stipulates that each component of a combination drug must make a contribution to the claimed effect in a significant patient population. POZEN believes that this requirement has been convincingly met in the clinical setting of migraine without nausea as well as in the overall population as a whole.

POZEN believes that a review of the data submitted in the MT 100 NDA contained in this document, supplemented by the independent analyses of the primary endpoint data from Studies MT100-301 and MT100-304 addressing the contribution of metoclopramide to the combination, should serve to confirm the efficacy of MT 100 as an acute treatment for migraine. In particular, the significant margin of efficacy of MT 100 over naproxen sodium alone in treatment of migraine attacks without nausea should support a role for MT 100 in treatment of this condition.

D. OVERALL RISK / BENEFIT CONSIDERATIONS

POZEN believes that the Division's opinion that the risk of TD with the use of MT 100 could be as high as 1% is not supported by a reasonable interpretation of the available data, as has been reviewed in this document. There may be a minimal risk of TD with the proposed use of MT 100, but extensive use of metoclopramide-containing products for the treatment of migraine in the UK has not been associated with the report of any cases. POZEN continues to believe that TD associated with the episodic use of metoclopramide in the treatment of migraine would occur exceedingly rarely, if at all.

POZEN commits to collaborate with the FDA to agree appropriate labeling for MT 100 intended to mitigate any risk of TD when MT 100 is used in the acute treatment of migraine. POZEN proposes that such labeling take into consideration the recommendations of its clinician advisory panel, as summarized in this document.

The potential benefits of MT 100 as an additional treatment option for patients in the United States should not be overlooked, nor should the comparative safety profile of MT 100. In the United States, the array of treatments available for migraine include various over-the-counter medications, many of which have not been evaluated in the manner required for prescription medications for migraine. In addition, narcotic analgesics are often used as non-specific treatments for migraine and may pose risks of medication abuse. If a migraine attack is not adequately treated with an OTC medication or the equivalent, the next specific option for migraine treatment is usually a drug of the triptan class. Many patients do not tolerate the side effects of triptans and the use of this class of drugs is contraindicated in some patients with migraine. Between November 1997 and February 2002, the FDA AERS system received 561 reports of cardiovascular events associated with use of one or more triptans, and that 49 of these events had a fatal outcome (Dodick 2004). There is a pressing medical need for additional effective and non-vasoactive treatments for migraine.

POZEN believes that the benefits of MT 100 in the treatment of all migraine attacks has been conclusively shown by the data obtained on its use in the treatment of over 3000 subjects evaluated in clinical trials. In addition, the greater degree of efficacy of MT 100 observed in the treatment of migraine attacks without nausea, a clinical presentation common in a large proportion of attacks, serves to further enhance the benefit-to-risk ratio of this treatment for an individual patient with migraine.

APPENDIX 1 **Reglan® Package Insert**

APPENDIX 2 **MHRA Document -- Postmarketing AEs with metoclopramide**

APPENDIX 3 **Information on Use of Metoclopramide for Treatment of Migraine in UK obtained from CompuFile Limited**

APPENDIX 4 **Consensus Statement by Clinician Advisory Panel**

APPENDIX 5 **Sustained Pain Response – Statistical Analyses of this Endpoint in Study 301 and Study 304**

APPENDIX 6 **Independent Analyses by Drs. Lipton and Kolodner**

REFERENCES