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RESEARCH**

APPLICATION NUMBER:

21-618

21-681

21-682

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

NDA/Serial Number: 21,618/000 (trichomoniasis indication)
21,681/000 (giardiasis indication)
21,682/000 (amebiasis indication)
250 mg and 500 mg tablet

Drug Name: Tinidazole

Indication(s): Trichomoniasis, Giardiasis, Amebiasis

Applicant: Presutti Laboratories, Inc.

Date(s): Application: July 16, 2003
Received: July 17, 2003
User Fee: May 17, 2004

Review Status: Standard Review

Biometrics Division: Division of Biometrics III (HFD-725)

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Keywords: NDA review, clinical studies, meta-analysis

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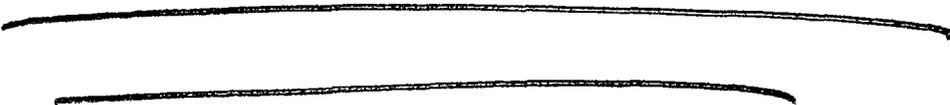
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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

This is a 505(b)(2) NDA containing published references and data summaries pertaining to the use of tinidazole for the treatment of trichomoniasis, giardiasis, and amebiasis. Although the quality of each published study is on average poor, lacking standard randomization methods and blinding procedures, collectively the studies support the claim that 2 g tinidazole is an effective treatment for the above mentioned indications.



1.2 Brief Overview of Clinical Studies

1.2.1 Trichomoniasis Indication

This submission contains a total of 35 published studies for the treatment of trichomoniasis using a single 2 g dose of tinidazole (TNZ). These 35 studies are comprised of 18 non-comparative studies, 3 dose ranging studies, and 14 comparative studies. The review of the trichomoniasis indication will focus only on the 14 comparative studies [Table 1.1]. Comparative treatments used in these 14 studies were placebo (n=3), 2 g metronidazole (MTZ) (n=5), 1.6 g MTZ (n=1), 200 mg tid x 10 days MTZ (n=1), 5 g x 10 days MTZ (n=1), 1.5 ornidazole (ORN) (n=2), and 2 g carnidazole (CARN) (n=1). Of these 14 studies, the Sponsor selected five studies to serve as pivotal in the NDA submission on the basis of size (number of patients enrolled and treated) and design (blinded).

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Table 1.1 Comparative trichomoniasis studies using a single 2 g tinidazole dose

Publication	Comparator**	Population	Design
Lyng, 1981*	PL (MP group only)	F, MP	DB, R (code)
O'Prasertsawat, 1992*	1.6 g MTZ	F, MP	DB, R (pt selected blinded box)
Hillstrom, 1977*	1.5 g ORN	F, MP	DB, R (random sampling numbers generated)
Chaisilwattana, 1980*	1.5 g ORN	F, MP	DB
Gabriel, 1982*	2 g MTZ	F	SB, R (method not discussed)
Rees, 1974	PL x 1 day	F	DB
Mati, 1974	PL	F	DB
Weidenbach, 1974	2 g MTZ	F	OL, R (method not discussed)
Anjaneyulu, 1977	2 g MTZ	F	R (method not discussed)
Rao, 1978	2 g MTZ	F	OL, R (method not discussed)
Bloch, 1985	2 g MTZ, 2 g benzoyl MTZ	F,MP	OL
Aimakhu, 1975	200 mg t.i.d x 10 days MTZ	F, MP	DB, R (assignment drawn from basket by nurse)
Beric, 1978	5 g x 10 days MTZ	F, MP	OL
Chaudhuri, 1980	2 g CARN	F, MP	DB, R (method not stated)

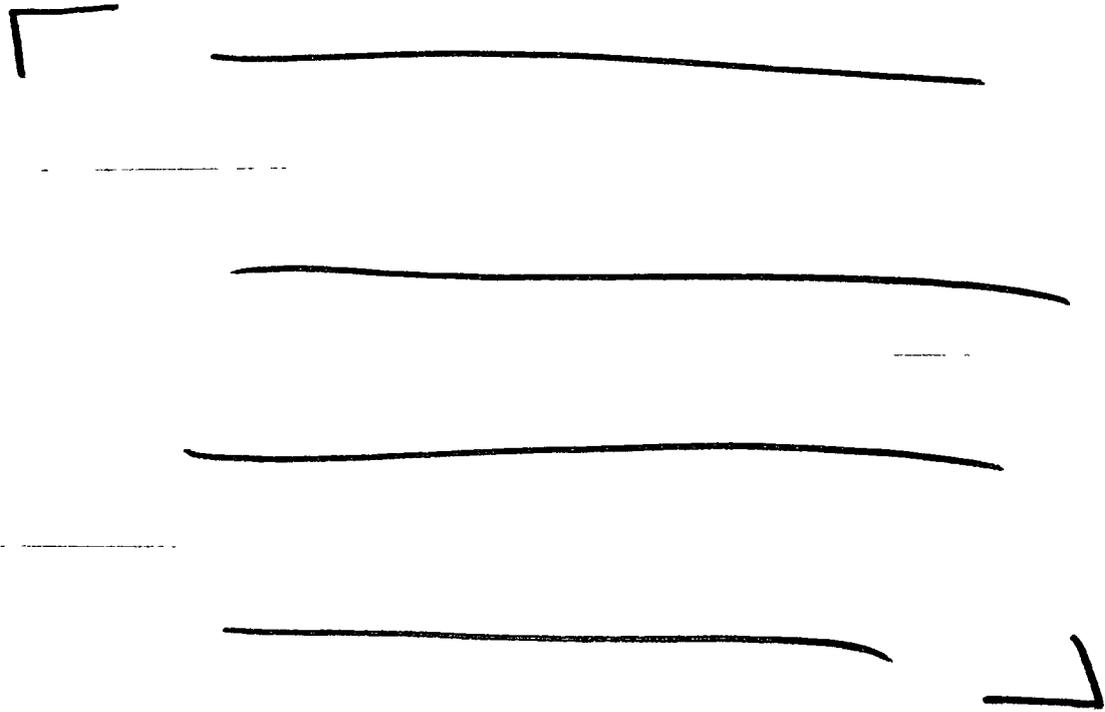
* selected by Sponsor as pivotal study

** Unless otherwise specified, all comparator treatments were given as a single dose

PL=placebo, MTZ=metronidazole, ORN=ornidazole, CARN=carnidazole

DB=double blind, SB=single blind, R=randomized (method), OL=open-label

F=adult female, MP=adult male partner



1.2.2 Giardiasis Indication

This submission contains 23 published clinical studies evaluating TNZ in the treatment of giardiasis in both children and adults. Of these 23 studies, 6 were non-comparative, 2 used multi-day TNZ treatment and 15 studies were comparative evaluating a single day treatment of TNZ. Fourteen of the 15 comparative studies evaluated a single 2.0 g (50 mg/kg in children) dose of TNZ versus an active comparator or placebo (including one comparing TNZ 2 g x 1 day against TNZ 150 mg bid x 7 days) and one study compared a single 1.5 g dose of TNZ versus an active comparator [Table 1.3]. Of these studies, the Sponsor selected four to serve as pivotal studies based on size and design.

Table 1.3 Comparative giardiasis treatment studies

Publication	TNZ Dose	Population	Comparator	Design
Jokipii, 1979*	2 g x 1 day	85 A	MTZ 2.4 g x 1 day, MTZ 2.4 g x 2 day	SB, R (alternate assignment)
Jokipii, 1982*	1.5 g x 1 day	100 A	ORN 1.5 g	SB, R (alternate assignment)
Kyronseppa, 1981*	2 g x 1 day	50 A	MTZ 2 g x 2 days	R (code)
Bakshi, 1978*	50 mg/kg x 1 day	186 C	MTZ 50 mg/kg x 1 day	SB, R (method not discussed)
Gadzer, 1977	50 mg/kg x 1 day	100 C	MTZ 50 mg/kg x 1 day	not discussed
Nigam, 1991	50 mg/kg x 1 day	75 C,A	MTZ 50 mg/kg x 1 day	R (code)
Krishnamurthy, 1978	50 mg/kg x 1 day	60 C	MTZ 50 mg/kg x 1 day	OL, R (code)
El Masray, 1978	2 g x 1 day	55 A	PL	not discussed
Jokipii, 1978	2 g x 1 day	45 A	TNZ 150 mg bid x 7 days	OL, NR
Farahmandian, 1978	50 mg/kg x 1 day	175 C,A	PL	OL, NR
Speelman, 1985	2 g x 1 day	30 C,A	MTZ 50 mg/kg x 1 day	SB, R (pt drew assignment from envelope)
Suntornpoch, 1981	50 mg/kg x 1 day	121 C	ORN 50 mg/kg x 1 day	OL, NR
Pengsaa, 1999	50 mg/kg x 1 day	113 C	ALB 400 mg x 3 days	R (method not discussed)
Sabchareon, 1980	2 g x 1 day	124 C	MTZ 2 g x 1 day, PL	not discussed
Bassily, 1987	2 g x 1 day	80 A	ORN 1 g x 1 day	SB, R

* selected by Sponsor as pivotal study

C= children, A=adults

ORN=ornidazole, MTZ=metronidazole, ALB=albendazole, PL=placebo

DB=double blind, SB=single blind, R=randomized (method), NR=not randomized, OL=open-label

1.2.3 Amebiasis Indication

1.2.3.1 Intestinal Amebiasis

This submission contains 26 published clinical reports evaluating tinidazole for the treatment of intestinal amebiasis. Twelve of these studies compared TNZ against MTZ, eight studies were non-comparative and six studies used a different dose of TNZ as the comparator treatment. The non-comparative studies and the studies with TNZ as the comparator were excluded from this review since they do not provide comparative efficacy and safety information for the proposed 2 g x 3 days dose of TNZ. Additionally, studies by Welch [1978] and Bassily [1987] were excluded because they included patients who had both giardiasis and amebiasis infections at the time of treatment. The study by Salles [1999], which used a suspension preparation of 0.5 ml/kg TNZ, was also excluded.

The remaining nine comparative clinical studies in intestinal amebiasis [Table 1.4] evaluated TNZ (2 g x 3 days or 600 mg bid x 5 days) against MTZ (2 g x 3 days, 400 mg tid x 5 days or 800 mg tid x 5 days). The Sponsor selected four comparative, randomized studies [Swami, 1977; Singh, 1977; Misra, 1977; and Bakshi, 1978] to serve as pivotal studies.

Table 1.4 Comparative studies in the treatment of intestinal amebiasis

Publication	TNZ Dose	Comparator	Design
Swami, 1977*	2 g x 3 days**	MTZ 2 g x 3 days **	OL, R ('randomization schedule'-no details provided)
Singh, 1977*	2 g x 3 days	MTZ 2 g x 3 days	OL, R (method not discussed)
Misra, 1977*	2 g x 3 days	MTZ 2 g x 3 days	OL, R (method not discussed)
Bakshi, 1978*	2 g x 3 days	MTZ 2 g x 3 days	SB, R (method not discussed)
Misra, 1974	600 mg bid x 5 days	MTZ 400 mg tid x 5 days	SB, R (method not discussed)
Joshi, 1975	600 mg bid x 5 days	MTZ 400 mg bid x 5 days	OL, R (method not discussed)
Pehrson, 1984	600 mg bid x 5 days	MTZ 800 mg tid x 5 days	OL, R (method not discussed) vague study-pilot design
Chunge, 1989	2 g x 3 days	MTZ 400 mg tid x 5 days	R (method not discussed)
Prakrashi, 1974	600 mg bid x 5 days	MTZ 400 mg tid x 5 days	OL, NR (alt pt assignment)

*selected as pivotal by Sponsor, **additional days of treatment required for some patients,

TNZ=tinidazole, MTZ=metronidazole, DB=double blind, SB=single blind, R=randomized (method), NR=not randomized OL=open-label

1.2.3.2 Amebic Liver Abscess

A total of 18 clinical studies using TNZ in the treatment of amebic liver abscess were identified by the Sponsor. Nine of these studies were comparative and nine were non-comparative. Seven of the nine comparative studies evaluated a 2 g x 2-5 days dose of TNZ versus 2 g x 2-5 days of MTZ (six studies) or 400 mg tid x 5 days MTZ (one study). The Sponsor has selected the seven studies, which evaluated a 2 g x 2-5 days TNZ treatment, as pivotal and the remaining two studies as supportive.

Table 1.5 Comparative studies in the treatment of amebic liver abscess

Publication	TNZ Dose	Comparator	Design
Mendis, 1984*	2 g x 3 days	400 mg tid x 5 days MTZ	DB, DD, R (code table)
Kundu, 1974*	2 g x 3 days	2 g x 3 days MTZ	OL, R (code table)
Khokhani, 1977*	2 g x 2 days	2 g x 2 days MTZ	OL, R (method not discussed)
Mathur, 1977*	2 g x 2 days	2 g x 2 days MTZ	OL, R (method not discussed)
Islam, 1978*	2 g x 3 days**	2 g x 3 days MTZ**	OL, R (method not discussed)
Simjee, 1985*	2 g x 5 days**	2 g x 5 days MTZ**	SB, R (method not discussed)
Bakshi, 1978*	2 g x 2 days	2 g x 2 days MTZ	OL, R (method not discussed)
Hatchuel, 1975	800 mg tid x 5 days	800 mg tid x 5 days MTZ	DB, R (method not discussed)
Lasserre, 1983	1 g bid x 1 day	1 g bid x 1 day ORN	DB, R (method not discussed)

*selected as pivotal by Sponsor

**additional days of treatment required for some patients

TNZ=tinidazole, MTZ=metronidazole, ORN=ornidazole, DB=double blind, DD=double dummy, SB=single blind, R=randomized (method), OL=open-label

1.3 Statistical Issues and Findings

To identify clinical controlled trials evaluating TNZ in the treatment of trichomoniasis, giardiasis and amebiasis, the Sponsor conducted literature searches using the Medline and Embase databases. These databases provide access to thousands of published trials in science and medicine and are therefore utilized in many systematic reviews and meta-analyses. Although these databases are quite extensive and widely used by the scientific community there can be biases when using these database. A primary concern with these database searches is of publication bias in which studies with favorable results were more likely to be submitted and accepted for publication compared to studies with less favorable results. The source of funding or other support for selected studies introduces additional publication bias. Negative studies sponsored by the pharmaceutical industry are less likely to be published than those supported by the government or by voluntary organizations, with investigators citing the data management by these companies as a reason for non-publication.

An additional concern with these databases is that they are more likely to contain studies conducted in English speaking countries than studies conducted in developing, non-English speaking countries. Whereas most of the major west European journals that are published in languages other than English are indexed in Embase or Medline, this is not the case for journals published in less developed countries. Among the 3000 to 4000 journals indexed by Medline, Embase, or the Science Citation Index, only about 2% are from the less developed world [Egger, 1998].

Another concern is multiple publication bias, where the same positive results are reported multiple times leading to an overestimation of treatment effect.

Inconsistencies among study entry criteria and endpoints are additional concerns regarding these database reviews and meta-analyses. Heterogeneity among study endpoints and outcomes can lead to uninterpretable meta-analyses results.

Statistical methods exist, which are discussed in detail in the reviewer's statistical methods section, to investigate the presence of heterogeneity and/or bias.

Aside from the general statistical concerns regarding database searches and meta-analyses, statistical issues identified during the review of this NDA include: improper randomization techniques used in several of the referenced studies, dated (1970's and 1980's) studies, lack of blinding in several studies, and insensitive diagnostic procedures used in several of the trichomoniasis studies.

Compared to today's clinical standards and Good Clinical Practices, the studies in this submission are of poor quality. Several of the referenced studies used insufficient randomization methods such as alternate treatment assignment (i.e. every other patient received TNZ), treatment selection by subject (i.e. two boxes, each containing one of the study treatments, placed in front of patient and patient asked to choose one), treatment assignment chosen from a basket by the unblinded study coordinator. Additionally, several of the studies were open-label, particularly in studies of amebic liver abscess and intestinal amebiasis, leading to treatment bias. The laboratory method used to diagnosis infection in the trichomoniasis studies varied between the culture method and the wet preparation method. Approximately one-half of the trichomoniasis comparative studies used the wet preparation method, which is considered to lack in sensitivity compared to culture diagnosis.

2. INTRODUCTION

2.1 Overview

This New Drug Application submitted by Presutti Laboratories, Inc. (Sponsor) is a 505(b)(2) application for the approval of tinidazole for the treatment of trichomoniasis, giardiasis, and amebiasis (to include liver abscess and intestinal amebiasis). Tinidazole, for the treatment of giardiasis, trichomoniasis, and amebiasis, has been in clinical use throughout most of the world for over 30 years and several reports have been published on its use. Studies/reports published in the scientific literature serve as the clinical submission for efficacy and safety in this NDA. The Sponsor was not required to conduct additional Phase III comparative studies.

Tinidazole is a second generation 5-nitroimidazole, similar to metronidazole, with activity against protozoa and anaerobic bacteria. Pfizer Laboratories Ltd originally developed tinidazole and has marketed the drug, in several countries excluding the United States and Canada, since the 1970's under the trade name Fasigyn®. Tinidazole is approved for use in the UK, Australia, Austria, Belgium, Costa Rica, El Salvador, Finland, France, Germany, Guatemala, Honduras, Italy, Japan, Mexico, Netherlands, Nicaragua, Panama, South Africa, Spain, Sweden and Switzerland for many indications including trichomoniasis, giardiasis, and amebiasis.

2.1.1 Brief Background on Trichomoniasis

Trichomoniasis is a common sexually transmitted disease (STD) due to infection with *Trichomonas vaginalis*, a flagellated protozoan. Trichomoniasis is a sexually transmitted disease that occurs in both women and men but is more common in women. The World Health Organization (WHO) estimates the worldwide prevalence of trichomoniasis is 170 million, which is greater than that of gonorrhea or chlamydia. In the US, the prevalence of trichomoniasis in women is 3-5 million; the incidence in men is unknown. Approximately 15% of women presenting to US STD clinics are found to have trichomoniasis. Trichomoniasis is found in most partners of those infected (14-60% of male partners and 67-100% of female partners). The risks associated with vaginal trichomoniasis are pelvic inflammatory disease, infection following gynecologic surgery, cervical inflammatory neoplasia, increased risk of HIV virus seroconversion, and amniotic fluid infections. Additionally, trichomoniasis is associated with adverse birth outcomes such as premature delivery or rupture of the membranes and low birth weight.

In the US, metronidazole is the only marketed FDA approved product for the treatment of trichomoniasis. The CDC recommends a treatment regimen of 2 g orally in a single dose [CDC MMWR, 1/23/98, 47 (RR-1); 1-118]. An alternative MTZ regimen is 500 mg twice daily for seven days. The FDA has approved 375 mg of MTZ twice a day for 7 days for treatment on the basis of PK equivalency of this regimen with metronidazole 250 mg three times a day for 7 days.

2.1.2 Selection of published studies on the treatment of trichomoniasis

Given the vast number of clinical trials conducted using tinidazole for the treatment of trichomoniasis, the Sponsor was not required to conduct further trichomoniasis trials. The Sponsor conducted a literature search for all trichomoniasis studies using TNZ using Medline (Medical Literature, Analysis, and Retrieval System Online) and Embase as the primary search databases. The Sponsor also reviewed references from TNZ review papers. From this search, the Sponsor identified 35 published reports (*Sponsor indicates in summary that 34 reports were identified but table 11.3, Volume 1.9 of 1.17 of NDA submission lists 35 studies*) using a single 2g dose of TNZ for the treatment of trichomoniasis. Of these studies, 14 were comparative and 9 were comparative and blinded (8 DB, 1 SB). The Sponsor selected five studies [Lyng, 1981; O'Prasertsawat, 1992; Chaisilwattana, 1980; Gabriel, 1982; Hillstom, 1977] as pivotal based on larger sample size and treatment blinding. The remaining four blinded comparative studies were chosen as supportive studies.

2.1.3 Brief Background on Giardiasis

Giardiasis is an infectious diarrheal disease caused by the parasite, *Giardia lamblia*, and is most commonly transmitted through oral-fecal contact, either directly from person to person by physical contact, or indirectly via food and water contaminated with feces. Giardiasis is one of the most common

intestinal parasitic diseases infecting up to 20% of the world's population. The disease is most prevalent in developing countries, where infections are associated with poor sanitary conditions, poor water quality control, and overcrowding. In the United States, the annual infection rate of giardiasis is approximately 100,000 cases. It occurs most commonly in campers and hikers from drinking fecal contaminated water, in children in day care centers, and in homosexual men.

There are several recommended treatments (metronidazole, quinacrine, tinidazole, furazolidone and paromomycin) [The Medical Letter, April 2002] in adults and children but only one US FDA approved treatment (furazolidone). Recommended metronidazole dosing in adults is 250 mg tid x 5 days and is 15 mg/kg tid x 5 days in children resulting in cure rates between 85 and 95%. Because of the potentially adverse effects on a fetus, pregnant women are advised not to take metronidazole during the first trimester of pregnancy. Furazolidone (given as 100 mg x 7-10 days in adults and 6 mg/kg qid x 7-10 days in children) and quinacrine (given as 100 mg tid x 5 days in adults and 2 mg/kg tid x 5 days in children) are both effective but are no longer commercially available in the US. Although not approved by the FDA for giardiasis, paromomycin (recommended dosing is 25-35 mg/kg/d x 7 days in adults and children) is available in the US.

NTZ kids

2.1.4 Selection of published studies on the treatment of giardiasis

Using Medline and Embase as primary databases, the Sponsor identified 15 comparative clinical studies using TNZ for the treatment of giardiasis. Fourteen of the 15 comparative studies evaluated a single 2.0 g (50 mg/kg in children) dose of TNZ versus an active comparator or placebo and 1 compared a single 1.5 g dose of TNZ versus an active comparator. Using size and design as selection criteria, the Sponsor selected four studies [Bakshi, 1978; Jokipii, 1982; Jokippi, 1979; Kryonseppa, 1981] to serve as pivotal for this indication. Three of these studies were single blind, one was open-label and all were randomized to either TNZ or active comparator. One study [Bakshi, 1978] studied children and the other three studied adults. Efficacy rates in the four pivotal studies ranged from 88 to 94% and rates in the non-pivotal studies ranged from 80 to 97%. (For completeness all 15 comparative studies will be included in this review.)

2.1.5 Brief Background on Amebiasis

Amebiasis is an infection caused by the protozoal organism *Entamoeba histolytica* and includes intestinal amebiasis and liver abscess. *E. histolytica* probably is second only to malaria as a protozoal cause of death. In developed countries, infection occurs primarily among travelers to endemic regions, recent immigrants from endemic regions, homosexual males, immunosuppressed persons, and institutionalized individuals. Transmission usually occurs by food-borne exposure, particularly when food handlers are shedding cysts or food is cultivated in feces-contaminated soil, fertilizer, or water. Less common means of transmission include contaminated water, oral and anal sexual practices, and direct rectal inoculation

through colonic irrigation devices.

The worldwide prevalence rate of amebiasis is approximately 10% with rates as high as 50% in areas of Central and South American, Africa and Asia and as low as 4% in the United States. In 1993, a total of 2970 cases of amebiasis were reported to the Centers for Disease Control and Prevention; 33% occurred in Hispanic immigrants and 17% in immigrants from Asia or the Pacific Islands. Amebic liver abscess is 7-12 times more common in men than in women, although the sex distribution is equal in children. The prevalence of amebic colitis and liver abscess is estimated at 40-50 million cases annually worldwide, resulting in 40,000-110,000 deaths. Young children appear to be at higher risk for severe invasive disease, resulting in a higher mortality rate.

Asymptomatic amebiasis is a risk factor for future development of invasive disease; therefore, affected patients should be treated with iodoquinol (FDA approved), paromomycin, or diloxanide furoate (available only through the CDC). Recommended treatment [The Medical Letter, April 2002] of intestinal amebiasis (i.e. colitis, liver abscess) is with metronidazole (FDA approved dose in adults is 750 mg tid x 7-10 days and 3-5 mg/kg in 3 doses x 7-10 days in children) or tinidazole (recommended (unapproved) dose in adults is 800 mg tid x 5 days and 60 mg/kg x 5 days in children) plus a luminal agent to eradicate colonization.

2.1.5.1 Selection of published studies on the treatment of intestinal amebiasis

The Sponsor identified a total of 26 published clinical reports, which studied tinidazole for the treatment of intestinal amebiasis. Of these 26 reports, 9 controlled studies were identified in which eight were randomized and two were blinded (single blind). The Sponsor selected four studies [Bakshi, 1978; Swami, 1977; Singh, 1977; Misra, 1977] to serve as pivotal studies. All of these studies evaluated the intended tinidazole dose of 2g/day x 3 days. One additional study [Chunge, 1989] was not chosen by the Sponsor as either pivotal or supportive but will be reviewed since it evaluated the proposed 2 g x 3 days TNZ treatment. The remaining three studies [Joshi, 1975, Misra, 1974, Pehrson, 1984, Prakrash, 1974] evaluated a split dose (600 mg/bid x 5 days) tinidazole regimen and were therefore not chosen as pivotal by the Sponsor. *For completeness, all nine comparative studies will be discussed in this review.*

2.1.5.2 Selection of published studies on the treatment of amebic liver abscess

The Sponsor identified 18 published clinical reports using tinidazole in the treatment of amebic liver abscess. Nine of these studies were comparative against MTZ and nine were non-comparative. Of the nine comparative studies, three were double-blind, one was single-blind and the rest were open-label. The Sponsor selected seven studies [Khokhani, 1977; Mathur, 1977; Islam, 1978; Simjee, 1985; Bakshi, 1978; Kundu, 1977; Mendis, 1984] to serve as pivotal based on dose of TNZ used (2 g x 3-5 days). Two other studies evaluated different doses of TNZ: 800 mg tid x 5 days [Hatchuel, 1975] and 1 g bid x 1 day [Lasserre, 1983] and were therefore selected as non-pivotal supportive studies by the Sponsor. *For completeness all nine comparative studies will be reviewed.*

2.2 Data Sources

This submission contains published clinical reports identified by the Sponsor through Medline and Embase database searches. Medline is the National Library of Medicine's primary database containing over 12 million references from over 4,600 worldwide journals. Embase, the Excerpta Medica database, is a bibliographic database covering over 3,800 worldwide journals on biomedical and pharmaceutical

fields. Search criteria for both databases included: tinidazole, trichomoniasis, giardiasis, amebiasis, and clinical studies. No other sources of clinical data were included in this submission.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Sponsor's Analyses

No formal statistical analyses were provided by the Sponsor. Summary tables, by indication, were provided, which contain treatment effect rates and exact test p-values. For each indication, the Sponsor selected four to seven studies to serve as pivotal based on relative sample size, dose of TNZ studied (2 g dose) and design (randomized, blinded, comparative). The Sponsor provided combined efficacy success rates as simple proportions of total successes over total treated for the studies selected as pivotal and combined efficacy rates for all controlled studies identified. The Sponsor did not provide any statistical analyses of combined study efficacy rates.

3.1.2 Reviewer's Analyses

3.1.2.1 Statistical Methods

Treatment success among the studies in trichomoniasis was defined as the microscopic absence of *T. vaginalis* infection at protocol-specified follow-up visit(s). In giardiasis, treatment success was generally defined as the absence of either *G. lamblia* trophozoites or cysts in follow-up stool samples. Among the intestinal amebiasis studies, treatment success was generally defined as the clearance of *E. histolytica* parasites from follow-up stool samples. Several of these studies also considered the clinical relief of symptoms associated with infection in determining treatment success. Studies in amebic liver abscess defined treatment success as relief of signs and symptoms along with normal radiological and laboratory findings.

Meta-analyses were performed on data groups pooled according to treatment indication, study type (pivotal or non-pivotal as chosen by Sponsor), comparator used (active or placebo), diagnostic test (trichomoniasis indication), population studies (giardiasis indication) or tinidazole dose. Since treatment outcome was binomial (cured or not cured) in all the selected studies, the risk difference was measured as the difference in success rates. Study event rates and rate differences and combined effect rates (point estimates) with respective 95% confidence intervals were calculated. Event rates were calculated as the ratio of success over total treated for each study arm. Study rate difference was calculated as the difference in event rates between the two treatment arms (TNZ-comparator). The chi-square test for homogeneity, derived from the Q statistic [DerSimonian, 1986], was used to test for between-study heterogeneity. When the Q statistic was significant the random effect model was used, otherwise the fixed effect model was used [DerSimonian, 1986]. The fixed effect model assumes that all studies came from a common population such that the only source of variance is the within-study variance. The fixed effects rate is calculated as the sum of each study's rate difference times the weight (inverse variance) divided by the sum of the weights. Under the random effects model, the assumption that studies did not originate from the same population is made and therefore variance comes from both the within-study differences as well as the between-study variance. The random effects rate is calculated as the sum of each study's rate difference times the weight divided by the sum of the weights where weight is the inverse of the sum of

the within study and between study variances. The test of difference in treatment rate for both fixed effects and random effects uses the z-value (combined effect rate/standard error).

To evaluate consistency among selected studies, tests for heterogeneity were performed using the Q statistic. This statistic is a cumulative sum of the squared distance of each study from the combined studies effect multiplied by the study's assigned weight [$\Sigma \text{ weight}_i (\text{individual outcome} - \text{combined outcome})^2$]. Weight is calculated as the inverse of the square of the standard error of the individual outcome. The Q statistic will follow a chi-square distribution for degree of freedom=k, where k=number of outcomes minus one under the null hypothesis that all studies originate from the same population. A significant p-value suggesting heterogeneity was further explored using graphical tests (funnel plots) and further pooling analyses. A positive test for heterogeneity requires the use of the random effects model to estimate the treatment effect rate. The fixed effect rate can be considered when the Q statistic is insignificant. The concern of sufficient power with the Q statistic can be addressed by comparing the fixed effects rate with the random effects rate. Both values should be approximately equal when a sufficiently powered Q statistic is insignificant.

Funnel plots, which are simple scatter plots of a study's effect estimates (x-axis) against its precision (y-axis), were analyzed to test selection bias among selected studies. Precision was measured as the inverse of the standard error of the log risk ratio. Risk ratio is calculated as the ratio of TNZ successes/total treated with TNZ to comparator successes/total treated with comparator. The effect estimate was plotted as the log of the risk ratio. This plotting method is based on the hypothesis that precision will increase as sample size increases when estimating the underlying treatment effect. The spread will narrow as precision increases among larger studies. In the absence of bias, the plot likely resembles a symmetrical inverted funnel; otherwise the plot shows an asymmetrical and skewed shape. Bias usually takes the form of a gap in the wide part of the funnel, which indicates the absence of small studies showing no benefit or harm. The funnel plot is a graphical test for any type of bias that is associated with sample size. The publication and location biases are more likely to affect smaller studies than larger trials and may thus lead to funnel plot asymmetry. Another source of asymmetry arises from differences in the methodological quality. Smaller studies, on average, are conducted and analyzed with less methodological rigors than larger studies, and trials of lower quality tend to show larger effects.

The Forest Plots presented in the following analyses illustrate individual study effect rates along with combined effect rates and respective confidence intervals. Solid squares were chosen to represent differences in effects rates, with larger squares representing studies with greater weight in the combined analyses. The square symbol is a proportional symbol representing the inverse of the standard error of the study. Solid diamond shapes and open boxes were chosen to represent the weighted combined effect rates calculated as described above. The software used for the meta-analyses was Comprehensive Meta-Analysis version 1.0.25.

3.1.2.2 Analyses of Trichomoniasis Studies

A total of 14 TNZ comparative trichomoniasis studies [Table 3.1] were identified consisting of 636 patients treated with TNZ and 619 patients treated with active control (AC) or placebo. Overall 600 TNZ patients and 525 comparator patients were cured of trichomoniasis following treatment. In general, TNZ appears to be non-inferior in all the active controlled studies and superior to placebo. Unless otherwise specified, all treatment durations were for one day.

Table 3.1 Summary of all 14 comparative trichomoniasis studies

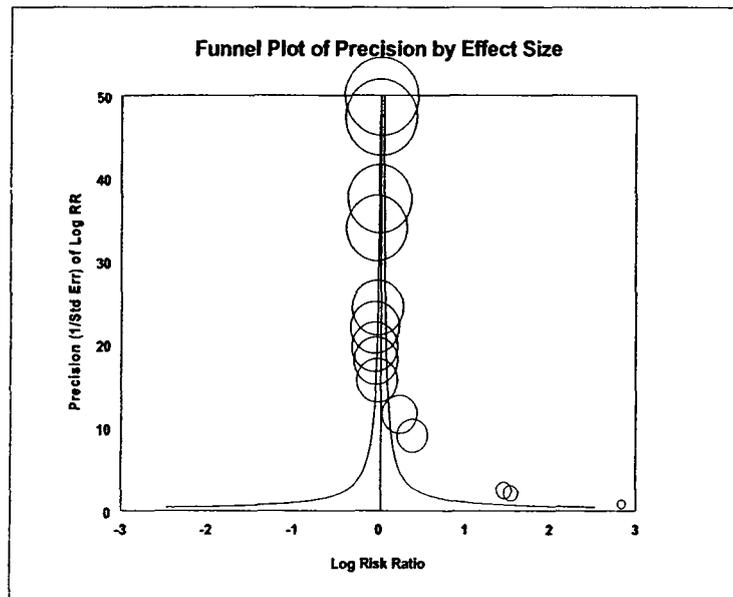
Publication	Location	#Pts	Design	Trt Arms	Successes	Follow-up	p-value
Lyng 1981*	Denmark	149F, 149M	DB,R	TNZ 2.0gF + 2.0gM (n=75) TNZ 2.0g F + placM (n=74)	(56/61) 91.8% (45/62) 72.6%	1-2 wk, 1 mo post intercourse	0.0085
O'Prasertsawat 1992*	Thailand	132F (67 MTZ, 65 TNZ)	DB,R	TNZ 2.0 g. MTZ 1.6g (split)	(65/65) 100% (66/67) 98.5%	6-16 days	NS
Gabriel 1982*	UK	95F (49 TNZ, 46 MTZ)	SB, R	TNZ 2.0g MTZ 2 0g	(40/42) 95.3% (39/40) 97.5%	14 days	NS
Chaisilwattana 1980*	Thailand	107 F (52 TNZ, 55 ORN)	DB, R	TNZ 2.0 ORN 1.5 g	(51/52) 98% (54/55) 98%	14 days	NS
Hillstrom 1977*	Sweden	90F, 52M	DB, R	TNZ 2.0g ORN 1.5g TNZ 2.0g	(41/43) 96% (45/45) 100% (37/40) 92.5%	1 wk 1 mo	NS NS
Chaudhuri 1980	Holland	77F, 77M (38 TNZ, 39 CARN)	DB, R	TNZ 2.0g CARN 2.0g	(36/38) 94.7% (39/39) 100%	1, 2 weeks	NS
Aimakhu 1975	Nigeria	50F (25 TNZ, 25 MTZ)	DB, R	TNZ 2.0 g MTZ 200 mg t.i.d. x 7d	(24/25) 96% (25/25) 100%	Day 15	NS
Mati 1974	Kenya	31F (16 TNZ, 15 PL)	DB, R	TNZ 2.0g PL	(16/16) 100% (4/15) 27%	7 days	<0.001
Rees 1974	Kenya	20 (TNZ 10, PL 10)	DB, R	TNZ 2.0 PL	(8/10) 80% (0/10) 0%	4, 5,7 days	<0.001
Anjaneyulu 1977	India	100 F (TNZ 50, MTZ 50)	OL	TNZ 2.0 g MTZ 2 g	(47/50) 94% (32/50) 64%	4,8, 12 days	<0.001
Beric 1978	Germany	204F (TNZ 104, MTZ 100)	OL	TNZ 2.0 g MTZ 5 g <u>over</u> 10 days	(103/104) 99% (97/100) 97%	8 days	NS

Bloch 1985	S. Africa	161 F (TNZ 59, MTZ 58, 44 BMTZ)	OL	TNZ 2.0 g	(57/59) 95%	7, 14 days	NS
				MTZ 2.0g	(58/58) 100%		
				BMTZ 2.0g	(44/44) 100%		
Rao 1978	Thailand	107 F (52 TNZ, 55 ORN)	OL, R	TNZ 2.0	(51/52) 98%	14 days	NS
				ORN 1.5 g	(54/55) 98%		
Weidenbach, 1974	Germany	64F (TNZ 43, MTZ 21)	OL, R	TNZ 2.0g	(40/43) 93%	1, 6 weeks	NS
				MTZ 2.0g	(20/21) 95%		

DB=double blind, SB=single blind, R=randomized, OL=open-label, TNZ=tinidazole, MTZ=metronidazole, ORN=ornidazole, BMTZ=benzoyl metronidazole, CARN=carnidazole, NS=not significant, placM=placebo arm in male partners only
P-value calculated using Fisher's Exact test of proportions
** selected as pivotal by Sponsor*

A funnel plot [Figure 3.1] of the 14 comparative trichomoniasis studies suggests that the larger studies have greater precision compared to the smaller studied and that overall the studies demonstrate a consistency between size and outcome. The smaller circles on the far right of the log risk ratio scale represent the three placebo controlled (PC) studies, which yielded a large positive risk ratio value. Upon removal of these three studies, the funnel plot shows a symmetric funnel plot centered at a log risk ratio of zero. This plot does not show evidence of publication bias; however this is a general conclusion, which can not be proven with absolute certainty.

Figure 3.1 Funnel plot analyses for 14 comparative trichomoniasis studies



The results of the pooled 14 comparative studies resulted in significant test for heterogeneity, which is due to variability in comparators, single day treatment doses of TNZ studied, and studies designs. Using random effect modeling, which takes into account the inter-study variability, the weighted combined rate difference effect rate was 0.1067, 95% CI [0.038, 0.176], p-value=0.002. Since it is difficult to draw meaningful interpretations from this pooled analysis of all 14 studies, separate analyses were performed looking at sub-groups of studies pooled according to study design and comparator.

3.1.2.2.1 Analyses of Blinded Studies

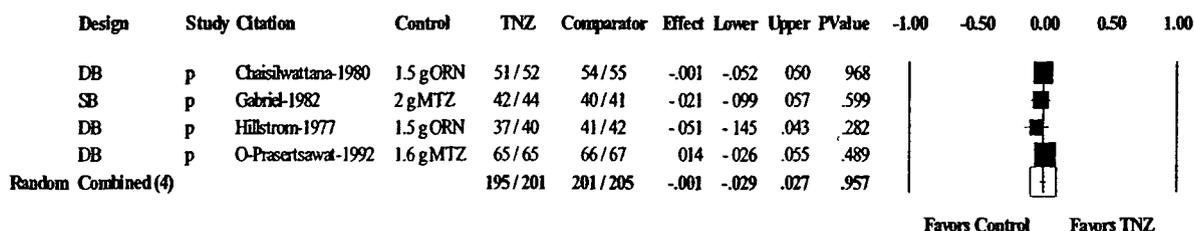
There were a total of nine blinded (8 DB, 1 SB) studies of which five were chosen as pivotal by the sponsor and four as supportive. The test for heterogeneity among these nine studies resulted in a p-value <0.0001 indicating inter-study variation likely due to variation in comparators used.

A meta-analyses of all active control blinded studies (n=6) resulted in an insignificant test for heterogeneity (p-value =0.6195). The combined fixed effects rates of these six studies was -0.008, 95% CI [-0.034, 0.018], p-value=0.550. These results suggest that TNZ performs as well as, with a non-inferiority margin <5%, comparator. Comparators used in these studies were 1.5 g ORN (n=2 studies), 1.6 g MTN (n=1 study), 2 g CRN (n=1 study), 2 g MTZ (n=1 study) and 200 mg tid x 7 days MTZ (n=1 study).

An analyses of the remaining three studies, which contained a placebo control group, resulted in a p-value<0.001 for heterogeneity, random effects rate=0.5477, 95% CI [0.076, 1.020], p-value=0.023. When omitting the Lyng [1981] study from this meta-analyses, since it did not contain a true placebo control (placebo control in male partners only, all females received TNZ), the Q statistic p-value=0.916, fixed effects rate 0.739, 95% CI [0.577, 0.901], p-value <0.0001.

A meta-analyses of the five pivotal studies (262 TNZ treated patients) selected by the Sponsor resulted in a Q statistic p-value of 0.042, however when omitting the Lyng [1981] study from the pooled analyses, the test for heterogeneity was insignificant with a p-value of 0.591. Given that the Lyng [1981] study was not an active controlled study, nor was it a true placebo controlled study (comparator was placebo in only one-half of the male partners) it is the cause of the observed inter-study variability. The random effects model (of all five pivotal studies) resulted in an effects rate of 0.195, 95% CI [-0.040, 0.064], p-value=0.645. When omitting the Lyng [1981] study, the fixed effects rate remained insignificant (-0.008), 95% CI [-0.029, 0.027], p-value=0.957 [Figure 3.2].

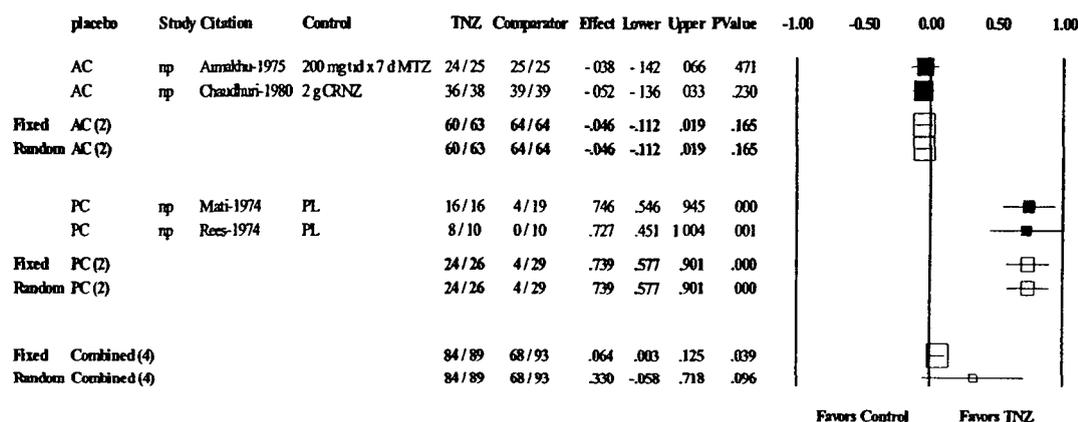
Figure 3.2 Combined analysis of four pivotal studies



Of the remaining blinded comparative studies [Chaudhuri, 1980; Aimakhu, 1975; Mati, 1974; Rees, 1974] not selected as pivotal, the overall efficacy success rates ranged from 80 to 100% with three of the

studies above 94%. Two of these studies were active controlled resulting in an insignificant test for heterogeneity with a p-value=0.847 and a combined random (same as fixed) effects rate of -0.046, 95% CI [-0.112, 0.019], p-value of 0.165. The remaining two studies were placebo controlled resulting in a Q statistic p-value of 0.916, combined random (same as fixed) effect rate of 0.739, 95% CI [0.577, 0.901], p-value <0.0001 [Figure 3.3].

Figure 3.3 Meta-analyses, by comparator, of four blinded non-pivotal studies

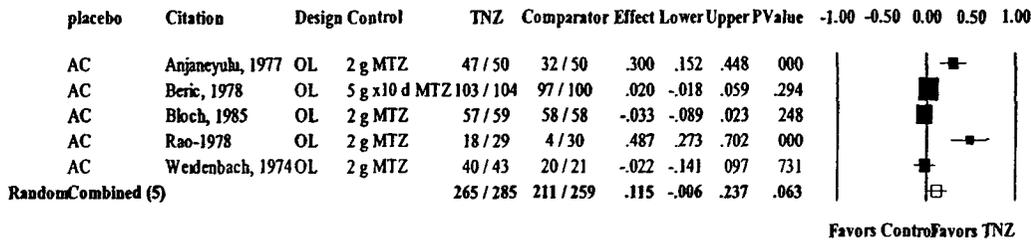


3.1.2.2.2 Analyses of Open-Label Studies

Five open-label studies [Anjaneyulu, 1977; Beric, 1978; Bloch, 1985; Rao, 1978; Weidenbach, 1974] evaluated the efficacy and safety of a single 2 g dose of tinidazole versus an active comparator in trichomoniasis. A single 2 g dose of MTZ was used as the comparator in every study except for one study [Beric, 1978], which used MTZ 5 g x 10 days. All studies resulted in tinidazole efficacy rates of at least 93% except one study [Rao, 1978], which had an efficacy rate of only 62% (18/29) compared with 13% (4/30) in the comparator arm. The cure rates in this study were presented as the clinical cure rates; however both treatment groups had 100% parasitological cure rates.

The variability among the five open-label studies was significant with a Q statistic p-value <0.0001. The combined random effects rate [Figure 3.4] was 0.115, 95% CI [-.006, 0.237], p-value=0.063. As shown in the figure below, the larger (comparatively) studies suggest similar cure rates between TNZ and the active comparator.

Figure 3.4 Combined analyses of open-label trichomoniasis studies

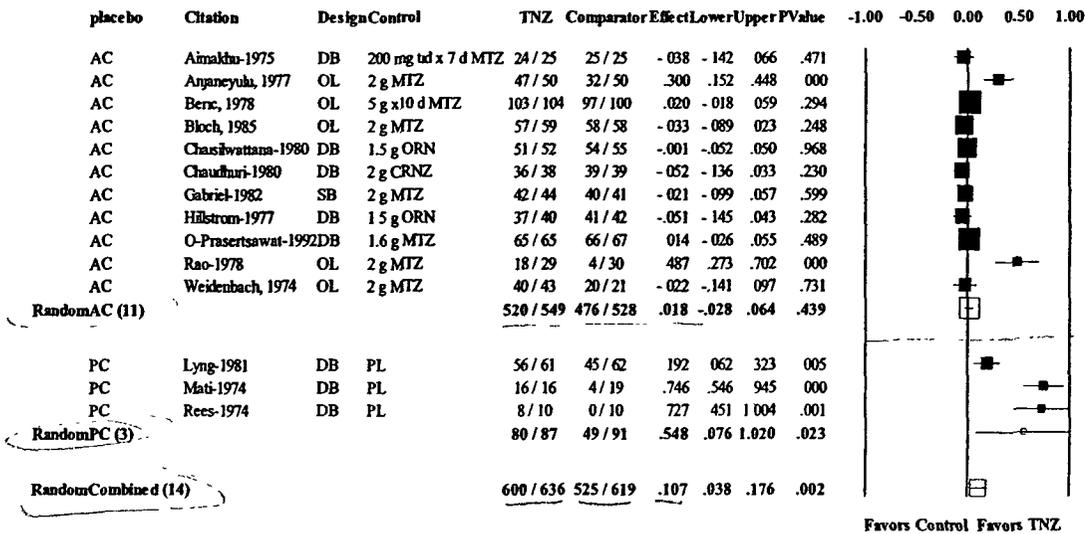


3.1.2.2.3 Analyses by Treatment Control

An analysis [Figure 3.5] sorting the studies by control used (active or placebo) resulted in similar success rates between TNZ and active control. Due to variability in active control, the Q statistic p-value for all 11 AC studies was <0.0001. The combined random effect rate for the AC studies was 0.018, 95% [-0.028, 0.064], p-value 0.439.

The Q statistic p-value was <0.0001 for all three placebo-controlled studies, however the p-value becomes insignificant (p=0.916) when omitting the Lyng [1981] study from the combined analysis. The three PC studies yielded a combined random effects rate of 0.192, 95% CI [0.062, 0.323], p-value=0.023, fixed effects rate among the PC studies when omitting the Lyng [1981] study was 0.739 95% CI [0.577, 0.901], p-value <0.0001.

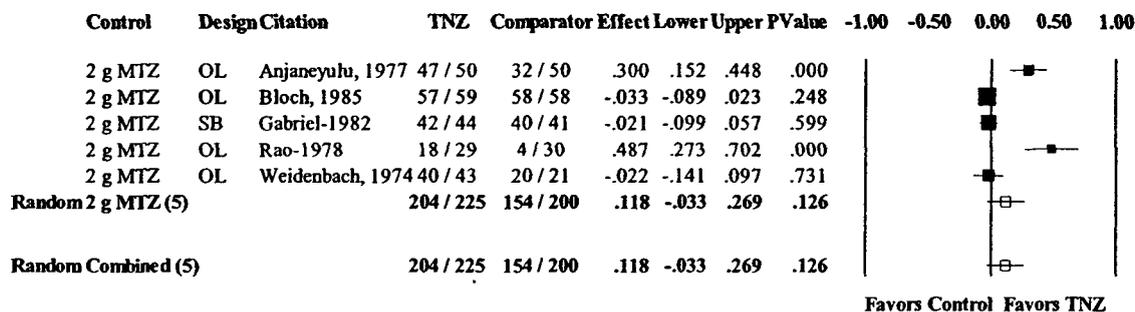
Figure 3.5 Analyses of trichomoniasis studies by comparator (active or placebo controlled)



A separate analysis [Figure 3.6] was performed combining the five studies that used the approved 2 g x 1 day metronidazole dose as the active comparator in the treatment of trichomoniasis. The test for

heterogeneity among these studies was significant and therefore the random effects model was used. The combined random effects rate was 0.118, 95% [-0.033, 0.269], p-value 0.126 suggesting that TNZ is non-inferior to 2 g x 1 day MTZ given that the lower limit of the CI falls within a conservative 4% margin.

Figure 3.6 Analyses of trichomoniasis studies with 2 g x 1 day MTZ as the comparator



3.1.2.2.4 Analyses by Diagnostic Used

Since there are multiple symptoms associated with trichomoniasis, which often resemble other vaginal infections, clinical testing is generally required for diagnosis. Wet preparation and culture are commonly used methods to identify trichomoniasis in vaginal secretions. Wet preparation is only 35 to 80% sensitive compared with culture (15) and the sensitivity is highly dependent on the expertise of the microscopist and on how the samples were processed. The current preferred method is culture in microaerophilic conditions, which has an estimated sensitivity rate between 85 and 95%.

An analyses was performed by pooling studies according to test used (culture, wet mount, or not stated). This analysis resulted in similar combined effects rates and insignificant p-values for all three sub-groups indicating the absence of a diagnostic test effect in the pooled analyses.

3.1.2.2.5 Summary of Meta-Analyses of Trichomoniasis Studies

The overall treatment effect of tinidazole for trichomoniasis was similar to active control and significantly better than placebo in all meta-analyses performed. An analysis pooling all studies (n=5) evaluating TNZ vs. the approved dose of MTZ (2g x 1 day) resulted in similar treatment effect rates suggesting non-inferiority of TNZ to MTZ.

Table 3.2 Meta-analyses of Trichomoniasis TNZ Studies

Meta-Analyses ¹	# of Studies	TNZ Success Rate	Comparator Success Rate	Treatment Effect*	p-value ²	95% CI	Q-statistic p-value
Blinded	9	0.954 (335/351)	0.872 (314/360)	0.116	0.023	(0.016, 0.215)	<0.001
Blinded AC	6	0.966 (255/264)	0.985 (265/269)	0.013	0.550	(-0.034, 0.018)	0.620
Blinded PC	3	0.920 (80/87)	0.539 (49/91)	0.548	0.023	(0.076, 1.020)	<0.001
Blinded PC ⁵	2	0.923 (24/26)	0.138 (4/29)	0.739	<0.001	(0.577, 0.901)	0.916
Open label	5	0.930 (265/285)	0.815 (211/259)	0.115	0.063	(-0.006, 0.237)	<0.001
AC	11	0.947 (520/549)	0.902 (476/528)	0.018	0.439	(-0.028, 0.065)	<0.001
PC	3	0.920 (80/87)	0.539 (49/91)	0.548	0.023	(0.076, 1.020)	<0.001
Pivotal	5	0.958 (251/262)	0.921 (246/267)	0.012	0.645	(-0.040, 0.064)	0.042
Pivotal ⁴	4	0.970 (195/201)	0.980 (201/205)	-0.001	0.957	(-0.029, -.027)	0.591
Non-pivotal ³	9	0.933 (349/374)	0.793 (279/352)	0.195	0.002	(0.070, 0.321)	<0.001
2g MTZ control	5	0.800 (204/255)	0.770 (154/200)	0.118	0.126	(-0.033, 0.269)	<0.001

AC=active controlled studies, PC=placebo controlled studies

Blinded AC=blinded active controlled studies, Blinded PC=blinded placebo controlled studies

¹ Criteria for pooling of studies

² P-value for Z-statistic (combined effects estimate/s.e)

³ Significant due to placebo controlled studies in the combined analysis

⁴ Meta-analyses omitting the Lyng [1981] study

⁵ Meta-analyses omitting the Lyng [1981] study

Fixed effects rate used if Q-statistic p-value is insignificant, otherwise random effects rate used

*Fixed or random effects estimate of TNZ-comparator

3.1.2.3 Analyses of Giardiasis Studies

The Sponsor identified a total of 15 comparative giardiasis treatment studies, with a total of 730 subjects assigned to TNZ and 546 subjects assigned to a comparator (active or placebo). Heterogeneity among all 15 pooled studies was observed with a p-value <0.0001. The test for heterogeneity was significant due to the amount of variability in study designs, comparators, and TNZ regimens. The combined random effects rate was 0.353, 95% CI [0.176, 0.530], p-value=0.0001 [Figure 3.7]. A funnel plot of these 15 studies [Figure 3.8] was generally symmetrical with the larger studies having greater precision and the average log risk ratio centered between zero and one suggesting the absence of selection bias. Placebo controlled (n=2) studies appear to the right of the log risk ratio, which is expected due to the significant difference in treatment success.

Table 3.3 Summary of all 15 comparative giardiasis studies

Publication	#Pts	Design	Treatment Arms	Successes	Follow-up	p-value *
Bakshi 1978*	186 children	SB,R,C (R is unclear)	TNZ 50mg/kg (mean dose=61.8mg/kg)	(83/94) 88%	4,8,12,16 days	<0.00122
MTZ 50mg/kg (mean dose=56.0mg/kg)			(43/92) 47%			
Jokipii 1982*	105 adults	SB,R,C (R by alternating-not random)	TNZ 1.5g	(45/50) 90%	1,2,4,8 wks	1.000
ORN 1.5g			(45/50) 90%			
Jokipii 1979*	85 adults	SB, R, C (R by alternating-not random)	TNZ 2.0g	(26/28) 93%	1,2,4,8 wks	0.001 ^b
MTZ 2.4g			(13/26) 50%			
MTZ 2.4g x 2d			(24/31) 77%			
Kryonseppa 1981*	50 adults	R,C (R according to code)	TNZ 2.0g	(22/25) 88%	2,4wks	0.464
MTZ 2.0g x 2d			(19/25) 76%			
Bassily 1987	80 adults	C	MTZ 500 mg/d x 10 days	(19/20) 95%	3 wks	v. MTZ: 0.641 v. ORN: 0.612
TNZ 2 g x 1 day			(27/30) 90%			
ORN 1 g x 1 day			(29/30) 97%			
El Masray 1978	75 adults & children	C	TNZ 2 g x 1 day	(53/55) 96%	3-5 wks	<0.001
PL			(2/20) 10%			
Farahmandian 1978	210 adults	C	TNZ 50 mg/kg (2 g max)	(156/165) 95%	4 days	<0.001
PL			(3/30) 10%			
Gadzer 1977	100 children	R, C	TNZ 50 mg/kg x 1 day (max 2 g)	(40/50) 80%	4,8,12,16 days	0.071
MTZ 50 mg/kg x 1 day			(18/30) 60%			
Jokipii 1978	45 adults	C	TNZ 150 mg bid x 7 days	(14/19) 74%	daily for 7 d, 2,4,8 wks	0.114
TNZ 2 g x 1 day			(24/26) 92%			
Krishnamurthy 1978	60 children	R, C	TNZ 50 mg/kg x 1 day	(29/30) 97%	4,8,12 days	<0.001

			MTZ 50 mg/kg x 1 day	(15/30) 50%		
Nigam 1991	75 children and adults	R, C	TNZ 50 mg/kg x 1 day	(39/40) 98%	4, 8, 12, 16 days	<0.001
			MTZ 50 mg/kg x 1 day	(19/35) 54%		
Pengsaa 1999	113 children	R, C	TNZ 50 mg/kg x 1 day	(49/51) 96%	1-2 wks	0.001
			ALB 400 mg QD x 3 days	(31/62) 50%		
Sabchareon 1980	124 children	C	TNZ 2 g x 1 day	(18/21) 86%	30 days	v. MTZ: 0.024 v. PL: <0.001
			MTZ 2 g x 1 day	(11/21) 52%		
			PL	(0/20) 0%		
Speelman 1985	Study 1 :33 adults and children	SB, R, C	TNZ 50mg/kg x 1 day	(16/17) 94%	4 wks	0.017
			MTZ 60 mg/kg x 1 day	(9/16) 56%		
	Study 2: 30 adults and children	SB, R, C	TNZ 50 mg/kg x 1 day	(15/15) 100%		1.000
			MTZ 50 mg/kg x 2 days	(14/15) 93%		
Suntornpoch 1981	121 children	C	TNZ 50 mg/kg x 1 day	(45/48) 94%	7,14, 21 days	1.000
			ORN 50 mg/kg x 1 day	(38/40) 95%		

* selected as pivotal by Sponsor

SB=single blind, R=randomized, C=controlled, TNZ=tinidazole, MTZ=metronidazole, ORN=ornidazole, PL=placebo, ALB=albendazole

a. 2-sided test of proportions of TNZ vs. comparator using Fisher's Exact Test

b. TNZ vs. MTZ 2.4 g (TNZ vs. MTZ x 2d was NS)

Figure 3.7 Combined analyses of all 15 comparative giardiasis

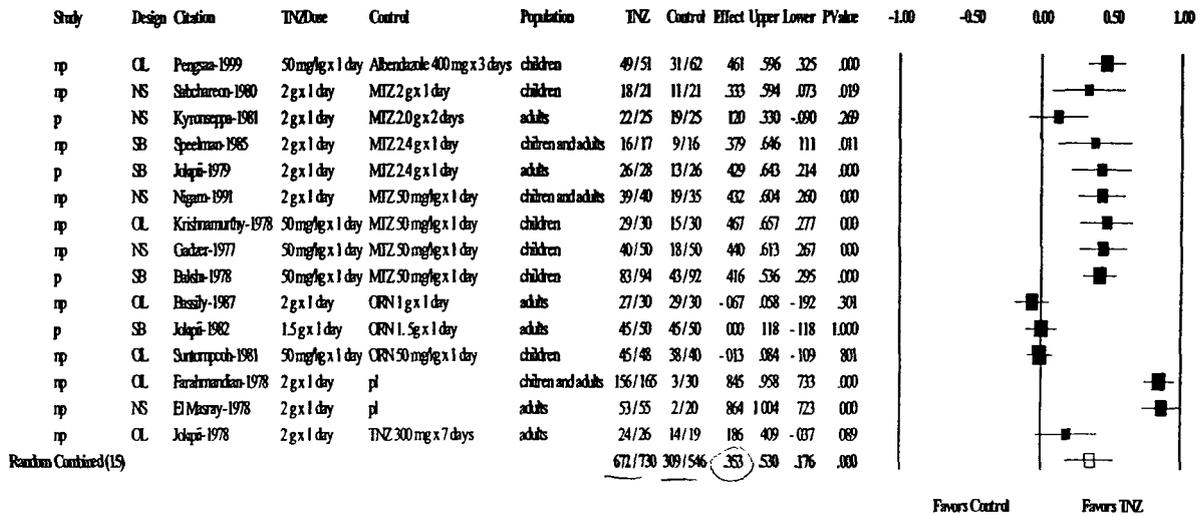
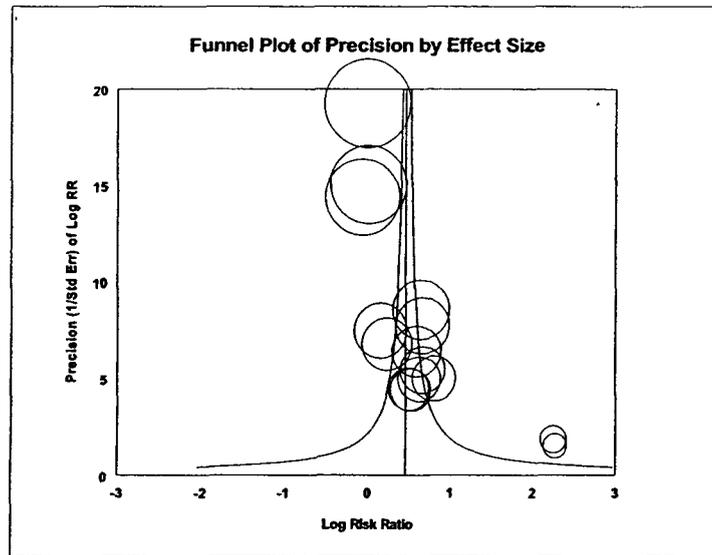


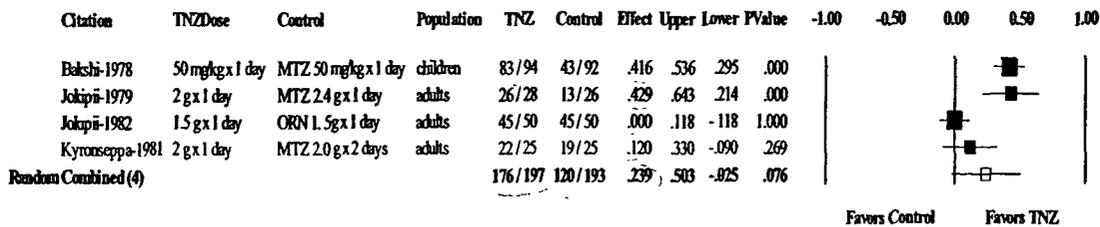
Figure 3.8 Funnel plot analyses of all 15 giardiasis studies



To further interpret these studies, an analysis of the Sponsor selected pivotal studies was performed. Two studies [Bakshi, 1978, Jokippi, 1979] suggested a greater treatment effect in the TNZ arm compared MTZ; however both studies were small in size, had vague randomization methods stated and were single blind. Additionally, this analysis yielded a positive test for heterogeneity ($p < 0.0001$) as well as an insignificant p-value (0.076) from the combined random effects rate of 0.239, 95% CI [-0.025, 0.503]) suggesting significant variability among the four studies. This is likely due to the variation in

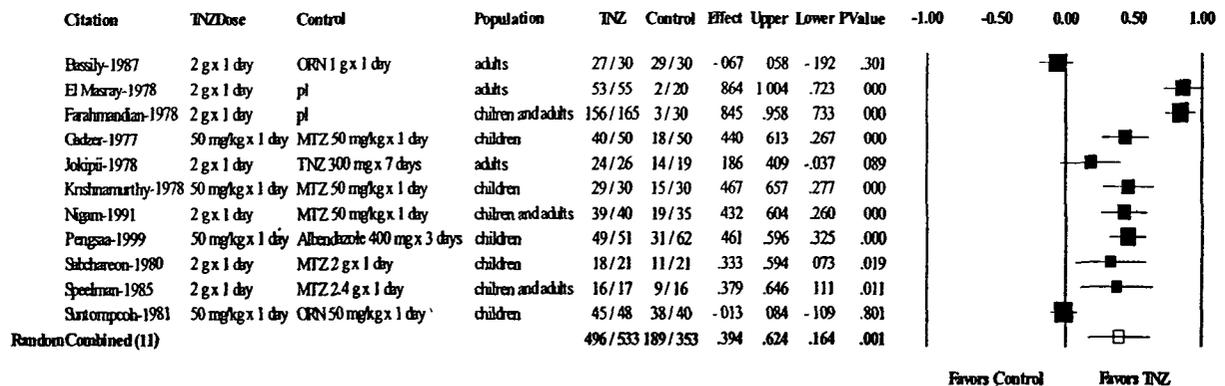
comparators used and in populations studied.

Figure 3.9 Combined analyses of sponsor selected pivotal giardiasis studies



Among the 11 Sponsor designated, non-pivotal studies, the test for heterogeneity yielded a significant p-value <0.0001, random effects rate 0.3941, 95% CI [0.164, 0.624], p-value=0.0008. This significant difference is attributable to the presence of two placebo controlled studies as well as differing comparators studied.

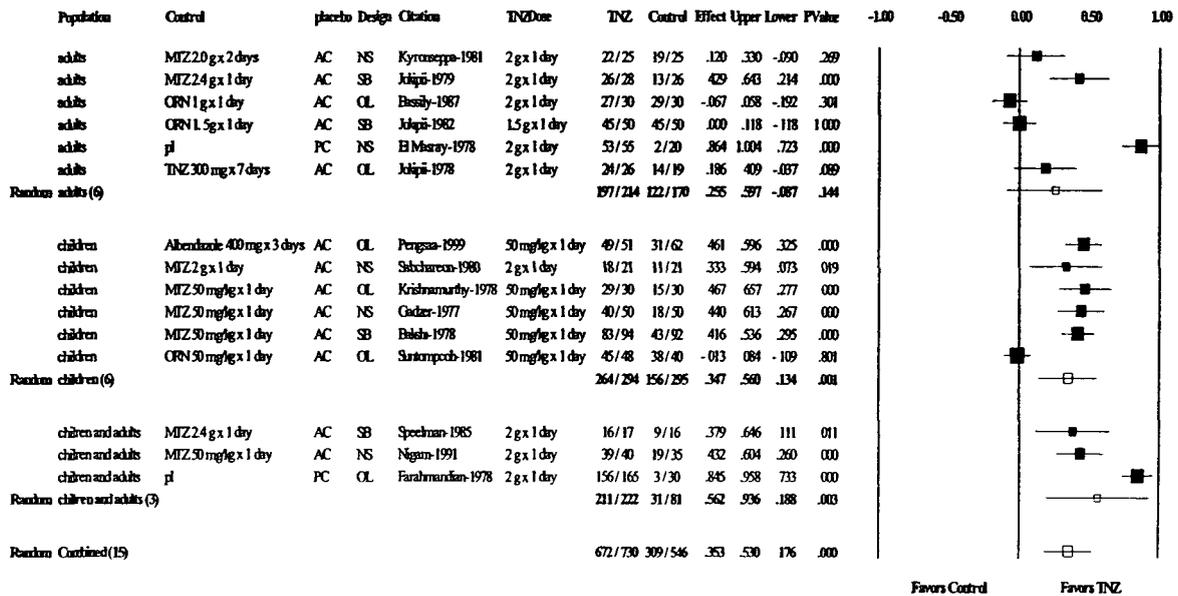
Figure 3.10 Combined analyses of non-pivotal giardiasis studies



3.1.2.3.1 Analyses by Study Population

Among the studies that treated only adults (n=6), there was significant heterogeneity (p<0.0001) due to the variation in active control (only one PC study) used. The random effects rate was 0.255, 95% CI [-0.087, 0.597], p-value=0.144. In studies treating only children (n=6), the random effects rate was 0.347, 95% CI [0.134, 0.560], p-value=0.0014 (test for heterogeneity p-value<0.0001 due to variation among active controls). Among the three studies that treated both adults and children, there was significant heterogeneity (p<0.0001) due to the Faramandian [1978], which was placebo controlled. Among all three adult and children treated studies, the random effects rate was 0.562 95% CI [0.188, 0.936], p-value=0.003. When removing the Faramandian [1978] study, the fixed effects rate was 0.417, 95% CI [0.272, 0.561], p-value<0.0001. Details of these analyses are in the figure below.

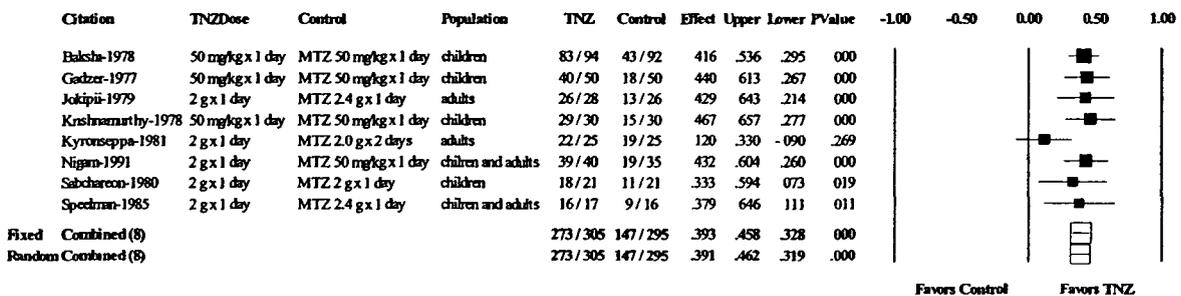
Figure 3.11 Analyses by study population



3.1.2.3.2 Analyses by Control

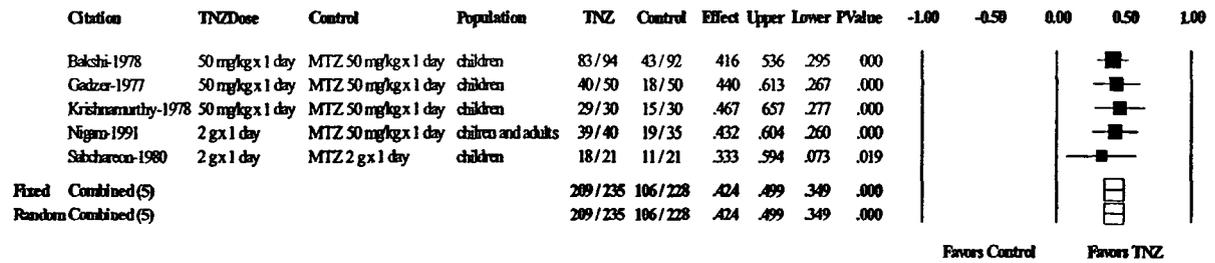
Eight studies evaluated TNZ vs. MTZ in the treatment of giardiasis for which all but two (these studies used MTZ 2.4 g x 1 day) used the standard 2 g x 1 day (50 mg/kg in children) dose. Combining these studies [Figure 3.12] resulted in an insignificant test for heterogeneity ($p=0.334$), random (same as fixed) effects rate=0.393, 95% CI [0.319, 0.462], p -value<0.001. A general trend favoring TNZ was demonstrated across studies for which both children and adults were treated.

Figure 3.12 Meta-analysis of all comparative studies with MTZ control



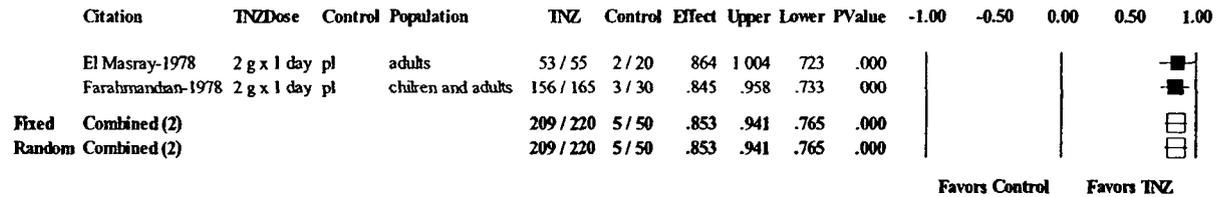
The following analysis looked at only those studies ($n=5$) which evaluated the proposed TNZ dose vs. 2 g x 1 day MTZ. This analysis resulted in an insignificant test for heterogeneity with a p -value=0.949 and a random (same as fixed) effects rate of 0.425, 95% CI [0.350, 0.499] with a significant p -value<0.0001.

Figure 3.13 Meta-analysis of five studies using proposed TNZ dose vs. 2 g x 1 day MTZ



Analysis of the two placebo controlled studies resulted in an insignificant test for heterogeneity ($p=0.843$), random (equal to fixed) effects rate 0.853, 95% CI [0.765, 0.941], $p<0.0001$. These two studies evaluated a single 2 g dose of TNZ one in children only and one in children and adults.

Figure 3.14 Meta-Analysis of two placebo-control giardiasis studies



3.1.2.3.3 Meta-Analyses of Giardiasis Studies

Several meta-analyses suggested that TNZ performed as well, if not superior, to MTZ in the treatment of giardiasis. Among the two PC trials, the combined treatment effects rate was significantly better in the TNZ group as compared to the placebo group. This analysis also resulted in an insignificant test for heterogeneity suggesting that the two studies were similar in treatment effect. A meta-analysis pooling five studies that evaluated 2 g x 1 day TNZ vs. 2 g x 1 day MTZ resulted in an insignificant test for heterogeneity and a significant fixed effect rate with a p -value <0.0001 . Other analyses, summarized in the table below, also show that TNZ performs as well, if not superior to MTZ for this indication.

Table 3.4 Meta-Analyses of Giardiasis Studies

Meta-Analyses**	# of Studies	Success Rate: TNZ	Success Rate: Comparator	Treatment Effect***	p-value*	95% CI	Q-statistic p-value
Non-pivotal	11	0.931 (496/533)	0.535 (189/353)	0.394	0.0008	(0.164, 0.624)	<0.0001
Pivotal	4	0.893 (176/197)	0.622 (120/193)	0.239	0.0760	(-0.025, 0.503)	<0.0001
AC	13	0.908 (463/510)	0.613 (304/496)	0.270	0.0001	(0.136, 0.403)	<0.0001
PC	2	0.950 (209/220)	0.100 (5/50)	0.853	<0.0001	(0.765, 0.941)	0.8432
Single blind ¹	4	0.899 (170/189)	0.598 (110/184)	0.299	0.0340	(0.023, 0.575)	<0.0001
Open label	6	0.943 (330/350)	0.616 (130/211)	0.313	0.078	(-0.035, 0.661)	<0.0001
MTZ control ²	5	0.889 (209/235)	0.465 (106/228)	0.424	<0.0001	(0.349, 0.499)	0.949
Adults only	6	0.921 (197/214)	0.718 (122/170)	0.255	0.1443	(-0.087, 0.597)	<0.0001
children only	6	0.898 (264/294)	0.529 (156/295)	0.347	0.0014	(0.1334, 0.560)	<0.0001
children & adults	3	0.950 (211/222)	0.383 (31/81)	0.562	0.0032	(0.188, 0.936)	<0.0001

AC=active controlled studies, PC=placebo controlled studies

* P-value for Z-statistic (combined effects estimate/s.e)

¹ All four single blind studies were active controlled. There were no blinded placebo controlled studies.

² Studies comparing TNZ 2 g x 1 day vs. MTZ 2 g x 1 day (50mg/kg x 1 day in children)

** Criteria for pooling of studies

***Fixed or random treatment effects (TNZ-comparator)

3.1.2.4 Analyses of Amebiasis Studies

3.1.2.4.1 Intestinal Amebiasis

A total of nine comparative studies [Table 3.5] using TNZ to treat intestinal amebiasis were identified with a total of 378 patients received TNZ and 359 received a comparator drug. The number of infection cures was 296/378 and 191/359 in the TNZ and comparator groups respectively. The random effects rate was 0.198, 95% CI [0.033, 0.363], p-value=0.019 (test for heterogeneity p-value<0.0001) [Figure 3.15].

Table 3.5 Summary of nine comparative intestinal amebiasis studies

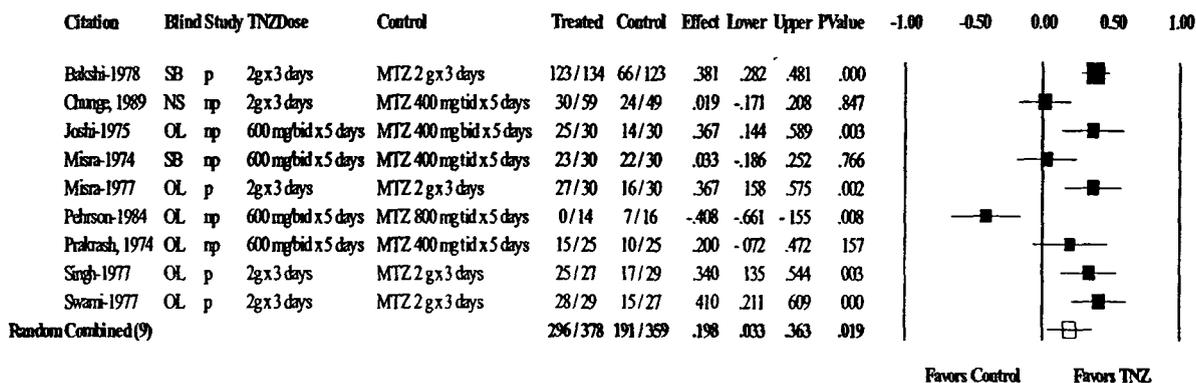
Publication	Design	Treatment Arms	Successes	Follow-up	p-value *
Bakshi 1978*	SB,R (R method not stated)	TNZ 2g/d x 3 days	(123/134) 91.7%	4,20,30 days	0.0000
		MTZ 2g/d x 3 days	(66/123) 53.6%		
Swami 1977*	R (R method not stated)	TNZ 2g/d x 3 days	(28/29) 96.5%	4,20,30 days	0.0003
		MTZ 2g/d x 3 days	(15/27) 55.5%		
Singh 1977*	R (R method not stated)	TNZ 2g/d x 3 days	(25/27) 92.6%	4,20,30 days	0.0031
		MTZ 2g/d x 3 days	(17/29) 58.6%		
Misra 1977*	R (R method not stated)	TNZ 2g/d x 3 days	(27/30) 90%	5,20,30 days	0.0015
		MTZ 2g/d x 3 days	(16/30) 53.3%		
Joshi 1975	R (R method not stated)	TNZ 600 mg bid x 5 days	(25/30) 83.3%	5 days	0.0029
		MTZ 400 mg bid x 5 days	(14/30) 46.7%		
Pehrson 1984	R, OL (R method not stated)	TNZ 600 mg bid x 5 days	(0/14) 0%	30 days	0.0078
		MTZ 800 mg tid x 5 days	(7/16) 44.1%		
Chunge 1989	R (R method not stated)	TNZ 2 g x 3 days	(30/59) 50.9%	3, 6 days	0.8467
		MTZ 400 mg tid x 5 day	(24/49) 49.0%		
Prakrash 1974	OL	TNZ 600 mg bid x 5 days	(15/25) 60%	6, 20, 30 days	0.1573
		MTZ 400 mg tid x 5 days	(10/25) 40%		
Swami 1977	R (R method not stated)	TNZ 2 g x 3 days	(28/29) 96.6%	4, 20, 30 days	0.0003
		MTZ 2 g x 3 days	(15/27) 55.5%		

P-value calculated using Fisher's Exact Test of proportions

** Selected as pivotal by Sponsor*

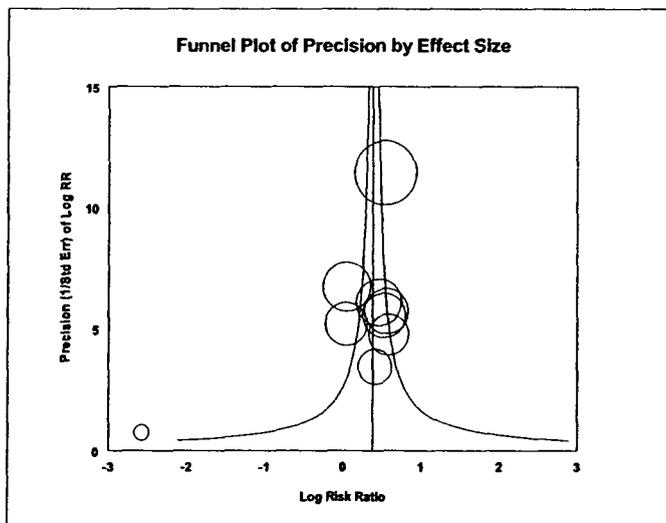
TNZ=tinidazole, MTZ=metronidazole, R=randomized, OL=open-label, SB=single blind

Figure 3.15 Meta-analyses of all nine comparative intestinal amebiasis studies



All nine studies in the funnel plot [Figure 3.16], except the Pehrson [1984] study (appears to the far left on the x-axis) are centered between a log risk ratio between zero and one, with increasing precision with increasing sample size. The Pehrson [1984] study reported a low treatment effect due to patients in the study having asymptomatic amebiasis for which a luminal agent is preferred (see medical review by Maureen Tierney, MD for detailed review of this study).

Figure 3.16 Funnel plot of all nine comparative intestinal amebiasis studies

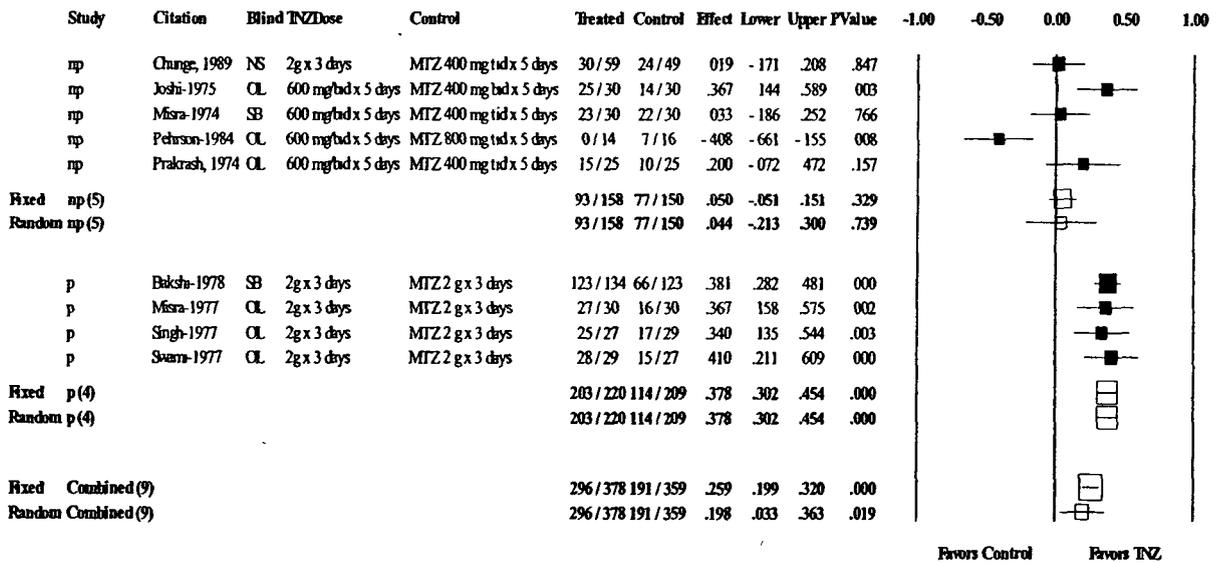


3.1.2.4.1.1 Analysis by Study Status

The four pivotal studies selected by the Sponsor resulted in an insignificant test for heterogeneity ($p=0.969$), fixed effects rate of 0.378, 95% CI [0.302, 0.454], $p\text{-value}<0.0001$. All four studies evaluated the proposed TNZ dose against a 2 g x 3 day dose of MTZ [Figure 3.17].

Heterogeneity was identified among the five non-pivotal studies with a p-value=0.0002. The random effects rate was 0.044, 95% CI [-0.213, 0.300], p-value=0.7394. Heterogeneity among these studies was likely due to the Pehrson [1984] study, for which patients enrolled appeared to have more asymptomatic amebiasis than active disease. Treatment with TNZ or MTZ is less effective in asymptomatic infection for which luminal agents are preferred. Given the difference in type of amebic infections in the Pehrson [1984] study it is appropriate to remove it from the combined analyses. After removal, the test for heterogeneity was insignificant with a p-value=0.084 and a random effects rate of 0.148, 95% CI [-0.030, 0.326], p-value=0.1025.

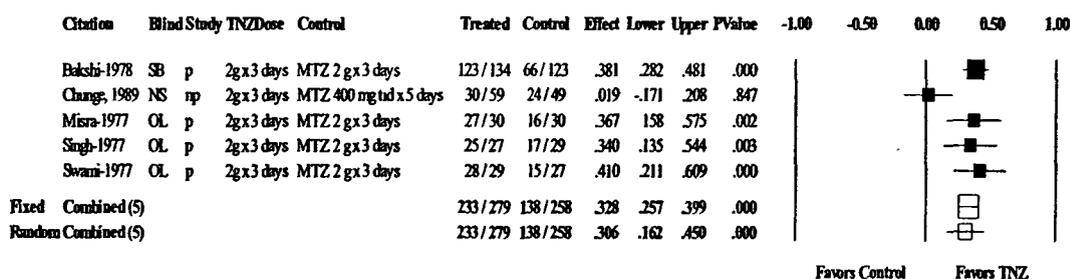
Figure 3.17 Combined analyses by study status



3.1.2.4.1.2 Analysis by Proposed TNZ Regimen

Two TNZ regimens (2 g x 3 days or 600 mg bid x 5 days) were studied in the nine studies submitted in intestinal amebiasis. Meta-analyses of the pooled studies that evaluated the proposed 2 g x 3 days dose of TNZ resulted in a positive test for heterogeneity (p=0.016). The random effects rate was 0.306, 95% CI [0.162, 0.450], p-value<0.0001 [Figure 3.18]. The comparator regimens among these five studies was MTZN 2 g x 3 days (n=4) and the fifth study evaluated MTZ 400 mg tid x 5 days. Omitting the fifth study [Chunge, 1989] from the analyses, the test for heterogeneity was insignificant (p=0.969), fixed effect rate was 0.378, 95% CI [0.302, 0.454], p-value<0.0001.

Figure 3.18 Analysis by Proposed TNZ Regimen



The remaining four studies compared TNZ 600 mg bid x 5 days and had the random effects rate 0.050, 95% CI [-0.307, 0.406], p-value=0.786 (test for heterogeneity p-value=0.0001). Three different regimens of MTZ were used as comparators in these four studies leading to the significant heterogeneity.

3.1.2.4.1.3 Summary of Meta-Analyses of Intestinal Amebiasis Studies

The meta-analyses of studies that evaluated the most common TNZ regimen (also regimen proposed by Sponsor for this indication) of 2 g x 3 days resulted in significantly more treatment success in the TNZ group compared to the MTZ group, however the analysis yielded a significant test for heterogeneity. When comparing TNZ 2 g x 3 days against MTZ 2 g x 3 days, the test for heterogeneity was insignificant and the treatment effect was significantly better in the TNZ group. Results of analyses by other doses and frequencies of MTZ and TNZ yielded insignificant differences in treatment success rates.

Table 3.6 Meta-Analyses of Intestinal Amebiasis Studies

Meta-Analyses**	# of Studies	Success Rate: TNZ	Success Rate: Comparator	Treatment Effect***	p-value*	95% CI	Q-statistic p-value
Pivotal ¹	4	0.923 (203/220)	0.545 (114/209)	0.378	<0.0001	(0.302, 0.454)	0.9693
Non-pivotal	5	0.589 (93/158)	0.513 (77/150)	0.044	0.7394	(-0.213, 0.300)	0.0002
Non-pivotal ²	4	0.646 (93/144)	0.522 (70/134)	0.148	0.1025	(-0.030, 0.326)	0.0840
Single blind	2	0.890 (146/164)	0.575 (88/153)	0.218	0.2868	(-0.183, 0.618)	0.0046
Open label	6	0.774 (120/155)	0.503 (79/157)	0.219	0.0812	(-0.027, 0.464)	<0.0001
MTZ control ³	4	0.923 (203/220)	0.545 (114/209)	0.378	<0.0001	(0.302, 0.454)	0.9693
MTZ control ⁴	3	0.596 (68/114)	0.538 (56/104)	0.063	0.3294	(-0.064, 0.190)	0.5330
TNZ 2 g x 3 days	5	0.835 (233/279)	0.535 (138/258)	0.306	<0.0001	(0.162, 0.450)	0.0163
TNZ 600 mg bid x 5 day	4	0.636 (63/99)	0.525 (53/101)	0.046	0.7855	(-0.307, 0.406)	0.0001

¹ All four pivotal studies used the same active control (MTZ 2 g x 3 days)

² Omitting Pehrson [1984] study

³ Active comparator was MTZ 2 g x 3 days (same four studies as the ones chosen as pivotal)

⁴ Active comparator was MTZ 400 mg tid x 5 days

* P-value for Z-statistic (combined effects estimate/s.e)

** Criteria for pooling of studies, ***Fixed or random treatment effects (TNZ-comparator)

3.1.2.4.2 Amebic Liver Abscess

Nine comparative studies [Table 3.7] using TNZ in the treatment of amebic liver abscess were identified consisting of a total of 181 patients received a TNZ treatment regimen while 194 received comparator. The overall random effects rate was 0.177, 95% CI [0.026 0.328], $p=0.022$, test for heterogeneity p -value <0.0001 [Figure 3.20]. Different doses of TNZ and MTZ studied contributed to the significant heterogeneity among studies.

Table 3.7 Summary of all nine comparative amebic liver abscess studies

Publication	Design	Treatment Arms	Successes	Follow-up	p-value
Mendis 1984*	R, DB	TNZ 2 g x 3 days	(13/16) 81.3%	5,10, 30 days	0.0070
		MTZ 400 mg tid x 5 days	(6/18) 33.3%		
Kundu 1977*	R, OL	TNZ 2 g x 3 days	(8/9) 88.9%	5, 10, 30 days	0.0156
		MTZ 2 g x 3 days	(3/9) 33.3%		
Kokhani 1977*	R, OL	TNZ 2 g x 2 days	(10/10) 100%	5, 10, 30 days	0.0023
		MTZ 2 g x 2 days	(5/14) 36.7%		
Mathur 1977*	R, OL	TNZ 2 g x 2 days	(10/10) 100%	5, 10, 13 days	0.4583
		MTZ 2 g x 2 days	(9/10) 86.4%		
Islam 1978*	R, OL	TNZ 2 g x 3-6 days	(15/16) 93.8%	10,12,30 days	0.2538
		MTZ 2 g x 3-10 days	(12/15) 80.0%		
Simjee 1985*	R, SB	TNZ 2 g x 5 days	(17/24) 90.1%	5d, 4wk,8wk	0.2264
		MTZ 2 g x 5 days	(25/27) 92.6%		
Bakshi 1978*	R, OL	TNZ 2 g x 2 days	(48/50) 96.0%	5, 10, 30 days	0.0034
		MTZ 2 g x 2 days	(37/49) 75.5%		
Hatchuel 1975	DB, R	TNZ 800 mg tid x 5 days	(13/14) 90.0%	20 days	0.4362
		MTZ 800 mg tid x 5 days	(15/15) 100%		
Lasserre 1983	DB, R	TNZ 1 g bid x 1 day	(33/35) 94.3%	6 mo	0.9544
		ORN 1 g bid x 1 day	(35/37) 94.6%		

TNZ=tinidazole, MTZ=metronidazole, ORN=ornidazole, R=randomized, SB=single blind, DB=double-blind, * selected as pivotal by Sponsor, P-value calculated using Fisher's Exact test of proportions

The funnel plot analyses [Figure 3.19] of these nine studies shows general consistency among study sample sizes and precisions however the three studies to the right of the zero log risk ratio (values between 2.44 and 2.67) may indicated the presence of selection or publication bias.

Figure 3.19 Funnel plot of all nine comparative amebic liver abscess studies

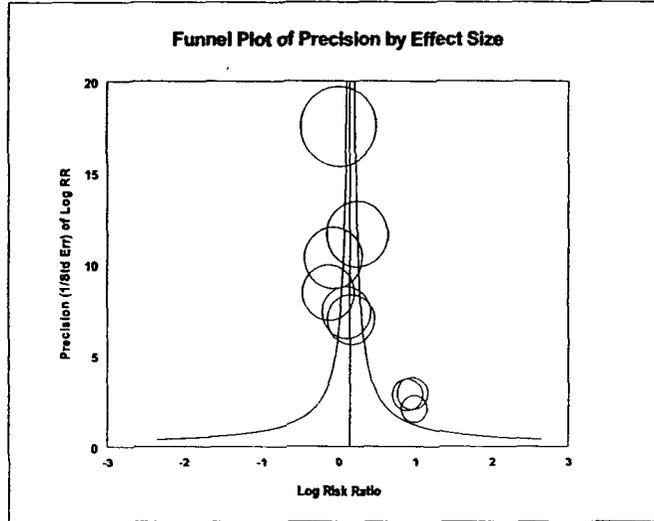


Figure 3.20 Combined analyses of all amebic liver abscess studies

Citation	BlindStudy	TNZDose	Control	TNZ	Control	Effect	Lower	Upper	PValue	-1.00	-0.50	0.00	0.50	1.00
Mahur-1977	CL	p	2g x 2 days	MITZ 2g x 2 days	10 / 10	9 / 10	.091	-.146	.328	.458				
Khokhani-1977	CL	p	2g x 2 days	MITZ 2g x 2 days	10 / 10	5 / 14	.588	.315	.861	.002				
Bakshi-1978	CL	p	2g x 2 days	MITZ 2g x 2 days	48 / 50	37 / 49	.205	.073	.337	.008				
Kundu-1974	CL	p	2g x 3 days	MITZ 2g x 3 days	8 / 9	3 / 9	.556	.185	.926	.016				
Islam-1978	CL	p	2g x 3 days	MITZ 2g x 3 days	15 / 16	12 / 15	.138	-.097	.372	.254				
Simjee-1985	SB	p	2g x 5 days	MITZ 2g x 5 days	17 / 21	25 / 27	-.116	-.311	.078	.226				
Mendis-1984	DB	p	2g x 3 days	MITZ 400 mg/tid x 5 days	13 / 16	6 / 18	.479	.189	.769	.005				
Hatchuel-1975	DB	np	800 mg tid x 5 days	MITZ 800 mg tid x 5 days	13 / 14	15 / 15	-.069	-.243	.105	.436				
Lassere-1983	DB	np	1g bid x 1 day	CRN 1g bid x 1 day	33 / 35	35 / 37	-.003	-.109	.103	.954				
Random Combined (9)					167 / 181	147 / 194	.177	.026	.328	.022				

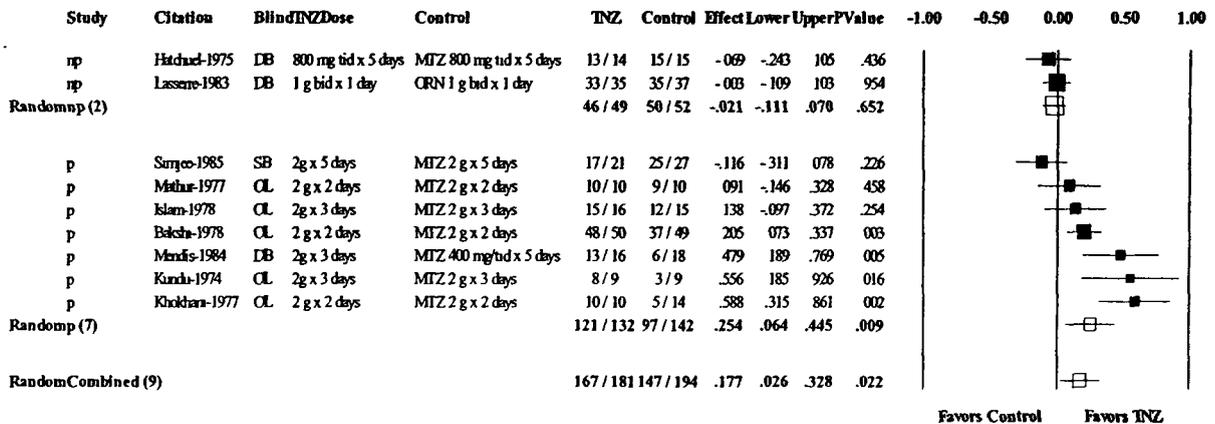
3.1.2.4.2.1 Analyses by Study Status

Heterogeneity (p=0.0002) was observed among the seven pivotal studies (selected by Sponsor) when pooled [Figure 3.21]. The combined random effects rate was 0.254, 95% CI [0.065, 0.445], p=0.009. All seven studies evaluated the 2 g dose of TNZ given between two and five days (proposed dose is 2 g TNZ x 3-5 days). There was considerable variation (range: -0.116, 0.588) in the calculated rate differences, which may be due to the small number of subjects in each study.

The two non-pivotal studies evaluated a different dose of TNZ (800 mg tid x 5 days and 1 g bid x 1 day) from the dose proposed by the Sponsor. Results of combining these two studies was a fixed effects rate

of -0.021, 95% CI [-0.111, 0.070], p-value=0.652 and insignificant (p=0.528) test for heterogeneity. Total patients studied between these two studies were 49 and 52 in the TNZ and MTZ/ORN groups respectively. A Forrest plot for all nine studies, pooled according to pivotal status, is shown below with the overall combined random effects slightly favoring TNZ.

Figure 3.21 Analyses according to study status



3.1.2.4.2.2 Analyses by Proposed TNZ Dose

An additional analysis, pooling only those studies (n=4), which evaluated the proposed TNZ dose (2 g x 3-5 days) resulted in a random effects rate of 0.245, 95% CI [-0.096, 0.586], and an insignificant p-value=0.160 (test for heterogeneity significant, p=0.0008). The comparators used in these four studies were MTZ 2 g x 3-5 days (n=3), and MTZ 400 mg tid x 5 days (n=1).

3.1.2.4.2.3 Analyses by Treatment Blind

Four studies in amebic liver abscess were blinded (3 DB, 1 SB) and the remaining (n=5) were open label. Among the blinded studies, the random effects rate was 0.044, 95% CI [-0.154, 0.242], p-value=0.6607 (p-value for Q statistic=0.0059). The five open-label studies were significant for heterogeneity (p=0.0045) with a random effects estimate of 0.107, 95% [-0.162, 0.376], p-value=0.4363.

3.1.2.4.2.4 Summary of Meta-Analyses of Amebic Liver Abscess Studies

The only meta-analyses, which yielded a significant p-value for the combined treatment effect, were the analyses of the Sponsor's pivotal studies and the open-label studies. Both analyses are difficult to interpret however since varying doses of TNZ were studied in both groups. A more informative analysis is that of all studies evaluating the proposed TNZ dose of 2 g x 3-5 days. The results of this analysis suggest that TNZ is non-inferior to MTZ, with a non-inferiority margin less than 10%.

Table 3.8 Meta-Analyses of Amebic Liver Abscess Studies

Meta-Analyses**	# of Studies	TNZ Success Rate	Comparator Success Rate	Treatment Effect***	P-value*	95% CI	Q-statistic p-value
Pivotal	7	0.917 (121/132)	0.683 (97/142)	0.254	0.0088	(0.064, 0.445)	0.0002
Non-pivotal	2	0.939 (46/49)	0.962 (50/52)	-0.021	0.6519	(-0.111, 0.070)	0.5278
Blinded ¹	4	0.884 (76/86)	0.835 (81/97)	0.044	0.6607	(-0.154, 0.242)	0.0059
Open label	5	0.958 (91/95)	0.680 (66/97)	0.288	0.0028	(0.099, 0.476)	0.0211
TNZ 2 g 3-5 days ²	4	0.855 (53/62)	0.667 (46/69)	0.245	0.1600	(-0.096, 0.586)	0.0008

¹ Comprised of 3 DB, 1 SB studies

² Proposed TNZ dose for treatment of amebic liver abscess is 2 g/day x 3-5 days (all but one study used MTZ 2 g/day x 3-5 days, the other dose was MTZ 400 mg tid/day x 5 days)

* P-value for Z-statistic (combined effects estimate/s.e)

** Criteria for pooling of studies

3.2 Evaluation of Safety

No formal safety analyses were performed given the nature of this submission. Refer to the medical safety review by Carl Kraus, MD.

The most reported adverse events associated with TNZ treatment, as summarize by the Sponsor in the submission, were metallic taste, nausea, vomiting, abdominal pain, anorexia, and weakness/fatigue. The frequency of these events was on average consistent among treatment indications.

Table 3.9 Most frequent adverse events associated with TNZ treatment

Adverse Event	Trichomoniasis	Giardiasis	Amebiasis
Metallic Taste	55/1536 (3.6%)	36/932 (3.8%)	60/842 (7.1%)
Nausea	61/1536 (4.0%)	19/932 (2.0%)	43/842 (5.1%)
Vomiting	19/1536 (1.3%)	17/932 (1.8%)	10/842 (1.2%)
Abdominal Pain	25/1536 (1.6%)	20/932 (2.1%)	11/842 (1.3%)
Anorexia	30/1536 (2.0%)	6/932 (0.6%)	21/842 (2.5%)
Weakness/fatigue	17/1536 (1.1%)	34/932 (3.6%)	11/842 (1.3%)

Adverse reactions with metronidazole, the most common active control studied against TNZ in the studies discussed and also the approved treatment for trichomoniasis and amebiasis, are nausea, headache, vomiting, diarrhea, epigastric distress, constipation and abdominal cramping.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Documentation of patient demographics was inconsistent among the published studies presented in this submission. It is not feasible to perform subgroup analyses using cited references.

Analyses by population studied (adults, children) was performed for giardiasis indication and discussed in section 3.1.2.3.1.

4.2 Other Special/Subgroup Populations

Given the nature of this submission and the quality of the studies cited therein, subgroup analyses were not feasible.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

As previously discussed, the Sponsor was not required to conduct new clinical efficacy trials but rather was allowed to submit literature references of previously conducted controlled efficacy studies in trichomoniasis (n=14 studies), giardiasis (n=15 studies) and amebiasis (n=18 studies). In this review, several meta-analyses were performed on these studies noting that although meta-analyses are useful to strengthen evidence of efficacy, there are potential for biases in data selection and potential for misinterpretation of analyses. Details of statistical concerns in this NDA and with the use of meta-analyses are discussed in detail in section 1.3. To summarize:

- This submission lacks in individual patient and study data since it relied solely on published literature. Without these data, it may be difficult to fully evaluate study quality and accuracy leading to difficulties in assessing study to study variation. Most of the references provided were of older published studies with limited detail pertaining to patient demographics, outcomes and study design.
- Treatment randomization methods varied from study to study with few studies utilizing statistically valid methods such as computer generated assignment codes.
- Few studies were double-blind [trichomoniasis: 8 (DB), 1(SB); giardiasis: 4 (SB); intestinal amebiasis: 2 (SB), amebic liver abscess: 3 (DB), 1 (SB)], adding potential treatment bias.
- Study heterogeneity was identified in several analyses, primarily due to variation in treatment doses and regimens, which was reduced when further sub-grouping of studies.
- Fundamental to all meta-analyses from database referenced studies is the concern for publication and selection bias. Studies with more favorable outcomes, or those performed in more developed countries, tend to be published more often than those studies showing no benefit with experimental treatment or that were written, or conducted in non-English speaking countries. Selecting studies with favorable results for inclusion in meta-analyses is a general concern. To assess for these potential biases in this review, funnel plots demonstrating treatment effect vs. study precision were examined. In the event there was evidence suggesting non-symmetry in these plots, studies were further examined (given the limitation in data) in attempt to understand the source(s) of variation. In most cases, deviations in symmetry were due to inappropriate pooling of active control and placebo control studies. In another instance, one study demonstrating a deviation from the others was found to be studying an entirely different patient

population and was thus removed from the meta-analyses.

- There is also concern regarding the use of older, weaker quality studies in the meta-analyses. Most of the comparative tinidazole studies were performed several years ago not having the same quality as current studies.

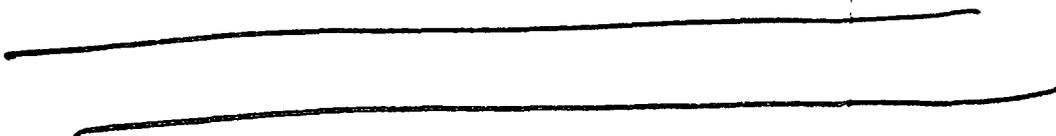
This review attempted to address these statistical concerns as best possible by performing multiple sensitivity analyses, testing for bias using funnel plotting method, and testing for heterogeneity among pooled studies. Random and fixed effect methods were used depending of the presence of heterogeneity.

In general, meta-analyses are not at the same level as prospective well-designed clinical trials for the purposes of evaluating drug efficacy. Meta-analyses are generally applied retrospectively and are therefore a post-hoc analyses tool dealing with similar statistical issues seen in observational and retrospective studies. However, there is strong evidence to support the efficacy of tinidazole for the treatment of trichomoniasis, giardiasis, and amebiasis based on the following conclusions:

- For each indication, the treatment effects across individual studies were in the same direction in favor of tinidazole or suggested non-inferiority of tinidazole to comparator.
- The meta-analyses of all selected studies (by indication) or sub-groups (by treatment dose or regimen, study population, and study design) provide sufficient evidence to support the efficacy of tinidazole. For giardiasis and amebiasis, there was stronger evidence in support of tinidazole over comparator.
- The studies utilized in the analyses were all controlled and most were randomized.
- There is a vast clinical experience with tinidazole at the proposed dose and durations for these indications.

5.2 Conclusions and Recommendations

This is a 505(b)(2) NDA containing published references and data summaries pertaining to the use of tinidazole for the treatment of trichomoniasis, giardiasis, and amebiasis. Although the quality of each published study is on average poor, lacking standard randomization methods and blinding procedures, collectively the studies support the claim that 2 g tinidazole is an effective treatment for the above mentioned indications.



SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: LaRee Tracy, M.A.

Date: April 21, 2004

Concurring Reviewers:

Statistical Team Leader: Karen Higgins, Sc.D.

cc:

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References

1. Egger, M., Smith G., Education and debate meta-analysis bias in location and selection of studies. *BMJ* 1998; 316: 61-66 (3 January)
2. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986; 7:177-188.

Trichomoniasis References:

3. Rees PH, McGlashan HE, Mubega V. Single-dose treatment of vaginal trichomoniasis with tinidazole. *E Afr Med J*; 51: 1974, 782-785.
4. Lyng, J., Christensen, J., A double-blind study of the value of treatment with a single dose tinidazole of partners to females with trichomoniasis. *Acta Obstet Gynecol Scand* 60:1981, 199-201.
5. Mati JKG, Wallace RJ. The treatment of trichomonal vaginitis using a single dose of tinidazole by mouth. *E Afr Med J*; 51: 1974, 883-888.
6. O-Prasertsawat, P., Jetsawangsi, T., Split-dose metronidazole or single-dose tinidazole for the treatment of vaginal trichomoniasis. *Sex Transm Dis* 19:1992, 295-297.
7. Weidenbach, A., Leix, H., Treatment of trichomonal vaginitis with a single dose of tinidazole. *Curr Med Res Opinion* 2:1974, 147-151.
8. Anjaneyulu, R., Gupte, S.A., Desai, D.B., Single-dose treatment of trichomonal vaginitis: A comparison of tinidazole and metronidazole. *J Int Med Res* 5:1977, 438-441.
9. Rao, H.T.M., Shenoy, D.R., Single-dose oral treatment of vaginal trichomoniasis with tinidazole and metronidazole. *J Int Med Res* 6:1978, 46-49.
10. Gabriel G, Robertson E, Thin RN. Single dose treatment of trichomoniasis. *Int Med Res* 1982;10:129-130.
11. Bloch, B., Smyth, E., The treatment of *Trichomonas vaginalis* vaginitis. *S Afr Med J* 67:1985, 455-457.
12. Aimakhu V. Vaginal trichomoniasis: one stat dose of tinidazole compared with a seven day course of metronidazole. *W Afr Med J*; April 1975: 97-100.
13. Beric B, Pribicevic V, Djordjevic M, Pavlovic N. Clinical investigations of the therapeutic action of tinidazole (Fasigyn) during the treatment of urogenital trichomoniasis in women and men (with comparative laboratory investigations of the action of metronidazole and tinidazole). *Zentralblatt fur Gynakologie*; 100(24): 1978, 1594-1598.
14. Hillstrom, L. Petterson, L., Palsson, E., Sandstrom, S.O., Comparison of ornidazole and tinidazole in

- single-dose Treatment of Trichomoniasis in Women. *Brit J Venereal Dis* 53:1977, 193-194.
15. Chaisilwattana P, Bhiraleus P, Patanaprinich P, Bhadrakom C. Double blind comparative study of tinidazole and ornidazole as a single dose treatment of vaginal trichomoniasis. *J Med Assoc Thailand* 1980; 63:448-452.
 16. Chandhuri P, Drogendyk AC. A double blind controlled clinical trial of carnidazole and tinidazole in the treatment of vaginal trichomoniasis. *Europ J Obstet Gynecol Reprod Biol*; 10: 1980, 325-328.
 17. Madico, G., Quinn, T., Rompalo, K., McKee, K, Gaydos, C. Diagnosis of *Trichomonas vaginalis* Infection by PCR Using Vaginal Swab Samples *Journal of Clinical Microbiolog*; 11: 1998, 3205-3210.
 18. 0095-1137/98/\$04.00+0

Giardiasis References:

19. Jokipii L, Jokipii AMM. Single-dose metronidazole and tinidazole as therapy for giardiasis: success rates, side effects and drug absorption and elimination. *J Infect Dis* 140:1979, 984-988.
20. Jokipii L, Jokipii, AMM. Treatment of giardiasis: Comparative evaluation of ornidazole and tinidazole as a single dose. *Gastroenterol* 83:1982, 399-404.
21. Kyronseppa H, Pettersson T. Treatment of giardiasis: relative efficacy of metronidazole as compared to tinidazole. *Scand J Infect Dis* 13:1981, 311-312.
22. Bakshi JS, Ghiara JM, Nanivadekar AS. How does tinidazole compare with metronidazole? A summary report of Indian trials in amoebiasis and giardiasis. *Drugs* 15 (Suppl 1): 1978, 33-42.
23. Gadzer AJ, Banerjee M. Single-dose treatment of children: A comparison of tinidazole and metronidazole. *Curr Med Res Opinion* 5:1977, 164-168.
24. Nigam P, Kapoor KK, Kumar A, et. al. Clinical profile of giardiasis and comparison of its therapeutic response to metronidazole and tinidazole. *JAPI* 1991; 39:613-615.
25. Krishnamurthy KA, Saradhambal V. Single dose therapy of giardiasis: A comparative study of tinidazole and metronidazole in pediatric patients. *Indian Pediatrics* 1978; 15: 51-56.
26. El Masray NA, Farid Z, Miner WF. Treatment of giardiasis with tinidazole. *Am J Trop Med Hyg* 1978; 27: 201-202.
27. Jokipii AMM, Jokippi L. Comparative evaluation of two dosages of tinidazole in the treatment of giardiasis. *Am J Trop Hyg* 1978; 27: 758-761.
28. Farahmandian I, Sheiban F, Sanati A. Evaluation of the effect of a single dose of tinidazole in giardiasis. July 1978. 139-140.
29. Speelman P. Single-dose tinidazole for the treatment of giardiasis. *Antimicrob Agents*

- Chemotherp 27: 1985, 227-229.
30. Suntornpoch V, Chavalittamrong B. Treatment of giardiasis in children with tinidazole, ornidazole and metronidazole. *SE Asian J Trop Med Pub Hlth* 1981; 12(2): 231-235.
 31. Pengsaa K, Sirivichayakul C, et. al. Albendazole treatment of giardia intestinalis infections in school children. *SE Asian J Trop Med Pub Hlth* 1999; 30(10): 78-83.
 32. Sabchareon A, Chongsuphajaisiddhi T, Attanath P. Treatment of giardiasis in children with quinacrine, metronidazole, tinidazole and ornidazole. *SE Asian J Trop Med Pub Hlth* 11: 1980, 280-284.
 33. Bassily S, Farid Z, El-Masry NA, Mikhail EM. Treatment of intestinal *E. histolytica* and *G. lamblia* with metronidazole, tinidazole and ornidazole: A comparative study. *J Trop Med Hyg* 90: 1987, 9-12.

Intestinal Amebiasis References:

34. Swami B, Lavakusulu D, Devi CS. Tinidazole and metronidazole in the treatment of intestinal amebiasis. *Cur Med Res Opinion* 1977; 5: 152-156.
35. Singh G, Kumar S. Short course of single daily dosage treatment with tinidazole and metronidazole in intestinal amebiasis: a comparative study. *Cur Med Res Opinion* 1977; 5: 157-160.
36. Misra NP, Gupta RC. A comparison of short course single daily dosage therapy of tinidazole with metronidazole in intestinal amebiasis. *J Int Med* 1977; 5: 434-437.
37. Bakshi JS, Ghiara JM, Nanivadekar AS. How does tinidazole compare with metronidazole? A summary report of Indian trials in amoebiasis and giardiasis. *Drugs* 15 (Suppl 1): 1978, 33-42.
38. Misra NP, Laiq SM. Comparative trial of tinidazole and metronidazole in intestinal amebiasis. *Cur Therap Res* 1974; 16: 1255-1263.
39. Joshi HD, Shah BM. A comparative study of tinidazole and metronidazole in the treatment of amoebiasis. *The Indian Practitioner* 28: 1975, 295.
40. Pehrson P, Bengtsson E. Treatment of non-invasive amoebiasis – a comparison between tinidazole and metronidazole. *Annals of Trop Med Parasitol* 1984; 78(5): 505-508.
41. Chung CN, Estamble BBA, Pamba HO, et al. Comparison of four nitroimidazole compounds for treatment of symptomatic amoebiasis in Kenya. *East Afr Med J* 1989; 66(11): 724-727.

Amebic Liver Abscess References:

42. Mendis S, Dharmasena BD, Jayatissa SK. Comparison of tinidazole and metronidazole in the

- treatment of hepatic amoebiasis: a controlled double blind study. *Ceylon Med J* 1984; 29: 97-100.
43. Kundu SC, Bhattacharjee TD, Desgupta DP, et. Al. Comparative evaluation of tinidazole and metronidazole in the treatment of amoebic liver abscess. *J Ind Med Assoc* 1977; 69(6): 127-129.
 44. Khokhani RC, Garud AD, Deodhar KP, et al. Comparative study of tinidazole and metronidazole in amoebic liver abscess. *Curr Med Res Opin* 5:1977; 161-163.
 45. Mathur SN, Itigi A, Krishnaveni RV. Tinidazole and metronidazole in the treatment of amebic liver abscess. *J Int Med Res* 1977; 5: 152-156.
 46. Islam N, Hasan M. Tinidazole and metronidazole in hepatic amoebiasis. *J Trop Med Hygiene* 1978; 20-22.
 47. Simjee AE, Gathiram V, Jackson T, Khan B. A comparative trial of metronidazole vs. tinidazole in the treatment of amoebic liver abscess. *S Afr Med J* 1985; 68:923-924.
 48. Bakshi JS, Ghiara JM, Nanivadekar AS. How does tinidazole compare with metronidazole? A summary report of Indian trials in amoebiasis and giardiasis. *Drugs* 15 (Suppl 1): 1978, 33-42.
 49. Hatchuel W. Tinidazole for the treatment of amoebic liver abscess. *SA Med J* 1975; 25: 1879-1881.
 50. Lasserre R, Jaroonevesama N, Kurathong S, Soh CT. Single day treatment of amebic liver abscess. *Am J Trop Med Hyg* 1983; 32: 723-726.

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/s/

LaRee Tracy
4/21/04 04:28:44 PM
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Karen Higgins
4/21/04 05:45:36 PM
BIOMETRICS

STATISTICAL REVIEW AND EVALUATION: 45 DAY MEETING REVIEW
(COMPLETED REVIEW FOR INTERNAL DISTRIBUTION ONLY)

NDA: 21,618
Name of Drug: _____™ (tinidazole)
Applicant: Presutti Laboratories, Inc.
Submission Date: July 15, 2003
Stamp Date: July 17, 2003

Indication(s): 1) Trichomoniasis, _____
2) Giardiasis
3) Amebiasis (intestinal and amebic liver abscess)

Number and Type of Controlled Clinical Studies (By Indication):

This NDA is a 505(b)(2) submission. All clinical studies provided in this submission come from published literature from over 30 years of clinical use of tinidazole outside of the United States. The sponsor provided a summary for all comparative studies and selected the larger, blinded (single or double), and randomized studies as pivotal.

For treatment of trichomoniasis with a single 2 g dose of tinidazole, over 34 published reports were identified. Of these reports, nine were blinded, randomized, comparative studies and the sponsor selected 5 of these 9 to use as pivotal studies. All nine studies will be reviewed.

For treatment of giardiasis with a single 2 g dose of tinidazole, 7 randomized, comparative clinical trials published reports were identified, of which 4 were chosen as pivotal. Three studies were single blind and no studies identified were double blind. All 7 references will be reviewed.

For the treatment of intestinal amebiasis, the sponsor identified 4 randomized clinical trials comparing the recommended tinidazole dose (2g/day x 3 days) to metronidazole (2g/day x 3days). Only one of the 4 studies was blinded (single).

For the treatment of amebic liver abscess, 18 studies were identified, 9 randomized, and 7 comparative to metronidazole. All 7 comparative studies were open-label except one double blind study and one single blind study. The sponsor chose the 7 comparative studies as pivotal.

Statistical Reviewer: LaRee Tracy, M.A.
Clinical Reviewer: Regina Alivisatos, M.D. (trichomoniasis indication)
Maureen Tierney, M.D. (giardiasis and amebiasis indication)
Carl Kraus, M.D. (safety)

Project Manager: Christina Chi, Ph.D.

45 Day Meeting Date: August 28, 2003
Date Draft Review Expected: March 17, 2004
ODE IV Goal Date: May 17, 2004
User Fee Date: May 17, 2004

A. ORGANIZATION AND DATA PRESENTATION	YES	N O	N/A	Comments
I. Is there a comprehensive table of contents with adequate indexing and pagination?	✓			
II. Are the original protocols, protocol amendments and proposed label provided	✓			Studies from published reports. Protocols/amendments not available.
III. Are patient profile listings (for all enrolled patients) provided in each study report?			✓	Detail not provided since clinical data is from published literature.
IV. Are adverse event listings by center and time of occurrence relative to enrollment date included?			✓	Safety summary across referenced studies
V. Have the data been submitted electronically?		✓		
a. If so, has adequate documentation of the data sets been provided?			✓	
b. Do the electronic data appear to accurately represent the data described in the study reports?			✓	
c. Can the data be easily merged across studies and indications?			✓	
d. Are inclusion/exclusion and evaluability criteria adequately coded and described?			✓	

B. STATISTICAL METHODOLOGY	YES	NO	N/A	Comments
I. Are all primary efficacy studies of appropriate design to meet basic approvability requirements, within current Divisional policy statements or to the extent agreed upon previously with the sponsor by the Division?	✓			Variable study designs and randomization methods. Applicability of each study will be considered on a case by case basis during the review.
II. For each study, is there a comprehensive statistical summary of the efficacy analyses which covers the intent-to-treat population, evaluable subject population and other applicable subgroups (age, gender, race, etc.)?	✓			Detail of statistical analyses varies among referenced studies. Applicability of each study will be considered on a case by case basis during the review.
III. Based on the summary analyses of each study, do you believe:	✓			
a. The analyses are appropriate for the type of data collected, the study design, and the study objectives (based on protocol objectives proposed labeling claims)?				
b. Intent-to-treat and evaluable patient analyses are properly performed?	✓			
c. Missing data has been appropriately handled?	✓			
d. Any multiplicity issues (e.g., regarding endpoints, time points, or multiple dose groups) have been adequately addressed?	✓			
e. If interim analyses were performed, were they planned in the protocol and were appropriate significance level adjustments made?			✓	
IV. Were sufficient and appropriate reference included for novel statistical approaches?			✓	

V. Are all of the pivotal studies complete?			✓	No additional studies conducted by the sponsor. All clinical data summarized from published reports.
VI. Have safety data been comprehensively and adequately summarized?	✓			

C. FILEABILITY CONCLUSIONS

From a statistical perspective this submission and indications therein, are reviewable with only minor further input from the sponsor.

The review of this NDA will require pooling data from across multiple studies published in the literature. The quality of these published studies will need to be carefully assessed to determine which studies are appropriate for pooling.

LaRee Tracy, M.A.
Statistical Reviewer
DBIII

Concur
Karen Higgins, Ph.D.
Statistics Team Leader
DB III

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