CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE for:

APPLICATION NUMBER: 050742

TRADE NAME: Mectizan

GENERIC NAME: Ivermectin

SPONSOR: Merck Research Laboratories

APPROVAL DATE: 11/22/96

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-742

Kenneth R. Brown, M.D.
Exetutive Director
Worldwide Regulatory Liaison
Biologics/Vaccines
Merck & Co., Inc
West Point, PA 19486-0004

NOV 22 1996

Dear Dr. Brown:

Reference is made to your March 29, 1996 new drug application (NDA) and your resubmission dated October 15, 1996, submitted under section 507 of the Federal Food, Drug, and Cosmetic Act for Tablet STROMECTOL® (ivermectin) 6-mg.

We acknowledge receipt of your amendments dated April 16, June 28, July 9, 16, 22, and 31, August 23, and 28, and October 4, 1996.

This new drug application provides for the treatment of strongyloidiasis and onchocerciasis.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 50-742. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Anti-Infective Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Ms. Pauline Fogarty
Regulatory Health Project Manager
(301) 827-2125

Sincerely yours,

David W. Feigal, Jr., M.D., M.P.H.
Acting Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

ENCLOSURE

MEDICAL OFFICER REVIEW OF NDA
NDA 50-742

Applicant: Merck Research Laboratories
Sumneytown Pike
West Point, PA 19486
Contact: Kenneth Brown, MD
Executive Director, Regulatory Affairs
(610) 397-2552

Date of submission: 29 March 1996
CDER stamp date: 1 April 1996
Date review completed: 23 September 1996

Drug identification:
Generic name: Ivermectin
Proposed trade name: Stromectol®

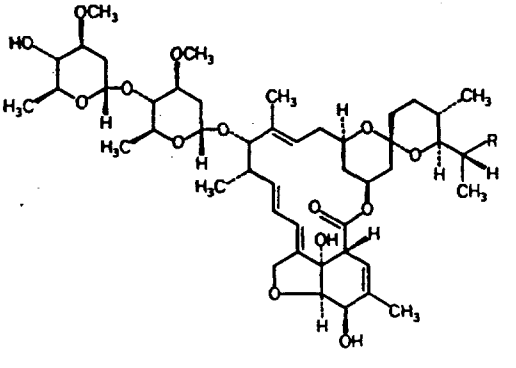
Molecular formulae: $C_{48}H_{74}O_{14}$ (component H_2B_{1a})
$C_{47}H_{72}O_{14}$ (component H_2B_{1b})

Molecular weights: 875.10 (component H_2B_{1a})
861.07 (component H_2B_{1b})

Chemical name:

5-O-demethyl-22,23-dihydroavermectin A_{1a};22,23-dihydroavermectin B_{1a}/5-O-demethyl-25-de(methylpropyl)-22,23-dihydro-25-(1-methylethyl) avermectin A_{1a};22,23-dihydroavermectin B_{1b}

Structural formula:



Component B_{1a}, R = C_2H_5 Component B_{1b}, R = CH_3

Ivermectin in the treatment of Strongyloidiasis

1. The disease
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10. Recommendations

Pharmacologic category: avermectin antiparasitic

Dosage form: 6-mg scored tablets

Route of administration: oral

Proposed INDICATIONS AND USAGE section:

Proposed DOSAGE AND ADMINISTRATION section:

Materials reviewed:

1. NDA 50-742, volume 1.1 and volumes 1.15-1.27

2. Additional information submitted 9 July 1996. 34 volumes. (included all information previously submitted as a Marketing Authorisation Application [MAA] to the French regulatory authority)

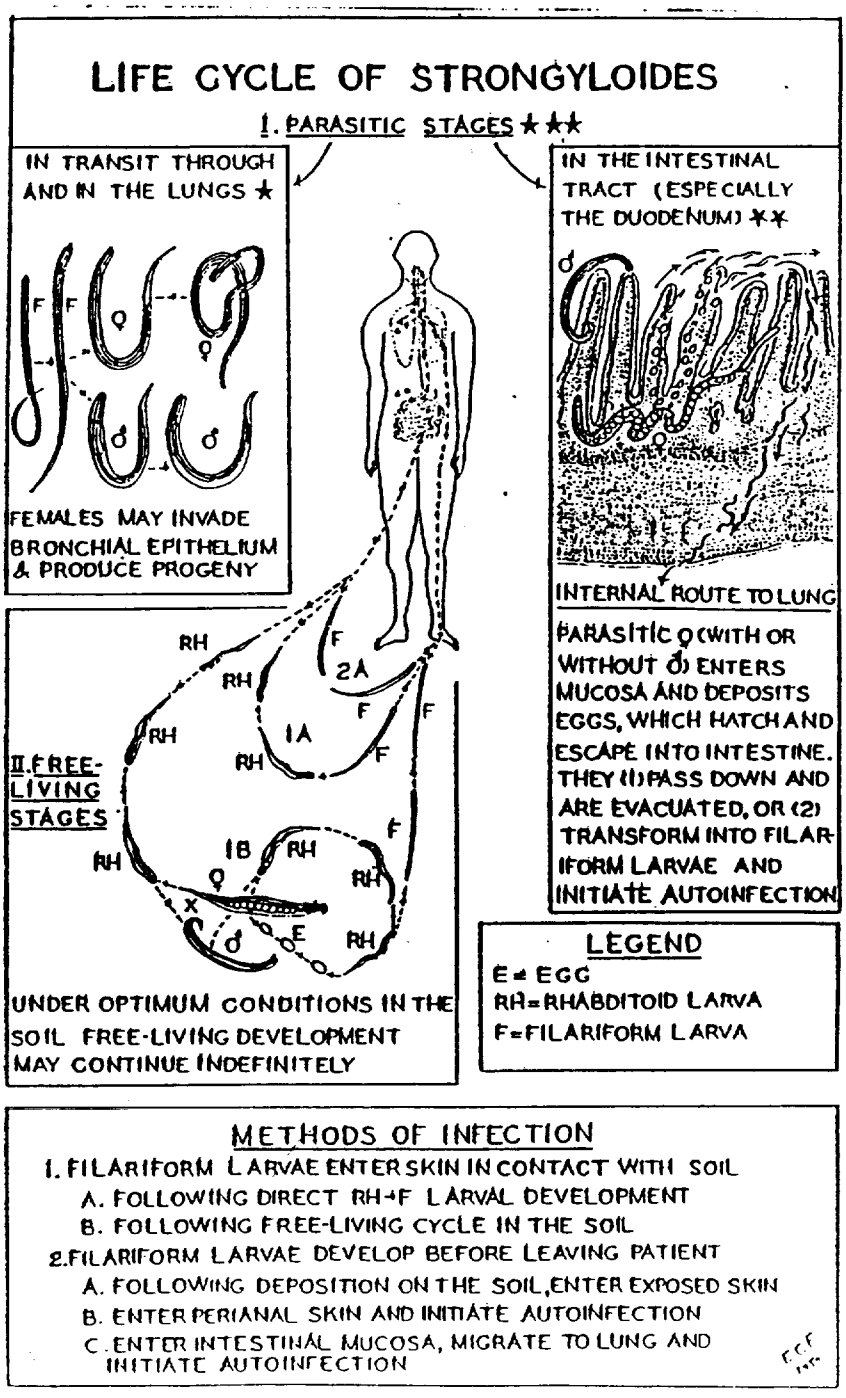
3. Safety Update report submitted 31 July 1996. 1 volume.

1. The disease

A. Life cycle:

Strongyloides stercoralis (heretofore referred to as SS) is a nematode parasite of the class Phasmidia, which also includes such human parasites as the hookworms (*Ancylostoma* and *Necator*), *Trichostrongylus*, and *Angiostrongylus*. These parasites all develop from the egg stage, through four successive larval stages, then finally mature to the adult stage. SS has a life cycle which is unique among all human helminth parasites in that it has a free-living phase of the life cycle and can also continually reinfect the same host.

The complete SS life cycle is demonstrated in the following diagram:



The following aspects of the life cycle are relevant to clinical trial design:

- The usual mode of transmission is via percutaneous penetration by an infective third-stage larva. Once this occurs, the pre-patent period (i.e., the time from initial infection to detection of SS larvae in the stool) is roughly 28 days. Therefore, if patients are treated for this infection but then return to a potentially-infectious environment, follow-up stool examinations beyond that time point will not be able to distinguish relapse of the original infection (i.e., drug failure) from re-infection.
- The adult female is not nearly as prodigious as most of her nematode relatives. It is estimated that the daily egg output of a mature female SS is approximately 30 eggs per day. (Comparatively, an adult *Ascaris lumbricoides* female lays approximately 200,000 eggs per day.) As a result, detection of SS larvae in the stool of an infected patient requires concentration methods. The most sensitive method for direct parasite detection is the Baermann technique, in which a relatively large stool specimen can be processed such that the larvae of SS, if present, will migrate out of the specimen. This technique was reportedly utilized for all parasitologic specimens processed in the trials submitted by the applicant for this indication.
- Because of this low-level shedding of larvae in the stool of the host, the definition of 'cure' should be based on more than a single negative stool examination. There does not, however, appear to be a consensus in the literature as to how many consecutive negative stools should be required, and over what period of time post-therapy they should be checked.
- Infection may persist for years, due to the internal autoreinfection aspect of the life cycle. Larvae hatched in the host intestine may undergo accelerated development into infective third-stage larve while still in the intestinal lumen. These infective larvae then penetrate the gut epithelium or perianal skin, enter the host circulation, and repeat the pulmonary → trachea→ gastrointestinal migration which results in the continued presence of sexually mature, parthenogenic female worms. Elderly adult veterans of the Second World War, particularly those who were prisoners of war in the Pacific theatre of operations, have been diagnosed with strongyloidiasis 30+ years after their initial exposure.
- Strongyloidiasis can become disseminated if the host becomes immunocompromised. The medical literature documents cases in which quiescent infections disseminate when the host is given immunosuppressive chemotherapy. The advent of the HIV epidemic has brought about an increased number of cases of disseminated strongyloidiasis in those geographic areas in which the two diseases are both present. Disseminated disease is notoriously difficult to eradicate via anthelminthic therapy alone.

B. Clinical manifestations

In general, the severity of clinical symptoms is related to the intensity of the infection. Low-level infections can be relatively asymptomatic. Heavy infections, particularly when disseminated, can be fatal.

The infected patient can manifest symptoms which correspond to the migration of the parasite. Initial penetration of infective larvae into the skin can provoke an intense pruritus which may lead to secondary bacterial infection. When the larvae enter the peripheral circulation, they are transported to the pulmonary capillaries where they migrate into the alveoli. This process may result in cough, wheezing, and bronchopneumonia-like pulmonary symptoms. Following arrival in the crypts of the small intestine, female worms rapidly mature and invade the tissues of the wall. The females move in a tortuous fashion at the base of the villi or in the deeper stroma, laying eggs as they proceed. These eggs promptly hatch and the first-stage (rhabditiform) larvae burrow towards the intestinal lumen. In light infections, intestinal symptoms may be mild. In heavy infections, the mucosa may be honeycombed by the adult worms and larvae, and sloughing of extensive patches may occur. Watery, mucous and blood-laden diarrhea can result. The patient may experience various degrees of abdominal pain with alternating bouts of diarrhea and constipation. Secondary bacterial infection, including bacterial sepsis, may result from such massive compromise of the intestinal epithelium. Leukocytosis and eosinophilia are common features of this illness. Cutaneous manifestations, particularly urticaria and larva currens (similar to larva migrans but more rapid in evolution) may also be seen.

In disseminated disease, a variety of clincial manifestations may result from the migration of the SS larvae. Pulmonary infiltrates and progressive respiratory compromise can result, which will progress despite the initiation of empiric antibacterial therapy. Central nervous system involvement has also been described. (NB: in this NDA, the applicant is not seeking a disseminated strongyloidiasis indication.)

C. Therapy

Currently, there is one FDA-approved agent for the treatment of strongyloidiasis: thiabendazole (Mintezol, Merck). This agent was approved for this indication in 1966 and remains the mainstay of therapy for this disease in the US. The approval of this indication was based on a total of 103 patients with strongyloidiasis treated by investigators in the United States, with a reported 89% cure rate, and an additional 296 cases of strongyloidiasis submitted from international clinical studies, with a reported cure rate of 99% (M. Albuerne, Medical Officer review of NDAs 16-096 and 16-097, dated 26 January 1967). These studies were presumably open-label and noncomparative, as there was no accepted, reasonably efficacious therapy for strongyloidiasis at that time. (Unfortunately, the nature of the trial design of the various studies submitted in support of this application is not discussed in Dr. Albuerne's review.)

Although thiabendazole is the only currently-approved drug for this indication, the precise mechanism of its anti-strongyloides activity is unclear. According to Grove in his reference textbook Strongyloidiasis: A major roundworm infection of man (London: Taylor & Francis, 1989):

> When the actions of thiabendazole on the various phases of infection with *S. ratti* in mice were investigated, the drug was found to have little effect on migrating larvae, nor did it eradicate adult worms from the intestinal tract. Excretion of eggs in the faeces was markedly reduced, however; this was shown to be due to impairment by thiabendazole of the fecundity of parasitic females in the gut. Thiabendazole had no effect on *S. stercoralis* filariform larvae in the muscles of mice...
> These findings suggest that thiabendazole cannot be relied upon in treatment. It appears to be inactive against both migrating larvae and intestinal adult worms, its apparent efficacy being due to a marked reduction in the fecundity of parasitic female adult worms. It is possible, however, that this action reduces considerably the intensity of infection. (Page 205-6)

On the other hand, there is evidence from animal studies that ivermectin has better larvicidal activity. In the chapter discussing the rat model of strongyloidiasis (which involves a different species, *Strongyloides ratti*), the above-referenced text discusses the anthelminthic activity of the avermectins:

> Avermectin B_1 acts by paralyzing worms and permitting host responses to remove the parasite. Paralysis of the worms occurs when avermectin B_1 stimulates the pre-synaptic release of gamma aminobutyric acid which blocks the post-synaptic transmission of nerve impulses. Avermectin was found to be effective against *S. ratti* and totally suppressed the fecal larval excretion. Avermectin acted on tissue migrating larvae and completely prevented the appearance of *S. ratti* in the small intestine. (Grove, *op. cit.* at page 325)

At present, thiabendazole appears to retain its activity against this parasite; drug resistance does not appear to be a siginificant problem. Tolerability, on the other hand, does appear to be an issue; epigastric distress, diarrhea, nausea, vomiting, dizziness and weakness are common thiabendazole-related adverse drug effects. The Mintezol product label calls for a dose of approximately 22 mg/kg, given BID for two consecutive days. (Note that the thiabendazole regimens in the studies detailed below are three-day regimens. Many parasitic disease experts, including the WHO, recommend a three-day thiabendazole regimen for the treatment of intestinal strongyloidiasis.) Gastrointestinal side-effects are sometimes severe enough to interfere with patient compliance with this regimen.

2. Overview of studies submitted in support of this indication.

The applicant has submitted five clinical studies in support of this indication.

Protocol/ location	Investigator	Ivermecin arms	Comparator	Study design	Patient-level data submitted?	Considered 'pivotal' by applicant?	Number randomized
004/Paris	Gentilini	single dose	albendazole BID X 3 days	open label random	Yes	Yes	ABZ 27 Iver X 1 29
014/USA (Tennessee)	Berk	single dose QD X 2	thiabendazole BID X 3 days	open label random	yes	no	Iver X 1 4 Iver X 2 6 Thiaben 6
015/USA (Massachu-setts)	Gann	single dose QD X 2	thiabendazole BID X 3 days	open label random	yes	no	Iver X 1 18 Iver X 2 19 Thiaben 16
020/Brazil	Dreyer	single dose QD X 2	thiabendazole BID X 3 days	open label random	yes	no	Iver X 1 17 Iver X 2 17 Thiaben 15
WHO study Zanzibar	Marti	single dose	albendazole BID X 3 days	open label random	no	yes	ABZ 209 Iver X 1 208

As can be seen above, of the two studies considered 'pivotal' by the applicant, only one has patient-level data submitted with the NDA. This was discussed with the applicant at the time of the Fileability determination, and the applicant agreed to attempt to recover some of these data.

3. Study 004 (Gentilini): An open, randomized study of efficacy, safety, and tolerability of ivermectin single dose vs. albendazole (three-day course) in the treatment of patients infected with *Strongyloides stercoralis*.

A. Study summary:
The following summmarizes this study (taken from pages D-2148-57, volume 1.21 of NDA):

II. SUMMARY OF PROTOCOL AND STUDY PROCEDURES

A. Protection of Human Subjects

This study was conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research.

B. Investigators

Prof. Marc Gentilini, M.D./Annick Datry, M.D.
Deparment De Medecine Tropicale—Parasitologie
Hopital De La Salpetriere
43 BD de l' Hopital
75013 Paris, France

C. Objective

To study the efficacy, safety, and tolerability of ivermectin vs. albendazole in the treatment of patients infected with *Strongyloides stercoralis*.

D. Patient Selection

Approximately 50 patients were entered into this study.

Patient Inclusions

1. Patients infected with *Strongyloides stercoralis.*
2. Patients were between 5 and 70 years of age.
3. An examination of the stool done 6 days or less before entry into the study was positive for *Strongyloides stercoralis* larvae or duodenal aspirates or jejunal biopsies were positive for the larvae.

D. Patient Selection (Cont.)

Patient Exclusions

1. Age under 5 or over 70 years.
2. Women of childbearing potential.
3. Medical history of mental illness, seizure, or other serious illnesses.
4. SGOT or SGPT greater than twice the upper normal limit, creatinine greater than 2.0 mg/100 mL or grossly abnormal BUN or urine analysis.
5. An abnormal ECG or history of an abnormal EEG.
6. Moderate or severe anemia, i.e., hemoglobin less than 10 g or hematocrit less than 30%; any abnormality of white blood cell count and/or differential (except eosinophilia).
7. Any past or concurrent medical illness which the investigator felt might influence either the outcome of the study or interpretation of the data accrued.

E. Study Design

General Description

This study was an open, randomized study of the efficacy, safety, and tolerability of a single ivermectin dose vs. albendazole for 3 days in the treatment of ambulatory patients who have an infection with *Strongyloides stercoralis*.

Although the study was open in design, stool specimens were examined by one single expert who was to remain blinded as to the treatment allocations.

E. Study Design (Cont.)

Patients who satisfied all inclusion criteria (except as noted in section III.B.2) and none of the exclusion criteria specified above were randomly allocated to receive either a single dose of ivermectin (target dose of 200 mcg/kg) or albendazole (200 mg b.i.d. for 3 days). It should be noted that the actual dose of ivermectin administered to patients in this study was approximately 170 mcg/kg (median 169 mcg/kg). The reason for this was that the dosage schedule (i.e., combinations of ivermectin 6-mg tablets by body weight) included in the protocol for the study was in error. The difference between the administered dose and the target dose is not considered meaningful [8].

The efficacy and safety of ivermectin was evaluated on the basis of physical examinations and laboratory tests prior to treatment and on Days 7 (5 to 9), 30 (26 to 34), and 90 (85 to 95) posttreatment.

In the event that mild or moderate reactions to drug treatment occurred, they could be treated with aspirin and antihistamines; other medications were not to be administered during the first week of drug administration except for necessary treatment of patients with severe allergic reactions.

Although not required by the protocol, patients remained in France throughout the study period, thus eliminating the confounding variable of reinfection.

Patient Allocation

After completion of the informed consent procedures and documentation of strongyloidiasis evidenced by stool examination, patients were randomized to receive either ivermectin or albendazole according to an allocation schedule. The patients were dosed at least 2 hours before breakfast.

During the week prior to the study, the patient was screened to assure that he/she was in good physical condition. The patient had a physical examination and a laboratory screen. Vital signs were recorded on Day -1 (the day before drug administration).

E. Study Design (Cont.)

Treatment

Ivermectin was provided as 6-mg commercial tablets. The dose closest to that calculated on the basis of body weight was utilized. A schedule of recommended combinations of these tablets for patients who weigh between 15 and 84 kg is shown in the following table (Table 1).

Table 1

Ivermectin Dosage Recommended Tablet Combinations
Based on Patient Body Weight

Patient Body Weight (kg)	Tablets (6 mg)
15 to 25	½
26 to 44	1
45 to 64	1½
65 to 84	2

Albendazole was provided as 200-mg tablets. Each patient in this group received two tablets each day for 3 days for a total of 6 tablets.

Failure to respond to therapy could be determined in 5 to 9 days, and although there were no provisions in the protocol for the retreatment of treatment failures, the investigator did retreat all treatment failures as follows:

- Ivermectin-treated patients who failed were treated with two doses of the same ivermectin dose as previously administered 24 hours apart.
- Albendazole-treated patients who failed were treated with a single dose of ivermectin in accordance with their body weight (Table 1).

F. Clinical Observations and Laboratory Measurements

The patient was evaluated medically for suitability for the study. Based on signs and symptoms of disease, the investigator categorized the patient's clinical illness as mild, moderate, or severe. Categorizing the patient's severity of illness was not formally required by the protocol; however, such an evaluation is in keeping with the exercise of good clinical judgment in comparing patients in this clinical setting.

Table 2 shows the schedule of clinical observations and laboratory measurements during the study.

Table 2

Schedule of Clinical Observations and Laboratory Measurements

	Prestudy	1	2	3	Day 7 (5 to 9)	Day 30 (26 to 34)	Day 90 (85 to 95)
Drug Administration		X or X	 or X	 X			
Physical Examination	X	X			X	X	X
Vital Signs	X	X			X		
Laboratory Safety	X				X		
Stool Examination	X				X	X	X
Eosinophilia+	X				X	X	X

+This test (i.e., hypereosinophilia) was not a specific protocol requirement nor was the information made part of a MRL analysis. However, the information was part of a sub-protocol at the investigative site and reported by the investigative team [11].

F. Clinical Observations and Laboratory Measurements (Cont.)

Observations and measurements relating to efficacy and safety are described below:

Efficacy Measurements

Baseline evaluation of *Strongyloides stercoralis* was to be established in each patient prior to study drug administration. Although the protocol allowed duodenal or jejunal biopsies for the determination of *S. stercoralis*, only examination of stool samples by the Baermann technique [10] was used in the study. All stool specimens were examined by one single expert who was to remain blinded as to the treatment allocations.

Although the protocol allowed for several diagnostic examinations for detection and quantification of *S. stercoralis* in stools, parasitological cure, the primary measure of efficacy, was assessed using three repeated Baermann stool examinations during each of the three follow-up periods on (Days 5 to 9, 26 to 34, and 85 to 95).

The Baermann technique [10] is a method examining a stool specimen suspected of having small numbers of Strongyloides larvae and uses the modified Baermann apparatus. The technique is dependent on the migration of active larvae out of the fecal material, through a wire gauze covered with gauze padding and into water, where they settle out. The procedure is as follows:

a. Fill a funnel (6-inch) with water (attach rubber tubing with a pinch clamp to the bottom of the funnel) and place the wire gauze, one or two layers of gauze padding on it, on the funnel.

b. Place 100 g (or other weighed amount) of fecal material on the gauze padding so that it is covered with water.

c. Allow the apparatus to stand for 2 or more hours, draw off 10 mL of fluid by releasing the pinch clamp, spin it down in a centrifuge and examine the sediment with a magnifier or low power microscope to count and confirm the species of the larvae.

F. Clinical Observations and Laboratory Measurements (Cont.)

Because the investigator gave actual counts (number of larvae per gm stool) for some of the patients and plus (+) or word designations for others, it was decided to use the following scheme to have consistency for all patients (Table 3).

Table 3

Scheme to Translate Between Larvae Counts, Word Designations and "Plus" Designations

Word Designations	Larvae Counts Per gm Stool	'Plus' Designations
Few	1 to 15	+
	16 to 30	++
Many	31 to 100	+++
	>100	++++

The above scheme is presented only for purposes of quantifying the level of infestation (intensity of infection) per patient and important only to determine comparability of treatment groups and to examine whether there is an interaction between intensity of infection and clinical outcome. This scheme was not specifically stated in the protocol; however, MRL believes that such an analysis between intensity of infection and outcome is valid. Since intensity of infection (in addition to age, sex, race, and severity of infection) was found to be not related to cure rate at the α=0.10 level of significance (see H. Statistical Planning and Analysis) it was dropped from the statistical model, leaving only treatment group.

F. Clinical Observations and Laboratory Measurements (Cont.)

Safety Measurements

A complete physical examination was done during the week preceding study drug administration and repeated at follow-up visit. Prestudy and follow-up samples for the laboratory safety studies on blood and urine included:

a.	Hematology:	Hematocrit Hemoglobin White blood cell count, total Differential counts will be made if WBC is abnormally low or high Blood smear for malaria parasites (saved until the follow-up examination is completed)
b.	Blood Chemistries:	Blood urea nitrogen Serum creatinine SGOT SGPT Total bilirubin Alkaline phosphatase
c.	Urinalysis:	Urinalysis was performed in patients with abnormal serum creatinine values or with signs/symptoms or urinary tract infection.

The investigator could carry out additional analyses as required by the hospital or as indicated for optimum patient care.

Vital signs (blood pressure and pulse rate, both supine and erect, respiration rate and temperature) were recorded on Day -1 and thereafter according to hospital routine for patients who remained in the hospital.

G. Evaluation Criteria

1. Evaluability

All patients whose data was received by August 30, 1991 were classified by the MRL clinical monitor as evaluable or unevaluable with respect to efficacy. These evaluations by the MRL monitor, although not specified in the protocol, were in keeping with the dictates of the protocol (i.e., inclusion and exclusion criteria) and the exercise of good clinical judgment. Thus, patients were considered evaluable for efficacy if:

a. Strongyloidiasis was documented on stool examination.

b. The patient did not receive other effective therapy during the study period.

c. The patient was compliant with therapy.

d. Adequate follow-up stool examinations were performed for determination of efficacy.

e. There was no violation of inclusion and/or exclusion criteria that would compromise efficacy evaluation.

2. Efficacy

As described earlier, baseline evaluation of *Strongyloides stercoralis* was to be established in each patient prior to study drug administration. Although the protocol allowed duodenal or jejunal biopsies for the determination of *S. stercoralis*, only examination of stool samples by the Baermann technique [10] was used in the study. All stool specimens were examined by one single expert who was to remain blinded as to the treatment allocations.

The primary measure of efficacy in this study was the absence of larvae in posttherapy Baermann fecal examinations. The detection of larvae on any posttreatment stool examination meant failure. Patients with adequate follow-up examinations which were all negative for larvae were considered cured. It should be noted that although not specified in the protocol, parasitological cure (i.e., stool exams negative for larvae) without resolution of symptoms was counted as a clinical failure.

G. Evaluation Criteria (Cont.)

3. Safety

All patients were evaluated for safety by physical examination and laboratory studies. In addition, the patient was questioned daily (by phone) regarding adverse experiences with particular attention to evidence of allergic reactions (rash, itching, and anaphylaxis). Adverse experiences were described and recorded by the investigator who determined the durations, seriousness, severity, and drug relationship as well as the eventual outcome of each adverse experience.

H. Statistical Planning and Analysis

Methods of Analysis

The primary measurement of efficacy was the cure rate. Logistic regression was used to determine if any concomitant factors, i.e., age, sex, race, severity of infection, intensity of infection, affected the cure rate. None of these factors was related to cure rate at the α=0.10 level of significance. Thus, all were dropped from the statistical model, leaving only treatment group. The treatment groups were compared using Fisher's exact test for the proportion of patients who were cured.

Baseline characteristics were analyzed using either Fisher's exact test or the Chi-square test of the Wilcoxon Rank Sum test, as appropriate. Confidence intervals were calculated using the method of Blyth and Still.

All statistical tests for treatment-group differences were two-tailed (α=0.05).

I. Clinical Supplies

Ivermectin in the form of commercial tablets (Lot 9H9476) were obtained through MSD-Chibret. Albendazole (200 mg, ZENTEL) tablets were obtained through a local pharmacy in Paris.

Medical officer comments: this protocol is an open-label, randomized trial of single-dose ivermectin vs. albendazole 200 mg BID X 3 days. It shares similarities with the other submitted studies in the NDA for this indication, particularly in that patients were required to have stools positive for SS by Baermann technique. This method of stool processing was also used for all followup examinations.

The dosing of albendazole is generally consistent with product labeling in those countries where it is approved for the treatment of strongyloidiasis (namely: Austrailia, France, Germany, India, South Africa, and Switzerland). Those labels do, however, specify that the dosing should be 400 mg daily as a single dose for three days; the Gentilini study utilized 200 mg BID for three days. It is also of note that the product label in Germany indicates that in 'severe' infections (not otherwise defined in the label) the dose of albendazole should be 800 mg qd for 3 days. Labels from both Germany and India call for a second corse of albendazole if the stools are still positive after 14-21 days. The Swiss label specifically states that albendazole at 400 mg QD X 3 days is "not suitable dosage for the therapy of immunocompromised patients".

It must also be noted that the dosing schedule for ivermectin used in this study deviates from that used in all the other submitted studies in support of this indication:

Protocol-specified Ivermectin Dosing Schedules

Gentilini study		*Berk, Gann, Dreyer, and Marti studies*	
Patient weight (kg)	*# of tablets*	*Patient weight (kg)*	*# of tablets*
15 to 25	*½*	*15 to 24*	*½*
26 to 44	*1*	*25 to 35*	*1*
45 to 64	*1½*	*36 to 50*	*1½*
65 to 84	*2*	*51 to 65*	*2*
		66 to 79	*2½*
		80 and over	*3*

The net result of this discrepancy is that the patients in the Gentilini study were relatively underdosed, compared to the other submitted studies. For example, a 55 kg subject enrolled in Gentilini would receive 1½ tablets, whereas the same subject in any other study would have received 2 tablets. This resulted in a median ivermectin dose of 169 µg/kg in this study. Since this discrepancy results in relative underdosing rather than overdosing, it is reasonable to combine results. If the opposite were true (i.e., subjects in the ivermectin arm of this study were relatively overdosed), then combining these results with those of the remaining submitted studies would be more problematic.

B. Deviations from protocol:
In reviewing the study summary and the original protocol, the following deviations were noted:

- the protocol calls for the entry stool to document *Strongyloides* infection to have been collected "six days or less before entry into the study"; however, the majority of enrollees in both arms of the study had their infection documented well before day -6. (One subject's entry stool was collected 100 days prior to enrollment.)

Medical officer comment: in general, stools collected earlier than 6 days prior to enrollment will be considered acceptable. However, a single stool over three months prior to entry seems to stretch this a bit. It is unclear why a repeat stool could not have been collected at the time the subject was enrolled and treated with study medication.

- the protocol calls for followup stools to be collected at days 7, 30, and 90 post-therapy; cure is defined as (Page D-2228 of vol 1.21) "the absence of detectable larvae in the follow-up stool examinations." However, many of the subjects only have stools recorded at/around the day 7 timepoint, then variably at the 30 and 90-day timepoints. No mention is made of how these subjects will be dealt with in evaluating efficacy.

Medical officer comment: because this study was conducted in France, where strongyloidiasis is not present, these subjects (all of whom remained in France for the duration of the study, according to the applicant [page D-2162])

are not subject to the confounding variable of reinfection post-therapy. Therefore, ANY positive stool post-therapy, no matter how many days out from therapy that may be, should be considered a failure. The applicant (Page D-2162) concurs with this assessment.

It is unclear whether the applicant required 'cured' subjects to have negative stools documented at <u>each</u> of these post-therapy time points. In other words, if the 30-day stool collection was missed, but the subject was shown to have a negative stool at day 90, was this subject called a 'cure'?

- the protocol makes no mention of a requirement for retreatment, but the investigator apparrently re-treated several patients with positive stools on follow-up.

Medical officer comment: some of these retreated patients were given a dose of ivermectin (either a repeat dose, or an initial dose if the subject had previously been given albendazole) as recently as seven days after their initial dosing regimen had been completed. In other studies submitted in support of this indication, this practice was <u>not</u> done and it is clear that some patients clear their parasites from the stool more slowly than others. In these promptly retreated subjects, it is difficult to definitively state that they failed their initial course of therapy.

C. Applicant's findings:

The applicant's interpretation of the results of this study are found on the following pages, which are taken from pages D-2158 to 2171 of volume 1.21 of the NDA:

III. RESULTS

A. Patient Characteristics

A summary of demographic information for both evaluable patients and all enrolled patients is provided in Table 4. There were no statistically significant differences in the characteristics of the two treatment groups. A detailed summary of each patient's treatment therapy may be found in Appendix 1.

Eleven of 29 patients in the ivermectin group (37.9%) and 11 of 27 patients in the albendazole group (40.7%) had secondary diagnoses. A detailed summary of each patient's secondary diagnoses may be found in Appendix 2.

Twelve patients (41.38%) in the ivermectin and 7 patients in the albendazole group (25.93%) received concomitant therapy during the study. No concomitant therapy had activity against *S. stercoralis* or might have modified symptoms related to *S. stercoralis* infection. A detailed summary of each patient's concomitant therapy may be found in Appendix 3.

As stated earlier in this report, the actual dose of ivermectin administered to patients in this study was approximately 170 mcg/kg (median 169 mcg/kg - see Table 5) instead of a targeted dose of 200 mcg/kg. The reason for this was that the dosage schedule (i.e., combinations of ivermectin 6-mg tablets by body weight) included in the protocol for the study was actually targeted at an approximate dose range of 150 to 171 mcg/kg ivermectin and not 200 mcg/kg. However, the difference between the administered dose of ivermectin and the target dose (200 mcg/kg) is not considered meaningful [8].

A. Patient Characteristics (Cont.)

Table 4

Baseline Characteristics

	All Patients		Evaluable Patients	
	IV*	ALB*	IV*	ALB*
Number of Patients	29	27	28	23
Mean Age (Age Range in Years)	36 (21-67)	36 (16-74)	36 (21-67)	36 (19-65)
Male (Age Range in Years)	(23-67)	(16-74)	(23-67)	(20-47)
Female (Age Range in Years)				
Sex				
Male	16 (55%)	15 (56%)	16 (57%)	11 (48%)
Female	13 (45%)	12 (44%)	12 (43%)	12 (52%)
Race				
Caucasian	6 (21%)	8 (30%)	6 (21%)	7 (30%)
Asian	6 (21%)	3 (11%)	6 (21%)	3 (13%)
Negro	14 (48%)	16 (59%)	13 (46%)	13 (57%)
Indian	1 (3%)	0	1 (4%)	0
Mulatto	2 (7%)	0	2 (7%)	0
Severity of Infection				
Mild	18 (64%)	19 (70%)	18 (67%)	15 (65%)
Moderate	9 (32%)	5 (19%)	8 (30%)	5 (22%)
Severe	1 (4%)	3 (11%)	1 (4%)	3 (13%)
No data	1 (4%)	0	1 (4%)	0
Intensity of Infection				
1+	12 (41%)	9 (33%)	12 (43%)	9 (39%)
2+	7 (24%)	6 (22%)	6 (21%)	6 (26%)
3+	8 (28%)	11 (41%)	8 (29%)	7 (30%)
4+	2 (7%)	1 (4%)	2 (7%)	1 (4%)

There were no significant differences between treatment groups.
* IV=ivermectin
ALB=albendazole

A. Patient Characteristics (Cont.)

Table 5

Ivermectin Dosage

AN	Ivermectin (mg)	Patient Body Weight (kg)	mcg/kg
	9	49	184
	9	59	152
	12	70	171
	12	67	179
	9	60	150
	9	64	141
	12	75	160
	9	59	152
	9	57	158
	9	51	176
	9	53	170
	12	78	154
	12	80	150
	12	73	164
	12	70	171
	12	65	185
	12	76	158
	9	61	147
	12	65	185
	9	60	150
	9	63	143
	12	67	179
	9	52	173
	12	81	148
	12	68	176
	12	65	185
	9	52	173
	12	71	169
	12	71	169
		Median	169
		Mean	164.6

B. Patient Accounting

1. Accounting for Patients in the Study

Table 6 presents a summary of patients who entered, completed, and discontinued the study by treatment group.

Table 6

Accounting for Patients in the Study by Treatment Group

Patients	Ivermectin Treatment	Albendazole Treatment
Total Patients Entered	29	27
Total Patients Completed	22	11
Total Patients Discontinued	7	16
Adverse Clinical Experience	0	0
Adverse Laboratory Experience	0	0
Lost to Follow-Up	0	0
Patient Death	0	0
Patient Uncooperative	1	2
No Therapeutic Regimen/Retreat	4	0
Protocol Deviation	1	0
No Therapeutic Response	1	0
No Therapeutic Response/Treatment Change	0	14

2. Accounting for Patients in the Analysis

Table 7 presents a summary of patients who were evaluable and nonevaluable in the efficacy and safety analysis.

B. Patient Accounting (Cont.)

Table 7

Accounting for Patients in the Analysis of Efficacy and Safety by Treatment Group

Patients	Ivermectin Treatment	Albendazole Treatment
Evaluable for Efficacy Analysis	28	23
Nonevaluable for Efficacy Analysis	1	4
Reason for Nonevaluable for Efficacy Analysis:		
Diagnosis to Treatment >30 days	1 (AN 24)	2 (AN 7, 19)
Inadequate Follow-Up Parasitology	0	1 (AN 16)
No Follow-Up Visits	0	1 (AN 28)
Evaluable for Safety	29	27

Patients who did not fulfill the criteria for efficacy evaluation outlined in Section II.G. were considered nonevaluable for efficacy. However, failure to satisfy the entrance criteria in Section II.D. did not necessarily exclude patients from the analyses of efficacy if the criteria for efficacy evaluation were satisfied. The inclusion criteria in Section II.D. required that the time period from diagnosis of strongyloidiasis (i.e., detection of larvae on stool examination) to initiation of therapy not exceed 6 days. In practice, this was often not possible.

Because the natural history of strongyloidiasis is one of persistence over time, patients who received study drug therapy within 30 days of a diagnostic stool examination were considered evaluable. In addition, if the period from diagnosis to therapy was greater than 30 days but a posttherapy stool examination was positive for *S. stercoralis* larvae, thus confirming that the patient was infected at the time of therapy since reinfection would not occur in France, the patient was considered evaluable.

It is recognized that these changes in entry and evaluation criteria differ from the requirements of the protocol; however, they are considered by MRL as consistent with the treatment of patients in nonendemic areas. As such, MRL believes that the alterations from the protocol as specified above do not impact on the validity of the results of this study.

B. Patient Accounting (Cont.)

Thirty patients (ivermectin-15, albendazole-15) with diagnosis to treatment periods of 7 to 30 days were considered evaluable. One patient (AN 57) had a diagnosis to treatment period of 39 days but was considered evaluable (failure) based on positive follow-up stool examination on Posttreatment Days 7 and 8. One patient (AN 21) had negative stool examinations following ivermectin therapy but symptoms recurred during follow-up. The patient was treated with other antistrongyloidiasis therapy based on the clinical picture. This patient was considered evaluable as a therapeutic failure.

Results of all parasitological examinations appear in Appendix 4.

Overall, 96% (28/29) of patients in the ivermectin treatment group and 85% (23/27) of the albendazole-treated patients were considered evaluable. Table 7 above identifies the reason for each patient being excluded from the efficacy evaluation.

C. Efficacy

There were a total of 51 evaluable patients in the study (Table 8), 28 in the ivermectin treatment group and 23 in the albendazole treatment group. A total of 79% (22/28) of patients were cured following ivermectin therapy compared to 43% (10/23) of those receiving albendazole. This difference in cure rates is statistically significant (p=0.02). Logistic regression analysis demonstrated that no other factor (age, sex, race, clinical severity of infection, and intensity of infection) was significantly related to treatment failure.

Table 8

Study Outcome -- Evaluable Patients

	Ivermectin (N=28)			Albendazole (N=23)		
	Cure	Percent	95% C.I.	Cure	Percent	95% C.I.
Overall	22/28*	79	(59, 91)	10/23	43	(24, 65)
Sex						
Male	13/16	81	(54, 95)	2/11	18	(3, 52)
Female	9/12	75	(43, 93)	8/12	67	(35, 89)
Race						
Caucasian	4/6	67	(24, 94)	4/7	57	(20, 88)
Asian	6/6	100	(52, 100)	2/3	67	(13, 98)
Negro	9/13	69	(39, 90)	4/13	31	(10, 61)
Indian	1/1	100	(5, 100)	0/0		
Mulatto	2/2	100	(20, 100)	0/0		
Severity of Infection						
Mild	14/18	78	(52, 93)	6/15	40	(17, 67)
Moderate	7/8	88	(47, 99)	2/5	40	(7, 83)
Severe	0/1	0	(0, 95)	2/3	67	(13, 98)
No data	1/1	100	(5, 100)	0/0		
Intensity of Infection						
1+	10/12	83	(51, 97)	5/9	56	(23, 85)
2+	5/6	83	(36, 99)	3/6	50	(14, 86)
3+	5/8	62	(26, 90)	2/7	29	(5, 70)
4+	2/2	100	(20, 100)	0/1	0	(0, 95)

* Significant difference between treatment groups (p<0.05)

C. Efficacy (Cont.)

If only those patients who met the entrance criteria of Section II.D. are considered for efficacy evaluation (i.e., if those patients with diagnosis to treatment periods of greater than 6 days are removed), 10 of 13 (76.9%) ivermectin-treated patients and 2 of 6 (33.3%) patients treated with albendazole were cured. These cure rates are not statistically different from those calculated when patients with a prolonged diagnosis to treatment interval are also considered evaluable (see above). The similarities in efficacy seen with these comparisons emphasizes the clinical equivalence of the two groups.

Similar results are seen if all patients, regardless of their efficacy evaluation status, are considered for analysis. Twenty-three of 29 (79%) patients were cured following ivermectin treatment versus 13 of 27 (48%) cured after albendazole (p=.03).

A single patient (AN 21 in the ivermectin group) developed recrudescent symptoms and was considered a failure despite negative stool examinations.

Table 9 presents a summary of the 17 patients who failed their initial course of therapy (4 ivermectin-treated; 13 albendazole-treated) and received a follow-up course of ivermectin. This information is offered for purposes of full disclosure only and is not brought to bear on the interpretation of this study.

C. Efficacy (Cont.)

Table 9

Summary of Patients Who Failed Initial Course of Therapy and Received a Follow-Up Course of Ivermectin

AN	Initial Treatment*	Second Treatment*	Days Between First and Second Treatment	Outcome†
	IV	IV	36	Cure
	IV	IV	181	Insufficient parasitology data to evaluate
	IV	IV	25	Cure
	IV	IV	111	Insufficient parasitology data to evaluate
	ALB	IV	184	Insufficient parasitology data to evaluate
	ALB	IV	20	Cure
	ALB	IV	11	Cure
	ALB	IV	9	Cure
	ALB	IV	42	Cure
	ALB	IV	10	Cure
	ALB	IV	11	Cure
	ALB	IV	41	Cure
	ALB	IV	24	Cure
	ALB	IV	39	Cure
	ALB	IV	11	Insufficient parasitology data to evaluate
	ALB	IV	10	Cure
	ALB	IV	40	Insufficient parasitology data to evaluate

* IV=Ivermectin
ALB=Albendazole

† Outcome is based on an evaluation of the parasitologic results available for the patient indicated. Cure implies parasitological cure and reflects negative stool examinations after the second course of treatment.

A quality assurance audit was performed on this study 3.5 years after the completion of the trial (reference Audit Information Sheet - Appendix 5). The MRL representative who conducted the audit found certain GCP compliance issues relating to insufficient documentation of informed consent, incomplete case report form documentation at the site, protocol compliance, incomplete regulatory documentation at the site and lack of study monitoring. Examples of the audit findings included:

C. Efficacy (Cont.)

- There was no record of drug supplied to the patients and no record of unused drug having been returned to MRL.
- There was no routine field monitoring conducted at this site.
- Lack of availability of patient consent forms for some patients (6) while others had consent forms which were not signed by the patients (3) and of those with signed forms some (4) were dated by the investigator and not the patient.
- Insufficient case report form documentation in MRL's Official Regulatory File and at the site (missing for 4 patients and incomplete for 38 patients).
- The 4 patients whose case reports were not submitted were entered in the study but were not reported to MRL. It is not clear at this time why data for 4 patients were not submitted to MRL; however, it may have resulted from MRL data cut-off dates imposed for the assembly of the French MAA. Data for these 4 patients are not included in this summary (60 patients were entered into the trial by the investigator rather than the 56 included in this write up). However, comparing the results of the trial for all 60 patients (which were published [10] in 1994) with the results summarized here indicate no substantive difference. In addition, as stated earlier, the investigator included an analysis of hypereosinophilia which was not a requirement of the protocol nor made part of MRL's analysis. Table 10 summarizes the differences in the two reports.

C. Efficacy (Cont.)

Table 10

Comparison Between MRL Data Received From Investigative Site and Data Published by the Investigative Team [10]

	MRL Summary			Publication		
Patient Accounting:	IV*	ALB*	ALL*	IV*	ALB*	ALL*
Patients Entered	29	27	56	32	28	60
Evaluable Patients (Efficacy)	28	23	51	29	24	53
Nonevaluable Patients (Efficacy)	1	4	5	3	4	7
Cure Rate (%)	22/28 (79)	10/23 (43)	N/A	24/29 (83)	9/24 (38)	N/A

* IV = Ivermectin; ALB = Albendazole; ALL = IV plus ALB

( ) = Percent cured

C. Efficacy (Cont.)

In the opinion of MRL, the lack of a complete file of case report forms at the investigative site does not affect the integrity of the information originally received from the investigator and used to produce this MRL summary.

Although not specified in the protocol, patients who failed initial therapy with either agent were retreated with ivermectin in an open, nonrandom manner (Reference Section II.E. Study Design). In addition, the investigator did not always follow the complete dictates of the protocol requirements dealing with examinations, vital signs, and laboratory tests and in some cases recordings of same were made to workbooks but never transferred to case report forms that were forwarded to MRL. The investigator did not maintain adequate regulatory documentation (e.g., no signed copy of the final approved protocol, no signed Normal Ranges for Laboratory Tests, no drug supply records, etc.).

Despite these regulatory compliance issues, MRL believes that the results of this study, that are reported in this summary, support the use of ivermectin in strongyloidiasis of the gastrointestinal tract and that the integrity of the data and conclusions drawn are generally consistent with the findings reported by the investigative group [11].

D. Safety

1. Adverse Experiences—Clinical

a. Overall Assessment of Clinical Adverse Experiences

All 56 patients, regardless of evaluability for efficacy, were included in this safety analysis. Three patients, one in the ivermectin group and two in the albendazole group, had clinical adverse experiences. There were no statistically significant differences in the frequency of adverse experiences between the two groups.

AN 3 in the ivermectin group experienced mild nausea, fatigue, dizziness, sleepiness, tremors, and mild vertigo study day one to two days after treatment each lasting 18 hours. The investigator considered them to be probably drug related.

D. Safety (Cont.)

in the albendazole group on the first day of treatment experienced mild vertigo lasting 24 hours and epigastric pain 72 hours duration which was also mild in intensity. Both events were considered possibly drug related. On the first day of albendazole treatment, experienced an increase in nausea and abdominal discomfort of moderate intensity lasting for 12 hours which the investigator considered possibly related to drug treatment.

b. Serious Clinical Adverse Experiences

There were no clinical adverse experiences that were considered serious by either the investigator or the clinical monitor.

c. Patients Discontinued Due to Clinical Adverse Experiences

No patient in this study was discontinued because of a clinical adverse experience.

2. Adverse Experiences—Laboratory

a. Overall Assessment of Laboratory Adverse Experiences

Three patients, 2 in the ivermectin and 1 in the albendazole group, had laboratory adverse experiences.

in the ivermectin group had an increase in SGPT and alkaline phosphatase 6 days posttreatment that was considered probably not related to ivermectin but more likely concomitant halofantrine treatment for malaria, which has been associated with such effects [12].

in the ivermectin group had anemia (hemoglobin 11.2%, hematocrit 33.5%) and leukopenia white count 2.74 ths/mm^3 31 days posttreatment considered probably related to ivermectin.

D. Safety (Cont.)

in the albendazole group had a very slight increase in SGPT (21 to 59 U/L, normal range 5 to 45). Since the patient had a laparotomy performed within the past month, drug relationship was difficult to establish and considered unknown by the investigator. Since no further follow-up tests were performed the outcome was also unknown, but the patient was clinically well at last visit.

b. Serious Laboratory Adverse Experiences

None of these laboratory adverse experiences was considered serious.

c. Patients Discontinued Due to Laboratory Adverse Experiences

No patients discontinued due to a laboratory adverse experience.

3. Adverse Experiences—Other (Special Examinations)

There were no other adverse experiences.

4. Clinical Safety Measurements

No clinically significant changes in clinical measures of safety were noted.

5. Laboratory Safety Measurements

No consistent or significant changes in laboratory measures of safety were noted.

D. Medical Officer findings: efficacy

Since this study took place in France, it is assumed that there is no possibility of re-infection and that any follow-up stool exam that is positive represents a treatment failure.

The following criteria were utilized to determine evaluability and efficacy:
A positive stool no more than 60 days prior to entry into study
Present for follow-up for the day 30 and day 90 (or later) timepoints
Have three consecutive negative stools to be called a cure.

Medical officer evaluation of enrolled patients by treatment group and patient number Gentilini study 004

Patient #	Evaluable?	Reason	Cure?	Reason
Treatment arm: Ivermectin X 1				
	yes		Yes	▬ stool up to day 95
	yes		Yes	▬ stool up to day 93
	yes		Yes	▬ stool up to day 85
	yes		No	✚ day 29; retreated
	yes		Yes	▬ stool up to day 102
	yes		Yes	▬ stool up to day 87
	yes		No	▬ day 28; ✚ day 93,94,95
	yes		Yes	▬ stool up to day 102
	no	lost to f/u		
	yes		Yes	▬ stool up to day 99
	no	lost to f/u		
	yes		Yes	▬ stool up to day 92
	yes		Yes	▬ stool up to day 155
	no	entry stool day -100		
	yes		Yes	▬ stool up to day 138
	yes		Yes	▬ stool up to day 103
	yes		Yes	▬ stool up to day 90
	yes		Yes	▬ stool up to day 124
	yes		Yes	▬ stool up to day 123
	yes		No	✚ day 25; retreated
	yes		Yes	▬ stool up to day 85
	yes		No	▬ day 105; ✚ day 106
	yes		Yes	▬ stool up to day 91
	yes		Yes	▬ stool up to day 92
	yes		No	▬ day 11; ✚ day 100, 101
	yes		Yes	▬ stool up to day 101
	yes		Yes	▬ stool up to day 87
	yes		Yes	▬ stool up to day 91
	yes		Yes	▬ stool up to day 90
Totals	**Evaluable 26**		**Cure 21 (81%)**	
	Unevaluable 3		**Fail 5 (19%)**	

Medical officer evaluation of enrolled patients by treatment group and patient number Gentilini study 004 (Continued)

Patient #	Evaluable?	Reason	Cure?	Reason
Treatment arm: Albendazole 200 mg BID X 3 days				
	yes		No	+ day 33; retreated
	yes		Yes	- stool up to day 89
	yes		Yes	- stool up to day 100
	yes		Yes	- stool up to day 197
	yes		No	+ day 8; retreated
	no	lost to f/u		
	yes		Yes	- stool up to day 166
	no	no pre-therapy stool recorded		
	yes		No	+ day 8; retreated
	yes		No	+ day 39, 40; retreated
	yes		No	+ day 9; retreated
	yes		Yes	- stool up to day 96
	no	lost to f/u		
	yes		Yes	- stool up to day 220
	yes		Yes	- stool up to day 131
	yes		No	+ day 7,8; retreated
	yes		No	+ day 29, 30, 31
	yes		Yes	- stool up to day 92
	yes		No	+ day 10; retreated
	yes		Yes	- stool up to day 58
	yes		No	+ day 29, 30, 31
	yes		Yes	- stool up to day 97
	no	retreated day 11 after - stool day 8		
	yes		No	+ day 5,6,7; retreated
	yes		Yes	- stool up to day 87
	no	lost to f/u		
	yes		No	+ day 31, 32; retreated
Totals	**Evaluable 22**		**Cure 12 (55%)**	
	Unevaluable 5		**Fail 10 (45%)**	

Results per medical officer
Gentilini study 004

	Ivermectin X 1	Albendazole
Enrolled, Total	29	27
Evaluable per Medical Officer	26	22
Cure at 30 days	24	12
Fail at 30 days	2	10
Cure at 90 days	21	10
Fail at 90 days	3	1
Lost to f/u from days 30 to 90	0	1
Cure day 90 (% of evaluable)	**21/26 (81%)**	**10/22 (45%)**

Medical Officer findings: Safety

The patient-level clinical and laboratory data was reviewed and the applicant's summary (see SectionC above) was corroborated.

The applicant mentions two subjects in the ivermectin arm who had adverse laboratory events that the investigator thought to be worthy of mention. One of these subjects ([redacted] was found to have anemia and leucopenia "probably related to ivermectin". Upon closer examination of the laboratory values reported in the ivermectin-treated subjects, the following was found:

Subject #	lab finding (day of study)	Comments
	AST 32→ 86 (d6); ALT 57→ 167 (d6)	reported by applicant; ? Secondary to Halfan
	Hgb 16.0→ 11.2; Hct 47→ 33 (d31) WBC 6.7→2.7 (d31) ALT 24→ 61 (d31)	reported by applicant
	WBC 3.2→ 2.5 (d29)	Not commented on by investigator
	WBC 5.3→ 3.7 (d6)→ 3.4 (d100)	""
	WBC 8.9→ 6.9 (d26)→ 5.6 (d98)	""
	WBC 6.5→ 4.3 (d7)	""
	WBC 5.9→ 4.3 (d8)→ 3.9 (d104)	""
	WBC 7.9→ 3.2 (d11)→ 4.2 (d41)→ 4.4 (d103)	""
	WBC 5.5→ 5.8 (d8)→ 4.5 (d37)→ 3.6 (d84)	""

Thus there were a total of 8 of the 29 ivermectin-treated subjects who had a drop in WBC count. Additional cases were found but these appeared to be related to resolution of elevated eosinophil counts following ivermectin treatment; these are not included in the above table. A similar pattern was not readily evident in the albendazole arm.

From this it would seem appropriate to mention 'decline in WBC count' as a laboratory adverse event that may be associated with ivermectin therapy.

4. Study 020 (Dreyer): An open, randomized study of efficacy, safety, and tolerability of ivermectin single dose (one or two day course) vs. thiabendazole (three-day course) in the treatment of patients infected with *Strongyloides stercoralis*.

A. Study summary: The applicant's synopsis of this study is presented below (taken from page D-2592-3, volume 1.22 of NDA):

MERCK RESEARCH LABORATORIES

PRODUCT: MK-0933, Ivermectin Tablets

PROTOCOL TITLE/NO.: An Open, Randomized Study of Efficacy, Safety, and Tolerability of Ivermectin Single Dose (One or Two Day Course) vs. Thiabendazole (Three-Day Course) in the Treatment of Patients Infected With *Strongyloides Stercoralis* #020

INVESTIGATORS: Dr. Gerusa Dreyer/Prof. Amaury Coutinho, Recife, Brazil

PRIMARY THERAPY PERIOD: May 91 to Dec 91 | **CLINICAL PHASE:** I- II- III-X

DURATION: Study duration - approximately 1 year (6-month enrollment, 6-month follow-up). Treatment period 1 to 3 days depending on treatment group.

PRIMARY OBJECTIVES: To study the efficacy, safety, and tolerability of ivermectin vs. thiabendazole in the treatment of patients infected with *Strongyloides stercoralis*.

STUDY DESIGN: Open, randomized trial in ambulatory patients with strongyloidiasis of the gastrointestinal tract. Following diagnostic studies and laboratory tests, patients received either a single dose of ivermectin, two single doses of ivermectin 1 day apart or thiabendazole twice a day for 3 days. Follow-up visits were held weekly for 4 weeks.

DIAGNOSIS/INCLUSION CRITERIA: Males and females between the ages of 5 and 70 years weighing at least 15 kg who have strongyloidiasis confirmed by stool examination.

PATIENT ACCOUNTING:	Total	Ivermectin 1x	Ivermectin 2x	Thiabendazole
ENTERED: Total	49	17	17	15
Male (age range years)	42 (4 to 64)	14 (18-37)	16 (4-63)	12 (18-64)
Female (age range years)	7 (7 to 51)	3 (17-27)	1 (44)	3 (7-51)
COMPLETED:	47	15	16	15
DISCONTINUED: Total	2	2	1	0
Adverse clinical experience	0	0	0	0
Adverse laboratory experience	0	0	0	0
Other	2	2	1	0

DOSAGE/FORMULATION NOS.: Single 200-mcg/kg ivermectin oral dose, two 200-mcg/kg oral doses of ivermectin 1 day apart or 3 days of 25 mg/kg b.i.d. oral treatment with thiabendazole. Commercial ivermectin obtained through MSD-Chibret; (Lot H7502) and commercial thiabendazole obtained locally.

EVALUATION CRITERIA: Parasitological: Minimum of three repeated stool examinations on Days 5 to 9, 16 to 19, 26 to 34, and at 3 and 6 months. Cure was defined as the absence of larvae in the follow-up stool examinations. However, since the study was conducted in a highly endemic area, a positive stool examination beyond 36 days posttreatment was not considered a clinical failure if all prior posttreatment stool examinations were negative. Safety evaluation was based on clinical symptoms, physical examination and follow-up laboratory studies.

STATISTICAL PLANNING AND METHODS: The primary measurement of efficacy was the cure rate. The treatment groups were compared for the proportion of patients who failed and the proportion of patients experiencing adverse experience using Fisher's exact test. Baseline characteristics were analyzed using Fisher's exact test, the chi-square test or the Wilcoxon Rank Sum test, as appropriate. Confidence intervals were calculated using the method of Blyth and Still. All statistical tests for treatment group differences were two-tailed (α=0.05).

RESULTS:

Efficacy:

There were no statistically significant differences in cure rates among the treatment groups (single-dose ivermectin-67%, two-dose ivermectin-82%, thiabendazole-87%).

Safety:

A summary of Adverse Experiences (AEs) follows:

Clinical Adverse Experience Summary

Treatment Group	Ivermectin Single-Dose (N=17)	Ivermectin Two-Dose (N=17)	Thiabendazole (N=15)
Patients with Clinical AEs	0	2 (11.8)	9 (60%)
Serious Clinical AEs	0	0	0
Discontinuations due to Clinical AEs	0	0	0
Drug-Related Clinical AEs	0	0	9 (60%)

The difference in the incidence of clinical adverse experiences (AEs) between the single-dose ivermectin group and the thiabendazole group was significant ($p<0.001$) as was the difference between the two-dose ivermectin and thiabendazole groups ($p=0.008$). There was no statistically significant difference in the incidence of clinical AE between the two ivermectin treatment groups ($p=0.48$). There was no laboratory AEs. There were no serious clinical AEs or serious laboratory AEs.

CONCLUSIONS: (1) Ivermectin (200 mcg/kg) as a single dose and as two doses on consecutive days and thiabendazole (25 mg/kg b.i.d. x 3 days) are effective therapies for strongyloidiasis of the gastrointestinal tract. (2) Ivermectin is generally well tolerated and is associated with fewer clinical adverse experiences than thiabendazole.

REGULATORY COMPLIANCE ISSUES: Regulatory compliance issues were found during an MRL audit conducted at this investigative site 3 years after the completion of the trial and these findings are reported in this summary. Despite these findings, MRL believes the results presented in this report support the use of ivermectin in the treatment of strongyloidiasis. In addition, the results reported herein enable one to evaluate principal outcomes with regard to both efficacy and safety.

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B. Deviations from protocol.

In reviewing the documentation of the conduct of this study, the following deviations from the stated protocol were detected:

- Inclusion criteria call for an examination of stool samples done 2 weeks or less before entry into study to be positive for *S.stercoralis* larvae. Of the 49 patients enrolled, 34 had their entry stool listed as being collected > 2 weeks prior to drug dosing. Many enrollees (10) had the only positive stool recorded pre-therapy over one month prior to enrollment. One subject was listed as having one positive stool pre-therapy, taken 102 days prior to study entry.

Medical officer comment: the issue of whether some patients can self-cure from intestinal strongyloidiasis is controversial. It is reasonable to assume that, if no intervening therapy was given during the 102 days that this patient had known strongyloidiasis prior to study entry, he still had the disease at the time of enrollment. However, it woould not seem unreasonable to expect a repeat stool collection at the time the patient was actually enrolled in the study (i.e., at day 0). Even if such a specimen had been collected and were negative, it would not necessarily indicate spontaneous cure, but rather indicate that light infections are sometimes difficult to diagnose, even with the Baermann technique.

- Sera were to be collected for specific IgG antibody studies, but these data were not presented because the collection of such specimens was not consistently adhered to during the conduct of the study.

- The protocol defined parasitological cure as the primary study endpoint, and called for stool specimens to be collected for analysis at the following time points [acceptable range] post-therapy: day 7 [5-9], day 18 [16-19], day 28 [26-34], and at months 3 and 6. However, (page D-2601) "several changes to the protocol were agreed to by MRL [applicant] and the investigator; however, the changes were not made into a formal protocol amendment." Two specific changes were agreed to: 1) patients who had "highly reproducible positive stool examinations (at least two of four pretreatment stool examinations positive) were selected for entry", and 2) "the follow-up period was restructured...conducting these [Baermann] studies approximately weekly with the final follow-up at approximately day 30."

Medical officer comment: as discussed earlier in this review, it is unreasonable to require continued negative stools when the treated patient returns to his home environment, where he is likely to be re-infected. Therefore, since the pre-patent period is approximately 28 days, it is reasonable to have the 30-day follow-up be the test-of-cure. However, given that light infections may show intermittently negative on stool examination, it is necessary to have three negative stools documented post-therapy in order to be called a cure. If repeated negative stools are obtained after the one-month timepoint in order to document three consecutive negative stools, then that patient will still be considered a cure.

The first change referred to by the applicant is also reasonable. The difficulty is that, of all the 34 enrolled patients mentioned above who have positive stools documented more than 14 days pre-enrollment, NONE have <u>two</u> documented positive pretreatment stools. Therefore, if the applicant were to be strictly held to these amended entry criteria, 34 of the 49 enrolled patients would be excluded from analysis. In the opinion of this medical officer, this is unreasonable.

- Criteria for evaluability were not defined in the original protocol, but the study summary (page D-2603 of volume 1.22) defines an evaluable patient as one who had: a) strongyloidiasis documented on stool examination; b) not received other anti-helminthic therapy during the study period; c) been compliant with therapy; and d) had at least four stool samples submitted during the one-month post-therapy follow-up period.

Medical officer comment: thus it appears that the evaluability criteria were altered retrospectively such that any positive stool, at any time prior to study entry, was considered adequate for enrollment and evaluability, as long as the patient denied intervening anti-helminthic therapy. Again, it does not seem unreasonable to expect that a stool sample could have been collected at the time the patient presented for randomization and drug initiation.

The applicant makes no mention of how enrolled subjects will be classified at the time of follow-up if they

have stools positive for SS AFTER the 30-day post-therapy time point. Are these subjects all to be considered failures? Are they all considered reinfections, and thus only the specimens up to and including the 30-day specimen are to be considered? How the applicant has dealt with this issue, on a patient-by-patient basis, is not clearly delineated in the submitted information.

C. Applicant's findings

The applicant's results are presented on pages D-2605-2616 of the study summary, volume 1.22 of the NDA. This study summary appears on the following 28 pages:

COMPREHENSIVE STUDY SUMMARY

An Open, Randomized Study of Efficacy, Safety, and Tolerability of Ivermectin Single Dose (One or Two Day Course) vs. Thiabendazole (Three-Day Course) in the Treatment of Patients Infected With *Strongyloides Stercoralis*

I. BACKGROUND

Tens of millions of people around the globe are currently infected with *Strongyloides stercoralis* [1]. It is widespread, not only in moist rainy areas of the tropics and subtropics, but also in some areas of southern and eastern Europe and Southeastern United States. *Strongyloides stercoralis* is an intestinal nematode that usually causes a limited intestinal infection. Patients may remain asymptomatic but recurrent cutaneous and gastrointestinal symptoms are common. The intestinal disease is rarely fatal and usually associated with eosinophilia.

Strongyloidiasis begins when infective larvae in contaminated soil penetrate intact skin and cause an itchy erythematous rash at the point of entry. The larvae are then carried in the bloodstream to the lungs where they ascend the bronchial tree before being swallowed. They then enter the small intestine where they penetrate the mucosa and mature into adult worms. Eggs shed by female worms are transformed into larvae that are excreted in the intestinal lumen. Most larvae are excreted in the stool, but some may penetrate the mucous membrane of the lower bowel or perianal skin resulting in autoinfection which intensifies and perpetuates the intestinal colonization [2].

This phenomenon of autoinfection is unique to *S. stercoralis* and is not found in the other nematode parasites commonly infecting humans. In this form, the disease can be perpetuated for an indefinite period of time. World War II veterans who had been former prisoners of war in Southeast Asia as well as Vietnam veterans have been diagnosed as having strongyloidiasis without being further exposed for periods of over 40 years [1].

I. BACKGROUND (CONT.)

Thiabendazole (TBZ) has been the "drug of choice" for treatment of strongyloidiasis for almost 30 years since it has a wide range of action and is readily absorbed from the G.I. tract. However, it also is responsible for frequent and sometimes serious side effects [3,4]. Albendazole, a more broad spectrum anthelmintic, has efficacy in strongyloidiasis similar or slightly less than that of thiabendazole. Albendazole is, however, better tolerated than thiabendazole. Both drugs require administration of multiple doses [3]. Treatment failures occur with both albendazole and thiabendazole and a few patients are not cured even when treated with increased amounts of drug for a long time. A single-dose drug with fewer side effects and increased efficacy would be useful in the treatment of strongyloidiasis.

Ivermectin, a derivative of avermectin ß, is an orally effective microfilaricidal agent. It is now the current drug of choice for treating patients infected with the nematode *Onchocerca volvulus*, which is a major cause of blindness in inhabitants of tropical areas [3].

More than 5.2 million people worldwide have received at least one single oral dose of ivermectin at levels up to 200 mcg/kg for onchocerciasis [5]. Ivermectin given as a single oral dose of 100, 150, or 200 mcg/kg has been found to be a relatively safe and effective microfilaricide reducing *O. volvulus* skin microfilariae counts to near zero for up to 12 months [6]. Based on the safety and tolerability evaluations from these studies, 150 mcg/kg was judged to be the optimal oral dosage [6]. Ivermectin was approved by the French Regulatory Agency for the treatment of onchocerciasis in October 1987.

There is substantial evidence to suggest that ivermectin may be a useful therapeutic alternative for treatment of strongyloidiasis. Ivermectin has demonstrated activity in animal models of infection [7]. More importantly, ivermectin has been shown to be effective against human strongyloidiasis in noncomparative studies [8,9]. Ivermectin was well tolerated and a single dose demonstrated good activity. Based on this experience, we have undertaken a randomized, comparative trial of ivermectin versus thiabendazole in the treatment of strongyloidiasis.

II. SUMMARY OF PROTOCOL AND STUDY PROCEDURES

A. Protection of Human Subjects

This study was conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research.

B. Investigator(s)

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C. Objectives

To study the efficacy, safety, and tolerability of one or two oral doses (200 mcg/kg) of ivermectin compared to a 3-day regimen of 25 mg/kg b.i.d. thiabendazole in the treatment of patients infected with *Strongyloides stercoralis*.

D. Patient Selection

Inclusion Criteria

1. Patients infected with *Strongyloides stercoralis*.
2. Patients were between 5 and 70 years of age.
3. An examination of the stool samples done 2 weeks or less before entry into the study was positive for *Strongyloides stercoralis* larvae.
4. No treatment for strongyloidiasis within the previous 3 months.

D. Patient Selection (Cont.)

Exclusion Criteria

1. Age under 5 or over 70 years or weight under 15 kg.
2. Women of childbearing potential (unless they have a negative HCG).
3. Medical history of mental illness, seizure, or other serious illnesses.
4. Abnormal levels of SGOT or SGPT, creatinine greater than 2.0 mg/100 mL or grossly abnormal BUN or urine analysis.
5. A history of an abnormal ECG.
6. Moderate or severe anemia, i.e., hemoglobin less than 10 g or hematocrit less than 30%; any abnormality of white blood cell count and/or differential (except eosinophilia).
7. Any past or concurrent medical illness which the investigator feels might influence either the outcome of the study or interpretation of the data accrued.

E. Study Design

This was an open, randomized study in ambulatory patients who had strongyloidiasis evidenced by microscopic stool examination or positive stool culture. Using a local allocation schedule patients were randomized into three groups of patients each to receive either ivermectin (single dose or two single doses 1 day apart) or thiabendazole (3 days of b.i.d. dosing).

During the 2 weeks prior to the study, the patient was screened to assure that he/she was in good physical condition. The patient had a physical examination and a laboratory screen. Vital signs were recorded on Day -1 (the same day as drug administration but before drug was administered), Day 1 (the first day of drug administration), and 7 days later. Generally prestudy vital signs were recorded on Day 1 prior to administration of study drug; however, there may have been occasion for vital signs to be recorded the day prior to the administration of study drug. Since all patients had no concurrent illness which the investigator felt might influence the interpretation of data collected, this deviation from protocol was viewed by MRL as inconsequential.

E. Study Design (Cont.)

Table 1

Recommended Dosage Schedules

Ivermectin Dosage Recommended Tablet Combinations for 200-mcg/kg Dose	
Patient Weight (kg)	Number of Tablets (6 mg)
15 to 24	½
25 to 35	1
36 to 50	1½
51 to 65	2
66 to 79	2½
80 and over	3

Thiabendazole (MINTEZOL®) Dosage Tablet Combinations for 50-mg/kg Dose	
Patient Weight (kg)	Number of Tablets (500 mg)
15.0 - 22.2	0.25 (½ tablet)
22.3 - 33.4	0.5 (1 tablet)
33.5 - 44.5	0.75 (1½ tablets)
44.6 - 55.7	1.0 (2 tablets)
55.8 - 66.8	1.25 (2½ tablets)
66.9 and over	1.5 (3 tablets)

F. Clinical Observations and Laboratory Measurements

Table 2 shows the schedule of clinical observations and laboratory measurements during the study. In addition, the patient was questioned daily (by phone) regarding the adverse experiences with particular attention to evidence of allergic reactions (rash, itching, and anaphylaxis).

Table 2

Schedule of Clinical Observations and Laboratory Measurements

	Days						
	Prestudy+	1	2	3	5-9	16-19	28-36
Drug Administration		X					
	or						
		X	X				
	or						
		X	X	X			
Physical Examination	X	X			X		
Vital Signs	X	X			X		
Laboratory Safety*	X				X		
Stool Examination	X				X	X	X
IgG++	X						X
Eosinophilia++	X				X		X

\+ Prestudy=During 2 weeks (14 days) preceding the first day of study drug administration.
++ Although these tests were suggested to be carried out in the protocol they were not done with any degree of consistency to allow for appropriate analysis.
* Blood chemistries were performed only if indicated after prestudy evaluations.

Observations and measurements related to efficacy and safety are described below.

F. Clinical Observations and Laboratory Measurements (Cont.)

Efficacy Measures

Baseline evaluation of *Strongyloides stercoralis* as determined by larval counts using a modification of the Baermann's technique [10] was to be established in each patient prior to drug administration. All stool specimens were examined by one single expert who was to remain blinded as to the treatment allocations.

Parasitological cure was the primary measure of efficacy. Although the protocol required follow-up stool examinations at Days 5 to 9, 16 to 19, 26 to 34, and at Months 3 and 6, both the investigator and MRL realized after finalization of the protocol that this design was not appropriate for an area of high endemicity because the risk of reinfection was considered to be high over this extended period (i.e., greater than 1 month). Therefore, several changes to the protocol were agreed to by MRL and the investigator; however, the changes were not made into a formal protocol amendment.

The following changes were instituted:

- Patients with highly reproducible positive stool examinations for *Strongyloides stercoralis* larvae (at least two of four pretreatment stool examinations positive) were selected for entry into the trial.

- The follow-up period was restructured, maintaining a high number of Baermann stool examinations but conducting these studies approximately weekly with the final follow-up at approximately Day 30 (range: Days 28 to 36).

MRL believes that these changes do not impact on the overall validity of this study; rather, it allows for appropriate clinical outcomes to be assessed in an area of high endemicity for *Strongyloides stercoralis*.

The Baermann technique [10] is a method of examining a stool specimen suspected of having small numbers of Strongyloides larvae and uses the modified Baermann apparatus. The technique is dependent on the migration of active larvae out of the fecal material, through a wire gauze covered with gauze padding and into water, where they settle out. The procedure is as follows:

1. Fill a funnel (6-inch) with water (attach rubber tubing with a pinch clamp to the bottom of the funnel) and place the wire gauze, one or two layers of gauze padding on it, on the funnel.

F. Clinical Observations and Laboratory Measurements (Cont.)

2. Place between 50 and 100 g of fecal material on the gauze padding so that it is covered with water. If the fecal material is too firm, break it up slightly.

3. Allow the apparatus to stand for 2 or more hours, draw off 10 mL of fluid by releasing the pinch clamp, spin it down in a centrifuge and examine the sediment with a magnifier or low power microscope to count and confirm the species of the larvae.

Although not outlined in the protocol, Ritchie's concentration, Kato or fresh stool counts were done for many patients; however, the larval counts obtained from the Baermann technique are the basis for evaluation of efficacy.

In addition, although not specified in the protocol, the intensity of infection at baseline was also assessed. Quantifying the level of infestation (intensity of infection) per patient was important only to determine comparability of treatment groups and to examine whether there was an interaction between intensity of infection and clinical outcome. Because the investigator gave actual counts (number of larvae per gm stool) for some of the patients and plus (+) or word designations for others, it was decided to use the following scheme to have consistency for all patients (Table 3).

Table 3

Scheme to Translate Between Larvae Counts, Word Designations and "Plus" Designations

Word Designations	Larvae Counts per gm Stool	"Plus" Designations
Few	1 to 15	+
	16 to 30	++
Many	31 to 100	+++
	> 100	++++

This scheme was not specifically stated in the protocol; however, MRL believes that such an analysis between intensity of infection and outcome is valid.

F. Clinical Observations and Laboratory Measurements (Cont.)

Safety Measures

A complete physical examination was done during the 2 weeks preceding study drug administration and repeated at follow-up visits. Prestudy and follow-up samples for the laboratory safety studies on blood and urine included:

a. Hematology:	Hematocrit Hemoglobin White blood cell count, total Differential counts were made if WBC was abnormally low or high
b. Blood Chemistries:	Blood urea nitrogen Serum creatinine SGOT SGPT Total bilirubin Alkaline phosphatase
c. Urinalysis:	Urinalysis was performed in patients with abnormal serum creatinine values or with signs/symptoms of urinary tract infection

The investigator could carry out additional analyses as required by the hospital or as indicated for optimum patient care.

Vital signs (blood pressure and pulse rate, both supine and erect, respiration rate and temperature) were recorded on Day 1.

G. Evaluation Criteria

1. Evaluability

All patients whose data was received by May 28, 1992 were classified by the MRL clinical monitor as evaluable or unevaluable with respect to efficacy. These evaluations by the MRL monitor, although not specified in the protocol, were in keeping with the dictates of the protocol (i.e., inclusion and exclusion criteria) and the exercise of good clinical judgment. Thus, patients were considered evaluable for efficacy if:

a. Strongyloidiasis was documented on stool examination.

G. Evaluation Criteria (Cont.)

b. The patient did not receive other anti-helminthic therapy during the study period.

c. The patient was compliant with therapy.

d. Adequate follow-up stool examinations were performed for determination of efficacy. At least four samples during the follow-up period (1 month) were required.

2. Efficacy

The primary measure of efficacy in this study was the absence of larvae in posttherapy Baermann fecal examinations. Cure was defined as the absence of larvae in the follow-up stool examinations. The detection of larvae on any stool examination past Day 6 up to 36 days posttreatment met the definition of treatment failure.

3. Safety

All patients were evaluated for safety by physical examination and laboratory studies. In addition, the patient was questioned daily (by phone) regarding adverse experiences with particular attention to evidence of allergic reactions (rash, itching, and anaphylaxis). Adverse experiences were described and recorded by the investigator who determined the duration, seriousness, severity, and drug relationship as well as the eventual outcome of each adverse experience.

H. Statistical Planning and Analysis

The primary measurement of efficacy was the cure rate. Logistic regression was used to determine if any concomitant factors, i.e., age, sex, race, severity of infection, intensity of infection, affected the cure rate. None of these factors was related to cure rate at the α=0.10 level of significance. Thus all were dropped from the statistical model, leaving only treatment group. The treatment groups were compared for the proportion of patients who were cured as well as for the proportion of patient's experiencing adverse experiences using Fisher's exact test.

Baseline characteristics were analyzed using either Fisher's exact test or the chi-square test of the Wilcoxon Rank Sum test, as appropriate. Confidence intervals were calculated using the method of Blyth and Still. All statistical tests for treatment group differences were two-tailed (α=0.05).

I. Clinical Supplies

Ivermectin in the form of commercial MECTIZAN tablets (Lot H7502) were obtained through MSD-Chibret. Commercial thiabendazole (500 mg, MINTEZOL) was obtained locally [4].

III. RESULTS

A. Patient Characteristics

A total of 49 patients were enrolled in the study. A summary of demographic information for all patients is provided in Table 4. There were no statistically significant differences in the characteristics of the three treatment groups. A detailed summary of each patient's treatment may be found in Appendix 1.

Table 4

Baseline Characteristics - All Patients (%)

	Ivermectin One Dose		Ivermectin Two Doses		Thiabendazole	
Number of Patients	17		17		15	
Mean Age	22		28		25	
Sex						
Male (age range - yrs)	14 (18-37)	(82%)	16 (4-63)	(94%)	12 (18-64)	(80%)
Female (age range - yrs)		(18%)		(6%)		(20%)
Race						
Caucasian	3	(18%)	4	(24%)	3	(20%)
Black	3	(18%)	0		0	
Mulatto	11	(65%)	13	(76%)	12	(80%)
Intensity of Infection*						
2+	8	(47%)	6	(35%)	10	(67%)
3+	7	(41%)	4	(24%)	2	(13%)
4+	2	(12%)	7	(41%)	3	(20%)

* = Comparisons between treatment groups of Intensity of Infection, although not specified in the protocol, were done in order to further ensure the detection of treatment-group differences.

Note: There were no significant differences between treatment groups.

A. Patient Characteristics (Cont.)

Most patients had other secondary diagnoses at entry into the study (single-dose ivermectin - 82.4%, two-dose ivermectin - 94.1%, thiabendazole - 60.0%). The majority of these diagnoses were gastrointestinal parasitic infections other than strongyloidiasis. Two patients in each ivermectin treatment group were diagnosed as having AIDS; 1 patient in the thiabendazole treatment group was HIV seropositive but asymptomatic. A detailed summary of each patient's secondary diagnoses may be found in Appendix 2.

Two of 17 patients (11.8%) receiving ivermectin single dose, 4 of 17 patients treated with ivermectin two doses (23.5%), and 2 of 15 patients receiving thiabendazole (13.3%) received concomitant drug treatment and/or prior antinematode therapy (Appendix 2). Of these patients, no patients in the single-dose ivermectin group, 2 patients in the two-dose ivermectin group and 1 patient in the thiabendazole group had previously received agents with antinematode activity. In the two-dose ivermectin group, AN 82 was treated with albendazole for 10 days ending 37 days prior to entry and AN 453, who was HIV-infected and also receiving AZT, was treated with 102 days of thiabendazole ending 37 days prior to enrollment and 6 days of albendazole ending 25 days prior to entry. The thiabendazole-treated patient received 3 days of mebendazole (200 mg/d) ending 71 days prior to entry. Positive stool examinations were documented in each of these 3 patients prior to initiation of study drug therapy.

There were significant differences between treatment groups with respect to secondary diagnoses, prior therapy, or concomitant therapy.

B. Patient Accounting

1. Accounting for Patients in the Study

Table 5 following is a summary of patients who entered, completed, and discontinued the study by treatment group.

Table 5

Accounting for Patients in the Study by Treatment Group

Patients	Ivermectin 1-Dose	Ivermectin 2-Dose	Thiabendazole
Total Patients Entered	17	17	15
Total Patients Completed	15	16	15
Total Patients Discontinued	2	1	0
Adverse Clinical Experiences	0	0	0
Adverse Laboratory Experiences	0	0	0
Lost to Follow-Up	2		
No Therapeutic Response		1*	

* = Although this patient [redacted] was discontinued from study because of "No therapeutic response" she is still considered evaluable for efficacy.

2. Accounting for Patients in the Analysis

Table 6 is a summary of patients who were included in the analysis of efficacy (evaluable patients) and safety.

Table 6

Accounting for Patients in the Analysis by Treatment Group

Patients	Ivermectin 1-Dose	Ivermectin 2-Dose	Thiabendazole
Evaluable for Efficacy Analysis	15	17	15
Nonevaluable for Efficacy Analysis	2	0	0
Reason for Nonevaluability for Efficacy Analysis:			
Inadequate Follow-Up Parasitology	2		
Evaluable for Safety Analysis	17	17	15

B. Patient Accounting (Cont.)

A total of 49 patients were enrolled in the trial (ivermectin one dose - 17, ivermectin two dose - 17, thiabendazole - 15). Of the 49 patients enrolled, 47 completed the study and 2 (both in the single-dose ivermectin group) were considered discontinued and nonevaluable for efficacy due to lack of follow-up

Patients who did not fulfill the evaluability criteria outlined in Section II.G. were considered nonevaluable for efficacy. In certain circumstances, failure to satisfy the entrance criteria in Section II.D. did not exclude patients from the analyses of evaluable patients if the evaluability criteria were satisfied. The inclusion criteria required that the time period from diagnosis (i.e., positive stool exam) to initiation of therapy not exceed 14 days. In practice, this was often not possible. Because the natural history of strongyloidiasis is one of persistence over time, patients who received study drug therapy within 30 days of a diagnostic stool examination were considered evaluable. Furthermore, 1 patient , single-dose ivermectin) had four of four positive stool examinations from Study Day -102 to Study Day -71. Because of the highly reproducible nature of this patient's infection status, this patient was also considered evaluable. Five patients in the trial were HIV-positive; some patients had a history of opportunistic infections. None of these HIV-positive patients had any evidence of extra-gastrointestinal disease. Because enrollment of patients with underlying disease who meet entry criteria is at the discretion of the investigators, these patients were considered evaluable. Lastly, patient (4 years, 10 months old at randomization) was considered evaluable despite an age of less than 5 years old at entry.

All patients in the two-dose ivermectin (17) and the thiabendazole (15) treatment groups were considered evaluable. Two patients (2/17, 11.8%) in the single-dose ivermectin group were considered nonevaluable for efficacy. The differences in patient evaluability among the three groups were not statistically significant. The 2 patient exclusions in the single-dose ivermectin group were lost to follow-up prior to any posttreatment outcome evaluation and were excluded from analysis of efficacy.

Three patients - two-dose ivermectin; thiabendazole) received antinematode therapy during the 3-month period prior to entry into the study. However, all patients completed this therapy at least 25 days before study

B. **Patient Accounting (Cont.)**

entry and had multiple positive stool examinations for *Strongyloides stercoralis* prior to initiation of study drug. Therefore, these patients were considered evaluable.

It is recognized that these changes in entry and evaluation criteria differ from the requirements of the protocol; however, they are considered by MRL as consistent with the treatment of patients with strongyloidiasis given the natural history of the disease. In addition, with the exception of the 2 patients in the single-dose ivermectin group who were excluded from the efficacy analysis (outcome in these patients could not be rendered), no data are excluded from the analysis of efficacy or safety. As such, MRL believes that the alterations from the protocol as specified above do not impact on the validity of the results of this study.

C. **Efficacy**

Ten of 15 (67%) evaluable patients in the single-dose ivermectin group were cured compared to 14/17 (82%) in the two-dose ivermectin group and 13/15 (87%) of patients treated with thiabendazole. There was no significant difference between treatment groups in the proportion of patients cured. A patient's likelihood of cure was not significantly related to age, sex, race, or intensity of infection. Cure rates with 95% confidence intervals for treatment groups and various subgroups are contained in Table 7.

C. Efficacy (Cont.)

Table 7

Cure Rate - Evaluable Patients

	Ivermectin						Thiabendazole		
	One Dose			Two Doses					
	Cure	N	PCT	Cure	N	PCT	Cure	N	PCT
Overall	10	15	67 (39, 87)	14	17	82 (56, 95)	13	15	87 (58, 98)
Sex									
Male	10	13	77 (46, 94)	13	16	81 (54, 95)	10	12	83 (51, 97)
Female	0	2	0	1	1	100	3	3	100 (29, 100)
Race									
Caucasian	2	2	100	4	4	100	3	3	100 (29, 100)
Black	1	2	50	0	0	0	0	0	0
Mulatto	7	11	64 (32,88)	10	13	77 (46, 94)	10	12	83 (51, 97)
Intensity of Infection*									
2+	5	6	83 (36, 99)	4	6	67 (24, 94)	8	10	80 (44, 96)
3+	4	7	57 (20, 88)	3	4	75	2	2	100
4+	1	2	50	7	7	100 (59,100)	3	3	100

There were no significant differences between treatment groups.
( )=95% confidence interval.
*=Comparisons between treatment groups of Intensity of Infection, although not specified in the protocol, was done in order to further ensure the detection of treatment group differences.

As stated earlier (Section II. F. of this report), parasitological cure was the primary measure of efficacy. Although the protocol required follow-up stool examinations at Days 5 to 9, 16 to 19, 26 to 34 and at Months 3 and 6, it was realized after finalization of the protocol that this design was not appropriate for an area of high endemicity because the risk of reinfection was considered to be high over this extended period (i.e., greater than 1 month).

C. Efficacy (Cont.)

Many patients (72%) had follow-up stool examinations beyond posttreatment Day 31. Among these patients, there was a mean follow-up period of 124 days (93 days Postday 31) with a mean of 5.4 stool examinations beyond Day 31. For those ultimately found to have positive stool examinations for *S. stercoralis* larvae during extended follow-up, it is not possible to distinguish between relapse and reinfection. For this reason, outcome at Days 28 to 36 is considered the primary measure of efficacy.

In order to estimate a "worst outcome" cure rate, efficacy was also evaluated by designating all patients with any positive stool examination at any posttreatment time point (beyond Day 5) as treatment failures. By this criteria, 10/15 patients (67%) in the single-dose ivermectin group, 10/17 (59%) of patients in the two-dose ivermectin group and 9/15 (60%) of patients in the thiabendazole treatment group were cured. As in the primary definition of efficacy, there was no significant difference between treatment groups in the proportion of patients cured and no other factor was significantly predictive of outcome. Although Postday 31 stool examinations were performed, none of the HIV-positive patients enrolled in the study failed therapy using this "worst case" definition. Again, this data is presented "for information purposes" only since in this highly endemic area one could not distinguish between relapse and reinfection.

A quality-assurance audit was performed by the MRL Clinical Quality Assurance Resources at the study site 3 years after the completion of the trial (reference - Audit Information Sheet, Appendix 3). The audit indicated certain regulatory compliance issues relating to source documentation and monitoring. Examples of audit findings included:

1. Source document laboratory results for hematology, blood chemistry, urinalysis and parasitological stool results were unavailable.
2. Numerous workbook to CRF transcription errors were noted in the reporting of total eosinophil counts for some patients.
3. There were no records of prestudy pregnancy or ECG results as required in the protocol inclusion/exclusion criteria.
4. IgG assay results for tests which were to be performed by the NIH as part of a substudy of this protocol were never reported.

C. Efficacy (Cont.)

5. The ERC approval of the study was based on a draft protocol and not the final version.

6. There was no routine monitoring.

The lack of a complete file of source documentation at the investigative site does not impinge on the integrity of the information originally received from the investigator during the conduct and subsequent completion of this study some 3 years before. Nor does it compromise the information used to produce this MRL summary. Despite these GCP-related findings, MRL believes that the basic scientific and medical conclusions drawn from this study and described in this summary are valid.

D. Safety

All 49 patients were evaluated for safety and tolerability.

1. Adverse Experiences - Clinical

a. Overall Assessment of Clinical Adverse Experiences

Table 8 below is a summary of the clinical adverse experiences (AEs).

Table 8

Clinical Adverse Experience Summary

Treatment Group	Ivermectin Single-Dose (N=17)	Ivermectin Two-Dose (N=17)	Thiabendazole (N=15)
Patients With Clinical AEs	0	2 (11.8%)	9 (60.0%)
Serious Clinical AEs	0	0	0
Discontinuations Due to Clinical AEs	0	0	0
Drug-Related Clinical AEs	0	0	9 (60.0%)

D. Safety (Cont.)

The difference in the incidence of clinical adverse experiences (AEs) between he single-dose ivermectin group and the thiabendazole group was significant ($p<0.001$) as was the difference between the two-dose ivermectin and thiabendazole groups ($p=0.008$). There was no statistically significant difference in the incidence of clinical AEs between the two ivermectin treatment groups ($p=0.48$). There were no serious clinical AEs and no discontinuations due to clinical AEs.

Table 9 lists clinical AEs by body system.

The difference in the incidence of clinical adverse experiences considered by the investigator to be possibly, probably, or definitely drug related between the thiabendazole treatment group and each of the ivermectin groups was statistically significant ($p<0.001$ for each comparison).

D. Safety (Cont.)

Table 9

Clinical Adverse Experiences by Body System

Body System/ Diagnosis	Ivermectin Single-Dose (N = 17)	Ivermectin Two-Dose (N = 17)	Thiabendazole (N = 15)
Patients with AE	0	2 (11.8%)	9 (60.0%)
Body as a whole:		1 (5.9%)	5 (33.3%)
Malaise			5 (33.3%) [5]
Abdominal Pain		1 (5.9%) [0]	
Digestive system:		2 (11.8%)	2 (13.3%)
Nausea			2 (13.3%) [2]
Anorexia		1 (5.9%) [0]	
Diarrhea		1 (5.9%) [0]	
Nervous system / psychiatric system			8 (53.3%)
Dizziness			6 (40.0%) [6]
Headache			2 (13.3%) [2]
Irritability			1 (6.7%) [1]
Mental acuity decrease			2 (13.3%) [2]
Paresthesia			1 (6.7%) [1]
Vertigo			2 (13.3%) [2]
Special senses:			1 (6.7%)
Tinnitus			1 (6.7%) [1]

N.B.: Patient counts and event counts may not be the same since some patients may have more than one clinical AE event.

[ ] Numbers in brackets are those patients who had clinical AEs which were considered possibly, probably, or definitely related to study drug.

D. Safety (Cont.)

The clinical AEs reported for 2 patients in the two-dose ivermectin group were considered not related to study drug. One patient experienced anorexia on Study Days 1 and 2 that was considered by the investigator to be probably not related to study drug. The second patient reported abdominal pain on Study Days 2 and 3 that was considered by the investigator to probably not be drug related and diarrhea on Study Day 14 considered to be definitely not related to ivermectin.

All clinical AEs in the thiabendazole group were considered by the investigator to be drug related (i.e., possibly, probably, or definitely). Psychiatric/nervous system complaints accounted for the most commonly affected body system with 8 patients (53.3% of patients in the group) reporting adverse events in this category. Six of the 8 patients (40.0% of the patients in the group) reported dizziness, making this the most frequently reported clinical AE among patients treated with thiabendazole.

Each patient who entered the trial was asked to give an overall tolerance assessment of their treatment. Seventeen of 17 (100%) patients in the single-dose ivermectin group found the treatment to be "well tolerated," compared to 17 of 17 patients (100%) in the two-dose ivermectin and 6 of 15 patients (40%) treated with thiabendazole. The difference between each ivermectin group and thiabendazole was statistically significant ($p<0.001$).

b. Serious Clinical Adverse Experiences

There were no adverse experiences that were considered serious by either the investigator or the clinical monitor.

c. Patients Discontinued Due to Clinical Adverse Experiences

No patient in this study was discontinued from study drug because of an adverse experience.

2. Adverse Experiences - Laboratory

a. Overall Assessment of Laboratory Adverse Experiences

No laboratory adverse experiences were noted during the course of this study.

D. Safety (Cont.)

b. Serious Laboratory Adverse Experiences

There were no serious laboratory adverse experiences during the course of this study.

c. Patients Discontinued Due to Laboratory Adverse Experiences

No patients required discontinuation of study drug due to a laboratory adverse experience.

3. Adverse Experiences - Other

There were no other adverse experiences.

4. Clinical Safety Measurements

No clinically significant changes in clinical measures of safety were noted.

5. Laboratory Safety Measurements

No consistent or significant changes in laboratory measures of safety were noted.

IV. DISCUSSION

Ivermectin is an 80:20 mixture of avermectin ß1a and avermectin ß1b, monocyclic lactones produced by the actinomycete *Streptomyces avermitilis*. While its mechanism of action is not fully understood, ivermectin appears to exert its activity by inducing a chloride current via a glutamate-gated channel in the parasite resulting in apparent paralysis and death [11]. It is an orally effective antiparasitic agent that has been used in veterinary medicine since 1981. Based on its efficacy and excellent safety profile, ivermectin has achieved widespread acceptance as the treatment of choice for onchocerciasis (river blindness) [3].

During trials aimed primarily at establishing ivermectin's efficacy in onchocerciasis, a number of uncontrolled observations suggested that ivermectin had significant activity against a number of gastrointestinal nematodes [12]. These clinical notes were consistent with the drug's activity in an animal model of strongyloidiasis [7]. Subsequently, noncomparative studies demonstrated that ivermectin was an effective

IV. DISCUSSION (CONT.)

agent against strongyloidiasis [8,9]. Based on these observations as well as the need for a more effective, less toxic therapy in strongyloidiasis, several studies, including this trial, were undertaken.

This comparative randomized trial evaluated ivermectin's efficacy. Inclusion criteria selected for patients with heavy larval burden, and a very sensitive technique for parasite detection was utilized. The primary measure of efficacy in this trial was the absence of *S. stercoralis* larvae on four posttherapy stool exams, the last examination being on Days 28 to 36. Although additional follow-up stool examinations were performed for many patients, later time points were not used because of the increasing ambiguity between relapse and reinfection. In fact, reinfection could occur even before the Day 31 time point, making this definition somewhat arbitrary. One month follow-up was chosen as a compromise between minimizing the risk of reinfection and the need for a follow-up period of reasonable length that incorporated an adequate number of stool examinations. It is also uncertain how quickly a patient's stool should be clear of larvae. A positive stool examination performed prior to the first time point (Day 7) was not considered sufficient to define a patient as having failed as long as at least four subsequent examinations were negative.

Cure rates of 67% (single-dose ivermectin), 82% (two-dose ivermectin), and 87% (thiabendazole) were observed, confirming ivermectin's activity in this infection. While the single-dose ivermectin group had a somewhat lower cure rate than the other therapeutic groups, none of the differences in cure rates among the treatment groups were statistically significant. The cure rates for both ivermectin treatment groups were lower than those reported in one noncomparative study [8]. These differences may reflect the follow-up that patients in this study underwent or the possible preselection of a patient population with a high intensity of infection based on the trial's entry criteria.

Although efficacy did not differ among treatment groups, the incidence of clinical adverse experiences was substantially lower among patients receiving ivermectin. No patient in the single-dose ivermectin group had a clinical adverse experience compared to 11.8% of patients treated with two doses of ivermectin and 60% of patients receiving thiabendazole. This higher incidence of adverse events among patients in the

IV. DISCUSSION (CONT.)

This difference was magnified when only those adverse experiences considered by the investigator to be drug-related (possibly, probably, or definitely related to study drug) were considered. None of the adverse clinical events in the ivermectin groups were considered drug-related compared to all the events in patients treated with thiabendazole. It is not possible to exclude some bias in the interpretation of the relationship between reported symptoms and drug therapy. It is important to note that a statistically higher incidence of adverse experiences was present when all events were considered regardless of relationship. The safety profile for thiabendazole seen in this study is also consistent with other published reports [3,4].

In onchocerciasis, many of the adverse effects that occur after ivermectin treatment are a result of the patient's immune response (Mazzotti reaction) to dead microfilariae and usually appear within three days of the dose [13]. The severity of the response is directly related to the initial intensity of *O. volvulus* infestation. The lack of Mazzotti-type reactions in this trial following treatment of strongyloidiasis is consistent with previous experience and would be predicted based on disease pathogenesis.

A criterion for entry into this trial was that patients have strongyloidiasis limited to the gastrointestinal tract. It is not possible to extrapolate ivermectin's efficacy in disseminated disease. Several patients were HIV-infected, including patients with a history of opportunistic infections. While these patients responded well to ivermectin therapy, the numbers of patients were small, and no conclusions regarding ivermectin efficacy in immunocompromised patients can be drawn from this study.

This study demonstrates that ivermectin is a generally well tolerated and effective therapy for strongyloidiasis of the gastrointestinal tract in immunocompetent patients. It is associated with significantly fewer clinical adverse experiences than thiabendazole with similar efficacy. In addition, ivermectin's simple dosing regimen offers substantial advantages over thiabendazole for patient compliance. Overall, the results of this trial suggest that ivermectin offers a significant advance in the treatment of strongyloidiasis.

V. CONCLUSIONS

1. Ivermectin (200 mcg/kg) as a single dose and as two doses on consecutive days and thiabendazole (25 mg/kg b.i.d. x 3 days) are effective therapies for strongyloidiasis of the gastrointestinal tract.

2. Ivermectin is generally well tolerated and associated with fewer clinical adverse experiences than thiabendazole.

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D. Medical officer findings.

As discussed above in the section entitled "Deviations from protocol", the medical officer agrees that patients with a documented stool examination positive for SS at any time prior to enrollment are considered evaluable. As mentioned, 10 of the 49 enrollees had > 30 days elapse between documentation of SS infection and enrollment in the trial. However, the medical officer cannot accept the outlier (patient [redacted] whose only positive stool pre-therapy is listed as being collected 102 days prior to enrollment.

The patient data, by treatment group and day of parasitologic follow-up, are presented in the following tables:

Disposition and patient follow-up by treatment arm and patient number Dreyer study 020

Timepoint	Ivermectin X 1	Ivermectin X 2	Thiabendazole
enrollment stool collected >60 days pre-treatment	1 (Patient [redacted]	0	0
enrollment stool collected >14 days but <60 days pre-treatment	10	14	9
enrollment stool collected ≤ 14 days pre-treatment	6	3	6
total enrolled	**17**	**17**	**15**
day 7 (range 5-9) post-initiation of therapy	**14** (zero ✚)	**17** (1 ✚)	**15** (1 ✚)
day 30 (range 26-34)	**14** (4 ✚)	**16** (1 ✚)	**15** (1 ✚)
day 90 (range 80-100)	**6** (zero ✚)	**14** (4 ✚)	**13** (5 ✚)
day 180 (range 160 or greater)	**2** (zero ✚)	**6** (1 ✚)	**2** (zero ✚)

Footnotes:

✚ denotes positive stool for *Strongyloides stercoralis* by Baermann technique

❶ denotes enrolled patient is HIV positive

If the criteria for evaluability and cure that are discussed above are utilized (specifically, the requirement for three consecutive negative stools to be called a cure, and the validity of the 30-day post-therapy timepoint because of the possibility of re-infection), the following results are obtained on a patient-by-patient basis:

Medical officer evaluation of enrolled patients
by treatment group and patient number
Dreyer study 020

Patient #	Evaluable?	Reason	Cure?	Reason
Treatment arm:	Ivermectin X 1			
	yes		No	✚ stool day 29
	yes		Yes	▬ stool up to day 169
	yes		Yes	▬ stool up to day 92
	yes		Yes	▬ stool up to day 101
	no	entry stool day -102		
	yes		No	✚ stool day 29
	yes		No	✚ day 21; only 1 ▬ stool thereafter
	yes		No	✚ stool day 29
	yes		Yes	▬ stool day 29
	yes		No	✚ stool day 29
	yes		Yes	▬ stool up to day 183
	yes		Yes	▬ stool up to day 81
	no	lost to f/u		
	yes		Yes	▬ stool up to day 99
	yes		Yes	▬ stool day 25
	yes		Yes	▬ stool day 29
	no	lost to f/u		
Treatment arm:	Ivermectin X 2			
	yes		Yes	▬ stool up to day 92
	yes		Yes	▬ stool up to day 115
	yes		Yes	▬ stool up to day 115
	yes		Yes	▬ to day 87 ✔
	yes		Yes	▬ stool up to day 84
	yes		Yes	▬ stool up to day 87 ✔
	yes		No	✚ day 21; ▬ X 2; ✚ day 101
	yes		Yes	▬ stool up to day 183
	yes		Yes	▬ stool up to day 183
	yes		Yes	▬ stool up to day 207
	yes		Yes	▬ stool up to day 28
	yes		Yes	▬ stool up to day 99
	yes		Yes	▬ stool up to day 93
	yes		Yes	▬ stool up to day 85 ✔
	yes		No	✚ day 29
	yes		Yes	▬ stool up to day 29 ✔
	yes		Yes	▬ stool up to day 192

Medical officer evaluation of enrolled patients by treatment group and patient number Dreyer study 020
(Continued)

Patient #	Evaluable?	Reason	Cure?	Reason
Treatment arm: Thiabendazole				
	yes		Yes	▬ stool up to day 191
	yes		Yes	▬ stool up to day 94
	yes		No	✚ day 17, 24; ▬ day 31-78 ✔
	yes		Yes	▬ stool up to day 93
	yes		No	✚ day 31
	yes		Yes	▬ stool up to day 186
	yes		Yes	▬ stool up to day 94
	yes		Yes	▬ stool up to day 92
	yes		Yes	▬ stool up to day 94
	yes		Yes	▬ stool up to day 93
	yes		Yes	▬ stool up to day 29 ✔
	yes		Yes	▬ stool up to day 85 ✔
	yes		Yes	▬ stool up to day 45 ✔
	yes		Yes	▬ stool up to day 82 ✔
	yes		Yes	▬ stool up to day 29

Footnotes:

❶ HIV + enrollee

✔ reinfection or relapse (stools ▬ X 3 at or including day 30 but again positive at later follow-up)

The totals of the above chart are presented below:

Dreyer study 020
Results per Medical Officer

	Ivermectin X 1	Ivermectin X 2	Thiabendazole
Enrolled Total	17	17	15
HIV +	2	2	1
Evaluable per M.O.	14	17	15
Cure at day 30 (%)	9 (64%)	15 (88%)	13 (87%)
Fail at day 30 (%)	5 (36%)	2 (12%)	2 (13%)
Reinfections/relapses (% of evaluables)	0	4 (24%)	5 (33%)

Medical officer findings: safety

In the applicant's summmary of the Dreyer study, a table on (applicant's) page D-2614 reveals that a significantly higher number of thiabendazole-treated subjects reported clinical adverse experiences. The computerized patient-level data to corroborate these findings were included in the NDA submission (pages D-2795-97) and were verified by the medical officer. As there were no deaths or discontinuations, nor were any events considered serious in nature, no case report forms were included in the NDA.

It is noteable that practically all of the adverse clinical events in the thiabendazole arm (19 evnets in 9 patients who reported them) were considered to be 'definitely' related to thiabendazole. This is somewhat striking; investigators are not usually so adamant in their desire to ascribe causality. This would have been more convincing had the study been conducted in a blinded fashion.

The applicant reports that there were no laboratroy adverse experiences in this study. Patients were assessed at one timepoint pre-therapy, and then once at day 7 or 8 post-therapy. Thus, the degree of follow-up is not nearly as long-term as it was in the Gentilini study. Upon review of the submitted information, the medical officer agrees that the investigator did not report any laboratory changes to be adverse events associated with study drug administration. There were, nonetheless, several laboratory perturbations that were noted upon medical officer review;

Subject #	lab finding (day of study)	Comments
Ivermectin X 1		
	AST 17→ 43 (d7)	
Thiabendazole		
	AST 18→ 38 (d8)	
	AST 17→ 43 (d8)	
	AST 19→ 38 (d8)	
	ALT 24→ 35 (d8)	
	WBC 4.7→ 2.2 (d7)	
Ivermectin X 2		
	AST 26→ 44 (d8)	
	AST 17→ 43 (d8)	
	AST 20→ 38 (d8)	

Thus it can be seen that the only laboratory effects of ivermectin that were seen in this small study with limited laboratory followup was mild elevation in transaminases, particularly AST. This observation holds for thiabendazole as well as both ivermectin arms. There were no apparrent perturbations in WBC count among the ivermectin-treated subjects in this study, as were noted previously in the Gentilini study. The lack of laboratory follow-up past the day 8 post-therapy timepoint makes it difficult to make any further comment on this matter.

5. Study 014 (Berk) and 015 (Gann): An open, randomized study of the efficacy, safety, and tolerability of ivermectin single dose and repeat dose (one day apart) vs. Thiabendazole (three-day course) in the treatment of patients infected with *Strongyloides stercoralis*.

These two studies were conducted in separate locations but utilized comparable protocols. Both study sites are in the United States. Both utilized Baermann technique for processing of all stool specimens. Timepoints of follow-up were relatively comparable. On this basis, it would seem to be reasonable to combine the two studies.

The following summary of these studies is taken from pages D-2983 thru 2996 of volume 1.23 of the NDA submission:

MK-0933 Prot. No. 014/015
Dr. Berk and Dr. Gann

COMPREHENSIVE STUDY SUMMARY

An Open, Randomized Study of Efficacy, Safety, and Tolerability of Ivermectin Single Dose and Repeat Dose (One Day Apart) vs. Thiabendazole (Three-Day Course) in the Treatment of Patients Infected With *Strongyloides Stercoralis*

I. BACKGROUND

Tens of millions of people around the globe are currently infected with *Strongyloides stercoralis* [1]. It is widespread, not only in moist rainy areas of the tropics and subtropics, but also in some areas of southern and eastern Europe and Southeastern United States. *Strongyloides stercoralis* is an intestinal nematode that usually causes a limited intestinal infection. Patients may remain asymptomatic but recurrent cutaneous and gastrointestinal symptoms are common. The intestinal disease is rarely fatal and usually associated with eosinophilia.

Strongyloidiasis begins when infective larvae in contaminated soil penetrate intact skin and cause an itchy erythematous rash at the point of entry. The larvae are then carried in the bloodstream to the lungs where they ascend the bronchial tree before being swallowed. They then enter the small intestine where they penetrate the mucosa and mature into adult worms. Eggs shed by female worms are transformed into larvae that are excreted in the intestinal lumen. Most larvae are excreted in the stool, but some may penetrate the mucous membrane of the lower bowel or perianal skin resulting in autoinfection which intensifies and perpetuates the intestinal colonization [2].

This phenomenon of autoinfection is unique to *S. stercoralis* and is not found in the other nematode parasites commonly infecting humans. In this form, the disease can be perpetuated for an indefinite period of time. World War II veterans who had been former prisoners of war in Southeast Asia as well as Vietnam veterans have been diagnosed as having strongyloidiasis without being further exposed for periods of over 40 years [1].

Thiabendazole (TBZ) has been the "drug of choice" for treatment of strongyloidiasis for almost 30 years since it has a wide range of action and is readily absorbed from the G.I. tract. However, it also is responsible for frequent and sometimes serious side effects [3,4]. Albendazole, a more broad spectrum anthelmintic, has efficacy in strongyloidiasis similar or slightly inferior to that of thiabendazole. Albendazole is, however, better

I. BACKGROUND (CONT.)

tolerated than thiabendazole. Both drugs require administration of multiple doses [3]. Treatment failures occur with both albendazole and thiabendazole and a few patients are not cured even when treated with increased amounts of drug for a long time. A single-dose drug with fewer side effects and increased efficacy would be useful in the treatment of strongyloidiasis.

Ivermectin, a derivative of avermectin ß, is an orally effective microfilaricidal agent. It has now been proven to be the current drug of choice for treating patients infected with the nematode *Onchocerca volvulus*, which is a major cause of blindness in inhabitants of tropical areas [3].

More than 5.2 million people worldwide have received at least one single oral dose of ivermectin at levels up to 200 mcg/kg for onchocerciasis [5]. Ivermectin given as a single oral dose of 100, 150, or 200 mcg/kg has been found to be a relatively safe and effective microfilaricide reducing *O. volvulus* skin microfilariae counts to near zero for up to 12 months [6]. Based on the safety and tolerability evaluations from these studies, 150 mcg/kg was judged to be the optimal oral dosage [6]. Ivermectin was approved by the French Regulatory Agency for the treatment of onchocerciasis in October 1987.

There is substantial evidence to suggest that ivermectin may be a useful therapeutic alternative for treatment of strongyloidiasis. Ivermectin has demonstrated activity in animal models of infection [7]. More importantly, ivermectin has been shown to be effective against human strongyloidiasis in noncomparative studies [8,9]. Ivermectin was well tolerated and a single dose demonstrated good activity. Based on this experience, we have undertaken a randomized, comparative trial of ivermectin versus thiabendazole in the treatment of strongyloidiasis.

II. SUMMARY OF PROTOCOL AND STUDY PROCEDURES

A. Protection of Human Subjects

This study was conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research.

B. Investigators

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C. Objectives

It should be noted that the primary objectives of the two protocols being combined in this report were identical in the expressed need to measure efficacy, safety, and tolerability of one or two oral doses (200 mcg/kg) of ivermectin compared to a 3-day regimen of thiabendazole (25 mg/kg b.i.d.) in the treatment of *Strongyloides stercoralis*. However, other treatment comparisons were listed among objectives in each study that rendered the two protocols somewhat different. These differences do not affect reporting on the cumulative experience for the primary objective stated above. The differences may be summarized as follows:

C. Objectives (Cont.)

Protocol Objective	Gann (Study 015)	Berk (Study 014)
Compare the efficacy, safety, and tolerance of one or two doses of ivermectin (200 mcg/kg) to 3 days of thiabendazole (25 mg/kg b.i.d.).	X	X
Compare declines in specific antibody titers over a 12-month period for the treatment groups specified.	X	
Compare the times for stool to become negative for the treatment groups specified.		X
Compare treatment results in hyperinfection syndrome for the treatment groups specified.		X

Although the above objectives were listed in each of the protocols as indicated, it was not possible to consistently execute measurements dealing with the Study 015-objective of antibody titers; and frequent stool collections and cultures required to compare the time rate of stools becoming negative for *S. stercoralis* could not be consistently executed as required in Study 014. In addition, "hyperinfection syndrome" was not encountered in Study 014 and therefore not addressed. Thus, only the objective comparing the efficacy, safety, and tolerance of one or two doses of ivermectin (200 mcg/kg) to 3 days of thiabendazole (25 mg/kg b.i.d.) was consistently addressed in both studies and this summary is limited to this single objective.

D. Patient Selection

Inclusion Criteria

1. Patients were between 5 and 80 years of age.
2. An examination of the stool samples done 2 weeks or less before entry into the study was positive for *Strongyloides stercoralis* larvae.
3. No clinical evidence of disseminated strongyloidiasis (Study 015).
4. No treatment for strongyloidiasis within the previous 6 months (Study 015).

Exclusion Criteria

1. Age under 5 or over 80 years.
2. Women of childbearing potential (unless they have a negative HCG).
3. Medical history of mental illness, seizure, or other serious illnesses.
4. Abnormal levels of SGOT or SGPT greater than twice above the upper normal limit, creatinine greater than 2.0 mg/100 mL or grossly abnormal BUN or urine analysis.
5. A history of an abnormal EKG or EEG (Study 015 only).
6. Moderate or severe anemia, i.e., hemoglobin less than 10 g or hematocrit less than 30%; any abnormality of white blood cell count and/or differential (except eosinophilia).
7. Any past or concurrent medical illness which the investigator feels might influence either the outcome of the study or interpretation of the data accrued.

E. Study Design

General Description

This was an open, randomized study in ambulatory patients who had strongyloidiasis evidenced by microscopic stool examination or by positive stool culture. Using a local allocation schedule patients were randomized into one of three groups to receive either ivermectin (single or two dose) or thiabendazole. Although duodenal aspirates and/or jejunal biopsies were permitted in Study 014 these tests were not routinely performed nor were they used as confirmation of strongyloidiasis. Only Baermann stool examinations were used to assess strongyloidiasis in patients in Studies 014 and 015.

Although the study was open in design, stool specimens were examined by one single expert who was to remain blinded as to the treatment allocations.

The safety of ivermectin was evaluated on the basis of physical examinations and laboratory tests prior to treatment and on Day 7 posttreatment. Study 014 allowed for an additional physical examination on Day 30 posttreatment.

In the event that mild or moderate reactions occurred, they could be treated with aspirin and antihistamines; other medications were not to be administered during the first week of drug administration except for necessary treatment of patients with severe allergic reactions.

Patient Allocation

After completion of the informed consent procedures and documentation of strongyloidiasis evidenced by stool examination, patients were randomized to receive either single dose of ivermectin, two single doses of ivermectin 1 day apart or 3 days of b.i.d. dosing with thiabendazole.

During the week prior to the study, the patient was screened to assure that he/she was in good physical condition. The patient had a physical examination and a laboratory screen. Vital signs were recorded on Day -1 (the day before or same day but before drug administration), Day 1 (the first day of drug administration), and 7 days later.

E. Study Design (Cont.)

Treatment

Ivermectin and thiabendazole (TBZ) were provided as 6- and 500-mg commercial tablets, respectively. The dose closest to that calculated on the basis of body weight was utilized in order to achieve the targeted dose of 200 mcg/kg of ivermectin or 50 mg/kg/day of thiabendazole. A schedule of recommended combinations of these tablets is shown on the following page (see Table 1).

E. Study Design (Cont.)

Table 1

Dosage Recommendation by Weight

Ivermectin Dosage Recommended Tablet Combinations for 200-mcg/kg Dose	
Patient Weight (kg)	Number of Tablets (6 mg)
15 to 24*	½
25 to 35	1
36 to 50	1½
51 to 65	2
66 to 79	2½
80 and over	3

Thiabendazole (MINTEZOL) Dosage Tablet Combinations for Daily 50-mg/kg Dose	
Patient Weight (kg)	Number of Tablets (500 mg)
13.3 to 22.2	0.25 (½ tablet)
22.3 to 33.4	0.5 (1 tablet)
33.5 to 44.5	0.75 (1½ tablets)
44.6 to 55.7	1.0 (2 tablets)
55.8 to 66.8	1.25 (2½ tablets)
66.9 and over	1.5 (3 tablets)

* Range not specified in either protocol; however, range was necessary to accommodate children down to 5 years of age.

F. Clinical Observations and Laboratory Measurements

Table 2 shows the schedule of clinical observations and laboratory measurements during the study. In addition, the patient was questioned daily (by phone) regarding adverse experiences with particular attention to evidence of allergic reactions (rash, itching, and anaphylaxis).

Table 2

Schedule of Clinical Observations and Laboratory Measurements

	Days					Months			
	Pre-study+	1	2	3	Day 7 (5 - 9)	1	3	6	12
Drug Administration		X							
	or								
		X	X						
	or								
		X	X	X					
Physical Examination	X	X			X				
Vital Signs	X	X			X				
Laboratory Safety	X				X				
Stool Examination++	X				X	X	X	X	X
IgG (ELISA)*	X						X	X	X
Eosinophilia**	X				X		X	X	X

\+ Prestudy within 14 days of treatment.

++ Stool examinations for Study 014 were to include Postdays 7, 14, 21, and 30 then monthly for 1 year; however, investigator was not able to consistently execute this schedule.

* Study 015 only; however, investigator not able to consistently execute this requirement.

** The analysis of eosinophilia was for Study 015 only. Although results were collected and submitted to MRL by the investigator the analysis was not performed by MRL. However, the investigator performed the analysis and concluded that eosinophil levels returned to normal in 90% of all subjects by 12 months [11].

F. Clinical Observations and Laboratory Measurements (Cont.)

Observations and measurements related to efficacy and safety are described below:

Efficacy Measures

All stool specimens were examined by individuals who were blinded to the patient's treatment.

Parasitological cure was the primary measure of efficacy and was assessed using repeated Baermann stool examinations during the follow-up period. Any positive Baermann stool examination after Day 6 was considered a treatment failure.

The Baermann technique [10] is a method of examining a stool specimen suspected of having small numbers of Strongyloides larvae and uses the modified Baermann apparatus. The technique is dependent on the migration of active larvae out of the fecal material, through a wire gauze covered with gauze padding and into water, where they settle out. The procedure is as follows:

a. Fill a funnel (six-inch) with water (attach rubber tubing with a pinch clamp to the bottom of the funnel) and place the wire gauze, one or two layers of gauze padding on it, on the funnel.

b. Place 50 to 100 g of fecal material on the gauze padding so that it is covered with water. If the fecal material is too firm, break it up slightly.

c. Allow the apparatus to stand for 2 or more hours, draw off 10 mL of fluid by releasing the pinch clamp, spin it down in a centrifuge and examine the sediment with a magnifier or low power microscope to count and confirm the species of the larvae.

The larval counts obtained from the Baermann technique are the basis for evaluation of efficacy. Counts were done for purposes of quantifying the level of infestation (intensity of infection) per patient and important only to determine comparability of treatment groups and examine whether there is an interaction between intensity of infection and clinical outcome. This approach was not specifically stated in the protocol; however, MRL believes that such an analysis between intensity of infection and outcome is valid. However, for purposes of assessing clinical efficacy, stool

F. Clinical Observations and Laboratory Measurements (Cont.)

exams for larvae were recorded only as positive or negative; no quantitative assessment of the intensity of infection, as reflected in the number of larvae, was made.

The investigators occasionally used "word" or "plus" designations to quantify the number of larvae. The following convention was applied to "word" or "plus" designations:

"Word" Designation	Larvae Counts/gm Stool	"Plus" Designation
Rare	1 to 15	+
Few	16 to 30	++
Moderate	31 to 100	+++
Heavy	>100	++++

Safety Measures

A complete physical examination was done during the week preceding study drug administration and 7 days posttreatment. Prestudy and follow-up samples for the laboratory safety studies on blood and urine included:

a. Hematology: Hematocrit
Hemoglobin
White blood cell count, total
Differential counts will be made if WBC is abnormally low or high.

b. Blood Chemistries: Blood urea nitrogen
Serum creatinine
SGOT (AST)
SGPT (ALT)
Total bilirubin
Alkaline phosphatase

c. Urinalysis: Urinalysis was performed in patients with abnormal serum creatinine values or with signs/symptoms of urinary tract infection.

F. **Clinical Observations and Laboratory Measurements (Cont.)**

The investigator could carry out additional analyses as required by the hospital or as indicated for optimum patient care.

Vital signs (blood pressure and pulse rate, both supine and erect, respiration rate and temperature) were recorded on Day 1 and Day 7.

G. **Evaluation Criteria**

1. **Evaluability**

All patients whose data were received by September 1992 were classified by the MRL clinical monitor as evaluable or unevaluable with respect to efficacy. These evaluations by the MRL monitor, although not specified in the protocol, were in keeping with the dictates of the protocol (i.e., inclusion and exclusion criteria) and the exercise of good clinical judgment. Thus, patients were considered evaluable for efficacy if:

a. Strongyloidiasis was documented on stool examination.

b. The patient did not receive other effective anthelmintic therapy during the study period.

c. The patient was compliant with therapy.

d. Adequate follow-up stool examinations were performed for determination of efficacy. See details in next section.

e. There was no violation of inclusion and/or exclusion criteria that would compromise efficacy evaluation.

2. **Efficacy**

The primary measure of efficacy in this study was the absence of larvae in posttherapy Baermann fecal examinations. Cure was defined as the absence of larvae in the follow-up stool examinations. The detection of larvae on any stool examination past 6 days posttreatment met the definition of treatment failure.

G. Evaluation Criteria (Cont.)

The original protocols called for a number of posttreatment stool examinations. Although a 12-month follow-up was planned at both sites, this was primarily related to a parallel serological study at one site (Study 015). Three- to 6-month follow-up was the main goal. In general, full compliance with follow-up examinations outlined in Table 2 was not possible; therefore, the criteria summarized earlier (II.G.1. Evaluability) was established for evaluability. Patients with stool samples that were positive for *Strongyloides stercoralis* larvae any time after posttreatment Day 6 were considered evaluable for efficacy regardless of the total number of posttreatment stool examinations.

It is recognized that these changes in evaluation criteria differ from the requirements of the protocol; however, they are considered by MRL as consistent with the treatment of patients with strongyloidiasis given the natural history of the disease. As such, MRL believes that the alterations from the protocol as specified above do not impact on the validity of the results of these studies.

3. Safety

All patients were evaluated for safety by physical examinations and laboratory studies. In addition, the patient was questioned daily for 3 days (by phone) regarding adverse experiences with particular attention to evidence of allergic reactions (rash, itching, and anaphylaxis). Adverse experiences were described and recorded by the investigator who determined the durations, seriousness, severity, and drug relationship as well as the eventual outcome of each adverse experience.

H. Statistical Planning and Analysis

Methods of Analysis

The primary measurement of efficacy was the cure rate. Logistic regression was used to determine if any concomitant factors, i.e., age, sex, race, severity of infection, intensity of infection, affected the cure rate. None of these factors was related to cure rate at the α=0.10 level of significance. Thus, all were dropped from the statistical model, leaving only treatment group. The treatment groups were compared for the proportion of patients who were cured using Fisher's exact test.

H. **Statistical Planning and Analysis (Cont.)**

Baseline characteristics were analyzed using either Fisher's exact test or the Chi-square test or the Wilcoxon Rank Sum test, as appropriate. Confidence intervals were calculated using the method of Blyth and Still for N>5. All statistical tests for treatment-group differences were two-tailed (α=0.05).

I. **Clinical Supplies**

Ivermectin in the form of 6-mg tablets (Lot C-W011 17420) was used in both studies and obtained through MRL facilities in West Point, PA. Thiabendazole (TBZ) tablets (500 mg MINTEZOL) were obtained through local drug supply houses [4].

B. Devaitions from protocol

Despite the similarity in protocol design and, most importantly, the similar methods of stool collection and evaluation, it should be pointed out that there are several important differences between these two study sites:

- the site for Dr. Berk's study was East Tennessee State University and its affiliated Vetrans Administration Medical Center. Thus, the enrolled subjects at this site were all elderly males, many of whom presumably were infected during their military service in the Pacific or SE Asia. (It should also be pointed out that this area of the United States is known to have low-level endemic strongyloidiasis. Therefore, although extremely unlikely, these study subjects would be potentially subject to re-infection post-therapy.)
- the site for Dr. Gann's study was a community health center in Lowell Massachusetts, a community with a large proportion of its population composed of immigrants from Southeast Asia. This group of enrollees were generally younger, evenly distributed with regards to sex, and with a single exception, entirely of Southeast Asian (predominantly Cambodian) origin.
- the Berk protocol allowed for the entry of patients with disseminated strongyloidiasis, because of the demographics of the patient population at the VAMC study site; the Gann protocol specifically excluded subjects with clinical evidence of disseminated strongyloidiasis.
- the Gann study specifically sought to follow and analyze specific anti-strongyloides antibody titers over the 12 months following therapy, whereas the Berk study did not.

The actual implementation of these studies was similar enough to allow for their combined analysis. However, the difference in demographics is striking:

Demographics of enrolled subjects
Studies 014 (Berk) and 015 (Gann)

Investigator, Site	Demographics		Ivermectin X 1	Ivermectin X 2	Thiabendazole
Berk, Tennessee	Males	Number enrolled	4	5	6
		Average age (yrs)	72	70	65
		Number of deaths	0	1	1
	Females	Number enrolled	0	0	0
		Average age (yrs)	–	–	–
		Number of deaths	–	–	–
Gann, Massachusetts	Males	Number enrolled	10	8	6
		Average age (yrs)	38	46	42
		Number of deaths	0	0	0
	Females	Number enrolled	8	11	10
		Average age (yrs)	30	33	32
		Number of deaths	0	0	0

The relatively small numbers of subjects enrolled by Dr. Berk makes the difference in these demographics less concerning. Furthermore, although this site was looking to enroll patients with disseminated disease, the applicant states that no such patients were enrolled. The two deaths noted in this group, patients [redacted] died at days 84 and 57 of the study, respectively. Neither of these deaths were considered to be drug related. Patient [redacted] had severe underlying COPD and prostatic cancer; patient [redacted] had coronary artery disease and COPD.

Comment: the case report forms for these two deaths were not submitted with the NDA.

In general, these investigators were more compliant than the previously-reviewed studies regarding the protocol requirements for maximum allowable time between documentation of a positive stool and enrollment in the study. Both protocols called for a maximum of two weeks to elapse between these two events. Dr. Berk did not violate this parameter; Dr. Gann enrolled 8 subjects whose stools had been collected between 2 and 4 weeks pre-enrollment. These 8 subjects were not excluded from the medical officer analysis. One Gann patient [redacted] was enrolled 79 days following her only pre-therapy stool collection; this patient was not considered evaluable for efficacy by the medical officer.

C. Applicant's findings

The applicant's summary of the results of these combined studies is found on the following pages, as excerpted from pages D-2997 to D-3022, volume 1.23 of the NDA:

III. RESULTS

A. Patient Characteristics

Summaries of demographic information for evaluable patients as well as all patients entered into the trial are provided in Tables 3 and 4, respectively. A detailed summary of each patient's treatment may be found in Appendix 1 (Summary of Therapy). There were no significant differences in the characteristics of the treatment groups.

Of all patients enrolled in the study, 8 of 22 patients in the single-dose ivermectin group had secondary diagnoses as did 15 of 24 in the two-dose ivermectin group and 12 of 22 patients receiving thiabendazole. Although more than half of the patients had secondary diagnoses, no single body system accounted for the majority of the secondary diagnoses recorded in these studies. A summary table of patients with secondary diagnoses may be found in Appendix 2.

A majority of patients (13 of 22 in the single-dose ivermectin group [59.1%], 12 of 24 patients in the two-dose ivermectin group [50.0%], and 15 of 22 patients in the thiabendazole group [68.2%]) received concomitant therapy during the study. No patient received concomitant therapy with activity against *S. stercoralis*. Two patients were treated with prednisone. [redacted] (Study 015) was chronically receiving 5 mg of prednisone per day and was considered evaluable. [redacted] (Study 014) was treated with 30 mg of prednisone daily, which was considered potentially immunosuppressive, and was considered nonevaluable based on this concomitant therapy.

A. Patient Characteristics (Cont.)

Table 3

Patient Characteristics - Evaluable Patients

	Ivermectin		
	One Dose	Two Doses	Thiabendazole
Number of Patients	14	19	17
Study (Protocol)			
Berk (014)	2	1	2
Gann (015)	12	18	15
Mean Age	40	42	42
Sex			
Male [Age Range-Years]	9 [17-79](64%)	7 [25-62](37%)	8 [25-72](47%)
Female [Age Range-Years]	5 [21-45](36%)	12 [17-50](63%)	9 [8-56](53%)
Race			
Caucasian	2 (14%)	2 (11%)	2 (12%)
Southeast Asian	12 (86%)	17 (89%)	15 (88%)
Intensity of Infection			
1+	4 (29%)	4 (21%)	3 (18%)
2+	2 (14%)	5 (26%)	4 (24%)
3+	2 (14%)	3 (16%)	6 (35%)
4+	6 (43%)	7 (37%)	4 (24%)
Follow-Up Stool Exam			
Mean Number	4.9	4.6	4.3
Mean Duration (Days)	274	288	289

There were no significant differences between treatment groups.

A. Patient Characteristics (Cont.)

Table 4

Patient Characteristics - All Patients

	Ivermectin		Thiabendazole
	One Dose	Two Doses	
Number of Patients	22	24	22
Study (Protocol)			
Berk (014)	4	5	6
Gann (015)	18	19	16
Mean Age	41	45	44
Sex			
Male [Age Range-Years]	14 [17-79](64%)	12 [25-81](50%)	12 [25-86](55%)
Female[Age Range-Years]	8 [18-45](36%)	12 [17-50](50%)	10 [8-56](45%)
Race			
Caucasian	4 (18%)	6 (25%)	6 (27%)
Southeast Asian	18 (82%)	18 (75%)	16 (73%)
Intensity of Infection*			
1+	6 (30%)	7 (32%)	5 (23%)
2+	2 (10%)	5 (23%)	6 (27%)
3+	3 (15%)	3 (14%)	6 (27%)
4+	9 (45%)	7 (32%)	5 (23%)
Follow-Up Stool Exam			
Mean Number	3.9	4.3	4.3
Mean Duration (Days)	240	237	244

* Intensity of infection may not have been recorded for certain patients (as in the case of a negative pretreatment stool examination). Percentages relative to total number with pretreatment intensity of infection recorded.

There were no significant differences between treatment groups.

B. Patient Accounting

1. Accounting for Patients in the Study

Table 5 is a summary of patients who entered, completed, and discontinued the study by treatment group.

Table 5

Accounting for Patients in the Study by Treatment Group

Patients	Ivermectin 1-Dose	Ivermectin 2-Dose	Thiabendazole
Total Patients Entered	22	24	22
Total Patients Completed	11	19	15
Total Patients Discontinued	11	5	7
Adverse Clinical Experience	0	0	1
Adverse Laboratory Experience	0	0	0
Lost to Follow-Up	9	4	3
Patient Death	0	1[1]	0
Patient Uncooperative	2	0	1
No Therapeutic Response	0	0	1
No Therapeutic Response/Death	0	0	1[2]

[1] Study 014, [redacted] Patient actually completed treatment course and died 57 days posttreatment of background diseases (coronary artery disease and chronic pulmonary disease).

[2] Study 014, [redacted] patient considered to have no therapeutic response and died on Study Day 84 as a result of underlying pulmonary disease; the death was considered to be not drug related.

2. Accountability for Patients in the Analysis

Table 6 is a summary of the number of patients who were included in the analyses of efficacy (evaluable patients) and safety.

B. Patient Accounting (Cont.)

Table 6

Accounting for Patients in the Analysis by Treatment Group

Patients	Ivermectin 1-Dose	Ivermectin 2-Dose	Thiabendazole
Evaluable for Efficacy Analysis	14	19	17
Nonevaluable for Efficacy Analysis	8	5	5
Reason for Nonevaluability for Efficacy Analysis:			
Pretreatment Stool Exam. Negative	2[1]	2[2]	0
Inadequate Follow-Up Parasitology	5[3]	3[5]	3[4]
Pretreatment Stool Exam. >30 days	1[6]	0	0
Patient Discontinued Too Early	0	0	1[7]
Patient on High Dose Immunosuppressive Treatment	0	0	1[8]
Evaluable for Safety Analysis	22	24	22

Patient Identities (Study/AN):

B. Patient Accounting (Cont.)

A total of 68 patients were enrolled in the trial (ivermectin one dose - 22, ivermectin two dose - 24, thiabendazole - 22). All 68 patients are included in the safety analysis; however, 50 (74%) are included in the efficacy analysis.

Patients who did not fulfill the evaluability criteria outlined in Section II.G.1. were considered nonevaluable for efficacy. In certain circumstances, failure to satisfy the entrance criteria in Section II.D. did not necessarily exclude patients from the analyses of evaluable patients if the evaluability criteria were satisfied. The inclusion criteria required that the time period from diagnosis (i.e., positive stool exam) to initiation of therapy not exceed 14 days. In practice, this was not always possible. Because the natural history of strongyloidiasis is one of persistence over time, patients who received therapy within 30 days of a diagnostic stool examination were considered evaluable.

It is recognized that these changes in entry/evaluation criteria differ from the requirements of the protocols; however, they are considered by MRL as consistent with the treatment of patients with strongyloidiasis given the natural history of the disease. As such, MRL believes that the alterations from the protocols as specified above do not impact on the validity of the results of this study.

The study protocols allowed the investigator to determine whether a patient's underlying disease or concomitant therapy would interfere with evaluation of study outcome (i.e., exclusion criteria). Two patients enrolled in the study received concomitant steroid therapy. One patient (Study 015, [redacted] was chronically treated with only 5 mg of prednisone per day; this patient was considered evaluable because of the low daily steroid dose. Study 014, [redacted] (30 mg prednisone per day) was considered an acceptable study candidate by the investigator. The patient was enrolled in the study and failed thiabendazole therapy. Because of likely immunosuppression, this patient was considered nonevaluable by the Merck clinical monitor (this MRL decision was made independent of the clinical outcome for this patient).

B. Patient Accounting (Cont.)

The daily doses of ivermectin and TBZ were based on each patient's body weight. Ivermectin and TBZ were supplied as 6-mg and 500-mg tablets, respectively, both of which are scored to allow administration of half tablets. Individual doses were determined using Table 1 in Section II.E. These dosing guidelines were designed to achieve as close to 200 mcg/kg/dose and 50 mg/kg/day as possible within the physical limits of tablet administration. Ivermectin was administered as single daily doses for 1 day or on 2 consecutive days. All patients randomized to receive thiabendazole were treated b.i.d. for 3 days. With the exception of 1 patient (Study 015, [redacted] all patients received dosages consistent with those recommended in Table 1. [redacted] was somewhat underdosed having received a maximum of only 33 mg/kg/day of thiabendazole on 1 day and a minimum of 22 mg/kg/day of thiabendazole on 2 days. This patient was considered a clinical cure having had repetitive negative stool examinations from 1 week posttherapy to 1-year posttherapy. [redacted] was considered evaluable for efficacy.

Several patients had minor modifications or errors in their thiabendazole dosage regimen. (both in Study 015) received their sixth doses of thiabendazole on Study Day 4 rather than on Study Day 3. (Study 015) received her last dose of thiabendazole on Study Day 5 rather than Study Day 4. (Study 015) was moderately underdosed. It appeared unlikely that any of these irregularities would significantly impact the patients' outcomes and no patient was considered nonevaluable solely on the basis of these dosing modifications.

A single patient (Study 014, was inappropriately re-entered into the study following a therapeutic failure with thiabendazole. He was assigned a new allocation number and was re-randomized to be retreated with thiabendazole, that was again ineffective. Because patient re-entry is not allowed and because the experience represented by is not an additional independent observation, is not considered an additional patient entry. Therefore is not included in any analysis. Safety data from is considered to be a part of the continuing observation for To insure full availability of data, information collected during the patient's treatment as is included in tabulated information as a second treatment phase for

B. Patient Accounting (Cont.)

Overall, 14 of 22 patients (63.6%) randomized to receive single-dose ivermectin, 19 of 24 patients (79.2%) in the two-dose ivermectin treatment group and 17 of 22 patients (77.3%) assigned to thiabendazole treatment were considered evaluable for efficacy. There were no significant differences among treatment groups in the percent of total patients considered evaluable for efficacy.

C. Efficacy

1. Evaluable Patients

All evaluable patients (14/14) in the single-dose ivermectin group were cured (100%) compared to 18 of 19 patients (95%) assigned to the two-dose ivermectin group and 16 of 17 (94%) of patients receiving thiabendazole. There were no significant differences between treatment groups in the proportion of patients cured. Cure was not significantly related to age, sex, race or intensity of infection. Table 7 contains the cure rates and 95% confidence intervals for evaluable patients.

The mean number of posttreatment stool examinations and total duration of days included in the follow-up period also did not differ among treatment groups.

2. All Patients

For the analysis of efficacy for all patients, patients without adequate posttreatment stool examinations were excluded as well as patients with negative pretreatment stool examinations.

Thus, the following patients were excluded from the "all-patients" analysis of efficacy:

- For single-dose ivermectin:

  014/005 - Negative pretreatment stool examination

  015/233 - No follow-up stool examination

  015/301 - No follow-up stool examination

  015/389 - Negative pretreatment stool examination

8.99

C. Efficacy (Cont.)

- For two-dose ivermectin:

  014/006 - Negative pretreatment stool examination

  015/262 - Negative pretreatment stool examination

- For the thiabendazole group:

  014/011 - Only posttreatment Day 9 stool examination

  014/016 - No follow-up stool examination

Thus, in the group of patients with adequate pretreatment and posttreatment stool examinations, 18 of 18 (100%) patients in the single-dose ivermectin group were cured compared to 21 of 22 (95%) patients in the two-dose ivermectin treatment group and 18 of 20 (90%) patients assigned to receive thiabendazole. The mean number of posttreatment stool examinations and total duration of days included in the follow-up period also did not differ among treatment groups. There was no significant difference between treatment groups in the proportion of patients cured. Cure was not significantly related to age, sex, race, or intensity of infection. Table 8 contains the cure rates and 95% confidence intervals for all patients with adequate follow-up stool examinations.

C. Efficacy (Cont.)

Table 7

Patients Cured - Evaluable Patients

	Ivermectin						Thiabendazole		
	One Dose			Two Doses					
	Cure	N	PCT	Cure	N	PCT	Cure	N	PCT
Overall	14	14	100 (58,100)	18	19	95 (72,100)	16	17	94 (69,100)
Study									
Berk	2	2	100	1	1	100	1	2	50
Gann	12	12	100 (53,100)	17	18	94 (72,100)	15	15	100 (58,100)
Sex									
Male	9	9	100 (43,100)	7	7	100 (34,100)	7	8	88 (51,99)
Female	5	5	100	11	12	92 (63,99)	9	9	100 (43,100)
Race									
Caucasian	2	2	100	2	2	100	1	2	50
Southeast Asian	12	12	100 (53,100)	16	17	94 (70,100)	15	15	100 (58,100)
Intensity of Infection									
1+	4	4	100	3	4	75	3	3	100
2+	2	2	100	5	5	100	4	4	100
3+	2	2	100	3	3	100	5	6	83 (36,99)
4+	6	6	100 (28,100)	6	7	86 (28,100)	4	4	100

There were no significant differences between treatment groups.
( ) = 95% confidence interval (for N>5).

C. Efficacy (Cont.)

Table 8

Patients Cured - All Patients With Adequate Follow-Up Stool Examination

	Ivermectin						Thiabendazole		
	One Dose			Two Doses					
	Cure	N	PCT	Cure	N	PCT	Cure	N	PCT
Overall	18	18	100 (66,100)	21	22	95 (74,100)	18	20	90 (71,98)
Study									
Berk	3	3	100	4	4	100	2	4	50
Gann	15	15	100 (62,100)	17	18	95 (72,100)	16	16	100 (62,100)
Sex									
Male	10	10	100 (53,100)	10	10	100 (53,100)	8	10	80 (57,95)
Female	8	8	100 (38,100)	11	12	92 (63,99)	10	10	100 (47,100)
Race									
Caucasian	3	3	100	5	5	100 (28,100)	2	4	50
Southeast Asian	15	15	100 (62,100)	16	17	94 (72,100)	16	16	100 (62,100)
Intensity of Infection									
1+	6	6	100 (34,100)	6	7	86 (57,99)	5	5	100
2+	2	2	100	5	5	100	4	4	100
3+	3	3	100	3	3	100	5	6	83
4+	7	7	100 (34,100)	7	7	100 (34,100)	4	5	80

There were no significant differences between treatment groups.
( ) = 95% confidence interval (for N>5).

C. Efficacy (Cont.)

A quality assurance audit was performed for Study 015, 1½ years after the completion of the trial (reference Audit Information Sheet - Appendix 3). Persons who conducted the audit found certain GCP compliance issues relating to organization of the study and study documentation. Examples of their audit findings included:

- Lack of availability of signed patient consent forms for 43% of all patients and of those with signed forms 23% either did not have a date indicated or the date that was indicated was not consistent with study start. It should be pointed out that almost all of the patients who entered the trial were Cambodian refugees who were for the most part illiterate. In addition, the investigator did not counter sign 81% of the patient consent forms as required by his IRB.

- Laboratory safety data reported to MRL had discrepant dates with regard to source laboratory reports and multiple laboratories were used during the conduct of the trial without the approval of MRL.

- Two additional patients were treated at this site and never reported to MRL. Both patients had nonserious adverse experiences reported which were judged by the investigator to be drug related. Both patients received TBZ. Efforts made to obtain formal case reports on these patients were unsuccessful. Data from these two patients are excluded from this summary.

- Finding a lack of complete supporting laboratory documentation for stool testing and some cases of Baermann results which were not reported to MRL. Subsequent to MRL learning about the lack of complete laboratory documentation for stool testing a second audit was performed wherein all patients' files were reviewed for the presence of laboratory reports of stool testing in support of the test results reported to Merck. This subsequent audit showed that 52% of the patients had incomplete supportive documentation on file for stool testing. In this group of 52%, one to four source reports were missing per patient, with most patients having had an average of 6 to 7 tests completed during the study course. Admittedly, these findings would be of great concern if the frequency of positive stool tests

C. Efficacy (Cont.)

were high; however, this is not the case for any of the three treatment groups in this study. All treatments in this study displayed, for the most part, negative stool tests. In general, what is not evident because of the "missing" information is confirmatory and repeated negative stool-testing results.

- After the prestudy visit there was no routine field monitoring conducted at this site.

- There was no record of accountability for unused drug at this site.

Comparing the results of Studies 015 and 014 with those published in 1994 [11,12], the results summarized here indicate no substantive difference. Table 9 summarizes the differences between the two published reports and the data in this summary.

C. Efficacy (Cont.)

Table 9

Comparison Between Data Received at MRL for Studies 014 and 015 vs. Two Independent Publications [11,12] by the Investigative Groups

Patient Accounting:	MRL Summary*			Publication*		
	IVx1	IVx2	TBZ	IVx1	IVx2	TBZ
Patients Entered - Total:	22	24	22	20	23	26
Berk (014)	4	5	6	4	5	7
Gann (015)	18	19	16	16	18	19
Evaluable Patients - Total:	14	19	17	20	23	26
Berk (014)	2	1	2	4	5	7
Gann (015)	12	18	15	16	18	19
Nonevaluable Patients - Total:	8	5	5	0	0	0
Berk (014)	2	4	4	0	0	0
Gann (015)	6	1	1	0	0	0
Cure Rate+ - Total:	14/14	18/19	16/17	20/20	22/23	22/26
Berk (014)	2/2	1/1	1/2	4/4	5/5	5/7
Gann (015)	12/12	17/18	15/15	16/16	17/18	17/19

* IV x 1 = Ivermectin single dose for 1 day.
IV x 2 = Ivermectin single dose for 2 days.
TBZ = Thiabendazole 50 mg/kg/day for 3 days.
\+ Cure rates for "MRL Summary" are for Evaluable Patients only.

C. Efficacy (Cont.)

It is not clear why the total number of patients in Table 8 who entered into Study 014 differs by 1 patient between the MRL report and the publication by Berk (Study 014) [12]; however, data for only 15 patients were ever received at MRL for this study. What remains a puzzle is that for Study 015, wherein both reports account for 53 patients; the number of patients per treatment group differs between the MRL summary and what appeared in the publication by Gann (Study 015) [11]. Again, a comparison of the MRL database used in preparation of this report with the case reports submitted by the investigator to MRL reveals no discrepancies.

The major difference between this MRL summary and the two publications is the exclusion of certain patients from the analysis of efficacy. Both investigators included all their patients in their efficacy evaluation; however, MRL, used the stringent criteria described earlier. Regardless of the approach taken for efficacy evaluation, the cure rates described in each of the publications and this summary are consistently comparable.

Despite these GCP-related findings, MRL believes that the basic scientific and medical conclusions drawn from these studies and described in this summary are valid in that the data have been published in a peer-reviewed journal and the fact that incomplete source documentation for some of the primary efficacy laboratory data is outweighed by the high frequency of negative stool testing results for all three treatment groups.

D. Safety

1. Adverse Experiences - Clinical

All patients were evaluated for safety and tolerability.

a. Overall Assessment of Clinical Adverse Experiences

Table 10 below is a summary of the clinical adverse experiences.

Table 10

Clinical Adverse Experience Summary

Treatment Group	Ivermectin Single-Dose (N=22)	Ivermectin Two-Dose (N=24)	Thiabendazole (N=22)
Patients with Clinical AE	3 (14%)	6 (25%)	19 (86%)
Serious Clinical AE	0	1 +	1 ++
Discontinued Due to Patient Death	0	1 +	0
Discontinuations Due to Clinical AE	0	0	1 *
Discontinued Due to No Therapeutic Response/ Death	0	0	1 ++
Drug-Related Clinical AE	3 (14%)	5 (21%)	18 (82%)

+ Study 014, - Patient actually completed treatment course and died 57 days posttreatment of background diseases (coronary artery disease and chronic pulmonary disease); the death was not drug related.

++ Study 014, - Patient died on Study Day 84 as a result of underlying pulmonary disease; the death was considered to be not drug related.

* Study 014, had study drug discontinued after 1 day of therapy due to severe nausea and moderate tinnitus considered by the investigator to be definitely related to study drug.

D. Safety (Cont.)

The difference in the incidence of clinical adverse experiences (AEs) between each of the ivermectin groups and the thiabendazole group was significant ($p<0.001$ for each comparison). There was no statistically significant difference in the incidence of clinical AEs between the two ivermectin treatment groups ($p=0.46$). There were two serious clinical AEs (both patient deaths) as summarized above; neither was considered drug related.

Drug-related (possibly, probably, or definitely related) clinical AEs were not significantly different between the two ivermectin treatment groups ($p=0.70$); however, the difference between each of the ivermectin groups and the thiabendazole group was significant ($p<0.001$ for each comparison).

Table 11 is a listing of clinical AEs by body system.

D. Safety (Cont.)

Table 11

Clinical Adverse Experiences By Body System

Body System/ Diagnosis	Ivermectin Single-Dose (N=22)	Ivermectin Two-Dose (N=24)	Thiabendazole (N=22)
Patients with AE	3 [3]	6 [5]	19 [18]
Body as a Whole	0	2 (8.3%) [1]	12 (54.5%) [11]
Asthenia/Fatigue			11 (50.0%) [11]
Death		1 (4.2%) [0]	1 (4.5%) [0]
Malaise			2 (9.1%) [2]
Abdominal Pain		1 (4.2%) [1]	
Digestive System	2 (9.1%) [2]	1 (4.2%) [1]	15 (68.2%) [15]
Anorexia	1 (4.5%) [1]		7 (31.8%) [7]
Constipation	1 (4.5%) [1]		
Diarrhea	1 (4.5%) [1]	1 (4.2%) [1]	1 (4.5%) [1]
Dyspepsia			2 (9.1%) [2]
Flatulence			1 (4.5%) [1]
Nausea		1 (4.2%) [1]	9 (40.9%) [9]
Salivation			1 (4.5%) [1]
Vomiting		1 (4.2%) [1]	3 (13.6%) [3]
Nervous System/Psychiatric System	0	2 (8.3%) [2]	15 (68.2%) [15]
Disorientation			4 (18.2%) [4]
Dizziness		2 (8.3%) [2]	9 (40.9%) [9]
Somnolence			7 (31.8%) [7]
Vertigo			1 (4.5%)[1]
Skin and Skin Appendage	3 (13.6%) [3]	2 (8.3%) [2]	1 (4.5%) [1]
Pruritus	1 (4.5%) [1]	2 (8.3%) [2]	1 (4.5%) [1]
Rash	1 (4.5%) [1]		
Urticaria	1 (4.5%) [1]		
Special Senses	0	0	1 (4.5%) [1]
Tinnitus			1 (4.5%) [1]

N.B.: Patient counts and event counts may not be the same since some patients may have more than one clinical AE event.

[ ] Numbers in brackets are those patients who had clinical AEs which were considered possibly, probably, or definitely related to study drug.

D. Safety (Cont.)

The organ system most commonly involved among patients treated with ivermectin reporting clinical adverse experiences was the skin (14% of patients receiving single-dose ivermectin and 8% of patients treated with two doses of ivermectin). Pruritus was the most frequent skin sign or symptom. Two patients in the two-dose ivermectin treatment group reported mild dizziness. No other clinical adverse experiences were reported by more than 1 patient treated with either ivermectin dosage regimen.

The organ systems most commonly involved in clinical adverse experiences reported by patients treated with TBZ were the digestive system and the nervous/psychiatric systems (both were identified in 68% of patients). Dizziness (9 patients), somnolence (7 patients) and disorientation (4 patients) were the most common symptoms within the nervous/psychiatric system. Nausea (9 patients) and anorexia (7 patients) were most frequent within the digestive system complaints. The single most frequently reported clinical adverse experience among patients treated with TBZ was asthenia/fatigue, occurring in 11 (50%) of patients.

Analysis was also performed considering only those adverse clinical experiences considered by the investigators to be drug related (relationship of the clinical event to the study drug was rated as possibly, probably or definitely related). Using this definition, 3 of the 22 patients (14%) in the single-dose ivermectin group had one or more drug-related clinical adverse experiences compared to 5 of 24 patients (21%) of patients treated with two doses of ivermectin and 18 of 22 patients (82%) in the thiabendazole group. The difference between the two ivermectin groups was not significant ($p=0.70$) but the difference between each of the ivermectin groups and the thiabendazole group was significant ($p<0.001$ for each comparison).

Most of the clinical AEs were considered drug related (possibly, probably, or definitely) regardless of the treatment group. Eight of the 9 (89%) clinical AEs among both ivermectin treatment groups and 18 of the 19 (95%) of the thiabendazole group were considered drug related. Thus, all clinical AEs with the exception of the two deaths were considered related to study drug.

D. Safety (Cont.)

Two patients were considered to have had one or more serious clinical adverse experiences probably or definitely not related to study drug; both were in Study 014. [redacted], a 64-year-old male in the thiabendazole treatment group; died as a result of underlying pulmonary disease; the patient's death was considered to be definitely not related to thiabendazole therapy. This patient was scored as "Discontinued Treatment Because of Lack of Therapeutic Response/Death". [redacted] was a 70-year-old male with coronary artery disease and chronic pulmonary disease randomized to receive two doses of ivermectin. The patient died on Day 57 of study; the patient's death was considered definitely not related to ivermectin therapy by the investigator. Although this patient (014/012) completed his treatment course, he was scored as discontinued from study because of AE (death).

b. Serious Clinical Adverse Experiences

Two serious clinical adverse experiences occurred during the trial. Both events were patient deaths (Study 014, Both events were considered definitely not related to study drug. Clinical descriptions of these patients are provided in the preceding paragraph.

c. Patients Discontinued Due to Clinical Adverse Experiences

One patient (Study 014, treated with thiabendazole had study drug discontinued after 1 day of therapy due to a clinical adverse experience. The patient reported severe nausea and moderate tinnitus on the first day of thiabendazole administration considered by the investigator to be definitely related to study drug. The patient's symptoms resolved following discontinuation of treatment. Reference the above for (Study 014) concerning patients who completed treatment course but were scored as discontinued because of either "Death" or "No Therapeutic Response/Death", respectively.

D. Safety (Cont.)

2. Adverse Experiences - Laboratory

a. Overall Assessment of Laboratory Adverse Experiences

No patients in the single-dose ivermectin or two-dose ivermectin treatment groups were noted to have any laboratory adverse experiences. One patient (Study 015 treated with thiabendazole (1 of 22, 4.5%) had elevations of AST, ALT, and alkaline phosphatase, which all returned to normal without intervention. These laboratory abnormalities were considered by the investigator to be possibly related to therapy with thiabendazole.

b. Serious Laboratory Adverse Experiences

There were no serious laboratory adverse experiences during the course of this study.

c. Patients Discontinued Due to Laboratory Adverse Experiences

No patients required discontinuation of study drug due to a laboratory adverse experience.

3. Adverse Experiences - Other

There were no other adverse experiences.

4. Clinical Safety Measurements

No clinically significant changes in clinical measures of safety were noted.

5. Laboratory Safety Measurements

No consistent or significant changes in laboratory measures of safety were noted.

IV. DISCUSSION

Ivermectin is an 80:20 mixture of avermectin ß1a and ß1b, monocyclic lactones produced by the actinomycete *Streptomyces avermitilis*. While its mechanism of action is not fully understood, ivermectin appears to exert its activity by inducing a chloride current via a glutamate-gated channel in the parasite resulting in apparent paralysis and death [13]. It is an orally effective antiparasitic agent which has been used in veterinary medicine since 1981. Based on its efficacy and excellent safety profile, ivermectin has achieved widespread acceptance as the treatment of choice for onchocerciasis (river blindness) [3].

During trials aimed primarily at establishing ivermectin's efficacy in onchocerciasis, a number of uncontrolled observations suggested that ivermectin had significant activity against a number of gastrointestinal nematodes [14]. These clinical notes were consistent with the drug's activity in an animal model of strongyloidiasis [7]. Subsequently, noncomparative studies demonstrated that ivermectin is an effective agent against strongyloidiasis [8,9]. Based on these observations as well as the need for a more effective, less toxic therapy in strongyloidiasis, several studies, including this trial, were undertaken.

This comparative randomized trial establishes conditions for evaluation of ivermectin's efficacy in strongyloidiasis. All patients evaluated for efficacy had microscopically documented *S. stercoralis* infection and all subsequent follow-up stool examinations utilized a very sensitive technique for parasite detection. Because the study was carried out in areas with a low risk for patient re-infection, the follow-up period was longer than that used in most previously published therapy trials in strongyloidiasis.

Cure rates of 100% (single-dose ivermectin), 95% (two-dose ivermectin) and 94% (thiabendazole) were observed in evaluable patients, confirming ivermectin's activity in this infection. There is no evidence that there is an advantage to two doses vs. a single dose of ivermectin in this patient population. It is important to note that no patient was severely immunocompromised or had evidence of infection beyond the gastrointestinal tract. It is not possible to extrapolate from this trial to these other patient populations.

IV. DISCUSSION (CONT.)

Although efficacy did not differ among treatment groups, the incidence of clinical adverse experiences was substantially lower among patients receiving ivermectin. Three of 22 patients (14%) treated with single-dose ivermectin were considered to have had drug-related clinical adverse clinical events as compared to 5 of 24 patients (21%) assigned to the two-dose ivermectin group and 18 of 22 patients (82%) receiving thiabendazole. The difference between the two ivermectin groups was not significant but the difference between each of the ivermectin groups and the thiabendazole group was significant. Because this study was not conducted using methods to blind both patients and investigators to the therapy each patient received (i.e., all laboratory personnel involved in Baermann stool examinations were to be blinded), it is not possible to exclude some bias in reporting and interpretation of adverse events. Several points suggest that these results are not due to such bias. Similar patterns of clinical adverse experiences are present at both sites and so are not specific to the investigator. Furthermore, when all clinical adverse experiences are considered rather than only those felt to be drug related, a significantly higher incidence of adverse events are still found in patients treated with thiabendazole. This analysis is independent of any interpretation of events by the investigators. Lastly, side effects in patients treated with thiabendazole is consistent with other published reports [3,4].

In onchocerciasis, many of the adverse effects that occur after ivermectin treatment are a result of the patient's immune response (Mazzotti reaction) to dead microfilariae and usually appear within 3 days of the dose [15]. The severity of the response is directly related to the initial intensity of *O. volvulus* infection. The lack of Mazzotti-type reactions in this trial following treatment of strongyloidiasis is consistent with previous experience and would be predicted based on disease pathogenesis.

This study demonstrates that ivermectin is a well tolerated and effective therapy for strongyloidiasis limited to the gastrointestinal tract in immunocompetent patients. It is associated with significantly fewer clinical adverse reactions than thiabendazole with similar efficacy. Overall, the results of this trial suggest that ivermectin offers a significant advance in the treatment of strongyloidiasis.

V. CONCLUSIONS

1. Ivermectin (200 mcg/kg) as a single dose and as two doses on consecutive days and thiabendazole (25 mg/kg b.i.d. x 3 days) are effective therapy for strongyloidiasis of the gastrointestinal tract.

2. Ivermectin is generally well tolerated and associated with fewer clinical adverse experiences than thiabendazole.

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Medical officer comments:

D. Medical officer findings

Medical officer evaluation of enrolled patients by treatment group and patient number Berk 014/Gann 015

Patient #	Evaluable?	Reason/Comment	Cure?	Reason	# ▬ stools
Treatment arm: Ivermectin X 1					
Berk					
	yes		Yes	▬ stool to day 233	6
	yes		Yes	▬ stool to day 264	6
	yes		Yes	▬ stool to day 126	3
	yes		Yes	▬ stool to day 138	3
Gann					
	yes	lost to f/u till day +97	Yes	▬ stool to day 232	3
	yes		Yes	▬ stool to day 191	4
	yes		Yes	▬ stool to day 357	5
	yes		Yes	▬ stool to day 381	5
	no	pre-Rx stool > 60 days			
	yes		Yes	▬ stool to day 370	5
	yes		Yes	▬ stool to day 366	5
	yes		Yes	▬ stool to day 182	4
	yes		Yes	▬ stool to day 189	4
	yes		Yes	▬ stool to day 379	5
	no	lost to f/u			
	yes		Yes	▬ stool to day 186	4
	yes		Yes	▬ stool to day 296	5
	no	lost to f/u			
	yes		Yes	▬ stool to day 252	5
	yes		Yes	▬ stool to day 236	3
	yes		Yes	▬ stool to day 196	5
	no	only 2 stools post-Rx			
Totals	enrolled 22 evaluable 18		Cure 18 Fail 0		

Medical officer evaluation of enrolled patients by treatment group and patient number Berk 014/Gann 015 (con't)

Patient #	Evaluable?	Reason/Comment	Cure?	Reason	# ▬ stools
Treatment arm:	Ivermectin X 2				
Berk					
	yes		Yes	▬ stool to day 35	5
	no	no + stool recorded			
	no	no f/u past day 23			
	no	only 2 stools post-Rx			
	yes		Yes	▬ stool to day 28	3
Gann					
	yes		Yes	▬ stool to day 365	5
	yes		Yes	▬ stool to day 363	5
	yes		Yes	▬ stool to day 372	5
	yes		Yes	▬ stool to day 378	4
	yes		No	✚ stool day 35	
	yes		Yes	▬ stool to day 215	5
	yes		Yes	▬ stool to day 180	4
	yes		Yes	▬ stool to day 365	5
	yes		Yes	▬ stool to day 329	5
	yes		Yes	▬ stool to day 350	5
	yes		Yes	▬ stool to day 225	5
	yes		Yes	▬ stool to day 331	5
	yes		Yes	▬ stool to day 183	4
	yes		Yes	▬ stool to day 267	5
	yes		Yes	▬ stool to day 102	3
	yes		Yes	▬ stool to day 231	4
	yes		Yes	▬ stool to day 187	4
	yes		Yes	▬ stool to day 208	5
	no	no pre-Rx stool +			

Totals	Enrolled 24	Cure	19
	Evaluable 20	Fail	1

Medical officer evaluation of enrolled patients by treatment group and patient number
Berk 014/Gann 015 (con't)

Patient #	Evaluable?	Reason/Comment	Cure?	Reason	# ▬ stools
Treatment arm:	Thiabendazole				
Berk					
	yes		Yes	▬ stool to day 339	7
	yes		No	✚ stool day 39, 46	
	no	only 1 stool post-Rx			
	no	only 1 stool post-Rx			
	yes		No	✚ stool day 91	
	no	lost to f/u			
Gann					
	yes		Yes	▬ stool to day 348	5
	yes		Yes	▬ stool to day 363	5
	yes		Yes	▬ stool to day 381	5
	yes		Yes	▬ stool to day 387	5
	yes		Yes	▬ stool to day 360	5
	yes		Yes	▬ stool to day 351	5
	yes		Yes	▬ stool to day 238	5
	yes		Yes	▬ stool to day 354	5
	yes		Yes	▬ stool to day 307	5
	yes		Yes	▬ stool to day 82	3
	yes		Yes	▬ stool to day 298	5
	yes		Yes	▬ stool to day 268	5
	yes		Yes	▬ stool to day 304	5
	yes		Yes	▬ stool to day 94	3
	yes		Yes	▬ stool to day 221	4
	yes		Yes	▬ stool to day 235	5

Totals:	Enrolled 22	Cure 17
	Evaluable 19	Fail 2

Study 014 (Berk)/ 015 (Gann)
Results per Medical Officer

		Ivermectin X 1		Ivermectin X 2		Thiabendazole	
		Berk	Gann	Berk	Gann	Berk	Gann
Enrolled, Total		4	18	5	19	6	16
Evaluable per M.O.		4	14	2	18	3	16
Cure at day 30		4	14	2	17	3	16
Fail at day 30		0	0	0	1	0	0
Cure at day 90		4	14	n/a	17	1	16
Fail at day 90		0	0	n/a	0	2	0
TOTALS (day 90)	Cure (%)	18/18 (100%)		17/18 (94%)		17/19 (89%)	
	Fail (%)	0		1/18 (6%)		2/19 (11%)	

Medical officer findings: safety

The applicant's summary of safety results for these combined studies is found on (applicant's) pages D-3012-17. In this, the applicant reports that there were 3 clinical ADE's in the single-dose ivermectin arm, 6 in the two-dose ivermectin arm, and 19 in the thiabendazole arm; this was reported to be a statistically significant difference between each of the ivermectin groups and the thiabendazole group.

The computerized patient listing for these adverse events was reviewed and compared with the tabular presentation found in the applicant's summary. The results as presented in Tables 10 and 11 of that summary were found to be consistent with the computerized patient listings. As can be seen in Table 11, the most commonly affected organ system in these clinical adverse events was skin and skin appendages in the ivermectin-treated patients, and nervous system and digestive system in the thiabendazole-treated patients.

As can be seen in Applicant's Table 10, there were two deaths and one discontinuation in these combined studies. (All three of these events were among the subjects enrolled by Dr. Berk.) Although information is given on these subjects in the text of the study summary, the case report forms for these three study subjects were not submitted with the NDA.

The patient population enrolled by Dr. Berk was considerably older and had many more co-morbidities than did the population of Cambodian immigrants enrolled by Dr. Gann. Thus is is not surprising to see these adverse outcomes predominantly in this group of enrollees. A brief synopsis of these 3 cases follows:

Early discontinuation:

Patient [redacted] Berk: a 59 year old white male with pre-existing hypertension, hemiparesis, s/p cerebrovascular accident, and a history of alcohol abuse. Patient randomized to thiabendazole and had severe nausea on the first day of drug administration. He also had moderately severe tinnitus. Both of these events were considered to be definitely related to thiabendazole administration and the patient was withdrawn from the study.

Death:

Patient [redacted] Berk: a 64 year old white male with COPD and prostate cancer, being treated concomitantly with multiple medications including steroids. This patient was treated with an initial three-day course of thiabendazole, with stools converting from 4+ positive to negative for *Strongyloides* larvae on days 10 and 25 post-therapy. He then was found to have larvae in the stool on day 39 post-therapy, and was started on a second course of thiabendazole on day 44. He completed this course of therapy. No further stools are recorded in the computerized listings, but the patient expired on study day 84, reportedly from his underlying pulmonary disease. The death was considered to be 'definitely not related' to study drug administration. (It is unclear whether this patient died of or with disseminated strongyloidiasis.)

Patient [redacted] Berk: a 70 year old white male with underlying coronary artery disease and COPD who was not taking concomitant steroids, randomized to the two-dose ivermectin arm. His stools were free of *Strongyloides* larvae by day 3 post-therapy and were negative on three further exams. The patient died on day 57 of study. The precise nature of this death is not clear from the study report, but the investigator stated that it was 'definitely not related' to study drug. A review of this patient's laboratory values only presents lab data from study days 1 and 9, even though the death was considered to have occurred while on study.

Laboratory adverse events which were considered worthy of mention by the investigator(s) include a single event in patient [redacted] a Gann patient in the thiabendazole arm who was found to have transaminase and alkaline phosphatase elevations on day 9 post-therapy that were 'possibly' drug-related. Upon review of these line listings, the following additional perturbations were noted:

Subject #	lab finding (day of study)	Comments
Ivermectin X 1		
Berk	serum creatinine 1.1→ 1.8 (d7)	
Gann	alkaline phosphatase 59→ 112 (d8)	
Gann	alkaline phosphatase 34→ 147 (d7)	
Gann	ALT 36→ 110 (d10)	
Ivermectin X 2		
Gann [redacted]	ALT 33→ 66 (d12)	
Thaibendazole		
Gann	alkaline phosphatase 111→ 218 (d7)	
Gann	AST 49→ 126 (d9) ALT 37→ 153 (d9) alkaline phosphatase 52→ 150 (d9)	As mentioned in applicant's summary

As can be seen from the above data, this study also reveals minor perturbations in transaminases and alkaline phosphatase levels but nothing else of note. It should be noted that the great majority of these patients only had post-therapy labs included from day 7-10, and nothing thereafter. This is of some concern, particularly in the case of the one patient (Berk [redacted]) who was considered to have died while in the study. No laboratory data from the time approaching the patient's ultimate demise is included in the computerized listings.

E. Conclusions

6. "WHO Study": A comparative trial of a single dose Ivermectin versus 3 days of albendazole for treatment of *Strongyloides stercoralis* and other soil transmitted helminth infections in children.

A. Study summary

This is a trial conducted under the auspices of the WHO in two villages on the island of Zanzibar, off the eastern coast of Africa. The applicant supplied study medication in the form of scored 6 mg tablets of ivermectin, which was dosed at 200 µg/kg as a single dose. The comparator drug, albendazole, was dosed at a fixed 400 mg qd for three days.

Although this study is submitted by the applicant as one of the 'pivotal' adequate and well-controlled investigations in support of the proposed product labelling for ivermectin, no primary patient data is submitted. The submission consists of a 20-page manuscript that has been submitted for publication in the American Journal of Tropical Medicine and Hygiene. (NB: subsequent to the filing of NDA 50-742, the applicant has reported that this manuscript has been accepted for publication in that same journal.) The applicant maintains that the patient-level data are not controlled by Merck, since the study was conducted not by Merck but by the WHO.

Study setting: two primary schools in two villages located in northern Zanzibar
Time of study: October to December 1994
Entry criteria:

- male and female students ≥ 10 years old, including schoolteachers
- oral informed consent
- stool positive by Baermann technique for larvae of *S. stercoralis*

Exclusion criteria:

- No consent
- fever or other signs of acute illness
- severe neurologic disorder
- severe liver disorder
- pregnancy

Randomization: a randomized list of sequential allocation was prepared in advance. After entering the trial, individuals were weighed and given their respective treatment, with either ivermectin at a dose of 200 µg/kg or the first dose of albendazole at a dose of 400 mg. Both drugs were administered in the presence of a study monitor with water. The subjects randomized to albendazole were given the subsequent daily doses under direct supervision so that compliance with the three-day regimen was assurred.

Medical officer comments: no information is presented to describe which weight ranges were administered which combinations of whole and half-tablets. For comparison to other studies submitted in support of this indication, it is important to know whether subjects of similar weights were dosed in a similar fashion. Also, the absorption of albendzole is significantly affected by co-administration with food. Since it is unclear whether anthelminthic activity against intestinal parasites is correllated with serum levels as opposed to intraluminal levels of albendazole (or metabolites), the importance of taking the comparator with vs. without food cannot be determined.

The applicant was asked to provide this information, and in response a fax was received by this medical officer on 26 August 1996. The following dosing information was provided by the principal investigator, Dr. H. Marti:

Patient weight (kg)	*Number of 6 mg tablets*
15 to 24	*½*
25 to 35	*1*
36 to 50	*1½*
51 to 65	*2*
66 to 79	*2½*
80 and over	*3*

This dosing schedule is identical to that used in the Dreyer, Berk, and Gann studies but is different from the schedule utilized in the Gentilini study. (The Gentilini dosing schedule caused an inadvertent underdosing in the ivermectin-treated subjects, who received on average 169 µg/kg rather than the targeted 200 µg/kg dose.)

In this same fax, Dr. Marti reaffirmed that both study medications were dosed with water only; therefore there was no food effect on drug absorption

Follow-up: subjects were queried regarding medication side-effects at day 3 of the study, using a questionnaire identical to that used at baseline. Three weeks following the first day of therapy, subjects were given a stool specimen container and instructed to return the following morning with a freshly-collected specimen. Upon submission of this specimen, the subjects were questioned again regarding side effects of medication, using the same questionnaire as previously. Each subject was then given another container and told to submit a second specimen the following day.

Endpoints: Subjects were considered cured if they had no evidence of *Strongyloides* larvae in both follow-up stool specimens, by Baermann technique. Individuals who did not provide both follow-up specimens were excluded from the efficacy analysis.

B. Applicant's findings

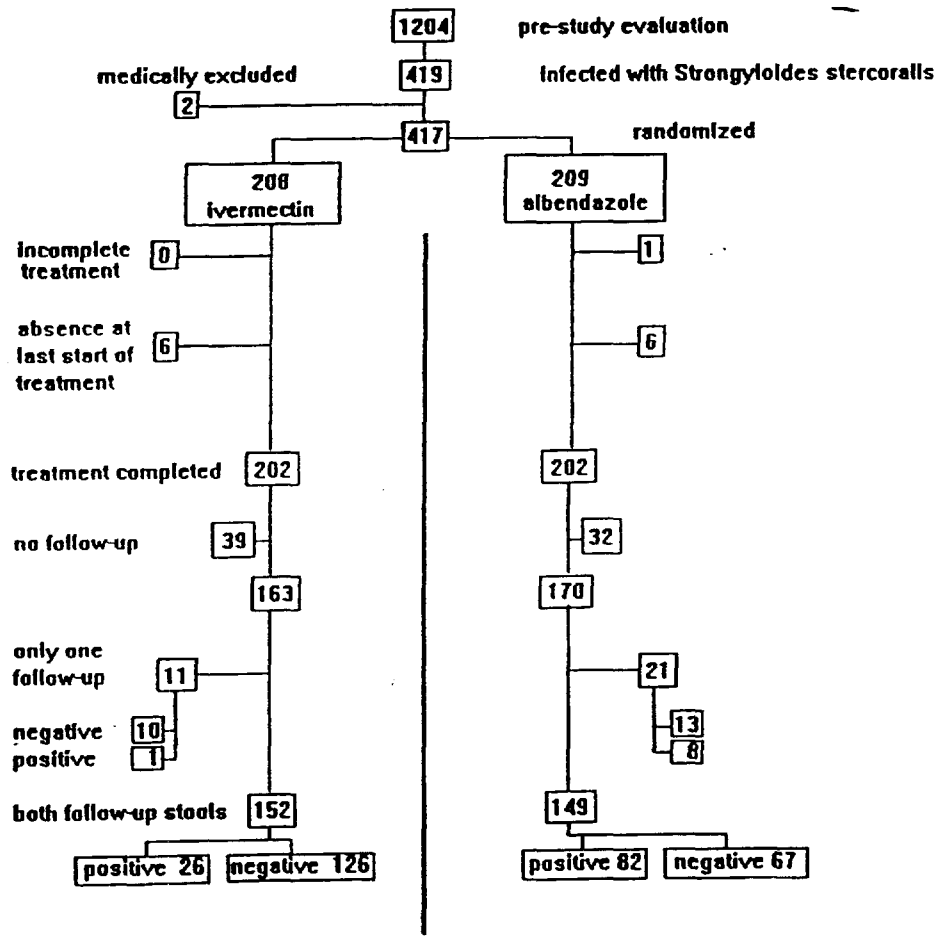
The applicant's findings are summarized in the ***Results*** section of the submitted manuscript, which begins on page D-3560 of volume 1.24 of the NDA. The following table, taken from this manuscript, presents the demographics and disposition of the subjects enrolled in this study:

Demographics and Disposition of Enrolled Subjects, WHO (Marti) study

Patients examined Males (age range 9-22 years) Females (age range 9-19 years)		545 (45.3%) 659 (54.7%)	
Pre-study evaluation		1204	
Patients infected with *S. stercoralis* Males Females		419 (34.8%) 207 (49.4%) 212 (50.6%)	
Excluded for medical reasons		2 (0.5%)	
	Treatment		
	Ivermectin	Albendazole	Total
Eligible for trial	208	209	417
Incomplete questionnaire or treatment, or Absence at last start of treatment	45	39	84
Evaluable for safety	163	170	333
Evaluable for efficacy (both follow-ups completed) Males Females	152 58 (38.2%) 94 (61.8%)	149 67 (45%) 82 (55%)	301 125 (41.5%) 176 (58.5%)

Medical officer comments: in reviewing the submitted manuscript, it is impossible to determine the precise accountability of all subjects randomized in this trial. For example, how many were excluded from analysis because of incomplete therapy? What does 'absence at last start of treatment' mean? How many patients were excluded form analysis because they presented with one positive follow-up stool, but did not have a second one collected? This question was asked of the applicant, who relayed it to the investigator. Dr. Marti supplied the following diagram in his fax communication of 26 August 96:

Subject allocation in Marti study, Zanzibar



As can be seen in this diagram, the investigator states that of the subjects who submitted one, but not the second, follow-up stool for examination, 10/11 were negative in the ivermectin arm versus 13/21 negative in the albendazole arm.

The efficacy results, as reported in the study manuscript, are presented in the following table (the results for the other intestinal parasitic infections are not included since they are not relevant to the NDA currently under review):

Applicant' s Efficacy Results, WHO (Marti) study

	Cure rate	
Parasite species	Ivermectin	Albendazole
Strongyloides stercoralis	82.9% (126/152)	45% (67/149)

Medical officer comment: the denominator in these cure rates is the number of subjects in each arm who returned for both follow-up stool analyses. If the subjects who presented for one follow-up stool are included, the rates become 83.4 % (136/163) for ivermectin, and 47.1% (80/170) for albendazole. Thus, the comparative results are not changed by the applicant's evaluability requirement of two documented follow-up stools.

It should be kept in mind that these efficacy data are base on a three-week post-therapy follow-up timepoint. As such, this is the shortest duration of post-therapy follow-up of any of the submitted studies in this portion of the NDA. The other study to be conducted in an endemic area (the Dreyer study, which was conducted in Brazil) attempted to gather follow-up stool samples at 30, 90, and 180 days post-therapy. Because of concerns over possible re-infection of study subjects, the 30-day endpoint was considered acceptable for this study (with a range of 26-34 days post-therapy). The Marti study pushes this primary study endpoint up to 21 days post-therapy.

The safety data presented in this study were generated by questionnaires that were completed for all study subjects at the time of enrollment, at the time of treatment, and three days following the start of treatment (which for the albendazole group would have been while still on therapy). Further safety information was collected by questionnaire at the three-week timepoint as well.

The treatment-emergent signs and symptoms, as shown in Table 5 of the submitted manuscript (page D-3573 of volume 1.24 of the NDA), are presented below (the table in the manuscript is entitled "Number of patients developing new signs and symptoms within three days after treatment [Adverse effects]"):

Applicant's Safety Results, WHO (Marti) Study

Symptom	Albendazole (N = 170)	Ivermectin (N = 163)
Abdominal distention	1	7‡
Chest pain/tightness	0	7‡
Loose stools	17	16
Headache	18	15
Cough, not with cold	8	11
Fever	7	10
Dizziness, vertigo	10	5
Nausea	6	5
Diffuse itching	6	3
Watery diarrhoea	3	2

‡ $p < 0.05$

C. Medical officer findings

The medical officer review of this submitted study, which the applicant considers 'pivotal' to the approval of this indication, must be confined to a critical reading of the manuscript. The applicant was unable to provide any source documentation from this study, since it was conducted under the auspices of the WHO rather than Merck Research Laboratories. The applicant participated in the conduct of the study only insofar as provision of study drug (ivermectin) was concerned.

In a sense, then, despite the fact that the applicant considers this study to be 'pivotal' to the strongyloidiasis indication, this clinical data is no different than the section of the NDA which provides literature references which support the approval of ivermectin for the strongyloidiasis indication (reviewed below). In fact, this study has not yet been published in a peer-reviewed journal whereas the remaining literature submitted has, at the very least, been scrutinized in this manner.

Medical officer comment: shortly after this NDA was submitted, the applicant informed DAIDP that the manuscript, which Dr. Marti had submitted for publication in November 1995, had been accepted for publication in the American Journal of Tropical Medicine and Hygiene. However, as the deadline for action on this NDA approaches, the paper has yet to appear in this journal. The medical officer thus took the liberty of calling Dr. McWilson Warren, editor-in-chief of the aforementioned journal, on 29 August 1996. Dr. Warren confirmed that the manuscript had been accepted for publication, and that the two peer reviewers had provided editorial comments but that the actual data presented in the manuscript was identical to that which was to go to press. He anticipated the appearance of the Marti paper in the December 1996 issue of the American Journal of Tropical Medicine and Hygiene.

If the reader refers back to the table on page 4 of this review, in which an overview of the submitted clinical studies is presented, it can be seen that the Marti study is, numerically, the study on which the strongyloidiasis indication rests. In terms of total patients randomized, the Marti study includes 417/591 or 71% of the subjects studied in this portion of the NDA.

Methodologically, the Marti study is similar enough to the other studies to allow for pooling of the efficacy data, particularly since Baermann analysis was used for all stool processing. However, there are two major methodologic differences between this study and the other four reviewed above:

- test-of-cure stool examination was done at three weeks post-initiation of therapy and at no other time; and
- cure/fail was determined on the basis of two stools collected within a few days of each other.

The reader will recall that, even in the other study performed in an endemic area (Dreyer, conducted in Brazil), a day 30 stool collection was considered acceptable by the medical officer if there were a total of 3 post-therapy stool collections documenting clearance of *Strongyloides* larvae from the stool. One would expect such a study as Marti to have a range of actual dates of stool collection, varying around the targeted three-week timepoint; thus, some of the submitted specimens were undoubtedly collected earlier than day 21 of the study. Since patient level data was not available for medical officer review, no further comment can be made.

D. Conclusions

The Marti study provides evidence of the short-term efficacy of single-dose ivermectin in the treatment of intestinal strongyloidiasis. Even though the test-of-cure (TOC) endpoint was shorter than in all the other submitted studies, the observed comparative efficacy of ivermectin versus albendazole makes it highly likely that a similar difference would have been seen had the TOC stool samples been collected one week later. Furthermore, the sensitivity of the TOC would have been improved had a third stool been collected in the post-therapy follow-up period. Unfortunately, this study did not incorporate a thiabendazole arm for active comparison with the agent currently approved for this indication in the US. Despite these shortcomings, this study is an important component of the the NDA submission because of the large number of subjects enrolled and the substantially higher degree of efficacy demonstrated as compared to the active control, albendazole.

7. Overview of literature references submitted in support of strongyloidiasis indication.

A. Applicant's findings

The applicant has submitted a total of 13 literature references in support of the strongyloidiasis indication. These references are broken down into compassionate treatments (4 references), anecdotal treatments (2 references), and non-applicant-sponsored treatment studies (7 references).

The applicant's summary of this literature, as found on pages D-3580-90 of volume 1.24 of the NDA, follows:

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The purpose of this document is to summarize information appearing in the literature that can be used to further support the use of ivermectin in the treatment of strongyloidiasis of the gastrointestinal tract. The information, as published, deals with the use of ivermectin in compassionate treatments, anecdotal treatments (i.e., patients whose strongyloidiasis was treated secondarily to a primary treatment concern, e.g., treatment for onchocerciasis) or non-MRL-sponsored treatment studies. In general, there were no safety problems encountered in the various citations covered that differed from what is presented in the safety analysis of ivermectin treatment of patients within stronglyloidiasis in this NDA. Thus, this summary deals only with presentation of efficacy data that supports the claim for the use of ivermectin in the treatment of *S. stercoralis* infection of the gastrointestinal tract.

In addition to citing references to the primary claim sought, this summary includes additional case reports dealing with disseminated *S. stercoralis* infections. However, these cases are presented for "information purposes" only since a claim is not being sought for this indication.

Many of the publications are in a foreign language; however, English summaries are provided for those citations that are used. Numbers in [ ] refer to the references that are attached to this report.

Following the summaries of the published communications there is a table that summarizes information obtained from these publications regarding the efficacy of ivermectin in the treatment of strongyloidiasis of the gastrointestinal tract.

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A. Compassionate Treatments [1 - 4]

Four compassionate treatments using ivermectin in the treatment of strongyloidiasis appear in the literature.

One patient (a 51-year-old male with Cushing's syndrome) previously underwent 3 successive 10-day courses of albendazole treatment, each with relapse. Ivermectin treatment (12 mg per day for 2 days) eliminated the parasites with findings still negative at one year follow-up. [1]

A 32-year-old female (former drug addict) with HIV presented with disseminated strongyloidiasis that was resistant to thiabendazole. The patient received a single dose of ivermectin (150 mcg/kg); however, intestinal obstruction was present along with severe electrolyte imbalance. These symptoms worsened and diffuse mesenteric adenopathy was found at laparotomy. The patient died of septic shock (*Pseudomonas aeruginosa)* with meningitis. The outcome of ivermectin treatment in this patient could not be determined. [2]

A 45-year-old male with strongyloidiasis that was resistant to various antiparasitic agents received multiple-dose ivermectin. The patient was given an initial dose of ivermectin 12 mg; after 1 week the parasite burden was reduced. The same dose of ivermectin was then given on 2 consecutive days. No parasites were detected in stool samples during 14 months of follow-up. [3]

A 40-year-old man who was unsuccessfully treated with thiabendazole every 3 - 4 months over an 8-year period was given a single dose of ivermectin (200 mcg/kg). Stool samples were clear of all larvae in 48 hours and remained negative for at least one year after ivermectin therapy. [4]

B. Anecdotal Treatments [5 - 6]

During a mass treatment program of onchocerciasis with ivermectin in the rain forest zone of Cameroon, 20 patients were found to have coincidental strongyloidiasis of the gastrointestinal tract. Based on examination of stools 1 month after treatment, ivermectin (single dose of 150 mcg/kg) provided a cure rate of 100% for stronglyloidiasis. [5]

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B. Anecdotal Treatments [5 - 6] (Cont.)

In a pilot study to determine the efficacy of single-dose ivermectin in the treatment of human gastrointestinal helminthiasis in a hyperendemic area of Central America, 12 randomly selected adults received a single-dose treatment of ivermectin (140 - 200 mcg/kg). Prior to treatment, 3 of the 12 subjects had *Strongyloides stercoralis* infestation; based on examination of stools 1 month following administration of ivermectin, all 3 were successfully treated. [6]

C. Non-MRL-Sponsored Treatment Studies [7 - 13]

One series involved 9 HIV-infected men, including 5 with AIDS-defining conditions, with evidence of strongyloides hyperinfection, who received either a single-dose ivermectin treatment (150-200 mcg/kg in 2 of 9 patients) or multiple doses of ivermectin (200 mcg/kg on Days 1, 2, 15 and 16 in 7 of 9 patients). All 7 patients who received multiple doses of ivermectin experienced sustained clinical and parasitological cures of their Strongyloides infections. One of 2 patients who received single-dose ivermectin relapsed on day 30 with both general, respiratory, and GI symptoms. This patient refused further treatment with ivermectin and died 4 days later with symptoms suggestive of sepsis and/or disseminated strongyloidiasis. The remaining 8 patients remained in remission during follow-up periods from 7 months to 3 years. [7]

In a second study, 70 patients (41 males and 29 females) with strongyloidiasis of the gastrointestinal tract were treated with ivermectin (6 mg on day one and another 6 mg 2 weeks later). The eradication of *S. stercoralis* was found in 60/68 (88.2%) 13 days after the first dose (i.e., prior to dose 2); in 59/65 (90.8%) 13 days after dose 2; in 49/54 (90.7%) 1-2 months later; in 47/47 (100%) 3-4 months later; and in 45/47 (95.7%) 5-6 months later. Comparison of patients who responded to those who did not respond showed significant differences between the groups in the amount of pre-existing symptoms, anti-HTLV-I, eosinophil count, and IgE. [8]

In a third study, in a highly endemic area of *S. stercoralis* infection, 23 patients with positive stool cultures for *S. stercoralis* were treated with ivermectin (single 6-mg tablet on day one followed by a 6-mg tablet 2 weeks later). Two weeks after the single treatment, and prior to dose 2, parasitological eradication occurred in 18 of 21 patients (85.7%). Two weeks after the second ivermectin dose one more patient showed parasitological eradication. [9]

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C. Non-MRL-Sponsored Treatment Studies [7 - 13] (Cont.)

In another clinical study, a series of 125 patients with strongyloidiasis of the gastrointestinal tract (78 males and 47 females) were treated with ivermectin 6 mg on day 1 followed by 6 mg on day 14. Parasitological eradication was achieved in 108 of 125 patients (86.4%). Of the 17 patients who showed persistence, 8 received a further course of ivermectin and all *S. stercoralis* in their feces was eradicated. It was noted by the authors that the positive rate of anti-HTLV-I in the resistant group was significantly higher (80.0%) than in the eradicated group (29.2%). **[10]**

A series of 54 patients (28 males and 26 females) in another study received ivermectin (6 mg on day 1 followed by 6 mg on day 14) for strongyloidiasis of the gastrointestinal tract. For the patients with follow-up stool examinations, the cure rate at 2 weeks after dose one (i.e., prior to dose 2) was 49 of 53 patients (92.5%) and at 2 weeks after the second dose was 48 of 50 patients (96.0%). **[11]**

An open trial of 100 patients with *S. stercoralis* infection of the gastrointestinal tract (57 males, 43 females, ages 3 - 94 years) was done comparing ivermectin to albendazole. Patients were treated with single-dose ivermectin (200 mcg/kg; N=53) or albendazole (400 mg for 3 days; N = 47). Efficacy was evaluated in 85 patients and cure rates were 42 of 43 patients in the ivermectin group (97.7%) versus 37 of 42 in the albendazole group (88.1%). The 6 treatment failures (1 ivermectin and 5 albendazole) were re-treated with ivermectin and were cured. **[12]**

In a series of 114 patients in Bangui, Central African Republic (56 males and 58 females, age range 5 to 70 years, mean age 26.3 some with mixed parasitic infestations but the majority with single parasitic infestations [strongyloidiasis, ascariasis and/or ancylostomiasis]), 53 patients (46%) were shown to have strongyloidiasis. All patients received a single dose of ivermectin (200 mcg/kg) and follow-up parasitology was evaluated at 7-10 days posttreatment and again at 15 days posttreatment. Patients with strondyloidiasis had negative stool examinations at both time points **[13]**.

Summary of Published Information That Supports the Use of Ivermectin in the Treatment of Strongyloidiasis of the Gastrointestinal Tract

INFO. TYPE	REFERENCE [ ]*	IVERMECTIN DOSE	CURE RATE (%)	COMMENT
COMPASSIONATE TREATMENT	1	12 mg/day x 2 days	1/1 (100)	Subject with Cushing's syndrome previously underwent 3 failures with albendazole
COMPASSIONATE TREATMENT	3	12 mg/day x 1 day + 12 mg/day x 2 days	1/1 (100)	After second treatment, definite cure with 14 mo. posttreatment follow-up
COMPASSIONATE TREATMENT	4	1 x 200 mcg/kg	1/1 (100)	Chronic strongyloidiasis unsuccessfully treated with TBZ over an 8-year period was cured with neg. stools for at least 1 yr. post therapy.
ANECDOTAL TREATMENT	5	1 x 150 mcg/kg	20/20 (100)	Data collected during mass treatment of onchocerciasis with ivermectin in Cameroon. Twenty patients had coincidental strongyloidiasis of the gastrointestinal tract.

* References [2] and [7] are excluded from this summary since they represent, respectively, treatments of disseminated disease and hyperinfection.

Summary of Published Information That Supports the Use of Ivermectin in the Treatment of Strongyloidiasis of the Gastrointestinal Tract (Cont.)

INFO. TYPE	REFERENCE [ ]*	IVERMECTIN DOSE	CURE RATE (%)	COMMENT
ANECDOTAL TREATMENT	6	140-200 mcg/kg	3/3 (100)	Three of 12 randomly selected adults in a hyperendemic area of Central America were positive for *S. sterocoralis* and treated with ivermectin (140-200 mcg/kg).
TREATMENT STUDIES	8	6 mg on Day 1 + 6 mg on Day 14		Stool examination at:
			60/68 (88)	13 days Postdose 1
			59/65 (91)	13 days Postdose 2
			49/54 (91)	1 - 2 months Postdose 2
			47/47 (100)	3 - 4 months Postdose 2
			45/47 (95.7)	5 - 6 months Postdose 2

* References [2] and [7] are excluded from this summary since they represent, respectively, treatments of disseminated disease and hyperinfection.

Summary of Published Information That Supports the Use of Ivermectin in the Treatment of Strongyloidiasis of the Gastrointestinal Tract (Cont.)

INFO. TYPE	REFERENCE [ ]*	IVERMECTIN DOSE	CURE RATE (%)	COMMENT
TREATMENT STUDIES	9	6 mg on Day 1 + 6 mg on Day 14	18/21 (86) 19/21 (90)	Stool examination at: Prior to Dose 2 Two weeks after Dose 2
TREATMENT STUDIES	10	6 mg on Day 1 + 6 mg on Day 14	108/125 (86)	8 of 17 who failed received an additional course of ivermectin and all 8 were cured
TREATMENT STUDIES	11	6 mg on Day 1 + 6 mg on Day 14	49/53 (92) 48/50 (96)	Stool examination at: Prior to Dose 2 Two weeks after Dose 2

* References [2] and [7] are excluded from this summary since they represent, respectively, treatments of disseminated disease and hyperinfection.

Summary of Published Information That Supports the Use of Ivermectin in the Treatment of Strongyloidiasis of the Gastrointestinal Tract (Cont.)

INFO. TYPE	REFERENCE [ ]*	IVERMECTIN DOSE	CURE RATE (%)	COMMENT
TREATMENT STUDIES	12	1 x 200 mcg/kg	42/43 (98)	Ivermectin treatment Albendazole (400 mg x 3 days) was the comparative agent in this trial and achieved a cure rate in 37 of 42 patients (88%). The six treatment failures (one ivermectin and five albendazole) were retreated with ivermectin and were cured.
TREATMENT STUDIES	13	1 x 200 mcg/kg	53/53 (100)	Follow-up stool exams conducted 7-10 days and 15 days posttreatment.

* References [2] and [7] are excluded from this summary since they represent, respectively, treatments of disseminated disease and hyperinfection.

REF #	CITATION
1	Loutan, L., Goumaz, M. and Gaillard, R. C. TRAITEMENT AVEC L'IVERMECTINE D'UNE HYPERINFESTATION A STRONGYLOIDES STERCORALIS CHEZ UN PATIENT AVEC SYNDROME DE CUSHING <TREATMENT OF A STRONGYLOIDES STERCORALIS HYPERINFESTATION WITH IVERMECTIN IN A PATIENT WITH CUSHING'S SYNDROME> *Schweiz. Med. Wochenschr.* 123(24): 1275, June 19, 1993 (French not translated; however, English summary provided, in Soc. Proc.)
2	Couprie, R., Maslo, C., Bouchaud, O., Matheron, S., Saimot, A. G. and Coulaud, J. P. ANGUILLULOSE DISSEMINEE AU COURS DE L'INFECTION PAR LE VIH: UNE NOUVELLE OBSERVATION <DISSEMINATED STRONGYLOIDIASIS IN A PATIENT WITH HIV INFECTION: A NEW CASE> *Presse Med.* 22(20): 968, June 5, 1993 (In Letters - French not translated; however, English summary provided)
3	Lyagoubi, M., Datry, A., Mayorga, R., Brucker, G., Hilmarsdottir, I., Gaxotte, P., Neu, D., Danis, M. and Gentilini, M. CHRONIC PERSISTENT STRONGYLOIDIASIS CURED BY IVERMECTIN *Trans. Roy. Soc. Trop. Med. Hyg.* 86(5): 541, Sept.-Oct. 1992 (In Short Reports)
4	de S. Wijesundera, M. and Sanmuganathan, P. S. IVERMECTIN THERAPY IN CHRONIC STRONGYLOIDIASIS. *Trans. Roy. Soc. Trop. Med. Hyg.* 86(3): 291, May-June 1992 (In Short Reports)
5	Moyou, S. R., Enyong, P. A. and Agnamey, P. RESULTS OF MASS IVERMECTIN TREATMENT ON THE ENDEMIC HELMINTHIASIS IN THE RAIN FOREST ZONE OF SOUTH WEST CAMEROON *Acta Leiden.* 59(1-2): 466, 1990 (Abstract in Soc. Proc.)

REF #	CITATION
6	Freedman, D. O., Zierdt, W. S., Lujan, A. and Nutman, T. B. THE EFFICACY OF IVERMECTIN IN THE CHEMOTHERAPY OF GASTROINTESTINAL HELMINTHIASIS IN HUMANS *J. Infect. Dis.* 159(6): 1151-1153, June 1989 (In Communications)
7	Torres, J. R, Isturiz, R., Murillo, J., Guzman, M. and Contreras, R. EFFICACY OF IVERMECTIN IN THE TREATMENT OF STRONGYLOIDIASIS COMPLICATING AIDS *Clin. Infect. Dis.* 17(5): 900-902, Nov. 1993
8	Shikiya, K., Zaha, O., Niimura, S., Nakamura, H., Nakayoshi, T., Kochi, A., Uehara, T., Uechi, H., Ohshiro, J., Kinjo, F. and Saito, A. IVERMECTIN NI YORU CHIRYOH NI TEIKOHSHITA FUNSENCHUUSHOHKANSHA NO KENTOH <IVERMECTIN AND DRUG-RESISTANCE IN PATIENTS WITH STRONGYLOIDIASIS> *Kansenshogaku Zasshi* 66(7): 935-943, July 1992 (Jap. with Engl. sum. Not translated)
9	Shikiya, K., Kinjo, N., Uehara, T., Uechi, H., Ohshiro, J., Arakaki, T., Kinjo, F., Saito, A., Iju, M. and Kobari, K. EFFICACY OF IVERMECTIN AGAINST STRONGYLOIDES STERCORALIS IN HUMANS *Intern. Med. Jpn.* 31(3): 310-312, Mar. 1992
10	[Clinical study on ivermectin against 125 strongyloidiasis patients] Shikiya K; Zaha O; Niimura S; Uehara T; Ohshiro J; Kinjo F; Saito A; Asato R. *Kansenshogaku Zasshi* Jan 1994, 68 (1) p13-20,
11	[Clinical study on ivermectin against Strongyloides stercoralis] Shikiya K; Uehara T; Uechi H; Ohshiro J; Arakaki T; Oyakawa T; Sakugawa H.; Kinjo F; Saito A; Asato R. *Kansenshogaku Zasshi* Sep 1991, 65 (9) p1085-90,

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REF #	CITATION
12	Scaglia, M., Gatti, S., Bruno, A., Bernuzzi, A. M., Cevini, C. and Gaxotte, P. IVERMECTIN VS ALBENDAZOLE IN THE TREATMENT OF STRONGYLOIDIASIS IN ITALIAN PATIENTS Am. J. Trop. Med. Hyg. 49(3, Suppl.): 262-263, Sept. 1993 (Abstract in Soc. Proc.)
13	Testa J, Kizimandji-Coton G, Delmont J, Di Costanzo B and Gaxotte P TRAITEMENT DE L'ANGUILLULOSE, DE L'ASCARIDIOSE ET DE L'ANKYLOSTOMIASE: PAR L'IVERMECTINE (MECTIZAN) A BANGUI (RCA) [TREATMENT OF STRONGYLOIDIASIS, ASCARIASIS AND ANCYLOSTOMIASIS WITH IVERMECTIN (MECTIZAN) IN BANGUI (CAR)] Med Afr Noire 37(5): 283-284, 1990 (French only. Not translated Only English summary)

B. Medical officer findings

1. Studies designed specifically to investigate strongyloidiasis

There are several studies in the literature which specifically examine the efficacy of ivermectin in the therapy of strongyloidiasis, in both immunocompromised as well as immunologically intact subjects.

Reference: Torres, J.R., et al. Efficacy of ivermectin in the treatment of strongyloidiasis complicating AIDS.
Source: Clin Infect Dis 17(5): 900-2, 1993.
Type of study: open-label, compassionate use series
Treatment arms: Single-dose 150-200 mcg/kg, N = 2
Multi-dose 200 mcg/kg on days 1,2,15, and 16, N = 7
Number of patients: 9
Method of diagnosis: Baermann technique of stools (N = 9); sputum examination (N = 3)
Follow-up timepoints: at least seven months; up to three years
Results: One patient with a CD4 count of 358 cells/mm3 and no evidence of disseminated infection was treated with a single dose and was cured; the other single-dose patient had a CD4 count of 52 cells/mm3 and evidence of disseminated disease (larvae in sputum); he refused further therapy and died with disseminated strongyloidiasis. The other seven patients were treated with multiple dose therapy. All were cured of their strongyloidiasis, including two other patients with larvae in sputum and CD4 counts below 100/mm3.
Comments: although open-label and compassionate in design, this study is of value because it utilizes Baermann technique for stool examination, and provides prolonged follow-up of all subjects. It is also a remarkable paper in light of the fact that immunosuppressed patients with disseminated strongyloidiasis have, in general, a very poor clinical response to thiabendazole. The results of the Torres study cited here should be compared to the recent review of the literature done by Celedon et al (Systemic strongyloidiasis in patients infected with the human immunodeficiency virus: a report of three cases and review of the literature. Medicine 73(5): 256-63, 1994) which documents 14 cases of HIV-associated strongyloidiasis, 12 of whom died despite therapy with multiple, often prolonged, courses of thiabendazole.

Reference: Scaglia M et al. Ivermectin vs. Albendazole in the treatment of strongyloidiasis in Italian patients.
Source: Abstract from 1993 annual meeting of the American Society of Tropical Medicine and Hygiene, in Am J Trop Med Hyg 49 (3, supplement): 262-3, 1993.
Type of study: open-label
Treatment arms: Ivermectin 200 mcg/kg single dose, N = 53
Albendazole 400 mg qd X 3, N = 47
Number enrolled: 100 patients with 'uncomplicated' strongyloidiasis
Method of diagnosis: 'coproparasitological exam' of fixed stool samples
Follow-up timepoints: one and three months post-therapy
Results: ten patients were lost to follow-up, and five died during the trial. Of the 43 evaluable ivermectin patients, 42 (98%) were cured. In the 42 evaluable albendazole patients, 37 (88%) were cured. Side effects were 'negligible' in both groups.
Comments: in this study, the efficacy of albendazole is considerably higher than in the previously-reviewed studies. However, since the Baermann technique was apparently not used, low-level failures in both arms may not have been detected.

Reference: Testa J, et al. Traitement de l'anguillulose, de l'ascaridiose, et de l'ankylostomiase par l'ivermectin (Mectizan) à Bangui (RCA).

Source: Médecine d'Afrique Noire 37(5): 283-4, 1990.
Type of study: open study
Treatment arms: Ivermectin 200 mcg/kg single dose, N = 114 (total); N = 53 (infected with *S. stercoralis*)
Number enrolled: 114
Method of diagnosis: Three stool examination techniques, including Baermann technique
Follow-up timepoints: 7-10 and 15 days post-therapy
Results: 53/53 patients with strongyloidiasis were cured at the 7-10 day endpoint; 18 of these 53 presented for the second (15-day) follow-up and all 18 were cured. No patients reported any adverse side-effects ("Aucun patient traité n'a décrit d'effets secondaires après la prise de l'ivermectine.")
Comments: multiple stool exam techniques make the possibility of false negatives unlikely; however, a 15-day endpoint is relatively short.

Reference: Naquira C, et al. Ivermectin for human strongyloidiasis and other intestinal helminths
Source: Am J Trop Med Hyg 40 (3): 304-9, 1989.
Type of study: double-blinded, escalating dose-ranging study in patients with strongyloidiasis in Peru
Treatment arms: patients were sequentially assigned to the following treatment groups:
Group A: Ivermectin 50 mcg/kg (N = 18)
Group B: Ivermectin 100 mcg/kg (N = 18)
Group C: Ivermectin 150 mcg/kg (N= 18)
Group D: Ivermecting 200 mcg/kg (N = 17) ☜dosage used in MRL studies
Group E: Ivermectin 100 mcg/kg qd on days one and four (N = 18)
Group F: Ivermectin 200 mcg/kg qd on days one and four (N = 20) ☜ close to MRL dosage
Number enrolled: 110
Method of diagnosis: 24-hour stool collections were processed using Baermann technique as well as additional methods.
Follow-up timepoints: days 17-24 and 30-38 post-therapy. (Eighteen of the subjects cured at the 30-day endpoint, who lived in an area of Peru considered nonendemic for strongyloidiasis, were followed additionally with three serial stool samples at day 90 post-therapy. The breakdown of these 18 patients by treatment group was not presented.)
Results: at 30 days post-therapy, the following cure rates were reported:
Group A: 10/15 (67%)
Group B: 11/15 (73%)
Group C: 16/17 (94%)
Group D: 16/17 (94%) ☜dosage used in MRL studies
Group E: 15/17 (88%)
Group F: 20/20 (100%)
Additionally, all 18 of the cured patients who were followed up at three months post-therapy were found to have remained cured of their infections.
Adverse events included constipation (4 subjects), elevation of transaminases, serum creatinine, and alkaline phosphatase (1 each).
Comments: Method of stool analysis is comprehensive and allows for comparison with 'pivotal' studies. Excellent follow-up. Despite conduct in an endemic area, used 30-day post-therapy endpoint (unlike Marti study). Would have been of benefit if applicant had been able to submit patient-level data for this study. Unfortunately, the two-dose regimens used in this study are not precisely the same as those used in the MRL-sponsored studies reviewed above (those doses were given in two consecutive days [i.e., days 1 and 2] rather than on days one and four.

The applicant has also submitted four references from the Japanese literature. All of these are authored by the same group of investigators located on Okinawa, and all have the same first author (Shikiya, K.). When arranged chronologically, these papers report successively larger numbers of subjects. Thus it is likely that these papers represent successive accumulations of subjects and therefore the numbers reported in each paper cannot be added together. The paper reporting the largest number of subjects, which presumably represents the cumulation of the investigative efforts of this group, will be reviewed and tabulated. (One of the four papers was actually published in English [Intern Med Jpn 31(3): 310-12, 1992] and will be relied upon for procedural details of this series of papers.)

Reference: Shikiya K et al, Clinical study on ivermectin against 125 strongyloidiasis patients.
Source: Kansenshogaku Zasshi 68(1): 13-20, 1994.
Type of study: Open label, noncomparative study in an endemic area (Okinawa)
Treatment arms: Ivermectin 6 mg as single dose with repeat dose 2 weeks later. (Approximate dose range was 70-160 mcg/kg for each dose.)
Number enrolled: 125 patients
Method of diagnosis: fecal samples were examined using the agar plate method
Follow-up timepoints: patients were seen and stools examined 2 weeks after the first and second doses, as well as at or after one month following the second dose.
Results: of the 125 patients dosed with a single 6 mg dose, 112 presented for the two-week followup and 95 (85%) were negative. Of those 95 (all of which were dosed with a second 6 mg dose at that two-week timepoint), 87 remained negative at the second follow-up stool. The 13 subjects lost to initial follow-up were all found to be negative at this four-week timepoint. Therefore, at four weeks following the initial dosing, the cure rate was (87 + 13)/119 or 84% (six other subjects were lost to follow-up at the four week timepoint, making the denominator 125-6 = 119). Side effects were reported by 9 (7.2%) patients following the first dosage, and included dizziness in 3, nause and diarrhea in 2 each, and several other minor side effects in single subjects. The English abstract also mentions that "although liver disjunction [sic] developed in 13.6% of the patients, no symptoms occurred and no special treatment was required."
Comments: dosing regimen is non-standard. Although each individual dose appears to relatively underdose the subjects (although data on the weight of the subjects does not appear in the article), when the total dose over 2 weeks is calculated, these subject received a roughly comparable dosing regimen (140-320 mcg/kg). Method of diagnosis is non-standard, although the agar plate method is considerably more sensitive than a simple stool smear or formalin-ether concentration. The approximate amount of stool used in the agar plate technique is less than that used for the Baermann technique, but is greater than the amount used for a typical formalin-ether concentration. It is also of note that 43 out of the 125 patients treated in this study were HTLV-1 positive and therefore, to various degrees, immunocompromised. The investigators found a statistically significant correllation between treatment failure and HTLV-1 status. Therefore, the overall eradication rate of 84% should be considered lower than would be expected had immunocompromised patients been excluded from enrollment.

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2. Studies not specifically designed to investigate strongyloidiasis

Additional studies appear in the literature which have resulted from studies designed primarily to determine the efficacy of ivermectin in the treatment of onchocerciasis. Many areas endemic for onchocerciasis are co-endemic for strongyloidiasis; thus, several teams of investigators have studied the efficacy of ivermectin against intestinal helminths in the context of mass treatment studies for onchocerciasis. The following studies were therefore not specifically designed as strongyloidiasis studies but nonetheless contribute efficacy information that is relevant to this portion of the NDA.

Reference: Moyou SR, et al: Results of mass ivermectin treatment on the endemic helminthiasis in the rain forest zone of southwest Cameroon.
Source: Abstract of poster in Acta Leiden 59 (1-2): 466, 1990.
Type of study: ancillary study in context of mass treatment campaign for onchocerciasis
Treatment arms: ivermectin 150 mcg/kg X 1
Number enrolled: a subset of 20 patients was found pre-therapy to have *Strongyloides* larvae in stool
Method of diagnosis: not elaborated.
Follow-up timepoints: single stool exam one month post-therapy
Results: 20/20 patients with *Strongyloides* larvae reported as cured
Comments: lack of description of method of stool exam probably indicates a simple stool smear was performed; therefore, low-level failures may not have been detected. Nonetheless, 30-day endpoint is best that can be asked for in this endemic area.

Reference: Freedman DO et al: The efficacy of ivermectin in the chemotherapy of gastrointestinal helminthiasis in humans.
Source: J Infect Dis 159(6): 1151-3, 1989.
Type of study: ancillary study in context of mass treatment campaign for onchocerciasis in Guatemala
Treatment arms: ivermectin 140-200 mcg/kg X 1
Number enrolled: 12 randomly selected adults submitted stools, 3 of which were infected with *Strongyloides*
Method of diagnosis: formalin-iodine concentration of stool and examination of entire sediment
Follow-up timepoints: one month post-treatment
Results: 3/3 strongyloidiasis patients were cured at the one-month timepoint
Comments: Number is small. Difference in stool examination technique makes possibility of false-negative single follow-up stool more likely. Nonetheless, these results are consistent with other studies using Baermann technique.

Reference: Taticheff S et al: Effect of ivermectin (Mectizan®) on intestinal nematodes
Source: Ethiopian Med J 32(1): 7-15, 1994
Type of study: ancillary study in context of mass treatment campaign for onchocerciasis in Ethiopia
Treatment arms: ivermectin 150 mcg/kg X 1
Number enrolled: 231 patients with onchocerciasis, of which 7 were infected with *Strongyloides*
Method of diagnosis: formalin-ether stool concentration
Follow-up timepoints: 15 and 90 days post-therapy
Results: 7/7 subjects were cured at the 3 month post-therapy timepoint
Comments: Number is small. Difference in stool examination technique makes possibility of false-negative single follow-up stool more likely. Nonetheless, these results are consistent with other studies using Baermann technique.

In addition to these references, the applicant has also submitted four articles that describe single case reports of individual patients treated with ivermectin for strongyloidiasis. Because of the case report nature of these references and the unusual clinical aspects of the particular cases that warranted publication, they are not considered to be directly relevant to the NDA and will not be critically reviewed.

The submitted literature references which support the strongyloidiasis indication are summarized below:

Summary of literature references supporting strongyloidiasis indication

Reference, location	Ivermectin dose	Comparator	Method of stool diagnosis	Efficacy at timepoint	HIV/HTLV Patients included?
Scaglia, Italy	200 mcg/kg X 1	Albendazole	not specified	at three months: IVER 42/43 (98%) ABZ 37/42 (88%)	"uncompli-cated"cases only
Testa, Central Africa	200 mck/kg X 1	none	Baermann	at 15 days: IVER 18/18 (100%)	not mentioned
Naquira, Peru	Gr A: 50 mcg/kg X 1 Gr B: 100 mcg/kg X 1 Gr C: 150 mcg/kg X 1 Gr D: 200 mcg/kg X 1 Gr E: 100 mcg/kg X 2 Gr F: 200 mcg/kg X 2	none	Baermann	at 30 days: Gr A: 10/15 (67%) Gr B: 11/15 (73%) Gr C: 16/17 (94%) Gr D: 16/17 (94%) Gr E: 15/17 (88%) Gr F: 20/20 (100%)	not mentioned
Shikiya, Okinawa	6 mg X 2, taken two weeks apart	none	agar plate	at 28 days after first dose: 100/119 (84%)	43/125 patients enrolled were HTLV-1 +
Torres, Venezuela	200 mcg/kg X 1 (n=2) 200 mcg/kg X 4 (n=7) Given days 1,2,15,16	none	Baermann	at ≥ 7 months: 1/2 single dose (50%) 7/7 multidose (100%)	all 9 were HIV+; 5 had CD4 ≤ 200/mm3
Moyou, Cameroon	150 mcg/kg X 1	none	not specified	at one month: IVER 20/20 (100%)	not mentioned
Freedman, Guatemala	140-200 mcg/kg X 1	none	Formalin/ iodine	at one month: IVER 3/3	not mentioned
Taticheff, Ethiopia	150 mcg/kg X 1	none	Formalin/ ether	at 90 days: IVER 7/7	not mentioned

The applicant seeks labeling that would indicate a single dose of 200 mcg/kg for the treatment of strongyloidiasis. When the above references are compiled by those which studied doses of 150-200 mcg/kg as a single dose, and also had at least 30 days of post-therapy follow-up, the efficacy rate is 97%:

References using 150-200 mcg/kg X 1
and providing ≥ 30 days of post-therapy follow-up

Reference	Patients cured/evaluable
Scaglia	42/43
Naquira	16/17 (150 mcg/kg X 1)
	16/17 (200 mcg/kg X 1)
Moyou	20/20
Freedman	3/3
Taticheff	7/7
TOTAL	104/107 (97%)

Not all of these studies utilized Baermann stool examinations, thus raising the possibility of false negatives. Furthermore, the ideal test-of-cure timepoint may well be longer than 30 days post-therapy. But, since all of these studies were performed in endemic areas where the possiblity of reinfection exists, this timepoint is accepted as being the most reasonable.

C. Conclusions

The published literature supports the applicant's contention that ivermectin at a dose of 200 mcg/kg X 1 is safe and effective in the therapy of uncomplicated strongyloidiasis.

8. Statistical considerations

Insert statsitical review and survival analysis here

9. Overall conclusions

The sponsor has submitted four separate clinical studies in support of the strongyloidiasis indication for which patient-level data (in the form of computerized case tabulations) has been made available. The consolidated results of these four studies, after the medical officer's review, are as follows:

Study	Ivermectin X 1		Ivermectin X 2		Albendazole		Thiabendazole	
	30 day	90 day	30 day	90 day	30 day	90 day	30 day	90 day
Gentilini	24/26	21/26			12/22	10/22		
Dreyer	9/14		15/17				13/15	
Berk	4/4	4/4	2/2				3/3	1/3
Gann	14/14	14/14	17/18	17/18			16/16	16/16
TOTALS	51/58 (86%)	39/44 (89%)	34/37 (92%)	17/18 (94%)	12/22 (55%)	10/22 (45%)	32/34 (94%)	17/19 (89%)

Additionally, the applicant has submitted the manuscript of a study conducted by the WHO in Zanzibar (the Marti study). This paper, along with the additional literature submitted in support of this indication, show the following results:

Study	Ivermectin X 1		Ivermectin X 2		Albendazole		Thiabendazole	
	30 day	90 day	30 day	90 day	30 day	90 day	30 day	90 day
Marti	126/152*				67/149*			
Literature (total)	104/107	49/50				37/42		
TOTALS	130/159 (82%)	49/50 (98%)			67/149 (45%)	37/42 (88%)		

The clincal data, taken as a whole, support the applicant's claim that a single 200 mcg/kg dose of ivermectin is safe and effective in the treatment of uncomplicated strongyloidiasis in the non-immunocompromised host. The statistical examination of these data performed by Dr. Sue Bell of CDER supports this claim. Therefore, the medical officer concludes that this indication should be granted to the applicant.

Ivermectin in the treatment of Onchocerciasis

1. The disease

A. Life cycle

Onchocerciasis is the term used for the clinical disease caused by the human nematode parasite *Onchocerca volvulus*. This human parasite is a vector-borne disease transmitted by the bite of the blackfly, *Simulium*. In Africa, the predominant vector species is *S. damnosum*. These insects require relatively high aquatic oxygen levels for their larval development. Thus, the life cycle of the vector is closely associated with breeding areas in fast-moving streams and rivers where rapids provide adequate oxygenation to support development of the water-borne larvae.
Because of the association of the vector with streams and rivers, the disease in humans is epidemiologically associated with these bodies of water and has been termed 'river blindness'. (See *Clinical manifestations*, below.)

Adult *O. volvulus* males and females are found in subcutaneous nodules of the infected human host. These nodules are usually palpable and removable; upon removal and digestion in collagenase, a typical onchocercal nodule can contain between 2-4 male and 3-6 female adults. The female measures 30-50 mm in length, whereas the male measures 20-40 mm. The worms become tightly coiled within these nodules, which are usually palpable, measure 5-15 mm in diameter, and characteristically are located on the hips, joints of the arms or legs (in African disease) or on the scalp (in Central American disease). Nodules are less likely to be found in caucasian patients. They have been found in children as young as one year of age in endemic areas. Adult *Onchocerca* can live for over eleven years and are capable of producing microfilariae for 9-10 years (Roberts JMD et al, Bull WHO 37: 195-212, 1967).

Adult females within these nodules are in a state of constant larviposition. First-stage larvae, known as microfilariae, are discharged into the fibrous tissue surrounding the nodule and escape into subcutaneous tissue. These microfilariae (abbreviated mf) are relatively long-lived and may survive in the skin for up to 30 months (Duke BOL, British Med Bull 28: 66, 1972). When an infected human is bitten by an appropriate *Simulium* vector, mf are ingested when the fly imbibes tissue juices from the skin. The ingested larvae penetrate the stomach of the fly and arrive in the thoracic muscles, where they undergo two molts and become infective third-stage larvae. These infective larvae migrate to the labium of the fly, where they await the fly's next blood meal. When the vector is feeding, infective larvae migrate down the proboscis and enter the skin of the human host during the feeding process. Following two additional molts, adult worms become sexually mature and mating pairs coil up into nodules. Nodule development takes place in proximity to the location of the infective *Simulium* bite; this is why location of nodules varies between African and American disease, as the biting habits of the local blackfly vectors varies by geographic area.

B. Clinical manifestations

Although the adult worms often cause macroscopic, palpable masses, these are not the lesions which produce clinical disease. It is the constant presence of migrating subcutaneous mf, the host immune reaction to these parasites, and the antigens released upon their demise which is the cause of the clinical disease known as onchocerciasis. The migrating mf cause an intensely pruritic dermatitis that has been variously characterized as licheniform, eczematoid, or pigmented. Adenolymphocoele ("hanging groin") and scrotal elephantiasis has also been described as a complication of this infection.

The most important clinical manifestation of this infection occurs when migrating mf invade the structures of the eye. The mf may invade the cornea and be associated with a punctate, vascular, or interstitial sclerosing keratitis. Concomitantly with the migration of the mf into the orbit, and particularly into the immediate vicinity of the optic nerve, the patient first complains of photophobia, with evidence of congestion and punctate hemorrhage around the limbus of the eye and congestion and edema of the conjunctiva. This is followed by inflammation of the iris, ciliary body, retina, and choroid, exudate in the vitreous, resulting in gradually increasing loss of vision. The final stage, that of complete blindness, results from the invasion of the optic nerve by the mf (Faust, Russel, and Jung: Clinical Parasitology, 8th edition, 1977).

It is estimated that some 20 million people in Subsaharan Africa are infected with onchocerciasis, as well as an additional one million people in scattered foci in Central and South America. This disease is considered to be the second most important infectious cause of blindness in Africa, following trachoma. Despite this prevalence in endemic

areas of the world, onchocerciasis is not considered a major imported tropical disease in the United States. According to the CDC, there are between 100 and 200 new cases annually in the United States (John Beach, CDC Parasitic Disease Drug Service, personal communication). From one quarter to one half of these cases are in immigrants who have come to the US from endemic areas. Among US citizens, those most likely to present with onchocerciasis are Peace Corps volunteers, missionaries, and others who had lived in endemic areas of the world for adequate amounts of time to acquire a parasite burden of sexually mature *Onchocerca* adults. The clinical manifestations of the disease are relatively chronic in nature, as opposed to other imported tropical diseases (such as malaria) in which the infected patient rapidly becomes clinically apparent.

In endemic areas of the world such as West Africa, onchocerciasis has a major socioeconomic impact because it incapacitates otherwise healthy, potentially productive adults. This is one of the three major factors which led to the WHO's decision to initiate an onchocerciasis eradication campaign in West Africa in the mid 1980's. The remaining two factors which made this disease a candidate for a concerted eradication effort are 1) the aforementioned focality of the disease (i.e. its close association with swiftly-flowing streams and rivers); and 2) the recognition that ivermectin was a suitable drug for use in population-based mass treatment programs.

C. Therapy

Drugs for the treatment of this disease are classified as either larvicidal or adulticidal. According to the fourth edition of Mandell's Principals and Practice of Infectious Diseases : "Traditionally, patients with skin disease have been treated with diethylcarbamazine (DEC). This drug kills microfilariae but has little effect on the adult worm. Severe reactions such as rash, fever, generalized body pains, keratitis, and iritis may occur...". DEC (Hetrazan, Lederle) was discovered in the 1940's and has been the mainstay of onchocerciasis therapy since the seminal articles on its effect on microfiladermia were published by Mazzotti in 1948. This drug was approved by the FDA in November 1950 and remains the only drug approved for this disease in the US to date.

Prior to the discovery of DEC, the only drug found to be effective in this disease was Suramin. This drug was synthesized in Germany in the 1920's as an antitrypanosomal drug, following the observation that some azo dyes possessed trypanocidal activity. It remains to this date the only drug recognized as having adulticidal activity in onchocerciasis. Suramin still has use in the therapy of African trypanosomiasis. It must be given by slow intravenous injection, and has a notorious side effect profile which includes peripheral neuropathy, albuminuria, leukopenia, shock, and renal failure. Because it has some larvicidal as well as adulticidal effects, treatment of onchocerciasis patients with suramin can evoke the constellation of signs and symptoms commonly referred to as the Mazzotti reaction (fever, pruritus, rash, adenitis, generalized body pains, arthralgia). Suramin is available in the US under an IND held by the Parasitic Disease Drug Service of the CDC.

The Mazzotti reaction was described in the context of clinical trials with DEC. In fact, this reaction is such a predictable consequence of DEC administration that it is frequently used as a diagnostic challenge test in cases where onchocerciasis is suspected on clinical grounds, yet parasitologic diagnosis by skin snip has been negative. The severity of this reaction is considered to be proportional to the intensity of the infection.

Because the Mazzotti reaction can be severe, the recommended dosing regimen for onchocerciasis (Mandell, Principles and Practice of Infectious Diseases, Fourth Edition, page 2536) calls for an initial low dose (50 mg/day) on day one, then 50 mg tid on day 2, then 100 mg tid on day 3, followed by 3 mg/kg tid for days 4-21. (NB: the current product labeling reads "In Bancroft's filariasis, onchocerciasis, and loiasis, the usual dose is 2 mg/kg of body weight 3 times a day immediately following meals... When the disease is in the acute stage, treatment should be maintained for 3 to 4 weeks." The DOSAGE AND ADMINISTRATION section then proceeds to state: "When, as a public health measure, it is desirable to treat large numbers of patients known to harbor microfilariae, the same dosage schedule may be given for 3 to 5 days."

The severity of the Mazzotti reaction and the need for multiple doses made DEC a suboptimal drug for use in mass eradication campaigns. For this reason, the initial onchocerciasis control efforts of the WHO were directed at the *Simulium* vector. This massive spraying campaign, which began in 1973, was initially successful in reducing transmission of the disease, but it became clear that ultimate success would not be achieved by this intervention alone. It was at this critical time in the WHO's Onchocerciasis Eradication Program that ivermectin was recognized as a

potentially important anthelminthic for human use.

Ivermectin had originally been developed by Merck in the 1970's for veterinary use. By 1986, ivermectin had been registered in 47 countries for animal use. It was labeled for the treatment of ectoparasites (ticks, mites, and lice) as well as nematode endoparasites in a variety of animal hosts (cattle, sheep, horses, pigs, and dogs).

Because ivermectin was found to be highly effective in the treatment of veterinary nematodes (including the horse parasite *Onchocerca cervicalis*), usually as a single dose, studies of its safety and efficacy in human parasitic disease were undertaken. These clinical studies began in 1980, and led to the marketing approval of ivermectin for human onchocerciasis in France in 1987. These clinical studies form the basis of the clinical studies section of this NDA. No clinical studies have been performed specifically in anticipation of an NDA filing with the FDA.

2. Overview of submitted application

The applicant has submitted the following clinical studies in support of the onchocerciasis indication:

1. Protocol 514: A multicenter, randomized, double-blinded, placebo-controlled comparative study of ivermectin (12 mg single dose, capsule formulation) versus DEC in the treatment of patients with onchocerciasis. This study enrolled 149 male patients in four locations in Africa. A dataset was provided to the statistical reviewer by the applicant for this study, but the medical officer was provided a study summary report in hard copy only. A 34-volume 'request for additional information' amendment was submitted to the NDA, dated 9 July 96, which included four volumes of individual patient data from this study.

2. Protocol 519: A multicenter, randomized, double-blinded, placebo controlled study of ivermectin at three doses (100, 150, or 200 mcg/kg single dose, capsule formulation) versus placebo in the treatment of onchocerciasis. This large phase 3 study enrolled 1156 males and 119 females at six locations in Africa. A dataset for this study was provided for the statistical reviewer, but the medical officer was provided a hard copy study summary only. The 9 July 96 'additional information' amendment to the NDA included 24 volumes of individual patient data from this study.

3. Protocol 545: An open study of ivermectin (150 mcg/kg single dose, capsule formulation) for the treatment of onchocerciasis in children 6-13 years old. This study was submitted to the French regulatory agency in 1988 as an efficacy supplement to the already-approved ivermectin label. A dataset was submitted to the statistical reviewer, but the hard copy summary of the Marketing Authorization Application was all that was submitted to the medical officer. The 9 July 96 NDA 'additional information' submission included 3 volumes of individual patient data from this study.

4. Protocol 548: A single-blind, placebo controlled study of the marketed tablet to assess the tolerability, safety, and efficacy of single dose ivermectin (150-220 mcg/kg) in the treatment of onchocerciasis. This study was performed in 46 male and 39 female patients in a single center (in Mali) by Dr. P. Vingtain. The dataset for up to the day 4 post-therapy timepoint was provided to the statistical reviewer, but no formal data analysis was provided by the applicant in the form of a completed study report. The 'additional information' submission to the NDA included one volume of individual patient data from this study. This study was not reviewed by the medical officer.

Several additional studies are referenced in the application, but the above four studies are the clinical trials upon which the application rests. The design of these onchocerciasis studies includes the following common features:

- the diagnosis of onchocerciasis is made on the basis of skin snips, using a standardized instrument
- the degree of microfiladermia is quantified in terms of number of microfilaria per gram of skin tissue, by taking the average of four anatomically separate snips taken from standardized locations on the patient's body
- patients were treated with ivermectin for a single dose (or comparator) and then followed serially for at least six months

- skin snips were repeated at specified times using the same technique as the baseline samples mentioned above
- response to therapy was measured as the decrease in microfiladermia from that seen at baseline.
- appropriate ophthalmological parameters, including number of visible intraocular microfilaria, were monitored

Although the density of microfilariae in skin snips is, in actuality, a surrogate endpoint for the more direct intraocular measurements of disease progression or regression, this is an appropriate endpoint. Such measurements are relatively well standardized and have been the accepted method for diagnosis and monitoring of onchocerciasis patients for many years. Thus it is appropriate to use this parameter as a measurement of response to therapy. The clinical studies cited above followed ophthalmological endpoints as well. Since the sponsor requests labeling that calls for repeated therapy at three month intervals, the primary endpoint of interest in these studies will be decrease in microfiladermia from baseline, at three months post-therapy.

Several of these studies define 'favorable response to therapy' as a patient whose microfilarial skin snip count has dropped below 5 mf/mg of tissue. The basis for this measurement lies in the fact that these studies were designed primarily to examine the feasibility of using ivermectin in the setting of mass eradication campaigns. If the density of microfiladermia in the population can be suppressed below a certain limit, it is thought that transmission of the infection back to the *Simulium* vector can be interrupted. If this is accomplished, then the transmission cycle has been broken and the eradication campaign has a much higher likelihood of success. Thus, for the purposes of mass eradication studies, the 5 mf/mg tissue parameter is an important endpoint. However, at the individual patient level, absolute eradication of microfiladermia is the more important endpoint.

3. Medical officer review of submitted application

A. Study 514: Double-blind comparative studies of ivermectin (MK-933), diethylcarbamazine citrate (DEC-C) and placebo in patients with onchocerciasis.

i. Applicant's summary

The clinical study report for study 514 is found on pages D-1441 to D-1520 of volume 1.19 of the NDA. The reader is referred to this document for the study report in its entirety; the synopsis of the study report is included on the following page:

MERCK SHARP & DOHME RESEARCH LABORATORIES

SYNOPSIS--CLINICAL STUDY REPORT

DATE: 16JAN87

PRODUCT:	Ivermectin (MK-933) Capsules Containing 6 mg MK-933 and Diethylcarbamazine Citrate (DEC-C) Capsules Containing 50 mg DEC-C and Matching Placebo Capsules	
PROTOCOL & #:	Double-Blind Comparative Studies of Ivermectin, Diethylcarbamazine Citrate and Placebo in Patients With Onchocerciasis	#514-09
INVESTIGATORS & STUDY #:	Dr. M. Lariviere; Dakar, Senegal Dr. M. Lariviere; Bamako, Mali Dr. K. Awadzi; Tamale, Ghana Dr. B. Greene; Grand Bassa County, Liberia	#5002
STUDY DESIGN:	Double-blind vs DEC-C and placebo; treatment assignment according to a randomized allocation schedule	DURATION: Single dose of ivermectin on Day 1, 2 daily doses of DEC-C on Days 1 through 8; efficacy follow-up for 1 year
DOSAGE:	Ivermectin patients received a single oral 12 mg dose on Day 1. DEC-C patients received 2 daily doses totaling 50 mg on Days 1 and 2 and 200 mg on Days 3 through 8.	

PATIENT POPULATION:		IVERMECTIN	DEC-C	PLACEBO
ENTERED:	MALE (Mean Age/Years)	50 (31.1)	50 (31.4)	49 (32.3)
	FEMALE (Mean Age/Years)	0	0	0
	TOTAL	50	50	49
COMPLETING STUDY:		44	45	44
WITHDRAWN:		6	5	5
	SAFETY (CLINICAL AND LABORATORY)	0	0	0
	Rx FAILURE	0	0	0
	OTHER	6	5	5
EVALUATED FOR EFFICACY (MAXIMUM):		47	49	46
ADVERSE EXPERIENCES (Patients)				
	CLINICAL	25	28	11
	LABORATORY	5	11	2

RESULTS:

EFFICACY: In this comparative study of ivermectin vs DEC-C vs placebo in hospitalized onchocerciasis patients, mean skin microfilaria (mf) densities decreased sharply by Day 2 in both ivermectin and DEC-C patients and reached almost identical low levels (~ 2% of pretreatment) by Day 8. The mf densities then decreased further in the ivermectin patients (some to 0) over the next 3 months but increased gradually in DEC-C patients to about 14% of pretreatment level in 3 months. Between 3 and 12 months posttreatment, the mf densities in ivermectin patients gradually increased to about 5% of the pretreatment level compared to 20% in the DEC-C patients at 12 months. There were essentially no changes with placebo treatment.

Both ivermectin and DEC-C eliminated mf from the anterior chamber of the eye. DEC-C-treated patients cleared mf faster than ivermectin-treated patients.

SAFETY: The incidence of clinical adverse experiences in the ivermectin-treated patients was slightly lower than in patients treated with DEC-C (50 vs 56%). More DEC-C patients had a worsening of systemic reactions than ivermectin patients. In addition, more DEC-C patients required steroids, anti-inflammatory drugs and analgesics than ivermectin patients to relieve symptoms of systemic reactions and clinical adverse experiences.

In general, ophthalmologic safety results were similar for ivermectin and DEC-C. DEC-C, however, caused an increase in severity of limbitis and punctate keratitis in more patients during the first 4 and 14 study days, respectively, than ivermectin.

None of the laboratory adverse experiences was considered serious by the investigators, and no patient was discontinued from the study due to adverse experience. The DEC-C-treated group had a greater percentage of patients with laboratory adverse experiences than the ivermectin-treated group. The percentage of patients with increased AST in the DEC-C group (22%) was significantly greater than in the ivermectin group (2%) and placebo group (4%); $p < 0.02$.

CONCLUSIONS: The following conclusions may be drawn from the data presented in this CSR: (1) Ivermectin given as a single 200 mcg/kg oral dose is an effective microfilaricide in the treatment of onchocerciasis and is at least as effective as the standard 8-day course of DEC-C; (2) The microfilaria level remains below 5 mf/mg skin for up to 9 months for a larger percentage of ivermectin patients than DEC-C patients, and the trend continues for at least 12 months; (3) Ivermectin has a better safety profile in onchocerciasis patients than DEC-C with respect to allergic and inflammatory reactions; and (4) The treatment of onchocerciasis with ivermectin is associated with a lower incidence of clinically significant deterioration of ophthalmologic parameters than DEC-C, i.e. up to Day 4 for limbitis and up to 2 weeks for punctate keratitis.

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ii. Medical officer comments on study 514.

This study was conducted in four separate sites in West Africa (Senegal, Mali, Liberia, and Ghana) during 1984 and 1985. Each study site contributed approximately 30 patients (ten in each treatment arm), with the exception of Dr. Awadzi in Ghana, who enrolled 59 patients. The results of each of these study sites were independently published in the peer-reviewed medical literature and form an important component of the medical literature describing the efficacy of ivermectin in this disease. The publications that resulted from this study include:

- Green BM et al: Comparison of ivermectin and diethylcarbamazine in the treatment of onchocerciasis. New England Journal of Medicine 313(3): 133-8, 1985.
- Lariviere M et al: Double-blind study of ivermectin and diethylcarbamazine in African onchocerciasis patients with ocular involvement. Lancet 2: 174-7, 27 July 1985.
- Diallo S et al: A double-blind comparison of the efficacy and safety of ivermectin and diethylcarbamazine in a placebo controlled study of Senegalese patients with onchocerciasis. Transactions of the Royal Society of Tropical Medicine and Hygiene 80: 927-34, 1986.
- Awadzi K et al: The chemotherapy of onchocerciasis XI: A double-blind comparative study of ivermectin, diethylcarbamazine, and placebo in human onchocerciasis in Northern Ghana. Annals of Tropical Medicine and Parasitology 80(4): 433-42, 1986.

Each of these references are included in the NDA submission, found on pages D-3746 to D-3785 of volume 1.24.

In general, the design of this study is excellent. After meeting the enrollment criteria, patients were randomly assigned to one of the three treatment arms, and were supplied with identical-appearing treatment kits which contained an eight day supply of medication consisting of: a single dose of ivermectin (at a dose of 12 mg) plus placebo; an eight-day course of DEC at a dose of 50 mg on day 1, 100 mg on day 2, and 200 mg daily for the remaining 6 days; or all placebo capsules. Each patient took the same number of identically appearing capsules in the morning and evening. Patients and investigators were blinded as to the identity of the study medication.

All enrolled patients were males with moderate to severe disease (defined as ≥20 mf per mg of skin) and evidence of mild to moderate ocular involvement. Patients were followed daily in-hospital for the first 2 weeks, then as outpatients on day 28 and at months 3,6,9, and 12 post-therapy. Parasitologic parameters followed included skin snips at specified anatomic locations, as well as several ophthalmologic parameters (visual acuity, peripheral visual fields, pupillary reflexes, color vision, slit-lamp exam of the anterior and posterior chamber, intraocular pressure, dilated fundus exam with photography, and fluorescein angiography).

The following comments pertain to the design and conduct of this study as it applies to this NDA submission:

✦ the formulation used was the capsule formulation whereas the NDA requests approval of the tablet formulation.
✦ the dose of ivermectin studied is a constant 12 mg dose, whereas the NDA requests dosing on a mcg/kg basis. As a rough estimate, the baseline demographic characteristics presented on page 22 of the study report (page D-1465 of Volume 1.19) give a mean weight of approximately 56 kg in the three treatment arms. This means the average enrollee received a dose of 214 mcg/kg, whereas the NDA requests a dose of 150 mcg/kg. Therefore, on average, the patients in this study received a higher dose of ivermectin than is requested.
✦ the protocol makes no mention of nodulectomy as a component of this study, but the literature reports that were generated from these studies specifically mention that onchocercal nodules were removed from numerous patients in all arms of the study at various times post-therapy. This is potentially important because the removal of actively larvipositing adult worms could cause a decrease in microfiladermia, which may confound the drug effect being studied. There appears to be no attempt to control for this in the efficacy analysis, or to stratify the analysis by number of nodules removed per patient. The graph presented on page 33 of the study report (page D-1476, volume 1.19) shows that the placebo group had a significant drop in microfiladermia at days 14 and 28. The applicant discusses this observation on page D-1477. No satisfactory explanation is provided for this observation, aside from the speculation that this was "partially due to the ongoing Onchocerciasis Control Programme in Ghana". Admittedly, the literature reports state that nodules were removed from patients no earlier than one month post therapy; thus, the observed drop in microfiladermia

seen in the placebo arms of the study preceded the nodulectomies that were performed. Nonetheless, nodulectomy was not planned to be a component of this study, according to the submitted study report. Since such a procedure could have affected the parasitological endpoint of interest, it should have been addressed in the study report.
✦ this is the only study submitted in this NDA which had a comparator arm using an FDA-approved drug for this indication (DEC-C). Since the methodology used in this study is essentially the same as that used in the larger phase 3 study 519, it is reasonable to compare the efficacy results of the DEC-C arm of this study with the efficacy results of the ivermectin arms of both this study as well as study 519.

iii. Conclusions

Study 514 supports the safety and efficacy of ivermectin in the therapy of onchocerciasis. The dose and formulation used in this study are not identical to that which the applicant proposes in the product labeling, but these differences do not invalidate the study. In this double-blinded, comparative, placebo-controlled study, the applicant has demonstrated that ivermectin has better efficacy than DEC-C, when expressed as reduction in geometric mean microfilariae per mg of skin from baseline. This difference persists beyond the three month post-therapy timepoint. Furthermore, study 514 demonstrates that ivermectin (even at this higher dose) causes less severe Mazzotti-type reactions than DEC-C, and that ivermectin does not exacerbate ophthalmological indices with the exception of a transient increase in the number of anterior chamber microfilaria seen.

Please see the overall conclusions to this section of the NDA review for efficacy and safety results of this study in comparison to the other studies submitted in this application.

B. Study 519: A multiclinic, double-blind study of ivermectin (MK-933) and placebo in patients with onchocerciasis.

i. Applicant's summary:

The applicant's comprehensive study summary for this study is found on pages D-1523 to D-1605, volume 1.19 of the NDA submission. The reader is referred to this document for a comprehensive description of the study. The synopsis of the clinical study report is included on the following page:

MERCK SHARP & DOHME RESEARCH LABORATORIES

SYNOPSIS--CLINICAL STUDY REPORT
DATE: 20JAN87 R 27FEB87
R 30JAN87

PRODUCT:	Ivermectin (MK-933) Oral Capsules Containing 0.75, 1.0 or 4.0 mg Ivermectin; Placebo	
PROTOCOL & #:	A Multiclinic, Double-Blind Study of Ivermectin (MK-933) and Placebo in Patients With Onchocerciasis	#519-00
INVESTIGATORS & STUDY #:	Six investigators in 6 countries	#5003
STUDY DESIGN:	A double-blind, randomized, placebo-controlled, multicenter study	DURATION: Single dose ivermectin or placebo Day 1; efficacy follow-up 3, 6 and 12 months posttreatment
DOSAGE:	Each patient received a single oral dose of ivermectin (100, 150 or 200 mcg/kg body weight) or placebo on Day 1 of the study.	

PATIENT POPULATION:		TOTAL	100 MCG/KG	150 MCG/KG	200 MCG/KG	PLACEBO
ENTERED:	MALE (Mean Age)	1156 (31.0)	295 (30.9)	276 (31.1)	297 (31.8)	288 (30.8)
	FEMALE (Mean Age)	119 (37.2)	23 (38.0)	44 (36.2)	25 (34.5)	27 (37.0)
	GENDER AND AGE UNKNOWN	3	1	2	0	0
	TOTAL	1278 (31.61)	319 (31.38)	322 (31.81)	322 (31.96)	315 (31.30)
WITHDRAWN:						
	SAFETY (CLINICAL AND LABORATORY)		0	0	0	0
	Rx FAILURE		0	0	0	0
	OTHER					
EVALUATED FOR EFFICACY (MAXIMUM):	Day 3	1009	254	249	254	252
	Month 3	942	238	237	238	229
	Month 6	917	237	230	223	227
ADVERSE EXPERIENCES (Patients)						
	CLINICAL		152	155	170	94
	LABORATORY		1	1	0	0

RESULTS:

EFFICACY: This multiclinic, double-blind study compared 3 dosage levels of ivermectin to placebo in hospitalized onchocerciasis patients. The median skin mf densities at Day 3 were 14.2, 8.4, 7.2 and 46.5 for the 100, 150, 200 mcg/kg and placebo treatment groups, respectively. The decrease continued to almost complete elimination of the mf at Months 3 and 6 for the ivermectin groups. During the same period, placebo patients had significantly smaller changes. The 200 mcg/kg group had a more rapid effect than 100 mcg/kg ($p < 0.05$). There was little difference between the 150 and 200 mcg/kg doses with respect to their microfilaricidal effect. In the elimination of microfilariae from the anterior chamber of the eye, ivermectin was significantly superior ($p < 0.001$) to placebo at Months 3 and 6.

SAFETY: All 3 doses (100, 150 and 200 mcg/kg) of ivermectin were generally well tolerated. However, the percentage of patients with clinical adverse experiences (primarily myalgia and headache) was slightly higher at the higher dose levels. None of these adverse experiences was considered serious.

Ivermectin treatment was generally superior to the placebo treatment regarding the percentages of patients with an improvement in limbitis, sclerosing keratitis, anterior chamber microfilaria, corneal live microfilaria, corneal dead microfilaria and punctate opacity especially in the reduction of microfilaria in the anterior chamber and cornea, at Months 3 and 6. Ivermectin was similar to placebo regarding changes in the other ophthalmologic variables.

Two ivermectin-treated patients had a laboratory adverse experience (not serious). One patient had a 'possibly' drug-related serum bilirubin elevation. Another patient had high urine WBCs. Both were rated as mild.

CONCLUSIONS: The following conclusions may be drawn from the data presented in this CSR: (1) Ivermectin given as a single oral dose at levels of 100, 150 and 200 mcg/kg is an effective microfilaricide in the treatment of onchocerciasis. Higher doses are associated with a more rapid onset of effect. (2) Ivermectin is associated with mild allergic and inflammatory reactions which increase slightly with higher doses. (3) Ivermectin does not seem to precipitate major ocular complications in patients with onchocerciasis. (4) Considering the efficacy and safety of the 3 dosage levels tested, 150 mcg/kg ivermectin represents an optimal dosage for the treatment of onchocerciasis. (5) Ivermectin administration is not needed more frequently than once in 6 months.

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ii. Medical officer comment on study 519

This multicenter study involved a total of 1278 patients at six study sites (five in West Africa [Liberia, Ghana, Ivory Coast, Togo, Mali] and one in Guatemala). Although it did not include an active comparator arm, it did enroll patients in a double-blinded, placebo controlled fashion to one of three dosages of ivermectin. The methodology used in this study was similar to that used in study 514. There were, however, some differences in the conduct of this study:

- ✦ Study 514 was conducted in males only whereas this study enrolled females as well as males.
- ✦ This study was to include patients from Guatemala along with West Africa (however, the Guatemala site was excluded from analysis because patients were enrolled without baseline parasitological parameters being recorded).
- ✦ This study only followed patients out to 6 months post-therapy. (It was designed to follow patients out to 12 months, but the cutoff date for data entry precluded the 12 month endpoint. Even though this study was conducted in 1986, no update providing the 12 month endpoint was submitted with the NDA).
- ✦ This study admitted patients to hospital for baseline studies and for 4 rather than 14 days following study drug administration. The patients were then followed as outpatients at months 3 and 6 post-therapy (unlike study 514, there was no one month post-therapy time point).
- ✦ The ophthalmologic evaluation of patients in this study did not include fluorescein angiography.

The results of this multicenter study were published in the medical literature under the following citation: White AT et al: Controlled trial and dose-finding study of ivermectin for treatment of onchocerciasis. Journal of Infectious Diseases 156(3): 463-70, 1987. This reference was included in the NDA submission (page D-3806-3813, volume 1.24).

In general, this is a well-designed study which shares many features of study 514 in terms of patient evaluation and monitoring. The following comments pertain to the design and conduct of this study as it applies to this NDA submission:

- ✦ Once again, the capsule formulation of ivermectin was used in this study. Capsules were provided in strengths of 4.0, 1.0, and 0.75 mg. These were combined with identically-appearing placebo capsules so that each patient in each of the four treatment arms (100, 150, or 200 mcg/kg, and placebo) received five capsules at the time of drug administration.
- ✦ Unlike study 514, this study contains treatment arms that are at and below the requested dose of 150 mcg/kg. Because these studies used similar methodology and parasitological endpoints, efficacy comparisons between this study and the DEC-C arm of study 514 would seem to be reasonable.
- ✦ Unlike study 514, there were no routine nodulectomies performed as part of this study. Therefore, there is no possibility of bias introduced into this study because of the removal of larvipositing adults.
- ✦ As mentioned previously, this study was designed to follow patients for 12 months following therapy but the data submitted with the NDA only go out to 6 months post-therapy. This discrepancy does not alter the importance of this study; as mentioned previously, the endpoint of interest in this application is degree of reduction of microfiladermia from baseline at three months post-therapy.

As presented in Table 13 of the Clinical Study Report (page D-1557, vol.1.19), the geometric mean percentage reduction from baseline of microfilariae per milligram of skin was 99.5% at 3 months post therapy for the 150 mcg/kg arm of this study, with an N of 237.

Because this study used the capsule formulation, which may be more bioavailable than the to-be-marketed tablet formulation (see Biopharmaceutics review of Dr. Philip Colangelo, DAIDP), it is also important to notice the results of the 100 mcg/kg arm of this study. This arm had an N of 238 at the 3 month post-therapy timepoint, and demonstrated a 98.2% reduction in microfilaria per milligram of skin tissue. Because the tablet formulation may be slightly less bioavailable, the 150 mcg/kg dose of tablet will most likely provide an efficacy rate that falls somewhere between a 99.5% and 98.2% reduction in microfiladermia at the 3 month timepoint. This should be compared with the efficacy results for the DEC-C arm of study 514:

	100 mcg/kg arm of study 519	DEC arm of study 514
N at entry	319	50
density of infection		
baseline (mf/mg, $\bar{x}$ [range])	47.3 (0.5-352.2)	57.1 (9.8-228.9)
day 4 (% of baseline)	26.3%*	3.8%
day 30	------	3%
3 month	1.8%	14%
6 month	2.9%	11%

* in study 519, this measurement was at day 3 post-therapy rather than day 4

Thus in this cross-study comparison, it appears that the lower dose of ivermectin still demonstrates a substantially higher efficacy rate in terms of clearance of microfiladermia at three months post-therapy. This comparison is also notable for the difference in rate of clearance between the two treatments at the 3-4 day post-therapy timepoint. One can see that DEC-C has a much more rapid killing effect on microfilariae, such that practically all the reduction in microfiladermia observed has taken place by day 4 post-therapy. In contrast, ivermectin clears microfilariae more gradually. The precise mechanism responsible for this difference in kinetics is not known, but this difference would seem to provide parasitologic evidence which corroborates the differential rates of Mazzotti reaction between the two treatment regimens.

In terms of safety, study 519 demonstrated that the 150 mcg/kg dose was, in general, better tolerated and less reactogenic than the 200 mcg/kg dose. Aside from disease-associated signs and symptoms, the ivermectin-treated patients had more musculoskeletal and nervous/psychiatric events than did the placebo-treated patients. These events appeared to show a dose-response effect. The adverse experience which was the most common 'nervous/psychiatric' event was headache.

iii. Conclusions

Ivermectin at a single dose of either 100 or 150 mcg/kg is safe and effective in the treatment of patients with onchocerciasis. Either dose is more efficacious and less reactogenic than the only currently-approved product, DEC-C.

C. Study 545: An open study of the tolerability, safety, and efficacy of single oral 150 mcg/kg doses of ivermectin (MK-933) in children 5 to 12 years of age with onchocerciasis.

i. Applicant's summary.

Following the marketing approval of ivermectin in France in 1987, the applicant proceeded to conduct a study of ivermectin therapy in children. The previous studies were conducted in adults only.

The Clinical Study Report for study 545 is found on pages D-1884 to D-2041C, volume 1.20 of the NDA. The synopsis of this report is found on the following page:

MERCK SHARP & DOHME RESEARCH LABORATORIES

SYNOPSIS--CLINICAL STUDY REPORT
DATE: 05JAN88
R 09MAR88

PRODUCT:	Ivermectin, Capsules (1, 3, 6 mg)	
PROTOCOL & #:	An Open Study of the Tolerability, Safety, and Efficacy of Single Oral 150 mcg/kg Doses of Ivermectin (MK-933) in Children 5 to 12 Years of Age With Onchocerciasis	#545-00
INVESTIGATOR & STUDY #:	Dr. M. Lariviere 75006 Paris Cedex 06 France	#5544
STUDY DESIGN:	Open study	**DURATION:** Patients were given 1 oral dose of ivermectin on Day 1; patients followed for 3, 6, and 12 months posttreatment
DOSAGE:	Ivermectin, 150 mcg/kg single oral dose	

PATIENT ACCOUNTING:

	IVERMECTIN
ENTERED: Total	103
Male (age range--years)	71 (6 to 13)
Female (age range--years)	32 (6 to 13)
COMPLETED STUDY:	103
WITHDRAWN:	0
EVALUATED FOR EFFICACY (MAXIMUM):	102

RESULTS:

EFFICACY: Ivermectin was effective in reducing skin microfilaria in children. The median decrease from baseline (median of 34.1 mf/mg skin) was significant at Day 3, Months 3 and 6 with changes of -29.3, -33.5, and -32.7 (mf/mg skin), respectively. Greatest reduction from baseline occurred at Month 3. The percentage of patients with a favorable response (< 5 mf/mg skin) was at least 70% for all visits.

SAFETY: Forty-seven clinical adverse experiences were reported in 36 (35.0%) patients. Forty-six were mild, 1 of edema was moderate, none was considered serious. The most commonly reported were headache (23.3%) and myalgia (8.7%) followed by peripheral edema (5.8%) and edema (4.9%). The majority of clinical adverse experiences had a drug relationship of "possibly." Most patients did not have any of the disease-associated signs and symptoms at baseline and remained symptom free after receiving ivermectin. The most frequent symptoms occured on Day 7 and were fever (49/49) and pruritus (16/19). Ivermectin did not precipitate major ophthalmologic deterioration. Patients with mild ocular involvement were generally improved over the 6-month period.

No laboratory adverse experiences were reported.

CONCLUSION: Based on 6-month data a single 150 mcg/kg oral dose of ivermectin is effective and generally safe and well tolerated in children 5 to 12 years of age with onchocerciasis.

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ii. Medical officer comments

This study was conducted so that community-based mass eradication campaigns could safely include children as well as adults. This is important not only so that the individual children might be spared the debilitating effects of infection with onchocerciasis, but also so that children cannot serve as reservoirs of disease within the population, making interruption of transmission all but impossible.

Features of the design and execution of this study that are of particular note include the following:

✦ children from ages 5 to 12 years, weighing 20 to 40 kg, were to be enrolled. These children had to have a baseline skin mf density of at least 10 mf/mg skin and no ocular involvement.

✦ The study was conducted by Dr. M. Lariviere in Odienne, Ivory Coast, West Africa. A total of 103 children were enrolled.

✦ Dosage of ivermectin was 150 mcg/kg, provided as capsule formulation. The capsules were provided in 1, 3, and 6 mg strengths. The study was open-label and there was no placebo control.

✦ Following enrollment, patients were hospitalized at the time of drug administration and observed for seven days, during which time clinical parameters (blood chemistries, CBC, urinalysis, skin biopsies, and ocular examinations) were performed. Following discharge, patients were seen in follow-up at 3, 6, and 12 months post-therapy.

✦ Skin biopsy and ocular examination techniques were identical to those utilized in studies 514 and 519 (no fluorescein angiography was performed).

In general, this study was designed and executed in a manner comparable to the previously-reviewed studies in adults. Thus, relative efficacies should be comparable across these studies.

As seen in table 9 of the Clinical Study Report (page D-1903, volume 1.20 of NDA), the reduction in skin microfilaria density, expressed as a percentage reduction in geometric mean microfilaria/mg of skin, was 99.3% at the 3 month post-therapy endpoint. This is similar to the results seen in adults at this dosage.

With regards to safety results in this study, ivermectin therapy appeared to evoke the same constellation of 'disease-associated' signs and symptoms as were seen in adults. Within the first 1-3 days post-therapy, approximately half of the children treated (49/103, 48%) had fever; 16% (16/103) had pruritus; and 2% (2/103) had lymph node enlargement. These symptoms resolved by the time of the 3 month follow-up visit. The ophthalmologic parameters revealed a similar pattern of response to ivermectin as seen in adults: a transient increase in anterior chamber and corneal microfilariae in some patients at the three day post-therapy timepoint. At the three and six-month timepoints, these ophthalmologic parameters have returned to baseline or improved.

Clinical adverse events, regardless of perceived relationship to drug administration, were reported in 36 of the 103 children, and included 47 events. The most common event reported was headache in 24 (23%) of the children, followed by edema (either peripheral or not otherwise specified) in 11 (11%), myalgia in 9 (9%), and abdominal pain, vomiting, and vertigo in one patient each. Clinical laboratory safety results were also similar to those seen in adults: one child had a decrease in WBC count of 50% or more from baseline, two had increases from baseline of 100% or more in ALT, and 5 had increases of 100% or more from baseline in AST.

iii. Conclusions

The safety and efficacy of ivermectin at a single dose of 150 mcg/kg appears to be the same for children 5-12 years of age as for adults.

D. Study 548: A single-blind, placebo-controlled study of the tolerability, safety, and efficacy of successive single oral doses of ivermectin approximately 150 to 220 mcg/kg in adults with onchocerciasis.

i. Applicant's summary

This study was designed to examine the efficacy and safety of the to-be-marketed tablet formulation of ivermectin, and compare the results with those of the capsule formulation. The applicant's Clinical Study Report can be found on pages D-1811 to D-1838, volume 1.19 of the NDA; the study synopsis is included on the following page:

MERCK SHARP & DOHME RESEARCH LABORATORIES

SYNOPSIS--CLINICAL STUDY REPORT
DATE: 02FEB87

PRODUCT:	Ivermectin, Tablet (6 mg Scored); Placebo	
PROTOCOL & #:	Phase III Onchocerciasis--A Single-Blind, Placebo-Controlled Study of the Tolerability, Safety and Efficacy of Successive Single Oral Doses of Ivermectin (MK-933) Approximately 150 to 220 mcg/kg in Adults With Onchocerciasis	#548-00
INVESTIGATOR & STUDY #:	Dr. P. Vingtain Institut D'Ophthalmologie Tropicale De L'Afrique B.P. 248, Bamako, Mali North Africa	#5545
STUDY DESIGN:	A single-blind, placebo-controlled study	DURATION: 3 years
DOSAGE:	Ivermectin, 150 to 220 mcg/kg; 5 successive single oral doses at 6-month intervals	

PATIENT POPULATION:	TOTAL	IVERMECTIN	PLACEBO
ENTERED:			
MALES (Mean Age--Years)	46	37 (31.1)	9 (30.3)
FEMALES (Mean Age--Years)	39	27 (37.9)	12 (26.5)
TOTAL	85	64	21
COMPLETING STUDY:	85	64	21
WITHDRAWN:	0	0	0
SAFETY (CLINICAL AND LABORATORY)			
Rx FAILURE			
OTHER			
EVALUATED FOR EFFICACY (MAXIMUM):	71	55	16
ADVERSE EXPERIENCES (Patients)			
CLINICAL	43	38	5
LABORATORY	0	0	0

RESULTS:

EFFICACY: No formal analysis of the data was performed. Summary statistics of the data for the first 4 days after the first dose suggest that ivermectin, administered in tablet form, reduced skin microfilaria counts to near 0 levels while skin microfilariae decreased only slightly in the placebo-treated patients. The proportion of patients with a favorable response (< 5 mf/mg skin) at Day 4 post-treatment was 53/55 (96.4%) and 2/16 (12.5%) for ivermectin- and placebo-treated patients, respectively.

SAFETY: Clinical adverse experiences reported by the investigator are listed below. All were transient, none was considered serious.

	MK-933	PLACEBO	TOTAL
Patients entered	64	21	85
Patients completed	64	21	85
Clinical AEs	38 (59.4%)	5 (23.8%)	43 (50.6%)

No laboratory AEs were reported.

CONCLUSION: Ivermectin, in a single oral dose of 150 to 220 mcg/kg in tablet form, appears to be safe and effective in reducing skin microfilaria counts to near 0 levels within 3 to 4 days.

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ii. Medical officer comments

This study is important because it is the only clinical study included in the NDA which utilizes the to-be-marketed formulation in the treatment of onchocerciasis. Unfortunately, the design and execution of this study are suboptimal:

- ✦ there is no direct comparator arm using the capsule formulation
- ✦ there is no attempt to collect any clinical pharmacokinetic information
- ✦ there are no data presented past the day 4 post-therapy timepoint, although the study design calls for the usual 3 and 6 month post-therapy timepoints.

The day 4 results from this study can be compared to the results seen in the above-reviewed capsule studies. Specifically, the percent geometric mean reduction from baseline in microfilariae/mg of skin tissue was 97.1% and the safety profile was similar to that seen in the previous studies.

DAY 4 POST-THERAPY RESULTS
ALL CLINICAL STUDIES OF ONCHOCERCIASIS

Study #	Treatment/ formulation	Dose	N	Geometric mean mf/mg skin			Percent of pre-Rx (Geo. Mean)
				pre-Rx	post-treatment		
					day 3	day 4	
514	Ivermectin capsules	12 mg	47	60.5		3.6	6%
	DEC-C	1350 mg	49	55.9		3.8	7%
519	Ivermectin capsules	100 mcg/kg	254	51.4	13.5		26.3%
		150 mcg/kg	249	47.8	8.1		16.8%
		200 mcg/kg	254	51.8	6.7		12.9%
545	Ivermectin capsules	150 mcg/kg	101	36.4	2.1		5.8%
548	Ivermectin tablets	150-220 mcg/kg	55	23.9		0.7	2.9%

The day 4 results from study 548 show somewhat better parasite killing than was seen in the previously-reviewed studies. This may in part be explained by the fact that the patients enrolled in study 548 did not have as heavy a parasite burden as did the patients enrolled in studies 514 and 519. Furthermore, one additional day between dosing and measurement of parasite killing would be expected to show more eradication of microfilariae in those patients seen at day 4 as opposed to day 3 post-therapy. At the very least, these data indicate that the tablet formulation appears to be at least as effective as the capsule formulation in eradicating skin microfilariae.

Safety results from study 548 showed a profile of disease-associated signs and symptoms that is similar to

that seen in the other ivermectin studies. For comparison purposes, the following table presents the results of the most characteristic disease-associated and treatment-associated signs and symptoms across studies:

Study #	Treatment	Disease-associated signs and symptoms			Treatment-associated signs and symptoms	
		skin pruritus	fever	arthralgia/ synovitis	headache	myalgia
514	Iver 12 mg	19/37 (51%)	11/29 (38%)	8/32 (25%)	13/50 (26%)	15/50 (30%)
	DEC	42/47 (89%)	25/34 (74%)	15/39 (38%)	19/50 (38%)	19/50 (38%)
519	Iver 100 mcg	83/317 (26%)	54/314 (17%)	27/316 (9%)	67/319 (21%)	67/319 (21%)
	Iver 150 mcg	83/318 (26%)	71/313 (23%)	30/319 (9%)	70/322 (22%)	57/322 (18%)
	Iver 200 mcg	99/319 (31%)	93/316 (29%)	33/319 (10%)	78/322 (24%)	66/322 (20%)
545	Iver 150 mcg	16/103 (16%)	49/103 (48%)	3/103 (3%)	24/103 (23%)	9/103 (9%)
548	Iver 150 mcg tablets	27/64 (42%)	13/61 (21%)	32/64 (50%)	35/64 (55%)	9/64 (14%)

As can be seen in this comparative table, the rates of disease-associated signs and symptoms seen in study 548 were somewhat higher than seen in study 519. This would be expected, as the killing of microfilariae (as indicated in the previous table) was fairly rapid in this study. DEC, in general, has the most rapid killing kinetics and is more reactogenic than ivermectin.

Even though the symptoms 'headache' and 'myalgia' are referred to as "Treatment-associated signs and symptoms" in this table, these symptoms are probably particular to onchocerciasis patients as well. They are presented as a separate category in this table because they are outside of the constellation of signs and symptoms that comprise the Mazzotti reaction. If headache and myalgia were truly treatment associated, one would expect to see a similar pattern of adverse events in the strongyloidiasis patients as well. This was not the case.

iii. Conclusions

Study 548 was the only study submitted in this NDA in which the to-be-marketed tablet formulation was studied in a field trial of onchocerciasis patients. Unfortunately, data were only submitted out to the day 4 post-therapy timepoint. Overall, the safety and efficacy of the tablet formulation appears to be comparable to that seen in the capsule formulation studies. From the results submitted, there does not appear to be any evidence that the bioinequivalence of the tablet, as discussed in the biopharmaceutics review of this NDA, is of any clinical significance. However, since the three month post-therapy timepoint was used as the primary endpoint for all other studies mentioned in this review, no further comment regarding comparative efficacy (tablet vs. capsule) can be made.

4. Medical officer review of literature

In addition to the clinical studies reviewed above, the NDA contains an extensive amount of literature submitted in support of the onchocerciasis indication. Several of these key references have been cited above, as they were the result of Merck-sponsored studies 514 and 519.

A separate volume of the NDA (vol. 1.25) is entitled "Published Clinical Literature". The index to this volume lists 404 references, all of which are submitted in abstract form. These references address a variety of aspects of the use of ivermectin in the treatment of onchocerciasis. The reader is referred to this volume if further specific information is sought. In general, these references support the use of ivermectin in mass treatment programs for onchocerciasis. Most of the investigations were performed with the tablet formulation, and the results of these studies are consistent with the results cited in the submitted clinical studies using the capsule formulation. Several abstracts refer to the use of ivermectin in returning travelers who have acquired onchocerciasis; these abstracts support the safety and efficacy of ivermectin in this setting, including the need for retreatment at 3 to 6-month intervals.

5. Statistical considerations

As mentioned previously, the applicant submitted electronic datasets for portions of the onchocerciasis studies reviewed above. These datasets were analyzed by Dr. Sue Bell of DAIDP. The reader is referred to Dr. Bell's portion of this NDA review for her findings. In general, her review confirmed the applicant's analysis of the data as presented in their Clinical Study Reports.

6. Conclusions regarding Onchocerciasis indication

Since its introduction into clinical use in the early 1980's, ivermectin has become the drug of choice for the treatment and control of onchocerciasis. The applicant has established the Mectizan Donation Program, through which ivermectin has been donated to the WHO's Onchocerciasis Control Programme since 1987. In the ensuing 8 years prior to the submission of this NDA, an estimated 36 million doses have been distributed to over 5.2 million persons in onchocerciasis-endemic areas of the world.

The studies submitted by the applicant demonstrate that the capsule version of ivermectin is more effective than DEC-C in eradicating skin microfilariae, is better tolerated than DEC-C in these patients, and maintains its activity for over three months following administration. The medical literature lends further support to these early clinical studies, and indicates that the tablet formulation (which has been in use worldwide since 1989) is as safe and efficacious as the original capsule version.

How, then, to address the Biopharmaceutical reviewer's findings of bioinequivalence between the capsule and the tablet? One possible way to resolve this finding would be to repeat the study, using a larger number of subjects to see if the initial bioequivalence finding was partially the result of small sample size. Unfortunately, the capsules are no longer available (and if any could be located they would be long since past their expiration date) and thus the study cannot be repeated. Is there another way to seek assurance from within the submitted studies that the tablet formulation is acceptable?

Studies 514 and 519 used identical methodology for assessing parasite burden and response to therapy. In fact, these studies share several investigators in common. Thus it is appropriate to do a cross-study comparison. Keeping in mind that Dr. Colangelo's biopharmaceutics review suggests that the tablet may be less than 80% of the capsule in terms of bioavailability, and that the requested dose for onchocerciasis is 150 mcg/kg, it is fortunate that the study design of study 519 included a 100 mcg/kg arm. If the tablet truly delivers only 75% of the dose delivered by the capsule, then the 100 mcg/kg arm is relevant since this represents 66% of the requested 150 mcg/kg dose. If this treatment arm of study 519 is compared to the DEC-C active control arm of study 514 (keeping in mind that this is the FDA-approved therapy for onchocerciasis), one sees that ivermectin compares quite favorably:

	100 mcg/kg arm of study 519	DEC arm of study 514
N at entry	319	50
density of infection		
baseline (mf/mg, x̄ [range])	47.3 (0.5-352.2)	57.1 (9.8-228.9)
day 4 (% of baseline)	26.3%*	3.8%
day 30	------	3%
3 month	1.8%	14%
6 month	2.9%	11%

* in study 519, this measurement was at day 3 post-therapy rather than day 4

Additional information pertinent to this issue has been included in the NDA, to include the day 4 results of study 548 and the large amount of medical literature that has been published since the introduction of the tablet formulation to the Onchocerciasis Control Programme.

Therefore it is the conclusion of this medical officer that the finding of bioinequivalence does not render this indication nonapprovable. The great preponderance of clinical information, as well as the cross-study comparison noted above, support the efficacy and safety of the tablet formulation of ivermectin at a dose of 150 mcg/kg in the treatment of onchocerciasis.

7. Recommendations

The onchocerciasis indication should be approved, at a single dose of 150 mcg/kg in adults and children over 15 kg in weight. The labeling should also state that repeated dosing at 3 month intervals is appropriate, since ivermectin has no activity against the adult parasites.

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HFD-520

cc:
NDA 50-742
HFD-520
HFD-520/SMO/Leissa BL 11/21/96
HFD-520/MO/Coyne
HFD-520/CSO/Fogarty
HFD-520/Chem/Timper
HFD-520/Micro/King
HFD-520/Pharm/Adeyemo
HFD-520/Biopharm/Colangelo
HFD-520/Stats/Bell
HFD-344/Thomas

Concurrence only:
ODE IV/OD/
HFD-520/ActDivDir/DFeigal 11-26-96
HFD-520/DepDivDir/LGavrilovich

16 Pages
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Medical officer comment:

The individual reports on each of these 15 elderly patients have been carefully reviewed. These patients all had extreme debility, and many appeared to have begun a downward clinical spiral well before the administration of ivermectin. There were no concomitant medications that appeared to have been administered that would suggest a possible drug-drug interaction. Thus, the medical officer agrees with the conclusions presented on page 12 of the Merck report.

Because this drug has been used in millions of patients at doses similar to that used in the Wentworth Lodge scabies outbreak, and appears to be exceedingly safe when used for its approved indications, it would seem to be unlikely that such a cluster of deaths would be directly attributable to ivermectin. The confounding medical conditions seen in these elderly institutionalized patients, along with the wide range in time between dosing and death, seem to argue convincingly against any direct association with ivermectin.

It should be noted that, although the reporting physician (Dr. Barkwell) may have performed a suboptimal epidemiological study in his investigation of these deaths, he at the very least should be recognized as seeing the importance of attempting some sort of retrospective case-control study. The investigation by Merck, while making great efforts to point out the inadequacies of Dr. Barkwell's analysis, made no attempt to perform a case-control study of a better design. If Dr. Barkwell's choice of a control group was inappropriate, then perhaps the Merck investigators might have chosen a more appropriate control group (perhaps age and sex-matched controls from within the Alzheimer's unit). Furthermore, Dr. Barkwell was the physician on-site both before and during the episode. His suspicion that his patients were declining and dying at a rate that exceeded the norm seen at his institution is a clinical hunch that merits recognition. It appears to be an unsubstantiated hunch, but the observation warranted a complete evaluation.

The Canadian Health Protection Branch (HPB), immediately following the reporting of this episode, placed a clinical hold on their emergency release program for ivermectin treatment of scabies. In preparing this Safety Update review, this medical officer contacted HPB both telephonically and by electronic mail. Following the Canadian investigation of this episode, HPB reached the same conclusions (i.e. that there was no causality identified) and has reinstituted the scabies emergency release program. There have been no further reports of ivermectin-related deaths from the Wentworth Lodge.

In conclusion, then, this medical officer agrees with the Merck report found above. There is insufficient information from this episode to warrant any addition to the Geriatric Use section of the ivermectin product labeling.

B. Nonfatal serious AE's: human use product

The one nonfatal serious AE reported to Merck during the reporting period is detailed in WAES report which describes the case of an 18-year old Cameroonian male who was treated with ivermectin in the context of an onchocerciasis eradication program. The patient experienced joint pains 24 hours following a single dose of ivermectin, then two days later was found unconscious. He was hospitalized where he was found to be febrile and comatose, with spastic hypertonicity. Microfilariae of *Loa loa* were detected in blood, urine and cerebrospinal fluid. Over the following week his clinical status steadily improved. No further information was available.

Medical officer comment:

It is unclear whether this case represents some sort of toxicity to ivermectin (unlikely), an immunologic event related to the response of the patient's onchocerciasis to ivermectin therapy(unlikely), or an encephalopathic event sometimes seen in patients who are infected with Loa loa when treated with an anthelminthic (most likely). The report comes from Yaounde, which is at the perimeter of the loiasis-endemic zone of Cameroon.

A relevant reference is included in Section 5 of the Safety Update: "Five cases of encephalitis during treatment of loiasis with diethylcarbamazine" by Carme et al, found in Am J Trop Med Hyg 48(6): 684-90, 1991. This article describes the rare phenomenon of treatment-induced encephalopathy when patients with high Loa loa microfilarial loads are treated with filaricidal drugs. Although this phenomenon is of theoretical concern in ivermectin-treated onchocerciasis patients from areas co-endemic for loiasis, it does not appear to be of significant

concern despite many years of use in such co-endemic areas.

C. Serious AE's due to agricultural/veterinary ivermectin exposure

Other formulations of ivermectin have been available in the US and elsewhere for several years. The agricultural product (abamectin) and the veterinary product (ivermectin for topical, injectable, and oral administration) are extensively used for control of nematodes and ectoparasites. Occupational exposures occur with these products: topical formulation sometimes splashes on the user's face or hands, and agricultural product can also come in contact with the user's skin during handling and preparation.

The following cases were reported in which patients had serious AE's after accidental (or intentional) exposure to these non-human formulations of ivermectin:

WAES 43 year old female from the UK with a history of delusional parasitosis had self-administered 6-gram doses of ivermectin (animal use) from 30 to 50 times over the course of one year. She also self-administered furosemide and steroids. She was admitted to a London hospital for a full evaluation for parasitic infection, was found to be cushingoid and hypokalemic, but checked out of hospital against medical advice. No follow-up was expected.

Medical officer comment:

The scenario commonly referred to as 'delusional parasitosis' infers that a patient, despite multiple failed attempts to discover a parasitologic etiology for their symptom complex, has remained convinced that he/she is infected with a parasite of some sort. Frequently, these patients are convinced they have an ectoparasite such as scabies or pediculosis. Other parasitic diseases implicated in this disorder include loiasis, onchocerciasis, strongyloidiasis, and myiasis. Many of these diseases are potentially treatable with ivermectin; thus, the use of ivermectin by these patients is not unusual. The unavailability of ivermectin on the US market has led some patients (and their physicians) to use veterinary product, according to internet correspondence reviewed by this medical officer.

If the history of the above patient is accurate, it would at the very least seem to attest to the relative safety of ivermectin. Aside from hypokalemia (which was most probably due to furosemide abuse), no other laboratory abnormalities were noted.

WAES A male of unknown age committed suicide in Germany by ingesting multiple pesticides, as well as ivermectin. The reporter is listed as the police department in Traunstein, Germany. No additional information is expected.

Medical officer comment:

Since this case involved exposure to multiple agents, it would be difficult to interpret even if extensive additional information were to become available.

WAES A male of unknown age used topical ivermectin for animal use on his cattle in Oklahoma. One day following use, the patient developed generalized body rash, swelling, and joint pains which resolved 3-4 days later. No accidental ingestion or topical exposure had been experienced prior to this event.

Medical officer comment:

The physician treating this patient did not ascribe any causative role to ivermectin, but the event was reported by the patient's wife. The symptoms experienced by this patient are similar to those experienced by onchocerciasis patients given ivermectin.

WAES A 41 year old Argentinian male ingested a bottle of avermectin for animal use (??dose) along with a liter of wine in an apparent suicide attempt. At the time of presentation to an emergency room, he "presented obnubilation (sic) and slight mydriasis as a consequence of an acute intoxication". Vital signs and exam were normal otherwise. Appropriate measures were undertaken (lavage, activated charcoal, saline purge) and the patient was

admitted to the ICU where he had an uneventful and complete recovery.

Medical officer comment:

Pupillary dilatation has not been described previously with ivermectin. It is unclear whether any other substances had been ingested which may have produced this effect. The noted slight mydriasis may well have been a physiologic response.

D. Serious AE's included in Annual Report to IND

The applicant submitted the annual report to IND on September 12, 1996. This report covers the period 18 July 95 to 17 July 96. Since the Safety Update to the NDA included the time period up to 31 May 96, this IND Annual Report captures an additional one and one-half month of AE reporting.

In addition to the deaths reported by Dr. Barkwell in Canada, which have been extensively reviewed above, the Annual Report to the IND lists the following deaths:

WAES	A 44 year old male patient with AIDS died of respiratory failure
WAES	An 83 year old male patient died of myocardial infarction

No narrative summary information was included for these two deaths.

E. Non-serious AE's included in Annual Report to IND related to exposure to veterinary ivermectin

The applicant has also included a number of reports of exposure to various veterinary formulations of ivermectin. A brief listing of the events as characterized in the narrative summaries follows:

WAES #	age/sex	exposure	event*
	41 M	topical	abdominal cramps, headache, increased ALAT
	?? F	topical	pregnant patient exposed at 16 weeks gestation
	50 F	ingestion	--
	46 M	ingestion	--
	30 F	ingestion	--
	36 M	injection	--
	?? M	topical	--
	3 ??	ingestion	--
	?? M	topical	--
	?? F	ingestion	see above (patient with delusional parasitosis)
	65 M	topical	"Felt ghastly, decidedly groggy"
	?? M	ingestion	intentional self-treatment of parasite infection
	35 M	injection	upset stomach
	30 M	injection	redness, swelling, and pain
	20 M	injection	--
	?? M	topical	splash in eyes resulted in erythema, irritation
	?? M	topical	splash in eyes resulted in irritation
	2 F	ingestion	--
	30 M	topical	splash in eyes without reaction
	9 M	ingestion	--
	43 F	topical	--
	?? F	topical	--
	?? M	topical	vomiting, diarrhea

Non-serious exposures to animal or agricultural ivermectin (con't)

WAES #	age/sex	exposure	event*
	80 M	topical	dry eyes, change in eyesight
	21 F	injection	--
	33 F	injection	--
	29 M	injection	--
	51 M	topical	--
	84 F	ingestion	--
	42 M	injection	hypotension, nausea, injection site swelling
	70 M	topical	erythema, swelling of hands, vertigo, paresthesia
	2 F	ingestion	--
	31 M	topical	nausea, anxiety, tremors
	37 F	topical	--
	?? F	injection	--
	50 M	injection	--
	34 M	topical	diarrhea
	?? M	ingestion	--
	??F	ingestion	--
	33 M	injection	numbness, swelling at site
	?? M	topical	shortness of breath
	56 M	ingestion	--
	?? ?	topical	rash
	25 F	topical	exposure in nursing female; no event reported
	23 F	inhalation	diarrhea, abdominal cramping, skin rash
	62 F	ingestion	--
	62 M	injection	rash, weight loss, fatigue
	2 F	ingestion	--
	?? F	injection	nervousness
	2 M	ingestion	--
	?? M	injection	swelling at site
	4 M	ingestion	--
	36 F	topical	splash into eyes; nausea, drowsiness ensued
	?? F	injection	--
	?? M	ingestion	--
	?? M	topical	headache, fever, skin tingling
	29 F	topical	urticaria, rash
	38 F	topical	splash into left eye led to severe pain, conjunctival edema, erythema, ulceration of cornea, nausea
	?? M	topical	stomach cramps, nausea, headache
	33 M	injection	swelling and pain at site
	?? F	ingestion	warm heart feeling, dry mouth
	75 M	ingestion	--
	?? F	ingestion	--
	2 F	ingestion	--
	30 F	ingestion	--
	2 F	ingestion	--
	33 F	ingestion	accidental exposure in pregnant woman
TOTALS:		Ingestion	25
		Topical	25
		Injection	17
		Inhalation	1

* Many of the reports have no associated adverse events reported, as depicted by the dashed lines.

Medical officer comments:

There are numerous ingestion events of the 25 total, particularly those in pediatric subjects, that are the result of accidental ingestion of veterinary ivermectin kept in the household for the family dog. In the majority of these, no adverse events have been reported. The exact amount of drug exposure in these cases is not reported; a variety of dose sizes are on the market that are intended for different weight ranges of dogs.

The most striking aspect to these reports is the apparent irritant effect of topical ivermectin when it is splashed into the eyes. Of the five such events reported, all had some degree of eye irritation; one actually proceeded to corneal ulceration. It is unclear whether this is due to ivermectin itself or one of the excipients in the formulation.

Several of these topical exposures resulted in systemic symptoms such as nausea and headache, suggesting that there may be some systemic absorption following such topical exposure.

3. Conclusions

This Safety Update raises no new concerns over the safety of human use ivermectin. The only finding of any significance in this update is the episode at Wentworth Lodge in Ontario, Canada.

Any reported cluster of deaths warrants close scrutiny, particularly when the initial report claimed to show a statistically significant association between ivermectin therapy and death. The applicant has thoroughly investigated this event, generating WAES forms that are striking in their complete clinical documentation of each patient involved. Reading each of these cases leads one to the conclusion that these elderly patients suffered from the debilities of old age.

4. Recommendations

The product labeling for ivermectin warrants no additional editing on the basis of the information submitted in this safety update. Therefore, no further action is indicated.

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Reviewing Medical Officer
HFD-520

cc:
NDA 50-742
HFD-520
HFD-520/SMO/Leissa BL 11/21/96
HFD-520/MO/Coyne
HFD-520/CSO/Fogarty
HFD-520/Chem/Timper
HFD-520/Micro/King
HFD-520/Pharm/Adeyemo
HFD-520/Biopharm/Colangelo
HFD-520/Stats/Bell
HFD-344/Thomas

Concurrence only:
ODE IV/OD/
HFD-520/ActDivDir/DFeigal 11-21-96
HFD-520/DepDivDir/LGavrilovich

Clin. Pharm. / Bio

SEP 3 1996

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA: 50-742

Submission Date: March 29, 1996

Product: Ivermectin 6 mg Tablets
(MECTIZAN®)

Sponsor: Merck Research Laboratories
West Point, PA

Type of Submission: Original NDA

Priority Category: 1P

OCPB Reviewer: Philip M. Colangelo, Pharm.D., Ph.D.

I. SYNOPSIS

Section 6, Human Pharmacokinetics and Bioavailability, contained the following studies that were conducted by the sponsor (see also Table I-1 for details):

- Radiolabeled Metabolic Disposition Study in Healthy Male Subjects
- Single Dose Proportionality Crossover Study in Healthy Male Subjects
- Bioavailability of Clinical Capsule, Market Image Tablet, and Oral Hydroalcoholic Solution in Healthy Male Subjects
- Single Dose Excretion into Breast Milk of Lactating Women

All of these studies were conducted between 1986 and 1988 to support the approval of the 6 mg tablets in France for the treatment of onchocerciasis. All initial tablet formulations used in these pharmacokinetics/biopharmaceutics studies did not include antioxidants. All tablet formulations used in the clinical efficacy strongyloides trials contained small amounts of antioxidants (i.e., final marketed formulation). Since the clinical efficacy studies for the strongyloides claim were conducted exclusively with the final market image tablet, no additional pharmacokinetics/biopharmaceutics studies were conducted with this formulation, i.e., either in association with the approval for treatment of strongyloides in France or with this current NDA submission. The results of *in vitro* dissolution testing showed comparable and acceptable rates of dissolution for the final market image 6 mg tablet (i.e., with antioxidants), the initial 6 mg tablet formulation (i.e., without antioxidants), and the clinical 6 mg capsule formulation used in the onchocerciasis trials.

Table I-1 **Table of Investigations**

Study No. [Ref.]	Study Objective/ Study Design	Dosage Forms	Formulation No. (Batch Size)	Dose	Number of Subjects (S) Patients(P)	Conclusions
2 [I-5]	Evaluation of (^{3}H)ivermectin absorption, distribution, metabolism and excretion/ Single-dose study	14-mg Ivermectin Capsule	R0933-DFC-002-A001 (14)	14 mg (200 µCi)	4S (All M)	Mean T_{max} for ivermectin was 6 h; corresponding $t_{½}$ was 11.8 h. C_{max} of tritiated metabolites was twice that of parent drug. Drug and metabolites are slowly secreted in bile and excreted in feces. No more than 1.0% of the dose was excreted in urine.
5537 [I-6]	Evaluation of dose proportionality/Single dose (SD), three-way crossover study	3-mg Ivermectin Tablet 6-mg Ivermectin Tablet	E-3806 (390) E-3807 (2305)	6 mg 12 mg 15 mg	12S (All M)	Following SD of 6, 12, and 15 mg, mean C_{max} and AUC were proportional to dose although substantial variability was observed.
5535 [I-7]	Evaluation of Phase III capsule and to-be-marketed tablet vs. oral solution/ Single-dose, three-way crossover study	6-mg Ivermectin Capsule 6-mg Ivermectin Tablet 0.6 mg/mL hydroalcoholic solution (40% ethanol)	E-6086 (200) E-3807 (2305) E-3798 (500 mL)	12 mg 12 mg 12 mg	12S (All M)	The oral solution showed higher (close to twice) bioavailability than either of the solid forms. The tablet formulation showed comparable bioavailability to the capsule formulation. The relative bioavailability of the capsule was 113% of the tablet.
5533 [I-8]	Estimation of ivermectin's secretion into human breast milk/Single-dose study	0.5-mg Ivermectin Capsule 2.5-mg Ivermectin Capsule	E-5885 (1000) E-5893 (1000)	5 mg 12 mg	12S (All F)	Orally administered ivermectin is secreted in human milk. The highest concentration observed was 18.5 ng/mL after the 12-mg dose. Drug was still detectable 14 days postdose.

It is noteworthy from Table I-1, that the batch size of ~2300 for the 6 mg tablets used in the bioavailability study (i.e., Lot No. 3807) represented only ~2-3% of the market/stability batches manufactured in 1987 (~83,000-97,000 tablets) and < 1% of the market/stability batches manufactured from 1989 to 1995 (~420,000-600,000 tablets). Thus, these percentages were substantially lower than the currently employed ratio of ~10% for bioavailability batch sizes to production batch sizes.

The results of the radiolabeled metabolic disposition study indicated that systemic exposure to drug-related radioactivity, determined as ^{3}H-metabolite(s) of ivermectin, appeared to be greater than that of parent ivermectin. The mean plasma Cmax for the ^{3}H-metabolite(s) was approximately twice that of ivermectin. Also, the ^{3}H-metabolite(s) persisted longer in plasma than that of parent ivermectin and appeared to be related to the slower rate of disappearance of the ^{3}H-metabolite(s), i.e., half-time of ~3 days compared to an effective T½ of ~12 hours for ivermectin. An effective T½ was determined rather than the true elimination T½ since the plasma drug concentration-time profiles showed evidence of enterohepatic recycling (see **Section VI. 1.** for details). No parent ivermectin was detectable in urine and only ~0.6% of the radioactive dose was recovered in the urine at 4 days postdose. The predominate pathway of excretion appeared to be fecal, with ~50% of the radioactive dose recovered in the feces at 5 days postdose. This suggested that some of the drug and/or metabolites are excreted in the bile and ultimately eliminated in the feces. Based on the mean half-time of radioactivity of ~3 days, it would take ~12 days (4 x half-time) to recover nearly all the radioactive dose (~95%) in the feces.

The results from the dose proportionality study (i.e., 6, 12, and 15 mg as tablets) suggested increases in systemic exposure to ivermectin that were approximately proportional to dose. However, the overall variability in the AUC(0-72) and Cmax data (i.e., as %CV) between subjects was wide, ranging from ~50-70% across all three doses. The statistical analysis (ANOVA) of the dose-adjusted AUC(0-72) data (i.e., to the 6 mg dose) detected a statistically significant difference in the 12 mg vs. 6 mg comparison ($p = 0.03$), with the 12 mg dose producing a lower estimate. No other significant differences were detected in the dose-adjusted AUC comparisons and none were detected in the dose-adjusted Cmax comparisons. This reviewer concurs with the sponsor's conclusion that the deviation from strict dose proportionality in AUC(0-72) between the 12 and 6 mg doses would not be expected to be clinically significant.

In order to verify the ~12 hour effective T½ estimated from the small number of subjects in the radiolabeled metabolic disposition study, this reviewer requested the sponsor to determine this parameter for the 6 and 12 mg doses in the dose proportionality study using the same calculation method as in the metabolic disposition study (see **Section VI. 2.** for details). The mean effective T½ estimates for the 6 and 12 mg doses were similar at 16.8 and 16.7 hours, respectively, and were longer than that determined in the metabolic disposition study. Thus, it appeared that the T½ of ivermectin was at least ~16 hours, if not potentially longer.

The results from the bioavailability trial (i.e., 2 x 6 mg clinical capsules vs. 2 x 6 mg market image tablets vs. oral solution 12 mg) showed significantly higher AUC(0-72) and Cmax estimates for the solution as compared to either the capsules or tablets (~2-fold higher). No statistically significant differences were detected by ANOVA between the mean AUC(0-72) and Cmax estimates. Mean Cmax values following single 12 mg doses were 50.6 ng/ml for the capsules and 46.6 ng/ml for the tablets, with mean Tmax at 3.7 and 3.6 hours, respectively. The sponsor did not provide an evaluation of bioequivalence between the tablet (as test formulation) and capsules (as reference formulation) using the 90% confidence intervals on the tablet/capsule ratios calculated based on the currently accepted two one-sided test procedure. Instead, posterior probabilities and 95% confidence intervals for AUC and Cmax were calculated (see **Section VI. 3.** for details) using the ratio of capsule/tablet, i.e., using the tablet as the reference instead of the test formulation. The sponsor concluded that any differences in systemic availability of the capsules vs. the tablets were most likely (i.e., ~90% probability) to be less than 30% and probably (i.e., ~80% probability) less than 25%. However, the sponsor failed to note that differences of 20% or less had only a ~70% probability of occurrence. The latter difference of 20% being that which the currently accepted two one-sided test procedure for evaluation of bioequivalence is based upon. The bioequivalence of the market image tablet relative to the clinical trials capsule formulation was evaluated by this reviewer using the currently accepted two one-sided test procedure, as mentioned above. The 90% confidence intervals for AUC(0-72), i.e., (66.8%, 117.1%) and Cmax, i.e., (75.3%, 120.5%) indicated that the systemic availability of ivermectin from the market image tablets was less than that from the clinical capsules. This finding of bioinequivalence should be weighed against the results of the clinical efficacy and safety in the onchocerciasis trials in order to determine the relevance.

The results from the breast milk excretion study indicated that ivermectin was present in the milk of lactating women after a single dose of 12 mg (as capsules), maximum milk concentrations occurred on the first day following the dose (mean 7.6 ng/ml at 4 hours), and had substantially decreased thereafter, but remained detectable (> ~0.1 ng/ml) for up to 14 days postdose. The maximum intake of drug by a nursing infant (3 kg body weight) was estimated to be ~3 mcg/kg on the first day of single dose ivermectin administration and represented a minimal intake as compared to the recommended adult dosages of 150-200 mcg/kg (i.e., ~2% of adult doses). The mean intake of drug at 14 days postdose, the end of the study, was estimated to be ~0.1 mcg/kg in a nursing infant (i.e., ~0.05%-0.07% of the adult doses).

The sponsor commented in the Clinical Summary Section of this NDA that in light of the limited information concerning the development of the blood brain barrier in newborn infants, that treatment with ivermectin in mothers who intend to breast feed be withheld until at least 1 week after the birth of the child. This recommendation was also provided for in the proposed labeling. Thus, it appeared that the sponsor considered drug exposure through ingestion of mother's milk to the nursing infant to be of minor consequence in infants with fully developed/intact blood brain barriers. The conclusions

appeared to be appropriate based on the results of this study and of the oral toxicity study conducted in neonatal monkeys (i.e., < 2 weeks old). In this species, which has been reported to be more predictive of the human response to ivermectin than rodent models, no evidence of toxicity was observed at doses up to 100 mcg/kg/day.

II. RECOMMENDATION

The studies in the Human Pharmacokinetics and Biopharmaceutics Section of this NDA have been reviewed by OCPB. In the bioavailability study (NDA Study No. 5535), the market image 6 mg ivermectin tablet formulation was found by this reviewer to be bioinequivalent to the capsule formulation used in the onchocerciasis clinical efficacy and safety trials. In light of the fact that ivermectin tablets have been distributed worldwide for the treatment of onchocerciasis, it is urged that the reviewing medical officer weigh this finding of bioinequivalence against the clinical evaluation (i.e., efficacy and safety) of ivermectin in the treatment of this disease. Comments 1 through 3 should be conveyed to and adequately addressed by the sponsor.

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III. BACKGROUND

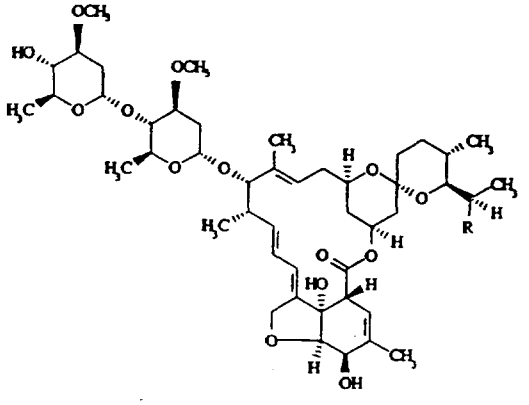
Ivermectin is a semisynthetic macrocyclic lactone in the avermectin series of anti-parasitic agents. It possesses potent anthelmintic activity and has been registered for agricultural/veterinary use since 1981 for the treatment of infestations by *Onchocerca* and *Strongyloides* species of nematodes. Ivermectin is not sold in the U.S. for human use, but it is used in the U.S. and abroad in many countries for the clinical treatment of onchocerciasis (a.k.a. river blindness). The 6 mg tablets are donated exclusively by the sponor and distributed worldwide through the World Health Organization's Onchocerciasis Control Program. In France, the drug was approved for use in onchocerciasis in 1988 and was more recently approved for use in strongyloides of the gastrointestinal tract in 1993.

The sponsor has filed this NDA to support the use of MECTIZAN® 6 mg tablets for the treatment of (1) onchocerciasis at a single dose of 150 mcg/kg (not to exceed 12 mg ivermectin/dose) and (2) strongyloides of the gastrointestinal tract at a single dose of 200 mcg/kg (not to exceed 18 mg ivermectin/dose) in humans.

IV. DRUG CHARACTERISTICS and DOSAGE FORMULATION

1. Physical and Chemical Characteristics

Ivermcetin is a mixture of two closely related homologues (H_2B_{1a} and H_2B_{1b}) of the class of compounds known collectively as avermectins. The mixture contains at least 90% H_2B_{1a} and less than 10% H_2B_{1b}. The chemical structures are as follows:



Molecular formulas and relative molecular masses:

H_2B_{1a} (R = C_2H_5): $C_{48}H_{74}O_{14}$; M.W. - 875.10

H_2B_{1b} (R = CH_3): $C_{47}H_{72}O_{14}$; M.W. - 861.07

Solubility is greatest in solvents of intermediate polarity. Ivermectin is insoluble in water (< 0.001 g/L), but freely soluble (> 200 g/L) in solvents such as methanol, ethyl acetate, and methylene chloride. It is soluble (10-100 g/L) in ethanol, diethyl ether, acetone, and aromatic hydrocarbons.

2. Dosage Formulations and Dissolution

a. Formulation History

During the course of the clinical program for onchocerciasis (i.e., to support registration in France in 1988), the initial formulations were capsules of varying strengths, ranging from mg ivermectin and also 14 mg [^{3}H]-labeled ivermectin. All capsules, except for the 14 mg [^{3}H]-labeled ivermectin capsules, contained microcrystalline cellulose and magnesium stearate as inert ingredients. The capsules were used in all Phase III clinical onchocerciasis safety and efficacy trials and in the following pharmacokinetics/biopharmaceutics NDA studies: metabolic disposition (as 14 mg [^{3}H]-labeled ivermectin), bioavailability, and excretion in human breast milk.

The 3 and 6 mg tablets replaced the capsules and these were used in the dose proportionality and bioavailability studies of the NDA. The tablet ingredients, which show proportionality in composition, were as follows:

Initial Tablet Formulations

Ingredient	**Amount (mg/tablet)**	**Amount (mg/tablet)**
Ivermectin		
Microcrystalline Cellulose, NF		
Pregelantinized Starch, NF		
Mg Stearate, NF		

A bioavailability/bioequivalence study was performed between the 6 mg tablet and the 6 mg clinical capsule to establish a link between the clinical trials and proposed marketing formulations. After the completion of the pharmacokinetics/biopharmaceutics studies with these tablets and prior to submission of the original French registration package, small amounts of antioxidants were added to prevent discoloration. Thus, the final market image 6 mg tablet contained the following ingredients:

Final Market Image Tablet Formulation

Ingredient	**Amount (mg/tablet)**
Ivermectin	
Microcrystalline Cellulose, NF	[redacted]
Pregelantinized Starch, NF	[redacted]
Mg Stearate, NF	[redacted]
Butylated Hydroxyanisole, NF	[redacted]
Citric Acid, USP	[redacted]
Total Weight	[redacted]

The addition of the antioxidants represented ~0.02% of the total tablet weight and the increase in microcrystalline cellulose from mg represented ~0.5% of the total tablet weight.

This final tablet formulation, which has been distributed for use in onchocerciasis, was used in the clinical safety and efficacy studies to support the eventual French registration of ivermectin for the strongyloidiasis indication. Thus, no additional pharmacokinetics/biopharmaceutics studies with this final formulation were deemed necessary by the sponsor. This was found to be acceptable by this OCPB reviewer (see also Dissolution below for further support).

b. Dissolution

The initial dissolution specifications for the market image tablet were as follows:

Dosage Form:	Compressed Tablet
Strength:	6 mg
Apparatus:	USP Apparatus II (paddle)
Medium:	Distilled water/n-propanol in ratio of 2:1
Volume:	900 ml
Agitation:	50 rpm
Temperature:	37°C
Sampling Time:	45 min
Analytical Method:	HPLC with UV detection (247 nm)
Dissolution (tentative):	Q = [redacted]% in [redacted] min

A non-polar medium (i.e., 33% v/v n-propanol) was required to maintain sink conditions since ivermectin is nearly insoluble in water (< 0.001 g/L). Since this medium apparently did not represent physiological conditions, the results of *in vitro* dissolution

testing would serve only as a quality control check of the tablet manufacturing process. During validation of this method, samples were repeated at 15, 30 , and 45 minutes (N = 12 for each time). The mean dissolution was 52% (RSD 36.8%), 89% (RSD 7.2%), and 98% (RSD 3.5%) at 15, 30, and 45 minutes, respectively. Thus, the specfication was set by the sponsor at [redacted]% dissolved (Q = [redacted]%) at [redacted] minutes since the dissolution gave an acceptable RSD only at this sampling time. The dissolution results for the final market image tablet and other dosage formulations (selected by the sponsor) used in various NDA studies are presented below for this method.

Ivermectin Dosage Forms: Mean % Dissolution (Range)

Dosage Form	Study Type	%Q at 15 min	%Q at 30 min	%Q at 45 min
3 mg Tablet* (N = 12)	PK - Dose Prop	104 (84-109)	104 (97-111)	106 (98-113)
6 mg Tablet* (N = 12)	PK - Dose Prop; Bioavail	97 (83-106)	101 (97-105)	104 (98-107)
0.5 mg Cap (N = 2)	PK - Excretion in Breast Milk	90 (89, 91)	93.5 (93, 94)	---
2.5 mg Cap (N = 6)	PK - Excretion in Breast Milk; Clinical -Oncho Trial	94 (83-101)	97.5 (89-102)	---
6 mg Cap (N = 12)	PK- Bioavail; Clinical - Oncho Trial	96 (92-103)	95 (90-105)	100 (90-106)
Market Image				
6 mg Tablet** (N = 6)	Clinical - Strongyloides	97 (88-101)	99 (99-100)	99 (98-100)
6 mg Tablet** (N = 6)	Clinical - Strongyloides	99 (91-106)	103 (100-108)	103 (100-107)

*Initial tablet formulations without antioxidants
**Final market image tablet formulation with antioxidants

Dissolution for the market image tablets and the other formulations presented in the table above was acceptable. In addition, dissolution results for the market image tablet formulation (i.e., with antioxidants) and the initial tablet formulation (i.e., without antioxidants) were comparable at all sampling times.

According to the sponsor, this initial dissolution method was employed to control and release ivermectin 6 mg tablets until March, 1994, when a more enviromentally

acceptable dissolution medium was developed. The medium employed use of the surfactant, sodium dodecyl sulfate (SDS), and was buffered to pH 7 with sodium phosphate. The current dissolution method and specification are as follows (changes in bold):

Dosage Form:	Compressed Tablet
Strength:	6 mg
Apparatus:	USP Apparatus II (paddle)
Medium:	**0.5% SDS/Distilled Water, 0.01M Monobasic Na Phosphate, pH 7**
Volume:	900 ml
Agitation:	50 rpm
Temperature:	37°C
Sampling Time:	45 min
Analytical Method:	HPLC with UV detection (247 nm)
Dissolution:	**Q = [redacted]% in [redacted] minutes**

This current method has been adequately validated with respect to accuracy, precision, linearity, stability of ivermectin in the dissolution medium, and analytical specificity. Dissolution in the two media (i.e., SDS vs. water/n-propanol) were acceptabe and comparable at 45 minutes for 3 production batches of tablets (i.e., 96% vs. 103%; 94% vs. 99%; 95% vs. 97%, N = 12 for each batch). Based on these results, the sponsor tightened the dissoultion specification for the SDS medium to Q = [redacted]% in [redacted] minutes. Dissolution at [redacted] minutes with the SDS medium for the commercial batches of ivermectin tablets manufactured after March 1994 ranged from % dissolved.

V. ANALYTICAL METHODS

The method to quantify ivermectin in plasma and milk was by HPLC with fluorescence detection. Since there was only minimal excretion in the urine, no urine assay was developed. In all studies included in Section 6 of this NDA, the concentrations of only the major component of ivermectin, i.e., H_2B_{1a}, were determined. Although the assay appeared to be selective enough to determine both the H_2B_{1a} and H_2B_{1b} components, the sponsor noted that at lower total drug concentrations, the levels of H_2B_{1b} fell below the limit of detection for the assay (~0.2 ng/ml). The validation of the assay in plasma and milk was acceptable, and assay performance, with respect to interday precision (%CV) of the quality control samples was also within acceptable limits (i.e., < ±20%) for each of the studies in Section 6. It is noteworthy to mention that the performance of the assay for all studies was evaluated using only 2 levels of quality control samples (i.e., low and high), instead of the currently accepted 3 levels of quality control samples (i.e., low, medium, and high). However, this does not represent a major deficiency in the analytical methodology.

It is also noteworthy that, for all the pharmacokinetics/biopharmaceutics studies included in Section 6, even though the limit of assay quantitation was ng/ml in plasma (as defined by the linear dynamic range of the assay), the sponsor reported a limit of detection ~0.2 ng/ml. Furthermore, no precision and accuracy data were provided to support this claim, and it was also apparent that the AUC estimates in the various studies were determined using plasma concentrations between ng/ml (i.e., extrapolation beyond the linear range of the assay). In general, this did not appear to effect the integrity of the AUC data or the overall results of the studies.

VI. HUMAN PHARMACOKINETICS STUDY SUMMARIES

1. Drug Metabolism Study #606: Metabolic Disposition
"An Open, Single-Dose Study in Healthy Subjects to Determine the Metabolic Disposition of Radiolabeled Ivermectin" (Report Date: January, 1986)

Objective:
To determine the absorption, metabolism, and elimination of radiolabeled ivermectin following single dose administration to healthy male volunteers.

Formulations/Treatments:
[^{3}H]-Ivermectin Capsules 14 mg (200 μCi) - Lot #R0933-DFC-002-A001
Ratio of Components: 91.8% H_2B_{1a}; ~8% H_2B_{1b}
Position of Label: [22,23-^{3}H]-Ivermectin H_2B_{1a}; no label on H_2B_{1b}

Subjects:
Four healthy male Caucasian subjects, age range 23-40 years (mean 30 yrs), weight range 60.0-75.0 kg (mean 65.7 kg)

Study Design and Methods:
Each subject received a single oral 14 mg dose of the radiolabeled capsule with 240 ml of water after an overnight fast of at least 8 hours. Blood samples for quantitation of parent ivermectin concentrations, i.e., H_2B_{1a} only, and drug-related radioactivity in plasma were collected serially from 0 (predose) to 72 hours (3 days) postdose. Urine and fecal samples for determination of parent and ^{3}H-metabolite(s) concentrations were collected at specified intervals for up to 96 hours (4 days) postdose for urine and 120 hours (5 days) for feces. Radiolabeled metabolite(s) concentrations were determined as the difference between total radioactivity and unlabeled H_2B_{1a} as measured by HPLC (see below).

Assay Methods, Validation, and Performance:
(i) Ivermectin (H_2B_{1a}) in Plasma and Urine - HPLC with Fluorescence Detection

Validated over linear dynamic range from 1-50 ng/ml in plasma. The limit of detection was reported to be ~0.2 ng/ml, but no data (i.e., accuracy and precision) was provided to substantiate this claim. The lower limit of quantification was 1.0 ng/ml, however, it appeared that the sponsor used plasma ivermectin concentrations between ng/ml to calculate the AUC estimates. Quality control (QC) samples were run with the clinical samples at two concentrations (low and high), instead of the preferred three concentrations (low, medium, high). The interday precision (%RSD) was acceptable for both the low (15 ng/ml) and high (35 ng/ml) QC's at 3.2% and 7.9%, respectively.

The assay of ivermectin in urine was the same as that in plasma. No urine assay validation or performance data was provided. According to the sponsor, no detectable levels of parent H_2B_{1a} could be determined in urine.

(ii) Total Radioactivity in Plasma, Urine, and Feces

Total drug-related radioactivity in these matrices was measured by conventional liquid scintillation counting. The potential for the radiolabel to associate with plasma water (i.e., ^3H_2O) was determined to be minimal, i.e., < 6% of the total radioactivity was found in plasma water.

Results:

The individual and mean plasma concentration data for parent ivermectin (H_2B_{1a}) and the ^{3}H-metabolites are illustrated in Figures 1 and 2, respectively. These figures indicated that, for all four subjects, individual ^{3}H-metabolite concentrations were higher and persisted longer in plasma than parent ivermectin and the between subject variability in both parent and ^{3}H-metabolite concentrations appeared to be wide. The postabsorptive phase of the ivermectin profiles suggested enterohepatic recycling (i.e., double peaks), which precluded accurate determination of the terminal phase rate constant (K) and T½ by conventional methods. The estimate of T½ was subsequently determined as the "effective" T½ using the single-dose method of Kwan, et. al. (*In: Pharmacokinetics, Chp 14, p 147-162, LZ Benet, G Levy, B Ferraiolo, eds, 1984*); see below for details. The pharmacokinetic parameters in plasma are summarized in the following table:

Mean ± SD (Range) Plasma Pharmacokinetic Parameters, N = 4

Parameter	**Ivermectin (H_2B_{1a})**	**^{3}H-Metabolite(s)***
Cmax	21.7±11.2 ng/ml (9.2 - 33.4) [CV 52%]	54.2±26.6 ng.eq/ml (28.2 - 88.7) [CV 49%]
Tmax	6.0±4.0 hr (4.0 - 12.0) [CV 67%]	7.0±3.9 hr (3.0 - 12.0) [CV 56%]
AUC(0-72)	329±196 ng.hr/ml (127-588) [CV 59.5%]	ND**
Effective T½* **	11.8# hr (9.8-14.3)	ND
Radioactive Half-Time	ND	2.9# days (2.0-3.4)

*Determined as the difference between the total radioactivity counts and unlabeled H_2B_{1a} measured by HPLC

**ND = Not determined

***Determined as (ln 2)/η, where $\eta = -(1/\tau) * [\ln(1 - (AUC(0\text{-}\tau)/AUC(0\text{-}72)))]$, and τ = 12 or 24 hr

#Harmonic Means

The mean plasma Cmax for the ^{3}H-metabolite(s) was approximately twice that of parent ivermectin. The mean Tmax estimates appeared to be similar for both species at ~6-7 hours, but may be actually shorter for the parent since in 3 subjects Tmax was 4 hours, but was 12 hours in the fourth subject. This same subject appeared to have a prolonged rate of appearance of the ^{3}H-metabolite(s) as Tmax was also 12 hours. The apparent elimination of the ^{3}H-metabolite(s) was substantially prolonged when compared to parent ivermectin, as evidenced by the half-time for radioactivity of ~3 days compared to the ~12 hour effective T½ estimated for ivermectin.

As noted by the sponsor, no detectable levels of parent ivermectin (i.e., H_2B_{1a}) could be determined in urine. The recovery of drug-related radioactivity in urine and feces are summarized in the following table:

Mean ± SD (Range) Cumulative Recovery of Total Radioactivity, N = 4

Time Postdose	**Urinary Recovery as % of Dose**	**Fecal Recovery as % of Dose**
24 hours (Day 1)	0.252±0.091 (0.153-0.331) [CV 36%]	29.03, 0.01* 0.06, 0.05**
48 hours (Day 2)	0.388±0.191 (0.206-0.632) [CV 49%]	17.49±29.22 (0.18, 1.18, 7.57, 61.04)
72 hours (Day 3)	0.500±244 (0.269-0.828) [CV 49%]	31.31, 8.76***
96 hours (Day 4)	0.606±0.311 (0-294-1.017) [CV 51%]	37.45±30.03# (7.84, 36.63, 67.89)
120 hours (Day 5)	Not Collected	48.62±18.3 (25.77, 43.60, 56.64, 68.45)

*Collected 24 hours postdose for subjects 1 and 2
**Collected predose (Day 0) for subjects 3 and 4
***Values for subjects 2 and 4; no sample for subject 3; no value reported for subject 1
#N = 3; no sample for subject 2

Urinary excretion of radioactivity appeared to be minimal, with a mean of ~0.6% of the radioactive dose recovered in the urine at 4 days postdose. Fecal recovery was greater with a mean of ~50% of the radioactive dose excreted in the feces at 5 days postdose. As Figure 3 illustrates, fecal excretion was minimal (i.e., < 10%) for up to ~2 days postdose in subjects 2, 3, and 4, and appeared to continue to increase through day 5, indicating that the length of the sample collection period was insufficient, i.e., based on half-time of radioactivity of ~3 days, it would take ~12 days (4 x half-time) to recover nearly all the dose (~95%) in the feces. For subject 1, fecal excretion was ~30% at 1 day postdose and appeared to remain constant at ~70% at the fourth and fifth days following the dose.

Reviewers Conclusions:
Systemic exposure to drug-related radioactivity, determined as ^{3}H-metabolite(s) of ivermectin, appeared to be greater than that of parent ivermectin (i.e., H_2B_{1a}). The mean plasma Cmax for the ^{3}H-metabolite(s) was approximately twice that of ivermectin. Also, the ^{3}H-metabolite(s) persisted longer in plasma than that of parent ivermectin and appeared to be related to the slower rate of disappearance of the ^{3}H-metabolite(s), i.e., half-time of ~3 days compared to an apparent/effective T½ of ~12 hours for ivermectin.

The postabsorptive phase of the parent ivermectin plasma concentration-time profiles suggested some enterohepatic recycling (i.e., double peaks), which precluded accurate determination of the terminal phase rate constants (K) and T½ by conventional methods. The estimate of T½ was subsequently determined as the "effective" T½, which employs an estimation of drug accumulation (i.e., AUC(0-τ)/AUC(0-inf) ratio) associated with the recycling process. In calculating the effective T½, the sponsor assumed: (1) that AUC(0-72) approximated the AUC(0-inf) since plasma ivermectin concentrations at 72 hours were either at or below the lower limit of quantification of the assay (i.e., 1.0 ng/ml) for all subjects, and (2) a dosing interval, τ, of either 12 or 24 hours. These assumptions and the method to determine T½ for parent ivermectin were appropriate for this study.

No parent ivermectin was detected in the urine and only ~0.6% of the radioactive dose was recovered in the urine at 4 days postdose. The predominate pathway of excretion appeared to be fecal, with ~50% of the radioactive dose recovered in the feces at 5 days postdose. The results suggested that some of the drug and/or metabolites are eliminated in the bile and ultimately excreted in the feces. Based on the mean half-time of radioactivity of ~3 days, it would take ~12 days (4 x half-time) to recover nearly all the

radioactive dose (~95%) in the feces.

FIGURE 1

INDIVIDUAL SUBJECT AND MEAN PLASMA CONCENTRATIONS OF IVERMECTIN

TREATMENT: ^{3}H-IVERMECTIN 14 MG, 200 MICRO Ci, ORAL

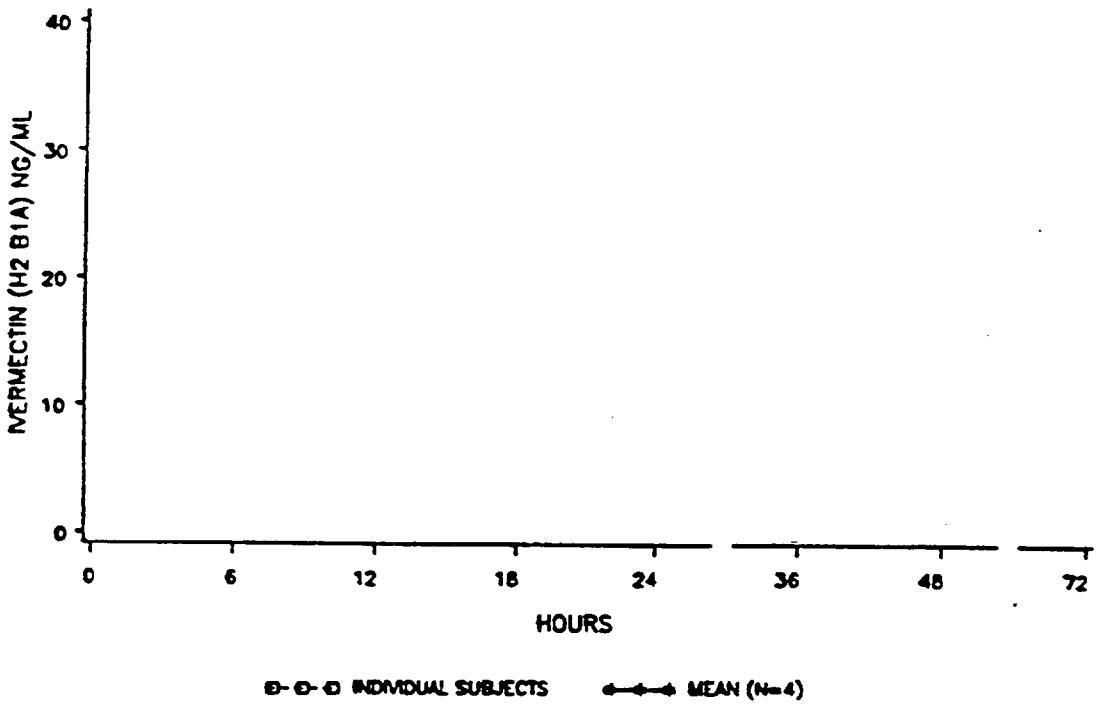


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FIGURE 2

INDIVIDUAL SUBJECT AND MEAN PLASMA CONCENTRATIONS OF ^{3}H-METABOLITES OF IVERMECTIN

TREATMENT: ^{3}H-IVERMECTIN 14 MG, 200 MICRO Ci, ORAL

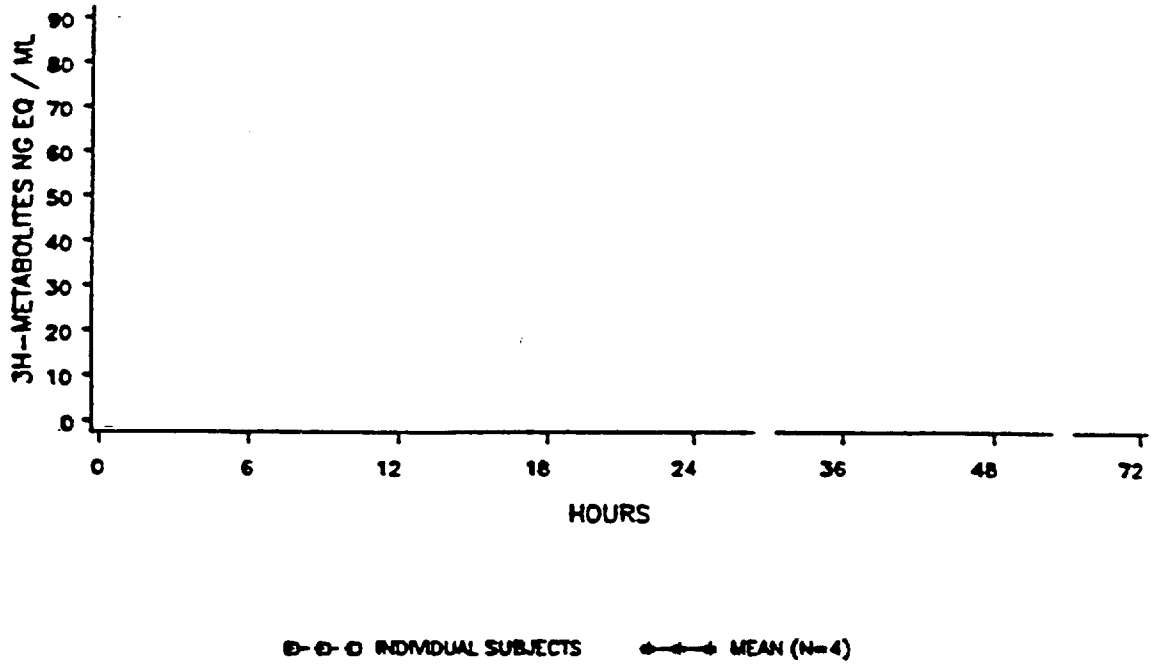

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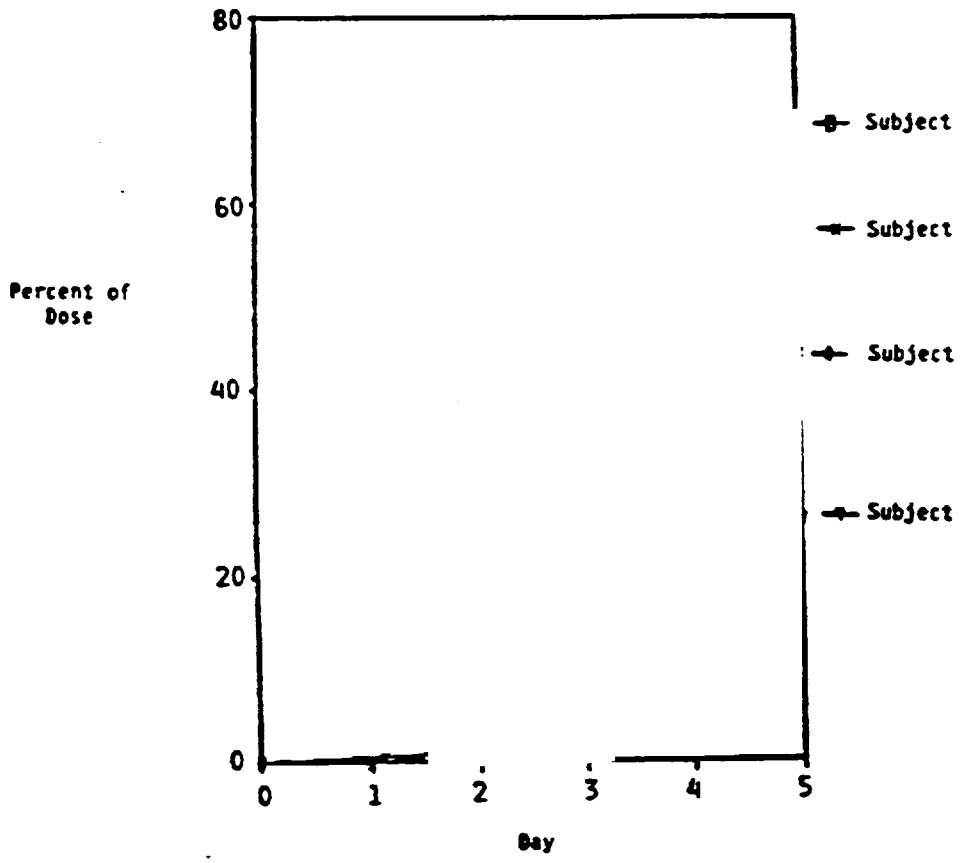
FIGURE 3

CUMULATIVE FECAL RECOVERY OF RADIOACTIVITY
FOLLOWING ADMINISTRATION OF ^{3}H-IVERMECTIN



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2. Drug Metabolism Study #615: Dose Proportionality
"An Open, Three Period, Single Dose, Crossover Study in Healthy Male Subjects to Determine the Effect of Dose on the Pharmacokinetics of Ivermectin Administered Orally as Tablets" (Report Date: June, 1986)

Objective:
To determine the effects of increasing the oral dose of ivermectin (from mg) on its pharmacokinetics.

Formulations/Treatments:
Ivermectin Tablets
6 mg - Lot #E-3807
3 mg - Lot #E-3806
The 6 mg tablet was the market image.
Dissolution at 30 minutes was acceptable.
See Table 1 for details of formulation and dissolution

Subjects:
Twelve healthy male Caucasian subjects, age range 21-41 years (mean 25.5 yrs), weight range 64.7-79.0 kg (mean 73.1 kg)

Study Design and Methods:
Open label, randomized, three period, crossover design. Each subject received the following three single dose treatments of ivermectin tablets with 240 ml of water after an overnight fast of at least 8 hours:

A: 6 mg (1 x 6 mg tablet)
B: 12 mg (2 x 6 mg tablets)
C: 15 mg (2 x 6 mg tablets + 1 x 3 mg tablet)

Each treatment was separated by a 12 to 15 day washout interval. Blood samples for quantitation of ivermectin concentrations, i.e., H_2B_{1a} only, in plasma were collected serially from 0 (predose) to 72 hours (3 days) postdose. No urine samples were collected.

Assay Methods, Validation, and Performance:
Ivermectin (H_2B_{1a}) in Plasma - HPLC with Fluorescence Detection
Linear dynamic range from 1-40 ng/ml. The limit of detection was reported to be ~0.2 ng/ml, but no data (i.e., accuracy and precision) was provided to substantiate this claim. The lower limit of quantification was 1.0 ng/ml, however, it appeared that the sponsor used plasma ivermectin concentrations between ng/ml to calculate the AUC estimates. Quality control (QC) samples were run with the clinical samples at two concentrations (low and high), instead of the preferred three concentrations (low, medium, high). The interday precision (%RSD) was acceptable for both the low (2.5 ng/ml) and high (30 ng/ml) QC's at 9.2% and 5.2%, respectively.

Data Analysis:
(i) Pharmacokinetic
AUC(0-72), Cmax, and Tmax were estimated by conventional model independent methods. It was observed that the postabsorptive phase of the ivermectin concentration-time profiles suggested enterohepatic recycling (i.e., double peaks), which precluded accurate determination of the terminal phase rate constant (K) and T½ by conventional methods. The estimate of T½ was subsequently determined for the 6 mg and 12 mg doses as the "effective" T½ using the single-dose method of Kwan, et. al. (*In: Pharmacokinetics, Chp 14, p 147-162, LZ Benet, G Levy, B Ferraiolo, eds, 1984*); see below for details.

(ii) Statistical
Statistical significance between the pharmacokinetic parameters AUC(0-72), Cmax, and Tmax

from the three dose levels was tested using an ANOVA for a three period design. Pairwise comparisons (i.e., 6 vs 12 mg, 6 vs 15 mg, 12 vs 15 mg) of the AUC(0-72) and Cmax estimates were performed using both the actual and dose-adjusted (for the 6 mg dose) values. For the dose-adjusted parameters, the 95% confidence intervals were also constructed for the geometric mean of the ratios (i.e., 12 mg:6 mg, 15 mg: 6 mg, and 12 mg:15 mg). The level of significance was assessed at $\alpha = 0.05$.

Results:

The mean plasma ivermectin (i.e., H_2B_{1a}) concentration-time data, unadjusted for dose, are illustrated in Figure 1 and suggested an increase with the increase in dose. The descriptive statistics for all pharmacokinetic parameters are summarized in the table below and the results of the ANOVA for Cmax and AUC(0-72) are presented in Tables 2 and 3, respectively. The individual and mean unadjusted AUC(0-72) and Cmax values are plotted as a function of dose in Figure 2.

Mean ± SD (Range) Pharmacokinetic Parameters (N = 12)

Parameter	**6 mg**	**12 mg**	**15 mg**
AUC(0-72) (ng.hr/ml)	347±195 (114-712) [CV 56%]	513±209 (306-900) [CV 41%]	820±555 (178-1871) [CV 68%]
Dose Adjusted* AUC(0-72)	347±195 (114-712)	257±104 (153-450)	328±222 (71-748)
Cmax (ng/ml)	18.3±9.7 (6.4-31.9) [CV 53%]	30.6±15.6 (13.9-68.4) [CV 51%]	48.5±35.2 (10.4-118.5) [CV 73%]
Dose Adjusted* Cmax	18.3±9.7 (6.4-31.9)	15.3±7.8 (7.0-34.2)	19.4±14.1 (4.2-47.4)
Tmax (hr)	3.9±0.79 (3-6) [CV 20%]	3.8±0.87 (3-6) [CV 23%]	3.8±1.19 (2-6) [CV 31%]
Effective T½ (hr)**	16.8 (14.0-21.0)	16.7 (13.3-20.5)	ND***

*Adjusted to 6 mg

**Determined as $(\ln 2)/\eta$, where $\eta = -(1/\tau) * [\ln(1 - (AUC(0-\tau)/AUC(0-72)))]$, and τ = 24 hr. Mean values expressed as harmonic means.

***Not determined

The increase in mean AUC(0-72) values approximated the increase in dose. However, the total variability in AUC(0-72) between subjects (i.e., %CV) was high across all 3 doses, especially the 15 mg dose. The range of AUC(0-72) values varied ~10-fold for the 15 mg dose and from ~3- to 6-fold for 6 mg and 12 mg (see Figure 2). The results in Table 3 indicated that no significant difference was detected between the mean unadjusted AUC(0-72) for the 6 and 12 mg doses ($p = 0.08$), but significance was attained between the 6 and 15 mg ($p < 0.01$) and the 12 and 15 mg ($p < 0.01$) comparisons. When adjusted for dose (6 mg), the mean adjusted AUC(0-72) for the 12 mg dose was significantly lower than that of the 6 mg dose ($p = 0.03$). No significant differences were detected for the other dose adjusted comparisons (i.e., 6 vs 15 mg or 12 vs 15 mg). Although the geometric mean of the ratios for adjusted AUC(0-72) were close to unity and the 95% confidence intervals for these ratios all included unity (see Table 3), there was wide variability between subjects for a given dose level. The individual dose adjusted AUC(0-72) ratios varied -fold, with ranges of for the mg ratio for the 15:6 mg ratio, and

for the 15:12 mg ratio.

Similar to AUC(0-72), the mean Cmax values also increased with the increase in dose. As the table above indicates, the overall variability in unadjusted Cmax between subjects (i.e., as %CV) was wide and similar in magnitude to that observed for unadjusted AUC(0-72). The Cmax values varied over ~10-fold range at the 15 mg dose and ~5-fold at 6 mg and 12 mg (see Figure 2). The results in Table 2 indicated that a significant difference was detected between the mean unadjusted Cmax for the three dose comparisons (i.e., $p = 0.04$ for 6 vs 12 mg; $p < 0.01$ for 6 vs 12 mg and 12 vs 15 mg). The same comparisons for the dose adjusted Cmax estimates were not statistically significant. The geometric mean of the ratios for adjusted Cmax were close to unity and the 95% confidence intervals for these ratios all included unity (see Table 2). The individual adjusted Cmax ratios varied -fold, with ranges of for the 12:6 mg ratio, for the 15:6 mg ratio, and for the 15:12 mg ratio.

Maximum plasma concentrations of ivermectin were attained, on average, within ~4 hours for all three dose levels and no significant differences were detected in Tmax between doses. The mean effective half-life estimates, calculated with $\tau = 24$ hr, were similar for the 6 mg and 12 mg doses at 16.8 and 16.9 hr, respectively. However, these T½ values were longer than those determined for the 4 subjects studied in the metabolic disposition study (i.e., mean T½ = 11.8 hr, range 9.8-14.3 hr).

Reviewers Conclusions:
The sponsor provided the following conclusions:

> Despite the substantial variability observed in the estimates of AUC(0-72) and Cmax following increasing single dose administration of 6, 12, and then 15 mg, this increase in dose did not result in unpredictably high plasma drug concentrations / systemic exposure to ivermectin.
>
> The statistical analysis of the unadjusted and dose adjusted AUC(0-72) data suggested some deviation from dose proportionality, but would not be expected to be clinically significant over this dosage range. The analysis of the unadjusted and dose adjusted Cmax data suggested dose proportionality was maintained across the three doses. The remarkable similarity in mean Tmax estimates suggested no dose related differences in the rate of drug absorption from the ivermectin tablets.

This reviewer is in agreement with the conclusions provided by the sponsor with respect to the assessment of dose proportionality.

With respect to the method to determine the "effective" T½ for ivermectin (i.e., $(\ln 2)/\eta$, where $\eta = -(1/\tau) * [\ln(1 - (AUC(0\text{-}\tau)/AUC(0\text{-}72)))]$ and $\tau = 24$ hr), the sponsor assumed that AUC(0-72) approximated AUC(0-inf) since plasma ivermectin concentrations at 72 hours were either at or below the lower limit of quantification of the assay (i.e., 1.0 ng/ml) for nearly all subjects at the 6 and 12 mg dose levels. Inspection of this concentration data revealed that 5 of 12 subjects at the 6 mg dose (~42%) and 7 of 12 subjects at the 12 mg dose (~58%) had plasma ivermectin concentrations at 72 hours postdose that were ~2 ng/ml or greater (actual range ng/ml). From this, it appeared that the assumption was not appropriate for approximately one-half of the subjects for whom T½ was estimated. Furthermore, inspection of the individual ln concentration-time profiles suggested that a sampling schedule beyond 72 hours postdose may be needed to adequately characterize the terminal phase and accurately determine T½. Thus, the estimates for effective T½ determined in this study and the metabolic disposition study may have underestimated the "true" T½ for ivermectin.

Table 1

Formulation and analytical measurements for 3 mg and 6 mg tablets of Ivermectin used in dose proportionality study.

Ivermectin (MK-933) is a mixture of no less than 80 % 22,23-dihydroavermectin-B_{1a} (H_2B_{1a}) and no more than 20 % 22,23-dihydroavermectin-B_{1b} (H_2B_{1b}). In this study, the drug was administered as the market image 6 mg, or submultiple 3 mg tablets.

	6 mg tablet	3 mg tablet
Lot number:	E-3807	E-3806
Formulation:		
Ivermectin human use grade (90.2%)	mg	mg
Microcrystalline Cellulose	mg	mg
Starch, pregelatinised	mg	mg
Magnesium Stearate	mg	mg
Total Weight	mg	mg

Assay Potency:

Assay method: FP-148

mean	5.82 mg/tablet	3.00 mg/tablet
range		

Dissolution test:

Test Method: FP-148[a]

time	% dissolution (N=12) mean (range)
min.	
min	
min	

a - The method used in the dissolution test was:
USP XXI, Method II (paddles at 50 rpm.)
in 900 ml of 33% v/v n-propanol in water.
5 ml samples were taken at 15, 30 and 45 minutes
and analyzed using assay procedure AM-211

FIGURE 1

MEAN IVERMECTIN CONCENTRATIONS IN PLASMA
AFTER SINGLE DOSE OF DRUG

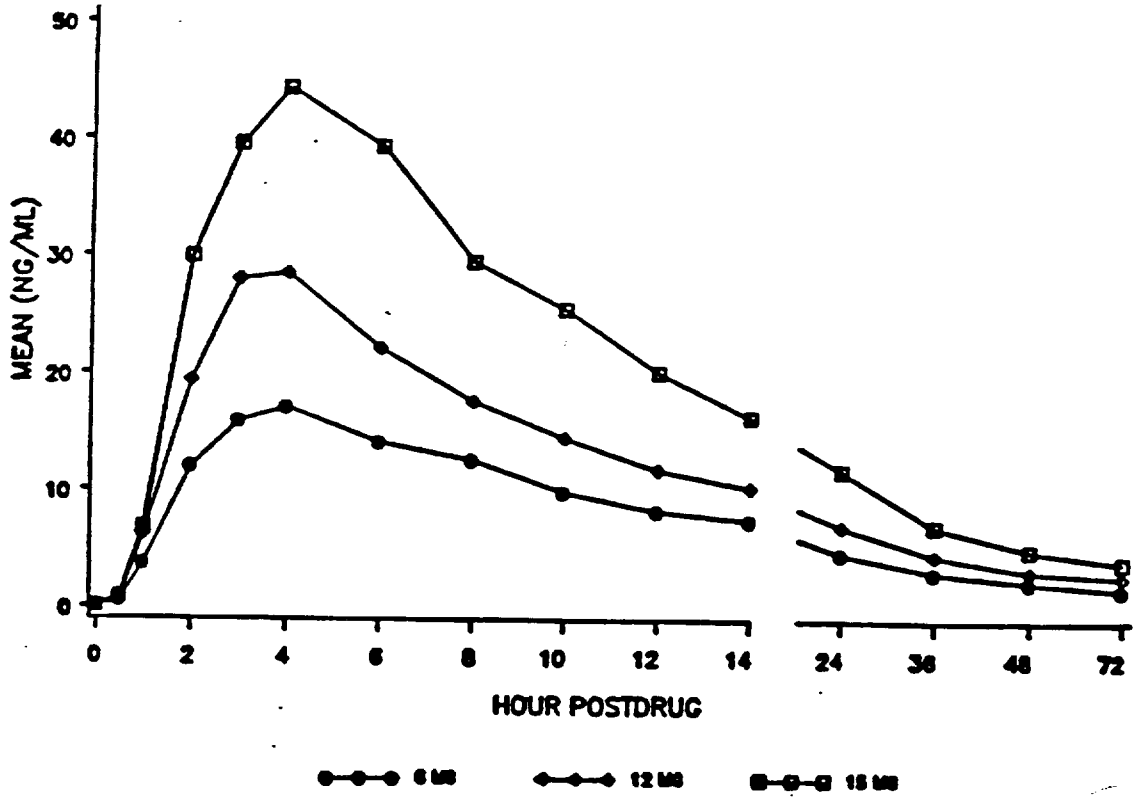

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TABLE 2

SUMMARY STATISTICS AND RESULTS FOR OBSERVED MAXIMUM PLASMA CONCENTRATION (C_{MAX}) OF IVERMECTIN AFTER 6, 12 AND 15 MG DOSES OF IVERMECTIN

	C_{MAX}-ACTUAL VALUES (NG/ML)			C_{MAX}-DOSE-ADJUSTED VALUES† (NG/ML)		
	6 MG	12 MG	15 MG	6 MG	12 MG	15 MG
N	12	12	12	12	12	12
Mean	18.3	30.6	48.5	18.3	15.3	19.4
Std	9.7	15.6	35.2	9.7	7.8	14.1
(Min, max)	(6.4, 31.9)	(13.9, 68.4)	(10.4, 118.5)	(6.4, 31.9)	(7.0, 34.2)	(4.2, 47.4)
Within subject std		13.6			5.2	
Overall treatment p-value		< 0.01			0.16	
Pairwise comparisons:						
6 mg	•	0.04	< 0.01	•	0.17	> 0.20
12 mg		•	< 0.01		•	0.07
Within subject std (log units)		N/A			0.35	
Overall treatment p-value (log units)		N/A			> 0.20*	
Geometric mean of the ratio of C_{max} after the following treatments:						
12 mg:6 mg					0.88	
15 mg:6 mg					0.92	
15 mg:12 mg		N/A			1.05	
95% CI for geometric mean of the ratio of C_{max} after the following treatments:						
12 mg:6 mg					(0.65, 1.19)	
15 mg:6 mg		N/A			(0.68, 1.25)	
15 mg:12 mg					(0.78, 1.42)	

† Dose adjusted to 6 mg
* All pairwise comparisons > 0.10

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TABLE 3

SUMMARY STATISTICS AND RESULTS FOR AREA UNDER THE 0- to 72-HOUR PLASMA CONCENTRATION CURVE (AUC) FOLLOWING ADMINISTRATION OF 6, 12 AND 15 MG DOSES OF IVERMECTIN

	AUC-ACTUAL VALUES (NG·HR/ML)			AUC-DOSE-ADJUSTED VALUES† (NG·HR/ML)		
	6 MG	12 MG	15 MG	6 MG	12 MG	15 MG
N	12	12	12	12	12	12
Mean	347	513	820	347	257	328
Std	195	209	555	195	104	222
(Min, max)	(114, 712)	(306, 900)	(178, 1871)	(114, 712)	(153, 450)	(71, 748)
Within subject std		220			92	
Overall treatment p-value		< 0.01			0.06	
Pairwise comparisons						
6 mg	•	0.08	< 0.01	•	0.03	> 0.20
12 mg		•	< 0.01		•	0.07
Within subject std (log units)		N/A			0.33	
Overall treatment p-value (log units)		N/A			> 0.20*	
Geometric mean of the ratio of AUC after the following treatments:						
12 mg:6 mg		N/A			0.81	
15 mg:6 mg					0.86	
15 mg:12 mg					1.07	
95% CI for geometric mean of the ratio of AUC after the following treatments:						
12 mg:6 mg		N/A			(0.61, 1.07)	
15 mg:6 mg					(0.65, 1.14)	
15 mg:12 mg					(0.81, 1.42)	

† Dose adjusted to 6 mg
* All pairwise comparisons > 0.10

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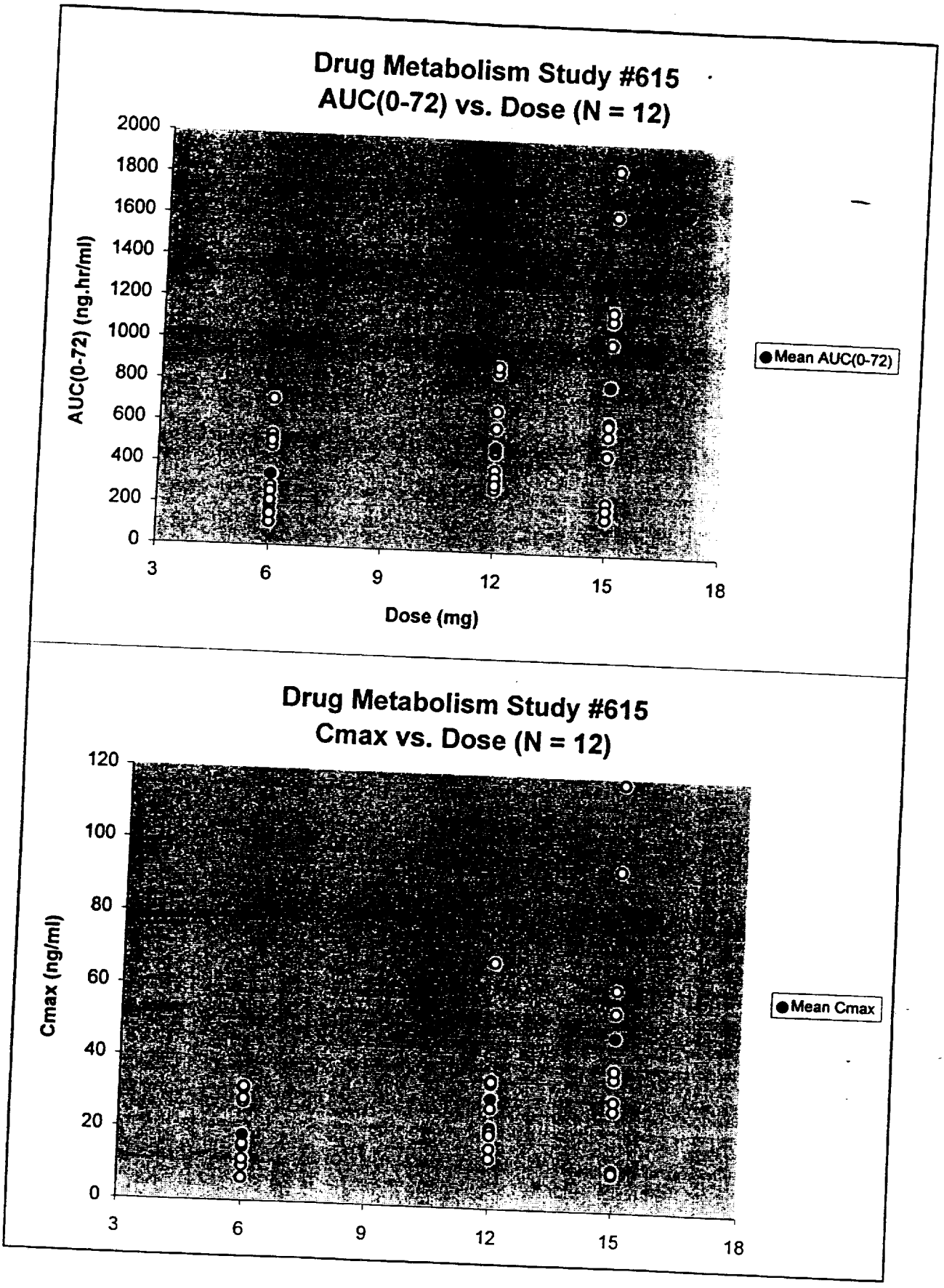
FIGURE 2


Drug Metabolism Study #615
AUC(0-72) vs. Dose (N = 12)
AUC(0-72) (ng.hr/ml)
2000
1800
1600
1400
1200
1000
800
600
400
200
0
3
6
9
12
15
18
Dose (mg)
Mean AUC(0-72)
Drug Metabolism Study #615
Cmax vs. Dose (N = 12)
Cmax (ng/ml)
120
100
80
60
40
20
0
3
6
9
12
15
18
Mean Cmax

3. Drug Metabolism Study #616: Bioavailability
"An Open, Three Period, Crossover Study in Healthy Subjects to Estimate the Relative Bioavailability of Ivermectin Administered as a Capsule and as a Tablet Compared to Ivermectin Administered as an Oral Solution" (Report Date: August, 1986)

Objective:
To estimate the relative bioavailability of a 12 mg single dose of ivermectin when administered as capsules, tablets, and an oral solution to healthy male subjects.

Formulations/Treatments:
Ivermectin Tablets 6 mg (market image) - Lot #E-3807

Ivermectin Capsules 6 mg - Lot #E-6086

Mean dissolution at 30 minutes was acceptable for both tablets and capsules. See Table 1 for details of formulations and dissolution.

Ivermectin Hydroalcoholic (40% Ethanol) Oral Solution 6 mg/10 ml - Lot #E-3798

Subjects:
Twelve healthy male Caucasian subjects, age range 22-48 years (mean 29.1 yrs), weight range 65-83 kg (mean 72.8 kg)

Study Design and Methods:
Open label, randomized, three period, crossover design. Each subject received the following three single dose treatments of ivermectin with either 250 ml (for the tablets and capsules) or 230 ml (for the oral solution) of water after an overnight fast of at least 8 hours:

A: 12 mg ivermectin oral solution (20 ml)
B: 12 mg ivermectin capsules (2 x 6 mg)
C: 12 mg ivermectin tablets (2 x 6 mg)

Each treatment was separated by at least a 13 day washout interval. Blood samples for quantitation of ivermectin concentrations, i.e., H_2B_{1a} only, in plasma were collected serially from 0 (predose) to 72 hours (3 days) postdose. No urine samples were collected.

Assay Methods, Validation, and Performance:
Ivermectin (H_2B_{1a}) in Plasma - HPLC with Fluorescence Detection

Linear dynamic range from ng/ml. The limit of detection was reported to be ~0.2 ng/ml, but no data (i.e., accuracy and precision) was provided to substantiate this claim. The lower limit of quantification was 1.25 ng/ml, however, it appeared that the sponsor used plasma ivermectin concentrations between ng/ml to calculate the AUC estimates. Quality control (QC) samples were run with the clinical samples at two concentrations (low and high), instead of the preferred three concentrations (low, medium, high). The interday precision (%RSD) was acceptable for both the low (6.25 ng/ml) and high (75 ng/ml) QC's at 8.7% and 5.7%, respectively.

Data Analysis:
AUC(0-72), Cmax, and Tmax were estimated by conventional model independent methods. The AUC and Cmax values were adjusted to the 12 mg dosages based on the assay potencies (see Table 1).

An ANOVA for a three period crossover design was used to determine statistical differences in the pharmacokinetic parameters between the three treatments. The most relevant statistical evaluations were those between the capsules and tablets since the capsules were used in the clinical onchocerciasis trials. The AUC(0-72) and Cmax data were log-transformed for the pairwise ANOVA comparisons of solution vs.

capsules, solution vs. tablets, and capsules vs. tablets. The 95% confidence intervals were also constructed for the geometric means of the ratios of solution:capsules, solution:tablets, and capsules:tablets for AUC and Cmax. In addition, posterior probabilities that the true mean difference in AUC and Cmax of the capsules vs. tablets comparison were less than 40, 35, 25, and 20% of the mean AUC and Cmax of the "standard", i.e., tablets, were calculated. It is noteworthy that the sponsor used the tablets, instead of the capsules, as the standard or reference treatment when calculating the posterior probabilities. Also, the sponsor did not perform an evaluation of bioequivalence between the tablets (i.e., as the test treatment) and the capsules (i.e., as the reference treatment) based on the currently accepted two one-sided test procedure.

Results:
The mean plasma ivermectin concentration-time data are illustrated in Figure 1, which suggested that the systemic availability of ivermectin from the 12 mg dose of the oral solution was greater than that from either the tablets or capsules, especially up to 24 hours postdose. The mean plasma concentrations resulting from administration of either the capsules or tablets appeared to be similar. The descriptive statistics for the pharmacokinetic parameters are summarized in the table below. The results of the ANOVA and other statistical tests for AUC(0-72) and Cmax are presented in Table 2.

Mean ± SD (Range) Pharmacokinetic Parameters (N = 12)

Parameter	**Ivermectin Oral Solution (12 mg/20 ml)**	**Ivermectin Capsules (2 x 6 mg)**	**Ivermectin Tablets (2 x 6 mg)**
AUC(0-72)* (ng.hr/ml)	1291±330 (954-1958) [CV 26%]	782±302 (304-1334) [CV 39%]	726±411 (287-1826) [CV 57%]
Cmax* (ng/ml)	82.9±25.4 (42.9-139.7) [CV 31%]	50.6±15.2 (26.3-71.0) [CV 30%]	46.6±21.9 (16.4-101.1) [CV 47%]
Tmax (hr)	4.0±0.9 (2.1-6.2) [CV 23%]	3.7±1.0 (2.0-6.1) [CV 27%]	3.6±0.7 (2.2-4.2) [CV 19%]

*Values for these parameters adjusted to the 12 mg dosages based on the assayed potencies given in Table 1

As evidenced from the data above, the mean AUC(0-72) and Cmax estimates resulting from single dose administration of the oral solution were ~2-fold higher than those for either the capsules or tablets. These same estimates were only slightly higher for the ivermectin capsules as compared to the tablets. Mean Tmax was similar for all three formulations at ~4 hours and no statistically significant differences were detected ($p > 0.20$). In Table 2, the ANOVA detected significantly higher AUC(0-72) and Cmax values for the oral solution vs. either the capsules or tablets ($p < 0.01$). No statistically significant differences were detected in the ANOVA between the capsules and tablets for either AUC(0-72) or Cmax ($p > 0.20$). The posterior probabilities for AUC and Cmax, calculated with the tablets as the standard instead of the test formulation, were 0.71 that the true mean difference (i.e., for capsules vs. tablets) in either parameter was less than 20% of the tablet means, 0.84 for less than a 25% difference, and 0.91 for less than a 30% difference. Thus, any differences in systemic availability of the capsules vs. the tablets were most likely (i.e., ~90% probability) to be less than 30% and probably (i.e., ~80% probability) less than 25%, but only marginally (i.e., ~70% probability) less than 20%. The latter difference of 20% being that which the currently accepted two one-sided test procedure for evaluation of bioequivalence is based upon.

The bioequivalence of the market image tablet relative to the clinical trials capsule formulation was evaluated by this reviewer by calculating the 90% confidence intervals based on the currently accepted

two one-sided test procedure. The ratios of the tablet (test) to capsule (reference) and the 90% confidence intervals (CI) are summarized in the table below.

Bioequivalence Summary of Ivermectin Tablets (N = 12) vs. Capsules (N = 12)

	AUC(0-72) Ratio*	90% CI for AUC(0-72)**	Cmax Ratio*	90% CI for Cmax**
Arithmetic Mean	0.97	(66.8%, 117.1%) Not Bioequivalent	0.96	(75.3%, 120.5%) Not Bioequivalent
S.D.	0.42		0.40	
Range				
Geometric Mean	0.88		0.88	

*Ratio of Tablets/Capsules
**CI calculated based on the two one-sided test procedure; bioequivalence acceptance criteria (80%, 125%)

These results indicated that, despite the apparent similarities in mean estimates of AUC(0-72) and Cmax, the ivermectin tablets failed to meet the criteria for bioequivalence when compared to the capsules. Thus, the systemic availability of ivermectin from the market image tablet formulation was less than that from the capsule formulation used in clinical trials.

Reviewers Conclusions:
The sponsor provided the conclusions that the bioavailability of ivermectin from the capsule used in clinical trials and the market image tablet formulations appeared to be similar, with any difference probably being less than 25%, and with drug from the capsule being slightly more bioavailable than that from the tablet.

Based on the statistical analyses of the pharmacokinetic data performed by the sponsor (i.e., ANOVA, posterior probabilities), these conclusions were valid. However, the results of the currently accepted two-one sided test procedure used to assess *in vivo* bioequivalence, conducted by this reviewer, indicated that the ivermectin tablets were not bioequivalent to the capsules. This finding of bioinequivalence should be tempered with the findings of the efficacy and safety in the [illegible] [OV 19%]

*Values for these parameters adjusted to the 12 mg dosages based on the assayed potencies given in Table 1

As evidenced from the data above, the mean AUC(0-72) and Cmax estimates resulting from single dose administration of the oral solution were ~2-fold higher than those for either the capsules or tablets. These same estimates were only slightly higher for the ivermectin capsules as compared to the tablets. Mean Tmax was similar for all three formulations at ~4 hours and no statistically significant differences were detected ($p > 0.20$). In Table 2, the ANOVA detected significantly higher AUC(0-72) and Cmax values for the oral solution vs. either the capsules or tablets ($p < 0.01$). No statistically significant differences were detected in the ANOVA between the capsules and tablets for either AUC(0-72) or Cmax ($p > 0.20$). The posterior probabilities for AUC and Cmax, calculated with the tablets as the standard instead of the test formulation, were 0.71 that the true mean difference (i.e., for capsules vs. tablets) in either parameter was less than 20% of the tablet means, 0.84 for less than a 25% difference, and 0.91 for less than a 30% difference. Thus, any differences in systemic availability of the capsules vs. the tablets were most likely (i.e., ~90% probability) to be less than 30% and probably (i.e., ~80% probability) less than 25%, but only marginally (i.e., ~70% probability) less than 20%. The latter difference of 20% being that which the currently accepted two one-sided test procedure for evaluation of bioequivalence is based upon.

The bioequivalence of the market image tablet relative to the clinical trials capsule formulation was evaluated by this reviewer by calculating the 90% confidence intervals based on the currently accepted

Table 1

Formulation and Analytical Measurements for Oral Solution and for 6 mg Capsules and Tablets of Ivermectin Used in the Bioavailability Study

Ivermectin (MK-933) is a mixture of no less than 80% 22,23-dihydroavermectin-B_{1a} (H_2B_{1a}) and no more than 20% 22,23-dihydroavermectin-B_{1b} (H_2B_{1b}).

	6 mg Tablet	6 mg Capsule	Solution
Lot number:	E-3807	E-6086	E-3798
Formulation:			
Ivermectin human use grade (90.2%)	mg	mg	mg
Microcrystalline cellulose	mg	mg	
Starch, pregelatinized	mg		
Magnesium stearate	mg	mg	
			ml
			ml
TOTAL	mg	mg	ml
Assay potency:			
Assay method:	FP-148	FP-89	FP-149
mean	5.82 mg/tablet	6.1 mg/capsule	5.9 mg/10 ml
range			
Dissolution test:			
Test method:	FP-148[a]	GM-39[b]	
	% dissolution (n=12) mean (range)		
Time			
min			
min			
min			

[a] USP XXI, Method II (paddles at 50 rpm) in 900 ml of 33% v/v n-propanol in water. 5 ml samples were taken at 15, 30, and 45 minutes and analyzed using assay procedure AM-211.

[b] USP XX, Method II (paddles at 50 rpm) in 900 ml of 33% v/v n-propanol in water. 5 ml samples were taken at 15, 30, and 45 minutes and analyzed using assay procedure AM-105.

FIGURE 1

MEAN PLASMA CONCENTRATIONS OF IVERMECTIN (H_2B_{1a})
(N = 12)

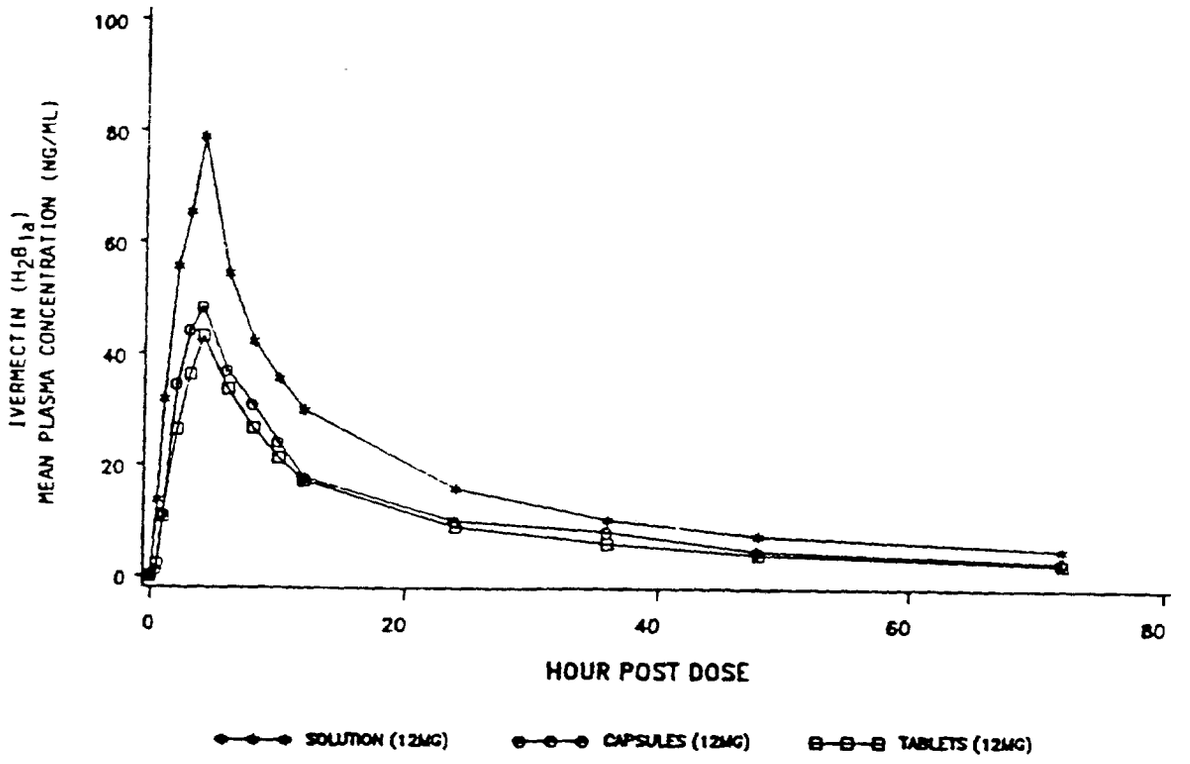


TABLE 2

SUMMARY STATISTICS AND RESULTS FOR AREA UNDER THE PLASMA CONCENTRATION-TIME CURVE FROM ZERO-HOUR TO INFINITY (AUC)[a] AND THE MAXIMUM PLASMA CONCENTRATION (C_{MAX})[a] FOLLOWING ADMINISTRATION OF 12 MG OF IVERMECTIN AS A SOLUTION IN 20 ML OF 40% ETHANOL, CAPSULES (2 x 6 MG) AND TABLETS (2 x 6 MG)

	AUC (NG·HR/ML)			C_{MAX} (NG/ML)		
	SOLUTION	CAPSULES	TABLETS	SOLUTION	CAPSULES	TABLETS
N	12	12	12	12	12	12
Mean	1291	782	726	82.9	50.6	46.6
Std	330	302	411	25.4	15.2	21.9
Min, max	954, 1958	304, 1334	286, 1826	42.9, 139.7	26.3, 71.0	16.4, 101.1
Within-subject std		274			17.1	
Overall treatment p-value		< 0.01			< 0.01	
Pairwise p-values						
Solution vs	—	< 0.01	< 0.01	—	< 0.01	< 0.01
Capsules vs		—	> 0.20		—	> 0.20
Posterior probability true mean difference (caps vs tabs) is less than:						
20% of std[b]		0.74			0.74	
25% of std		0.84			0.84	
30% of std		0.91			0.91	
40% of std		0.97			0.97	
Log Units						
Within subject std		0.33			0.28	
Overall treatment p-value		< 0.01			< 0.01	
Pairwise p-values:						
Solution vs	—	< 0.01	< 0.01	—	< 0.01	< 0.01
Capsules vs		—	> 0.20		—	> 0.20
Geometric Mean/95% Confidence Interval:						
Solution to capsules		1.73/(1.28, 2.34)			1.65/(1.28, 2.12)	
Solution to tablets		1.96/(1.43, 2.61)			1.88/(1.46, 2.41)	
Capsules to tablets		1.13/(0.84, 1.52)			1.14/(0.89, 1.46)	

[a] See Section II.b.2. for additional information on the pharmacokinetic parameters and assay of samples

[b] Mean of tablets

21NOV86

4. Protocol No. 539: Human Plasma and Milk Levels
"An Open, Single-Dose Study in Healthy Lactating Women to Determine Ivermectin Levels in Plasma and Milk" (Report Date: April, 1986)

Objective:
To determine milk and plasma concentrations of ivermectin in lactating women following a single 12 mg oral dose of ivermectin capsules.

Formulations/Treatments:
Ivermectin Capsules 2.5 and 0.5 mg

Mean dissolution at [redacted] minutes was acceptable for both strengths (i.e., Q = [redacted]% for [redacted] mg; [redacted]% for [redacted] mg)

Subjects:
Twelve healthy, nonpregnant, lactating African women who were not breast feeding or contributing to milk banks, age range 17-37 years (mean 24 ± 7 yrs), weight range 40-65 kg (mean 54 ± 8 kg). Although women weighing less than 50 kg or under 18 years of age were to be excluded, the study investigator allowed 3 women weighing 40-44 kg and another 4 women 17 years of age to participate in the study.

Study Design and Methods:
Open label design in which each subject received a single 12 mg dose of ivermectin capsules (i.e., 4 x 2.5 mg + 4 x 0.5 mg; total of 8 capsules) at least one hour before breakfast. The subjects were hospitalized for 14 days following drug administration and blood and milk samples for quantitation of ivermectin concentrations, i.e., H_2B_{1a} only, were collected as follows:

Blood
Day 1: Predose, 1, 4, and 12 hours postdose
Days 2 and 3: Predose (i.e., within 1 hour before breakfast)

Milk
Day 1: Predose, 1, 4, and 12 hours postdose
Days 2 through 14: Predose (i.e., within 1 hour before breakfast)

Assay Methods, Validation, and Performance:
Ivermectin (H_2B_{1a}) in Plasma - HPLC with Fluorescence Detection
Linear dynamic range from 1-40 ng/ml. The limit of detection was reported to be ~0.2 ng/ml, but no data (i.e., accuracy and precision) was provided to substantiate this claim. The lower limit of quantification was 1.0 ng/ml, based on the range of the assay. Quality control (QC) samples were run with the clinical samples at two concentrations (low and high), instead of the preferred three concentrations (low, medium, high). The interday precision (%RSD) was acceptable for both the low (2.5 ng/ml) and high (30 ng/ml) QC's at 10.4% and 3.0%, respectively.

Ivermectin (H_2B_{1a}) in Milk - HPLC with Fluorescence Detection
Linear dynamic range from 0.1-8 ng/ml. The limit of detection was reported to be ~0.05 ng/ml, but no data (i.e., accuracy and precision) was provided to substantiate this claim. The lower limit of quantification was 0.1 ng/ml, based on the range of the assay. Quality control (QC) samples were run with the clinical samples at two concentrations (low and high), instead of the preferred three concentrations (low, medium, high). The interday precision (%RSD) was acceptable for both the low (0.5 ng/ml) and high (6.0 ng/ml) QC's at 10.6% and 4.6%, respectively.

Data Analysis:
No pharmacokinetic parameters from either plasma or milk were determined by the sponsor.

Results:

Plasma

The plasma concentration data are provided in Table 1. Plasma levels of ivermectin (H_2B_{1a}) were quantifiable (i.e., > 1.0 ng/ml) in all women from 1 hr postdose on Day 1 through predose on Day 3. Maximum plasma concentrations were observed at 4 hrs postdose on Day 1 with a mean of 23 ng/ml and ranged from 5.0 to 62 ng/ml. Plasma drug concentrations decreased substantially by Day 3 (47 hrs postdose) for all but one subject [redacted], who had an elevated concentration of 69 ng/ml. The total variability in the plasma concentration data was wide at each timepoint (i.e., CV's of ~65% and greater).

Milk

The concentrations of ivermectin in milk are provided in Table 2 with the mean data plotted against time in Figure 1. Coincident with the plasma data, the mean maximum drug concentrations in milk were also observed at 4 hrs postdose on Day 1 at 7.6 ng/ml and ranged from ng/ml. The highest ivermectin milk concentration was observed in subject [redacted] at 18.5 ng/ml which occurred at 12 hours postdose on Day 1. Mean milk concentrations decreased by Day 2 postdose to 1.3 ng/ml and remained approximately at this level through Day 6 postdose. From Days 7 through 14, milk concentrations decreased further and remained between ng/ml. On Day 14 postdose, milk levels were quantifiable (i.e., > 0.1 ng/ml) in 9 of the 12 subjects with a mean concentration of 0.6 ng/ml. Similar to the plasma concentration data, the total variability in ivermectin milk concentrations between subjects was also wide (i.e., CV's from ~60 to ~160%).

The sponsor estimated that the maximum intake by a nursing 3 kg infant on Day 1 would be ~3 mcg/kg, based on the maximum ivermectin concentration in milk determined in this study to be ~19 ng/ml (i.e., subject [redacted] and the daily consumption of ~500 ml of milk. This 3 mcg/kg "dose" represented ~2% of the recommended adult dosages for onchocerciasis and strongyloides (i.e., 150-200 mcg/kg). Mean intake of ivermectin through the mother's milk would be lower on Days 2 through 14 ranging from mcg/kg.

Reviewers Conclusions:

The sponsor concluded that ivermectin was present in the milk of lactating women after a single dose of 12 mg, maximum milk concentrations occurred on the first day after the dose, and had substantially decreased thereafter, but remained detectable for up to 14 days postdose. The maximum intake of drug by a nursing infant (3 kg body weight) was estimated to be ~3 mcg/kg on the first day of single dose ivermectin administration and represented a minimal intake as compared to the recommended adult dosages of 150-200 mcg/kg. The mean intake of drug at 14 days postdose, the end of the study, was estimated to be ~0.1 mcg/kg (~0.05%-0.07% of the adult dosages) in a nursing infant.

The sponsor also commented in the Clinical Summary Section of this NDA that in light of the limited information concerning the development of the blood brain barrier in newborn infants, that treatment with ivermectin in mothers who intend to breast feed be withheld until at least 1 week after the birth of the child. This recommendation was also provided for in the proposed labeling.

Thus, it appeared that the sponsor considered drug exposure through ingestion of mother's milk to the nursing infant to be of minor consequence in infants with fully developed/intact blood brain barriers. The conclusions are appropriate based on the results of this study and of the oral toxicity study conducted in neonatal monkeys (i.e., < 2 weeks old). In this species, which has been reported to be more predictive of the human response to ivermectin than rodent models, no evidence of toxicity was observed at doses up to 100 mcg/kg/day.

TABLE 1

PLASMA LEVELS OF IVERMECTIN (H_2B_{1a}, NG/ML) FOLLOWING AN ORAL DOSE OF IVERMECTIN (12 MG)

SUBJECT NUMBER	DAY 1, PREDOSE	DAY 1, 1 HOUR	DAY 1, 4 HOUR	DAY 1, 12 HOUR	DAY 2, 23 HOUR	DAY 3, 47 HOUR
N						
Mean ± SD:	N.D.	13 ± 9	23 ± 15	12 ± 11	6 ± 4	12 ± 22
Median	N.D.	10	19	7	4	4

N.S. = No sample.
N.D. = None detected.
[a] Sample marked as plasma but was a milk sample.
[b] Above range of standard line--assay repeated on a smaller sample volume.
[c] Marked as Day 2, seven-hour Plasma 6. Plasma 6 should be Day 3.
[d] An additional sample supplied marked Day 1, seven-hour. No drug was detected in this sample.

TABLE 2

MILK LEVELS OF IVERMECTIN (H_2B_{1a}, NG/ML) FOLLOWING AN ORAL DOSE OF IVERMECTIN (12 MG)

	SAMPLE NO.								
SUBJECT NO.	DAY 1, PREDOSE 1	DAY 1, HOUR 1 2	DAY 1, HOUR 4 3	HOUR 12 4	DAY 2 5	DAY 3 6	DAY 4 7	DAY 5 8	DAY 6 9
N	10	11	12	12	12	12	12	10	12
Mean ± SD:	N.D.	1.6 ± 1.8	7.6 ± 4.5	4.0 ± 5.3	1.3 ± 2.1	1.3 ± 1.3	1.7 ± 1.9	1.2 ± 1.1	1.2 ± 1.1
Median	N.D.	0.9	7.2	2.5	0.9	0.7	1.0	0.7	1.0

N.S. = No sample
$N.D._b$ = None detected
b = Above range of standard line—assay repeated on a smaller sample volume

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TABLE 2 (CONT.)

MILK LEVELS OF IVERMECTIN (H_2B_{1a}, NG/ML) FOLLOWING AN ORAL DOSE OF IVERMECTIN (12 MG)

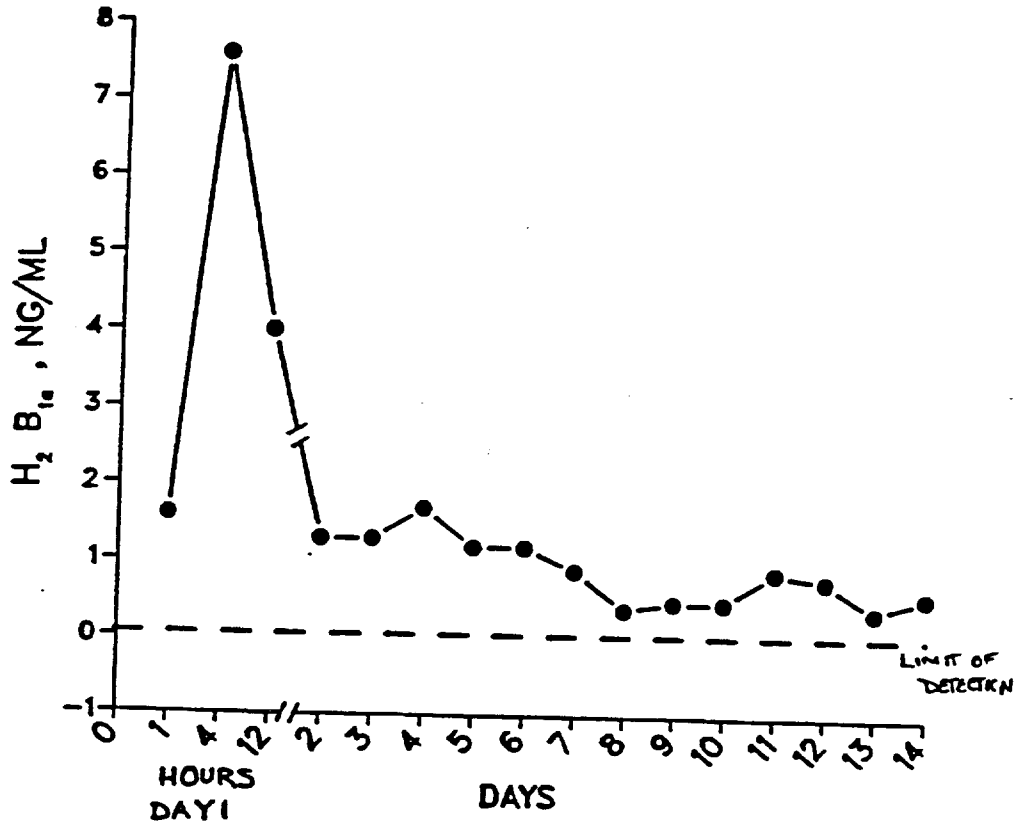
	SAMPLE NO.							
	DAY 7	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14
SUBJECT NO.	10	11	12	13	14	15	16	17
N	12	10	12	11	10	12	10	12
Mean ± SD:	0.9 ± 0.8	0.4 ± 0.4	0.5 ± 0.6	0.5 ± 0.5	0.9 ± 0.7	0.8 ± 1.0	0.4 ± 0.5	0.6 ± 0.8
Median	0.9	0.3	0.3	0.5	0.7	0.3	0.2	0.3

N.S. = No sample
$N.D_b$ = None detected
b = Above range of standard line—assay repeated on a smaller sample volume

18DEC86

FIGURE 1

MEAN IVERMECTIN (H_2B_{1a}) LEVELS IN MILK FOLLOWING 12 MG ORAL DOSE



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VII. IN VITRO METABOLISM

As a follow-up to the radiolabeled metabolic disposition study (see **Section VI.**), the sponsor attempted to characterize further the metabolite profile of ivermectin using the urine, feces, and plasma samples collected from the subjects in this study. A number of polar and non-polar (or "drug-like") metabolites were tentatively identified or postulated. In urine, a group of polar metabolites were identified, with the major metabolite postulated to be a hydroxylated derivative of H_2B_{1a}. Another group of at least 7 "drug-like" metabolites were also postulated and resembled those identified in the livers of pigs. In feces, the "drug-like" metabolites were the primary group identified (~40-50% of extractable residue), with the monosaccharide of H_2B_{1a} being a major derivative of this group. The sponsor noted that all "drug-like" metabolites observed in the feces were also present in the urine, only at much lower levels. The unmetabolized drug was also a major component of the extractable radioactivity in feces (~25-70%). In plasma, only trace amounts of parent ivermectin were detected and ~80% of the extractable radioactivity existed as non-polar metabolites, with the majority postulated to be derivatives of the monosaccharide of H_2B_{1a}. Approximately 12 polar metabolites in plasma were postulated, but the nature of these metabolites were not investigated any further.

The sponsor did not provide any data or related results of *in vitro* hepatic metabolism studies of ivermectin in human liver miscrosomal or other hepatic tissues. It appeared that the *in vitro* metabolism of ivermectin was investigated in rats and other animal species. In rat liver microsomes, CYP3A and possibly CYP1A1 may be involved.

In summary, although the data are not definitive, it appeared that ivermectin is metabolized to a number of metabolites and most likely by the liver. In light of the one-time dosage regimen for either onchocerciasis or strongyloides, the potential for a drug-metabolism or drug-drug interaction would be expected to be minimal.

VIII. COMMENTS TO BE SENT TO SPONSOR

1. For the bioavailability study (NDA Study No. 5535), the sponsor was asked to re-evaluate the bioequivalence of the to be marketed tablet formulation relative to that of the capsule formulation used in clinical trials using 90% confidence intervals calculated on the geometric means of the tablet/capsule AUC and Cmax ratios based on the currently accepted two one-sided test procedure. In the initial NDA submission, the sponsor calculated posterior probabilities and 95% confidence intervals using the to be marketed tablets as the reference, instead of the test formulation. The request was made since it is standard practice for the to be marketed tablet to be considered as the test formulation and the clinical capsules as the reference formulation. However, the sponsor responded by providing 90% confidence intervals on the capsule/tablet ratios, i.e., the opposite of what was requested, and essentially the same as was performed in the initial submission.

2. Has the influence of food on the systemic availability of ivermectin been assessed ? The sponsor may want to consider examining this since ivermectin, like albendazole, is nearly insoluble in water and appears to be poorly absorbed following oral administration. Yet, administration of albendazole with food for the treatment of systemic parasitic diseases is recommended since systemic exposure appears to be substantially increased. If no such data or related results exist, then it is recommended that the sponsor provide a statement in the labeling to indicate that the effect(s) of food on the systemic availability of ivermectin has not been studied.

3. Labeling Comment:
Under CLINICAL PHARMACOLOGY, *Pharmacokinetics*, the last sentence in this section currently reads:

Since in the dose proportionality study (NDA Study No. 5537), apparent/effective half-lives of 16.8 and 16.7 hours were recently calculated for the 6 and 12 mg doses, respectively, it is recommended to change the current wording to:

Philip M. Colangelo 9/3/96
Philip M. Colangelo, Pharm.D., Ph.D.
Office Clinical Pharmacology/Biopharmaceutics,
Division of Pharmaceutical Evaluation III

RD/FT signed by Frank Pelsor, Pharm.D., Team Leader F. Pelsor

Clin Pharm/Biopharm Review Attendees 08/29/96: Dr. Nicholas Fleischer (HFD-880), Dr. Henry Malinowski (HFD-860), Mr. John Hunt (HFD-870)

cc:
Div. File - NDA 50-742
HFD-520 (P. Coyne, MO)
HFD-520 (P. Fogarty, CSO)
//
//
HFD-340 (Viswanathan)
HFD-205 (FOI)
HFD-880 (Division File)
HFD-880 (Pelsor, Colangelo)
Drug file (Clarence Bott, HFD-870, PKLN RM 13B-31)

Pharm/Tox

AUG 5 1996

SEETHALER

520

Review and Evaluation of Pharmacology and Toxicology Data
Division of Anti-Infective Drug Products, HFD-520

NDA: 50-742 (formerly NDA 20-721)

DRUG: Mectizan (Ivermectin)

CATEGORY: Anti-parasitic agent

SPONSOR: Merck Research Laboratories
Sumneytown Pike
West Point, PA 19486

CONTACT PERSON: Kenneth R. Brown, M.D., Regulatory Liaison
Phone 610-397-2552

NUMBER OF VOLUMES: 34

DATE OF SUBMISSION: March 29, 1996

DATE CDER RECEIVED: April 3, 1996

DATE ASSIGNED: April 8, 1996

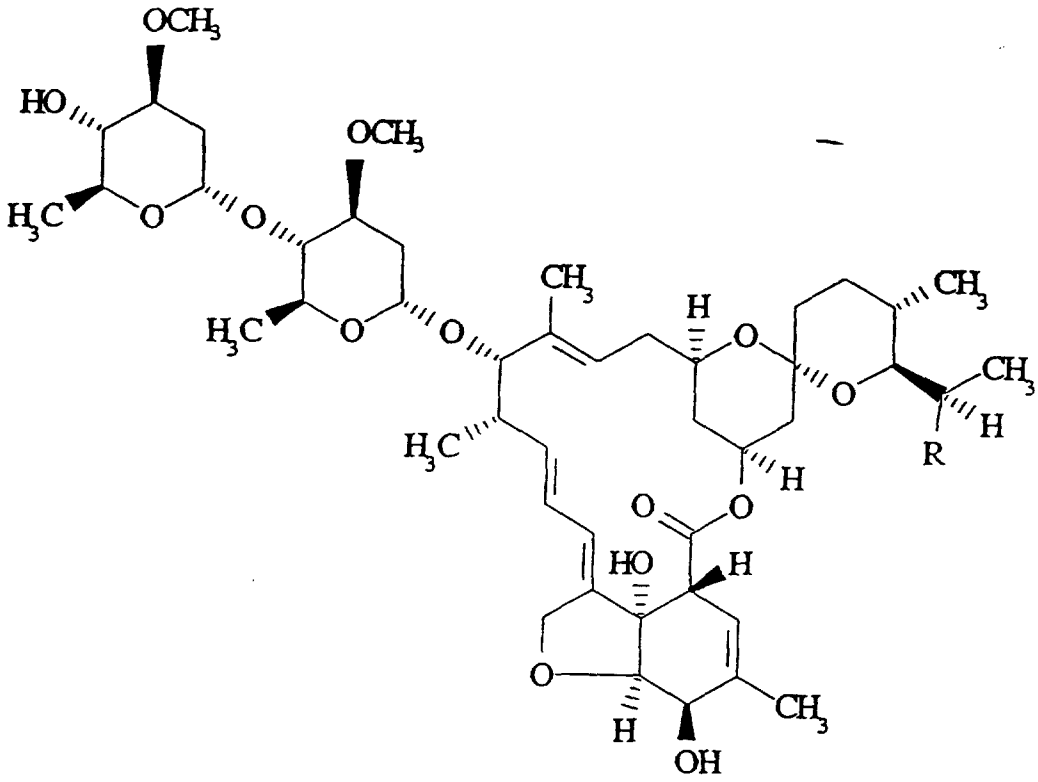
DATE REVIEW STARTED: June 17, 1996

DATE FIRST DRAFT COMPLETED: July 26, 1996

DATE REVIEW ACCEPTED BY TEAM LEADER: July 30, 1996

INTRODUCTION/OVERVIEW

Ivermectin is derived from the avermectins, a class of broad-spectrum antiparasitic agents isolated from the fermentation products of *Streptomyces avermitilis*. It is a mixture of two semisynthetic macrocyclic lactones, which are designated as H_2B_{1a} (ethyl analog) and H_2B_{1b} (methyl analog). The mixture contains at least 90% of the ethyl analog, and not more than 10% of the methyl analog. The structure of ivermectin is shown on the next page. Ivermectin is also known by the sponsor's code number MK 0933, and by the trade name, Mectizan. The drug will be marketed in a tablet dosage form, containing 6 mg of active ingredient.



Molecular formulas and relative molecular masses:

H_2B_{1a} (R = C_2H_5): $C_{48}H_{74}O_{14}$; M.W. - 875.10

H_2B_{1b} (R = CH_3): $C_{47}H_{72}O_{14}$; M.W. - 861.07

Ivermectin has been used in Africa and elsewhere to treat onchocerciasis (river blindness) and strongyloidiasis (a nematode infection of the gastrointestinal tract). Previous human experience has shown that the compound is highly efficacious and generally, well-tolerated. It is approved in France and several other countries for human use, and in the United States for veterinary use. In the U. S. it is used for prophylaxis against heartworm in dogs, and as an anthelmintic in several species of farm animals.

This NDA seeks approval of Mectizan for the treatment of river blindness in a single oral dose of 150 mcg/kg, and for the treatment of strongyloidiasis in a single oral dose of 200 mcg/kg.

PRECLINICAL SAFETY STUDIES

This NDA contains reports of a large number of toxicology studies on ivermectin, that were conducted between 1977 and 1995. The data from most of these studies have been previously reviewed by the Center for Veterinary Medicine (USFDA), and are summarized in the next section. The previously unreviewed studies, are reviewed in this section.

1. Ascending Dose Oral Toxicity Study in Rhesus Monkeys

This was a GLP study conducted by the sponsor in West Point, PA between March and September of 1985 (study TT-85-013-0). Eight rhesus monkeys were caged individually and maintained under appropriate environmental conditions. At the start of the study, the animals were two to three years old and weighed between 2.4 and 3.2 kilograms. Two males and two females received MK-0933, while four other animals (two of each sex) received another compound (MK-0936). The compounds were administered orally, by gavage, in sesame oil (5 ml/kg). The doses tested were 0.2, 0.5, 1, 2, 4, 6, 8, 12, and 24 mg/kg with intervals of two to three weeks between doses. Body weights and food consumption were recorded, and the animals were observed for signs of toxicity. The eyes were examined for mydriasis. Also, blood was drawn periodically for measurement of plasma drug concentrations.

Emesis was observed in these animals, with a dose-related incidence at doses of 2 mg/kg and higher. Mydriasis was seen at doses of 6 mg/kg and above. Decreased activity and/or sedation occurred at 24 mg/kg. After the minimum toxic dose of 2 mg/kg, the peak plasma drug concentrations were highest at 24 hours and averaged 110 nanograms/ml. No postmortem or microscopic observations were reported for this study.

2. Two Week Oral Toxicity Study in Immature Rhesus Monkeys

This was a GLP study conducted for the sponsor by (study TT-85-9033). Immature rhesus monkeys (4/sex/group) were caged individually and maintained under appropriate environmental conditions. At the start of the study, the animals were 13 to 21 months old, and weighed between 1.9 and 3.2 kilograms. MK-0933 in sesame oil was administered once daily, by nasogastric intubation, at doses of 0, 0.3, 0.6, or 1.2 mg/kg/day (1 ml/kg) for 14-16 days. Evaluations for treatment-related effects were based on observations, body weights, hematology, serum chemistries, ophthalmogic examinations, gross pathology, organ weights, and microscopic histopathology.

There were no treatment-related findings in these animals. Increases in serum transaminases occurred in three animals, but these increases were attributed to hepatitis-like viral infections.

3. Two Week Oral Toxicity Study in Neonatal Rhesus Monkeys

This was a GLP study conducted for the sponsor by —

(study TT-86-9005). Three groups of neonatal rhesus monkeys (5 males and 3 females/group) were maintained on a bottled infant formula in individual incubators in the nursery. The animals were examined by a veterinarian, and deemed to be in clinically acceptable condition. At the start of the study, the animals were 7 to 13 days old, and weighed between 400-600 grams. MK-0933 in sesame oil was administered once daily, by nasogastric intubation, at doses of 0, 0.04, or 0.1 mg/kg/day (1 ml/kg) for 14 days. Evaluations for treatment-related effects were based on observations, body weights, food consumption, hematology, serum chemistries, ophthalmogic examinations (including pupillary light responses), gross pathology, organ weights, and microscopic histopathology.

No treatment-related effects were observed in this study.

The Mectizan tablets described in this NDA carry a three year expiration date. It has been determined that a loss of potency of approximately 5-10% occurs during three years of storage at room temperature. The loss of potency is due to the formation of unidentified oxidative degradation products in the tablets. The following two studies were performed to evaluate the safety of the degradation products.

4. Two Week Oral Toxicity Study of Stored Tablets in Rats

This was a GLP study conducted by the sponsor in West Point, PA during June and July of 1995 (study TT-95-043-0). Mectizan tablets that had been stored for three years, were ground into a powder with a mortar and pestle. The crushed powder was suspended in 0.5% aqueous methylcellulose, and the suspension was assayed for concentration and uniformity. The suspension was administered orally to Sprague-Dawley rats (15 males, 15 females) once daily for 14 days. The suspension was given in a volume (5 ml/kg) that corresponded to 10 mg/kg of ground tablet, and a dose of 0.5 mg/kg of ivermectin. Another group of rats (15/sex) received a comparable volume of 0.5% methylcellulose, and served as a control group. Evaluations for treatment-related effects were based on observations, body weights, food consumption, hematology, serum chemistries, ophthalmogic examinations, urinalysis, gross

pathology, organ weights, and microscopic histopathology.

No treatment-related effects were seen in this study.

5. Two Week Oral Toxicity Study of Stored Tablets in Monkeys

This was a GLP study conducted by the sponsor in West Point, PA during July of 1995 (study TT-95-044-0). Mectizan tablets that had been stored for three years, were ground into a powder and suspended in 0.5% aqueous methylcellulose, as described above. The suspension was administered orally, through a nasogastric tube, to rhesus monkeys (4 males, 4 females) once daily for 14 days. The suspension was given in a volume (5 ml/kg) that corresponded to 10 mg/kg of ground tablet, and a dose of 0.5 mg/kg of ivermectin. Another group of animals (4/sex) received 0.5% methylcellulose, and served as a control group. The monkeys were approximately two years old, and weighed from 2.4 to 3.4 kilograms at the start of the study. Evaluations for treatment-related effects were again based on observations, body weights, food consumption, hematology, serum chemistries, ophthalmogic examinations, urinalysis, gross pathology, organ weights, and microscopic histopathology.

No treatment-related effects were seen in this study.

TOXICOLOGY PROFILE OF IVERMECTIN

The following summary of ivermectin toxicity has been derived from the CVM reviews of the earlier submissions, and from the current NDA.

Acute Toxicity

The median lethal doses (LD50s) were reported as follows:
11.6 mg/kg oral-male mice
24.6-87.2 mg/kg oral-female mice (several different studies)
42.8-52.8 mg/kg oral-male rats
44.3-52.8 mg/kg oral-female rats
2.3 mg/kg oral-infant rats (1-2 day old pups)
406 mg/kg dermal-rabbits (both sexes)

The signs of toxicity observed in rodents were ptosis, bradypnea, ataxia, tremors, and loss of the righting reflex.

A study was conducted in dogs using single oral doses of 5-80 mg/kg. Mydriasis, ataxia, and tremors occurred at 10 mg/kg. Two of the four dogs dosed at 80 mg/kg, became comatose and died.

In experiments with cattle, subcutaneous doses of up to 6 mg/kg were well-tolerated. However, in a group of four calves that

received 8 mg/kg sc (40 times the therapeutic dose), one calf died and two others were sacrificed moribund. The compound was thought to have caused CNS depression in these cattle.

Subchronic Toxicity

A 14-week study was conducted in rats (20/sex/group) at doses of 0, 0.4, 0.8, and 1.6 mg/kg/day orally. (The animals used in this study, were derived from dams that had also been treated with the compound). The no-effect level was 0.4 mg/kg/day. At higher doses, the following gross and microscopic signs of toxicity were observed: enlarged spleens with congestion of the red pulp and extramedullary hematopoiesis, iron-positive pigment in renal tubular epithelium, hepatocellular vacuolation and pigment in Kupffer cells. Reactive hyperplasia of the bone marrow was seen in the animals with enlarged spleens, suggesting possible intravascular hemolysis.

In dogs (4/sex/group), a 14-week study was conducted at doses of 0, 0.5, 1, and 2 mg/kg/day orally. The no-effect level was 0.5 mg/kg/day. The signs seen at higher doses were salivation, mydriasis, anorexia, dehydration, tremors, and ataxia. Some of the animals became recumbent, and four of the eight dogs in the high-dose group were sacrificed in poor condition.

Reproductive Toxicity

Several teratology studies were conducted in mice (20-25 dams/group) at doses of 0, 0.1, 0.2, 0.4, 0.8, and 1.6 mg/kg/day orally, during gestation days 6-15. Tremors and convulsions were seen in some dams following doses of 0.2 mg/kg/day. Some maternal deaths occurred at doses of 0.4 mg/kg/day and higher. Teratogenic effects were seen at doses of 0.4 mg/kg/day and above. Cleft palate occurred in the fetuses from the 0.4, 0.8, and 1.6 mg/kg/day groups. Exencephaly was seen in the 0.8 mg/kg group.

A teratology study was conducted in rats (25 dams/group) with oral doses of 0, 2.5, 5, and 10 mg/kg/day during gestation days 6-17. There were some maternal deaths, and some pre-implantation loss in the high-dose group. Incomplete bone ossification occurred in the 5 and 10 mg/kg/day groups. Cleft palate and "wavy ribs" were seen in the 10 mg/kg group.

In rabbits (16 dams/group) the teratology study was conducted with oral doses of 0, 1.5, 3, and 6 mg/kg/day during gestation days 6-18. In the high-dose group, there were losses in maternal body weights, and some abortions. There was also an increase in the number of dead fetuses. Cleft palate and clubbed forepaws occurred in the fetuses from the 3 and 6 mg/kg groups.

Some additional reproduction studies that were conducted in rats

showed that ivermectin produced adverse effects in neonates (delayed development, increased pup mortality). These effects occurred at maternal doses of 1.6 mg/kg/day and above. It was also shown that the compound was secreted in the milk of lactating rats.

No chronic toxicology studies on ivermectin have been reported. Ivermectin was non-mutagenic when tested (with or without metabolic activation) in the Ames Salmonella mutation assay, the mouse lymphoma (L5178) assay, and the unscheduled DNA synthesis test in human fibroblasts. Carcinogenicity studies have not been conducted with the compound.

PHARMACOKINETIC STUDIES

MK-0933 was administered orally (in sesame oil) to two groups of mice, in doses of 0.1 or 0.5 mg/kg/day for 35 days (Study TT-82-071-0). Peak plasma drug concentrations were 5 and 20 nanograms/ml, in the low- and high-dose groups respectively. At necropsy, analysis of brain tissue, revealed MK-9033 concentrations of 35 ppb in some animals (because of technical difficulties encountered in the brain assay, the value of 35 ppb may or may not be reliable).

In an acute study in mice, a single oral dose of MK-0933 (51 mg/kg) was administered in sesame oil (Study TT-82-088-0). This dose was lethal to four of 30 animals, while other animals became moribund. At various times after dosing, blood was drawn from surviving animals, and some animals were sacrificed for analysis of brain tissue. The peak drug concentrations found in this study were 5000 nanograms/ml in plasma, and 400 ppb in brain.

In another study, MK-0933 in sesame oil was administered orally by gavage to two groups of four female Beagle dogs at doses of either 0.5 or 2 mg/kg/day for 35 days (Study TT-82-070-0). Peak plasma drug concentrations of 175 and 1500 nanograms/ml occurred during the third week of the study, but then declined during the last two weeks of the study. One dog in the 2 mg/kg/day group developed tremors, ataxia, and depression, and was sacrificed moribund on day 24. In this animal, the drug was detected in the cerebrospinal fluid at a concentration of 3 nanograms/ml. In the other seven animals sacrificed on day 35, the drug was not detected in the CSF (detection limit 1 ng/ml).

The pharmacokinetic data obtained in human studies is presented in Table I-1 (attached).

CONCLUSIONS/RECOMMENDATIONS TO SPONSOR

Ivermectin appears to be neurotoxic, presumably through an effect on GABA neurons. The compound appeared to be more toxic in rodents than in subhuman primates, especially with regard to CNS effects such as tremors and ataxia. In mice, effects were seen at doses as low as 0.2 mg/kg/day; in monkeys, mild toxicity (emesis) was observed following a dose of 2 mg/kg, which is 10 times higher than the recommended human dose of 200 mcg/ml. At these doses, peak plasma drug levels were 5.5 times higher in the monkeys than in humans (110 versus 20 nanograms/ml).

Ivermectin is teratogenic in mice, rats, and rabbits, and should be labeled as Pregnancy Category C. It is also excreted in the milk of lactating animals and humans.

Ivermectin has been shown to be effective in the treatment of onchocerciasis and strongyloidiasis, and this drug will be extremely useful in the control of these parasitic diseases. An adequate margin of safety has been demonstrated between the dose toxic to subhuman primates, and the intended single (one-time) human therapeutic dose. Approval of this NDA is recommended.

The drug should not be used by pregnant women or nursing mothers, unless it can be shown that the benefits of therapy, clearly outweigh the risks to the fetus.

Kenneth Seethaler

Kenneth Seethaler, Ph.D., D.A.B.T.
Pharmacologist, HFD-520

cc: Original NDA 50-742
HFD-340
HFD-520
HFD-520/Pharm/K.Seethaler
HFD-520/MO/P.Coyne
HFD-520/Micro/J.King
HFD-520/Chem/J.Timper
HFD-520/CSO/P.Fogarty
HFD-520/Biopharm/P.Colangelo
HFD-520/Biostat/S.Bell

8/5/96

Concurrence Only:
HFD-520/L.Gavrilovich
HFD-520/R.Osterberg 7/30/96

Ivermectin
Synopsis of Application
I. Synopses
I. Human Pharmacokinetics and Bioavailability Documentation

Table I-1 Table of Investigations

Study No. [Ref.]	Study Objective/ Study Design	Dosage Forms	Formulation No. (Batch Size)	Dose	Number of Subjects (S) Patients(P)	Conclusions
2 [I-5]	Evaluation of (^{3}H)ivermectin absorption, distribution, metabolism and excretion/ Single-dose study	14-mg Ivermectin Capsule	R0933-DFC-002-A001 (14)	14 mg (200 µCi)	4S (All M)	Mean T_{max} for ivermectin was 6 h; corresponding $t_{½}$ was 11.8 h. C_{max} of tritiated metabolites was twice that of parent drug. Drug and metabolites are slowly secreted in bile and excreted in feces. No more than 1.0% of the dose was excreted in urine.
5537 [I-6]	Evaluation of dose proportionality/Single dose (SD), three-way crossover study	3-mg Ivermectin Tablet 6-mg Ivermectin Tablet	E-3806 (390) E-3807 (2305)	6 mg 12 mg 15 mg	12S (All M)	Following SD of 6, 12, and 15 mg, mean C_{max} and AUC were proportional to dose although substantial variability was observed.
5535 [I-7]	Evaluation of Phase III capsule and to-be-marketed tablet vs. oral solution/ Single-dose, three-way crossover study	6-mg Ivermectin Capsule 6-mg Ivermectin Tablet 0.6 mg/mL hydroalcoholic solution (40% ethanol)	E-6086 (200) E-3807 (2305) E-3798 (500 mL)	12 mg 12 mg 12 mg	12S (All M)	The oral solution showed higher (close to twice) bioavailability than either of the solid forms. The tablet formulation showed comparable bioavailability to the capsule formulation. The relative bioavailability of the capsule was 113% of the tablet.
5533 [I-8]	Estimation of ivermectin's secretion into human breast milk/Single-dose study	0.5-mg Ivermectin Capsule 2.5-mg Ivermectin Capsule	E-5885 (1000) E-5893 (1000)	5 mg 12 mg	12S (All F)	Orally administered ivermectin is secreted in human milk. The highest concentration observed was 18.5 ng/mL after the 12-mg dose. Drug was still detectable 14 days postdose.

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STATISTICAL REVIEW AND EVALUATION

NDA: 50-742
Generic Drug Name: Ivermectin
Drug Trade Name: MECTIZAN®
Formulation: oral tablets
Drug Class: 1P
Applicant: Merck Research Laboratories

SEP 2 6 1996

Indications: 1. Strongyloidiasis of the gastrointestinal tract
2. Onchocerciasis (a.k.a. River blindness)

User Fee Date: October 1, 1996

Documents Reviewed: NDA Volumes 1, 28, 29, 30, 31, 32 dated March 29, 1996 submitted as NDA
NDA Volumes 3, 7, 29, and 34 dated July 9, 1996 submitted as NDA
Safety Update Report dated July 31, 1996 submitted for NDA 50-742
Dataset provided August 23,1996 for Strongyloidiasis studies.
Dataset provided September 3,1996 for Onchocerciasis studies.
Draft of Medical Officer's strongyloidiasis review.

Type of Review: Clinical

Medical Officer: Phillip Coyne, M.D., HFD-520
Statistical Reviewer: B. Sue Bell, Ph.D., HFD-725
Project Manager: Pauline Fogarty, HFD-520

0. Executive Summary

The applicant is requesting approval of ivermectin for the treatment of strongyloidiasis and of onchocerciasis. The recommended dosages are a single oral dose of approximately 200 or 150 µg of ivermectin per kg of body weight for strongyloidiasis and onchocerciasis, respectively. Ivermectin is to be supplied as 6 mg white, scored tablets.

In support of the strongyloidiasis indication, five studies were submitted with two studies that used albendazole as the comparator being considered pivotal by the applicant. The Medical Officer considers negative stools through 30 days of follow-up to represent a cure. Ivermectin was statistically superior to albendazole in both pivotal studies with lower bounds on the 95% confidence intervals of the difference in proportion cured of 10% and 27%. However, in two U.S. studies and in one French study comparing single-dose and double-dose ivermectin with thiabendazole, ivermectin was not statistically comparable to thiabendazole based upon the DAIDP's Points to Consider document that requires that the lower bound be greater than or equal to -10% if the cure rate is greater than or equal to 90%. These studies were very small resulting in very wide confidence intervals. Except for one treatment arm in one study, the point estimates of the proportion cured by an ivermectin treatment was either equal to or slightly greater than the point estimate of the proportion cured by thiabendazole. In contrast, statistical analysis based on time to treatment failure showed that both single-dose and double-dose ivermectin treatments were slightly better than thiabendazole based upon a comparison of the 95% confidence intervals of cure rates. Graphs provided in the section titled Medical Officer's Integrated Summary of Efficacy show the consistency of the study results. Concerning safety, ivermectin was shown to be extremely safe in these studies and to have a better safety profile than thiabendazole.

Therefore, based upon statistical review of the data provided by the sponsor and revised by the reviewing medical officer, it is recommended that ivermectin be approved for the indication of strongyloidiasis.

In support of the onchocerciasis indication, 4 studies were submitted for review. The one pivotal study was a multicenter, double-blind clinical trial with comparison to both a placebo group and a diethylcarbamazine citrate (DEC-C) treatment group. The medical officer considers the reduction in geometric mean of microfilaria (mf) density at one month to be the primary outcome with reductions at 3 months and 6 months being of secondary importance. These time points are relevant because of the label's recommendation for possible retreatment at three months. Using nonparametric statistical methods to compare the percent of baseline mf count shows that ivermectin is statistically superior to DEC-C at all three time points with a p-value of 0.0001. Further, DEC-C treatment causes severe systemic reactions as the result of the killing of the microfilaria. The number of ivermectin-treated patients with such reactions was statistically less. All other studies were placebo controlled trials which demonstrated that ivermectin was superior with very few and very minor adverse clinical experiences.

It must be noted that the onchocerciasis clinical trials used a capsule that was found to be bioinequivalent to the tablets in the clinical pharmacology/biopharmaceutics. Otherwise, the statistical review of the applicant's data supports approval of ivermectin for the treatment of onchocerciasis.

I. Background

"MECTIZAN® (Ivermectin) is a semisynthetic, anthelmintic agent for oral administration. Ivermectin is derived from the avermectins, a class of highly active broad-spectrum anti-parasitic agents isolated from the fermentation products of *Streptomyces avermitilis*."

"The drug has been registered for agricultural and veterinary use since 1981."

"In 1987, ivermectin was approved in France for the treatment of onchocerciasis and is now considered the drug of choice for the treatment of that infection." "As of mid-1995, greater than 36 million ivermectin treatments (representing >5.2 million patients) have been administered for onchocerciasis."

"In November 1993, the French government approved the use of ivermectin for strongyloidiasis."

Ivermectin is available in 6-mg tablets. The applicant recommends administration of a single oral dose where the dosage is dependent upon the indication and the weight of the patient. The applicant considers the single dose regimen to be one of the advantages of ivermectin since other agents used to treat these indications require a multi-dose regimen.

II. Strongyloidiasis of the gastrointestinal tract

"Strongyloidiasis occurs chiefly in tropical and subtropical regions of the world. However, endemic regions also exist in southeast USA, Japan and southern and eastern Europe. Severe disseminated disease may occur in immunocompromised patients."

"The therapeutic arsenal available at present for the treatment of strongyloidiasis is limited to thiabendazole and albendazole. Thiabendazole is effective in 75-96% of cases; however, it is frequently associated with considerable clinical adverse reactions. Albendazole, the therapeutic alternative, is well tolerated and has a cure rate of 42-100%, depending on the dose schedule and length of follow-up."

***REVIEWER COMMENT**: Exact statistical methods implemented in the software package StatXact3 will be used to calculate 95% confidence intervals for the difference in cure rates for this indication. Because of the relatively small sample sizes and high cure rates, the data from the majority of studies for this indication do not satisfy the assumptions for using the normal approximation to the binomial distribution. The Marti study does have sufficient sample size for use of the normal approximation.*

II.A. Labeling claims and primary studies

"The recommended dosage of MECTIZAN for the treatment of strongyloidiasis is a single oral dose designed to provide approximately 200 µg of ivermectin per kg of body weight." "Patients should take tablets with water. In general, additional doses are not necessary. However, a follow-up stool examination to verify eradication of infection should be performed."

"Two controlled clinical studies using albendazole as the comparative agent were carried out in international sites where albendazole is approved for the treatment of strongyloidiasis of the gastrointestinal tract, and three controlled studies were carried out in the US and internationally using thiabendazole as the comparative agent. Efficacy, as measured by cure rate, was defined as the absence of larvae in follow-up stool examinations. Based on this criterion, efficacy was significantly greater for MECTIZAN (a single dose of 170 to 200 µg/kg) than for albendazole (200 mg b.i.d. for 3 days). MECTIZAN administered as a single dose of 200 µg/kg for 1 day was as efficacious as thiabendazole administered at 25 mg/kg b.i.d. for 3 days."

The applicant considers the Gentilini study and the Marti study as the two pivotal studies. Both pivotal studies compared Ivermectin to Albendazole.

***REVIEWER COMMENT**: Since the applicant is making a labeling claim that ivermectin is "as efficacious as thiabendazole," the studies comparing ivermectin to thiabendazole are also reviewed in detail.*

II.B. Applicant's Analysis

II.B.1. Protocol 004 (Gentilini/Datry)

Protocol title:
"An Open, Randomized Study of Efficacy, Safety and Tolerability of Ivermectin Single Dose vs. Albendazole (3-day course) in the Treatment of Patients Infected With *Strongyloides Stercoralis* (Study 004)."

Publication based upon data collected:

Datry A, Hilmarsdottir I, Mayorga-Sagastume R, Lyagoubi M, Gaxotte P, Biligui S, Chodakewitz J, Neu D, Danis M, Gentilini M. Treatment of *Strongyloides stercoralis* infection with ivermectin compared with albendazole: results of an open study of 60 cases. Trans Roy Soc Trop Med Hyg, 1994;88:344-345.

II.B.1.a. Study Design

This study was an "Open, randomized trial in otherwise healthy ambulatory patients to compare the efficacy, safety and tolerability of ivermectin versus albendazole in the treatment of strongyloidiasis of the gastrointestinal tract." "Although the study was open in design, stool specimens were examined by one single expert who was to remain blinded as to the treatment allocations." The study was conducted in France.

Patients received either a single dose of ivermectin (target dose of 200 µg/kg) or albendazole (200 mg b.i.d. for 3 days). Because the ivermectin dosage schedule included in the protocol was in error, the actual dose of ivermectin was approximately 170 µg/kg. "The difference between the administered dose and the target dose is not considered meaningful."

Patients were included who were between 5 and 70 years of age and who were infected with *Strongyloides stercoralis (SS)*. Infection status was determined by stool examination using the Baermann technique. Please refer to the Medical Officer's review for more details of the inclusion/exclusion criteria and for details of the visit procedures.

***REVIEWER COMMENT**: The published article also mentioned the exclusion of patients who had received any other antifilarial drug in the 6 months, or other antihelmintic treatment in the 72 hours, preceding the study.*

"After completion of the informed consent procedures and documentation of strongyloidiasis evidenced by stool examination, patients were randomized to receive either ivermectin or albendazole according to an allocation schedule. The patients were dosed at least 2 hours before breakfast."

REVIEWER COMMENT: According to the published article, informed oral consent was given rather than written consent. The applicant's audit found no patient consent forms for 6 patients, 3 forms had not been signed by the patients, and 4 of the signed forms were dated by the investigator.

The applicant's study report considered all patients whose data was received by August 10, 1991. The evaluability criteria were that strongyloidiasis was documented on stool examination, the patient did not receive any other effective therapy during the study period, the patient was compliant with therapy, adequate follow-up stool examinations were performed for determination of efficacy, and there was no violation of inclusion and/or exclusion criteria that would compromise efficacy evaluation.

REVIEWER COMMENT: The published article reports on 60 patients entered into the trial while the applicant's report is for 56 patients. The applicant suggests that the discrepancy may have resulted from a cut-off date imposed for the assembly of the French MAA.

"The efficacy and safety of ivermectin was evaluated on the basis of physical examinations and laboratory tests prior to treatment and on Days 7 (5-9), 30 (26 to 34), and 90 (85 to 95) posttreatment." Aspirin and antihistamines were permitted for mild or moderate reactions to drug treatment. "Other medications were not to be administered during the first week of drug administration except for necessary treatment of patients with severe allergic reactions."

"The primary measure of efficacy in this study was the absence of larvae in posttherapy Baermann fecal examinations. The detection of larvae on any posttreatment stool examination meant failure. Patients with adequate follow-up examinations which were all negative for larvae were considered cured. It should be noted that although not specified in the protocol, parasitological cure (i.e., stool exams negative for larvae) without resolution of symptoms was counted as a clinical failure." Clinical failures were retreated using ivermectin.

REVIEWER COMMENT: Contrary to the protocol, 2 ivermectin and 9 albendazole patients were retreated after having a positive stool examination. A sensitivity analysis will be performed on the Medical Officer's data to assess the impact of showing the 6 albendazole patients, who were retreated as early as 10 days after initial treatment, as non-evaluables in contrast to treatment failures. The other 3 albendazole patients and the 2 ivermectin patients were retreated approximately a month after initial therapy which was sufficient time for the drugs to demonstrate efficacy.

In a quality assurance audit performed by the applicant 3.5 years after the completion of the trial, "certain GCP compliance issues relating to insufficient documentation of informed consent, incomplete case report form documentation at the site, protocol compliance, incomplete regulatory documentation at the site and lack of study monitoring" were found.

II.B.1.b. Efficacy Results

Applicant's results

"A total of 79% (22/28) of patients were cured following ivermectin therapy compared to 43% (10/23) of those receiving albendazole. This difference in cure rates is statistically significant (p=0.02). Logistic regression analysis demonstrated that no other factor (age, sex, race, clinical severity of infection, and intensity of infection) was significantly related to treatment failure." If those patients whose diagnosis was greater than 6 days prior to treatment are removed, similar results are seen with 76.9% (10 of 13) of the ivermectin-treated patients being cured and 33.3% (2 of 6) of the albendazole-treated patients being cured.

***REVIEWER COMMENT**: The difference between the percent cured for the two treatments is 43% with a 95% confidence interval of $_{28.23}$ [8% , 66%] $_{79\%,43\%}$. This indicates that ivermectin cured a statistically greater percent of patients than albendazole in this study population.*

"Similar results are seen if all patients, regardless of their efficacy evaluation status, are considered for analysis." In this intent-to-treat analysis, 79% (23 of 29) of ivermectin-treated patients are cured and 48% (13 of 27) of albendazole-treated patients are cured.

***REVIEWER COMMENT**: The difference between the percent cured for the two treatments in the intent-to-treat analysis is 31% with a 95% confidence interval of $_{29.27}$ [6% , 62%] $_{79\%,48\%}$. This indicates that ivermectin cured a statistically greater percent of intent-to-treat patients than albendazole in this study population.*

As can be seen in Table 1, there is "no substantive difference" between the outcomes of the 56 patients included in the applicant's report compared with the outcomes of the 60 patients included in the published report.

Table 1: Comparison between applicant's data received from investigative site and data published by the investigative team for protocol 004.

	Applicant Summary			Publication		
Patient Accounting:	IV*	ALB*	ALL*	IV*	ALB*	ALL*
Patients Entered	29	27	56	32	28	60
Evaluable patients (Efficacy)	28	23	51	29	24	53
Nonevaluable Patients (efficacy)	1	4	5	3	4	7
Cure Rate (%)	22/28 (79)	10/23 (43)	N/A	24/29 (83)	9/24 (38)	N/A

* IV = Ivermectin; ALB = Albendazole; ALL = IV plus ALB

( ) = Percent cured

Medical Officer's results

Using a test of cure at 30 days post treatment and evaluating those patients with any recent positive stool examination taken pretreatment without intervening treatment, the Medical Officer found that ivermectin cured 24 of 26 (92%) evaluable patients and albendazole cured 12 of 22 (55%) evaluable patients. A 95% confidence interval of the difference in proportion cured is $_{26.22}$ [10% , 65%] $_{92\%,55\%}$. A lower bound greater than zero indicates that ivermectin cured a statistically greater proportion of patients diagnosed with strongyloidiasis than albendazole. Because the risk of reinfection in France is very low, a 90 day follow-up is considered to evaluate the potential for relapse. At 90 days, the Medical Officer found that ivermectin cured 21 of 26 (81%) and albendazole cured 10 of 21 (48%). A 95% confidence interval of the difference in proportion cured $_{26.21}$ [3% , 64%] $_{81\%,48\%}$ which continues to indicate that ivermectin cures a statistically greater proportion than albendazole.

II.B.1.c. Safety Results

No patients were discontinued due to adverse clinical or laboratory experiences. One patient from the ivermectin group experienced mild nausea, fatigue, dizziness, sleepiness, tremors, and mild vertigo for one to two days after treatment. Although probably related to the study drug, it was not considered serious.

II.B.2. Protocols 014/015 (Berk and Gann)

Protocol title:
"An Open, Randomized Study of Efficacy, Safety and Tolerability of Ivermectin Single Dose and Repeat Dose (One day apart) vs. Thiabendazole (Three-day course) in the Treatment of Patients Infected With *Strongyloides Stercoralis.*"

Publications based upon data collected:

Gann PH, Neva FA, Gam AA. A randomized trial of single- and two-dose ivermectin versus thiabendazole for treatment of Strongyloidiasis. J Infect Dis, 1994;169:1076-1079.

Salazar SA, Berk SH, Howe D, Berk SL. Ivermectin vs. Thiabendazole in the treatment of Strongyloidiasis. Infect Med, 1994;11:50-59.

II.B.2.a. Study Design

"Open, randomized trial in ambulatory patients with strongyloidiasis of the gastrointestinal tract. Following diagnostic studies and laboratory tests, patients received either a single dose of ivermectin, two single doses of ivermectin 1 day apart or thiabendazole twice a day for 3 days. Follow-up visits were weekly for 1 month and monthly for 1 year (Study 014), or at Week 1, and Months 1, 3, 6, and 12 (Study 015)." "Although the study was open in design, stool specimens were examined by one single expert who was to remain blinded as to the treatment allocations." The primary therapy period was from May 1990 through December 1991. The Berk study (014) was conducted using patients from a Veterans Administration Medical Center in Mountain Home, Tennessee. The Gann study (015) was conducted in where there is a large population of refugees from Cambodia and Laos.

Dosages were a single 200-mcg/kg ivermectin oral dose, two 200-mcg/kg oral doses of ivermectin 1 day apart or 3 days of 25 mg/kg b.i.d. oral treatment with thiabendazole.

"After completion of the informed consent procedures and documentation of strongyloidiasis evidence by stool examination, patients were randomized ..."

***REVIEWER COMMENT**: The applicant [page 1549 of volume 30] reported that 4 of the 68 patients who were randomized had negative pretreatment stool examinations and were therefore considered nonevaluable. Because 2 of these 4 patients had at least one positive pretreatment stool examination, the Medical Officer considered these 2 patients to be evaluable.*

"Parasitological cure was the primary measure of efficacy and was assessed using repeated Baermann stool examinations during the follow-up period. Cure was defined as the absence of larvae in the follow-up stool examinations. A single positive stool after Day 6 was defined as a therapeutic failure." "The primary measurement of efficacy was the cure rate."

Patients were included who were between 5 and 80 years of age and who were infected with *Strongyloides stercoralis*. Infection status was determined by stool examination using the Baermann technique. Please refer to the Medical Officer's review for more details of the inclusion/exclusion criteria and for details on the visit procedures.

REVIEWER COMMENT: *There were inconsistencies between the protocols that required one year of follow-up and a statement in the study report that "Three- to 6-month follow-up was the main goal." The evaluability criteria never explicitly stated what was considered "adequate follow-up stool examinations. The Medical Officer concluded that 30 days was appropriate for test of cure.*

A subsequent audit by the applicant "showed that 52% of the patients had incomplete supportive documentation on file for stool testing. In this group of 52%, one to four source reports were missing per patient, with most patients having had an average of 6 to 7 tests completed during the study course. Admittedly, these findings would be of great concern if the frequency of positive stool tests were high; however, this is not the case for any of the three treatment groups in this study."

REVIEWER COMMENT: *There were discussions concerning the lack of signed informed consent documents for 43% of all patients. It was concluded that oral consent had been given, and that the problems had arisen because "almost all patients who entered the trial were Cambodian refugees who were for the most part illiterate." The journal article by Gann et al specifically stated that the medical interviews were conducted in Cambodian.*

II.B.2.b. Efficacy Results

Applicant's results

"All evaluable patients (14/14) in the single-dose ivermectin group were cured (100%) compared to 18 of 19 patients (95%) assigned to the two-dose ivermectin group and 16 of 17 (94%) of patients receiving thiabendazole. There were no significant differences between treatment groups in the proportion of patients cured. Cure was not significantly related to age, sex, race or intensity of infection."

REVIEWER COMMENT: *The difference between the percent cured for the single-dose ivermectin group and the thiabendazole group is 6% with a 95% confidence interval of* $_{14.17}$ [-12% , 24%] $_{100\%,94\%}$. *The difference between the percent cured for the double-dose ivermectin group and the thiabendazole group is 1% with a 95% confidence interval of* $_{19.17}$ [-20% , 21%] $_{95\%,94\%}$. *In the DAIDP Points to Consider document , equivalence, when the better of the two agents has a cure rate greater than 90%, is established when the lower bound of the 95% confidence interval around the difference in the outcomes is not less than -10%. The lower bounds of -12% and -20% miss this threshold for establishing equivalency. However, it should be noted that the studies were small which led to wide confidence intervals.*

In a modified intent-to-treat analysis, the applicant included all patients "with adequate pretreatment and posttreatment stool examinations." In this population, "18 of 18 (100%) of the single-dose ivermectin group were cured compared to 21 of 22 (95%) patients in the two-dose ivermectin treatment group and 18 of 20 (90%) patients assigned to receive thiabendazole."

Table 2 presents the number of patients by treatment group who entered the study and the number of patients considered nonevaluable for clinical efficacy by reason for exclusion.

Table 2: Accounting by applicant of patients entered into protocols 014 and 015.

Patients	Ivermectin 1-dose	Ivermectin 2-dose	Thiabendazole
Entered into Studies	22	24	22
Nonevaluable for Efficacy	8	5	5
Reason for nonevaluability for efficacy			
Pretreatment stool exam negative	2	2	0
Inadequate follow-up parasitology	5	3	3
Pretreatment stool exam > 30 days	1	0	0
Patient discontinued too early	0	0	1
Patient on high dose immunosuppressive treatment	0	0	1
Evaluable for Efficacy Analysis	14	19	17
Cure Rate (%)	14/14 (100)	18/19 (95%)	16/17 (94%)
Evaluable for Safety Analysis	22	24	22

Medical Officer's results

Using a test of cure at 30 days post treatment and evaluating those patients with any recent positive stool examination taken pretreatment without intervening treatment, the Medical Officer found that single-dose ivermectin cured 18 of 18 (100%) evaluable patients, double-dose ivermectin cured 19 of 20 (95%) evaluable patients, and thiabendazole cured 18 of 19 (95%) evaluable patients. A 95% confidence interval of the difference in proportion cured between single-dose ivermectin and thiabendazole is $_{18.19}$ [-20% ,37%] $_{100\%,95\%}$. A 95% confidence interval of the difference in proportion cured between double-dose ivermectin and thiabendazole using the exact method is $_{20.19}$ [-28% , 30%] $_{95\%,95\%}$.

Because the risk of reinfection in the U.S. is very low, a 90 day follow-up is considered to evaluate the potential for relapse. At 90 days, the Medical Officer found that single-dose ivermectin cured 18 of 18 (100%), double-dose ivermectin cured 17 of 18 (94%), and thiabendazole cured 17 of 19 (89%). A 95% confidence interval of the difference in proportion cured by single-dose ivermectin versus thiabendazole at 90 is $_{18.19}$ [-16% , 43%] $_{100\%,89\%}$. A 95% confidence interval of the difference in proportion cured by double-dose ivermectin versus thiabendazole at 90 days is $_{18.19}$ [-23% , 39%] $_{94\%,89\%}$.

II.B.2.c. Safety Results

Two patient deaths that were not considered related to the study drugs were reported. One patient on two-dose of ivermectin died 57 days posttreatment of coronary artery disease and chronic pulmonary disease. One patient on thiabendazole died on study day 84 as a result of underlying pulmonary disease.

One patient on thiabendazole had his treatment discontinued after 1 day of therapy due to severe nausea and moderate tinnitus. The investigator considered these clinical adverse events to be definitely related to the study drug.

"The difference in the incidence of clinical adverse experiences (AEs) between each of the ivermectin groups and the thiabendazole group was significant ($p<0.001$ for each comparison)." For clinical adverse experiences that were considered possibly, probably, or definitely related to study drug, there were 3 of 22 (14%) patients on single-dose ivermectin, 5 of 24 (21%) on two-dose ivermectin, and 18 of 22 (82%) on thiabendazole.

II.B.3. Protocol 020 (Dreyer)

Protocol title:
"An Open, Randomized Study of Efficacy, Safety and Tolerability of Ivermectin Single Dose (One or Two Day Course) vs. Thiabendazole (Three-day Course) in the Treatment of Patients Infected With *Strongyloides Stercoralis*."

II.B.3.a. Study Design

"Open, randomized trial in ambulatory patients with strongyloidiasis of the gastrointestinal tract. Following diagnostic studies and laboratory tests, patients received either a single dose of ivermectin, two single doses of ivermectin 1 day apart or thiabendazole twice a day for 3 days. Follow-up visits were held weekly for 4 weeks." The study was conducted in Recife, Brazil between May 1991 and December 1991.

Patients received either a single 200 µg/kg ivermectin oral dose, two 200-mcg/kg oral doses of ivermectin one day apart or 3 days of 25 mg/kg b.i.d. oral treatment with thiabendazole.

Patients were included who were between 5 and 70 years of age and who were infected with *Strongyloides stercoralis*. Infection status was determined by stool examination using the Baermann technique. Please refer to the Medical Officer's review for more details of the inclusion/exclusion criteria and for details of the visit procedures.

"The primary measure of efficacy in this study was the absence of larvae in posttherapy Baermann fecal examinations. Cure was defined as the absence of larvae in the follow-up stool examinations. The detection of larvae on any stool examination past Day 6 up to 36 days posttreatment met the definition of treatment failure." "Since the study was conducted in a highly endemic area, a positive stool examination beyond 36 days posttreatment was not considered a clinical failure if all prior posttreatment stool examinations were negative." "All stool specimens were examined by one single expert who was to remain blinded as to the treatment allocations."

II.B.3.b. Efficacy Results

Applicant's results

"Ten of 15 (67%) evaluable patients in the single-dose ivermectin group were cured compared to 14/17 (82%) in the two-dose ivermectin group and 13/15 (87%) of patients treated with thiabendazole. There was no significant difference between treatment groups in the proportion of patients cured. A patient's likelihood of cure was not significantly related to age, sex, race, or intensity of infection."

REVIEWER COMMENT: *The difference between the percent cured for the single-dose ivermectin group and the thiabendazole group is -20% with a 95% confidence interval of* $_{15,15}$ *[-56% , 16%]* $_{67\%,87\%}$. *The difference between the percent cured for the double-dose ivermectin group and the thiabendazole group is -5% with a 95% confidence interval of* $_{17,15}$ *[-36% , 27%]* $_{82\%,87\%}$. *The small study size results in very wide confidence intervals with lower bounds well below the -15% required by DAIDP's Points to Consider to establish comparability.*

"In order to estimate a ""worst outcome"" cure rate, efficacy was also evaluated by designating all patients with any positive stool examination at any posttreatment time point (beyond Day 5) as treatment failures. By this

criteria, 10/15 patients (67%) in the single-dose ivermectin group, 10/17 (59%) of patients in the two-dose ivermectin group and 9/15 (60%) of patients in the thiabendazole treatment group were cured."

REVIEWER COMMENT: *The "worst outcome" results use the definition of failure that was used by Berk and Gann (protocols 014 and 015). The lower cure rates would be expected because of the risk of reinfection.*

Table 3 presents the number of patients by treatment group who entered the study and the numbers included in the clinical and safety analyses. Because Recife, Brazil is an endemic area, the cure rates for any treatment failures after 36 days could have been due to reinfection.

REVIEWER COMMENT: *The Medical Officer used 30 days as test of cure.*

Table 3: Accounting by applicant of patients entered into protocol 020 (Dreyer).

Patients	Ivermectin 1-dose	Ivermectin 2-dose	Thiabendazole
Entered into Study	17	17	15
Discontinued study	2	1	0
Completed study	15	16	15
Evaluable for Efficacy Analysis	15	17	15
Cure Rate (failure if positive stool days 6-36) (%)	10/15 (67%)	14/17 (82%)	13/15 (87%)
Cure Rate (failure if positive stool after day 5) (%)	10/15 (67%)	10/17 (59%)	9/15 (60%)
Evaluable for Safety Analysis	17	17	15

Medical Officer's results

Using a test of cure at 30 days post treatment and evaluating those patients with any recent positive stool examination taken pretreatment without intervening treatment, the Medical Officer found that single-dose ivermectin cured 9 of 14 (65%) evaluable patients, double-dose ivermectin cured 15 of 17 (88%) evaluable patients, and thiabendazole cured 13 of 15 (87%) evaluable patients. A 95% confidence interval of the difference in proportion cured between single-dose ivermectin and thiabendazole is $_{14,15}$ [-59% , 16%] $_{65\%,87\%}$. A 95% confidence interval of the difference in proportion cured between double-dose ivermectin and thiabendazole using the exact method is $_{17,15}$ [-31% , 39%] $_{88\%,87\%}$.

Because the risk of reinfection in Brazil is high, a 90 day follow-up is considered to evaluate the potential for reinfection. At 90 days, the Medical Officer found that single-dose ivermectin cured 6 of 11 (55%), double-dose ivermectin cured 10 of 16 (63%), and thiabendazole cured 8 of 14 (57%). A 95% confidence interval of the difference in proportion cured by single-dose ivermectin versus thiabendazole at 90 days follow-up is $_{11,14}$[-50%,45%] $_{55\%,57\%}$. A 95% confidence interval of the difference in proportion cured by double-dose ivermectin versus thiabendazole at 90 days follow-up is $_{16,14}$ [-36% , 47%] $_{63\%,57\%}$.

II.B.3.c. Safety Results

There were no serious clinical adverse events or discontinuations due to clinical adverse events.

There was a statistically significant difference between the incidence of clinical adverse experiences between the ivermectin groups and the thiabendazole group (P<0.001). None of the 17 patients who received ivermectin in a single-dose reported a clinical adverse experience. Two of the 17 patients who received ivermectin in two doses reported clinical adverse experiences that the investigator considered unrelated to the study drug. Nine of the 15 patients who received thiabendazole reported clinical adverse experiences with 8 patients having psychiatric/nervous system complaints and 6 of the 8 reporting dizziness.

"Each patient who entered the trial was asked to give an overall tolerance assessment of their treatment. Seventeen of 17 (100%) patients in the single-dose ivermectin group found the treatment to be "well tolerated," compared to 17 of 17 patients (100%) in the two-dose ivermectin and 6 of 15 patients (40%) treated with thiabendazole."

II.B.4. World Health Organization Study (Marti et. al.)

Protocol title:
"A Comparative Trial of a Single Dose Ivermectin versus 3 days of Albendazole for Treatment of *Strongyloides Stercoralis* and Other Soil Transmitted Helminth Infections in Children."

Publication based upon data collected:

Marti HP, Haji HJ, Savioli L, Chwaya HM, Mgeni AF, Hatz C. A comparative trial of a single dose ivermectin versus 3 days of albendazole for treatment of *Strongyloides stercoralis* and other soil transmitted helminth infections in children. Am J Trop Med and Hyg, (submitted November 1995).

II.B.4.a. Study Design

"A randomized trial carried out in rural Zanzibar comparing a single dose 200 µg/kg ivermectin and 400 mg daily for 3 days of albendazole for treatment of strongyloidiasis and other intestinal nematodes." The study was conducted October-December 1994. The participants were students at least 10 years old enrolled in either one of two primary schools. Included were students with *S. stercoralis* detected in a stool sample provided by the student. Stool samples were evaluated in the laboratory on the same day as collection using the Baermann technique. Excluded were students from whom consent was not given, who had fever or other signs of acute illness, severe neurological disorders, severe liver disorders, or were pregnant.

A randomization list for the sequential allocation of the drugs was prepared in advance. Treatments were administered under the supervision of a medical assistant. Three weeks after the end of treatment, the subjects were given a stool container and asked to bring a fresh specimen the following morning.

A standardized questionnaire was used by the medical assistant to assess side effects at baseline, at 3 days after start of treatment, and at 3 weeks after the end of treatment.

II.B.4.b. Efficacy results

Applicant's results

A total of 419 children were found to be infected with S. Stercoralis and were eligible for the trial. Of these, 2 children were excluded for medical reasons, 13 had incomplete treatments, 32 had incomplete follow-ups and 71 had no follow-up. The loss to follow-up was primarily attributed to an unforeseen closure of a school just before the holidays, so that many pupils did not return to school. Of the 301 evaluable participants, 152 received a single dose of ivermectin, while 149 were treated with 3 days of albendazole.

"Cure rates for *S. stercoralis* were significantly better with ivermectin than with albendazole (82.9% vs 45.0%)."

Medical Officer's results

Patient level data was not available for this study. Please refer to the Medical Officer's report for a qualitative assessment of this study.

II.B.4.c. Safety Results

No severe adverse effects were recorded among the students in either treatment group. "109 children (32.7%) experienced adverse effects of either medication: 29.4% in the ivermectin group and 35.9% in the albendazole group (n.s.). None of them was sufficiently incapacitated to be unable to perform normal daily activities. Abdominal distension and chest tightness or pain were recorded significantly more often after ivermectin medication."

II.B.5. Dose ranging study (Naquira, et. al.)

Publication based upon data collected:

Naquira C, Jimenez G, Guerra JG, Bernal R, Nalin DR, Neu D, Aziz M. Ivermectin for human strongyloidiasis and other intestinal helminths. Am J Trop Med Hyg, 1989;40:304-309.

II.B.5.a. Study Design

"Seventy-four males and 36 females aged 11-74 years who had stool examinations positive for S. Stercoralis larvae within 7 days of the study and who gave informed consent were assigned to 1 of 6 dose groups. All received matching placebos on day 1 and then on day 3 a single oral dose of ivermectin. Sequential groups of about 18 patients received single doses of 50, 100, 150, or 200 µg/kg ivermectin, followed on day 4 by another matching placebo or, in 2 of the groups by another dose of ivermectin (100-100 or 200-200 µg/kg)." (page 2511 of volume 1.32)

"Ivermectin dose was assigned according to a double-blinded sequential dose allocation schedule."

II.B.5.b. Efficacy results

Applicant's results

Table 4 presents the numbers and percents of patients treated and cured by dose level. "Strongyloidiasis cure rates were significantly higher in recipients of doses > 150 mcg/kg, but did not vary significantly above that dose."

Table 4: Cure rate (%) of strongyloidiasis patients treated with single ivermectin doses of 50-200 mcg/kg or with 2 doses of 100 or 200 mcg/kg in study conducted by Naquira et. al.

Total dose (mcg/kg)	Patients cured/ total patients (%) — Days post-treatment 3	30
50	12/18 (67%)	10/15 (67%)
100	2/18 (11%)	11/15 (73%)
150	7/18 (39%)	16/17 (94%)
200	11/17 (65%)	16/17 (94%)
100 (x2)	11/18 (61%)	15/17 (88%)
200 (x2)	9/20 (61%)	20/20 (100%)
All Doses	52/109 (48%)	89/101 (88%)

Medical Officer's results

Patient level data was not available for this study. Please refer to the Medical Officer's report for a qualitative assessment of this study.

II.B.5.c. Safety Results

"Clinical and laboratory adverse effects were chiefly mild and self-limited among the 200 patients in this study." "There were 3 deaths of patients with severe complicating diseases: 1 with perforated gastric carcinoma, 1 with leukemia who developed a hematologic blast crisis, and 1 with Klebsiella meningitis. These patients died at 10, 3, and 18 days after therapy, respectively."

II.C. Medical Officer's Integrated Summary of Efficacy

The applicant provided patient level data for the Gentilini (004), Dreyer (020), Berk (014), and Gann (015) studies. The protocols for these studies were fairly consistent including the use of blinded examination of patient stools using the Baermann technique to assess infection with *Strongyloides stercoralis*. Patients in these studies were followed for an extended period with stool examinations generally occurring at 30, 60, and 90 days. However, these protocols had some inconsistencies in their definitions of evaluable patients and of test of cure.

The Medical Officer reviewed all the patient records provided and made an independent assessment of evaluability and cure. Basically, any patient with a positive stool within a couple of months prior to treatment was considered evaluable. A few patients had been excluded by the sponsor because they had both positive and negative stools prior to treatments. Because it is possible for the Baermann technique to misdiagnose light cases and because Strongyloidiasis is not known to be eliminated without treatment, the Medical Officer considered these patients to be evaluable. A few patients were excluded who had positive stool examinations more than 100 days prior to entry into the study. Refer to the Medical Officer's report for further discussion on evaluability criteria.

For consistency, the primary efficacy outcome was defined as a test of cure at 30 days post treatment with

a secondary outcome at 90 days. The study by Dreyer was conducted in Brazil where Strongyloidiasis is endemic to the area so there is the possibility of reinfection. The other studies were conducted in France by Gentilini and in the United States by Berk and Gann where risk of reinfection is small.

For further analysis, the patient outcome data from the Gentilini, Dreyer, Berk, and Gann studies are being pooled by treatment regimen. The studies started with very similar protocols. The Medical Officer has applied consistent criteria for evaluability and outcome assessment in his review. Respectively, for 30 days follow-up and for 90 days follow-up, Table 5 and Table 6 compare the ivermectin treatment regimens with the comparator treatments for each study and for the data pooled by treatment. Figure 1 and Figure 2 each provide a graphical view of the 95% confidence intervals of the difference in treatment outcomes.

REVIEWER COMMENT: *DAIDP's Points to Consider document suggests when a standard treatment has 90% efficacy or higher then the lower bound on the 95% confidence interval of the difference in the cure rates should not be below -10% for approval. As can be seen in the following tables, ivermectin is statistically better than albendazole. Although ivermectin's cure rates are comparable to thiabendazole's, the lower bounds are generally around -20% at 30 days post treatment. The confidence intervals are wide because of the small sample sizes.*

Table 5: Summary of Medical Officer's assessment of efficacy at 30 days post treatment

	Ivermectin cured/evaluable (%)	Comparator cured/evaluable (%)	95% CI of treatment difference
Ivermectin 1 dose versus Thiabendazole			
Pooled Treatments	51/58 (88%)	31/34 (92%)	[-22% , 16%]
Berk (014) & Gann (015)	18/18 (100%)	18/19 (95%)	[-20% , 37%]
Dreyer (020)	9/14 (65%)	13/15(87%)	[-59%, 16%]
Ivermectin 2 doses versus Thiabendazole			
Pooled Treatments	34/37 (92%)	31/34 (92%)	[-19% , 23%]
Berk (014) & Gann (015)	19/20 (95%)	18/19 (95%)	[-28% , 30%]
Dreyer (020)	15/17 (88%)	13/15 (87%)	[-31% , 39%]
Ivermectin 1 dose versus Albendazole			
Gentilini (004)	24/26 (92%)	12/22 (55%)	[10% , 65%]
Marti (WHO)	126/152 (83%)	67/149 (45%)	[27% , 49%]

Figure 1: 95% Confidence Intervals of Differences in Proportions Cured of Strongyloidiasis at 30 Days Post Treatment

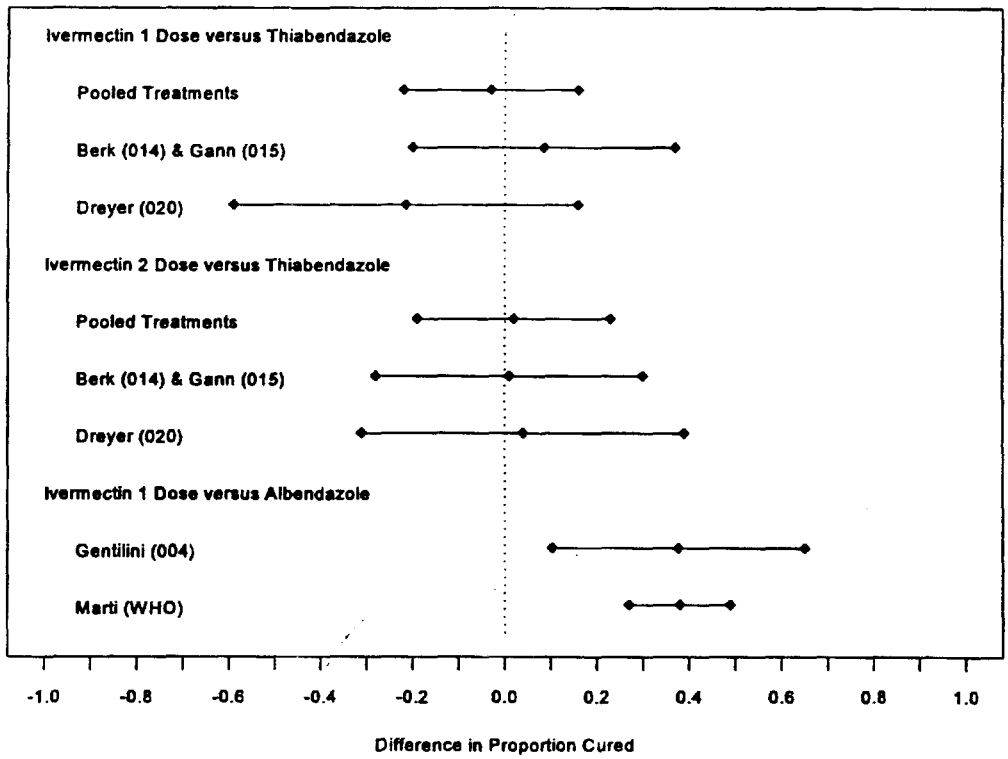
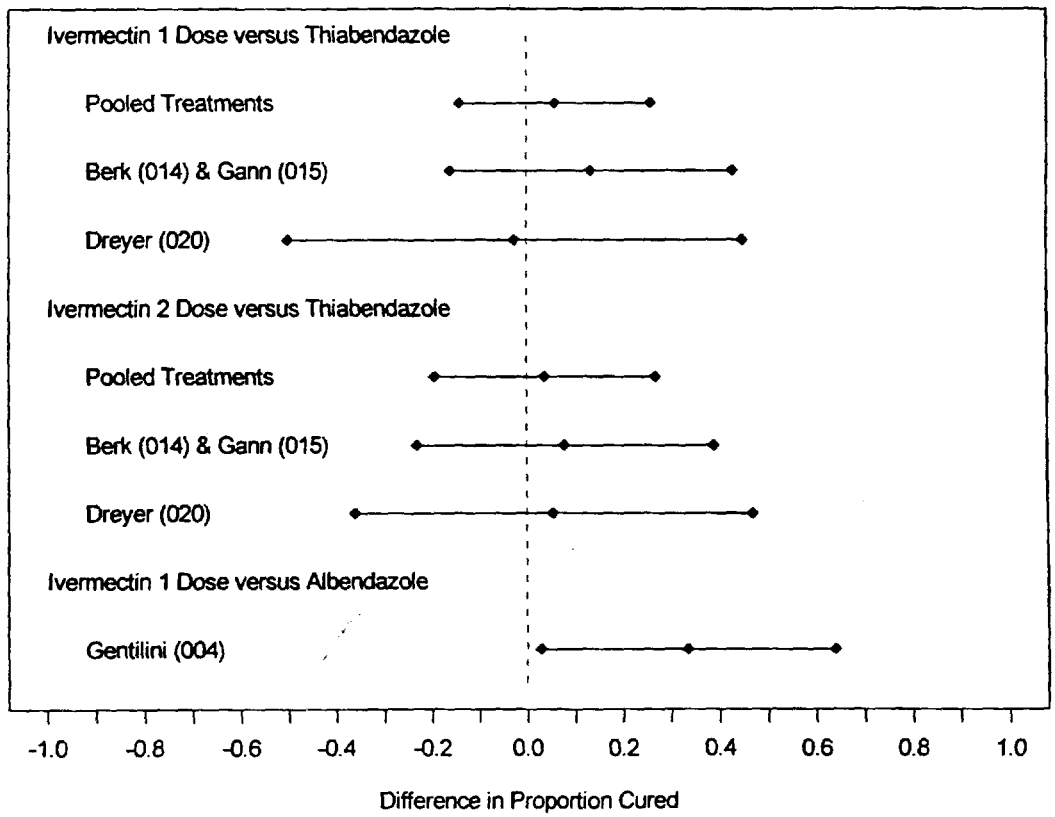


Table 6: Summary of Medical Officer's assessment of efficacy at 90 days post treatment

	Ivermectin cured / evaluable (%)	Comparator cured / evaluable (%)	95% CI of treatment difference
Ivermectin 1 dose versus Thiabendazole			
Pooled Treatments	45 / 55 (82%)	25 / 33 (76%)	[-14% , 28%]
Berk (014) & Gann (015)	18 / 18 (100%)	17 / 19 (89%)	[-16% , 43%]
Dreyer (020)	6 / 11 (55%)	8 / 14(57%)	[-46%, 37%]
Ivermectin 2 doses versus Thiabendazole			
Pooled Treatments	27 / 34 (79%)	25 / 33 (76%)	[-21% , 29%]
Berk (014) & Gann (015)	17 / 18 (94%)	17 / 19 (89%)	[-23% , 39%]
Dreyer (020)	10 / 16 (63%)	8 / 14 (57%)	[-31% , 44%]
Ivermectin 1 dose versus Albendazole			
Gentilini (004)	21 / 26 (81%)	10/21 (48%)	[4% , 61%]

Figure 2: 95% Confidence Intervals of Differences in Proportions Cured of Strongyloidiasis at 90 Days Post Treatment



A survival analysis can be used to analyze the time to an event. In this case, the event is a positive stool on follow-up examination. A Kaplan-Meier analysis is a non-parametric method that can be used to estimate the proportion cured and to provide a confidence interval about the proportion cured. For this analysis, patients were pooled across studies by treatment regimen. In the Gentilini study, a few patients were retreated within a week or so of initial treatment. For the survival analysis, these patients are treated both as treatment failures and as if they were lost to follow-up at that time (i.e. censored).

REVIEWER COMMENT: *Six patients were retreated with albendazole within 10 days of initial treatment. It is possible that the drug had not had sufficient time to complete its cure. It is a more conservative case to treat these patients as losses rather than as failures of albendazole. Note that in the Marti study albendazole only cured 45%. At 30 days, Albendazole cures 55% if the early retreatments are treated as losses and 43% if the early retreatments are treated as failures.*

Based on the Kaplan-Meier method, the 95% confidence interval on the percent cured at end of follow-up is the following for each treatment: albendazole [33%,76%] if retreatments are failures and [49% , 96%] if retreatments are losses, single-dose ivermectin [68%,92%], double-dose ivermectin [66%,94%], and thiabendazole [62%,92%]. Figure 3 and Figure 4 each provide a graphical view of the survival curves for each of the treatments first with the Gentilini early retreatments treated as failures and second treated as losses.

Figure 3: Kaplan-Meier Analysis of Time to Treatment Failure for Strongyloidiasis with early Gentilini retreatments treated as treatment failures

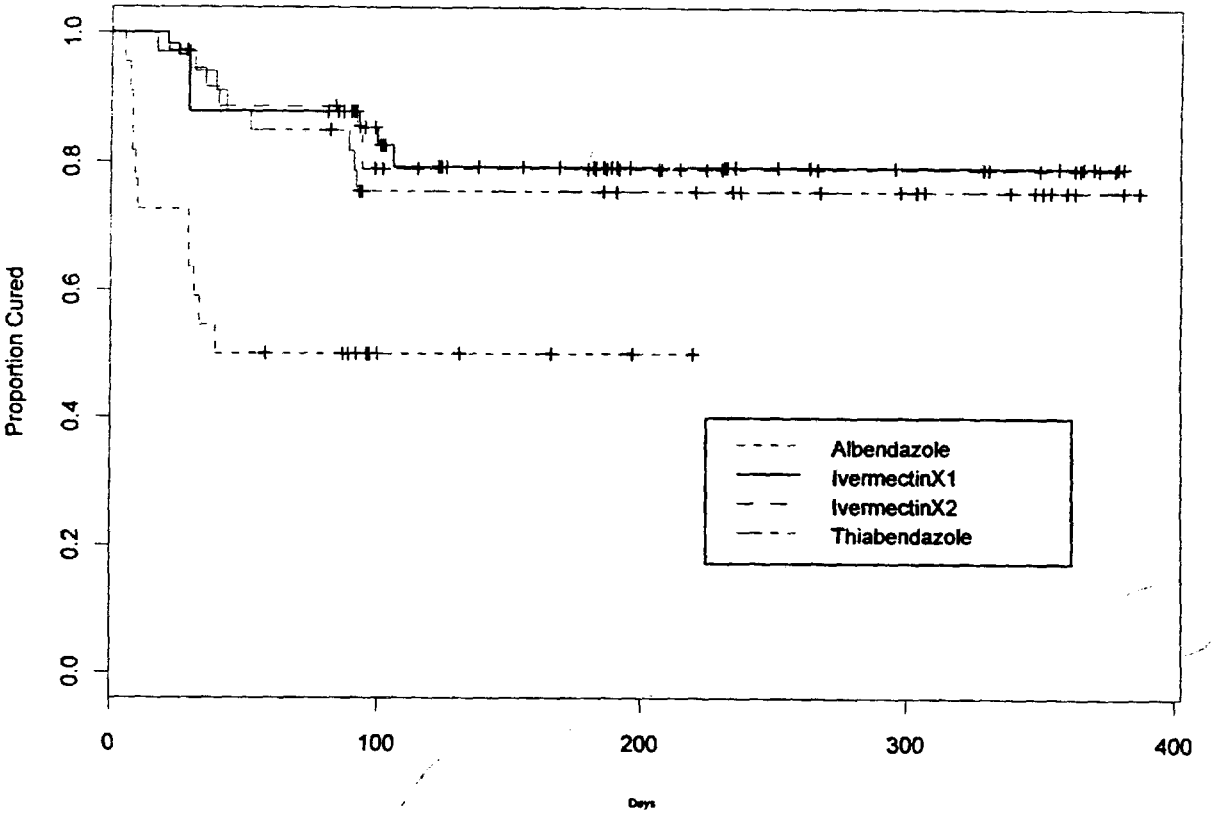
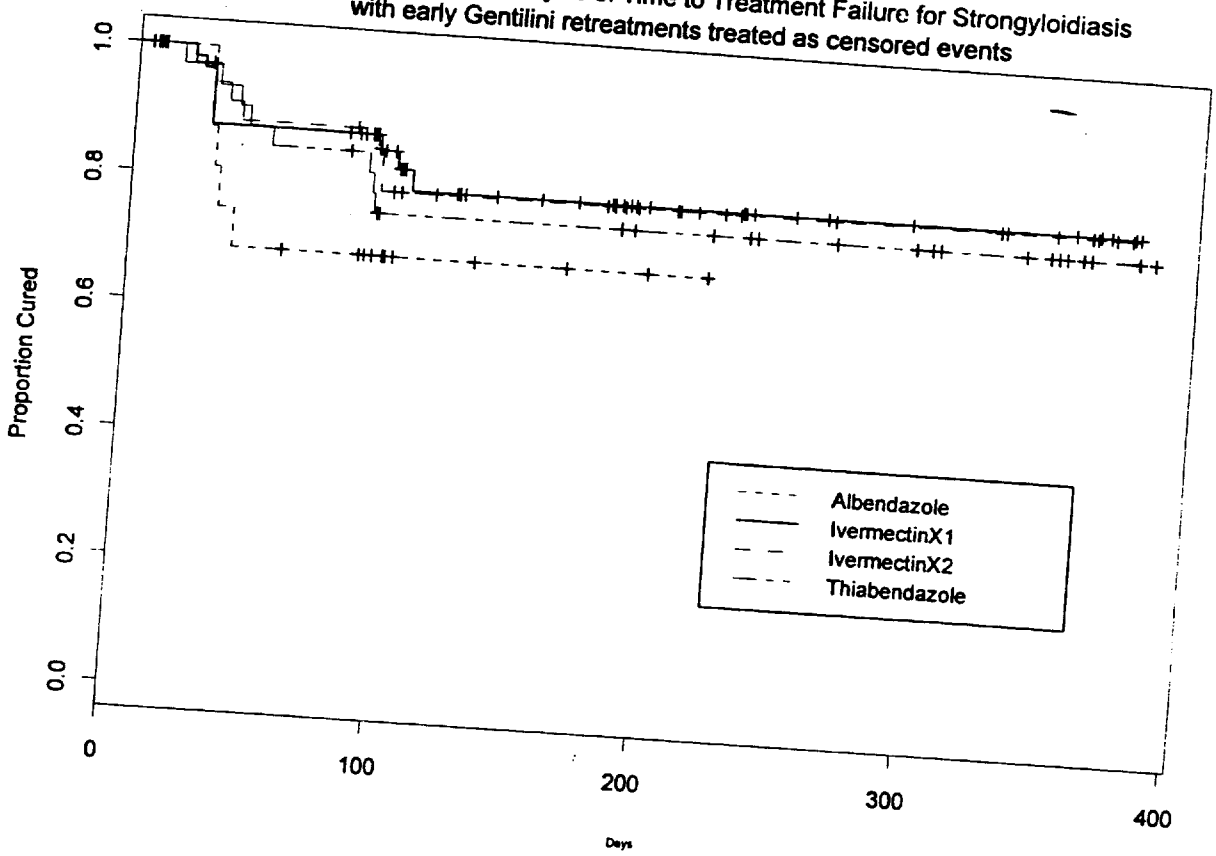


Figure 4: Kaplan-Meier Analysis of Time to Treatment Failure for Strongyloidiasis with early Gentilini retreatments treated as censored events



REVIEWER COMMENT: *As the graphs illustrate, albendazole is closer in effectiveness to the other treatments when the early retreatments are treated as losses rather than as failures. However, even with this perhaps overly conservative approach, ivermectin still demonstrates effectiveness at least as good as the alternatives.*

III. Onchocerciasis (a.k.a. River blindness)

"Onchocerciasis is a major filarial disease and one of the major causes of blindness in Third World countries. This disease, caused by the filarial parasite Onchocerca volvulus, is transmitted to humans by blackflies of the genus Simulium."

"The clinical manifestations of the disease, largely due to the host's immune response to the dead microfilaria, range from itching, weight loss, disfiguring skin changes, and eye damage which can lead to blindness."

"Efforts to reduce transmission of onchocerciasis by vector control have proven unsuccessful and chemotherapy of this disease has been limited to the two drugs DEC and Suramin. These drugs often have serious side effects and must be administered under close supervision making them impractical candidates for mass chemotherapy."

"During the development of ivermectin for animal health, it was discovered that the drug was highly effective against the microfilariae of *Onchocerca cervicalis* in horses. Thus, it was postulated that ivermectin may have activity in man against *Onchocerca volvulus*, the causative agent of onchocerciasis, also known as river blindness."

"In 1987, ivermectin was approved in France for the treatment of onchocerciasis and is now considered the drug of choice for the treatment of that infection."

III.A. Labeling claims and primary studies

"The recommended dosage of MECTIZAN for the treatment of onchocerciasis is a single oral dose designed to provide approximately 150 µg of ivermectin per kg of body weight." "Patients should take tablets with water. In mass distribution campaigns in international treatment programs, the most commonly used dose interval is 12 months. For the treatment of individual patients, retreatment may be considered at intervals as short as 3 months."

"The evaluation of MECTIZAN in the treatment of onchocerciasis is based on the results of clinical studies involving 1278 patients. In a double-blind, placebo-controlled study involving adult patients with moderate to severe onchocercal infection, patients who received a single dose of 150 µg/kg MECTIZAN experienced an 83.2% and 99.5% decrease in skin microfilariae count (geometric mean) 3 days and 3 months after the dose, respectively. A marked reduction of >90% was maintained for up to 12 months after the single dose."

"In a separate open study involving pediatric patients ages 5 to 12, similar decreases in skin microfilariae counts were observed for up to 12 months after dosing."

REVIEWER COMMENT: *Applicant provided two sets of data for each of the following studies. The efficacy dataset only provided basic demographic data and support for the density outcome of mf/mg of skin by relative study day. The second dataset provided adverse clinical experiences. Note that systemic responses were excluded from the dataset since these were considered to be the result of effective treatment rather than unexpected adverse clinical experiences.*

The statistical reviewer verified that results reported in the NDA submission were consistent with results produced by analysis of these datasets. Since the medical officer did not reclassify individual patients as to evaluability or cure status, statistical reanalysis of the data was limited to application of alternative statistical analysis to assess the robustness of the findings based upon the submitted data.

III.B. Protocol 514 (Document 5002) Studies by Lariviere (509, 510), Awadzi (511), Green (512)

Protocol title:
"Double-Blind Comparative Studies of Ivermectin, Diethylcarbamazine Citrate and Placebo in Patients with Onchocerciasis."

III.B.1. Study Design

The study was a double-blind, double-dummy, comparative study of ivermectin, diethylcarbamazine citrate (DEC-C) and placebo. Treatment assignment was according to a randomized allocation schedule. Ivermectin patients received a single oral 12 mg (two 6 mg capsules) dose on Day 1. DEC-C patients received 2 daily doses totaling 50 mg on Days 1 and 2 and 200 mg on Days 3 through 8. The synopsis of the clinical study report was dated 16Jan87. The study subjects were hospitalized onchocerciasis patients located in Senegal, Mali, Ghana, and Liberia. The outcome was a measure of microfilaria density that was the combined measurements from 4 skin snips taken at the right and left iliac crest and at the right and left calf.

III.B.2. Efficacy Results

Applicant's results

"In this comparative study of ivermectin vs DEC-C vs placebo in hospitalized onchocerciasis patients, mean skin microfilaria (mf) densities decreased sharply by Day 2 in both ivermectin and DEC-C patients and reached almost identical low levels (~ 2% of pretreatment) by Day 8. The mf densities then decreased further in the ivermectin patients (some to 0) over the next 3 months but increased gradually in DEC-C patients to about 14% of pretreatment level in 3 months. Between 3 and 12 months posttreatment, the mf densities in ivermectin patients gradually increased to about 5% of the pretreatment level compared to 20% in the Dec-C patients at 12 months. There were essentially no changes with placebo treatment."

"Both ivermectin and DEC-C eliminated mf from the anterior chamber of the eye. DEC-C-treated patients cleared mf faster than ivermectin-treated patients."

Figure 5 was provided by the applicant to graphically show the difference in the affect of the treatments on the reduction in the geometric mean of microfilaria densities (mf/mg skin) over the one year of follow-up. Table 7 shows the results for the outcomes that the Medical Officer considered primary and secondary.

REVIEWER COMMENT: *The Medical Officer considered the reduction in the geometric mean of the mf/mg one month posttreatment to be the primary outcome for assessment of efficacy. Of secondary interest was the reduction at 3-months and 6-months posttreatment because of the labeling suggestion of possible retreatment at 3-months posttreatment.*

As the applicant noted in the submission [page D-1473 of volume 1.19], the data is neither normally distributed nor log-normally distributed. The applicant appropriately performed nonparametric analysis of the data in addition to reporting the geometric mean for consistency with other publications in this field. In this reviewer's nonparametric analysis of the data, results were consistent with the applicant in that there was not a statistically significant difference between ivermectin and DEC-C in the actual reductions in the density (mf/mg). An alternative to analyzing the actual reductions in microfilaria counts is to analyze the effect of the treatments on the ratio of the microfilaria count at a follow-up time point to the microfilaria count at baseline before treatment. The applicant referred to this measure as percentage of pretreatment. Analysis of this measure resulted in a statistically significant difference in the percentage of pretreatment baseline at all three time points (p-value = 0.0001) based upon a Wilcoxon Rank Sum analysis of the data provided by the applicant.

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III.B.2. Efficacy Results

Applicant's results

"In this comparative study of ivermectin vs DEC-C vs placebo in hospitalized onchocerciasis patients, mean skin microfilaria (mf) densities decreased sharply by Day 2 in both ivermectin and DEC-C patients and reached almost identical low levels (~ 2% of pretreatment) by Day 8. The mf densities then decreased further in the ivermectin patients (some to 0) over the next 3 months but increased gradually in DEC-C patients to about 14% of pretreatment level in 3 months. Between 3 and 12 months posttreatment, the mf densities in ivermectin patients gradually increased to about 5% of the pretreatment level compared to 20% in the Dec-C patients at 12 months. There were essentially no changes with placebo treatment."

"Both ivermectin and DEC-C eliminated mf from the anterior chamber of the eye. DEC-C-treated patients cleared mf faster than ivermectin-treated patients."

Figure 5 was provided by the applicant to graphically show the difference in the affect of the treatments on the reduction in the geometric mean of microfilaria densities (mf/mg skin) over the one year of follow-up. Table 7 shows the results for the outcomes that the Medical Officer considered primary and secondary.

REVIEWER COMMENT: *The Medical Officer considered the reduction in the geometric mean of the mf/mg one month posttreatment to be the primary outcome for assessment of efficacy. Of secondary interest was the reduction at 3-months and 6-months posttreatment because of the labeling suggestion of possible retreatment at 3-months posttreatment.*

As the applicant noted in the submission [page D-1473 of volume 1.19], the data is neither normally distributed nor log-normally distributed. The applicant appropriately performed nonparametric analysis of the data in addition to reporting the geometric mean for consistency with other publications in this field. In this reviewer's nonparametric analysis of the data, results were consistent with the applicant in that there was not a statistically significant difference between ivermectin and DEC-C in the actual reductions in the density (mf/mg). An alternative to analyzing the actual reductions in microfilaria counts is to analyze the affect of the treatments on the ratio of the microfilaria count at a follow-up time point to the microfilaria count at baseline before treatment. The applicant referred to this measure as percentage of pretreatment. Analysis of this measure resulted in a statistically significant difference in the percentage of pretreatment baseline at all three time points (p-value = 0.0001) based upon a Wilcoxon Rank Sum analysis of the data provided by the applicant.

Figure 5: Geometric mean of microfilaria densities (mf/mg skin) of onchocerciasis where the treatments are ivermectin, DEC-C, and placebo.

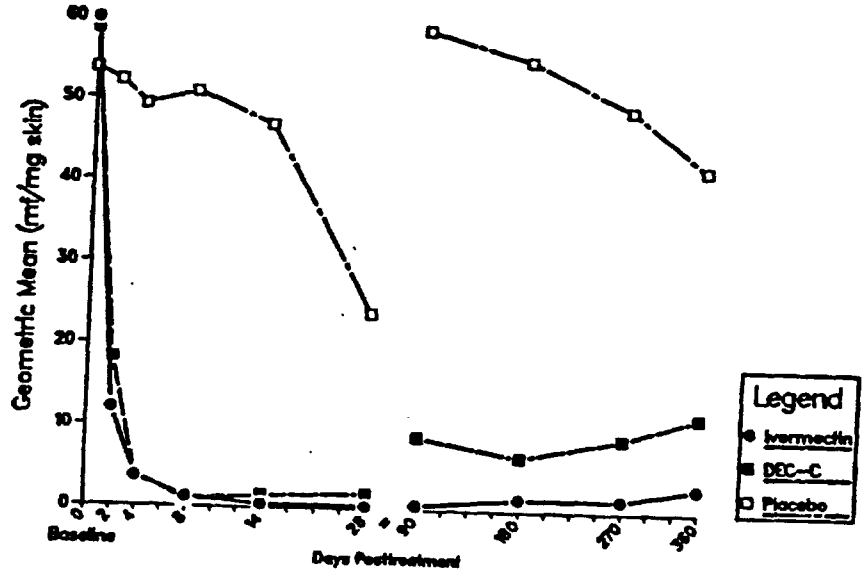


Table 7: Summary of skin microfilaria density (mf/mg skin) between-treatment comparisons (pages D-1475 and D-1478 of volume 1.19)

	Number of evaluable patients Median Change from Pretreatment Percentage of Pretreatment @			Between-Treatment Comparisons		
Visit	Ivermectin	DEC-C	Placebo	Ivermectin vs DEC-C	Ivermectin vs Placebo	DEC-C vs Placebo
Day 28	38 -61.7 1%	39 -56.9 3%	36 -24.9 37%	N.S.	***	***
Month 3	26 -68.6% 1%	29 -49.1 14%	26 -10.1 86%	N.S.	***	***
Month 6	44 -49.9 2%	45 -43.2 11%	43 -3.1 92%	N.S.	***	***

@ Geometric mean of the percentage of pretreatment mf counts calculated as (follow-up mf count / baseline mf count) * 100%.
*** Significant difference between the respective treatment groups regarding median change from baseline, $p \leq 0.001$
N.S. Difference between respective treatments was not significant, $p > 0.05$

In addition to the analysis of reduction in microfilaria density, the applicant performed an analysis using as a test of cure a success being a reduction in the mf/mg of skin to less than 5 mf/mg skin. "It is generally believed, among the onchocerciasis experts, that a patient becomes "noninfective" and will no longer serve as a host for transmission of onchocerciasis when the microfilaria is reduced to less than 5 mf/mg skin." [page D-1479 of volume 1.19]. Based on this criteria, ivermectin cured 36/38 (95%), 23/26 (88%), 31/44 (70%) at day 28, month 3, and month 6, respectively, while DEC-C cured 25/39 (64%), 8/29 (28%), and 16/45 (36%) at day 28, month 3, and month 6, respectively. [page D-1480 of volume 1.19]

REVIEWER COMMENT: *The 95% confidence intervals about the difference in proportions with a favorable response are* $_{38,39}$ *[11% , 50%]* $_{95\%,64\%}$ *,* $_{26,29}$ *[37% , 85%]* $_{88\%,26\%}$ *,* $_{44,45}$ *[13% , 57%]* $_{70\%,36\%}$ *for day 28, month 3, and month 6, respectively. This reviewer performed the analysis also using cut points of 2.5 and 1.0 mf/mg with ivermectin showing even greater efficacy in comparison to DEC-C.*

III.B.3. Safety results

"The incidence of clinical adverse experiences in the ivermectin-treated patients was slightly lower than in patients treated with DEC-C (50 vs 56%). More DEC-C patients had a worsening of systemic reactions than ivermectin patients. In addition, more DEC-C patients required steroids, anti-inflammatory drugs and analgesics than ivermectin patients to relieve symptoms of systemic reactions and clinical adverse experiences." The most commonly reported clinical adverse experience was myalgia in 30% of the ivermectin-treated patients and 38% of the DEC-C-treated patients. Headache closely followed being reported by 26% of the ivermectin-treated patients and by 38% of the DEC-C-treated patients [page D-1503 of volume 1.19].

"In general, opthalmologic safety results were similar for ivermectin and DEC-C."

"None of the laboratory adverse experiences was considered serious by the investigators, and no patient was discontinued from the study due to adverse experience." There was not a statistically significant difference between the number of ivermectin-treated patients and number of DEC-C-treated patients with any adverse laboratory experiences. The only statistically significant lab difference was AST that increased in 2% of the ivermectin-treated patients and 22% of the DEC-C-treated patients ($0.001<p<0.01$).

III.C. Protocol 519 (Documents 5003/5004) Studies by Green, Awadzi, Lariviere, Schulz-Key, Vingtain, Zea-Flores

Protocol title:
"A Multiclinic, Double-Blind Study of Ivermectin and Placebo in Patients with Onchocerciasis."

Protocol 5003 reported the results through 6 months of follow-up. Protocol 5004 is the posttreatment follow-up through 12 months and includes all CRF data received as of June 30, 1987.

III.C.1. Study Design

The study included 6 investigators (Greene, Awadzi, Lariviere, Schulz-Key, Vingtain, and Zea-Flores) in 6 countries (Liberia, Ghana, Ivory Coast, Togo, Mali, and Guatemala). The study was a double-blind, randomized, placebo-controlled, multicenter study comparing 3 dosage levels of ivermectin to placebo in hospitalized onchocerciasis patients. Each patient received a single oral dose of ivermectin (100, 150, or 200 mcg/kg body weight) or placebo on Day 1 of the study. Efficacy follow-up was through 12 months posttreatment.

REVIEWER COMMENT: *Note that three of the investigators (Lariviere, Awadzi, and Greene) and three sites*

(Liberia, Ghana, and Mali) are the same as for both protocols 514 and 519. Further, these studies were being conducted at the same time (cutoff date for 514 was December 26, 1985 [page D-1449 of volume 1.19] and the cutoff data for 519 was February 28, 1986 [page D-1551 of volume 1.19]. This raises a question as to whether there is sufficient independence of the studies from the two protocols to serve as independent confirmation of the results.

"The overall efficacy assessment was based on reduction from baseline skin microfilaria density and the percentage of patients with a favorable response. Favorable response is defined as microfilaria reduced to less than 5 mf/mg skin after the study drug administration."

Patients whose baseline microfilaria-density was less than 10 mf/mg skin were excluded rather than the 20 mf/mg that was specified in the protocol. The less stringent criterion was used "to avoid the exclusion of too many patients". Because at six months Dr. Lariviere retreated 75 of his patients whom he felt were not responding to therapy, his center was excluded from the efficacy analysis at 12 months. The skin snip assays were not performed according to the protocol for Dr. Zea-Flores center, so the medical monitor decided to exclude this center from the per-protocol efficacy analysis as well.

III.C.2. Efficacy Results

Applicant's results

Table 8 summarizes the efficacy of three dose levels of ivermectin and of placebo at day 3, month 3, and month 6 posttreatment. [page D-1561 of volume 1.19]. This study did not capture data at month 1 posttreatment. There was not a statistically significant difference among the ivermectin treatments while there was a highly statistically significant difference ($p \leq 0.001$) between each ivermectin treatment and placebo at each time point.

Table 8: Summary of skin microfilaria density (mf/mg skin) between-treatment comparisons for protocol 519.

	Number of patients evaluable for efficacy Median change from pretreatment Percentage of pretreatment @			
Visit	100 mcg ivermectin	150 mcg ivermectin	200 mcg ivermectin	Placebo
Day 3				
N	254	249	254	252
Median	-32.6	-34.0	-40.5	-2.9
%	26.2%	16.8%	12.9%	91.4%
Month 3				
N	238	237	238	229
Median	-47.9	-45.2	-48.0	-15.5
%	1.8%	0.5%	0.4%	60.8%
Month 6				
N	237	230	223	227
Median	-43.5	-43.4	-48.4	-18.0
%	2.9%	1.5%	1.1%	54.4%

@ Geometric mean of the percentage of pretreatment values

III.C.3. Safety Results

"Clinical adverse experiences (drug related or not drug related) were reported in 152 (47.6%), 155 (48.1%), 170 (52.8%) and 94 (29.8%) patients in the 100, 150, 200 mcg and placebo groups, respectively." "None of the adverse experiences was considered serious by the investigators and no patient was discontinued from the study because of the adverse reactions." [page D-1586 of volume 1.19]. The two most common adverse clinical events were myalgia and headache [page D-1590 of volume 1.19]. Myalgia was reported by 21%, 17.7%, 20.5%, and 13% of the patients in the 100, 150, 200 mcg, and placebo, respectively. Headache was reported by 21%, 21.7%, 24.2%, and 10.2% of the patients in the 100, 150, 200 mcg, and placebo, respectively. "Myalgia and headache are probably reactions caused by the death of the skin microfilaria, which explains their frequent occurrences among the patients receiving ivermectin.

Only two patients, one in each of the 100 and 150 mcg groups, had any adverse laboratory experiences after receiving the study drug. The patient in the 100 mcg group had high urine WBCs, and the patient in the 150 mcg group had increased total serum bilirubin. [page D-1593 of volume 1.19]

III.D. Protocol 548 (Document 5545) - Study by Vingtain

Protocol title:
"A single-blind, placebo-controlled study of the tolerability, safety, and efficacy of successive single oral doses of ivermectin (MK-933) approximately 150 to 220 mcg/kg in adults with onchocerciasis""

III.D.1. Study Design

The study was conducted as a single-blind, placebo-controlled study. The synopsis of the clinical study report was dated 02Feb87. The intent was for the study to continue over a 3 year period, but "only data at the day 4 visit were in-house" at the time this report was prepared.

The dose level of ivermectin was 150 to 220 mcg/kg of body weight. Five successive single oral doses at 6-month intervals were to be administered.

Evaluability criteria was that baseline microfilaria counts be ≥ 10 mf/mg skin rather than 20 mg/mg skin that was specified in the protocol.

III.D.2. Efficacy Results

Applicant's results

"No formal analysis of the data was performed. Summary statistics of the data for the first 4 days after the first dose suggest that ivermectin, administered in tablet form, reduced skin microfilaria counts to near 0 levels while skin microfilariae decreased only slightly in the placebo-treated patients. The proportion of patients with a favorable response (<5 mf/mg skin) at Day 4 posttreatment was 53/55 (96.4%) and 2/16 (12.5%) for ivermectin- and placebo-treated patients, respectively."

In the study, 64 patients (37 males and 27 females) were treated with ivermectin and 21 patients (9 males and 12 females) were treated with placebo. All 85 patients completed the study. Seventy-one patients (55 ivermectin-treated and 16 placebo-treated) were evaluated for efficacy. Nine patients from the ivermectin group and five patients from the placebo group were excluded because either their baseline microfilaria counts were too low or the patient lacked posttreatment skin microfilaria measurements.

REVIEWER COMMENT: *The difference between the percent cured in the ivermectin-treated group versus*

the placebo-treated group is 85% with a 95% confidence interval of $_{55.16}$ *[63% , 105%]* $_{96\%,13\%}$*.. Clearly, ivermectin is statistically more efficacious than placebo.*

III.D.3. Safety Results

The investigator reported clinical adverse experiences for 38 of 64 (59%) ivermectin-treated patients and for 5 of 21 (24%) placebo-treated patients. No laboratory adverse experiences were reported.

III.E. Protocol 545 (Document 5544) - Study by Lariviere

Protocol title:
"An open study of the tolerability, safety, and efficacy of single oral 150 mcg/kg doses of ivermectin (MK-933) in children 5 to 12 years of age with onchocerciasis."

III.E.1. Study Design

This was an open study of 103 children (71 male and 32 female) aged 6 to 13 who had onchocerciasis without eye involvement and were otherwise in good health. Fifty-four of the 103 (52.4%) patients had a secondary diagnosis of malaria.

Patients were given 1 oral dose of 150 mcg/kg of ivermectin on Day 1. Patients were followed for 3, 6, and 12 months posttreatment. All patients were hospitalized for at least seven days following administration of ivermectin.

"Evidence for the efficacy of the study drug was obtained from skin biopsy samples taken on Days 3, 4, or 5 and subsequently during follow-up examinations at three, six, and twelve months after study drug administration." The relative day ranges for the visits were -14 to predose for the pretreatment visit, 1 to 7 for the Day 3 visit, 65 to 125 for Month 3 visit, and 141 to 225 for Month 6 visit. "If a patient had multiple data within a day range, the valid data from the last visit in that interval were used in the analysis."

III.E.2. Efficacy Results

Applicant's results

"Ivermectin was effective in reducing skin microfilaria in children. The median decrease from baseline (median of 34.1 mf/mg skin) was significant at Day 3, Months 3 and 6 with changes of -29.3, -33.5, and -32.7 (mf/mg skin), respectively. Greatest reduction from baseline occurred at Month 3. The percentage of patients with a favorable response (< 5 mf/mg skin) was at least 70% for all visits."

Based on an all-patients-treated analysis, as of Day 3, 74 of 101 (73.3%) patients had a favorable response. As of Month 3, 95 of 102 (93.1%) patients had a favorable response. As of Month 6, 89 of 102 (87.3%) patients had a favorable response.

For the per-protocol analysis, one patient was excluded because a baseline skin biopsy was not performed. A second patient was excluded from the Month 6 analysis because the follow-up skin biopsy was not performed.

III.E.3. Safety Results

"Forty-seven clinical adverse experiences were reported in 36 (35.0%) patients. Forty-six were mild, 1 of

edema was moderate, none was serious. The most commonly reported were headache (23.3%) and myalgia (8.7%) followed by peripheral edema (5.8%) and edema (4.9%). The majority of clinical adverse experiences had a drug relationship of ""possibly."" Most patients did not have any of the disease-associated signs and symptoms at baseline and remained symptom free after receiving ivermectin."

"No laboratory adverse experiences were reported."

IV. Integrated Safety Summary

Combining the clinical adverse experiences of patients treated for strongyloidiasis under protocols 004, 014, 015, and 020 [page J-88 of volume 1.1], 4 of 68 (6%) single-dose ivermectin patients experienced an adverse clinical event compared with 8 of 41 (20%) double-dose ivermectin-treated patients, 28 of 37 (76%) thiabendazole-treated patients [page D-91 of volume 1.28], and 2 of 27 (7%) of albendazole-treated patients. No patients were discontinued from the ivermectin or albendazole treatment regimens due to adverse experiences. One patient was discontinued from thiabendazole treatment due to nausea.

For onchocerciasis, the disease-associated signs and symptoms were presented separately from unexpected events that were considered clinical adverse experiences (AEs). "No clinical AEs were considered serious by the investigators." "Clinical AEs, regardless of relationship to study drug, were reported in significantly more ivermectin-treated patients regardless of dose (49.5%) than placebo patients (29.5%)." The applicant states the these results "may be consistent with the profile of reactions caused by death of skin microfilaria" [page J-121 of volume 1.1]. Myalgia was reported in 18% (218/1209) of the patients, and headache was reported in 22.7% (274/1209) of the patients [page J-127 of volume 1.1].

The applicant submitted a safety update report dated July 31, 1996 that included specific details concerning the 15 deaths in a Canadian nursing home that were considered by the reporting physician to be possibly ivermectin related. There does not appear to be any pattern in the timing of the deaths or the causes of death to indicate a relationship to ivermectin. The ages of the patients ranged from 77 to 90 with 7 males and 8 females. The first death occurred 17 days after treatment and was due to pneumonia. The other deaths occurred 40 to 176 days after treatment. The most common cause of death was cerebral vascular accident with 4 deaths occurring from 45 to 140 days after treatment. The second most common cause of death was pneumonia with 3 deaths occurring from 17 to 123 days after treatment. Other causes of death included Alzheimer's disease, congestive heart failure, coronary artery disease, myocardial infarction, renal failure, and respiratory infection.

REVIEWER COMMENT: *In the Onchocerciasis studies only 2 of 1437 patients were over 65. One experienced eye pain 3 days posttreatment. The other reported no adverse clinical experiences. In the Strongyloidiasis studies, 10 patients were over 65 years of age. Of these only one patient reported clinical adverse experiences. The adverse experiences reported were somnolence, tremor, vertigo, asthenia, nausea, and dizziness 1 to 2 days posttreatment.*

V. Summary and Conclusions

V.A. Strongyloidiasis of the gastrointestinal tract

1. Based upon the evidence presented in the Gentilini study 004, the single target dose of 200 µg/kg of ivermectin was statistically more efficacious than albendazole (200 mg b.i.d. for 3 days) in the treatment of strongyloidiasis in patients 5 to 70 years of age (95% confidence interval $_{26.22}$ [10%,65%] $_{92\%,54\%}$). Further, the World Health Organization's study in children replicated the results with a 95% confidence interval of $_{152.149}$ [27%,49%] $_{83\%,45\%}$.

Ivermectin and albendazole appear to be equally safe with no serious adverse clinical or laboratory experiences noted for either treatment.

This reviewer concludes that the applicant has demonstrated that a single-dose treatment of ivermectin has statistically superior efficacy and comparable safety to albendazole.

2. Using a test of cure as negative stools through 30 days of follow-up, neither single-dose of 200 µg/kg nor double-dose (200 µg/kg for 2 days) treatments of ivermectin met the DAIDP's Points to Consider document's criteria for establishing comparable efficacy to thiabendazole (25 mg/kg b.i.d. for 3-days). Because thiabendazole's pooled cure rate was 92%, a lower bound on the 95% confidence interval of the difference in the rates should be no less than -10%. Except for the single-dose ivermectin arm of the Dreyer study, all the remaining point estimates of cure rates for ivermectin equaled or exceeded the point estimates of the cure rates for thiabendazole. The small sample sizes of the studies resulted in very wide confidence intervals.

In contrast, the 95% confidence intervals for the cure rates based upon a Kaplan-Meier analysis of the data were slightly better for the ivermectin-treated patients than for thiabendazole-treated patients with [68%,92%], [66%,94%], [62%,92%] for single-dose ivermectin, for double-dose ivermectin, and for thiabendazole, respectively.

In regards to safety, the ivermectin-treated patients consistently reported statistically fewer clinical adverse experiences than the thiabendazole-treated patients (p-value < 0.001).

Because ivermectin demonstrated both a statistically better safety profile than thiabendazole and statistically comparable efficacy based upon survival analysis methods, this reviewer considers ivermectin to be a satisfactory alternative to thiabendazole for the treatment for strongyloidiasis.

V.B. Onchocerciasis

Based upon evidence presented in protocol 514 for the treatment of onchocerciasis, a single oral dose of 12 mg capsules of ivermectin was statistically comparable to DEC-C administered at a daily dosage of 50 mg for two days followed by 200 mg daily for six days in the reduction of microfilaria density at one month posttreatment. Ivermectin maintained a lower level of microfilaria density through the one year of follow-up than DEC-C. Both treatments resulted in a statistically greater reduction in microfilaria density than placebo. The safety profile for the two drugs was also comparable except a statistically greater proportion of DEC-C patients experienced systemic reactions associated with the microfilaricidal action of the treatments.

The second study presented in support of the claim was protocol 519 that was a dosing study comparing ivermectin with placebo. There was not a statistical difference between the 100, 150, and 200 µg/kg dose levels of ivermectin in reduction in microfilaria density at 3 days, 3 months, and 6 months posttreatment.

Because protocol 514 demonstrated that ivermectin was at least comparable in efficacy with DEC-C but with a better safety profile and a much simpler dosing regimen and because the ivermectin results were replicated in other clinical trials, this reviewer concludes that ivermectin provides a statistically satisfactory alternative to DEC-C for the treatment of onchocerciasis.

B. Sue Bell, Ph.D.
Mathematical Statistician, DOB IV

Concur: Daphne Lin, Ph.D.
Acting Team Leader, DOB IV

Ralph Harkins, Ph.D.
Division Director, DOB IV

cc:
Archival: NDA 50-742
HFD-520
HFD-520/D. Feigal
HFD-520/B. Leissa
HFD-725/R. Harkins
HFD-725/D. Lin
HFD-520/Medical Officer/P. Coyne
HFD-520/Pharm/K.Seethaler
HFD-520/Micro/J. King
HFD-520/Chem/J. Timper
HFD-520/Project Manager/P. Fogarty
HFD-880/Biopharm/P.Colangelo
HFD-725/BioStat/S. Bell
HFD-344/Clin Inv/M. Thomas
Chron
This review contains 29 pages, 8 tables, and 5 figures.

micro

NDA 50-742
Mectizan
Merck

Division of Anti-Infective Drug Products (HFD-520)
Clinical Microbiology Review Notes #1

NDA # 50-742 **DATE COMPLETED: 10/4/96**

SPONSOR(IND)/APPLICANT(NDA): Merck

SUBMISSION REVIEWED: Proposed draft labeling

PRODUCT NAMES(S):
Proprietary: Mectizan

Non-Proprietary/USAN: Ivermectin

DISPENSED: X Rx ___ OTC

INITIAL SUBMISSION:
Received by CDER: N/A
Received by Reviewer:
Review Completed:

AMENDMENT(S)
Received by CDER: 9/30/96
Received by Reviewer: 10/3/96
Review Completed: 10/4/96

Related Documents: The complete NDA

REMARK(S):

This review is written to bring disposition of this NDA to closure from the microbiological perspective. Microbiological review of this application was administratively waived at the request of the Supervisory Microbiologist at the time the NDA was filed. No technical review of microbiological data was proposed because the application was perceived to contain no microbiological data. Indeed, no technical data have been reviewed in accordance with administrative agreements determined at the time the NDA was filed.

Nevertheless, proposed draft labeling was brought to my attention; the proposed draft labeling contains a MICROBIOLOGY section which was not requested by a FDA Microbiologist. These labeling statements have not been verified in accordance with administrative agreements noted above. However, these labeling statements are likely to be accurate

scientifically because Merck has previously demonstrated a strong commitment to providing basic scientific information to the FDA; on the other hand, these labeling statements have not been reviewed for inaccuracy due to gratuitous juxtaposition of otherwise true statements. Overall, no outstanding microbiological issues have been raised within the context of the administrative agreements pertaining to this application.

CONCLUSIONS and/or RECOMMENDATIONS:

No outstanding microbiological issues have been raised within the context of the administrative agreements pertaining to review of this application.

James R. King 10/4/96

James R. King
Microbiologist, HFD-520

SMicro/ASheldon

DepDir/LGavrilovich

cc: Orig. NDA # 50-742
HFD-473
HFD-520/DepDir/LGavrilovich
HFD-635
HFD-520/SMicro/ASheldon T5 10/4/96
HFD-502
HFD-520
HFD-520/Micro/KIng
HFD-520/MO/Coyne
HFD-520/Pharm/
HFD-520/Chem/
HFD-520/CSO/Fogarty

Printed for signatures prior to draft concurrence; 10/4/96

Chem

JUL 22 ...

DIV

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: ~~20-721~~ 50-742 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 6/14/96

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	COMPLETED DATE
ORIGINAL	3/29/96	4/1/96	6/14/96

NAME & ADDRESS OF APPLICANT:

Merck Research Laboratories
P.O. Box 4, BLA-20
Sumneytown Pike
West Point, PA 19486

CONTACT: **Kenneth R. Brown, M.D., Regulatory Affairs**
610-397-2552

DRUG PRODUCT NAME

Proprietary: Mectizan
Established: Ivermectin
Code #: MK-0933

PHARMACOLOGICAL CATEGORY/INDICATION:

Treatment of strongyloides of the gastrointestinal tract and onchocerciasis.

DOSAGE FORM: Tablets, immediate release

STRENGTHS: 6 mg

ROUTE OF ADMINISTRATION: Oral

Rx/OTC: Rx

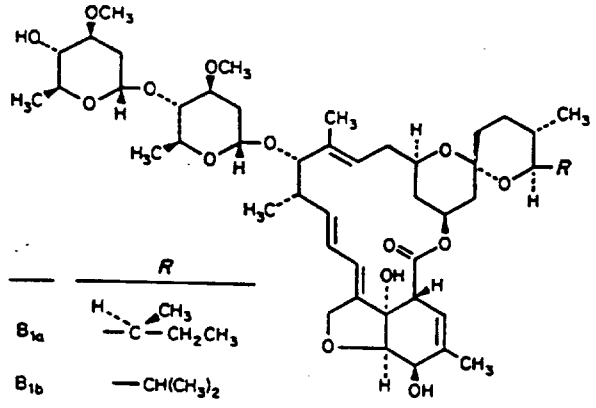
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Ivermectin: A mixture of ivermectin component B_{1a} and ivermectin component B_{1b}.

Ivermectin: CAS-70288-86-7;
Ivermectin component B_{1a}: CAS-70161-11-4;
Ivermectin component B_{1b}: CAS-70209-81-3.

Ivermectin component B_{1a}: $C_{48}H_{74}O_{14}$. Component of Ivermectin. (2aE,4E,8E)-(5'S,6S,6'R,7S,11R,13R,15S,17aR,20R,20aR,20bS)-6'-(S)-sec-Butyl-3',4',5',6,6',7,10,11,14,15,17a,20,20a,20b-tetradecahydro-20,20b-dihydroxy-5',6,8,19-tetramethyl-17-oxospiro[11,15-methano-2H,13H,17H-furo[4,3,2-pg][2,6]-benzodioxacyclooctadecin-13,2'-[2H]pyran]-7-yl 2,6-dideoxy-4-O-(2,6-dideoxy-3-O-methyl-α-L-*arabino*-hexopyranosyl)-3-O-methyl-α-L-*arabino*-hexopyranoside.

Ivermectin component B_{1b}: $C_{47}H_{72}O_{14}$. Component of Ivermectin. (2aE,4E,8E)-(5'S,6S,6'R,7S,11R,13R,15S,17aR,20R,20aR,20bS)-3',4',5',6,6',7,10,11,14,15,17a,20,20a,20b-Tetradecahydro-20,20b-dihydroxy-6'-isopropyl-5',6,8,19-tetramethyl-17-oxospiro[11,15-methano-2H,13H,17H-furo[4,3,2-pq][2,6]-benzodioxacyclooctadecin-13,2'-[2H]pyran]-7-yl 2,6-dideoxy-4-O-(2,6-dideoxy-3-O-methyl-α-L-*arabino*-hexopyranosyl)-3-O-methyl-α-L-*arabino*-hexopyranoside.



SUPPORTING DOCUMENTS:

Two original IND were made for ivermectin by Merck & Co. The first IND was filed on 9/13/84 in order to administer ivermectin to persons infected with S. stercoralis or Ascaris lumbricoides or other gastrointestinal nematodes. The second, IND was filed on 7/17/90 to specifically determine the safety and efficacy of ivermectin in patients who were infected with S. stercoralis and other intestinal nematodes. Following the filing of the second IND the first was withdrawn on 12/28/90.

RELATED DOCUMENTS:

DMF

CONSULTS:

5/21/96: A consult for environmental assessment was prepared by this reviewer and submitted to Nancy Sager, Environmental Scientist, CDER.

5/21/96: 2 method validation packages were prepared and submitted: Nick Falcone, FDA U.S. Customs House, room 900, 2nd & Chestnut St., Philadelphia PA 19106; Hank Drew, DDA, room 1002, 1114 Market St., St. Louis, MO 63101.

5/21/96: A consult was prepared and submitted for suitability of the trade name in the labeling to the Labeling and Nomenclature Committee.

5/20/96: A consult was submitted for the fermentation process controls to HFD-160, Dr. Peter Cooney.

An establishment evaluation request was submitted at the time of this review; The EER number is 10248. The pertinent sites to be inspected are:

Fermentation is performed

Extraction, crystallization, and isolation of avermectins are performed at

Hydrogenation and final purification steps are performed utilizing the facilities located at

The manufacturing and packaging for ivermectin tablets are conducted at the facility

REMARKS/COMMENTS:

Ivermectin is a semisynthetic, antihelmintic agent for oral administration. Ivermectin is derived from the avermectins, a class of highly active broad-spectrum antiparasitic agents isolated from fermentation products of *Streptomyces avermitilis*. The drug has been registered for agricultural and veterinary use since 1981.

CONCLUSIONS & RECOMMENDATIONS:

The application is not approvable with regard to chemistry, manufacturing, and controls. The consults itemized on the previous page are incomplete at this time: environmental assessment; fermentation process consult; 2 method validation packages; consult for suitability of the trade name in the labeling to the Labeling and Nomenclature Committee; establishment evaluation request. Comments to the firm with deficiencies to the application are cited in the sections: Synthesis; Process Raw Materials; Drug Product Component Composition; Excipients; Stability; Labeling.

JTh 6/14/96

J. Timper, Review Chemist

NDA 20-721
HFD-520/Division File
HFD-520/SBRoy/Teamleader
HFD-520/JTimper/Chem 6/14/96
HFD-520/PCoyne/MO
HFD-520/KSeethaler/Pharm
HFD-520/DKing/Micro
HFD-520/SBell/Stat
HFD-520/PColangelo/Biopharm
HFD-520/Cintron/CSO
HFC-130/JAllen

7/22/96

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA 50-742 CHEM.REVIEW #2 REVIEW DATE: 9/16/96
Revision: 9/20/96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment (BZ)	8/28/96	8/29/96	9/4/96

NAME & ADDRESS OF APPLICANT:

Merck Research Laboratories
P.O. Box 4, BLA-20
Sumneytown Pike
West Point, PA 19486

CONTACT: Kenneth R. Brown, M.D., Regulatory Affairs; 610-397-2552

DRUG PRODUCT NAME
Proprietary: Mectizan
Established: Ivermectin
Code # MK-0933
Chem. Type/Ther. Class: 1P

PHARMACOLOGICAL CATEGORY/INDICATION:
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STRENGTHS: 6 mg

ROUTE OF ADMINISTRATION: Oral

Rx/OTC: Rx

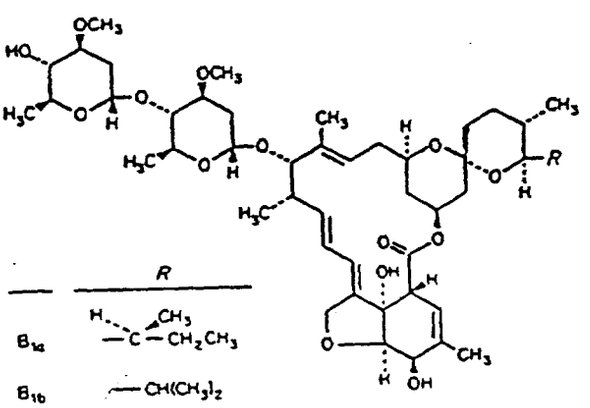
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Ivermectin: A mixture of ivermectin component B_{1a} and ivermectin component B_{1b}.

Ivermectin: CAS-70288-86-7;
Ivermectin component B_{1a}: CAS-70161-11-4;
Ivermectin component B_{1b}: CAS-70209-81-3.

Ivermectin component B_{1a}: $C_{48}H_{74}O_{14}$. Component of Ivermectin. (2aE,4E,8E)-(5'S,6S,6'R,7S,11R,13R,15S,17aR,20R,20aR,20bS)-6'-(S)-sec-Butyl-3',4',5',6,6',7,10,11,14,15,17a,20,20a,20b-tetradecahydro-20,20b-dihydroxy-5',6,8,19-tetramethyl-17-oxospiro[11,15-methano-2H,13H,17H-furo[4,3,2-pg]-[2,6]benzodioxacyclooctadecin-13,2'-[2H]pyran]-7-yl 2,6-dideoxy-4-O-(2,6-dideoxy-3-O-methyl-α-L-arabino-hexopyranosyl)-3-O-methyl-α-L-arabino-hexopyranoside.

Ivermectin component B_{1b}. $C_{47}H_{72}O_{14}$. Component of Ivermectin. (2aE,4E,8E)-(5'S,6S,6'R,7S,11R,13R,15S,17aR,20R,20aR,20bS)-3',4',5',6,6',7,10,11,14,15,17a,20,20a,20b-Tetradecahydro-20,20b-dihydroxy-6'-isopropyl-5',6,8,19-tetramethyl-17-oxospiro[11,15-methano-2H,13H,17H-furo[4,3,2-pq][2,6]-benzodioxacyclooctadecin-13,2'-[2H]pyran]-7-yl 2,6-dideoxy-4-O-(2,6-dideoxy-3-O-methyl-α-L-arabino-hexopyranosyl)-3-O-methyl-α-L-arabino-hexopyranoside.



SUPPORTING DOCUMENTS:
Two original INDs were made for ivermectin by Merck & Co. The first, IND , was filed on 9/13/84 in order to administer ivermectin to persons infected with S. stercoralis or Ascaris lumbricoides or other gastrointestinal nematodes. The second, IND was filed on 7/17/90 to specifically determine the safety and efficacy of ivermectin in patients who were infected with S. stercoralis and other intestinal nematodes. Following the filing of the second IND the first was withdrawn on l 2/28/90.

RELATED DOCUMENTS:

DMF

CONSULTS:

5/21/96: A consult for **environmental assessment** (EA) was prepared by this reviewer and submitted to Nancy Sager, Environmental Scientist, CDER.

9/3/96: A consult with the response by the firm to the findings of the first consulted EA review was prepared by this reviewer and submitted to Nancy Sager, Environmental Scientist, CDER. The FONSI was completed 9/16/96. (**Complete, acceptable**)

5/21/96: 2 **method validation packages** were prepared and submitted: Nick Falcone, FDA U.S. Customs House, room 900, 2nd & Chestnut St., Philadelphia PA 19106; Hank Drew, DDA, room 1002, 1114 Market St., St. Louis, MO 63101. The method validation packages are not complete at the time of this review.

5/21/96: A consult was prepared and submitted for suitability of the trade name in the labeling to the **Labeling and Nomenclature Committee.**

6/20/96 (**Complete, acceptable**) The committee reply stated no reasons to object to the product name, Mectizan.

5/20/96: A **consult was submitted for the fermentation process controls** to HFD-160, Dr. Peter Cooney.

9/3/96: A consult with the response by the firm to the findings of the first consulted review was prepared by this reviewer and submitted to HFD-160, Dr. Peter Cooney.

9/11/96: (**Complete, acceptable**) The second consulted review of the fermentation process consulted review was completed with recommendation that the information is acceptable.

6/14/96: An **establishment evaluation request** was submitted at the time of this review; The EER number is 10248. The pertinent sites to be inspected are: Fermentation is performed Extraction, crystallization, and isolation of avermectins are performed at Hydrogenation and final purification steps are performed utilizing the facilities located at . The manufacturing and packaging for ivermectin tablets are conducted at the facility in
NDA 20-721; J.Timper; Chemistry review #1; page 4 Mectizan (Ivermectin); Merck & Co., Inc. **This is OPEN at this time.**

REMARKS/COMMENTS:

This NDA 50-742 was first assigned the number NDA 20-721. In June, 1996 the product number was changed to conform to the numbering for fermentation products. The firm should provide a translated copy of the drug substance batch records and address the lack of impurity controls in the drug substance fermentation and subsequent synthetic step.

CONCLUSIONS & RECOMMENDATIONS:

There are still a few remaining deficiencies. The method validation work is open. The establishment inspection request is open. The firm's request for 24 months stability dating is not supported by the data; the stability data supports 12 months expiration dating.

9/20/96

J. Timper,

9/25/96

NDA 50-742
HFD-520/Division File
HFD-520/BDunn/Teamleader (Acting)
HFD-520/JTimper/Chem 9/20/96
HFD-520/PCoyne/MO
HFD-520/KSeethaler/Pharm
HFD-520/DKing/Micro
HFD-520/SBell/Stat
HFD-520/PColangelo/Biopharm
HFD-520/Cintron/CSO
HFC-130/JAllen

TO: NDA 50-742
DATE: 10/7/96
RE: ADDENDUM TO REVIEW #2

The firm was requested to use the uninverted systematic chemical name. The prohibitive length and room on the labeling was given as explanation for the request. The response is adequate.

> The firm has proposed the inverted form of the systematic chemical name developed by Chemical Abstracts Service (CAS), in general accordance with the rules established by the International Union of Pure and Applied Chemistry (IUPAC) and the International Union of Biochemistry (IUB), and employed in the current issues of CA. The name proposed is the names of two components of a mixture of at least 90% of
>
> 5-*O*-demethyl-22,23-dihydroavermectin A_{1a}
>
> and less than 10% of
>
> 5-*O*-demethyl-25-de(1-methylpropyl)-22,23-dihydro-25-(1-methylethyl)avermectin A_{1a}.

The drug product components are correctly given in the labeling section, "DESCRIPTION". The chemical structure is given correctly.

JTim 10/7/96

J. Timper

NDA 50-742
HFD-520/Division File
HFD-830/BDunn/Deputy Div. Director, DNDC III
HFD-520/JTimper/Chem
HFD-520/PCoyne/MO
HFD-520/KSeethaler/Pharm
HFD-520/DKing/Micro
HFD-520/SBell/Stat
HFD-520/PColangelo/Biopharm
HFD-520/Fogarty/CSO
HFC-130/JAllen

BDunn 10/7/96

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA 50-742 **CHEM.REVIEW** #3 **REVIEW DATE:** 10/7/96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment BC	10/4/96	10/7/96	9/30/96

NAME & ADDRESS OF APPLICANT:

Merck Research Laboratories
P.O. Box 4, BLA-20
Sumneytown Pike
West Point, PA 19486

CONTACT: Kenneth R. Brown, M.D., Regulatory Affairs; 610-397-2552

DRUG PRODUCT NAME
Proprietary: Mectizan
Established: Ivermectin
Code # MK-0933
Chem. Type/Ther. Class: 1P

PHARMACOLOGICAL CATEGORY/INDICATION:
Treatment of strongyloides of the gastrointestinal tract and onchocerciasis.

DOSAGE FORM: Tablets, immediate release

STRENGTHS: 6 mg

ROUTE OF ADMINISTRATION: Oral

Rx/OTC: Rx

SUPPORTING DOCUMENTS:
IND was filed on 9/13/84 in order to administer ivermectin to persons infected with S. stercoralis or Ascaris lumbricoides or other gastrointestinal nematodes. IND was filed on 7/17/90 to specifically determine the safety and efficacy of ivermectin in patients who were infected with S. stercoralis and other intestinal nematodes.

RELATED DOCUMENTS:
FDA memorandum to Dr. Dunn from J.Timper regarding NDA 50-742 dated 9/27/96.
Letter to Philadelphia Regional Office from Merck, dated 9/18/96.

REMARKS/COMMENTS:

This review is of Merck's fax, dated September 30, 1996. There was a telephone conversation with Merck Research Laboratories on 9/26/96. A fax was sent on 9/27/96 to summarize the FDA comments to the firm in that phone call.

In the fax, the firm has adopted controls at the extraction of avermectin step that occurs at This control monitors the impurity B_{2a} to be less than 1.1% in the wet cake. The firm should commit to submit the results of the on-going investigation of process failures at this step. The firm states in the fax that they will reject batches that show visible impurities or fail the B_{2a} specification.

CONCLUSIONS & RECOMMENDATIONS:

The few remaining chemistry concerns should be addressed by the firm. The method validation work is open. The firm's request for 24 months stability dating is not supported by the data. The stability data support 15 months expiration dating.

JTim 10/7/96

J. Timper

NDA 50-742
HFD-520/Division File
HFD-830/BDunn/Deputy Div. Director, DNDC III
HFD-520/JTimper/Chem
HFD-520/PCoyne/MO
HFD-520/KSeethaler/Pharm
HFD-520/DKing/Micro
HFD-520/SBell/Stat
HFD-520/PColangelo/Biopharm
HFD-520/Fogarty/CSO
HFC-130/JAllen

TO: NDA 50-742
DATE: 10/7/96
RE: ADDENDUM TO REVIEW #3

A memorandum dated October 4, 1996 was received by HFD-520. The memorandum recommends to withhold application. It states the following deviations from GMPs:

- Batch records are not routinely reviewed by Quality Assurance prior to product release.
- A limited review of batch production records found failures which were not investigated to determine their cause nor were methods instituted to prevent their reoccurrence.
- Failure to validate changes made to established manufacturing processes and access their effect on stability.

See attached.

J. Timper

NDA 50-742
HFD-520/Division File
HFD-830/BDunn/Deputy Div. Director, DNDC III 10/7/96
HFD-520/JTimper/Chem
HFD-520/PCoyne/MO
HFD-520/KSeethaler/Pharm
HFD-520/DKing/Micro
HFD-520/SBell/Stat
HFD-520/PColangelo/Biopharm
HFD-520/Fogarty/CSO
HFC-130/JAllen

(685)

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair (HFD-530), 9201 Corporate Blvd, Room N461

From: **Division of** Anti-Infective Drug Products **HFD-520**

Attention: Bonnie B. Dunn, Ph.D. **Phone:** 827-2003

Date: October 4, 1996

Subject: Request for Assessment of a Trademark for a Proposed New Drug Product

Proposed Trademark: Stromectol **NDA/ANDA#** 50-742

Established name, including dosage form:
Ivermectin; 6 mg immediate release tablet

Other trademarks by the same firm for companion products:

Mectizan (same drug product but donated else where than the U.S.). Merck does not want to use the same name as that used else where in the world because they don't want to confuse the donated drug program name with the "for sale" drug program in the U.S. According to Frank Ricci of Merck Research Laboratories, this name is already registered in the U.S. and France.

Indications for Use (may be a summary if proposed statement is lengthy):

Treatment of strongyloides of the gastrointestinal tract and onchocerciasis (gastrointestinal nematodes).

Initial Comments from the submitter (concerns, observations, etc.):

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev. December 95

Consult #685 (HFD-520)

STROMECTOL ivermectin immediate release tablet, 6 mg

There were no look-alike/sound-alike conflicts or misleading aspects noted with the proposed proprietary name. However, the Committee believes the established name for the product is (ivermectin tablets) immediate release. The USP does not specifically recognize the term "immediate release" and to be in conformance with the USP established name conventions, "immediate release" should either not be used at all or appear outside of the parenthesis.

The Committee has no reason to find the proposed proprietary name unacceptable.

D Yoring 11/18/96, Chair
CDER Labeling and Nomenclature Committee

cc: Original NDA 50-742
HFD-520/Div. File
HFD-830/Chem/DunnB
HFD-520/Chem/TimperJ
HFD-520/Chem/KatagueD
HFD-520/PM/FogartyP

6 1 OCT 22 1996

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA 50-742 **CHEM.REVIEW #4** **REVIEW DATE:** 10/22/96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment BC	10/15/96	10/16/96	10/17/96

NAME & ADDRESS OF APPLICANT:

Merck Research Laboratories
P.O. Box 4, BLA-20
Sumneytown Pike
West Point, PA 19486

CONTACT: Kenneth R. Brown, M.D., Regulatory Affairs; 610-397-2552

DRUG PRODUCT NAME
Proprietary: Stromectol
Established: Ivermectin
Code # MK-0933
Chem. Type/Ther. Class: 1P

PHARMACOLOGICAL CATEGORY/INDICATION:
Treatment of strongyloides of the gastrointestinal tract and onchocerciasis.

DOSAGE FORM: Tablets, immediate release

STRENGTHS: 6 mg

ROUTE OF ADMINISTRATION: Oral

Rx/OTC: Rx

SUPPORTING DOCUMENTS:
IND was filed on 9/13/84 in order to administer ivermectin to persons infected with S. stercoralis or Ascaris lumbricoides or other gastrointestinal nematodes. IND was filed on 7/17/90 to specifically determine the safety and efficacy of ivermectin in patients who were infected with S. stercoralis and other intestinal nematodes.

REMARKS/COMMENTS:

The name "Mectizan" has been revised by the firm to be Stromectol. The purpose was to avoid confusion in marketing. There was a consult to the Committee for Drug Product Labeling and it was found acceptable. The formal review of the trade name will be submitted to the file when it arrives.

The review #4 is the evaluation of the response by the firm to the FDA fax (dated October 9, 1996) sent by Pauline Fogarty. This fax contained deficiencies noted to the firm in chemistry review #3.

CONCLUSIONS & RECOMMENDATIONS:

Recommend approval after acceptable establishment inspections. The research needed to understand the production failures at the avermectins extraction and purification step should be provided in a phase 4 submission.

J.T. 10/22/96

J. Timper

NDA 50-742
HFD-520/Division File
HFD-830/BDunn/Deputy Div. Director, DNDC III BBD 10/29/96
HFD-520/JTimper/Chem
HFD-520/PCoyne/MO
HFD-520/KSeethaler/Pharm
HFD-520/DKing/Micro
HFD-520/SBell/Stat
HFD-520/PColangelo/Biopharm
HFD-520/Fogarty/CSO
HFC-130/JAllen

EA ▽ Fonsi

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

MECTIZAN®

(ivermectin tablets)

NDA 50-742 [redacted]

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
(HFD-520)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-721

MECTIZAN® (ivermectin tablets)

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for **MECTIZAN® (ivermectin tablets), Merck Research Laboratories** has conducted a number of environmental studies and prepared an environmental assessment in accordance with 21 CFR 25.31a(a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Ivermectin is a semi-synthetic drug which will be administered orally in the treatment of strongyloidiasis and onchocerciasis. The active moiety is used in the U.S. in approved veterinary products. The Center for Veterinary Medicine reviewed an environmental assessment and issued a finding of no significant impact for the approval of ivermectin products. Approval of this product for human use will result in a very small incremental increase in the use of this active moiety over that which is currently used for veterinary purposes.

The drug substance will be manufactured at Merck facilities in Elkton, VA, Danville, PA and Barceloneta, PR. The drug product will be manufactured at a Merck facility in Haarlem, Holland. The finished drug product will be used in hospitals, clinics and by patients in their homes throughout the United States.

Ivermectin may enter the environment from excretion by patients, from disposal of pharmaceutical waste or from emissions from manufacturing sites.

The environmental fate and effects of this active moiety have been studied extensively because of its use as a veterinary product. Rapid photodegradation and oxidative degradation in soil have been identified as environmental depletion mechanisms. Effects on standard test organisms have been observed at concentrations as low as 0.01 ppb.

Disposal may result from production waste such as out of specification lots, returned goods and user disposal of empty or partly used product and packaging. Pharmaceutical waste will be sent to licensed incineration facility. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic procedures. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release.

The small incremental increase in the use of this drug that will result from this approval does not change the Agency's previous conclusion that a finding of no significant impact is appropriate. The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

9/12/96
DATE

PREPARED BY
Nancy B. Sager
Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

9/13/96
DATE

CONCURRED
Charles P. Hoiberg, Ph.D.
Division Director, Office of New Drug Chemistry-1
Center for Drug Evaluation and Research

Attachment: Environmental Assessment

1. Date

January 1, 1996

2. Name of Applicant/Petitioner:

Merck Research Laboratories
Merck & Co., Inc.

3. Address:

Sumneytown Pike
West Point, PA 19486-0004

4. Description of the Proposed Action:

a. Requested Action

Merck Research Laboratories, Division of Merck and Co., Inc. has filed a New Drug Application for MECTIZAN™ (ivermectin), indicated for the treatment of strongyloidiasis (threadworm infection) of the gastrointestinal tract and onchocerciasis (river blindness). MECTIZAN will be available in tablet form (6 mg) packaged in an aluminum foil strip. The composition of the foil

strip is as follows (outside to inside); lacquered coating, aluminum foil (30 microns), primer, polyethylene sealant.

At the projected annual US patient usage, the maximum incremental production of ivermectin required is estimated to be extremely small (Confidential Appendix III, Part 1). This amount is only a very small percentage (less than 0.1%) of the estimated amount of ivermectin used for human health purposes worldwide and represents an even much smaller percentage of the ivermectin produced for previously approved veterinary uses.

b. Need for the Action

MECTIZAN (ivermectin), a semisynthetic anthelmintic agent, offers effective therapy for the treatment of strongyloidiasis and onchocerciasis. While endemic in the tropics, these diseases also occur to a limited extent in the United States especially where unsanitary, crowded conditions prevail.

Strongyloidiasis is caused by the parasitic worm, *Strongyloides stercoralis*. The recommended dosage of MECTIZAN for treatment of strongyloidiasis is a single oral dose designed to provide approximately 200 micrograms of ivermectin per kg of body weight. In general, additional doses will not be necessary.

Onchocerciasis is caused by a parasitic worm, *Onchocera volvulus* and is a leading cause of blindness in certain tropical regions. The recommended dosage of MECTIZAN for treatment of onchocerciasis is a single oral dose designed to provide approximately 150 micrograms of ivermectin per kg of body weight. In mass distribution campaigns in international treatment programs, the most commonly used dose interval is 12 months. For treatment of individual patients, retreatment may be considered at intervals as short as 3 months.

c. The Locations Where the Product will be Produced and Types of Environments Adjacent to those Locations

The bulk drug substance (ivermectin) will be manufactured in the applicant's facilities. The fermentation steps will take place at the Merck Manufacturing Division facilities in Elkton, Virginia and Danville, Pennsylvania (as avermectin broth). The avermectin broth produced at the Elkton facility will be shipped to the facility in Danville, Pennsylvania. The Danville site will complete the isolation and purification of avermectin. The avermectin will be shipped to the Merck Manufacturing Division facility in Barceloneta, Puerto Rico for conversion to ivermectin (drug substance).

The drug product (MECTIZAN) will be manufactured and packaged at the applicant's facility in Haarlem, Holland. Returned goods will be disposed of at the Merck Manufacturing Division facility in West Point, Pennsylvania.

The types of environments present at the locations mentioned above, specific to the vicinity of drug substance (avermectin and ivermectin) manufacturing or drug product (MECTIZAN) manufacturing and packaging, are described in the following sections.

1) Elkton, Virginia

Route 340 South (P.O. Box 7)
Elkton, VA 22827

a) Geographic Conditions

The Elkton plant is located on the south fork of the Shenandoah River approximately three miles south of Elkton, Virginia in Rockingham County. Coordinates of the plant's location are latitude 38° 23' N and longitude 78° 39' W. The town of Elkton is located approximately 3 miles northeast of the plant, has a population of less than 1,935 people according to the 1990 U.S. Census Bureau.

The site is approximately 58 acres and employs about 700 people. The surrounding neighborhood includes Merck's chemical operations, farmland, wooded acres, and residential homes.

b) Air Resources

The plant is located in Virginia's Air Quality Control Region II which is in attainment with the National Ambient Air Quality Standards (NAAQS) for sulfur oxides, nitrogen oxides, total suspended particles and ozone. State air regulations generally incorporate standards and procedures required by the United States Environmental Protection Agency (USEPA). The Prevention of Significant Deterioration (PSD), the New Source Performance Standards (NSPS), and the National Emission Standard for Hazardous Air Pollutants (NESHAPS) regulations have been incorporated into the state air regulations. The plant is approximately two kilometers from a Class I Area (Shenandoah National Park). Prevailing winds near the plant are from the south-southwest.

The mean summer temperature is 23°C (73°F) and the mean winter temperature is 1°C (33°F). Annual rainfall is about 34 inches.

c) Water Resources

Separate sanitary, process and storm water sewer systems are maintained by the plant. The sanitary wastes, after solids separation and chlorination, are mixed with the process waste for additional treatment in the plant's waste water treatment facility. Water from the storm water system and non-contact cooling water is mixed with the waste water treatment plant effluent and discharged to the South Fork of the Shenandoah River through the plant's VPDES outfall. There are no injection wells on the plant's property, and the only surface water within 1000 feet of the plant is the South Fork of the Shenandoah River. The 100-year flood plain elevation at the plant is approximately 973 feet above mean sea level. One well supplies the plant's potable water needs with an additional well as backup.

d) Land Resources

The terrain surrounding the plant is valley flatland. The Elkton plant is underlain by carbonate rocks of the Rome and Elbrook formations, surficial deposits consist of fluvial sand and gravel, and regolith of residual clays. The bedrock strata beneath the plant are tilted and strike north 57° and dip to the northwest 45°. Handling and disposal of solid waste streams at the Elkton plant is subject to, and in compliance with, the Federal Resource Conservation and

Recovery Act (RCRA), the Virginia Solid Waste Management Regulations and the Virginia Hazardous Waste Management Regulations, which are administered by the Department of Environmental Quality.

2) Danville, Pennsylvania

P.O. Box 600
Danville, Pennsylvania 17821

a) Geographic Conditions

The Danville plant is located on a 180 acre site in the Susquehanna River Valley approximately 70 miles north of Harrisburg, Pennsylvania in the Borough of Riverside. The plant is located adjacent to the south bank of the North Branch of the Susquehanna River. Coordinates of the plant's location are latitude 40° 57' N and longitude 76° 38' W.

b) Air Resources

Annual rainfall at the Williamsport Airport (approximately 30 miles from the plant) is 41 inches. The mean summer temperature is 22°C (72°F), while the mean winter temperature is -2°C (28°F). The entire state of Pennsylvania has no significant nitrogen dioxide

pollution. The entire state of Pennsylvania is included in the Northeast Transport Region. The Danville plant is located in Northumberland County which is in attainment with the standards for the National Ambient Air Quality Standards (NAAQS) for all criteria pollutants except ozone. The state has incorporated into its regulations the new source performance standards (NSPS), the National Emission Standards for Hazardous Air Pollutants (NESHAPS), and the National Ambient Air Quality Standards (NAAQS). There are no Class I Areas within 50 km of the plant. Prevailing winds near the plant are from the west-northwest direction.

c) Water Resources

Separate sanitary, process, and storm sewers are maintained at the plant. The sanitary sewer flows to Danville's wastewater treatment plant, while the process sewer flows to the plant's waste water treatment facility. Water from the storm sewer merges with the effluent from the plant's waste water treatment system, and the combined streams are discharged to the Susquehanna River through the plant's National Pollutant Discharge Elimination System (NPDES) outfall. The only surface water within 1000 feet of the plant is the North Branch of the Susquehanna River. There are no injection wells on the plant property, and the 100-year flood plain elevation at the plant is approximately 460 feet above mean sea

level. The plant derives its potable water entirely from an on-site treatment plant which uses the North Branch of the Susquehanna River as its source. The plant potable water quality meets all requirements of the Federal Safe Drinking Water Act and the Pennsylvania Safe Drinking Water Act.

d) Land Resources

The Danville site is located within the Appalachian Mountain Section of the Valley and Ridge Physiographic Province. General topographic trends of the region include long, continuous ridges separated by valleys of varying width. The Danville site lies on a fairly flat region around which the North Branch of the Susquehanna River flows. Montour Ridge is located directly across the river from the Danville site, and rises to an elevation above 1000 feet above mean sea level. Elevations on the Danville site range from approximately 450 to 470 feet above mean sea level, with the steepest slopes occurring along the banks of the river.

3) Barceloneta, Puerto Rico

Merck Sharp & Dohme
Quimica de Puerto Rico
Road #2, Kilometer 56.7
Barceloneta, Puerto Rico

a) Geographic Conditions

The Merck Sharp & Dohme Quimica de Puerto Rico, Inc. (MSDQ) facility is located on a 166 acre site in Barceloneta, Puerto Rico. The city of Barceloneta contains a population of approximately 20,000 people and is located 38 miles due west of San Juan and three miles south of the Atlantic Ocean. The MSDQ plant is located at km 56.7 along state Highway 2. Coordinates of the plant's location are latitude 18° 25' N and longitude 66° 32' W.

b) Air Resources

Puerto Rico generally has attained National Ambient Air Quality Standards (NAAQS) although there are problems with particulates in the Cataño air basin. The Barceloneta plant is located in the Barceloneta air basin. The state requires new source permits and operating permits for all point sources. Puerto Rico has been delegated authority over the National Emission Standards for Hazardous Air Pollutants Program (NESHAPS).

Meteorological data for the area is collected at the Isla Verde Airport in San Juan (about 47 miles east of Barceloneta). Annual rainfall is near 60 inches and the mean ambient temperature varies

between 24 and 28°C (76 and 82°F). An easterly trade wind is the predominant wind pattern.

c) Water Resources

The entire fresh water requirements for the plant are supplied by one pumped well and two artesian wells. The artestian wells are used as the primary source of plant water. No other well, or surface water bodies, are located within 1000 feet of the facility. The plant potable water quality meets all requirements of the federal Safe Drinking Water Act. Separate sewer systems exist for sanitary, process and storm water runoff. Process waste water flows into the plant's pretreatment system and then to the Barceloneta Regional Wastewater Treatment Plant (BRWTP). Sanitary waste from the plant joins the effluent from the pretreatment system and the combined streams flow to the BRWTP.

Storm water from the plant is collected in an independent trench system, consisting of concrete dikes and swales and directed away from the facility. Surface water runoff from portions of the plant discharge to the sinkhole system which is described in the land resources section below. The MSDQ plant is located approximately 1.25 miles west of the Manati River and 70 meters (230) feet above mean sea level. The plant is located well above the 100-year flood plain.

d) Land Resources

The plant is located in an inter-mogote depression. The depression is elongated east-west over a distance of 2 km. The mogotes are asymmetrical hills that are built of massive thick-bedded members of the Aymamon Limestone. A series of sink holes and secondary depressions are located to the east and tend in a northwesterly direction from the site. Bedrock beneath the plant site consists primarily of moderately solutioned, recrystallized limestone of the Aymanmon Formation. In depressions between mogotes and ridges, the limestone is overlain by the quaternary blanket sands. The blanket deposits consist mostly of silty or sandy clay which underwent rapid deposition in a subaerial fluvial plain environment. Based on soil borings from the site, 20 percent of the soil is sand. Red-brown to yellow silty clay comprises the dominant soil found in the borings. Land use surrounding the plant includes industrial and mixed industrial. Other industries lie north and west of the facility, the community of Trinidad lies north of the facility, and the rest of the surrounding area is undeveloped.

4) Haarlem, Holland

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

a) Geographic Conditions

The MSD plant in Haarlem, Holland is located in the municipality of Haarlem, near the North Sea coast and approximately 20 km (13 miles) from the city of Amsterdam. The plant is located east of the city of Haarlem on 18 hectare (45 acres) of land near the river Spaarne. The plant is located in the area of Waarderpolder, which is dedicated to industrial activity only. The population of Haarlem is approximately 150,000 people.

b) Air Resources

Dutch government laws prescribe emission standards for hazardous air pollutants. No significant air pollution generating industries are located in the vicinity. Annual rainfall is about 0.75 meter (30 inches). Mean January temperature is 5-8°C (40-45°F). Prevailing wind directions are west and south-west (sea wind) at a windforce of 3 to 8 Beaufort.

c) Water Resources

All water used for consumption, process, and sanitary equipment is obtained from the official county supplier. Water quality meets standards of potable water. Water for firefighting can be withdrawn from the River Spaarne. There are no injection wells on the plant property. The sanitary and storm sewer system are directly coupled to the municipal sewer system, while the process effluents are treated before discharge into the municipal sewer. The discharge of wastewater into the municipal sewer is covered by an agreement with the Hoogheemraadschap van Rynland. All wastewater is treated in the public wastewater treatment plant managed by the Hoogheemraadschap van Rynland. The effluent from the treatment plant is discharged into the River Spaarne.

d) Land Resources

The land of the industrialized zone where the plant is located is reclaimed ("polder"). The soil is composed of layers of clay, sand, and peat.

5) West Point, Pennsylvania

Sumneytown Pike
P.O. Box 4
West Point, PA 19486-0004

a) Geographic Conditions

The West Point plant is located on a site (~450 acres) in Upper Gwynedd Township, Montgomery County, which is approximately 30 miles northwest of Philadelphia. The center of the West Point plant is located near latitude 40° 12' 54" N and longitude 75° 17' 59" W. Land use surrounding the plant is primarily residential and agricultural with other industrial sites approximately one-half mile away.

b) Air Resources

Air quality in this area is in compliance with the Environmental Protection Agency's (EPA) National Ambient Air Quality Standards (NAAQS) of the Clean Air Act for total suspended particulates, sulfur oxides, and nitrogen oxides. This compliance is based on monitoring and reporting by the Pennsylvania Department of Environmental Protection (PA DEP) under the requirements of the State Implementation Plan. At this time,

Montgomery County does not meet the ozone standard set forth by the NAAQS. The West Point plant lies within the outer zone of the Southeast Pennsylvania air basin. Pennsylvania is part of the EPA Region III and PA DEP is responsible for implementing the State Implementation Plan which includes new stationary source permits for manufacturing. Meteorological data for the region is collected at the Philadelphia International Airport. Annual rainfall is approximately 42 inches (107 cm) and the mean ambient monthly temperature varies between 33 and 77°F (0.5-25°C). Predominant winds are from west to southeast.

c) Water Resources

Potable water is supplied to the plant operations via an on-site storage tank which is supplied by on-site wells and a public water supplier, North Wales Water Authority. The North Wales Water Authority operates two public wells within a half-mile of the plant property.

Stormwater drainage is controlled using detention basins which maintain site runoff at levels estimated for undeveloped property and to minimize erosion. This runoff is discharged into either the Towamencin Creek or the Wissahickon Creek.

Wastewater generated as a result of on-site incineration activity will be discharged to the Upper Gwynedd Township Authority Wastewater Treatment Plant (UGTA). The UGTA discharges treated effluent to the Wissahickon Creek.

The location of the discharge from the UGTA is downstream from the West Point site. Pennsylvania DEP limits the wasteload allocation and water pollutant limits (established by the Pennsylvania Water Toxics Management Strategy) from the UGTA by means of the National Pollutant Discharge Elimination System discharge permit. This wasteload allocation and water pollutant limit are used to determine the allowable contribution limits from the West Point site to the publicly owned treatment works. The treated wastewater is also regulated by the UGTA under permit and local ordinance.

d) Land Resources

The plant is underlain by Triassic age sedimentary rocks, mapped as the Brunswick and Lockatong formations. These formations occur as layered beds of red and very dark gray shale with occasional layers of sandstone. Although these rocks generally have low primary porosities, permeability is maintained and improved by the presence of fractures and joint sets.

The plant site elevation is about 361 feet above mean sea level (United States Geologic Survey datum).

d. The Location Where the Product will be Used and Disposed Of

MECTIZAN is intended for use throughout the United States. Ivermectin and other ingredients used to formulate MECTIZAN will enter the environment primarily in domestic sewage which is highly diluted during routine wastewater processing. Environmental concentrations of ivermectin resulting from the use of MECTIZAN tablets will be many orders of magnitude below levels of environmental significance. When compared to the expected environmental concentration (US-use) for treatment of strongyloidiasis and onchocerciasis, aquatic toxicity endpoints from studies conducted with ivermectin produce differences (assessment factors) which are well in excess of 1000.

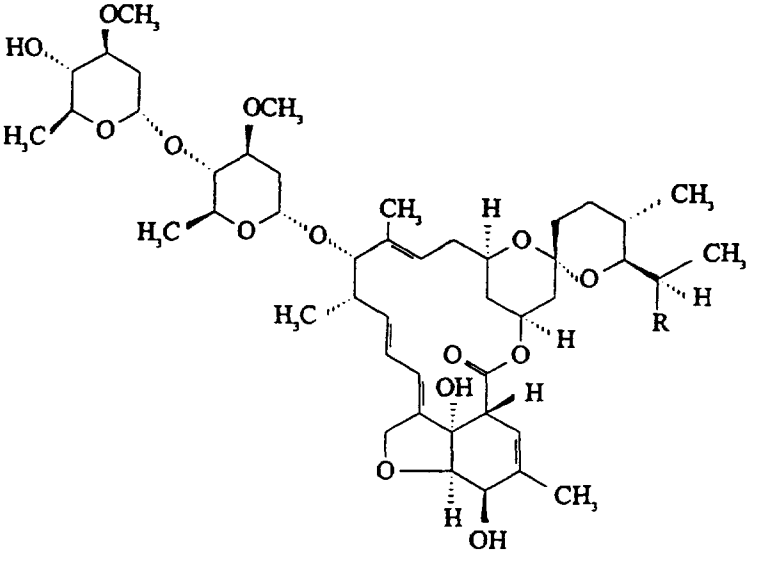
Merck & Co., Inc. has a returned goods policy which involves the return of any unused market packages to the West Point, Pennsylvania facility for disposal. This results essentially in a single controlled location for product disposal. Thermal destruction is used to treat wastes containing finished product. On-site incineration facilities are used to handle the majority of this

waste. Any off-site incineration is conducted at a permitted facility.

5. Identification of Chemical Substances that are the Subject of the Proposed Action

Ivermectin is produced by fermentation (*Streptomyces avermitilis*) and subsequent chemical hydrogenation and is a mixture of two closely related homologues belonging to a class of compounds known as avermectins. The chemical names of the two homologues are: 22,23-dihydroavermectin B_{1a} ($R=C_2H_5$) and 5-O-Demethyl-25-de(1-methylpropyl)-22,23-dihydro-25-(1-methyl ethyl) avermectin B_{1a} ($R=CH_3$). The latter is also known as 22,23-dihydroavermectin B_{1b}. The Chemical Abstracts Registry (CAS) number assigned to ivermectin is 70288-86-7.

The structure and properties of ivermectin are given below. Formulation ingredients and excipients are listed in Confidential Appendix - Part 2.



Molecular Formula	Molecular Weight
(R = C_2H_5) $C_{48}H_{74}O_{14}$	875.10
(R = CH_3) $C_{47}H_{72}O_{14}$	861.07

Ivermectin contains at least 90% of the compound in which R in the above structure is the ethyl group and less than 10% of the compound in which R is the methyl group. [Note: Ivermectin was previously defined as containing at least 80% of the compound in which R is the ethyl group and less than 20% in which R is the methyl group. Based on a historical data review and process capability, the component proportion was changed to that indicated.] Ivermectin is a white to yellowish-white crystalline powder and has an ill-defined melting point of about 155°C. The

material is optically active and has a specific rotation $[\alpha]_D^{20°C}$, of approximately -19° (C=2.5, CH_3OH).

The ultraviolet absorption spectrum in methanol is characterized by a maximum at 245 nm and clearly defined shoulders at ~237 and ~254 nm. Ivermectin is very insoluble in water: The concentration of a saturated aqueous solution is 4 ppm.

Ivermectin has been shown to be stable for at least six months when stored under ambient conditions. In solution, ivermectin is photolabile.

Ivermectin contains at least 95% of the two compounds shown above as determined by UV absorption and liquid chromatography.

Based on radioactivity measurements, the octanol-water (pH 7 buffer) partition coefficient, K_D, for ivermectin is 1651.

The present assessment supplements ivermectin data with data generated with avermectin B_1. The structure of avermectin B_1 (AVM) only differs from that of ivermectin (IVM) by a double bond at position 22,23. Ivermectin is produced from avermectin by catalytic reduction of this double bond. Physical properties of ivermectin and avermectin are compared below.

Comparison of IVM and AVM Physical Properties

Physical Properties	IVM	AVM
Molecular Weight[a]	875	873
Octanol/Water Partition Coef.	1,651	9,900
K_{oc}[b]	12,600-15,700	≥4,000
Aqueous Solubility[c]	4 ppm	8 ppb
E (λmax), Methanol	30,100 (245)	31,850 (243)

[a] Molecular weight of the B_{1a} component

[b] Different soils used

[c] Different methods used

Both compounds possess low water solubility, high octanol/water partition coefficients and high K_{oc} values. Compounds with K_{oc} values >1000 are considered to be immobile in soil.

Additional information concerning the molecular structure, chemical names, laboratory codes, generic name, trade name, physical-chemical properties as well as a summary of the environmental fate and effects data for ivermectin can be found in Appendix I.

6. Introduction of Substances into the Environment:

A summary of the permit numbers applicable to the manufacture of MECTIZAN (ivermectin), discussed below, is given in Confidential Appendix III - Part 3.

a. As a Result of the Manufacture of MECTIZAN (ivermectin), 6 mg

1) Elkton, Virginia

a) Air Emissions Controls and Citations - Bulk Drug Substance Manufacture

The fermentation step generates fermentation off-gases that contain typical respiration byproducts, including carbon dioxide (CO_2). The on-site incinerator emissions consist of typical combustion products.

Air emissions are subject to, and in compliance with, the Virginia Regulations for the Control and Abatement of Air Pollution. The on-site trash incinerator is in compliance with the Commonwealth of Virginia Regulations for the Control and Abatement of Air Pollution. No new permit limits are anticipated as a result of the proposed action and approval will not impact the facility's ability to comply with all applicable permit conditions.

b) Liquid Emissions Controls and Citations - Bulk Drug Substance

The manufacturing process generates aqueous waste streams from fermentor vents, fermentor sample funnels, equipment washes and floor drains. All aqueous waste is collected via piping or collection sump in a 20,000 gallon collection tank or directly transferred to either holding tanks or tank trucks. From the collection tank, the waste can be transferred either to an evaporator system to concentrate the liquid waste prior to shipment off-site or directly to a tank truck. The liquid waste is then sent to the applicant's Danville, Pennsylvania facility for treatment and disposal. The specifics of wastewater treatment employed at the Danville facility are described in the section (2) below. On a limited case-by-case basis, liquid wastes that have been determined through process knowledge and detailed analysis to contain less than a threshold concentration of avermectins will be sewered to the site's advanced activated sludge system (wastewater treatment plant).

Effluent from the facility's wastewater treatment plant is discharged directly to the Shenandoah River under the Virginia Pollutant Discharge Elimination System (VPDES) Permit #VA0002178 (expiration date: 6/6/99). The VPDES permit is administered by the Virginia Department of Environmental Quality. The effluent currently has maximum daily limits of TSS $\leq$5338 kg/d and COD $\leq$17,246 kg/d and pH limits between 6.5 and 9.5. No new permit

limits are anticipated as a result of the proposed action and approval will not impact the facility's ability to comply with all applicable permit conditions.

c) Solid Waste Controls and Citations - Bulk Drug Substance Manufacture

Burnable, non-hazardous, solid wastes containing "de minimis" amounts of avermectin may consist of paper, aluminum, plastic, and drums. Such wastes are incinerated on-site or sent to a permitted incineration facility able to accept such waste streams. Other non-hazardous wastes which cannot be recycled are disposed of at a state licensed landfill.

Disposal of non-hazardous solid waste is subject to and in compliance with Permit #183 (no expiration date) issued under the Virginia Solid Waste Management Regulations. There are no numerical permit limits on solid waste generation and no additional permit conditions are anticipated as a result of the proposed action.

d) Employee Protection

Material Safety Data Sheets (MSDS) are available on-site for all chemicals as required by the Occupational Safety Act of 1971, the Hazards Communication Act of 1985 and Title 29 Code of Federal Regulations (CFR) Part 1910. Employees associated with the

manufacture of drug product have appropriate MSDSs available for their review. Employee protective clothing, such as gloves, uniforms and safety glasses are used during the packaging process to assure compliance with the Occupational Safety Act of 1971 and the Hazard Communication Act of 1985 and Title 29 CFR Subpart I.

2) Danville, Pennsylvania

a) Air Emission Controls and Citations - Bulk Drug Substance Manufacture

The fermentation step generates fermentation off-gases that contain typical respiration byproducts, including carbon dioxide (CO_2). Air emissions generated from the avermectin isolation consist of volatile organic compounds (such as hexane, methanol, ethanol, and toluene) and dust. Volatile organic emissions from the avermectin production process are controlled by condensers. Dust in the process building will be filtered with HEPA filters to control the introduction of avermectin and dust into the ambient air with an efficiency greater than 99.9%.

Air emissions applicable to the production of avermectin are in compliance with the regulations of the Pennsylvania Department of Environmental Protection (Title 25, Part I, Subpart C, Article III,

Air Resources) and Operating Permit #49-313-032C (expiration date: 10/31/99).

b) Liquid Emissions Controls and Citations - Bulk Drug Substance Manufacture

The avermectin manufacturing process generates two types of liquid-waste streams: one, a combination of solvent-based waste streams, the other, a combination of aqueous waste streams.

The solvent-based waste streams from the avermectin manufacturing process are generated in the isolation step and in the recovery of solvents used for the isolation. They contain discarded organic compounds (e.g., avermectin) dissolved in solvents such as toluene, methanol, ethanol, hexane. Solvent-based liquid streams will be recovered within the process to the extent feasible to minimize any potential release of organic compounds to the environment. Solvent-based wastes will either be sent off-site for disposal to a permitted facility, or disposed of in an on-site permitted incinerator. The incineration process is subject to and in compliance with the Pennsylvania Rules and Regulations for the Protection of the Environment, Title 25, Part I, Subpart C, Article I, Land Resources, Chapter 75, Solid Waste Management and Article III, Air Resources and 40 CFR Parts 264 and 265, Standards Applicable to Owners and Operators of Hazardous Waste

Treatment, Storage and Disposal Facilities. The incineration process is also subject to and in compliance with the site's hazardous waste (RCRA) permit #PAD003043353 and Operating Permit #49-301-018 (expiration date: 4/30/98).

The aqueous-based waste streams consist of spent fermentation broth and wash waters that contain unconsumed fermentation nutrients, unrecovered by-products and traces of avermectins and dissolved solvents such as hexane, methanol, ethanol, and toluene. The aqueous-based streams are treated using caustic in an on-site high pressure, high temperature reactor designed to destroy residual avermectins. The effluent from the high pressure reactor is further treated in an on-site two-stage biological waste water treatment plant before being discharged into the North Branch of the Susquehanna River. The final plant effluent is discharged under the requirements of and in compliance with NPDES Permit No. PA 0008419 (expiration date: 9/99) which is administered by the Pennsylvania Department of Environmental Protection. The amount of avermectin released into the Susquehanna River is below levels of environmental concern based on toxicity testing.

c) Solid Waste Controls and Citations - Bulk Drug Substance Manufacture

Dry solid waste (such as paper, trash, and HEPA filters) from the avermectin production process is disposed of by either on-site or

off-site incineration. On-site incineration of solid waste is subject to and operated in compliance with the regulations for air emissions of the Pennsylvania Department of Environmental Protection (Title 25, Part I, Subpart C, Article III, Air Resources).

d) Employee Protection

Material Safety Data Sheets (MSDS) are available on-site for all chemicals required by the Occupational Safety Act of 1971 and the Hazards Communication Act of 1985. Employees associated with the manufacturing of avermectin have appropriate MSDS available for their review. Employee protective clothing, such as gloves, uniforms, and safety shoes, and protective equipment, such as safety glasses, are used during the manufacturing process to assure compliance with the Occupational Safety Act (OSHA) of 1971 and the Hazards Communication Act of 1985.

To minimize worker exposure to avermectin, the following monitoring activities are conducted:

(1). At least bi-annual monitoring of dust levels for avermectin where avermectin powder is handled; and

(2) At least monthly wipe test on equipment, floors and production bottles in the production area.

3) Barceloneta, Puerto Rico

a) Air Emission Controls and Citations - Bulk Drug Substance Manufacture

Air emissions generated during the production process will consist of volatile organic compounds such as ethanol, formamide, and toluene which will be controlled as appropriate by condensers. Exhaust air in the process building and the formulation and sterile areas will be filtered. Air emissions are subject to and in compliance with the Puerto Rico Environmental Quality Board under the "Regulations for the Control of Atmospheric Pollution." Manufacture of drug substance is also in compliance with conditions under permit number PFE-09-1291-1668-I-II-0.

b) Liquid Emissions Controls and Citations - Bulk Drug Substance Manufacture

The manufacturing process generates two types of liquid waste streams: a combination of solvent-based waste streams, and a combination of aqueous waste streams.

The solvent-based streams are generated in the chemical processing steps. They will contain discarded organic compounds dissolved in solvents such as ethanol, formamide, toluene and water. The solvent-based streams will be destroyed by incineration. The on-

site incineration process will be subject to and in compliance with the Puerto Rico Environmental Quality Board (EQB) Regulations for the Control of Atmospheric Pollution and the U.S. EPA regulations for the control of hazardous waste, 40 CFR Parts 264 and 265. Currently, the solvent incinerator operates under a permit number PRD 090028101 issued by the EQB Hazardous Waste Program and under EQB Permit No. PFE-09-1291-1668-I-III-0 issued by the EQB Air Program

The aqueous-based waste stream consists of wash waters generated by equipment washings. Holding tanks are provided to contain these washes prior to testing and disposal. Depending on the ivermectin concentration, the holding tank contents will be managed in one of two ways:

(1) Contents are tested for ivermectin and recycled through a filter until a specified level is reached, and then are discharged to the chemical sewer; or

(2) contents are incinerated.

Effluent from the Barceloneta plant is discharged to the Barceloneta Regional Wastewater Treatment Plant (BRWTP) under permit #GOA-93-202-045. The BRWTP operates under the requirements of NPDES permit #0002137 which is administered by EPA.

c) Solid Waste Controls and Citations - Bulk Drug Substance Manufacture

Solid wastes, such as paper, trash, and HEPA-type filters etc., generated at the Barceloneta plant as a result of drug substance manufacture are subject to, and in compliance with, the regulations for solid waste disposal of the Puerto Rico Environmental Quality Board (EQB).

Non-hazardous solid waste (general trash, paper and plastics) is disposed of on-site in a solid waste incinerator. The incinerator is subject to and in compliance with the Regulations for the Control of Solid Waste administered by the EQB and permits PFE-09-1291-1668-I-III-O issued by the EQB Air Program and SI-93-0004 (expiration date: 4/14/96) issued by the EQB Solid Waste Program.

d) Employee Protection

Material Safety Data Sheets are available on-site for all chemicals required by the Occupational Safety Act of 1971 and the Hazards Communications Act of 1985. Employees associated with the manufacturing of drug product have appropriate MSDSs available for their review. Employee protective clothing (such as gloves, uniforms, safety glasses, safety shoes, and protective equipment) is used during the manufacturing process of drug product to assure compliance with the Occupational Safety Act of 1971 and the

Hazards Communication Act of 1985. To minimize worker exposure to ivermectin, the following monitoring activities will be conducted:

(1) At least semi-annual monitoring of dust levels where ivermectin powder is handled;

(2) Wipe tests are performed to verify the cleanup of spills in the manufacturing area.

4) Haarlem, Holland

a) Air Emissions Controls and Citations - Drug Product Formulation and Primary Packaging

Air emissions generated during the formulation of human ivermectin consist of volatile organic compounds (such as ethanol) and dust. Air from the process building, formulation area sterile facility is exhausted through HEPA-type filter prior to discharge to the atmosphere to control particulate emissions of ivermectin powder (drug substance). The manufacturing is regulated, and in compliance with the Air Pollution Act.

b) Liquid Emissions Controls and Citations - Drug Product Formulation and Primary Packaging

Liquid waste streams containing ivermectin are generated in the formulation and packaging of the drug product. Small quantities of organic solvents, such as ethanol and water, from equipment cleaning and wipedowns are generated. Waste organic solvents are collected and sent to the Rotterdam incinerator. The disposition of organic solvents is in compliance with the Hazardous Waste Act and the Waste Act.

Any aqueous waste resulting from manufacturing the drug product will be collected and treated with an activated carbon purification unit to remove the ivermectin. The wastes will then enter the plant's general waste system which includes domestic sewerage and will go via a neutralization pit (pH >6.5) to the municipal sewerage treatment plant. This plant operates under the control of the Hoogheemraadschap van Rynland. MSD has a permit #1420('86)V26580 (granted June 11, 1987 with no expiration date) from the municipality for entering the sewerage treatment plant with their plant effluent. The wastewater discharge is regulated by, and in compliance with, the "Wet Verontreiniging Oppervlaktewateren" which includes the Waste Water Regulations. Spent activated carbon from the filter system will be collected in

plastic bags, put into drums, and handled as a hazardous waste as described below.

c) Solid Emissions Controls and Citations - Drug Product Formulation and Primary Packaging

Solid waste resulting from production and packaging of the drug product, such as HEPA-type filters and spent activated carbon, will be combined with other plant trash and transferred via closed vehicle to the Rotterdam incinerator. A permit for transport and incineration is issued by the provincial authorities under the laws regulating transport and processing of solid wastes.

Management of solid waste from manufacturing is regulated, and in compliance with, the "Wet Milieubeheer" which includes: the Air Pollution Act; the Hazardous Waste Act; the Waste Act; and the Waste Regulation.

d) Employee Protection

Material Safety Data Sheets (MSDS) are available for all chemicals required by the Dutch Safety Law (Arbo Law) and the Dutch Safety Rules for Industry and Workshops. Employees associated with the formulation and packaging of ivermectin have appropriate MSDS available for their review. As additional worker protection,

monthly swab tests are performed for ivermectin on equipment, floors, and production bottles in the production area.

Manufacturing is regulated by, and in compliance, with the Dutch Safety Law (Arbo Law) and the Dutch Safety Rules for Industry and Workshops.

5) West Point, Pennsylvania

a) Air Emission Controls and Citations - Drug Product Disposal

The on-site incineration facility employs necessary operating conditions as to ensure compliance with permitted emission levels. As a contingency, off-site incineration will be conducted at a permitted facility.

The air emission controls for the disposal of this product meet the requirements of the Pennsylvania Air Pollution Control Regulations under Title 25 of the Pennsylvania Code, Part I - Department of Environmental Protection (PA DEP), Chapters 121-141.

Approval of the proposed action will not impact the facility's ability to comply with the above stated requirements. No new permit limits are anticipated as a result of the proposed action.

b) Liquid Waste Controls and Citations - Drug Product Disposal

The liquid from incineration operation will be discharged into the site wastewater collection system and will undergo pretreatment along with other sanitary waste. This wastewater is discharged for further treatment to the UGTA. The treated effluent is discharged from the UGTA under NPDES Permit Number PA 0023256. This permit is administered by PA DEP.

The wastewater is subject to, and in compliance with, the pretreatment standards for existing sources of the Pharmaceutical Manufacturing Category under Title 40 of the Code of Federal Regulations Part 439. The wastewater is also regulated by the UGTA and is in compliance with the existing contract and the "Rules and Regulations Governing the Discharge of Sanitary and Industrial Wastewaters into the Public Sewers of Upper Gwynedd Township Authority." These regulations are based on the requirements of the Federal Clean Water Act and Pennsylvania Clean Streams Law. The current contract with UGTA (expiration 9/30/98) limits plant effluent to a flow (calculated from a monthly average) of 1.255 million gal/day; BOD = 250 mg/L (daily maximum); TSS = 300 mg/L; and pH between 5.5 - 9.0. Approval of the proposed action will not impact the facility's ability to comply with the above stated requirements and no new permit limits are anticipated as a result of the proposed action.

c) Solid Waste Controls and Citations - Drug Product Disposal

Appropriate controls for the disposal of unused market packages are utilized as part of the site solid waste management program. The waste is incinerated at permitted disposal facilities. Ash generated from the on-site incineration process is disposed of at a permitted facility and is monitored to confirm its acceptability with prevailing solid waste regulations.

Solid waste management at the West Point plant requires conformance with conditions set forth in Permits 400674 (expiration date: 1/25/2003) and 400459 (expiration date: 6/16/2005) issued by PA DEP and Permit PAD002387926 (expiration date: 4/15/2002) issued by both EPA and PA DEP. These requirements assure comprehensive control for management of waste throughout the plant including returned market packages. The requirements of the Pennsylvania Code, Title 25, Part I - Department of Environmental Protection, Chapter 75, are the primary regulations which impact solid waste management. The regulations are subject to the requirements of the Federal Resource Conservation and Recovery Act, the Federal Hazardous and Solid Waste Amendments, and the Pennsylvania Solid Waste Management Act.

Approval of the proposed action will not impact the facility's ability to comply with the above stated requirements.

d) Employee Protection

Material Safety Data Sheets are available on-site for all chemicals required by the Occupational Safety Act of 1971, the Hazards Communication Act of 1985 and Title 29 Code of Federal Regulations Part 1910.1200. Employees associated with the manufacture of drug substance have appropriate MSDSs available for their review. Employee protective clothing, such as gloves, uniforms, and safety glasses are used during the manufacturing process to assure compliance with the Occupational Safety Act of 1971 and the Hazard Communication Act of 1985 and Title 29 Code of Federal Regulations, Subpart I.

b. As a Result of the Use of MECTIZAN (ivermectin)

The projected use of MECTIZAN (ivermectin) for the treatment of strongyloidiasis and onchocerciasis involves oral administration of a single dose consisting of one to three 6 mg tablets depending on the patient's body weight. The annual demand for MECTIZAN (ivermectin), 6 mg for use in the treatment of strongyloidiasis and onchocerciasis in the United States will be very low. Based on the indicated dose, this corresponds to an extremely small quantity of

ivermectin annually on an incremental use basis (see Confidential Appendix III - Part 1). This amount is only a very small percentage (less than 0.1%) of the estimated amount of ivermectin used for human health purposes worldwide and represents an even much smaller percentage of the ivermectin produced for veterinary use. Human health use of ivermectin will not result in emissions to either the terrestrial or atmospheric compartments.

c. As a Result of the Disposal of MECTIZAN 6 mg (Ivermectin, MSD)

The Merck West Point, Pennsylvania incineration facilities will be used to treat returned product. On-site incineration facilities will handle the majority of this waste with resulting combustion efficiency of at least 99.9% on an hourly basis. In the event that the West Point facility is unable to accept such waste, the wastes will be disposed of at an alternate permitted off-site facility. The expected emissions from the disposal site are described below.

(1) Air Emissions - Particulates and vapors (carbon dioxide, water vapor, etc.) are expected to be emitted into the atmosphere from the incineration of returned goods. The on-site West Point facility incineration operation is in compliance with all applicable standards and permit limits. Any off-site incineration will be conducted at an equivalent, permitted facility.

(2) Liquid Emissions - Any wastewater generated from the incinerator operation will be discharged into the sanitary sewer which undergoes on-site pretreatment for equalization and is discharged for off-site biological wastewater treatment at the UGTA.

(3) Solid Emissions - All returned and outdated market packages and residual ivermectin waste from operations at West Point will be incinerated at on-site or off-site facilities permitted to handle such waste streams.

d. Effect of Application Approval on Compliance with Current Emissions Requirements

Merck & Co., Inc. states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of ivermectin at its facilities in Elkton, Virginia; Danville, Pennsylvania; and Barceloneta, Puerto Rico and the production of MECTIZAN (ivermectin) at Haarlem, Holland as well as emission requirements set forth in applicable federal, state, and local statutes and regulations applicable to the production of ivermectin at its facilities in Elkton, Virginia; Danville, Pennsylvania; and Barceloneta, Puerto Rico and the production of MECTIZAN at

Haarlem, Holland and the incineration of returned goods at its facility in West Point, Pennsylvania.

7. Fate in the Environment

MECTIZAN (ivermectin) is derived from the avermectins, a class of highly active broad-spectrum antiparasitic agents isolated from fermentation broths of *Streptomyces avermitilis*. Environmental assessments have previously been prepared in connection with the approval of the use of avermectins in veterinary and agricultural applications. Environmental Assessments for ivermectin submitted to the FDA (CVM) have universally resulted in "findings of no significant impact" (FONSIs). Moreover, detailed assessment of ivermectin's effect on the environment has been a major component of the overall program to develop ivermectin as an antiparasitic drug for food producing animals. Extensive studies have been conducted. These were specifically designed to determine the extent of ivermectin's impact on the environment. Ivermectin's mobility, distribution and stability in soil and water were measured. Other studies investigated the drug's effect on a variety of environmentally important organisms including bacteria, invertebrates, fish, plants, etc. Combined with the clinical use pattern of ivermectin in livestock and man, these provide the means to assess ivermectin's environmental impact.

Information which supports the present Environmental Assessment can also be found in assessments prepared for previously approved products including:

Product	NADA	Approved
IVOMEC (ivermectin) Injection for Cattle	128-409	02/13/84
EQVALAN (ivermectin) Paste for Horses	134-314	05/21/84
IVOMEC (ivermectin) Injection for Swine	135-008	07/22/86
IVOMEC (ivermectin) Pour-On for Cattle	140-841	12/04/90

Relevant sections of those assessments have been summarized and are included herein.

a. Photodegradation

Halley (1990) used a high-pressure xenon arc lamp to simulate sunlight and calculated that ivermectin would photodegrade near the surface of open, flat bodies of water under clear skies in summer and winter sunlight with half lives of 12 and 39 hours, respectively. This rapid photodegradation in water should effect

swift elimination of ivermectin from the aquatic environment. Based upon data from a preliminary study, ivermectin undergoes photodegradation as a thin, dry film on glass with an estimated $t_{1/2}$ of about 3 hours in summer sunlight (Yeager and Halley, 1988). Avermectin B_{1a} possesses an absorption maximum similar to that of ivermectin (Sec. 5), with less intense longer wavelength absorption at approximately 290 and 350 nm (Halley, 1990), and photodegrades on soil TLC plates with a half life of 21 hours (Ku and Jacob, 1983a). Rapid photodegradation is consistent with the rapid loss of avermectin B_{1a} from cotton leaves (Bull et al., 1984).

b. Soil Binding

Ivermectin has been classified as "tightly bound" to soil [K_{OC} 12,578 with clay loam soil (Iowa)] and hence considered immobile (Halley, 1985). Consequently, the possibility of translocation of ivermectin through soil from one site to another in the environment is remote. It was also demonstrated that toxicity of ivermectin (Ostlind and Cifelli, 1980) and avermectin B_1 (Forbis, 1989) toward Daphnia is greatly attenuated (99%) in the presence of soil. These results agree with the known immobolization of ivermectin (Halley, 1985) and avermectin B_1 (Ku and Jacob, 1983a) on soil. When ivermectin was partitioned between water and Iowa soil, a soil to water distribution of 333 was found, predicting that 99.7%

of the drug would be bound, with only 0.3% in solution (Halley, 1985).

c. Fate in Soil and Vegetation

Laboratory studies (Bull et al., 1984) have shown that under aerobic conditions in soil [^{3}H]avermectin B_{1a} degrades to at least thirteen radioactive products; half lives for the drug (at 1 ppm) in Lufkin fine sandy loam, Houston clay and coarse sand soils are 14-28, 28-56, and 56 days, respectively. The major degradation product is an approximately 1:2.5 equilibrium mixture of 8a-hydroxyavermectin B_{1a} (an acetal) and the corresponding ring-opened aldehyde. At all treatment levels in Lufkin fine sandy loam, 90% degradation of [^{3}H]avermectin B_{1a} occurs within 168 days of exposure. Avermectin B_{1a} is strongly adsorbed by ditch-bottom sludge (Vonk and Van den Hoven, 1985) and other soil types and is immobile (Ku and Jacob, 1983b).

Low levels ($\leq$0.1 ppm) of radioactivity were found in the leaves and stems of cotton seedlings grown in Lufkin fine sandy loam containing 10 ppm of [^{3}H]avermectin B_{1a}; some radioactivity ($\geq$3 ppm) was found on the seedling roots, but whether it was absorbed or adsorbed was not determined (Bull et al., 1984). Little radioactivity from labeled avermectin B_{1a} or its degradates was taken into the vascular system of the cotton seedlings. This low

level of uptake is consistent with the observed lack of phytotoxicity for a number of other plant species grown in soil containing avermectin B_1. The observed lack of pronounced systemic insecticidal activity for ivermectin and avermectin B_1 also indicates little or no uptake of these compounds by plants.

Tritiated avermectin B_{1a} was found to undergo rapid depletion and degradation when applied to the leaves of cotton plants (Bull et al., 1984). Little more than half of the applied radioactivity was still present on the leaf at 2 days post treatment, and only one-third of this was avermectin. At this time, roughly 5% of the applied radioactivity was found within the leaves. By eight days post treatment, only 13% of the applied radioactivity was found on the leaf surfaces, and only 15% of this residue was avermectin; 8% of the dose was within the leaves. The authors suggest that the rapid loss of applied labeled avermectin B_{1a} and its instability are related to the known photolability of this compound. A non-polar photodegradation product of avermectin B_{1a} has been identified as the $\Delta^{8,9}$-isomer (Ku and Jacob, 1983).

The slight uptake by cotton seedlings of radioactivity from soil containing [^{3}H]avermectin B_{1a}, reported by Bull et al. (1984), suggests that if soil were to contain the close structural analog ivermectin, uptake of the latter by plants grown in the soil would also be minor. Data from Bull et al. (1984) concerning lack of

uptake of radioactivity by grass from a plot treated with [^{14}C]avermectin B_{1a} ant bait formulation also support this contention. In addition, studies comparing the pesticidal activities of directly applied vs. systematically applied (soil) avermectin demonstrated little or no uptake of the agent from soil.

Moye and coworkers (1987) reported radioactive residues in crops (sorghum, lettuce, carrots and turnips) grown in three types of soil to which [^{14}C]avermectin B_{1a} had been applied 3 to 12 times at 0.025 to 0.030 lb/acre/application. Radioassay of the crops indicated a maximum total residue of 14 ppb. As only 4.4% of the total radioactive residue in a lettuce leaf was extractable with acetone, it is clear that most of the residual radioactivity is either chemically different from avermectin B_{1a} or present in a strongly bound form (probably incorporated into the vegetable matter as small molecules resulting from breakdown of the avermectin B_{1a}).

Iwata et al. (1985) reported that the initial rate of avermectin B_{1a} degradation on citrus fruits and leaves is very rapid. Total residue dissipation half lives were 50 days (lemon leaves), 58 days (orange rind) and 36 days (lemon rind). Comparison of total radioactive residues with percentage avermectin B_{1a} showed continuing degradation of the actual avermectin B_{1a} present in the residues. Comparison of pulp and rind radioactive residues indicated lack of translocation from the rind into the edible portion of the fruits.

Residue levels (total radioactivity) were less than 0.004 mcg/g (limit of detection) in new growth leaves from tips of branches whose mature leaves had been immersed in a [^{3}H]avermectin B_{1a} solution (3 mg/mL) 91 days earlier. It is reasonable to assume that the extent of translocation (both leaf to leaf, and rind to pulp) of ivermectin would also be very slight. Ivermectin would also be expected to exhibit a short persistence on fruit surfaces because of photodegradation

d. Fate Summary

Photodegradation, combined with oxidative degradation in soil under aerobic conditions, will diminish the extent of environmental contamination by ivermectin. Human drug use of ivermectin is unlikely to result in contamination of surface water and, as movement of ivermectin through soil is slight, contamination of surface and subterranean water is highly improbable. Binding of ivermectin to soil sediment in water greatly reduces its effective concentration. Based on the discussion of soil binding, soil metabolism and photodegradation, it can be predicted that ivermectin present in the environment would not be expected to undergo significant movement or translocation, and should not accumulate. Given its environmental fate characteristics, ivermectin will be readily eliminated from the aquatic environment.

8. Effect on the Environment:

a. Aquatic Toxicity

The effects of ivermectin, avermectin and related compounds upon a number of aquatic species (including Daphnia), as determined in laboratory tests, are reported in Table 1. Ivermectin and avermectin B_1 show comparable aquatic toxicity. However, ivermectin is more toxic to daphnids than is avermectin B_1. Daphnia, the freshwater aquatic species most sensitive to ivermectin, have been used for risk assessment purposes. The concentrations at which toxicities are observed in these tests should be regarded as "worst-case" values because factors (i.e., binding to soil and other particulate matter, and photodegradation) known to reduce exposure under field conditions are absent. Ivermectin and avermectin show comparable mammalian toxicity (Lankas and Gordon, 1989).

1) Daphnia

a) Toxicity

The 48-hr LC_{50}, 48-hr NOEL and calculated 21-day MATC values for ivermectin toward Daphnia are 0.025, ~0.010 and 0.004 ppb, respectively (see Table 1). As indicated in 7.b., the presence of

soil in the test system reduced the toxicity of ivermectin and avermectin B_1 toward Daphnia.

It is clear that the environmental fate characteristics of ivermectin, and the very limited use of the drug in humans, make it highly unlikely that environmental concentrations as a result of the proposed action will reach levels toxic to any aquatic species, including Daphnia. Data in Table 1 also support the view that ivermectin-related compounds such as its monosaccharide and aglycone and feces/soil column percolates which contain ivermectin degradation/metabolites are much less toxic than the parent compound (based on 48-hr. LC_{50} data for the former, and 48-hr. NOEL data for the percolates). Avermectin B_1 is less toxic toward Daphnia than is ivermectin, and the known degradation products of avermectin B_{1a} (i.e., the $\Delta^{8,9}$ isomer and the 8a-hydroxy compound) are also much reduced in toxicity toward Daphnia compared to their parent compound (Forbis, Georgie and Burgess, 1985a and b, respectively).

2) Fish

a) Toxicity

Fish are at least 100-fold less sensitive to the toxicity of ivermectin than are Daphnia. Ivermectin 96-hr LC_{50} values, corrected for

assay, (Table 1) for rainbow trout and bluegill sunfish are 3.0 and 4.8 ppb, respectively, far higher (factor of at least several orders of magnitude) than the extremely low concentrations that might occur with ivermectin in ponds and streams because of the use of this drug in the treatment of strongyloidiasis and onchocerciasis. In general, the acute toxicity of avermectin toward fish [e.g., LC_{50} values of 3.6 and 9.6 ppb for rainbow trout (Sousa, 1981) and bluegill sunfish (Wilson, 1981), respectively] is similar to that exhibited by ivermectin.

b) Bioconcentration in Sunfish

The bioconcentration of [^{3}H]avermectin B_{1a} by the bluegill sunfish is modest and occurs gradually (Forbis and Franklin, 1983). In water containing 0.099 mg of test compound per liter (0.099 ppm) the daily bioconcentration factor for whole fish was only 19 to 69, with an uptake tissue concentration for whole fish of 1.9 to 6.8 ppb; accumulation ceased by about day ten. A 95 percent clearance rate of radioactivity for whole fish was found for a 14-day depuration period; the whole-fish concentration dropped from 6.8 to 0.32 (day 14). This bioconcentration value of less than 100 and the rapid rate of depuration are favorable, as they demonstrate that concentration and retention of avermectin B_{1a} (and hence ivermectin) in fish should not be an environmental concern.

3) Toxicity Toward Other Aquatic Species

The toxicity of ivermectin and avermectin toward other aquatic species is also presented in Table 1. Ivermectin has a moderate effect upon the growth characteristics of *Chlorella pyrenoidosa*, a fresh water unicellular, non-motile chlorophyte, at the relatively high concentrations of 1 to 10 ppm (Halley et al., 1989). Avermectin B_1 exhibits 14- and 9-day EC_{50} values of 3,900 and 100,000 ppb, respectively, with duckweed and a freshwater algae, *Selenastrum capricornutum* (see Table 1).

TABLE 1

EFFECT OF IVERMECTIN,
AVERMECTIN AND RELATED COMPOUNDS UPON AQUATIC SPECIES

COMPOUND	SPECIES	EFFECT	REFERENCES
Ivermectin	Daphnia	48-hour LC_{50} 0.025 ppb	Halley et al., 1989
Ivermectin (H_2B_{1a}) monosaccharide	Daphnia	48-hour LC_{50} 0.400 ppb	Halley et al., 1989
Ivermectin (H_2B_{1a}) aglycone	Daphnia	48-hour LC_{50} >17 ppb[a]	Halley et al., 1989
Ivermectin	Daphnia	48-hour NOEL ~0.010 ppb	Halley et al., 1989
Feces from ivermectin-dosed steer[b]/soil column percolates	Daphnia	48-hour NOEL ~3.2 ppb[c]	Halley et al., 1989
Ivermectin	Bluegill Sunfish	96-hour LC_{50} 4.8 ppb	Forbis, A.D., 1983
Ivermectin	Rainbow Trout	96-hour LC_{50} 3.0 ppb	McAllister, W.A., 1986
Avermectin B_1	Daphnia	48-hour LC_{50} 0.34 ppb	Surprenant & LaBlanc, 1981
Avermectin B_{1a}	Bluegill Sunfish	Estimated Lethal Threshold 6.7 ppb, NOEL 2.3 ppb (Dynamic 7-Day Toxicity Study)	Forbis, 1983
Avermectin B_1	Carp	96-hour LC_{50} 42 ppb	Douglas and Pell, 1985

TABLE 1 (Continued)

Avermectin B_1	Channel Catfish	96-hour LC_{50} 24 ppb	McAllister et al., 1985
Avermectin B_1	Mysid Shrimp	96-hour LC_{50} 0.022 ppb	Surprenant, D., 1988a
Avermectin B_1	Sheepshead Minnow	96-hour LC_{50} 15 ppb	Ward, 1985
Avermectin B_1	Oyster	48-hour EC_{50} 430 ppb	Ward, 1983
Avermectin B_1	Bluegill Sunfish	96-hour LC_{50} 9.6 ppb	Wilson, 1981
Avermectin B_1	Rainbow Trout	96-hour LC_{50} 3.6 ppb	Sousa, J.V., 1981
$\Delta^{8,9}$-Avermectin B_{1a} (photochemical degradation product of avermectin B_{1a})	Daphnia	48-hour LC_{50} 14 ppb	Forbis et al., 1985a
8α-Hydroxyavermectin B_{1a} (aerobic soil degradation product of avermectin B_{1a})	Daphnia	48-hour LC_{50} 26 ppb	Forbis et al., 1985b
Avermectin B_1	Daphnia (Life Cycle)	21-day MATC 0.03-0.09 ppb ACR[d] 6.5	Surprenant, D.C., 1984
Ivermectin	Daphnia (Life Cycle)	Estimated MATC 0.004 ppb	Calculated value[e]

TABLE 1 (Continued)

Avermectin B_1	Mysid shrimp (Life Cycle)	28-day MATC 0.0035-0.0095 ppb ACR 3.8	Surprenant,D.C.,1988b
Avermectin B_1	Rainbow Trout (ELS)	MATC 0.52-0.96 ppb ACR 4.6	McAllister, W.A., 1986
Avermectin B_1	Duckweed	14-day EC_{50} 3900 ppb	Hollister, 1981a
Avermectin B_1	*Selenastrum capricornutum*	9-day EC_{50} 100,000 ppb	Hollister, 1981b
Ivermectin	*Chlorella pyrenoidosa*	Maximum Growth Rate, No Effect at 10,000 ppb	Halley et al., 1989

Notes:

[a] LC_{50} could not be determined accurately as the highest concentration of the aglycone studied was 17 ppb.

[b] Feces from steers dosed with radiolabeled ivermectin were mixed with soil and applied to the tops of soil columns. Water was allowed to percolate through the columns; collected water contained no (<0.010 ppb) ivermectin, which binds to top of column.

[c] Because the low concentrations of ivermectin-related compounds in the feces/soil column percolates limited the extent of testing, sufficient data could not be collected to calculate the LC_{50} value accurately.

[d] ACR = Acute to Chronic Ratio; LC_{50}/MATC (Maximum Acceptable Toxicant Concentration).

[e] An estimated MATC for ivermectin was calculated from the 21-day MATC for avermectin (0.03 to 0.09 ppb; geometric mean of 0.052 ppb) and the ratio of the ivermectin and avermectin 48-hr. LC_{50} values for Daphnia (0.025 and 0.34 ppb, respectively): X/52 = 25/340; X = 0.004 ppb.

b. Other

An overview of the pharmacology of ivermectin and information on the toxicity of ivermectin to soil microbes, plants, various aquatic organisms, nematodes, arachnids, insects, and annelids, as well as a literature review, can be found in the Environmental Assessment for IVOMEC® (ivermectin) Injection for Swine (NADA 135-008). The present Environmental Assessment supplements this with recent information on ivermectin and supporting information on avermectin B_1.

The low phytotoxicity toward six plant species (cucumber, lettuce, soybean, perennial ryegrass, tomato, and wheat) has been demonstrated with ivermectin in both a seed germination and root elongation study (Feutz and Stuerman, 1995a) and a seedling growth study (Feutz and Stuerman, 1995b,). The results (NOEC values) from the studies are presented below. All NOEC values were based on mean measured concentrations.

Table 2: Seed Germination and Root Elongation Phytotoxicity Study with Ivermectin

Species	NOEC, ppm	
	Germination	Root Elongation
Cucumber	≥980	98
Lettuce	≥980	≥980
Soybean	≥930	≥930
Perennial Ryegrass	≥980	98
Tomato	≥980	≥980
Wheat	≥930	≥930

Table 3: Seedling Growth Phytotoxicity Study with Ivermectin in Sand

Species	NOEC, ppm		
	Shoot Length	Shoot Weight	Root Weight
Cucumber	0.68	0.68	≥790
Lettuce	6.9	0.68	≥790
Soybean	≥790	6.9	≥790
Tomato	0.68	0.68	0.68
Wheat	6.9	0.68	0.56

In addition, a seedling growth study was conducted with perennial ryegrass in sand and sandy loam soil (Feutz and Stuerman, 1995b). The low phytotoxicity of ivermectin to perennial ryegrass was further reduced by approximately 2000-fold, as measured by

the NOEC for shoot weight (the most sensitive parameter) in sandy loam soil relative to that in sand.

Table 4 Seedling Growth Phytotoxicity Study for Perennial Ryegrass with Ivermectin

Growth Medium	NOEC, ppm		
	Shoot Length	Shoot Weight	Root Weight
Sand	7.7	0.57	≥780
Sandy Loam Soil	≥1100	≥1100	≥1100

Both ivermectin and avermectin are toxic toward a wide variety of agricultural pests including the Mexican bean beetle, Southern army worm, aphids, and mites. The effect of ivermectin upon animal ectoparasites including flies, fleas, lice, ticks, and mites has also been determined (Fisher and Mrozik, 1984). A review article by Strong and Brown (1987) discusses the avermectins in insect control.

Avermectin B_1 has no effect upon nitrification in humic sandy or loam soils at up to 0.4 mg/kg soil, or 0.4 ppm (Barug and Van Agteren, 1985). There was no effect upon nitrification or respiration (Halley et al., 1989) for soil containing 30 ppb of fecal ivermectin and metabolites from subcutaneously dosed (300

mg/kg) steers. These are much greater concentrations than would be found in the environment from human health use.

Avermectin B_1 was found to impair the total gas production and the methane production of anaerobic methane-forming bacteria above a concentration of 1000 mg/L (Hanstveit, et al., 1985) (1000 ppm, the NOEC). The EC_{50} for total gas production was determined (by extrapolation) to be >>3200 mg/L; a significant inhibition of methane production rate could not be detected. These are concentrations far above any anticipated to arise in the environment.

The LC_{50} earthworm toxicity for ivermectin is 315 mg/kg soil (315 ppm) and the corresponding 96-hr. NOEL is 12 ppm (Halley et al., 1989). These are much greater concentrations than would be found in the environment from human health use.

c. Effects Summary

Because of 1) the very limited amount of ivermectin introduced into the environment through its use as an anthelmintic for humans, and 2) its rapid elimination from the environment, there will be no undesirable, adverse effect of this drug with respect to aquatic species or other life forms in the environment.

d. Toxicology

Ivermectin has been tested for acute oral toxicity in a variety of laboratory animal species (Lankas and Gordon, 1989). Acute toxic effects are characterized by signs of CNS toxicity including tremors, mydriasis, and lethargy. The acute oral LD_{50} values range from about 80 mg/kg in dogs to about 30 mg/kg in mice. The dermal LD_{50} values for ivermectin following 24-hour occluded exposure in rabbits and rats are 406 mg/kg and >660 mg/kg, respectively. The oral LD_{50} of ivermectin in mice is approximately 30 mg/kg.

In assessing the toxicity of ivermectin, it is important to note that rodents, and mice in particular, are poor models for predicting effects of ivermectin in humans. For example, doses of ivermectin of 0.2 mg/kg produce clinical signs of drug effects (tremors and ataxia) in mice (Lankas and Gordon, 1989). This dose (0.2 mg/kg) of ivermectin is used to treat onchocerciasis infections in humans. Since 1982, millions of people have been treated for onchocerciasis (0.15 - 0.2 mg/kg) with no serious drug-related adverse effects.

A comparison of acute exposure data in rhesus monkeys with humans suggests that primates are a better model for predicting the effects of ivermectin exposure in humans. In monkeys, the minimum acutely toxic oral dose is 2 mg/kg based on a 25%

incidence of emesis in treated animals (Lankas and Gordon, 1989). Peak plasma levels at this dose were 110 ng/ml or about 5-fold the human therapeutic plasma concentration. Doses of 8-24 mg/kg in monkeys produced mydriasis and sedation in addition to emesis with no deaths, despite plasma levels up to 680 ng/ml. These signs are similar to those reported in a carefully documented case of a child after accidental ingestion of about 8 mg/kg ivermectin. Emesis, mydriasis, and sedation were reported in this individual followed by complete recovery. Therefore, the primate is a better model for predicting the effects of human exposure to ivermectin than rodents. In addition, a 2-week repeat dose study in monkeys with ivermectin administered at dosage levels up to 1.2 mg/kg/day produced no evidence of toxicity.

Ivermectin was not genotoxic *in vitro* in the Ames microbial mutagenicity assay (*Salmonella typhimurium* strains) with and without rat liver activation, the mouse lymphoma cytotoxicity and mutagenicity assays and in the unscheduled DNA synthesis assay in human fibroblasts. Ivermectin had no adverse effects on fertility in rats at doses of up to eighteen times the maximum human dose (based on mg/kg/day). Long-term studies in animals have not been performed to evaluate the carcinogenic potential of ivermectin.

Developmental toxicity studies conducted with ivermectin in rats, rabbits, and mice have shown that the drug is not selectively toxic

to the fetus. No-effect levels for embryo/fetal toxicity were at or near those that produced severe maternotoxicity (Lankas and Gordon, 1989). Therefore, a risk assessment for developmental effects based on maternal exposure will provide even greater safety margins for developmental toxicity. This is supported by target animal safety studies conducted in a variety of domestic animal species treated at 2-fold or 3-fold the recommended use level of ivermectin with no evidence of developmental toxicity. In addition, extensive clinical use of ivermectin in these same species with over a billion doses administered to cattle, sheep, horses, swine, and dogs has confirmed the safety of this drug in pregnant animals. There are, however, no adequate and well-controlled studies in pregnant women.

e. Pharmacology

Ivermectin is metabolized in the liver and ivermectin and/or its metabolites are excreted almost exclusively in the feces over an estimated 12 days with less than 1% of the administered dose excreted in the urine. The plasma half-life of ivermectin in man is about 12 hours.

Ivermectin inhibits signal transmission from the ventral cord interneurons to the excitatory motor neurons in nematodes by stimulating release of the inhibitory neurotransmitter, gamma-

aminobutyric acid (GABA) from presynaptic nerve terminals. In arthropods, a similar mechanism inhibits signal transmission at the neuromuscular junction. Ivermectin does not readily penetrate the CNS of mammals, and thus, does not interfere with mammalian GABA-dependent neurotransmission.

In animal species studied (dog, swine, cattle, sheep), liver and fat contained the highest residues of ivermectin and little was found in muscle and kidneys. The unaltered drug was the major residue in the liver. The high degree of extractability indicates that there are few, if any, macromolecularly bound drug or metabolite residues. In various species, virtually all of the excreted drug-residue was eliminated in the feces.

9. Use of Resources and Energy

The raw materials used to manufacture MECTIZAN (ivermectin) are common organic compounds and pharmaceutical excipients which are generally regarded as safe (GRAS). The amounts of these which will be used for production of the human dosage form will be insignificant compared to the amounts consumed for other applications. Energy requirements for dosage form production is nominal and without environmental impact. Energy will also be used to transport the drug product and to dispose of wastes associated with this production, but the amounts involved will also

be negligible. The land to be used for production of the drug substance and the dosage form is already committed to production of other similar products.

Approval of the intended use of ivermectin for the treatment of strongyloidiasis and onchoceriasis will have no effect on any endangered or threatened species or upon property listed or eligible to be listed in the National Registry of Historic Places.

10. Mitigation Measures

The measures taken to avoid potential adverse environmental impacts associated with the manufacture of MECTIZAN (ivermectin) include proper disposal of liquid and solid waste as described in Section 6 of this Environmental Assessment. Moreover, the distribution, use and destruction of returned goods takes place under highly regulated and controlled conditions which further mitigate against adverse environmental consequences.

11. Alternatives to the Proposed Action

MECTIZAN (ivermectin) has been demonstrated to be generally well tolerated in the treatment of both strongyloidiasis and onchocerciasis. From an environmental prospective, use of MECTIZAN will result in negligible release of drug substance or

active metabolites and thus poses no environmental risk. Approval of MECTIZAN (ivermectin) for the indicated use is therefore preferable to non-approval, the only alternative to the proposed action.

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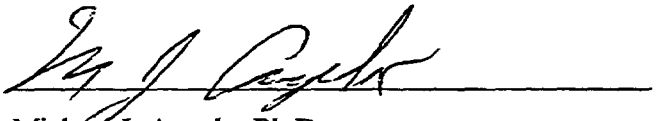
13. Certification:

The undersigned official certifies that the information presented is true, accurate and complete to the best of the knowledge of the firm responsible for preparation of the environmental assessment.



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Yeager, R.L. and B.A. Halley. 1988. "Photodegradation of Ivermectin (MK-0933) (H_2B_{1a} Component) as a Dry Thin Film by Sunlight", Internal Report - Merck Research Laboratories.

15. Supporting Information

a. Approved Ivermectin Products

Information which supports the present Environmental Assessment can be found in assessments prepared for the following previously approved products:

•IVOMEC® (ivermectin) Injection for Cattle, NADA 128-409; Approved 2/13/84 Federal Register, Vol. 49, No. 30, February 13, 1984, p. 5344

•EQVALAN® (ivermectin) 1.87% Paste for Horses, NADA 134-314; Approved 5/21/84 Federal Register, Vol. 49, No. 104, May 29, 1984, p. 22275

•IVOMEC® (ivermectin) Injection for Swine, NADA 135-008; Approved 7/22/86 Federal Register, Vol. 51, No. 136, July 16, 1986, p. 25686

•IVOMEC® (ivermectin) Pour-on for Cattle, NADA 140-841; Approved 12/04/90

Appendix I

A. Drug Substance Information Summary

1. Nomenclature

International Non-Proprietary Name

Ivermectin

U.S. Adopted Name

Ivermectin

Chemical Name

Ivermectin is a mixture of two closely related homologues belonging to a class of compounds known as avermectins.

Ivermectin contains

90% (min): 22,23-dihydroavermectin B_{1a}

10% (max): 22,23-dihydroavermectin B_{1b}

Laboratory Codes

MK-0933

Other Names

MECTIZAN™

Eqvalan®

Ivomec®

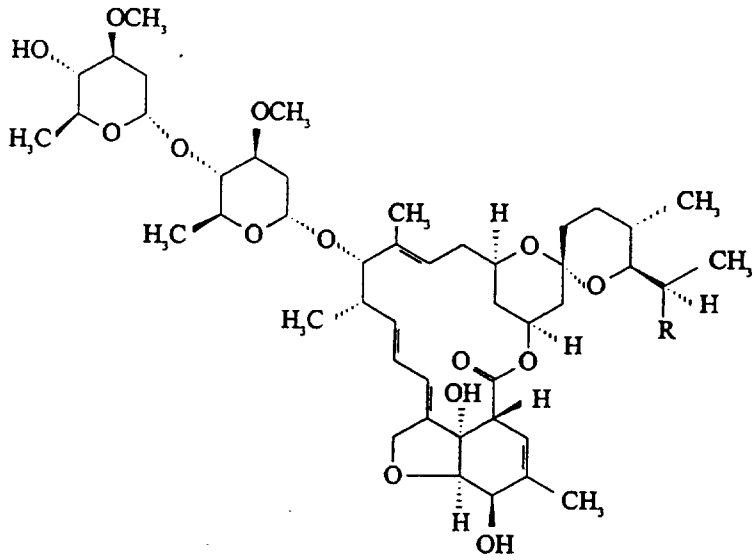
Heartgard 30®

Chemical Abstracts Service (CAS) Registry No.

70288-86-7

2. Description

Structural Formula



component B_{1a}: $R = C_2H_5$

component B_{1b}: $R = CH_3$

Molecular Formula/Molecular Weight

component B_{1a}	$C_{48}H_{74}O_{14}$	875.10
component B_{1b}	$C_{47}H_{72}O_{14}$	861.07

3. Environmental Fate

a. Solubility, Aqueous

4 mg/L

b. n-Octanol-Water Partitioning

$K_D = 1651$

c. Thermal Behavior

Melting Point ~155°C

d. UV - Visible Spectrum (Methanol)

Maximum at 245 nm with shoulders at ~237 and ~253 nm with A1%1cm values of about 382, 349 and 248 respectively.

e. Photolysis

Ivermectin is susceptible to photodegration in aqueous media. Calculated half-lives under clear sky conditions are

summer	12 hours
winter	39 hours

4. Environmental Effects

a. Aquatic Toxicity

There is an extensive body of literature on the aquatic toxicity of ivermectin and the avermectins. Representative studies with ivermectin are summarized below:

1) *Daphnia magna*

48-hour LC_{50} = 0.025 mcg/L
NOEL ~ 0.010 mcg/L

2) Bluegill Sunfish *(Lepomis macrochirus)*

96-hour LC_{50} = 4.8 mcg/L

3) Rainbow Trout *(Oncorhynchus mykiss)*

96-hour LC_{50} = 3.0 mcg/L

b. Toxicity to Earthworms

96-hour LC_{50} = 315 mg/kg soil

NOEL = 12 mg/kg soil

Appendix II

MSDS

MATERIAL SAFETY DATA SHEET

PRODUCT NAME: IVERMECTIN **PAGE: 1 OF 9**
PLANT MSDS CODE: PR-020 **Date: 1/96**

1. Chemical Product and Company Identification

Manufacturer---------- **MERCK SHARP & DOHME**
QUIMICA DE PUERTO RICO, INC.
P.O. BOX 601
BARCELONETA, PUERTO RICO; 00617

Emergency Telephone Number---- **(809) 846-3620 (P.R.)**
1-908-594-5555 (U.S.)

Label Name---------- Ivermectin

Chemical Name---------- Ivermectin (active ingredient) is a mixture of not less than 80% component B_{1a} (5-O-demethyl-22,23-dihydro-avermectin A_{1a}) and not more than 20% component B_{1b} (5-O-demethyl-de(1-methylpropyl)-22,23-dihydro-25-(1-methylethyl) avermectin A_{1a}).

Synonyms---------- Ivomec

Material Statistical Number---- Not available

Material Product Number-------- SP-2097

Intended Use---------- Antiparasitic agent

2. Composition/Information on Ingredients

Component	Molecular Formula	Molecular Weight	CAS Number	Percent (%)
Ivermectin Comp. Bla	$C_{48}H_{74}O_{14}$	875	70288-86-7	ca. 100
Comp. Blb	$C_{47}H_{72}O_{14}$	861	(mixture)	

EC Label---------- Not applicable

3. Hazards Identification

Appearance---------- Clear, moist, off-white to slightly yellow powder

Emergency Overview---------- CAUTION!
Antiparasitic agent.
Toxic if swallowed.
Harmful in contact with skin
May be harmful if inhaled.
Very toxic to aquatic organisms.

*** Continued on next page ***

Avoid contact of spilled material with soil. Do not allow any water potentially contaminated with ivermectin including storm water, runoff from spills and fire fighting activities and contaminated wastewater to enter any waterway, drain or sewer.

Potential Health Effects------- Overexposure to ivermectin may cause drowsiness, depressed motor activity, slowed breathing, dilation of the pupils, tremors, vomiting, anorexia and incoordination.

4. First-Aid Measures

Eye Contact---------- Flush with plenty of water for 15 minutes. Seek medical attention if irritation occurs.

Skin Contact---------- Wash with soap and water. Seek medical attention if symptoms appear.

Inhalation---------- In case of accidental overexposure, get to fresh air. If irritation occurs get medical attention.

Ingestion---------- If ingested, call a physician or Poison Control Center immediately. Drink one or two glasses of water and induce vomiting by gently touching the back of the throat with finger. Repeat until vomit fluid is clear. Do not induce vomiting or give anything by mouth to an unconscious person.

Note to Physicians---------- Since ivermectin is believed to produce effects that mimic enhancement of GABA activity in animals, it is probably wise to avoid drugs that enhance GABA activity (barbiturates, benzodiazepines, valproic acid) in patients with potentially toxic ivermectin exposure.

5. Fire-Fighting Measures

Flash Point ($^{o}C/^{o}F$)---------- Not applicable

Flash Point Test Method-------- Not applicable

*** Continued on next page ***

Flammable Limits-LEL (%)———	Not applicable
-UEL (%)———	Not applicable
Autoignition Temperature (°C/°F)-	Not available
Oxidizing Properties————	Not available
Combustibility Information——	Not available
Dust Explosivity Information——	Not available
Shock Sensitivity————	Not available
Fire/Explosion Hazards————	Material will burn if ignited. Can form explosive mixture with air in dusty conditions.
Extinguishing Media————	Use water spray or all purpose dry chemical. Water contaminated with ivermectin should be contained and not discharged to any waterway.
Special Fire Fighting Procedures-	Avoid creating significant airborne dust. Use full protective clothing and self-contained respiratory apparatus. Contain all water potentially contaminated with ivermectin. All exposed personnel and equipment should be decontaminated at the site.
Hazardous Decomposition Products Resulting From a Fire--	If involved in a fire, toxic gases including carbon monoxide and carbon dioxide may be generated.

6. Accidental Release Measures

Personal Precautions————	Immediately contact emergency personnel. Keep unnecessary personnel away. Use suitable protective equipment. (Section 8) Follow all fire fighting procedures (Section 5).
Environmental Precautions———	Ivermectin is very toxic to certain aquatic species. Avoid contact of spilled material with soil. Do not allow any water potentially contaminated with ivermectin including storm water, runoff from spills and fire fighting activities and contaminated wastewater to enter any waterway, drain or sewer.

*** Continued on next page ***

PRODUCT NAME: IVERMECTIN **PAGE: 4 OF 9**
PLANT MSDS CODE: PR-020 **Date: 1/96**

Methods for Cleaning Up——— If emergency personnel are unavailable, vacuum or carefully scoop up spilled material and place in an appropriate container for disposal by incineration. Avoid contact of spilled material with soil. Do not allow any water potentially contaminated with ivermectin including storm water, runoff from spills or fire fighting activities and contaminated wastewater to enter any waterway, drain or sewer. Residual surface material should be removed with towels moistened with methanol.

For additional assistance in the U.S., CHEMTREC provides a toll-free Hotline for chemical emergencies regarding spills, leaks, exposure or accidents: 1-800-424-9300.

7. Handling and Storage

Handling——— Compound should be handled in a contained area with access limited to authorized personnel and managed so that material is prevented from entering unregulated areas.

Storage——— Store in a tightly closed container in a cool, dry well ventilated location.

Other——— Protective clothing must be removed prior to leaving the controlled area. Showers are required after handling the material at the end of the workday. Always wash hands with soap and water prior to eating, drinking, or smoking.

8. Exposure Controls/Personal Protection

Exposure Guidelines

Component	OSHA Permissible Exposure Limit (PEL)	ACGIH Threshold Limit Value (TLV)	Merck Exposure Control Limit (ECL)
Ivermectin	Not established	Not established (8hr-TWA)	0.08 mg/m^3

*** Continued on next page ***

PRODUCT NAME: IVERMECTIN **PAGE: 5 OF 9**
PLANT MSDS CODE: PR-020 **Date: 1/96**

Engineering Controls	
Ventilation----------	Local exhaust ventilation must be provided where dust may enter the workroom environment. Containment areas should have dedicated exhaust and dust collection systems (HEPA filters or collectors).
Personal Protective Equipment	
Respiratory----------	An approved, properly fit tested, HEPA filtered cartridge respirator, or a respirator of greater protection, is required for handling the powder.
Hands/Arms----------	Latex gloves, or gloves providing greater protection, are required.
Eye/Face----------	Safety glasses are required. Goggles, face shield or other full-face protection is required if potential exists for direct exposure to dust or aerosols.
Additional Protective Equipment-	Full body garments should be worn when handling this compound. Disposable clothing including tyvek suits, head cover, and shoe protectors should be worn.

9. Physical and Chemical Properties

Appearance----------	Clear, moist, off-white to slightly yellow powder
Odor/Threshold Level (ppm)----	Odorless
pH----------	Not applicable
Boiling Point/Range (^{o}C/^{o}F)----	Not applicable
Melting Point/Range (^{o}C/^{o}F)----	Approx. 150^{o}C (302^{o}F)
Solubility in water----------	Negligible
Partition Coefficient (Kow)----	Not available
Specific Gravity (Water=1)----	Not applicable
Vapor Density (Air=1)----------	Not applicable

*** Continued on next page ***

Vapor Pressure (mmHG @ °C/°F)---	Not applicable
Volatile Components (% w/w)----	0%

10. Stability and Reactivity

Stability----------	Stable compound under reasonably foreseeable conditions of storage and use.
Conditions to Avoid----------	None known
Incompatibilities----------	Can be hydrolyzed by strong caustic solution.
Hazardous Polymerizations-------	None known
Hazardous Decomposition Products-	If involved in a fire, toxic gases including carbon monoxide and carbon dioxide may be generated.

11. Toxicological Information

Primary Route(s) of Entry------

Inhalation: Yes
Ingestion: No
Skin Contact: Yes

Toxicity Data

IVERMECTIN

TEST	SPECIES	ROUTE	RESULT
LD50	Mouse	Oral	25 mg/kg
LD50	Mouse	Intraperitoneal	30 mg/kg
LD50	Rat	Oral	50 mg/kg
LD50	Rat	Intraperitoneal	55 mg/kg
LD50	Rat (infant)	Oral	2 to 3 mg/kg
LC50	Rat	Inhalation	*
LD50	Rat	Dermal	More than 660 mg/kg
LD50	Rabbit	Dermal	406 mg/kg
LD50	Dog	Oral	About 80 mg/kg
LD50	Rhesus monkey	Oral	More than 24 mg/kg
Irritation	Rabbit	Ocular	Very slightly irritating
Irritation	Rabbit	Dermal	Non-irritating

*Maximum attainable concentration of 5.11 mg/liter produced transient irritation of mucous membranes but no deaths or other signs of toxicity after 1 hour exposure.

*** Continued on next page ***

PRODUCT NAME: IVERMECTIN **PAGE: 7 OF 9**
PLANT MSDS CODE: PR-020 **Date: 1/96**

Effects of Acute Exposure

Eye Contact————	Slightly irritating to the eyes in animal studies.
Skin Contact————	Non-irritating in animal studies. Prolonged or repeated contact may cause irritation, and/or drying and cracking of the skin.
Inhalation----------	An acute inhalation study demonstrated a low order of toxicity in animals by this route but this is accounted for by the large particle size of the sample used in this test. Inhalation is considered the primary route of exposure to the dry solid compound.
Ingestion----------	Ivermectin is considered highly toxic in acute animal studies although rodents were shown to be more sensitive to ivermectin compared to other species. Ivermectin is used at a therapeutic dose of 0.2 mg/kg, without signs of toxicity, in a variety of species (including humans). Based upon studies in animals and cases of accidental ingestion in humans, overexposure to ivermectin may cause drowsiness, depressed motor activity, slowed breathing, dilation of the pupils, tremors, vomiting, anorexia and incoordination.
Effects of Chronic Exposure——	There were no gross or histologic changes observed in dogs treated with ivermectin for 3 months or in monkeys treated for 2 weeks. Changes in the spleen, bone marrow and kidneys were reported in rats treated for 3 months. Signs of toxicity reported in these repeat-dose studies were similar to those observed following acute overexposure. The lowest no-effect level reported was 0.4 mg/kg/day. Ivermectin produced developmental toxicity in animals only at or near dose levels that were maternally toxic. No evidence of genotoxicity was found in a battery of assays.

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Carcinogen Designation———— Not listed as a carcinogen by NTP, IARC or OSHA.

Medical Conditions Aggravated by Exposure– None known

12. Ecological Information

Environmental Fate———— Ivermectin photodegrades rapidly in the environment and is metabolized in the soil. Water solubility is limited and it binds to soil very tightly. It does not bioconcentrate in fish and is not taken up from soil into plants. Both aquatic and terrestrial studies confirm the rapid degradation of ivermectin in the environment and its lack of accumulation and persistence.

Environmental Effects———— Ivermectin is very toxic to certain aquatic species.

LC50 - Daphnia magna, 48 hours = 0.025 ppb
NOEL (No-Observable-Effect Level) - Daphnia magna = 0.010 ppb
LC50 - rainbow trout, 96 hours = 3.0 ppb
LC50 - bluegill sunfish, 96 hours = 4.8 ppb

13. Disposal Considerations

Waste Disposal Information—— Ivermectin is very toxic to certain aquatic species. Avoid contact of spilled material with soil. Do not allow any water potentially contaminated with ivermectin including storm water, runoff from spills and fire fighting activities and contaminated wastewater to enter any waterway, drain or sewer. Residual surface material should be removed with towels moistened with methanol.

Incinerate all spill materials and residues at temperatures greater than 600°C.

*** Continued on next page ***

PRODUCT NAME: IVERMECTIN **PAGE: 9 OF 9**
PLANT MSDS CODE: PR-020 **Date: 1/96**

14. Transport Information

Shipping Description

U.S. DOT	Toxic solid, organic, N.O.S. (ivermectin), 6.1, UN2811, PGII
IATA/ICAO	Toxic solid, organic, N.O.S. (ivermectin), 6.1, UN2811, PGII
IMO	Toxic solid, organic, N.O.S. (ivermectin), Class 6.1, UN2811, II
ADR-RID	Not available

15. Regulatory Information

U.S. Federal Regulations	Not available
International Regulations	Not available
State Regulations	Not available

16. Other Information

Date Prepared	June 1989
Last Revision Date	January 1996
MSDS Coordinator	1-908-423-7926 Merck & Co, Inc. One Merck Drive P.O. Box 100, WS2F-48 Whitehouse Station, NJ 08889-0100 U.S.A.

Disclaimer: While this information and recommendations set forth are believed to be accurate as of the date hereof, MERCK & CO, INC. makes no warranty with respect hereto and disclaims all liability from reliance thereon.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

MEMORANDUM

DATE: October 4, 1996

FROM: Albert T. Sheldon, Jr. Ph.D.
Team Leader, Microbiology
Division of Anti-infective Drug Products
HFD-520

SUBJECT: Mectizan NDA # 50-742

TO: NDA File

Mectizan was submitted to the Division of Anti-infective Drug Products on March 29, 1995. The document was reviewed by the Supervisory Microbiologist prior to assignment and it was determined that no microbiological data had been submitted with the document. There were two possible administrative decisions that could be made regarding the fileability of this submission. The first was to make the NDA nonfileable because a microbiology section was not submitted with the NDA. This class 1P drug would then have been returned to the applicant with a portion of the user fees deducted according to convention. The other possibility was to accept the NDA even though the microbiology section was missing.

The possibility of accepting the Mectizan NDA was discussed with the medical officer. The focus of the discussion was to determine what additional information could have been required for microbiology that would cast doubt on the efficacy of ivermectin. It was reasoned that the establishment of microbiological efficacy was provided for in the clinical study since the establishment of efficacy was based on microscopic examination of stool (*Strongyloidiasis*) samples or skin microfilariae (*Onchocerciasis*) geometric mean counts. Thus, clinical and microbiological efficacy could be assessed. The problem was then viewed from the labeling perspective. The question was asked " What statements were being made in the microbiology section of the package insert (PI) that require verification?" In fact, no microbiology section was provided for in the original PI. The information that was included in the PI, at the request of the FDA, was "reviewed" by microbiology. The information appears reasonable but verification of the truthfulness must reside with the person requesting its inclusion. From the microbiological perspective the NDA can be approved.

Albert T. Sheldon Jr. Ph.D.

MEMORANDUM OF TELEPHONE CONVERSATION

NDA 50-742

Drug: Ivermectin
DATE: November 21, 1996
SUBJECT: CMC issues/Phase 4 commitments

BETWEEN: Representative of Merck & Co, Inc.

Kenneth Brown, Regulatory Affairs
Frank Recci, Regulatory Affairs

Danville, PA:

David Long, Tech. Operations
John Graves, Tech. Operations
Michael Kovach, Tech. Operations
Randy Hall, Plant Manager

Rahway, NJ:

Richard Steinbach, CMC
James Buckley, CMC

AND: Representatives of the Division of New Drug Chemistry:
Bonnie Dunn, Ph.D., Chemistry

Representatives of the Division of Anti-Infective Drug Products:

James Timper, Chemistry
Pauline Fogarty, Project Management Staff

Background: An approvable letter was issued on October 8, 1996, with CMC issues to be addressed by the applicant. On October 15, 1996, the applicant responded to the approvable letter. Upon review of the response Mr. James Timper felt that further elaboration was required, however, this could be accomplished through a phase 4 commitment. The attached was faxed to the applicant and a teleconference was held in which the issues were discussed.

Merck stated that:

1. The particulate impurities found in failed batches of avermectins bulk intermediate have been identified as triglycerides and phospholipids that are produced in competition with the avermectins in the fermentation step.

2. The observation of the insoluble brown particles in the avermectins bulk intermediate would warrant rejection of the batch for human use.

3. They would submit to the NDA representative chromatograms showing the resolution and detection limit of the process impurity B_{2a}.

DAIDP agreed: that the applicant's explanation was satisfactory. Therefore, the application can be approved without a phase 4 commitment.

The teleconference concluded amicably.

Pauline Fogarty
Regulatory Health Manager

cc: NDA 50-742
Div.File
HFD-520/Coyne
HFD-520/Leissa
HFD-520/Timper 11/22/96
HFD-830/ESheinin
HFD-830/BDunn 11/22/96
HFD-520/Fogarty
TELECON/PF.11/22/96
50-742.chem/11/22/96

Concurrence Only:

HFD-520/JBona

Ivermectin 50-742

Commitment: Attempt to provide an in-process control to assure that failed batches of the avermectins bulk are identified.

This can be demonstrated by providing information on the following:

I. An HPLC chromatogram of the avermectins toluene extraction could be an adequate in-process control when the chromatograms of failed batches are significantly different than the chromatograms of acceptable batches. Please provide a representative chromatogram of a failed and acceptable batch.

(1) Please identify those aspects of the chromatogram that identify a possible failure.
(2) In the failed batch chromatograph, please identify the impurity B_{2a}.

II. An HPLC chromatogram could be an adequate in-process control for release of the finished, purified avermectins intermediate bulk, when the chromatograms of acceptable batches are significantly different than batches that contain visible brown particles.

(1) Please provide a chromatogram of an acceptable and a failed batch.
(2) Please identify new peaks or enhanced peaks in the chromatograms of failed batches.
(3) Please identify the impurity B_{2a}.

III. Continue the effort to identify the compounds that constitute the brown particles found in the failed batches of avermectins bulk. Provide evidence of the resolution of the impurities in the chromatogram which is used to control the isolation of avermectins.

BSD 11/18/96

11/18/96