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120 Guatemalans with parasitologically proven cutaneous leishmaniasis were randomly and equally divided into 3 treatment groups: those receiving sodium stibogluconate (Pentostam), 20 mg antimony/kg/day iv for 20 days; those receiving ketoconazole (600 mg/day po for 28 days; and those receiving placebo treatment. All patients tolerated the treatments well with the exception of 2 patients in the ketoconazole group who prematurely stopped their medication; 1 developed abdominal pain and nausea and the other developed a generalized erythematous papular rash. Thirteen weeks after beginning treatment, the number of patients from each group with completely healed and parasitologically negative lesions were as follows: sodium stibogluconate, 33 (83%); ketoconazole, 14 (37%); and placebo, 10 (25%). The response rates for those with infections due to Leishmania braziliensis braziliensis were: sodium stibogluconate, 17 (94%); ketoconazole, 6 (32%); and placebo, 1 (7%). The response rates for those with infections due to Leishmania mexicana mexicana were: sodium

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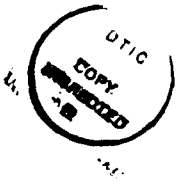
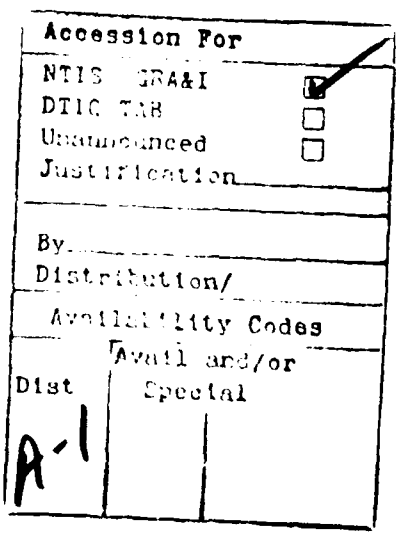
stibogluconate, 4 (50%); ketoconazole 8 (80%); and placebo, 6 (38%). High dose sodium stibogluconate appears to be well tolerated and effective aginst infections caused by L. b. braziliensis but less so against infections caused by L. m. mexicana, and ketoconazole appears to be effective against infections caused by L. m. mexicana but less so for infections caused by L. b. braziliensis.





FOREWORD

Citations of commercial organizations and trade names in this report do not constitute an official Department of the Army endorsement or approval of the products or services of these organizations.

The investigator(s) have abided by the National Institutes of Health Guidelines for Research Involving Recombinant DNA Molecules (April 1982) and the Administrative Practices Supplements.

TABLE OF CONTENTS

TABLES

FIGURES

INTRODUCTION

The recommended treatment for American cutaneous leishmaniasis (ACL) is one of two available pentavalent antimony compounds, sodium stibogluconate (Pentostam, Burroughs Wellcome) and meglumine antimonate (Glucantime, Specia). Despite the wide use of these antimonials, little reliable information is available on their optimum dose or their toxicity at higher doses.

In 1990 we reported that for Guatemalan cutaneous leishmaniasis 850 mg of antimony (equivalent to approximately 15 mg antimony/kg) for 15 days was very well tolerated and produced a clinical and parasitological response in 73% of patients by 13 weeks.[1] Reactivation of infections during 12 months of follow-up in 9% of patients lowered the final response rate to 64%. Others have shown that patients can tolerate up to 20 mg antimony/kg/day for 20 days with only minimal hepatic and cardiac injury.[2--3]

In an attempt to improve on our previously reported response rate of 64% and to better characterize the toxicity of high dose antimony, in this study we treated patients with sodium stibogluconate (20 mg antimony/kg/day iv) for 20 days.

Despite the wide acceptance of antimonials in the treatment of leishmaniasis, there is a pressing need for alternative therapies. Antimonials are expensive and require parenteral injection. In this day of hepatitis and adult immunodeficiency syndrome, oral drugs are increasingly attractive. Studies in Panama have shown that ketoconazole is equally effective as moderate dose antimony for leishmaniasis caused by Leishmania braziliensis panamensis.[4]

Ketoconazole is an imidazole drug that has shown remarkable success in the treatment of superficial and systemic mycoses.\5/ Ketoconazole interferes with the biosynthesis of ergosterol, a major fungal sterol critical to membrane integrity, thus inhibiting the 14-demethylation of lanosterol, a precursor in the ergosterol pathway. Blockage of this pathway results in ergosterol-poor organisms that are unable to maintain their plasma membranes. The selective effect of ketoconazole on fungi and Leishmania is due to the fact that ergosterol is of little importance to mammalian membranes, and cholesterol, the critical membrane sterol for mammals, is available from the diet.\6/

Ketoconazole has been used in clinical trials for mycotic infections since 1978, and more than 1 million patients have received the drug with few adverse effects. Although it appears to block adrenal steroid synthesis, no cases of hypoadrenalism have been reported. Skin rashes, nausea, vomiting, and anorexia have been the problems most commonly reported. Ketoconazole may interact with alcohol to increase susceptibility to nausea. Mild asymptomatic and reversible serum transaminase elevations have been observed in up to 15% of patients, but the incidence of serious hepatic injury has been estimated to be only 1 in 15,000 patients.\7/ Three deaths, all from hepatic failure, have been attributed to ketoconazole, for a mortality rate of 1 in 333,333 patients. Each person continued to take ketoconazole despite the appearance of jaundice.\8/

MATERIALS AND METHODS

Patient population

Guatemalan males who sought treatment for suspected leishmaniasis at any of our 4 clinics were evaluated. Eligibility for the study included a confirmed diagnosis of leishmaniasis, no previous treatment with antimonials or imidazoles, no serious concomitant medical problems, and no visible evidence of mucosal involvement. In contrast to our 1990 clinical study, which involved only military personnel, this study included 21 civilians and 99 soldiers. Persons who met the study requirements were offered the opportunity to enter the study. Informed consent was obtained from each person.

Treatment groups

120 subjects were assigned randomly and equally to 1 of 3 treatment groups: those receiving sodium stiboguconate (20 mg pentavalent antimony/kg/day iv for 20 days); those receiving ketoconazole (600 mg po each evening for 28 days); and those receiving placebo treatment. Half of the patients assigned to the placebo group received saline infusions similar to the sodium stibogluconate infusions, and half received tablets similar to ketoconazole.

Patient evaluation

Diagnosis of cutaneous leishmaniasis was made by thin smears of lesion scrapings or culture of lesion aspirates as described before.\9/ Only patients with positive cultures or clearly distinguishable amastigotes were entered into the study.

Isolates were characterized by isoenzyme electrophoresis as described before.\10/ The following enzymes were used: glucose phosphate isomerase, mannose phosphate isomerase, phosphogluconate dehydrogenase, phosphoglucomutase, and peptidase D.

Patients were evaluated at 1, 2, 3, 4, 6, 9, 13, 26, and 52 weeks after the start of therapy. Clinical response was defined as a lesion that completely reepithelialized and had no evidence of inflammation or induration. Aspirates for culture of all lesions and scrapings of open lesions were taken at the end of therapy and at the 9-week follow-up examination. A reactivated lesion was defined as the appearance of a lesion within or at the border of a previous lesion; new lesions were defined as those that appeared after treatment began and occurred away from any previous lesions. Since most of our patients remained in the endemic area during and after treatment, the appearance of new lesions was not necessarily taken as evidence of treatment failure.

If a patient's lesion was not completely reepithelialized by the 13-week follow-up examination, the patient was removed from the study and treated with meglumine antimonate (20 mg antimony/kg/day) for 20 days. Patients with clinically healed but parasitologically positive lesions at the 9-week examination were not retreated.

Before beginning treatment, on the last day of treatment, and at the 9-week examination patients had the following tests performed: hemoglobin, hematocrit, platelet count, white blood cell count, aspartate aminotransferase, alanine aminotransferase, direct and indirect bilirubin, creatinine, and electrocardiogram. In addition, patients treated with antimony or placebo injections had the liver function tests repeated on days 7 and 14 and had the electrocardiograms repeated on days 2, 4, 7, 9, 11, 14, 16 and 18. Patients who received ketoconazole or placebo tablets also had liver function tests repeated on day 14.

RESULTS

Patient characteristics

Four patients who were eligible for the study and who were offered the chance to participate declined because they preferred not to receive experimental therapy.

One hundred and twenty study subjects were enrolled. Randomization successfully allocated patients with similar characteristics into the 3 treatment groups (Table 1.)

All but 2 of the 120 patients received their treatments without interruption. Both patients who prematurely interrupted their treatments were receiving ketoconazole (see the section below on adverse effects for details). For the purposes of data analysis, data on these 2 patients is not included.

Clinical and parasitological response

Figure 1 shows the response rates of patients in the 3 treatment groups. A number of patients had complete reepithelialization of their lesions but cultures either on the last day of treatment or at the 9-week examination were still positive. In order to show both clinical response rates as well as clinical plus parasitological response rate, in Figures 1, 2, and 3, each treatment group is represented by 2 lines. The lower, bold, line represents the percentage of patients that had complete reepithelialization of their lesions and negative cultures at the end of treatment and at 9 weeks. The upper, narrow, line represents the percentage of patients that had a complete clinical response, irrespective of the results of cultures.

Figure 2 shows response rates for the 52 patients infected with L. b. braziliensis. Patients who received sodium stibogluconate usually responded rapidly, and by the end of 20 days of treatment all patients were parasitologically negative and 30% had completely closed their lesions. By 13 weeks only 1 patient (7%) had not responded both clinically and parasitologically. This patient had 3 large ulcers; 2 had closed completely by the 13th week, but 1 was only 70% reepithelialized. Cultures of all 3 lesions were negative. He may have continued to improve without further treatment, but in compliance with the study protocol he was dropped from the study and treated successfully with meglumine antimonate.

At the time of this report, only 14 of the 18 patients infected with L. b. braziliensis and treated with sodium stibogluconate have

returned for their follow-up examinations at 26 and 52 weeks. Of this group, none has had reactivations of their lesions.

Patients infected with L. b. braziliensis and treated with ketoconazole did not respond as well as those treated with sodium stibogluconate but responded better than those treated with placebo. At the 13-week examination, the clinical response rate for the ketoconazole group was significantly less than that for the sodium stibogluconate group ($p<0.01$; Fisher's exact test) but was significantly greater than that for the placebo group ($p<0.03$). The rates for ketoconazole clinical plus parasitological responses were also significantly less than that for sodium stibogluconate ($p<0.01$) but not significantly greater than that for placebo ($p<0.09$).

Patients who received placebo treatment and who were infected with L. b. braziliensis did not do well. At 13 weeks only 3 were clinically cured, but 2 of these had positive cultures. By 26 weeks 2 of the 3 had reactivations of their lesions.

Figure 3 shows the response rates for the 34 patients infected with L. m. mexicana. In contrast to patients infected with L. b. braziliensis, patients infected with L. m. mexicana responded better to ketoconazole than to sodium stibogluconate, although this difference was not statistically significant ($p<0.09$). The response rate for ketoconazole was significantly greater than that for placebo when either clinical or clinical plus parasitological response was considered ($p<0.02$ and $p<0.02$, respectively). The difference between sodium stibogluconate and placebo was not significant ($p<0.33$).

Of the 99 patients who have returned for their 52-week follow-up examination, the vast majority have returned to a leishmania-endemic area. Despite this only 2 have developed new lesions of

leishmaniasis. One had received sodium stibogluconate and had a new lesion due to L. b. braziliensis, and the other was treated with ketoconazole and was infected with L. m. mexicana.

Thirteen (11%) of the patients developed small papules at the edge of healed lesions after treatment was completed. In 4 cases the papules grew rapidly, ulcerated within 4 weeks, and provided positive cultures. In the remaining 9 cases the papules remained stable for the duration of our follow-up, and all cultures were negative. Since stable papules did not appear to be a bad prognostic sign, for the purposes of this study we have not considered them to signify reactivation of lesions.

Figures 4 and 5 show the mean change in lesion size from 2 weeks before to 13 weeks after starting treatment. Figure 4 depicts data for patients infected with L. b. braziliensis and Figure 5 shows data for patients infected with L. m. mexicana.

Laboratory test and adverse effects

Table 2 lists the laboratory values before, at the end of, and 9 weeks after treatment.

Note that results for alkaline phosphatase are not included in the summary, although they are given in annex 2, which lists all laboratory values. The laboratory that ran our specimens changed analytic procedures for alkaline phosphatase several times, making it impossible to compare results from patient to patient or even for the same patient from 1 time period to another.

Six (15%) of the 40 patients who received sodium stibogluconate developed elevated transaminases. Aspartate aminotransferase and

alanine aminotransferase values were equally elevated, but neither direct nor indirect bilirubin values were ever elevated, no patients developed jaundice, and no patients complained of right upper quadrant pain. The highest aspartate aminotransferase value was 358 IU (upper limit of normal = 55 IU). The course of elevated transaminase values was irregular. Often the highest values were not on the last day of treatment, and in several cases, the values dropped despite continued therapy. We believe that a number of instances of elevated values were due to the concurrent ingestion of alcohol.

One patient in the sodium stibogluconate group and 2 patients in the ketoconazole group developed anemia during treatment. In all 3 cases the patients developed fever and chills and blood smears were positive for Plasmodium vivax. Treatment of the malaria resolved the anemia.

Note that the 600 electrocardiograms taken during this study are still being analyzed. The results will be ready within the next 2 months. Preliminary analysis shows that t-wave suppression was very common in the sodium stibogluconate group, but no cases occurred of t-wave inversion or concave st-segments.

Table 3 shows the adverse reactions reported by patients. Adverse reactions were reported by 21 patients who received sodium stibogluconate, 7 patients who received ketoconazole, and 4 patients who received placebo. The majority of the adverse reactions were minor and did not require medical attention, and none were severe enough to pose a threat the patient.

For the sodium stibogluconate group, 5 patients had 7 adverse reactions significant enough to warrant medical intervention. For

the ketoconazole group, 3 patients reported 4 moderate adverse reactions, and for the placebo group, 1 patient reported moderately severe epigastric pain. In only 2 patients, both of whom received ketoconazole, were the adverse reactions severe enough to lead to the premature termination of treatment.

The first patient developed a generalized pruritic papular erythematous rash on the 17th day of treatment with ketoconazole. The patient had no urticaria or wheezing, and his blood pressure remained normal. Although in the opinion of the treating physician the rash did not require the termination of ketoconazole, the patient decided to withdraw from the study. The rash spontaneously resolved 3 days after cessation of ketoconazole. The patient was successfully treated with meglumine antimonate.

The second patient developed epigastric pain and nausea 2 hours after the second dose of ketoconazole. Two hours after the onset of these symptoms the patient vomited several times and had diarrhea. Ketoconazole was stopped for 2 days, during which the patient had no gastrointestinal symptoms. Ketoconazole and antacids were restarted and the patient again developed moderately severe epigastric pain, but this time did not vomit or have diarrhea. The patient was able to continue ketoconazole until the 16th dose when the epigastric pain increased substantially and he again vomited once. The patient was withdrawn from the study and treated successfully with meglumine antimonate. One day after ketoconazole was stopped the gastrointestinal symptoms resolved.

DISCUSSION

Treatment with high dose (20 mg/kg/day for 20 days) sodium stibogluconate in this clinical trial proved very effective against infections due to L. b. braziliensis but not more effective than placebo against infections caused by L. m. mexicana. In our clinical trial of 1990, we reported that only 64% of patients infected with L. b. braziliensis had clinical and parasitological responses to 850 mg antimony/day for 15 days (225 mg/kg total dose).[1]

The higher dose of sodium stibogluconate used in this study is apparently more effective than the lower dose used in the 1990 study for infections caused by L. b. braziliensis. Adverse effects such as arthralgias, nausea, headaches, and phlebitis were more common with the higher dose, but these were never more than moderately severe and did not require the premature termination of antimony.

Dosages of antimony of 20 mg/kg, which for an adult is equivalent to 12 to 15 ml/dose, require that the drug be given by intravenous infusion. Dosages of 850 mg, equivalent to 8.5 to 10 ml/dose, can be given by injection into the muscle. Although intravenous infusions can be less painful than intramuscular injections, they require special equipment and training. For clinics that are properly equipped, intravenous infusions pose no special problems. Cutaneous leishmaniasis, however, usually occurs in remote areas far from well equipped clinics. To the extent that it is advantageous to decentralize the treatment of cutaneous leishmaniasis in developing countries, higher dosage regimens of antimony are a drawback.

In contrast to our impressive results with sodium stibogluconate for infections caused by L. b. braziliensis, this drug was not significantly better than placebo for infections caused by the other major species of Leishmania in Guatemala, L. m. mexicana. Although infections by L. m. mexicana are traditionally considered benign, in our experience in Guatemala, they can cause significant morbidity if treatment is not available or is restricted to antimonials. Of 18 patients who we have treated with at least 2 courses of antimonials, 16 were infected with L. m. mexicana, and of 5 patients who have required at least 3 courses of antimonials, all 5 were infected with L. m. mexicana.

The tradition belief that L. m. mexicana infections, once healed, never reactivate also does not apply to Guatemalan infections. In our experience untreated or undertreated L. m. mexicana infections often run a cyclical course. They will ulcerate and stay open for several months, then reepithelialize and stay closed for several months, and then ulcerate again. Such cycles can continue for at least 7 years in our experience. Of the 12 patients in the present study infected with L. m. mexicana who received placebo treatment and did not respond, 5 (42%) at some point in their follow-up healed their lesions before developing reactivations.

Given the cyclical nature of L. m. mexicana infections and their poor response to antimonials, it is encouraging that ketoconazole appears to be effective.

Table 1. Characteristics of patients by treatment group

Characteristic	Treatment group		
	Pentostam (n=40)	Ketoconazole (n=38)	Placebo (n=40)
Age (years)	19.1 ± 0.6	20.2 ± 1.2	21.3 ± 1.4
Number lesions/patient	1.6 ± 0.2	1.5 ± 0.1	1.5 ± 0.2
Mean area of ulceration (cm^2)	1.5 ± 0.3	2.2 ± 0.4	2.0 ± 0.4
Mean age of lesions (days)	73.7 ± 34	68.3 ± 10	59.1 ± 7
Infecting species [1]			
L. m. mexicana	8	10	16
L. b. braziliensis	18	19	15
Unknown	12	9	9

1. Provisional

Table 2. Laboratory values before, during, and after treatment

Laboratory test	Treatment group		
	Pentostam (n=40)	Ketoconazole (n=38)	Placebo (n=40)
Serum creatinine (mg/100ml)			
Before treatment	0.75	0.75	0.85
Last day of treatment	0.79	0.81	0.79
9 weeks	0.76	0.83	0.82
# with abnormalities on last day of treatment *	0	0	0
Aspartate aminotransferase (IU)			
Before treatment	20	17	15
Last day of treatment	35	14	15
9 weeks	20	15	18
# with abnormalities on last day of treatment *	3	0	0
Alanine aminotransferase (IU)			
Before treatment	20	16	14
Last day of treatment	34	14	15
9 weeks	19	17	17
# with abnormalities on last day of treatment *	3	0	0
Indirect Bilirubin (mg/100ml)			
Before treatment	0.27	0.23	0.29
Last day of treatment	0.24	0.26	0.30
9 weeks	0.25	0.28	0.26
# with abnormalities on last day of treatment *	0	0	0

Table 2. Continued

Laboratory test	Treatment group		
	Pentostam (n=40)	Ketoconazole (n=38)	Placebo (n=40)
Direct Bilirubin (mg/100ml)			
Before treatment	0.29	0.28	0.33
Last day of treatment	0.24	0.36	0.30
9 weeks	0.31	0.31	0.26
# with abnormalities on last day of treatment *	0	0	0
Platelets (#/mm^3 X 1000)			
Before treatment	227	228	228
Last day of treatment	207	224	222
9 weeks	216	206	218
# with abnormalities on last day of treatment *	0	0	0
Hemoglobin (gm/100 ml)			
Before treatment	14.9	14.4	14.4
Last day of treatment	14.2	13.9	14.7
9 weeks	14.8	14.1	14.8
# with abnormalities on last day of treatment *	0	0	0
Hematocrit (%)			
Before treatment	45	43	43
Last day of treatment	43	42	44
9 weeks	44	42	45
# with abnormalities on last day of treatment *	1	2	0

Table 2. Continued

Laboratory test	Treatment group		
	Pentostam (n=40)	Ketoconazole (n=38)	Placebo (n=40)
White blood cells (#/mm^3)			
Before treatment	7070	6992	7491
Last day of treatment	6795	7540	7823
9 weeks	6831	7808	7609
# with abnormalities on last day of treatment *	0	0	0

* Number of patients with values at the last day of treatment outside of the normal range for the testing laboratory.

Table 3. Adverse Reactions Reported by Patients

Treatment group/ Adverse reaction	Severity * Mild	Moderate	Severe	Total
Pentostam				
Nausea	3	2	0	5
Anorexia	4	0	0	4
Headache	1	2	0	3
Rash	1	0	0	1
Arthralgias	5	1	0	5
Phlebitis	8	2	0	10
Ketoconazole				
Nausea	1	1 **	0	2
Abdominal pain	1	1	0	2
Headache	1	1	0	2
Dizziness	1	0	0	1
Rash	0	1 **	0	1
Placebo				
Abdominal pain	2	1	0	3
Nausea	1	0	0	1
Anorexia	1	0	0	1

* Mild: No need for medical attention
Moderate: Required medical attention, but posed no danger to patient
Severe: Required immediate medical attention to prevent danger to patient

** Adverse reaction led to the premature termination of the study drug

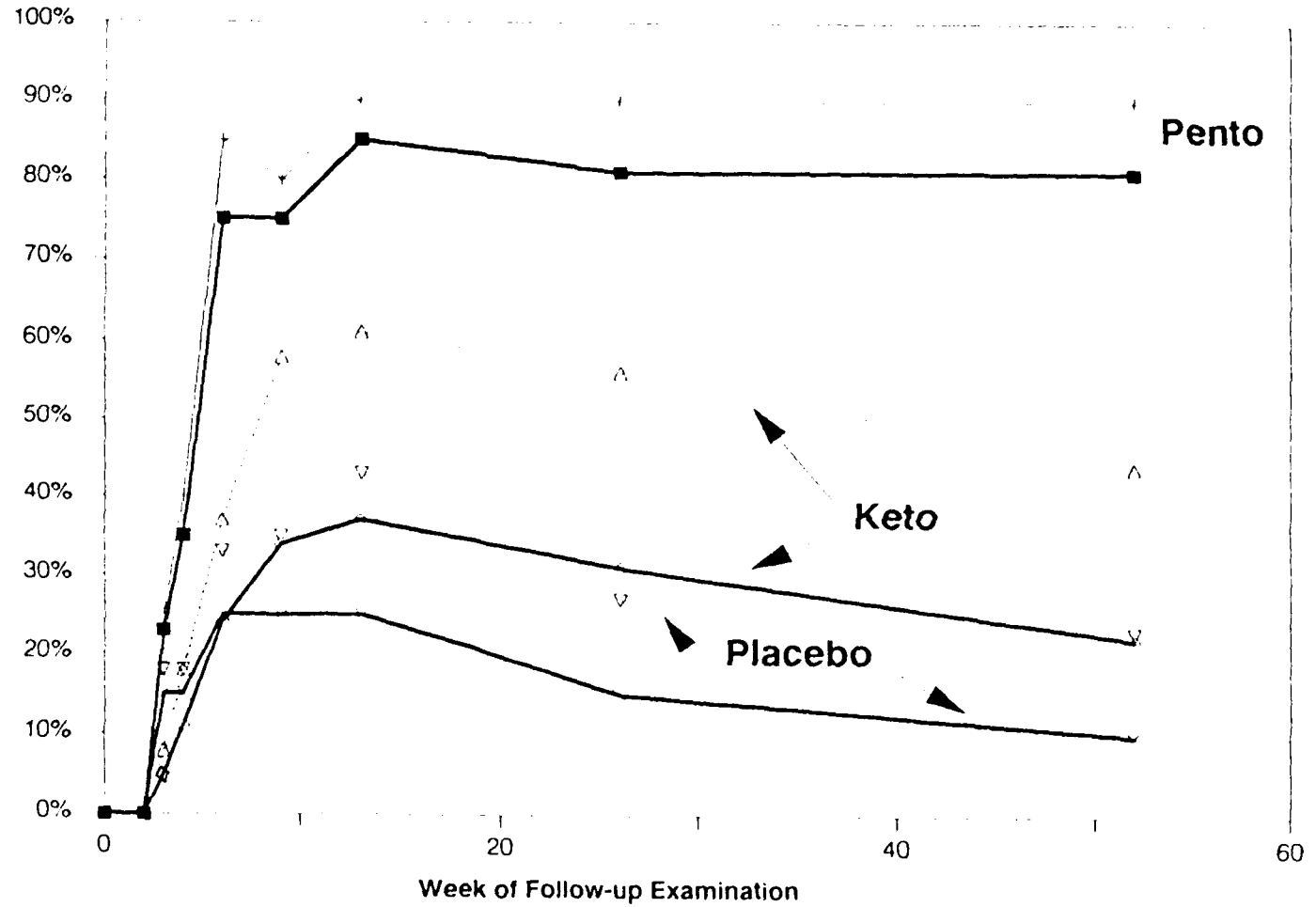
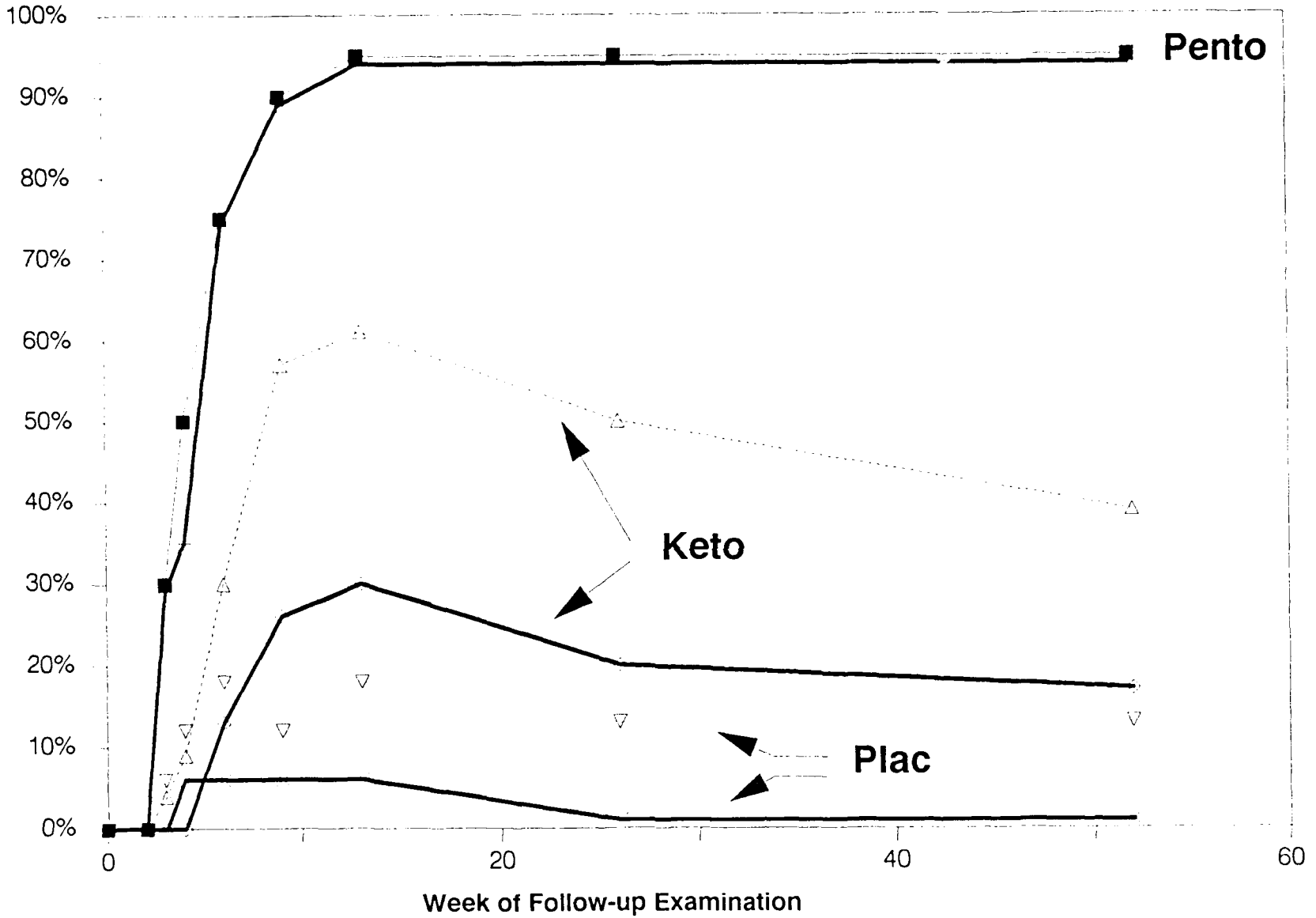
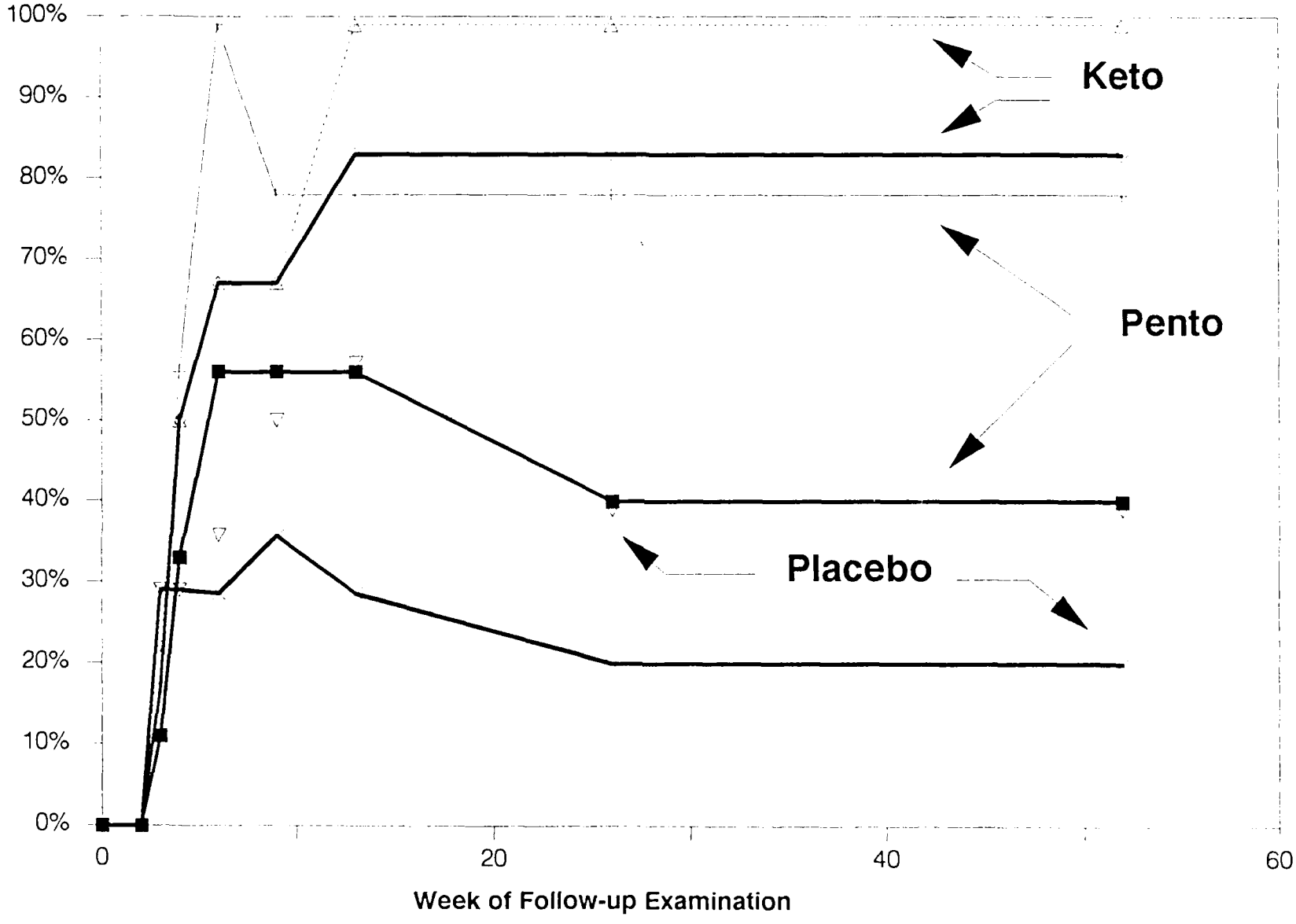


Figure 1. Percent of patients who responded to treatment with sodium stibogluconate, ketoconazole, or placebo by week of follow-up examination. Each of the 3 treatment groups is represented by 2 lines. The lower bold line represents the percentage of patients that had complete reepithelialization of their lesions and negative cultures at the end of treatment and at 9 weeks. The upper narrow line represents the percentage of patients that had a complete clinical response, irrespective of the results of cultures. Patients who did not respond by the 13-week examination were removed from the analysis and treated with meglumine antimonate.



Bold line = clinical and parasitological response
Narrow line = clinical response (cultures may have been positive)

Figure 2. Percent of patients infected with L. b. braziliensis who responded to treatment. See Figure 1 for explanation.



Bold line = clinical and parasitological response
Narrow line = clinical response (cultures may have been positive)

Figure 3. Percent of patients infected with L. m. mexicana who responded to treatment. See Figure 1 for explanation.

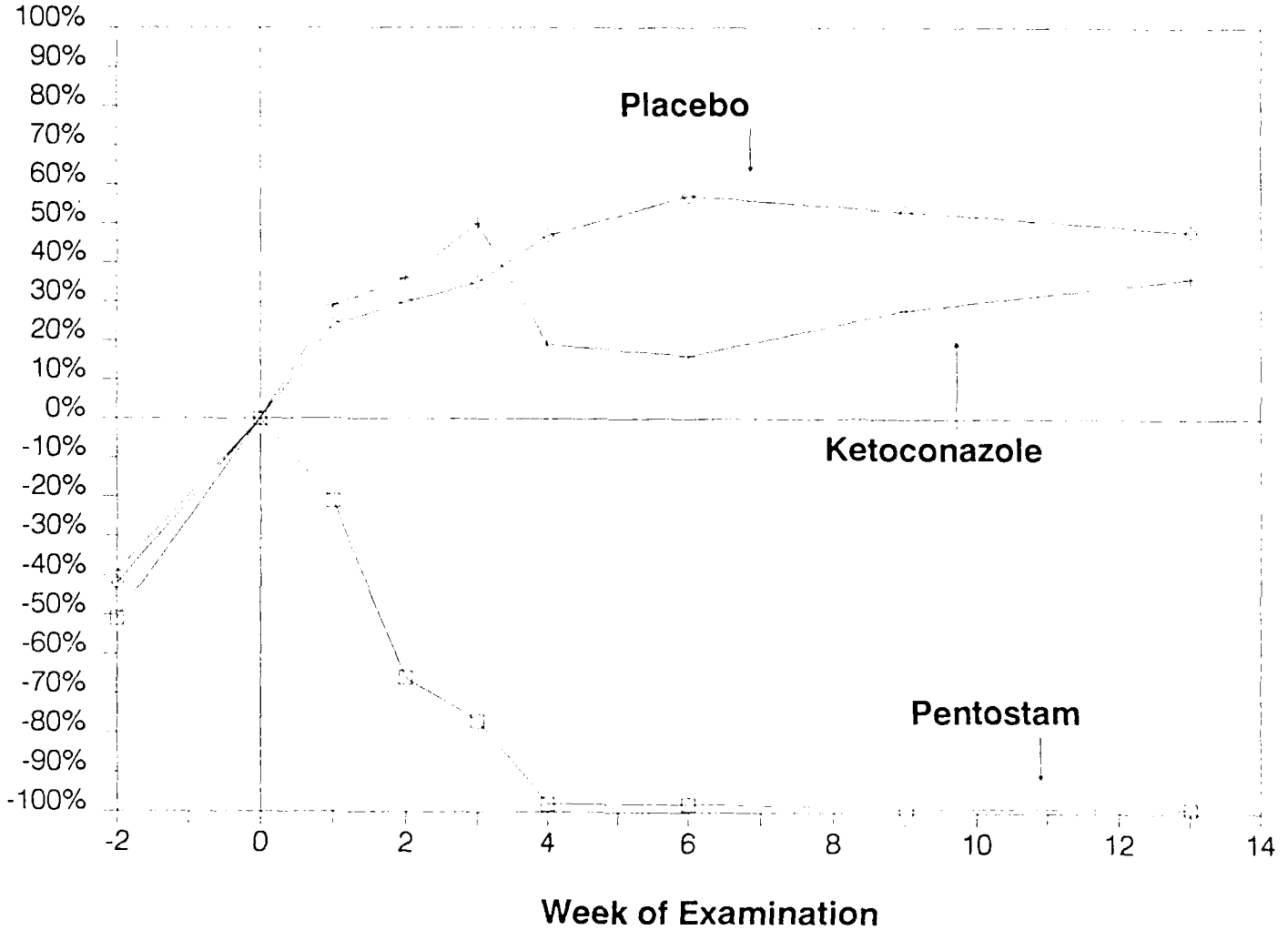


Figure 4. Change in lesion size from 2 weeks before to 13 weeks after starting therapy for patients infected with L. b. braziliensis.

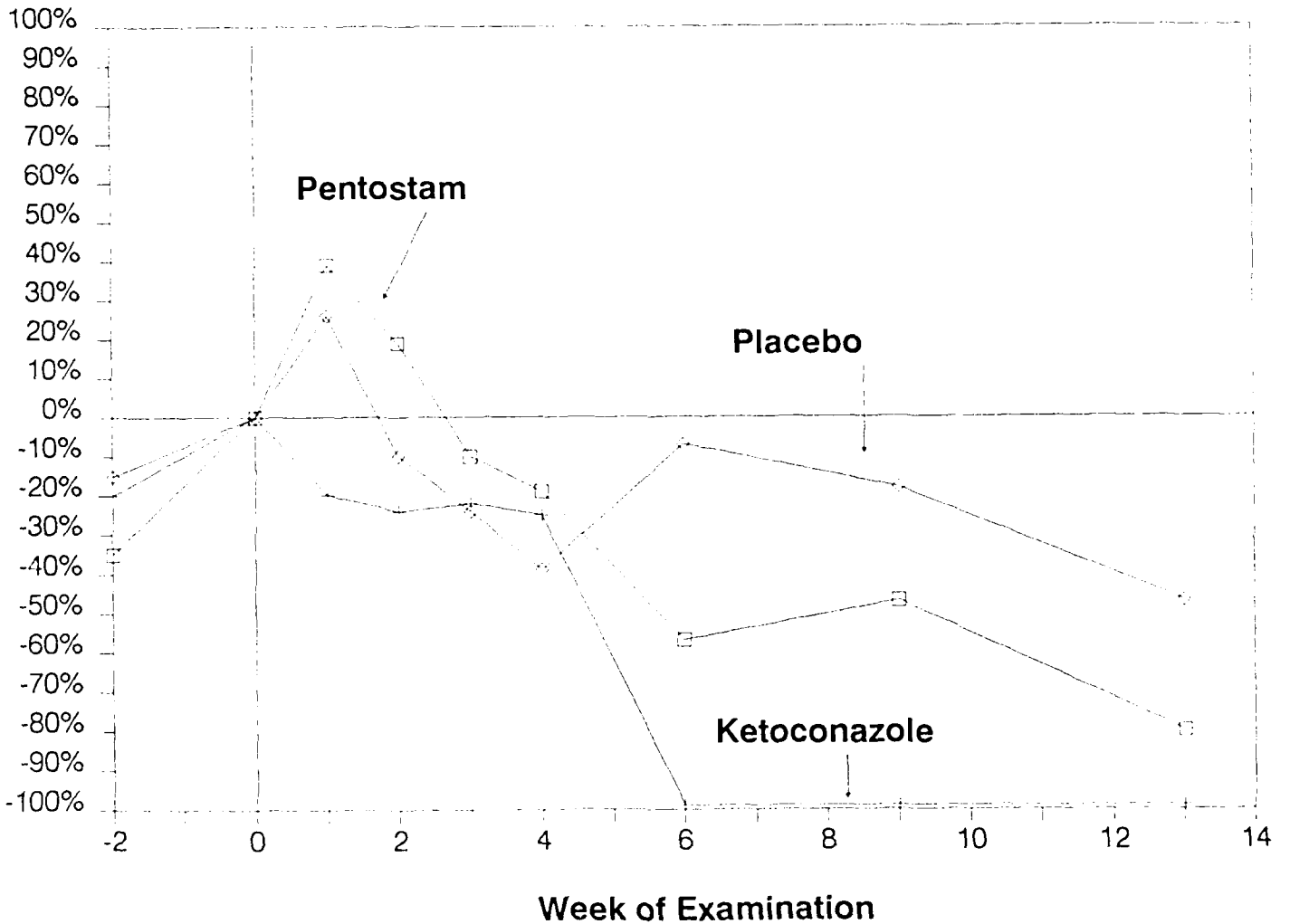


Figure 5. Change in lesion size from 2 weeks before to 23 weeks after starting therapy for patients infected with L. m. mexicana.

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ANNEX 1: LIST OF ADVERSE REACTIONS BY TREATMENT GROUP

ADVERSE REACTIONS SUMMARY SHEET
STUDY OF PENTOSTAM/KETOCONAZOLE/PLACEBO
DEC 2, 1989

Pentostam

ID	Severity[1]	Adverse Reaction
GA-225	Moderate	Pain and edema after Pentostam injection extravasated. Resolved in 48 hours with application of cold packs. Treatment not interrupted.
GA-245	Moderate	Headache. Approximately 9 hours after the 7th dose the patient developed a moderately severe headache that lasted 2 to 4 hours. Aspirin alleviated most of the pain, but the headache returned for the next 5 days, always about 9 hours after a dose. Treatment was not interrupted.
GA-246	Mild	Local pain at the site of injection. Treatment was not interrupted
GA-270	Mild	Local pain at the site of injection. Treatment was not interrupted
GA-290	Mild	Arthralgias. Began 18th day of treatment and involved the shoulder and knee joints. Resolved 2 days after stopping treatment.
GC-256	Mild	Nausea, anorexia, and headache. Began on day 15 of treatment and continued for the remaining 5 days of treatment and for 1 day more. No specific medication prescribed, and treatment was not interrupted.
GC-257	Mild	Rash. Began on the 3rd day of treatment and lasted for 12 days. Papular, pruritic rash of the upper arms and trunk. Treatment was not interrupted.
GC-275	Mild	Local pain at the site of injection. Began on day 12 of treatment and lasted for 4 days. Treatment was not interrupted.
GC-323	Mild	Local pain at the site of injection. Began on day 5 of treatment and lasted 20 days. Treatment was not interrupted.
GC-330	Mild	Local pain at the site of injection. Began on day 20 of treatment and lasted for 10 days. Treatment was not interrupted.
GC-334	Mild	Fever. Began on 9th day of treatment and lasted for 6 days. Blood smear positive for P. vivax and patient improved with chloroquine.
GC-348	Mild	Arthralgias. Began on day 11 of treatment in the shoulders. On day 16 the pain spread to include the knees. Resolved 3 days after stopping treatment
GC-353	Mild	Arthralgias. Began on 12th day of treatment and involved the shoulders. Resolved 2 days after stopping treatment.
GC-355	Moderate	Nausea, anorexia, and fainting spell. Five days after starting medicine, patient lost his appetite and felt nausea. On the 6th day of treatment, he fainted and was unconscious for a few minutes several hours after his injection. He recovered without problems and continued with his treatment.

GC-360	Mild	Nausea and anorexia. Ten days into treatment, the patient developed mild nausea and anorexia that lasted for 15 days (10 days of treatment and for 5 days more).
GC-368	Mild	Local pain at the site of injection. The pain was mild and resolved without further problems.
GC-370	Mild	Arthralgias. After 14 days of treatment, the patient developed joint pain of the wrist and elbow of the right arm. The pain lasted for 10 days and resolved 5 days after stopping therapy.
GC-373	Moderate	Headache, nausea, anorexia, and arthralgias. After 5 days of treatment, the patient developed moderately severe headaches that required aspirin. He also complained of mild nausea and anorexia. The three symptoms lasted for a total of 20 days, and resolved 5 days after stopping treatment. This patient also developed athralgias after the 15th day of treatment and lasted for 10 days.
GC-379	Moderate	Extravasation of drug. Six hours after the 7th dose, the patient developed edema, pain, and erythema of the hand where the intravenous injection had been placed. The reaction resolved over 3 days with application of cold packs.
GG-001	Mild	Local pain at site of injection. Began on day 15 of treatment and lasted 5 days. Required treatment with hot packs and aspirin. Treatment was not interrupted. Note: this was described as moderate in severity on the original case report forms, but on review, we now believe that this represented a mild adverse reaction.
GG-007	Mild	Local pain at the site of injection. Began on dat 5 of treatment and lasted for 4 days. Treatment was not interrupted.

1. Mild: No medical attention necessary
   Moderate: Medical attention necessary, but condition not dangerous
   Severe: Dangerous if no medical attention available

ADVERSE REACTIONS SUMMARY SHEET
STUDY OF PENTOSTAM/KETOCONAZOLE/PLACEBO
DEC 2, 1989

Ketoconazole

ID	Severity[1]	Adverse Reaction
GA-219	Mild	Nausea/vomiting. Approximately 2 hours after the 16th dose, the patient developed a headache with nausea and vomited 2 times. The nausea continued for 24 hours and the headache lasted for 48 hours. The symptoms resolved without any medications. Treatment was not interrupted.
GA-286	Mild	Abdominal pain. Two hours after the 21st dose the patient developed mild abdominal pain that lasted for 2 days. The symptom resolved with no medical intervention. Treatment was not interrupted.
GE-023	Mild	Headache. One hour after the 2nd dose the patient felt a moderately severe headache that lasted about 3 hours. These headaches came back after the 3rd and 4th dose, but then resolved spontaneously.
GE-030	Moderate	Rash. On the 17th day of treatment, patient noted a generalized pruritic rash over his whole body that began 1 hour after taking the pills. There was no urticaria or wheezing and the blood pressure remained normal. Although in the opinion of the treating physician the rash could have been managed with antihistiminics, the patient insisted on terminating treatment with ketoconazole. The rash resolved spontaneously 3 days after it began.
GG-010	Mild	Dizzyness. About 3 hours after the 18th dose, the patient felt light-headed. The symptoms lasted for about 1 hour and resolved spontaneously. Treatment was not interrupted.
GG-014	Moderate	Headache. On the second day of treatment the patient began to complain of moderately severe headaches that began just after taking ketoconazole and lasted for 4 to 8 hours. The headaches continued for 26 days and resolved the day after the medication was stopped.
GG-018	Moderate	Nausea and abdominal pain. After the second dose the patient developed epigastric pain, vomited, and had diarrhea. The patient stopped treatment for 2 days during which he had no symptoms. When treatment was restarted, the patient again developed moderately severe epigastric pain, but this time did not vomit or have diarrhea. After the 16th dose the epigastric pain increased and the patient vomited once. Treatment was terminated prematurely because of these adverse reactions, and the symptoms resolved.

1. Mild = No medical attention necessary
   Moderate = Medical attention necessary, but not dangerous
   Severe = Dangerous if no medical attention available

ADVERSE REACTIONS SUMMARY SHEET
STUDY OF PENTOSTAM/KETOCONAZOLE/PLACEBO
DEC 2, 1989

Placebo

TABLETS

ID	Severity[1]	Adverse Reaction
GA-248	Mild	Abdominal pain. Six hours after the 4th dose of placebo tablets the patient complained of mild stomach pain. No medical treatment was required, and the symptoms resolved in 48 hours.
GE-031	Moderate	Abdominal pain. The patient had chronic abdominal pain, but 11 days after starting treatment the patient developed worsening epigastric pain that lasted 7 days.
GC-290	Mild	Abdominal pain. Began on day 19 of treatment and lasted for 12 days (for the rest of treatment and then 3 days more). Resolved without specific medication and treatment was not interrupted.

INJECTIONS

GC-359	Mild	Nausea and anorexia. One day after stopping his medication, patient complained of nausea and loss of appetite. This resolved without treatment in 6 days.

1. Mild = No medical attention necessary
   Moderate = Medical attention necessary, but not dangerous
   Severe = Dangerous if no medical attention available

ANNEX 2: LIST OF LABORATORY VALUES BY TREATMENT GROUP

ID	GRUPO	RAMA	CUAL	DATOS PERS	CONS	TRATA	REAC ADV	0 CREAT	21D CREA	29D CREAT	9S CREA	0 TGO	8D TGO	14D TGO	21D TGO	29D TGO	9S TGO
GC-368	10	P	A					0.60	0.80		0.70	20	7	15	13		19
GA-277	10	P	A					0.90	0.70		0.70	25	26	20	20		22
GA-300	10	P	A					0.50	0.40		0.80	9	28	36	87		35
GC-355	10	P	A					0.60	0.67		0.80	36	80	57	30		32
GC-360	10	P	A					0.80	0.83		0.40	26	41	43	28		11
GC-373	10	P	A					0.70	0.50		0.90	26	24	20	20		9
GC-383	10	P	A					1.10	0.90		0.70	11	32	45	30		36
GC-370	10	P	A					0.30	0.50		0.80	11	19	19	26		5
GA-290	10	P	A					0.80	0.60		90	14	28	15	11		3
GA-246	10	P	A					0.90	0.90		0.66	19	51	47	37		20
GA-287	10	P	A					0.70	0.70		90	10	17	22	11		18
GA-298	10	P	A					0.80	0.90		1.	24	26	11	22		21
GA-283	10	P	A					0.70	0.70		0.90	10	12	5	74		41
GA-258	10	P	A					0.80	0.50		0.50	10	52	42	100		25
GA-263	10	P	A					0.80	0.50		0.68	9	36	28	5		38
GA-274	10	P	A					0.68	1.01		0.80	17	22	30	20		17
GC-353	10	P	A					0.70	0.70		0.50	30	30	8	38		19
GC-379	10	P	A					0.90	0.60		0.90	11	15	22	13		19
GC-348	10	P	A					0.09	0.60		0.15	17	60	43	5		17
GA-270	10	P	A					0.70	0.88		0.60	15	26	9	16		30
GC-306	10	P	A	X	X	X	-	0.80	1.10		0.68	15	26	60	26		26
GC-334	10	P	A	X	X	-	X	0.82	0.89		0.70	15	32	13	36		24
GG-001	10	P	A	X	X		X	0.60	0.80		1.00	19			26		17
GC-257	10	P	A	X	X	X	X	0.87	1.03			30	36	19	17		22
GG-011	10	P	A	X	X	-	-	1.06	0.83		0.84	34	50	41	43		17
GC-323	10	P	A	X	X	-	X	0.73	0.76		0.60	27	17	19	11		7
GC-282	10	P	A	X	X	X	-	1.03	1.31		0.91	13	53	358	46		24
GC-256	10	P	A	X	X	X	X	1.15	1.05		0.71	45	65	70	36		20
GC-310	10	P	A	X	X	X	-	0.90	0.73		0.74	41	11	15	39		13
GG-005	10	P	A	X	X	-	-	0.40	0.90		1.02	15	12	39	22		19
GA-245	10	P	A	X	X	-	X	1.00	0.60		0.86	15	32	53	102		18
GC-329	10	P	A	X	X	-	-	0.58	0.80		0.80	17	19	36	32		26
GC-275	10	P	A	X	X	X	-	0.78	0.79		0.80	28	200	39	39		24
GC-288	10	P	A	X	X	X	-	0.79	0.97		0.90	13	24	20	15		13
GA-225	10	P	A	X	X	X	X	0.80	1.20		1.00	15	102	51	50		9
GG-007	10	P	A	X	X	-	X	0.70	0.70		1.00	26	17	11	30		36
GC-321	10	P	A	X	X	-	-	0.73	0.70		0.79	30	9	51	68		13
GC-338	10	P	A	X	X	-	-	0.70	0.50		0.64	11	60	90	39		7
GC-281	10	P	A	X	X	X	-	0.92	1.21		0.89	17	38	36	43		19
GC-330	10	P	A	X	X	-	X	0.70	0.80		0.60	19	22	22	59		13
PENTOSTAM																	
max								1.15	1.31		1.02	45	200	358	102		41
min								0.09	0.40		0.15	9	7	5	5		3
mean								0.75	0.79		0.76	20	37	41	35		20

ID	0 TGP	8D TGP	14D TGP	21D TGP	29D TGP	9S TGP	0 FA	8D FA	14D FA	21D FA	29D FA	9S FA	0 BILI INDIR	8D BILI INDIR	14D BILI INDIR	21D BILI INDIR	29D BILI INDIR	9S BILI INDIR
GC-368	26	11	30	13		19	26	28	31	31		39	0.20	0.20	0.20	0.30		0.20
GA-277	28	55	26	17		24	55	31	57	50		47	0.20	0.22	0.20	0.20		0.10
GA-300	5	26	28	68		22	24	44	39	44		36	0.50	0.60	0.40	0.40		0.40
GC-355	39	97	66	26		38	48	22	247	320		66	0.18	0.26	0.10	0.50		0.20
GC-360	34	43	70	36		13	240	234	316	237		44	0.20	0.20	0.30	0.10		0.20
GC-373	25	34	30	20		5	40	55	60	60		50	0.14	0.70	0.14	0.12		0.20
GC-383	9	20	51	15		22	37	26	31	33		38	0.30	0.20	0.20	0.30		0.20
GC-370	17	20	53	24		3	42	28	39	46		37	0.20	0.60	0.20	0.14		0.20
GA-290	9	20	10	13		7	47	44	33	55		68	0.20	0.20	0.20	0.10		0.50
GA-246	19	60	49	47		28	31	37	44	26		23	0.3	0.2	0.1	0.12		0.28
GA-287	14	15	15	9		15	39	39	41	59		27	0.70	0.10	0.2	0.10		0.20
GA-298	28	57	15	39		26	62	37	62	59		44	0.20	0.20	0.20	0.40		0.30
GA-283	15	17	15	93		30	50	38	26	48		50	0.14	0.10	0.10	0.10		0.40
GA-258	5	34	68	91		30	47	33	33	178		57	0.10	0.06	0.80	0.10		0.20
GA-263	9	27	70	30		38	39	44	48	30		300	0.16	0.22	0.17	0.12		0.20
GA-274	19	26	39	26		20	66	35	48	48		50	0.40	0.30	0.20	0.20		0.30
GC-353	36	80	13	34		15	60	64		250		62	0.12	0.14	0.28	0.10		0.40
GC-379	7	43	39	13		7	55	50	52	53		73	0.30	0.20	0.20	0.30		0.20
GC-348	15	65	60	9		11	10	17	28	39		24	0.20	0.22	0.17	0.15		0.40
GA-270	11	19	13	18		38	227	277	44	50		64	0.30	0.40	0.30	0.30		0.24
GC-306	10	15	40	7		11	33	33	42	66		46	0.30	0.40	0.20	0.30		0.20
GC-334	19	47	29	29		15	42	33	39	46		22	0.20	0.10	0.30	0.40		0.20
GG-001	18			38		11	28			37		35	0.50			0.30		0.20
GC-257	27	33	22	13		17	55	39	37	33			0.60	0.20	0.40	0.32		0.15
GG-011	55	40	28	53		17	53	65	62	117		59	0.20	0.26	0.40	0.30		0.36
GC-323	39	22	15	12		17	44	50	42	35		59	0.40	0.33	0.30	0.70		0.20
GC-282	13	51	299	60		26	31	33	42	35		28	0.14	0.22	0.04	0.20		0.20
GC-256	38	94	41	33		19	62	90	57	57		33	0.50	0.40	0.10	0.20		0.08
GC-310	19	9	26	15		11	22	60	33	37		42	0.10	0.60	0.37	0.20		0.40
GG-005	17	11	11	19		23	44	37	46	45		68	0.10	0.40	0.30	0.20		0.10
GA-245	20	42	36	102		14	39	35	31	35		35	0.20	0.30	0.30	0.20		0.30
GC-329	15	13	80	34		45	35	55	46	32		55	0.60	0.30	0.50	0.20		0.20
GC-275	28	240	80	22		11	50	62	77	59		28	0.14	0.22	0.24	0.08		0.20
GC-288	5	36	38	19		13	46	37	42	37		55	0.16	0.02	0.10	0.14		0.30
GA-225	15	116	76	53		11	28	24	31	33		53	0.16	0.26	0.59	0.28		0.40
GG-007	32	15	17	24		21	11	48	38	35		35	0.20	0.20	0.30	0.40		0.40
GC-321	24	11	45	68		20	42	39	48	53		50	0.20	0.50	0.55	0.50		0.20
GC-338	13	30	89	34		5	44	35	42	24		24	0.30	0.40	0.20	0.08		0.12
GC-281	10	39	34	28		15	39	37	48			37	0.25	0.16	0.10	0.08		0.20
GC-330	17	17	28	49		11	40	66	62	42		84	0.60	0.50	0.30	0.20		0.40
PENTOSTA																		
max	55	240	299	102		45	240	277	316	320		300	0.70	0.70	0.80	0.70		0.50
min	5	9	10	7		3	10	17	26	24		22	0.10	0.02	0.04	0.08		0.08
mean	20	42	46	34		19	51	53	56	66		52	0.27	0.28	0.26	0.24		0.25

ID	0 BILI DIREC	8D BILI DIREC	14D BILI DIREC	21D BILI DIREC	29D BILI DIREC	9S BILI DIREC	0 PLAQ	21D PLAQ	29D PLAQ	9S PLAQ	0 HB	21D HB	29D HB	9S HB	0 HT	21D HT	29D HT	9S HT
GC-368	0.30	0.20	0.20	0.10		0.20	150	215			15.3	15.0			46	45		
GA-277	0.50	0.15	0.20	0.20		0.20	200	250		225	15.6	16.0		15.3	47	48		46
GA-300	0.80	0.50	0.20	0.20		0.20	175	260		180	16.0	16.0		15.5	48	48		46
GC-355	0.12	1.00	0.40	0.40		0.08	250	270		225	15.3	14.3		15.0	46	43		45
GC-360	0.10	0.20	0.50	0.10		0.20	230	280		190	15.6	14.3		12.7	42	43		37
GC-373	0.14	0.15	0.11	0.10		0.40	210	125		180	13.3	13.6		12.6	40	41		38
GC-383	0.10	0.20	0.20	0.10		0.20	180	150		190	16.0	16.0		16.1	48	47		47
GC-370	0.20	0.30	0.30	0.24		0.16	290	230		280	14.6	15.3		16.6	47	47		49
GA-290	0.20	0.20	0.20	0.40		0.40	250	150		200	15.0	15.3		16.0	45	46		46
GA-246	0.5	0.3	0.28	0.6		0.28	225	180		200	16.0	17.0		16.0	49	50		48
GA-287	0.30	0.20	0.30	0.50		0.20	276	250		250	14.6	14.0		14.0	44	42		42
GA-298	0.20	0.20	0.20	0.20		0.20	150	150		160	15.0	15.0		14.6	45	45		44
GA-283	0.16	0.20	0.40	0.30		0.80	228	220		180	16.3	15.6		14.0	49	47		43
GA-258	0.10	0.30	1.00	0.10		0.20	200	250		225	17.0	16.3		15.0	51	49		45
GA-263	0.20	0.14	0.14	0.24		0.10	260	250		190	14.0	14.0		15.0	42	42		45
GA-274	0.30	0.20	0.30	0.60		0.30	225	160		225	14.2	14.0		18.6	43	42		47
GC-353	0.12	0.14	0.16	0.20		0.60	200	175		280	12.6	12.6		13.0	38	38		39
GC-379	0.10	0.30	0.10	0.10		0.10	180	140		260	16.0	15.3		15.3	48	46		46
GC-348	0.18	0.16	0.18	0.14		0.20	200	250		200	12.6	10.0		12.6	38	30		38
GA-270	0.50	0.60	0.60	0.20		0.24	230	200		270	15.0	14.6		15.0	45	44		45
GC-306	0.20	0.20	1.00	0.40		0.30	250	180			15.3	14.0		14.6	46	42		44
GC-334	0.60	0.20	0.20	0.30		0.36	150			165	13.3	12.0		14.0	40	36		42
GG-001	0.20			0.20		0.20	275	200		210	15.8	14.0		14.0	49	43		43
GC-257	0.50	0.20	0.80	0.46		0.85	200	200			14.3	13.3			43	40		
GG-011	0.10	0.22	0.50	0.30		0.20	190	180		290	15.3	13.3		15.3	46	40		46
GC-323	0.10	0.24	0.10	0.20		0.80	225	180		275	14.0	13.3		15.0	42	41		45
GC-282	0.36	0.20	0.38	0.30		0.30	250	325		200	11.0	11.6		15.0	33	35		45
GC-256	0.20	0.50	0.50	0.10		0.32	220	200			15.6	13.6			47	41		
GC-310	0.20	0.20	0.54	0.20		0.10	140			260	14.3	11.6		14.3	43	35		42
GG-005	0.20	0.30	0.30	0.10		0.40	300	225		175	15.5	15.0		14.6	47	45		44
GA-245	0.60	0.50	0.20	0.30		0.30	325	200		225	16.0	15.3		15.3	48	46		46
GC-329	0.60	0.20	0.30	0.40		0.20	250	140		300	14.0	13.3		14.0	42	40		42
GC-275	0.22	0.20	0.42	0.20		0.60	180	200			16.6	14.0			50	42		
GC-288	0.36	0.28	0.50	0.42		0.50	160			200	15.6			15.0	47			45
GA-225	0.40	1.00	0.56	0.20		0.40	380	250		200	16.3	14.3		16.3	50	43		49
GG-007	0.30	0.20	0.20	0.20		0.30	300			145	13.4	14.0		13.0	40	42		39
GC-321	0.10	0.40	0.30	0.30		0.30	210	170		250	12.0	13.0		15.0	36	39		45
GC-338	0.50	0.30	0.10	0.28		0.23	250			180	15.0			14.0	45			42
GC-281	0.51	0.36	0.32	0.28		0.20	300	230		170	16.6	14.3		14.3	50	43		43
GC-330	0.10	0.50	0.10	0.50		0.20	200	200		200	14.3	15.0		15.0	43	45		45
PENTOSTA																		
max	0.80	1.00	1.00	0.60		0.85	380	325		300	17.0	17.0		18.6	51	50		49
min	0.10	0.14	0.10	0.10		0.08	140	125		145	11.0	10.0		12.6	33	30		37
mean	0.29	0.30	0.34	0.27		0.31	227	207		216	14.9	14.2		14.8	45	43		44

ID	0 GB	21D GB	29D GB	9S GB	0 PMN	21D PMN	29D PMN	9S PMN	0 LINF	21D LINF	29D LINF	9S LINF	0 EOS	21D EOS	29D EOS	9S EOS	0 MONOS	21D MONOS	29D MONOS	9S MONOS
GC-368	5700	8500			67	59			33	40			0	0			0	1		
GA-277	9600	8500		8000	77	72		68	23	26		30	0	2		2	0	0		0
GA-300	7800	6400		8200	60	62		70	40	36		26	0	0		2	0	2		2
GC-355	8600	6400		7500	68	68		62	30	32		35	0	0		3	2	0		0
GC-360	6800	6300		5150	68	68		68	28	32		32	2	0		0	0	0		0
GC-373	5600	7000		7100	60	59		38	36	38		58	2	3		4	2	0		0
GC-383	6600	5350		9900	64	56		66	32	42		30	4	2		2	0	0		1
GC-370	5650	7000		7000	65	66		69	34	30		28	0	0		0	2	2		2
GA-290	7000	5100		8250	68	81		70	32	16		18	0	0		8	0	3		4
GA-246	8900	5800		6950	64	40		46	34	48		42	0	2		5	2	0		6
GA-287	7100	8100		6800	56	68		70	37	32		29	6	0		1	1	0		0
GA-298	5750	7800		6700	44	66		61	40	34		38	16	0		1	0	0		0
GA-283	5400	7200		5100	54	70		54	46	25		46	0	3		0	0	2		0
GA-258	9750	5350		6150	62	65		47	30	32		32	2	2		20	2	0		0
GA-263	6150	9400		6180	62	64		65	36	28		35	2	8		0	0	0		0
GA-274	4100	5650		6200	53	64		60	44	36		38	0	0		0	3	0		2
GC-353	8600	4900		7200	54	60		50	34	40		50	10	0		0	4	0		0
GC-379	7000	8500		7400	68	48		60	30	40		38	2	10		0	0	1		2
GC-348	9050	7550		5350	68	50		64	26	45		36	6	4		0	0	1		0
GA-270	9850	8000		7100	66	71		63	34	25		33	0	4		2	0	0		2
GC-306	7200	9400		6950	62	65		63	36	35		34	0	0		1	1	0		0
GC-334	6300	7200		6400	60	64		56	40	28		30	0	6		12	0	2		2
GG-001	7100	4400		6500	65	65		70	33	32		28	0	2		2	0	1		0
GC-257	5000	6000			66	62			30	34			2	2			0	0		
GG-011	12200	5400		6650	68	66		70	32	30		30	0	2		0	0	0		0
GC-323	5800	6950		10000	58	54		64	36	43		36	2	0		0	4	0		0
GC-282	7300	7800		6650	52	60		62	36	35		32	6	2		4	4	0		2
GC-256	7000	5700			60	55			38	45			0	0			0	0		
GC-310	5000	6600		8500	62	60		75	38	37		23	0	1		2	0	2		0
GG-005	7800	6200		7300	71	72		61	27	26		31	0	2		8	0	0		0
GA-245	8100	6600		6300	65	64		66	35	36		34	0	0		0	0	0		0
GC-329	6950	5050		5900	63	60		50	35	40		46	0	0		0	1	0		4
GC-275	6000	6400			66	64			32	34			0	0			0	0		
GC-288	5000			7100	66			65	34			35	0			0	0			0
GA-225	5600	6300		5900	60	63		48	32	34		44	6	0		0	0	1		7
GG-007	7150	6900		5200	68	70		66	29	28		33	0	0		1	3	0		0
GC-321	4600	8000		4150	55	60		65	43	35		34	2	0		0	0	0		0
GC-338	6500			6200	64			57	36			43	0			0	0			0
GC-281	8900	8100		7200	66	63		56	24	33		34	4	1		6	2	3		2
GC-330	8300	6400		6800	63	65		61	35	35		39	0	0		0	2	0		0
PENTOSTA																				
max	12200	9400		10000	77	81		75	46	48		58	16	10		20	4	3		7
min	4100	4400		4150	44	40		38	23	16		18	0	0		0	0	0		0
mean	7070	6795		6831	63	63		61	34	34		35	2	2		2	1	1		1

ID	GRUPO	RAMA	CUAL	DATOS PERS	CONS	TRATA	REAC ADV	0 CREAT	21D CREA	29D CREAT	9S CREA	0 TGO	8D TGO	14D TGO	21D TGO	29D TGO	9S TGO
GE-021	10	K	C					0.70		0.60	0.90	13		9		7	12
GC-343	10	K	C					0.40		0.48		7		6		10	
GA-256	10	K	C					0.70		0.50	1.00	13		19		15	18
GG-030	10	K	C					0.60		0.50	0.60	9		12		7	10
GG-019	10	K	C					0.80		1.20	0.80	20		12		9	30
GG-027	10	K	C					0.80		0.80	1.20	10		14		15	9
GG-018	10	K	C					0.60				51					
GG-025	10	K	C					0.60		0.80	1.10	7		10		17	15
GG-017	10	K	C					0.50		0.75	0.60	19		5		9	10
GG-023	10	K	C					0.60		0.80	0.60	12		22		7	5
GE-022	10	K	C					0.90		0.70		7		13		15	
GG-014	10	K	C					0.60		1.10		7		6		11	
GG-013	10	K	C					0.50		0.60		19		5		12	
GE-036	10	K	C					0.72		0.41	0.80	18		9		18	24
GG-016	10	K	C					0.74		1.20	0.60	24		13		28	15
GG-020	10	K	C					1.00		0.90		11		15		35	
GG-024	10	K	C					0.80		0.90	0.80	40		12		5	7
GC-341	10	K	C					0.90		0.74	0.80	10		8		9	7
GG-015	10	K	C					0.52		1.20	0.80	19		12		14	12
GE-002	10	K	C	X	X	X	-	0.92		0.95	0.80	17		13		30	11
GC-280	10	K	C	X	X	X	-	0.88		0.87	0.95	7		22		24	18
GC-269	10	K	C	X	X	X	-	0.83		1.00	0.90	10		7		11	13
GC-285	10	K	C	X	X	X	-	1.02		1.20	1.20	15		22		17	19
GC-319	10	K	C	X	X	-	-	0.60		0.64	1.03	30		15		11	21
GC-314	10	K	C	X	X	X	-	0.68		0.86	0.83	55		45		15	9
GG-006	10	K	C	X	X	-	-	1.00		0.67	0.90	26		45		13	22
GC-333	10	K	C	X	X	-	-	0.89		0.70	0.80	13		13		19	17
GC-316	10	K	C	X	X	-	-	0.74		0.81		15		17		13	
GE-030	10	K	C	X	X	-	X	0.70		0.60		14		9		13	
GC-296	10	K	C	X	X	X	-	0.69		1.00	1.00	13		15		19	21
GE-023	10	K	C	X	X	-	X	0.60		0.72	0.50	15		22		17	22
GA-288	10	K	C					0.80		0.70	0.50	5		7		11	5
GG-003	10	K	C	X	X	-	-	0.80		0.69	1.04	19		8		20	20
GC-274	10	K	C	X	X	X	-	0.94		1.00	0.80	11		11		9	11
GC-335	10	K	C	X	X	-	-	0.82		0.70	0.90	7		19		15	7
GG-010	10	K	C	X	X	-	X	0.60		0.93	0.60	11		16		17	22
GC-308	10	K	C	X	X	X	-	0.71		0.74	0.77	17		15		19	18
GC-292	10	K	C	X	X	X	-	0.87		1.20		7		11		11	
GA-242	10	K	C	X	X	-	-	0.97		0.80	0.60	13		13		13	10
GA-219	10	K	C	X	X	X	X	1.05		0.82	1.03	43		24		5	13
Ketoconazole																	
max								1.05		1.20	1.20	55		45		35	30
min								0.40		0.41	0.50	5		5		5	5
mean								0.75		0.81	0.83	17		15		14	15

ID	0 TGP	8D TGP	14D TGP	21D TGP	29D TGP	9S TGP	0 FA	8D FA	14D FA	21D FA	29D FA	9S FA	0 BILI INDIR	8D BILI INDIR	14D BILI INDIR	21D BILI INDIR	29D BILI INDIR	9S BILI INDIR
GE-021	11		7		10	10	28		28		30	30	0.06		0.04		0.10	0.40
GC-343	9		9		15		39		21		40		0.10		0.22		0.18	
GA-256	26		10		15	32	25		40		35	48	0.10		0.12		0.20	0.32
GG-030	22		25		9	15	37		30		37	28	0.20		0.20		0.20	0.10
GG-019	13		16		9	20	42		42		46	35	0.20		0.20		0.30	0.14
GG-027	5		11		8	15	31		29		24	28	0.50		0.20		0.40	0.70
GG-018	52						84						0.30					
GG-025	5		11		13	9	28		26		33	42	0.28		0.20		0.20	0.50
GG-017	19		8		11	15	198		30		42	37	0.50		0.20		0.30	0.40
GG-023	14		12		5	9	42		35		31	31	0.10		0.20		0.10	0.20
GE-022	5		9		18		17		28		33		0.14		0.02		0.10	
GG-014	15		5		11		13		26		138		0.21		0.12		0.20	
GG-013	17		7		10		19		40		40		0.24		0.10		0.10	
GE-036	15		7		15	30	32		19		50	28	0.10		0.09		0.14	0.20
GG-016	13		15		36	15	211		48		42	35	0.70		0.30		0.30	0.40
GG-020	15		19		25		37		30		33		0.30		0.30		0.14	
GG-024	47		10		7	13	50		44		46	42	0.10		0.20		0.30	0.20
GC-341	8		6		6	10	28		30		31	31	0.02		0.4		0.2	0.18
GG-015	15		17		15	16	320		42		37	35	0.40		0.20		0.20	0.10
GE-002	17		13		30	9	42		39			44	0.14		0.39		0.33	0.60
GC-280	11		17		9	30	37		48		50	46	0.20		0.26		0.15	0.30
GC-269	7		11		7	11	42		50		46	59	0.40		0.22		0.08	0.20
GC-285	17		13		5	13	42		22		55	53	0.02		0.36		0.20	0.20
GC-319	18		20		13	49	17		30		42	26	0.12		0.62		0.40	0.20
GC-314	25		32		17	15	28		88		57	50	0.30		0.50		0.50	0.80
GG-006	28		32		13	19	33		35		31	33	0.10		0.70		0.40	0.50
GC-333	9		7		11	11	24		48		50	22	0.30		0.40		0.20	0.12
GC-316	15		19		22		33		48		46		0.50		0.27		0.50	
GE-030	7		19				26		26				0.04		0.18		0.16	
GC-296	11		9		17	18	55		53		57	49	0.24		0.13		0.50	0.30
GE-023	12		26		16	16	17		22		28	45	0.08		0.16		0.30	0.17
GA-288	10		19		9	20	39		48		26	37	0.20		0.30		0.20	0.20
GG-003	17		20		23	20	42		26		35	62	0.20		0.24		0.35	0.10
GC-274	13		9		9	9	26		42		37	24	0.10		0.18		0.04	0.03
GC-335	3		20		17	7	53		33		37	24	0.20		0.20		0.30	0.20
GG-010	17		17		15	16	28		24		37	38	0.25		0.36		0.50	0.30
GC-308	7		7		20	20	33		73		37	44	0.20		0.50		0.60	0.20
GC-292	5		15		5		44		55		59		0.24		0.31		0.30	
GA-242	24		15		13	39	55		44		39	50	0.36		0.30		0.30	0.30
GA-219	51		22		7	7	48		66		33	15	0.50		0.20		0.20	0.14
Ketocona																		
max	52		32		36	49	320		88		138	62	0.70		0.70		0.60	0.80
min	3		5		5	7	13		19		24	15	0.02		0.02		0.04	0.03
mean	16		15		14	17	51		39		42	38	0.23		0.26		0.26	0.28

ID	0 BILI DIREC	8D BILI DIREC	14D BILI DIREC	21D BILI DIREC	29D BILI DIREC	9S BILI DIREC	0 PLAQ	21D PLAQ	29D PLAQ	9S PLAQ	0 HB	21D HB	29D HB	9S HB	0 HT	21D HT	29D HT	9S HT
GE-021	0.36		0.36		0.20	0.02	120		180	185	14.0		13.3	14.0	42		40	41
GC-343	0.20		0.22		0.12		140		250		14.0		13.0		42		39	
GA-256	0.40		0.18		0.20	0.30	280		200	190	14.0		10.6	14.3	42		32	43
GG-030	0.60		0.20		0.30	0.10	175		250	260	13.3		14.0	14.2	40		43	43
GG-019	0.30		0.10		0.50	0.16	160		200		12.0		14.0		36		42	
GG-027	0.20		0.10		0.30	0.20	200			190	15.0			16.3	45			49
GG-018	0.30						150				16.6				50			
GG-025	0.08		0.20		0.10	0.50	250		150	175	16.0		15.0	14.6	48		45	43
GG-017	0.30		0.20		0.90	0.20	300		190	200	13.0		13.6	14.3	39		41	43
GG-023	0.20		0.20		0.60	0.30	240		190	175	14.5		13.0	14.0	44		39	42
GE-022	0.22		0.28		0.4		150				15.0				45			
GG-014	0.18		0.26		0.80		325		290		15.3		15.0		46		45	
GG-013	0.12		0.10		0.12		300			160	14.3			15.2	43			46
GE-036	0.30		0.16		0.14	0.20	300		300	280	16.0		14.3	16.0	48		43	48
GG-016	0.20		0.50		0.90	0.60	180		160	190	15.6		14.3	14.3	47		43	43
GG-020	0.20		0.20		0.16		120		200		14.6		14.6		44		44	
GG-024	0.08		0.10		0.30	0.20	200		175	160	14.0		12.6	13.0	42		37	39
GC-341	0.02		0.3		0.4	0.14	170		200	150	15.0		14.6	14.3	45		44	43
GG-015	0.20		0.10		0.60	0.20	200			225	10.3			11.4	31			34
GE-002	0.56		0.15		0.25	0.10	300			170	15.6		14.4	15.6	47		43	47
GC-280	0.38		0.26		0.35	0.10	325		200	250	14.3		12.3	12.0	43		37	36
GC-269	0.30		0.36		0.20	0.50			300		15.0		14.3		45		43	
GC-285	0.28		0.09		0.30	0.30	200		280	170	15.0		16.6	15.6	45		50	47
GC-319	0.36		0.28		0.50	0.20			190	220			13.6	16.0			41	48
GC-314	0.80		0.30		0.70	0.70			200	150	13.5		10.6	8.3	41		31	25
GG-006	0.30		0.10		0.53	0.40	225		200	225	17.0		12.6	14.0	51		38	42
GC-333	0.40		0.30		0.60	0.28	160		225	170	10.0		13.3	14.6	30		40	44
GC-316	0.20		0.38		0.30				220		16.6		14.0		50		42	
GE-030	0.26		0.42		0.34		190				15.6				47			
GC-296	0.36		0.43		0.40	0.30	300			300	13.0		13.3	13.0	39		40	39
GE-023	0.28		0.30		0.30	0.17	125		200	205	15.0		14.0	14.2	45		43	43
GA-288	0.30		0.20		0.20	0.30	290		210	160	15.0		16.0	16.0	45		47	47
GG-003	0.10		0.28		0.10	0.90	492		200	190	13.4		15.8	10.3	40		48	31
GC-274	0.32		0.32		0.22	0.19	294		260	275	15.6		15.0	14.0	47		45	42
GC-335	0.10		0.40		0.10	0.40	190		195	183	15.3		15.0	15.6	46		45	47
GG-010	0.28		0.32		0.30	0.30	250		150	225	15.0		12.3	16.0	45		37	48
GC-308	0.30		0.30		0.25	0.20	150			200	12.0			13.3	36			40
GC-292	0.28		0.25		0.50		190		250		15.0		15.3		45		46	
GA-242	0.21		0.20		0.20	0.90	280		250	300	13.3		13.3	15.0	40		41	45
GA-219	0.30		0.30		0.20	0.36	300		480	250	14.3		14.6	14.6	43		44	44
Ketocona																		
max	0.80		0.50		0.90	0.90	492		480	300	17.0		16.6	16.3	51		50	49
min	0.02		0.09		0.10	0.02	120		150	150	10.0		10.6	8.3	30		31	25
mean	0.28		0.25		0.36	0.31	228		224	206	14.4		13.9	14.1	43		42	42

ID	0 GB	21D GB	29D GB	9S GB	0 PMN	21D PMN	29D PMN	9S PMN	0 LINF	21D LINF	29D LINF	9S LINF	0 EOS	21D EOS	29D EOS	9S EOS	0 MONOS	21D MONOS	29D MONOS	9S MONOS
GE-021	7250		6100	8300	60		58	60	40		36	38	0		4	2	0		2	0
GC-343	5000		9500		55		36		40		42		5		20					
GA-256	8950		12500	7500	82		70	66	13		23	24	4		0	8	1		2	1
GG-030	6600		5100	7200	59		60	68	28		40	30	8		0	1	2		0	1
GG-019	4350		4900		50		56		40		44		0		0		0		0	
GG-027	6200			6800	53			52	35			48	0			0	2			0
GG-018	11000				70				30				0				0			
GG-025	6200		8250	5800	62		48	55	35		34	45	3		18	0	0		0	0
GG-017	6800		7500	7100	64		59	68	34		41	28	1		0	0	0		0	0
GG-023	5500		7200	7800	66		75	70	22		22	28	8		0	2	4		2	0
GE-022	6000				64				30				6				0			
GG-014	7350		7050		52		60		40		36		8		4		0		0	
GG-013	6200			9700	48			53	38			39	12			5	0			3
GE-036	6400		7350	6800	61		50	60	39		28	32	0		22	8	0		0	0
GG-016	5550		5350	10000	70		62	68	30		38	30	0		0	0	0		0	0
GG-020	4900		7000		56		63		39		35		3		0		2		1	
GG-024	7600		7300	10900	78		70	62	22		30	38	0		0	0	0		0	0
GC-341	5150		7100	7400	44		63	58	50		29	32	6		9	10	0		0	0
GG-015	8250			6800	71			72	26			32	1			4	0			2
GE-002	9300		9500	7600	66		66	58	32		34	40	0		0	2	0		0	0
GC-280	8000		10510	3500	60		60	64	30		40	30	8		0	2	0		0	2
GC-269	5200		8250		66		73		32		24		0		0		0		2	
GC-285	5800		5350	8600	66		57	60	34		40	35	0		1	3	0		2	2
GC-319			6500	7850			60	64			38	34			0	0			0	2
GC-314	5100		7400	7000	57		63	64	40		32	33	1		4	3	2		1	0
GG-006	7550		6900	5250	66		66	67	31		30	28	0		0	3	3		4	1
GC-333	5900		7500	6500	57		60	50	40		35	46	3		4	3	0		1	0
GC-316	8000		6000		63		57		35		34		0		9		2		0	
GE-030	6000				40				57				3				0			
GC-296	11350		7250	8500	70		50	68	23		38	26	2		9	3	2		3	3
GE-023	6050		7100	6725	54		68	68	42		38	30	2		2	1	2		2	0
GA-288	5900		7300	6500	54		60	58	40		36	40	4		4	0	0		0	2
GG-003	7800		10000	13250	41		68	72	36		25	26	22		7	0	1		0	2
GC-274	9800		7550	6800	54		62	70	36		32	28	6		2	0	0		2	2
GC-335	9100		10900	8400	66		61	58	30		39	41	2		0	1	2		0	0
GG-010	5600		5900	5200	64		61	68	36		36	30	0		0	2	0		3	0
GC-308	5000			10000	64			60	36			35	0			5	0			0
GC-292	5600		7700		68		62		32		34		0		3		0		1	
GA-242	11500		7000	11100	74		70	74	22		25	26	0		3	0	0		0	0
GA-219	8900		8000	9350	64		64	65	34		30	32	2		4	2	0		0	1
Ketocona																				
max	11500		12500	13250	82		75	74	57		44	48	22		22	10	4		4	3
min	4350		4900	3500	40		36	50	13		22	24	0		0	0	0		0	0
mean	6992		7540	7808	61		61	63	34		34	33	3		4	2	1		1	1

ID	GRUPO	RAMA	CUAL	DATOS PERS	CONS	TRATA	REAC ADV	0 CREAT	21D CREA	29D CREAT	9S CREA	0 TGO	8D TGO	14D TGO	21D TGO	29D TGO	9S TGO
GC-365	10	K	B					0.68		1.00	0.90	7		20		13	25
GG-028	10	K	B					1.30		1.00	0.70	9		19		9	13
GG-029	10	K	B					0.80		0.50	1.20	15		5		15	3
GA-248	10	K	B					0.70		0.80	1.10	13		25		32	17
GG-022	10	K	B					1.30		0.60	0.80	10				21	34
GE-031	10	K	B					1.00		0.90	0.80	36		8		32	30
GE-041	10	K	B					0.80		0.60		11		12		19	
GG-026	10	K	B					0.60		0.90	0.90	13		20		9	13
GG-021	10	K	B					0.70		1.00	0.90	11		13		10	5
GG-012	10	K	B					1.12		0.90	0.72	22		19		21	9
GG-004	10	K	B	X	X	-	-	0.90		1.00		2		8		15	
GC-298	10	K	B	X	X	X	-	0.46		1.10		15		7		17	
GE-005	10	K	B	X	X	X	-	1.30		1.10		14		11		5	
GC-290	10	K	B	X	X	X	X	0.87		1.10	0.69	9		13		9	9
GG-009	10	K	B	X	X	-	-	0.72		1.11	1.00	9		15		13	35
GA-221	10	K	B	X	X	X	-	0.87		0.92	1.20	51		28		24	40
GG-008	10	K	B	X	X	-	-	1.00		0.30	1.00	19		5		17	9
GA-236	10	K	B	X	X	X	-	1.10		0.85	0.79	17		30		30	41
GC-279	10	K	B	X	X	X	-	0.87		0.79		7		13		7	
GG-002	10	K	B	X	X	-	-	1.00		0.72		13		24		17	
GA-276	10	P	D					0.93	0.90		0.80	13	9	12	28		15
GC-377	10	P	D					0.60	0.50			15	26	9	20		
GC-359	10	P	D					0.80	0.64		0.70	6	30	15	20		7
GC-342	10	P	D					0.80	0.56			9	13	20	8		20
GA-264	10	P	D					0.50	0.80		0.40	10	15	11	9		9
GA-293	10	P	D					0.60	0.90		0.90	34	7	29	11		5
GA-281	10	P	D					1.10	0.70		0.50	7	13	20	9		13
GC-345	10	P	D					0.88	0.26			11	15	9	8		
GC-366	10	P	D					0.90	0.90		0.80	17	10	6	11		13
GC-387	10	P	D					1.00	1.00		0.60	7	20	20	9		28
GC-286	10	P	D	X	X	X	-	0.87	1.13		0.70	11	13	13	17		16
GC-295	10	P	D	X	X	X	-	0.60	0.88		0.90	7	17	9	7		17
GC-326	10	P	D	X	X	-	-	0.85	0.92		0.60	11	9	20	17		15
GC-278	10	P	D	X	X	X	-	0.92	0.90			11	5	17	11		
GC-332	10	P	D	X	X	-	-	0.89	0.86			26	9	7	17		17
GC-327	10	P	D	X	X	-	-	0.49	0.60		0.60	26	9	13	5		24
GC-317	10	P	D	X	X	-	-	0.59	0.65			41	47	18	9		
GC-277	10	P	D	X	X	X	-	1.08	0.52		1.16	11	11	15	9		19
GC-309	10	P	D	X	X	X	-	0.71	1.30		0.73	22	19	9	18		29
GE-017	10	P	D	X	X	-	-	0.94	0.89		0.82	17	11	32	19		13
PLACEBO																	
max								1.30	1.30		1.20	51	47	32	28		41
min								0.46	0.26		0.40	2	5	5	5		3
mean								0.85	0.79		0.82	15	15	15	13		18

ID	0 TGP	8D TGP	14D TGP	21D TGP	29D TGP	9S TGP	0 FA	8D FA	14D FA	21D FA	29D FA	9S FA	0 BILI INDIR	8D BILI INDIR	14D BILI INDIR	21D BILI INDIR	29D BILI INDIR	9S BILI INDIR
GC-365	20		24		15	26	46		42		39	42	0.60		0.30		0.20	0.10
GG-028	7		22		15	7	59		57		68	77	0.10		0.30		0.50	0.40
GG-029	20		9		19	15	44		53		62	62	0.20		0.40		0.20	0.10
GA-248	7		22		39	22	24		39		22	26	0.08		0.30		0.20	0.19
GG-022	5				12	24	31				38	42	0.81				0.20	0.10
GE-031	22		13		16	20	17		28		22	20	0.16		0.20		0.20	0.24
GE-041	15		14		19		32		33		26		0.30		0.25		0.21	
GG-026	9		15		11	11	24		42		31	33	0.10		0.20		0.30	0.10
GG-021	13		9		12	7	26		37		31	26	0.20		0.60		0.30	0.80
GG-012	24		22		25	7	55		64		56	64	0.50		0.40		0.30	0.10
GG-004	3		10		8		33		20				0.40		0.16		0.23	
GC-298	15		20		22		28		42		62		0.08		0.10		0.20	
GE-005	9		5		11		44		28		58		0.40		0.20		0.40	
GC-290	7		17		3	13	39		48		68	44	0.51		0.50		0.30	
GG-009	9		14		20	23	39		55		48	40	0.36		0.20		0.20	0.30
GA-221	28		36		38	55	42		26		42	48	0.10		0.40		0.16	0.20
GG-008	11		9		10	11	35		26		12	38	0.20		0.20		0.30	0.40
GA-236	15		32		28	32	33		53		50	53	0.10		0.20		0.30	0.51
GC-279	5		13		5		37		28		31		0.12		0.08		0.75	
GG-002	5		15		22		28		34		28		0.50		0.30		0.17	
GA-276	15	5	13	10		15	26	24	33	28		35	0.20	0.20	0.20	0.20		0.10
GC-377	11	8	13	15			42	24	33				0.20	0.20	0.60	0.45		
GC-359	13	34	17	19		9	25	201	234	221		92	0.32	0.30	0.30	1.00		0.90
GC-342	10	5	26	12		15	30	26	26	29		15	0.06	0.08	0.10	0.10		0.16
GA-264	25	11	19	12		13	46	35	35	240		46	0.16	0.18	0.12	0.20		0.30
GA-293	45	5	13	9		11	35	38	59	26		8	0.20	0.20	0.30	0.40		0.20
GA-281	9	11	15	20		9	24	24	42	25		26	0.20	0.20	0.20	0.28		0.20
GC-345	13	12	10	10			37	22	25	40			0.20	0.30	0.22	0.23		
GC-366	21	19	7	9		13	42	37	37	44		53	0.20	0.30	0.50	0.30		0.30
GC-387	7	38	13	5		15	31	26	35	35		48	0.40	0.30	0.20	0.50		0.10
GC-286	13	17	32	15		14	42	39	58	39		44	0.90	0.14	0.10	0.28		0.12
GC-295	11	28	13	13		9	46	42	46	73		55	0.26	0.25	0.08	0.30		0.10
GC-326	9	5	19	19		10	55	40	59	42		28	0.50	0.20	0.10	0.20		0.10
GC-278	7	5	15	17			26	24	37				0.15	0.20	0.10	0.14		
GC-332	20	13	7	19		13	34	44	33	37		24	0.50	0.20	0.30	0.30		0.20
GC-327	34	12	17	3		24	35	64	66	40		70	0.50	0.20	0.40	0.40		0.20
GC-317	17	55	20	13			50	39	52	62			0.30	0.40	0.50	0.20		
GC-277	11	9	9	11		20	50	55	68	53		25	0.12	0.08	0.16	0.26		0.30
GC-309	11	9	5	19		34	44	46	79	55		33	0.20	0.10	0.40	0.60		0.40
GE-017	15	11	27	11		13	33	33	37	39		31	0.30	0.30	0.20	0.34		0.40
PLACEBO																		
max	45	55	36	20		55	59	201	234	240		92	0.90	0.40	0.60	1.00	0.75	0.90
min	3	5	5	3		7	17	22	20	25		8	0.06	0.08	0.08	0.10	0.16	0.10
mean	14	16	16	13		17	37	44	47	63		42	0.29	0.22	0.27	0.33	0.28	0.26

ID	0 BILI DIREC	8D BILI DIREC	14D BILI DIREC	21D BILI DIREC	29D BILI DIREC	9S BILI DIREC	0 PLAQ	21D PLAQ	29D PLAQ	9S PLAQ	0 HB	21D HB	29D HB	9S HB	0 HT	21D HT	29D HT	9S HT
GC-365	0.20		0.30		0.20	0.10	200		290		13.3		14.3		40		43	
GG-028	0.90		0.20		0.30	0.20	160		150	260	15.3		14.0	14.3	46		42	43
GG-029	0.40		0.30		0.40	0.30	250		220		11.6		16.4	17.0	35		50	52
GA-248	0.28		0.40		0.40	0.14	280		300	230	14.0		15.0	15.6	42		45	47
GG-022	0.89				0.20	0.70	260		220	150	15.6		15.0	15.6	47		45	47
GE-031	0.20		0.20		0.32	0.10				215	12.2			13.6	39			41
GE-041	0.50		0.30		0.15				225		12.8		14.3		40		43	
GG-026	0.20		0.20		0.10	0.20	190		260	260	15.0		15.0	15.3	45		45	46
GG-021	0.10		0.10		0.10	0.60	170		200	200	12.6		14.3	16.0	38		43	48
GG-012	0.30		0.60		0.20	0.47	200		225	260	15.0		14.3	15.0	45		43	45
GG-004	0.10		0.13				509				16.0				48			
GC-298	0.20		0.20		0.90		225				16.6		16.6		50		50	
GE-005	0.30		0.50		0.20						15.6				47			
GC-290	0.30		0.25		0.70		170		260		15.3		13.6	16.0	46		41	48
GG-009	0.39		0.20		0.20	0.30	200		225	112	16.0		14.6	14.0	48		44	42
GA-221	0.20		0.30		0.65	0.20	190		200		13.0		13.3	16.0	39		40	48
GG-008	0.70		0.18		0.10	0.30				175	16.0		14.5	15.0	48		43	45
GA-236	0.40		0.30		0.50	0.30			250	250	15.0		16.3	15.0	45		47	45
GC-279	0.24		0.52		0.15		350		180		15.6		16.6		47		50	
GG-002	0.10		0.30		0.14		301		300		16.4		12.0		50		36	
GA-276	0.20	0.50	0.30	0.50		0.14	150	200		280	15.3	15.6		15.6	46	47		47
GC-377	0.20	0.10	0.10				225				13.0				39			
GC-359	0.15	0.15	0.30	0.30		0.30	275	160		290	13.6	14.6		14.6	41	44		44
GC-342	0.56	0.40	0.30	0.30		0.10	190	150		150	11.3	12.8		15.6	34	39		47
GA-264	0.14	0.12	0.36	0.30		0.30	200	290		180	12.0	13.6		11.6	36	41		35
GA-293	0.60	0.40	0.30	0.30		0.20	150	150		250	16.0	15.6		15.6	48	47		47
GA-281	0.20	0.20	0.20	0.24		0.30	150	200		180	17.0	16.0		14.0	52	48		43
GC-345	0.30	0.39	0.20	0.18			195	260			13.6	12.6			41	38		
GC-366	0.20	0.20	0.20	0.20		0.10	200			225	14.3			14.0	43			42
GC-387	0.20	0.10	0.10	0.10		0.30	170	150		220	14.0	15.0		16.0	42	44		48
GC-286	0.61	0.42	0.35	0.38		0.27	190			210	14.0			14.5	42			44
GC-295	0.30	0.20	0.58	0.40		0.30	215	190		200	12.0	15.3		12.6	36	46		38
GC-326	0.10	0.20	0.10	0.20		0.30	280			170	16.0			14.6	48			44
GC-278	0.56	0.30	0.32	0.46			350	260			14.3	14.0			43	42		
GC-332	0.30	0.20	0.50	0.40		0.20	250	225		200	16.6	16.0		14.6	50	47		44
GC-327	0.40	0.30	0.20	0.20		0.20	190	120		275	14.0	15.0		13.3	42	45		40
GC-317	0.50	0.30	0.10	0.20				180			14.0	14.3			42	43		
GC-277	0.36	0.32	0.20	0.30		0.20	325	300		180	14.0	13.6		14.3	43	41		43
GC-309	0.40	0.40	0.20	0.10		0.20	150	275		250	12.6	14.6		14.3	38	44		43
GE-017	0.20	0.10	0.10	0.31		0.20		250		303	16.0	15.0		16.0	48	46		48
PLACEBO																		
max	0.90	0.50	0.60	0.50	0.90	0.70	509	300	300	303	17.0	16.0	16.6	17.0	52	48	50	52
min	0.10	0.10	0.10	0.10	0.10	0.10	150	120	150	112	11.3	12.6	12.0	11.6	34	38	36	35
mean	0.33	0.27	0.27	0.28	0.31	0.26	228	210	234	218	14.4	14.6	14.7	14.8	43	44	44	45

ID	0 GB	21D GB	29D GB	9S GB	0 PMN	21D PMN	29D PMN	9S PMN	0 LINF	21D LINF	29D LINF	9S LINF	0 EOS	21D EOS	29D EOS	9S EOS	0 MONOS	21D MONOS	29D MONOS	9S MONOS
GC-365	7400		6500		56		58		42		40		0		2		2		0	
GG-028	9800		6100	5100	61		55	52	34		45	46	4		0	0	1		0	2
GG-029	4200		5800	5850	50		62	66	32		36	34	18		2	0	0		0	0
GA-248	6850		7350	9250	59		70	73	41		25	20	0		4	3	0		1	4
GG-022	6050		7200	6600	59		61	58	38		38	36	1		1	2	2		0	4
GE-031	8300			10350	44			71	30			23	24			3	2			2
GE-041	5100		7100		51		66		28		26		11		6		10		2	
GG-026	4900		11700	13550	44		70	72	40		30	28	14		0	0	1		0	0
GG-021	8900		7500	9500	64		64	66	33		34	32	1		1	2	2		1	2
GG-012	10900		6800	7400	73		63	60	26		33	36	0		2	2	0		2	0
GG-004	7500				56				32				12				0			
GC-298	8600		5650		62		48		30		40		0		7		0		5	
GE-005	7900				68				32				0				0			
GC-290	4300		8250	11100	58		60	65	38		37	32	0		2	3	2		0	0
GG-009	8400		11900	8500	40		67	70	48		26	22	4		5	5	4		2	2
GA-221	4900		7750	4500	60		52	42	40		46	52	0		0	3	0		0	3
GG-008	8850		7200	8300	66		74	66	32		24	31	2		2	2	0		0	1
GA-236	7800		8600	6450	60		71	60	35		27	38	5		0	0	0		0	0
GC-279	8750		8900		64		70		10		30		2		0		0		0	
GG-002	8400		14800		61		67		20		19		18		12		1		0	
GA-276	7750	5700		8000	64	64		69	32	36		30	2	0		0	0	0		0
GC-377	6800				66				32				1				1			
GC-359	5500	5500		6150	57	59		64	41	40		36	2	1		0	0	0		0
GC-342	6400	6500		11500	56	64		34	34	36		40	8	0		26	1	0		0
GA-264	8600	7750		6450	60	63		54	35	34		46	3	1		0	0	0		0
GA-293	6250	5800		4800	70	68		60	26	32		40	4	0		0	0	0		0
GA-281	5650	7000		5800	57	62		66	42	35		32	0	0		0	0	2		2
GC-345	5200	6250			64	44			36	40			0	16			0	0		
GC-366	5700			8200	64			59	36			40	0			1	0			0
GC-387	10300	5600		6450	57	50		58	34	46		40	9	2		0	0	2		2
GC-286	6900			7600	64			74	34			22	0			2	0			2
GC-295	8450	4700		6300	68	60		62	27	38		38	3	1		0	0	0		0
GC-326	7250			6200	59			55	39			43	0			2	2			0
GC-278	9700	9350			64	63			34	32			0	2			2	0		
GC-332	9100	14500		9200	71	76		67	20	21		33	6	0		0	1	0		0
GC-327	8200	8650		7600	69	60		58	31	40		42	0	0		0	0	0		0
GC-317	7250	8700			60	74			40	23			0	0			0	0		
GC-277	7400	10000		7150	70	68		60	28	31		35	0	0		3	2	1		0
GC-309	5350	6200		7200	52	69		66	44	29		34	0	1		0	0	0		0
GE-017	14100	7200		5600	69	61		60	30	37		38	0	0		0	1	1		2
PLACEBO																				
max	14100	14500	14800	13550	73	76	74	74	48	46	46	52	24	16	12	26	10	2	5	4
min	4200	4700	5650	4500	40	44	48	34	10	21	19	20	0	0	0	0	0	0	0	0
mean	7491	7463	8182	7609	60	63	63	62	33	34	33	35	4	2	3	2	1	0	1	1