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TITLE: EVALUATION OF SODIUM STIBOGLUCONATE (PENTOSTAM) AND KETOCONAZOLE IN THE TREATMENT OF AMERICAN CUTANEOUS LEISHMANIASIS

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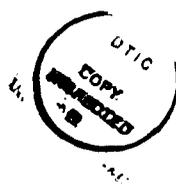
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stibogluconate, 4 (50%); ketoconazole 8 (80%); and placebo, 6 (38%). High dose sodium stibogluconate appears to be well tolerated and effective against infections caused by L. b. braziliensis but less so against infections caused by L. m. mexicana,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



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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.

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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 stibogluconate (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 to 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

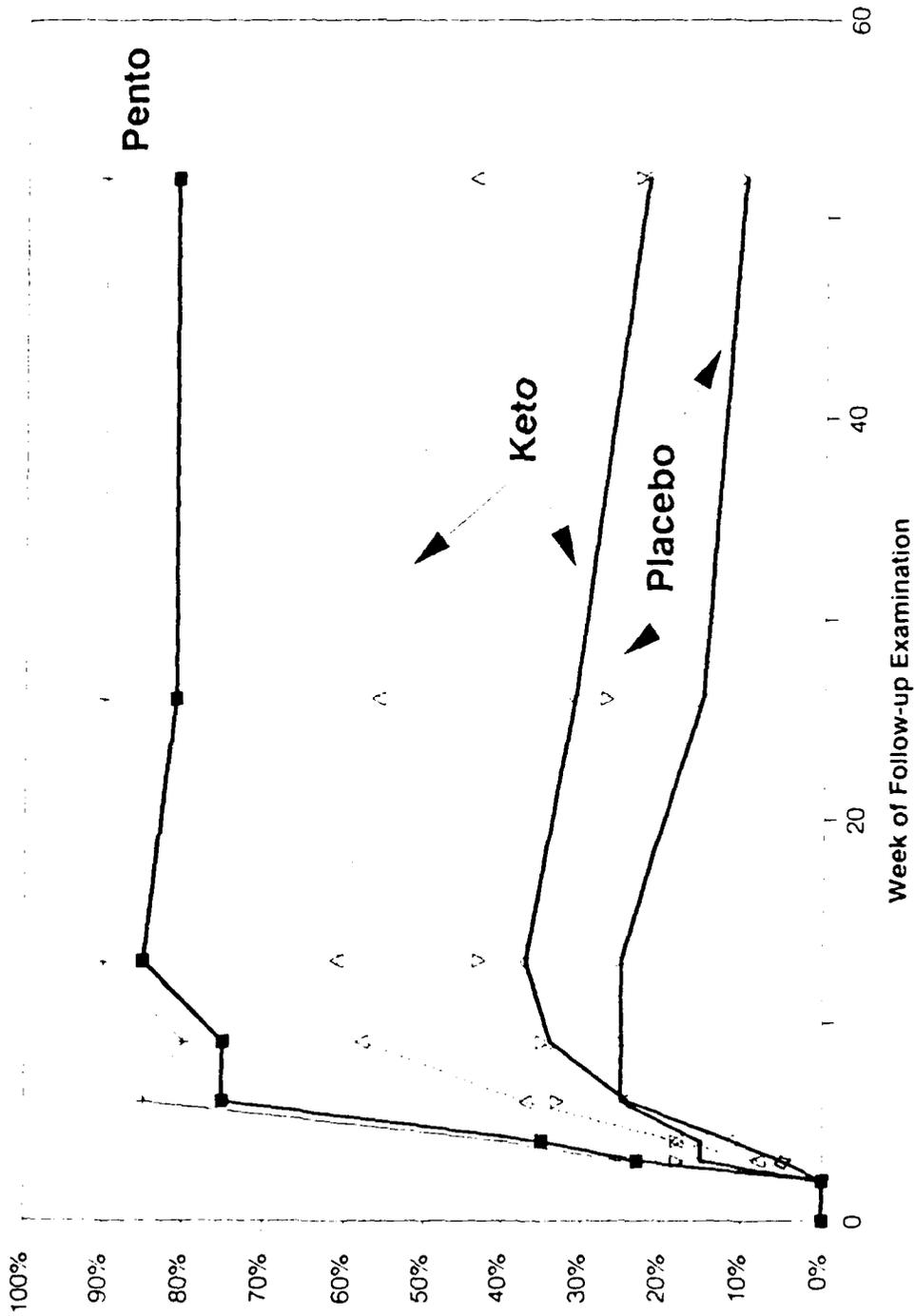
* Number of patients with values at the last day of treatment outside of the normal range for the testing laboratory.

Table 3. Adverse Reactions Reported by Patients

Treatment group/ Adverse reaction	Severity *			Total
	Mild	Moderate	Severe	
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

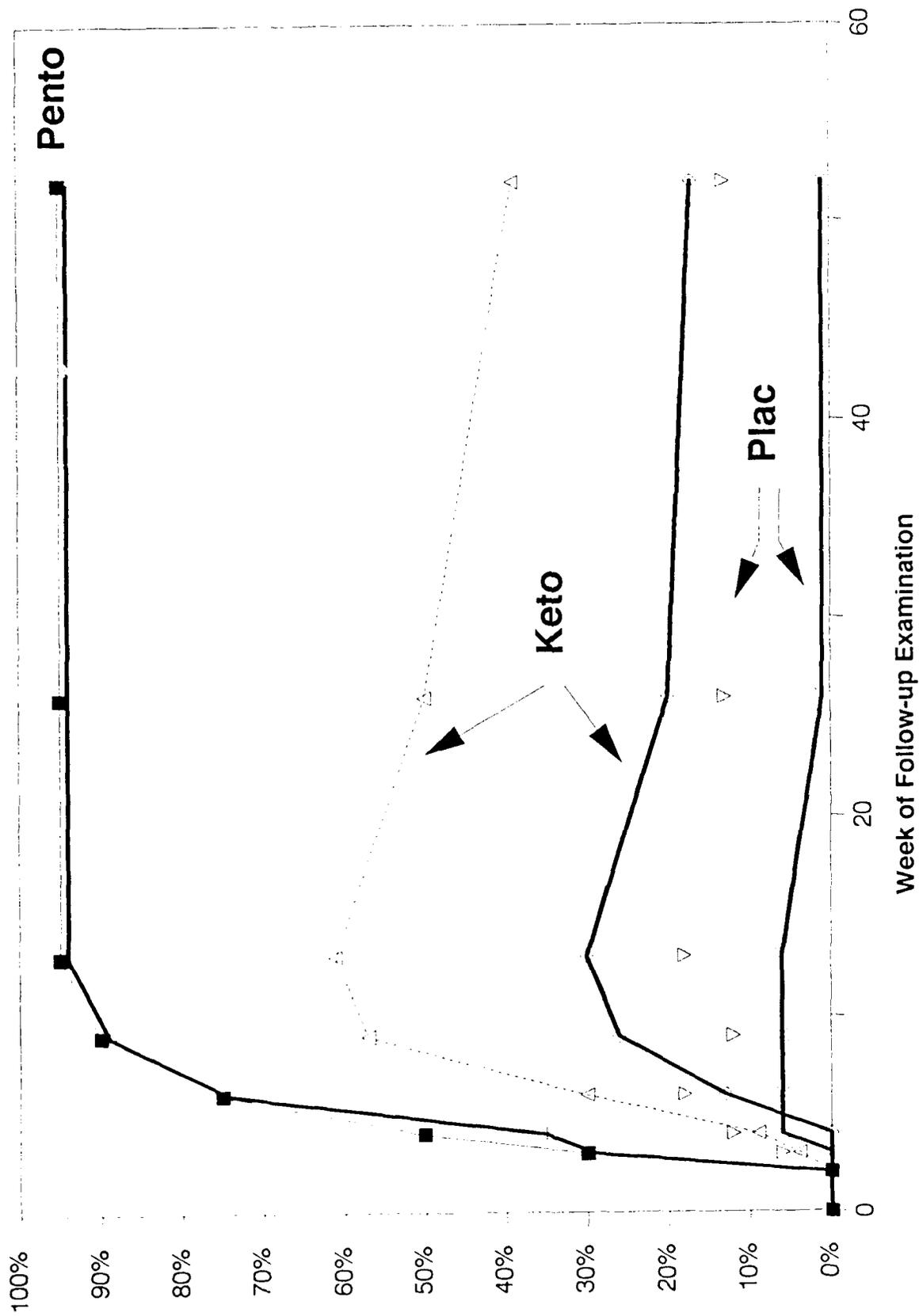
* Mild: No need for medical attention
 Moderate: Required medical attention, but posed no danger to patient
 Severe: Required immediate medical attention to prevent danger to patient

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



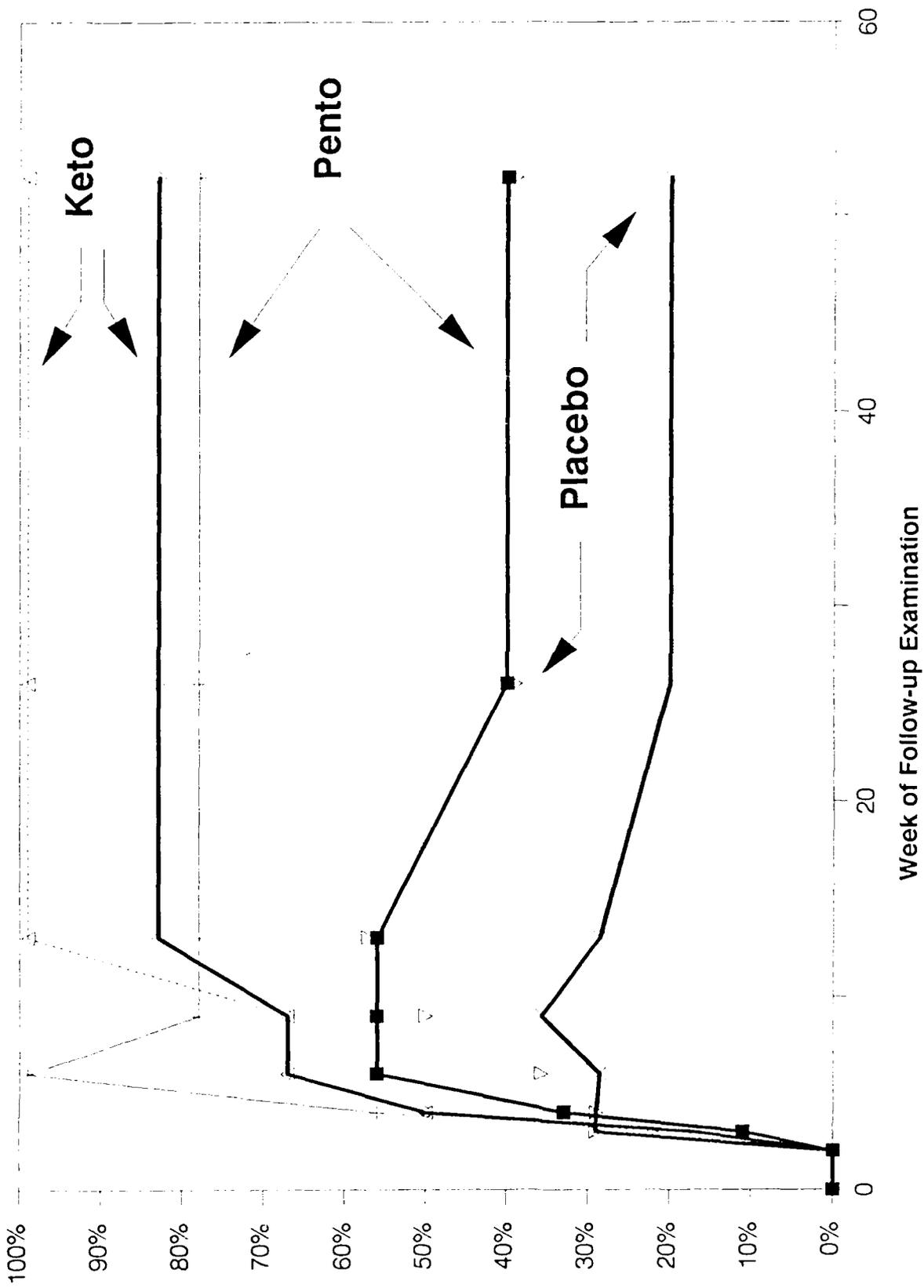
Bold line = clinical and parasitological response
Narrow line = clinical response (cultures may have been positive)

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.

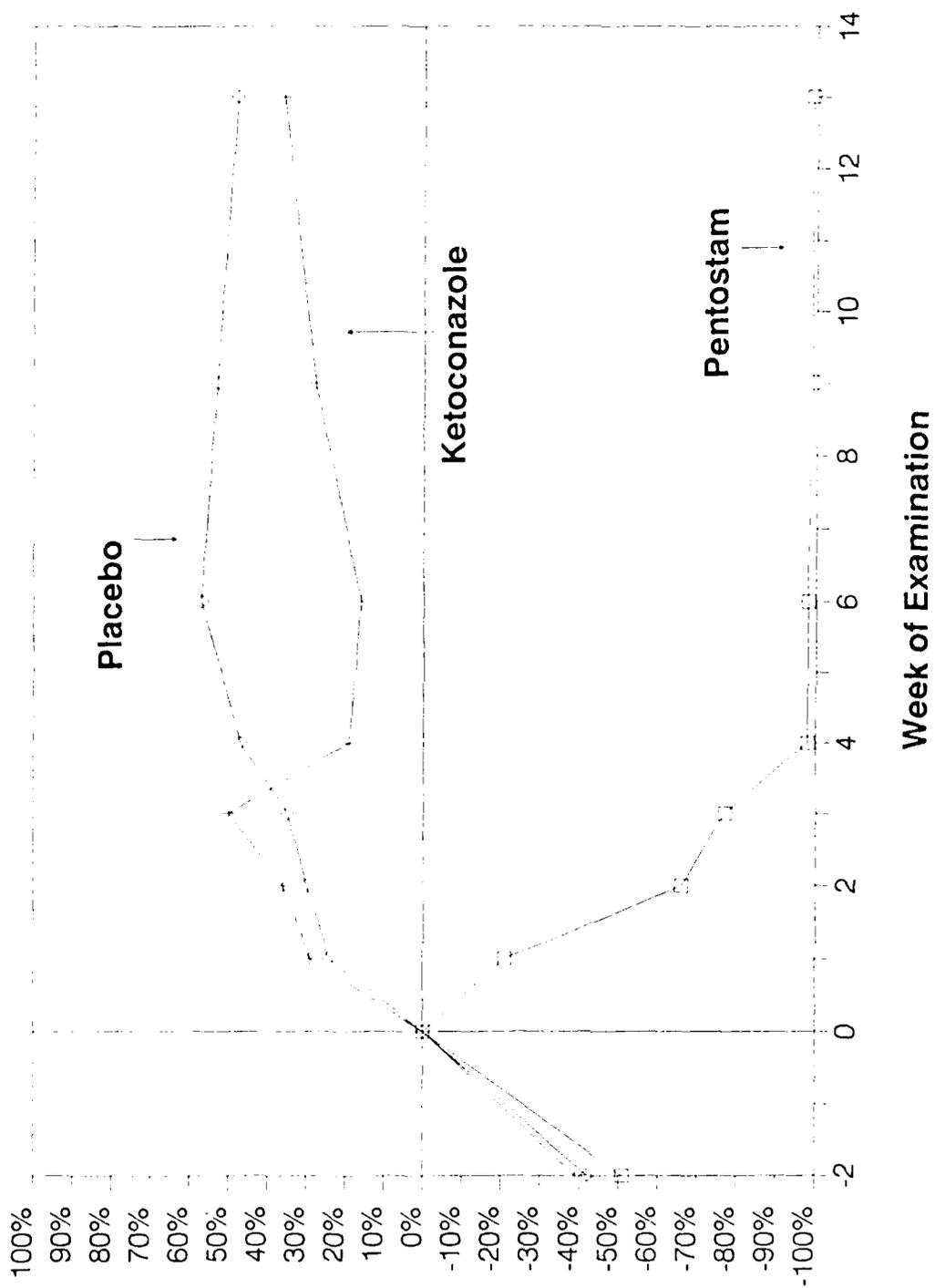


Figure 4. Change in lesion size from 2 weeks before to 13 weeks after starting therapy for patients infected with L. b. braziliensis.

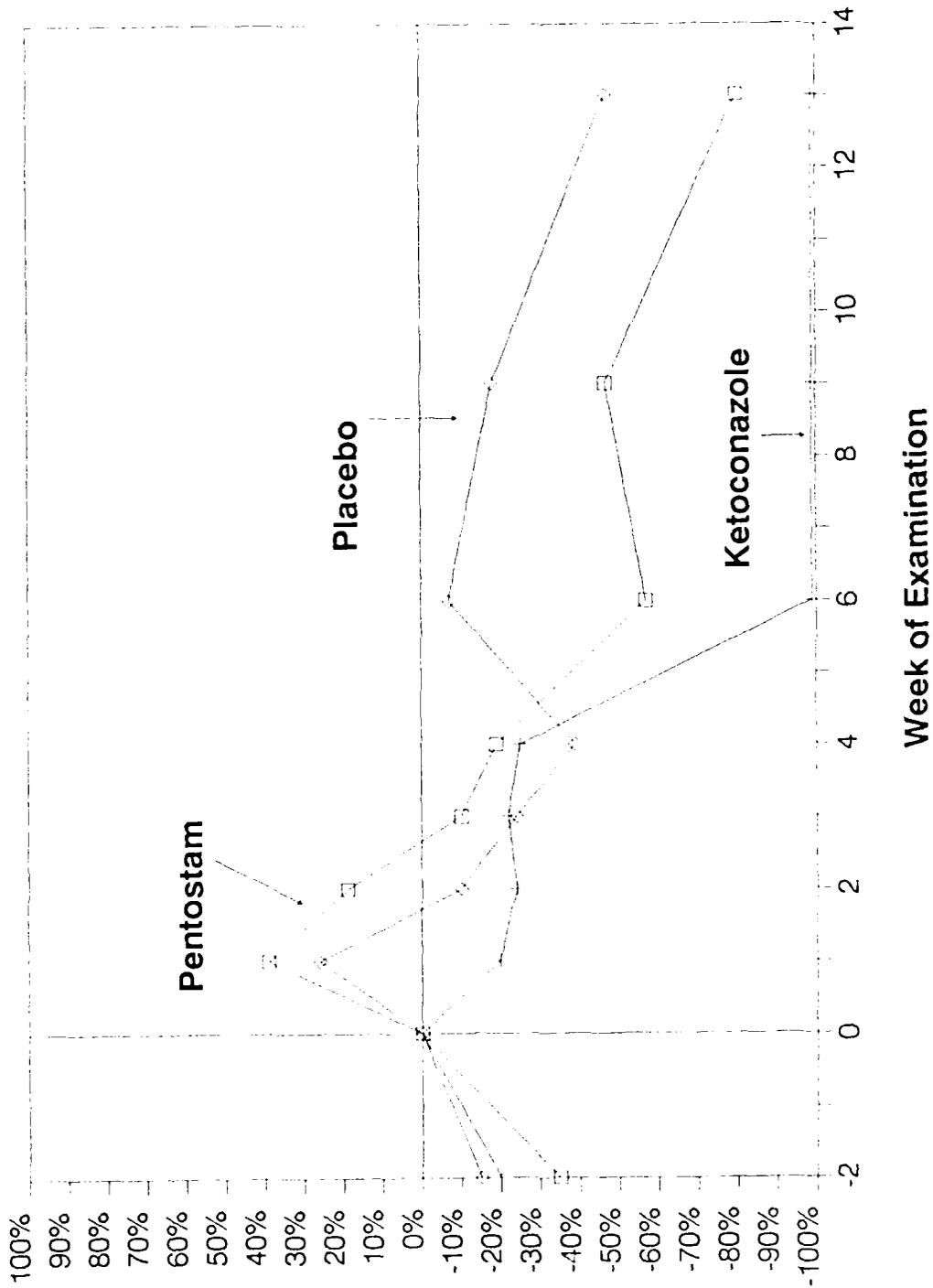


Figure 5. Change in lesion size from 2 weeks before to 23 weeks after starting therapy for patients infected with L. m. mexicana.

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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 <i>P. vivax</i> 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.

Pentostam (page 2)

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.

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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 antihistimincs, the patient insisted on terminating treatment with ketoconazole. The rash resolved spontaneously 3 days after it began.
GG-010	Mild	Dizziness. 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.
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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 CONS TRATA REAC ADV	0		80		140		210		290		95	
					TGO	CREA	TGO	CREA	TGO	CREA	TGO	CREA	TGO	CREA	TGO	CREA
GC-368	10	P	A		0.60	0.80	20	0.70	7	15	13	19	19	19	19	19
GA-277	10	P	A		0.90	0.70	25	0.70	26	20	20	22	22	22	22	22
GA-300	10	P	A		0.50	1.40	9	0.80	28	36	87	35	35	35	35	35
GC-355	10	P	A		0.60	0.67	36	0.80	80	57	30	32	32	32	32	32
GC-360	10	P	A		0.80	0.83	26	0.40	41	43	28	11	11	11	11	11
GC-373	10	P	A		0.70	0.50	26	0.90	24	20	20	9	9	9	9	9
GC-383	10	P	A		1.10	0.90	11	0.70	32	45	30	36	36	36	36	36
GC-370	10	P	A		0.30	0.50	11	0.80	19	19	26	5	5	5	5	5
GA-290	10	P	A		0.80	0.60	14	0.90	28	15	11	3	3	3	3	3
GA-246	10	P	A		0.90	0.90	19	0.65	51	47	37	20	20	20	20	20
GA-287	10	P	A		0.70	0.70	10	0.90	17	22	11	18	18	18	18	18
GA-298	10	P	A		0.80	0.90	24	1.00	26	11	22	21	21	21	21	21
GA-283	10	P	A		0.70	0.70	10	0.90	12	5	74	41	41	41	41	41
GA-258	10	P	A		0.80	0.50	10	0.50	52	42	100	25	25	25	25	25
GA-263	10	P	A		0.80	0.50	9	0.68	36	28	5	38	38	38	38	38
GA-274	10	P	A		0.68	1.01	17	0.80	22	30	20	17	17	17	17	17
GC-353	10	P	A		0.70	0.70	30	0.50	30	8	38	19	19	19	19	19
GC-379	10	P	A		0.90	0.60	11	0.90	15	22	13	19	19	19	19	19
GC-348	10	P	A		0.09	0.60	17	0.15	60	43	5	17	17	17	17	17
GA-270	10	P	A		0.70	0.88	15	0.60	26	9	16	30	30	30	30	30
GC-306	10	P	A	X	0.80	1.10	15	0.68	26	60	26	26	26	26	26	26
GC-334	10	P	A	X	0.82	0.89	15	0.70	32	13	36	24	24	24	24	24
GG-001	10	P	A	X	0.60	0.80	19	1.00	32	13	26	17	17	17	17	17
GC-257	10	P	A	X	0.87	1.03	30	0.84	36	19	17	22	22	22	22	22
GG-011	10	P	A	X	1.06	0.83	34	0.60	50	41	43	17	17	17	17	17
GC-323	10	P	A	X	0.73	0.76	27	0.60	17	19	11	7	7	7	7	7
GC-282	10	P	A	X	1.03	1.31	13	0.91	53	358	46	24	24	24	24	24
GC-256	10	P	A	X	1.15	1.05	45	0.71	65	70	36	20	20	20	20	20
GC-310	10	P	A	X	0.90	0.73	41	0.74	11	15	39	13	13	13	13	13
GG-005	10	P	A	X	0.40	0.90	15	1.02	12	39	22	19	19	19	19	19
GA-245	10	P	A	X	1.00	0.60	15	0.86	32	53	102	18	18	18	18	18
GC-329	10	P	A	X	0.58	0.80	17	0.80	19	36	32	26	26	26	26	26
GC-275	10	P	A	X	0.78	0.79	28	0.79	200	39	39	24	24	24	24	24
GC-288	10	P	A	X	0.79	0.97	13	0.90	24	20	15	13	13	13	13	13
GA-225	10	P	A	X	0.80	1.20	15	1.00	102	51	50	9	9	9	9	9
GG-007	10	P	A	X	0.70	0.70	26	1.00	17	11	30	36	36	36	36	36
GC-321	10	P	A	X	0.73	0.70	30	0.79	9	51	68	13	13	13	13	13
GC-338	10	P	A	X	0.70	0.50	11	0.64	60	90	39	7	7	7	7	7
GC-281	10	P	A	X	0.92	1.21	17	0.89	38	36	43	19	19	19	19	19
GC-330	10	P	A	X	0.70	0.80	19	0.60	22	22	59	13	13	13	13	13
PENTOSTAM																
max					1.15	1.31	45	1.02	200	358	102	41	41	41	41	41
min					0.09	0.40	9	0.15	7	5	5	3	3	3	3	3
mean					0.75	0.79	20	0.76	37	41	35	20	20	20	20	20

ID	0 TGP		80 TGP		140 TGP		210 TGP		290 TGP		9S TGP		0 BILI INDIR		80 BILI INDIR		140 BILI INDIR		210 BILI INDIR		290 BILI INDIR		9S BILI INDIR									
	TGP		TGP		TGP		TGP		TGP		TGP		FA	FA	FA	FA	FA	FA	FA	FA	FA	FA	FA	INDIR								
GC-368	26	11	30	13	26	28	31	31	31	31	39	39	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	
GA-277	28	55	26	17	55	31	57	50	50	47	47	47	0.20	0.22	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	
GA-300	5	26	28	68	24	44	39	44	44	36	36	36	0.50	0.60	0.40	0.40	0.40	0.40	0.40	0.40	0.40	0.40	0.40	0.40	0.40	0.40	0.40	0.40	0.40	0.40	0.40	
GC-355	39	97	66	26	48	22	247	320	320	66	66	66	0.18	0.26	0.10	0.50	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	
GC-360	34	43	70	36	240	234	316	237	237	44	44	44	0.20	0.20	0.30	0.10	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	
GC-373	25	34	30	20	40	55	60	60	60	50	50	50	0.14	0.70	0.14	0.12	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	
GC-383	9	20	51	15	37	26	31	33	33	38	38	38	0.30	0.20	0.20	0.30	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	
GC-370	17	20	53	24	42	28	39	46	46	37	37	37	0.20	0.20	0.20	0.10	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	
GA-290	9	20	10	13	47	44	33	55	55	68	68	68	0.3	0.2	0.1	0.12	0.28	0.28	0.28	0.28	0.28	0.28	0.28	0.28	0.28	0.28	0.28	0.28	0.28	0.28	0.28	
GA-246	19	60	49	47	31	37	44	26	26	23	23	23	0.70	0.10	0.2	0.10	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	
GA-287	14	15	15	9	39	39	41	59	59	27	27	27	0.20	0.20	0.20	0.40	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	
GA-298	28	57	15	39	62	37	62	59	59	44	44	44	0.14	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10	
GA-283	15	17	15	93	50	38	26	48	48	50	50	50	0.10	0.06	0.80	0.10	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	
GA-258	5	34	68	91	47	33	33	178	178	57	57	57	0.16	0.22	0.17	0.12	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	
GA-263	9	27	70	30	39	44	48	30	30	50	50	50	0.40	0.30	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	
GA-274	19	26	39	26	66	35	48	48	48	50	50	50	0.12	0.14	0.28	0.10	0.40	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30	
GC-353	36	80	13	34	60	64	48	48	48	62	62	62	0.30	0.20	0.20	0.30	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	
GC-379	7	43	39	13	55	50	52	53	53	73	73	73	0.20	0.22	0.17	0.15	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	
GC-348	15	65	60	9	10	17	28	39	39	24	24	24	0.30	0.40	0.30	0.30	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	
GA-270	11	19	13	18	227	277	44	50	50	64	64	64	0.30	0.40	0.20	0.30	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	
GC-306	10	15	40	7	33	33	42	66	66	46	46	46	0.30	0.40	0.20	0.30	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	
GC-334	19	47	29	29	42	33	39	46	46	22	22	22	0.20	0.10	0.30	0.40	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	
GG-001	18			38	28			37	37	35	35	35	0.50	0.50	0.30	0.40	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	
GC-257	27	33	22	13	55	39	37	33	33	59	59	59	0.60	0.20	0.40	0.32	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	
GG-011	55	40	28	53	53	65	62	117	117	59	59	59	0.20	0.26	0.40	0.30	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	
GC-323	39	22	15	12	44	50	42	35	35	59	59	59	0.40	0.33	0.30	0.70	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	
GC-282	13	51	299	60	31	33	42	35	35	28	28	28	0.14	0.22	0.04	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	
GC-256	38	39	41	33	62	90	57	57	57	33	33	33	0.50	0.40	0.10	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	
GC-310	19	9	26	15	22	60	33	37	37	42	42	42	0.10	0.60	0.37	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	
GG-005	17	11	11	19	44	37	46	45	45	68	68	68	0.10	0.40	0.30	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	
GA-245	20	42	36	102	39	35	31	35	35	35	35	35	0.20	0.30	0.30	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	
GC-329	15	13	80	34	35	55	46	32	32	55	55	55	0.60	0.30	0.50	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	
GC-275	28	240	80	22	50	62	77	59	59	28	28	28	0.14	0.22	0.24	0.08	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	
GC-288	5	36	38	19	46	37	42	37	37	55	55	55	0.16	0.02	0.10	0.14	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30	
GA-225	15	116	76	53	28	24	31	33	33	53	53	53	0.16	0.26	0.59	0.28	0.40	0.40	0.40	0.40	0.40	0.40	0.40	0.40	0.40	0.40	0.40	0.40	0.40	0.40	0.40	
GG-007	32	15	17	24	11	48	38	35	35	35	35	35	0.20	0.20	0.30	0.40	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	
GC-321	24	11	45	68	42	39	48	53	53	50	50	50	0.20	0.50	0.55	0.50	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	
GC-338	13	30	89	34	44	35	42	24	24	24	24	24	0.30	0.40	0.20	0.08	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	
GC-281	10	39	34	28	39	37	48	48	48	37	37	37	0.25	0.16	0.10	0.08	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	
GC-330	17	17	28	49	40	66	62	62	62	84	84	84	0.60	0.50	0.30	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	
PENTOSTA																																
max	55	240	299	102	240	277	316	320	320	300	300	300	0.70	0.70	0.80	0.70	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	
min	5	9	10	7	10	17	26	24	24	22	22	22	0.10	0.02	0.04	0.08	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	
mean	20	42	46	34	51	53	56	66	66	52	52	52	0.27	0.28	0.26	0.24	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	

ID	0		80		140		210		290		95		0		210		290		95		
	BILI DIREC	PLAQ	PLAQ	PLAQ	HB	HB	HB	HT	HT	HT	HT										
GC-368	0.30	0.20	0.20	0.20	0.20	0.10	0.20	0.20	0.20	0.20	150	215	15.3	15.0	15.3	46	45	46	45		
GA-277	0.50	0.15	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	200	250	15.6	16.0	15.3	47	48	47	48		
GA-300	0.80	0.50	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	175	260	16.0	16.0	15.5	48	48	48	48		
GC-355	0.12	1.00	0.40	0.40	0.40	0.40	0.08	0.08	0.08	0.08	250	270	15.3	14.3	15.0	46	43	46	43		
GC-360	0.10	0.20	0.50	0.10	0.20	0.10	0.20	0.20	0.20	0.20	230	280	15.6	14.3	12.7	42	43	42	43		
GC-373	0.14	0.15	0.11	0.10	0.10	0.10	0.40	0.40	0.40	0.40	210	125	13.3	13.6	12.6	40	41	40	41		
GC-383	0.10	0.20	0.20	0.10	0.20	0.10	0.20	0.20	0.20	0.20	180	150	16.0	16.0	16.1	48	47	48	47		
GC-370	0.20	0.30	0.30	0.24	0.20	0.24	0.16	0.16	0.16	0.16	290	230	14.6	15.3	16.6	47	47	47	47		
GA-290	0.20	0.20	0.20	0.40	0.20	0.40	0.40	0.40	0.40	0.40	250	150	15.0	15.3	16.0	45	46	45	46		
GA-246	0.5	0.3	0.28	0.6	0.28	0.6	0.28	0.28	0.28	0.28	225	180	16.0	17.0	16.0	49	50	49	50		
GA-287	0.30	0.20	0.30	0.50	0.20	0.50	0.20	0.20	0.20	0.20	276	250	14.6	14.0	14.0	44	42	44	42		
GA-298	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	150	150	15.0	15.0	14.6	45	45	45	45		
GA-283	0.16	0.20	0.40	0.30	0.20	0.30	0.80	0.80	0.80	0.80	228	220	16.3	15.6	14.0	49	47	49	47		
GA-258	0.10	0.30	1.00	0.10	0.20	0.10	0.20	0.20	0.20	0.20	200	250	17.0	16.3	15.0	51	49	51	49		
GA-263	0.30	0.14	0.14	0.24	0.10	0.24	0.10	0.10	0.10	0.10	260	250	14.0	14.0	15.0	42	42	42	42		
GA-274	0.30	0.20	0.30	0.60	0.30	0.60	0.30	0.30	0.30	0.30	225	160	14.2	14.0	18.6	43	42	43	42		
GC-353	0.12	0.14	0.16	0.20	0.12	0.20	0.60	0.60	0.60	0.60	200	175	12.6	12.6	13.0	38	38	38	38		
GC-379	0.10	0.30	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10	180	140	16.0	15.3	15.3	48	46	48	46		
GC-348	0.18	0.16	0.18	0.14	0.20	0.14	0.20	0.20	0.20	0.20	200	250	12.6	10.0	12.6	38	30	38	30		
GA-270	0.50	0.60	0.60	0.40	0.20	0.40	0.24	0.24	0.24	0.24	230	200	15.0	14.6	15.0	45	44	45	44		
GC-306	0.20	0.20	1.00	0.20	0.30	0.20	0.30	0.36	0.36	0.36	150	180	13.3	12.0	14.0	46	42	46	42		
GC-334	0.60	0.20	0.20	0.30	0.20	0.30	0.20	0.20	0.20	0.20	275	200	15.8	14.0	14.0	49	43	49	43		
GG-001	0.20	0.20	0.80	0.46	0.20	0.46	0.20	0.20	0.20	0.20	200	200	14.3	13.3	14.3	43	40	43	40		
GC-257	0.50	0.20	0.20	0.50	0.30	0.50	0.20	0.20	0.20	0.20	190	180	15.3	13.3	15.3	46	40	46	40		
GG-011	0.10	0.22	0.50	0.30	0.20	0.30	0.20	0.20	0.20	0.20	290	180	14.0	13.3	15.0	42	41	42	41		
GC-323	0.10	0.24	0.10	0.20	0.20	0.20	0.80	0.80	0.80	0.80	225	180	11.0	11.6	15.0	33	35	33	35		
GC-282	0.36	0.20	0.38	0.30	0.30	0.30	0.30	0.30	0.30	0.30	250	325	15.6	13.6	14.3	47	41	47	41		
GC-256	0.20	0.50	0.50	0.10	0.20	0.10	0.32	0.32	0.32	0.32	220	200	14.3	11.6	14.3	43	35	43	35		
GC-310	0.20	0.20	0.54	0.20	0.10	0.20	0.10	0.10	0.10	0.10	140	200	15.5	15.0	14.6	47	45	47	45		
GG-005	0.20	0.30	0.30	0.10	0.20	0.10	0.40	0.40	0.40	0.40	300	225	16.0	15.3	15.3	48	46	48	46		
GA-245	0.60	0.50	0.20	0.30	0.30	0.30	0.30	0.30	0.30	0.30	325	200	14.0	13.3	14.0	42	40	42	40		
GC-329	0.60	0.20	0.30	0.40	0.20	0.40	0.20	0.20	0.20	0.20	250	140	16.6	14.0	15.0	50	42	50	42		
GC-275	0.22	0.20	0.42	0.20	0.20	0.20	0.60	0.60	0.60	0.60	180	200	16.6	14.0	16.6	47	42	47	42		
GC-288	0.36	0.28	0.50	0.42	0.20	0.42	0.50	0.50	0.50	0.50	160	200	16.3	14.3	16.3	50	43	50	43		
GA-225	0.40	1.00	0.56	0.20	0.20	0.20	0.40	0.40	0.40	0.40	380	250	13.4	14.0	13.0	40	42	40	42		
GG-007	0.30	0.20	0.20	0.30	0.30	0.30	0.30	0.30	0.30	0.30	300	170	12.0	13.0	15.0	36	39	36	39		
GC-321	0.10	0.40	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30	210	170	15.0	15.0	14.0	45	45	45	45		
GC-338	0.50	0.30	0.10	0.28	0.23	0.28	0.23	0.23	0.23	0.23	250	180	16.6	14.3	14.3	50	43	50	43		
GC-281	0.51	0.36	0.32	0.28	0.20	0.28	0.20	0.20	0.20	0.20	300	230	14.3	15.0	15.0	43	45	43	45		
GC-330	0.10	0.50	0.10	0.50	0.20	0.50	0.20	0.20	0.20	0.20	200	200	17.0	17.0	18.6	51	50	51	50		
PENTOSTA	0.80	1.00	1.00	0.60	0.85	0.60	0.85	0.85	0.85	0.85	380	325	11.0	10.0	12.6	33	30	33	30		
max	0.10	0.14	0.10	0.10	0.08	0.10	0.08	0.08	0.08	0.08	140	125	14.9	14.2	14.8	45	43	45	43		
min	0.29	0.30	0.34	0.27	0.31	0.27	0.31	0.31	0.31	0.31	227	207									
mean																					

ID	GRUPO	RAMA	CUAL	DATOS CONS TRATA REAC ADV	0		21D		29D		9S		0		80		14D		21D		29D		9S	
					CREAT	CREA	CREAT	CREA	CREAT	CREA	TGO													
GE-021	10	K	C		0.70	0.90	0.60	0.90	0.60	0.90	13	7	13	9	7	12								
GC-343	10	V	C		0.40	0.48	0.50	0.50	0.48	0.48	7	10	7	6	10	12								
GA-256	10	K	C		0.70	1.00	0.50	1.00	0.50	1.00	13	15	13	19	15	18								
GG-030	10	K	C		0.60	0.60	0.50	0.60	0.50	0.60	9	7	9	12	7	10								
GG-019	10	K	C		0.80	1.20	1.20	0.80	1.20	0.80	20	9	20	12	9	30								
GG-027	10	K	C		0.80	1.20	0.80	1.20	0.80	1.20	10	15	10	14	15	9								
GG-018	10	K	C		0.60	0.60	0.60	0.60	0.60	0.60	51	17	51	10	17	15								
GG-025	10	K	C		0.60	1.10	0.80	1.10	0.80	1.10	7	9	7	5	9	10								
GG-017	10	K	C		0.50	0.60	0.75	0.60	0.75	0.60	19	12	19	22	7	5								
GG-023	10	K	C		0.60	0.60	0.80	0.60	0.80	0.60	12	15	12	13	15									
GE-022	10	K	C		0.90	0.70	0.70	0.70	0.70	0.70	7	11	7	6	11									
GG-014	10	K	C		0.60	1.10	1.10	0.60	1.10	0.60	7	12	7	5	12									
GG-013	10	K	C		0.50	0.60	0.60	0.60	0.60	0.60	19	18	19	9	18	24								
GE-036	10	K	C		0.72	0.41	0.41	0.80	0.41	0.80	18	24	18	13	28	15								
GG-016	10	K	C		0.74	1.20	1.20	0.60	1.20	0.60	24	15	24	15	35									
GG-020	10	K	C		1.00	0.90	0.90	0.90	0.90	0.90	11	5	11	15	5	7								
GG-024	10	K	C		0.80	0.80	0.90	0.80	0.80	0.80	40	10	40	12	5	7								
GC-341	10	K	C		0.90	0.80	0.74	0.80	0.74	0.80	19	9	19	8	9	7								
GG-015	10	K	C		0.52	1.20	1.20	0.80	1.20	0.80	19	14	19	12	14	12								
GE-002	10	K	C	X	0.92	0.95	0.95	0.80	0.95	0.80	17	30	17	13	30	11								
GC-280	10	K	C	X	0.88	0.87	0.87	0.95	0.87	0.95	7	24	7	22	24	18								
GC-269	10	K	C	X	0.83	1.00	1.00	0.90	1.00	0.90	10	11	10	7	11	13								
GC-285	10	K	C	X	1.02	1.20	1.20	1.20	1.02	1.20	15	22	15	22	17	19								
GC-319	10	K	C	X	0.60	0.64	0.64	1.03	0.64	1.03	30	11	30	15	11	21								
GC-314	10	K	C	X	0.68	0.86	0.86	0.83	0.86	0.83	55	15	55	45	15	9								
GG-006	10	K	C	X	1.00	0.67	0.67	0.90	0.67	0.90	26	13	26	45	13	22								
GC-333	10	K	C	X	0.89	0.70	0.70	0.80	0.70	0.80	13	19	13	13	19	17								
GC-316	10	K	C	X	0.74	0.81	0.81	0.80	0.74	0.80	15	13	15	17	13									
GE-030	10	K	C	X	0.70	0.60	0.60	0.60	0.70	0.60	14	13	14	9	13									
GC-296	10	K	C	X	0.69	1.00	1.00	1.00	0.69	1.00	13	19	13	15	19	21								
GE-023	10	K	C	X	0.60	0.72	0.72	0.50	0.60	0.50	15	22	15	22	17	22								
GA-288	10	K	C	X	0.80	0.70	0.70	0.50	0.80	0.50	5	11	5	7	11	5								
GG-003	10	K	C	X	0.80	0.69	0.69	1.04	0.69	1.04	19	20	19	8	20	20								
GC-274	10	K	C	X	0.94	1.00	1.00	0.80	0.94	0.80	11	9	11	11	9	11								
GC-335	10	K	C	X	0.82	0.70	0.70	0.90	0.82	0.90	7	15	7	19	15	7								
GG-010	10	K	C	X	0.60	0.93	0.93	0.60	0.60	0.60	11	17	11	16	17	22								
GC-308	10	K	C	X	0.71	0.74	0.74	0.77	0.71	0.77	17	19	17	15	19	18								
GC-292	10	K	C	X	0.87	1.20	1.20	0.80	0.87	0.80	7	11	7	11	11									
GA-242	10	K	C	X	0.97	0.80	0.80	0.60	0.97	0.60	13	13	13	13	13	10								
GA-219	10	K	C	X	1.05	0.82	0.82	1.03	0.82	1.03	43	5	43	24	5	13								
ketoconazole																								
max																								
min																								
mean																								
1.05																								
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ID	0		80		140		210		290		9S		0		80		140		210		290		9S	
	TGP	TGP	TGP	TGP	FA	FA	FA	FA	FA	FA	FA	FA	INDIR	BILI	INDIR									
GE-021	11	7	10	10	28	28	28	30	30	0.06	0.04	0.10	0.40											
GC-343	9	9	15	15	39	21	21	40	40	0.10	0.22	0.18	0.40											
GA-256	26	10	15	32	25	40	35	48	48	0.10	0.12	0.20	0.32											
GG-030	22	25	9	15	37	30	37	28	28	0.20	0.20	0.20	0.10											
GG-019	13	16	9	20	42	42	46	35	35	0.20	0.20	0.30	0.14											
GG-027	5	11	8	15	31	29	24	28	28	0.50	0.20	0.40	0.70											
GG-018	52				84					0.30	0.20	0.20	0.50											
GG-025	5	11	13	9	198	26	33	42	42	0.28	0.20	0.20	0.50											
GG-017	19	8	11	15	198	30	42	37	37	0.50	0.20	0.30	0.40											
GG-023	14	12	5	9	42	35	31	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	28	0.10	0.09	0.14	0.20											
GG-016	13	15	36	15	211	48	42	35	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	42	0.10	0.20	0.30	0.20											
GC-341	8	6	6	10	28	30	31	31	31	0.02	0.4	0.2	0.18											
GG-015	15	17	15	16	320	42	37	35	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	46	0.20	0.26	0.15	0.30											
GC-269	7	11	7	11	42	50	46	59	59	0.40	0.22	0.08	0.20											
GC-285	17	13	5	13	42	22	55	53	53	0.02	0.36	0.20	0.20											
GC-319	18	20	13	49	17	30	42	26	26	0.12	0.62	0.40	0.20											
GC-314	25	32	17	15	28	88	57	50	50	0.30	0.50	0.50	0.80											
GG-006	28	32	13	19	33	35	31	33	33	0.10	0.70	0.40	0.50											
GC-333	9	7	11	11	24	48	50	22	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	26	46			0.04	0.18	0.16												
GC-296	11	9	17	18	55	53	57	49	49	0.24	0.13	0.50	0.30											
GE-023	12	26	16	16	17	22	28	45	45	0.08	0.16	0.30	0.17											
GA-288	10	19	9	20	39	48	26	37	37	0.20	0.30	0.20	0.20											
GG-003	17	20	23	20	42	26	35	62	62	0.20	0.24	0.35	0.10											
GC-274	13	9	9	9	26	42	37	24	24	0.10	0.18	0.04	0.03											
GC-335	3	20	17	7	53	33	37	24	24	0.20	0.20	0.30	0.20											
GG-010	17	17	15	16	28	24	37	38	38	0.25	0.36	0.50	0.30											
GC-308	7	7	20	20	33	73	37	44	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	50	0.36	0.30	0.30	0.30											
GA-219	51	22	7	7	48	66	33	15	15	0.50	0.20	0.20	0.14											
Ketocona	52	32	36	49	320	88	138	62	62	0.70	0.70	0.60	0.80											
max	3	5	5	7	13	19	24	15	15	0.02	0.02	0.04	0.03											
min	16	15	14	17	51	39	42	38	38	0.23	0.26	0.26	0.28											

ID	0		80		140		210		290		9S		0		210		290		9S		
	BILI	DIREC	PLAQ	PLAQ	HB	HT	HB	HT	HB	HT	HB	HT									
GE-021	0.36		0.36		0.20	0.02	0.20	0.02	0.10	0.50	120	180	14.0	42	13.3	40	15.0	45	14.0	41	
GC-343	0.20		0.22		0.12		0.12		0.10	0.50	140	250	14.0	42	13.0	39	16.0	50	14.0	41	
GA-256	0.40		0.18		0.20	0.30	0.20	0.30	0.90	0.20	280	200	14.0	42	10.6	32	14.6	48	14.3	43	
GG-030	0.60		0.20		0.30	0.10	0.30	0.10	0.60	0.30	175	250	13.3	40	14.0	43	13.0	39	14.3	43	
GG-019	0.30		0.10		0.50	0.16	0.50	0.16	0.4	0.30	160	200	12.0	36	14.0	42	15.0	45	14.0	49	
GG-027	0.20		0.10		0.30	0.20	0.30	0.20	0.80	0.20	190	190	15.0	45	16.3		15.0		16.3		
GG-018	0.30								0.12	0.12	150	150	16.6	50			15.0	48		43	
GG-025	0.08		0.20		0.10	0.50	0.10	0.50	0.90	0.20	250	150	16.0	48	15.0	45	13.6	39	14.6	43	
GG-017	0.30		0.20		0.60	0.30	0.60	0.30	0.4	0.30	300	190	13.0	39	13.0	41	13.0	41	14.3	43	
GG-023	0.20		0.20		0.28		0.28		0.26	0.26	240	190	14.5	44	13.0	39	14.0	44	14.0	42	
GE-022	0.22		0.10		0.80		0.80		0.16	0.16	150	150	15.0	45							
GG-014	0.18		0.10		0.12		0.12		0.30	0.30	325	290	15.3	46	15.0	45	15.0	46	15.0	46	
GG-013	0.12		0.16		0.14	0.20	0.14	0.20	0.30	0.30	300	300	14.3	43	14.3	43	16.0	43	15.2	46	
GE-036	0.30		0.50		0.90	0.60	0.90	0.60	0.16	0.16	300	300	16.0	48	14.3	43	14.3	43	16.0	48	
GG-016	0.20		0.20		0.20	0.16	0.20	0.16	0.30	0.30	180	160	15.6	47	14.3	43	14.3	47	14.3	43	
GG-020	0.20		0.10		0.30	0.20	0.30	0.20	0.30	0.30	120	200	14.6	44	14.6	44	12.6	42	13.0	39	
GG-024	0.08		0.10		0.4	0.14	0.4	0.14	0.60	0.20	200	175	14.0	42	14.6	44	14.6	44	14.3	43	
GC-341	0.02		0.3		0.25	0.10	0.25	0.10	0.35	0.10	200	200	15.0	45	14.6	44	14.6	44	14.3	43	
GG-015	0.20		0.15		0.35	0.10	0.35	0.10	0.20	0.20	170	200	10.3	31	11.4	34	11.4	34	11.4	34	
GE-002	0.56		0.26		0.36	0.20	0.36	0.20	0.50	0.50	300	200	14.3	43	14.4	47	12.3	43	12.0	37	
GC-280	0.38		0.09		0.30	0.30	0.30	0.30	0.70	0.70	325	200	15.0	45	14.3	43	14.3	43	15.0	47	
GC-269	0.30		0.28		0.50	0.20	0.50	0.20	0.30	0.30	200	300	15.0	45	14.3	43	14.3	43	15.0	47	
GC-285	0.28		0.30		0.30	0.30	0.30	0.30	0.30	0.30	200	280	15.0	45	16.6	47	16.6	47	15.6	46	
GC-319	0.36		0.30		0.70	0.70	0.70	0.70	0.30	0.30	200	190	13.5	41	13.6	40	13.6	40	16.0	48	
GC-314	0.80		0.30		0.53	0.40	0.53	0.40	0.60	0.28	225	200	17.0	51	10.6	31	10.6	31	16.0	48	
GG-006	0.30		0.30		0.30	0.60	0.30	0.60	0.30	0.28	160	225	10.0	30	12.6	38	12.6	38	14.0	42	
GC-333	0.40		0.30		0.30	0.30	0.30	0.30	0.30	0.30	225	170	10.0	30	13.3	40	13.3	40	14.6	44	
GC-316	0.20		0.38		0.34		0.34		0.30	0.30	190	220	16.6	50	14.0	42	14.0	42	14.0	44	
GE-030	0.26		0.42		0.40	0.30	0.40	0.30	0.30	0.30	300	300	15.6	47	13.3	39	13.3	39	13.0	39	
GC-296	0.36		0.30		0.30	0.17	0.30	0.17	0.20	0.20	125	200	13.0	39	14.0	43	14.0	43	14.2	43	
GE-023	0.28		0.20		0.20	0.30	0.20	0.30	0.20	0.30	290	210	15.0	45	16.0	47	16.0	47	16.0	47	
GA-288	0.30		0.28		0.10	0.90	0.10	0.90	0.22	0.19	492	200	15.0	45	15.8	48	15.8	48	10.3	31	
GG-003	0.10		0.32		0.40	0.40	0.40	0.40	0.25	0.20	294	260	15.6	47	15.0	45	15.0	45	14.0	42	
GC-274	0.32		0.30		0.30	0.30	0.30	0.30	0.25	0.20	190	195	15.3	46	15.0	45	15.0	45	15.6	46	
GC-335	0.10		0.30		0.25	0.20	0.25	0.20	0.30	0.30	250	150	15.0	45	12.3	37	12.3	37	16.0	47	
GG-010	0.28		0.25		0.50	0.50	0.50	0.50	0.20	0.20	150	200	12.0	36	13.3	40	13.3	40	13.3	40	
GC-308	0.30		0.20		0.20	0.90	0.20	0.90	0.30	0.30	190	250	15.0	45	15.3	46	15.3	46	15.0	45	
GC-292	0.28		0.30		0.20	0.36	0.20	0.36	0.20	0.36	280	250	13.3	36	13.3	36	13.3	36	15.0	45	
GA-242	0.21		0.50		0.90	0.90	0.90	0.90	0.20	0.36	300	480	14.3	43	14.6	44	14.6	44	14.6	44	
GA-219	0.30		0.50		0.90	0.90	0.90	0.90	0.20	0.36	492	480	17.0	51	16.6	50	16.6	50	16.3	49	
Ketocona	0.80		0.09		0.10	0.02	0.10	0.02	0.36	0.31	120	150	10.0	30	10.6	31	10.6	31	8.3	25	
max	0.02		0.25		0.36	0.31	0.36	0.31			228	224	14.4	43	13.9	42	13.9	42	14.1	42	
min	0.28																				
mean																					

ID	0	210	290	95	0	210	290	95	0	210	290	95	0	210	290	95
	GB	GB	GB	GB	PMN	PMN	PMN	PMN	LINF	LINF	LINF	LINF	EOS	EOS	EOS	EOS
GE-021	7250	6100	8300	60	58	60	36	38	40	36	38	0	4	2	0	0
GC-343	5000	9500		55	36	40	42		40	42		5	20		2	0
GA-256	8950	12500	7500	82	70	66	23	24	13	23	24	4	0	8	2	1
GG-030	6600	5100	7200	59	60	68	40	30	28	40	30	8	0	1	2	1
GG-019	4350	4900		50	56		44		40	44		0	0		0	0
GG-027	6200		6800	53	52		48		35	48		0	0		2	0
GG-018	11000			70					30			0			0	0
GG-025	6200	8250	5800	62	48	55	34	45	35	34	45	3	18	0	0	0
GG-017	6800	7500	7100	64	59	68	41	28	34	41	28	1	0	0	0	0
GG-023	5500	7200	7800	66	75	70	22	28	22	22	28	8	0	2	4	2
GE-022	6000			64			30		30			6			0	0
GG-014	7350	7050		52	60		36		40	36		8	4		0	0
GG-013	6200		9700	48	53		39		38	39		12	5		0	3
GE-036	6400	7350	6800	61	50	60	28	32	39	28	32	0	22	8	0	0
GG-016	5550	5350	10000	70	62	68	30	30	30	38	30	0	0	0	0	0
GG-020	4900	7000		56	63		35		39	35		3	0		2	1
GG-024	7600	7300	10900	78	70	62	30	38	22	30	38	0	0	0	0	0
GC-341	5150	7100	7400	44	63	58	29	32	50	29	32	6	9	10	0	0
GG-015	8250		6800	71			26		26	32		1	4		0	2
GE-002	9300	9500	7600	66	66	58	34	40	32	34	40	0	0	2	0	0
GC-280	8000	10510	3500	60	60	64	30	30	30	40	30	8	0	2	0	2
GC-269	5200	8250		66	73		32		32	24		0	0		0	2
GC-285	5800	5350	8600	66	57	60	34		34	40	35	0	1	3	0	2
GC-319		6500	7850		60	64	38	34	40	38	34	0	0	0	2	2
GC-314	5100	7400	7000	57	63	64	32	33	40	32	33	1	4	3	0	2
GG-006	7550	6900	5250	66	66	67	30	28	31	30	28	0	0	3	2	1
GC-333	5900	7500	6500	57	60	50	40	35	40	35	46	3	4	3	3	1
GC-316	8000	6000		63	57		35		35	34		0	9		1	0
GE-030	6000			40			57		57			3			2	0
GC-296	11350	7250	8500	70	50	68	23	26	23	38	26	2	9	3	3	3
GE-023	6050	7100	6725	54	68	68	42	30	42	38	30	2	2	1	2	0
GA-288	5900	7300	6500	54	60	58	40	40	40	36	40	4	4	0	0	2
GG-003	7800	10000	13250	41	68	72	36	26	36	25	26	22	7	0	1	2
GC-274	9800	7550	6800	54	62	70	36	28	36	32	28	6	2	0	2	2
GC-335	9100	10900	8400	66	61	58	30	41	30	39	41	2	0	1	2	0
GG-010	5600	5900	5200	64	61	68	36	30	36	36	30	0	0	2	0	0
GC-308	5000		10000	64			36		36	35		0	5		3	0
GC-292	5600	7700		68	62		32		32	34		0	3	5	0	0
GA-242	11500	7000	11100	74	70	74	22	26	22	25	26	0	3	0	1	0
GA-219	8900	8000	9350	64	64	65	34	32	34	30	32	2	4	2	0	1
Ketocona																
max	11500	12500	13250	82	75	74	57	48	57	44	48	22	22	10	4	3
min	4350	4900	3500	40	36	50	13	24	13	22	24	0	0	0	0	0
mean	6992	7540	7808	61	61	63	34	33	34	34	33	3	4	2	1	1

ID	GRUPO	RAMA CUAL	DATOS CONS TRATA REAC ADV	0	210	290	95	0	80	140	210	290	95
				CREAT CREA	CREAT CREA	CREAT CREA	CREA	TGO	TGO	TGO	TGO	TGO	TGO
GC-365	10	K		0.68	1.00	1.00	0.90	7		20		13	25
GG-028	10	K		1.30	1.00	1.00	0.70	9		19		9	13
GG-029	10	K		0.80	0.50	1.20	1.20	15		5		15	3
GA-248	10	K		0.70	0.80	1.10	1.10	13		25		32	17
GG-022	10	K		1.30	0.60	0.80	0.80	10		8		21	34
GE-031	10	K		1.00	0.90	0.80	0.80	36		8		32	30
GE-041	10	K		0.80	0.60	0.60	0.60	11		12		19	13
GG-026	10	K		0.60	0.90	0.90	0.90	13		20		9	13
GG-021	10	K		0.70	1.00	0.90	0.90	11		13		10	5
GG-012	10	K		1.12	0.90	0.72	0.72	22		19		21	9
GG-004	10	K		0.90	1.00	1.00	1.00	2		8		15	15
GC-298	10	K		0.46	1.10	1.10	1.10	15		7		17	17
GE-005	10	K		1.30	1.10	1.10	0.69	14		11		5	9
GC-290	10	K		0.87	1.10	1.10	1.00	9		13		13	35
GG-009	10	K		0.72	1.11	1.00	1.00	9		15		24	40
GA-221	10	K		0.87	0.92	1.20	1.20	51		28		17	9
GG-008	10	K		1.00	0.30	1.00	1.00	19		5		30	41
GA-236	10	K		1.10	0.85	0.79	0.79	17		30		7	7
GC-279	10	K		0.87	0.79	0.79	0.79	7		13		17	17
GG-002	10	K		1.00	0.90	0.80	0.80	13		24		17	15
GA-276	10	P		0.93	0.90	0.80	0.80	13		12		28	15
GC-377	10	P		0.60	0.50	0.70	0.70	15		9		20	7
GC-359	10	P		0.80	0.64	0.80	0.80	6		30		20	20
GC-342	10	P		0.80	0.56	0.80	0.80	9		13		8	20
GA-264	10	P		0.50	0.80	0.40	0.40	10		15		9	9
GA-293	10	P		0.60	0.90	0.90	0.90	34		7		11	5
GA-281	10	P		1.10	0.70	0.50	0.50	7		13		9	13
GC-345	10	P		0.88	0.26	0.80	0.80	11		15		8	13
GC-366	10	P		0.90	0.90	0.80	0.80	17		10		11	13
GC-387	10	P		1.00	1.00	0.60	0.60	7		20		9	28
GC-286	10	P		0.87	1.13	0.70	0.70	11		13		17	16
GC-295	10	P		0.60	0.88	0.90	0.90	7		17		7	17
GC-326	10	P		0.85	0.92	0.60	0.60	11		9		17	15
GC-278	10	P		0.92	0.90	0.60	0.60	11		5		11	17
GC-332	10	P		0.89	0.86	0.60	0.60	26		9		9	24
GC-327	10	P		0.49	0.60	0.60	0.60	26		13		5	24
GC-317	10	P		0.59	0.65	1.16	1.16	41		47		9	19
GC-277	10	P		1.08	0.52	0.73	0.73	11		15		9	19
GC-309	10	P		0.71	1.30	0.82	0.82	22		19		18	29
GE-017	10	P		0.94	0.89	0.82	0.82	17		11		19	13
PLACEBO				1.30	1.30	1.20	1.20	51		47		28	41
max				0.46	0.26	0.40	0.40	2		5		5	3
min				0.85	0.79	0.82	0.82	15		15		13	18
mean													

ID	0		80		140		210		290		95	
	TGP	INDIR	FA	FA								
GC-365	20		24		42		42		39		42	
GG-028	7		22		57		57		68		77	
GG-029	20		9		53		53		62		62	
GA-248	7		22		39		39		22		26	
GG-022	5								38		42	
GE-031	22		13		28		28		22		20	
GE-041	15		14		33		33		26		20	
GG-026	9		15		42		42		31		33	
GG-021	13		9		37		37		31		26	
GG-012	24		22		64		64		56		64	
GG-004	3		10		20		20					
GC-298	15		20		42		42		62			
GE-005	9		5		44		44		58			
GC-290	7		17		48		48		68		44	
GG-009	9		14		55		55		48		40	
GA-221	28		36		26		26		42		48	
GG-008	11		9		35		35		12		38	
GA-236	15		32		53		53		50		53	
GC-279	5		13		37		37		31		31	
GG-002	5		15		28		28		28		28	
GA-276	15		5		26		26		24		35	
GC-377	11		8		42		42		33			
GC-359	13		34		25		25		201		234	
GC-342	10		5		30		30		26		29	
GA-264	25		11		46		46		35		35	
GA-293	45		5		35		35		38		59	
GA-281	9		11		24		24		24		42	
GC-345	13		12		37		37		22		25	
GC-366	21		19		42		42		37		37	
GC-387	7		38		31		31		26		35	
GC-286	13		17		42		42		39		58	
GC-295	11		28		46		46		42		46	
GC-326	9		5		55		55		40		59	
GC-278	7		5		26		26		24		37	
GC-332	20		13		34		34		44		33	
GC-327	34		12		35		35		64		66	
GC-317	17		55		50		50		39		52	
GC-277	11		9		50		50		55		68	
GC-309	11		9		44		44		46		79	
GE-017	15		11		33		33		33		37	
PLACEBO	45		55		59		59		201		234	
max	3		5		17		17		22		20	
min	14		16		37		37		44		47	
mean												

ID	0		80		140		210		290		0		210		290		0		210		290		0		210		290	
	BILI	DIREC	PLAQ	PLAQ	PLAQ	PLAQ	HB	HB	HB	HB	HT	HT	HT	HT	HT	HT	HT	HT										
GC-365	0.20		0.30		0.20	0.10	0.20	0.10	200	290	13.3	14.3	200	290	13.3	14.3	200	290	13.3	14.3	40	43	40	43	40	43	40	43
GG-028	0.90		0.20		0.30	0.20	0.30	0.20	160	150	15.3	14.0	160	150	15.3	14.0	160	150	15.3	14.0	46	42	46	42	46	42	46	42
GG-029	0.40		0.30		0.40	0.30	0.40	0.30	250	220	11.6	16.4	250	220	11.6	16.4	250	220	11.6	16.4	35	50	35	50	35	50	35	50
GA-248	0.28		0.40		0.40	0.14	0.40	0.14	280	300	14.0	15.0	280	300	14.0	15.0	280	300	14.0	15.0	42	45	42	45	42	45	42	45
GG-022	0.89		0.20		0.20	0.70	0.20	0.70	260	220	15.0	15.0	260	220	15.0	15.0	260	220	15.0	15.0	47	45	47	45	47	45	47	45
GE-031	0.20		0.30		0.32	0.10	0.32	0.10	225	215	12.2	13.6	225	215	12.2	13.6	225	215	12.2	13.6	39	41	39	41	39	41	39	41
GE-041	0.50		0.30		0.15		0.15		190	225	12.8	14.3	190	225	12.8	14.3	190	225	12.8	14.3	40	43	40	43	40	43	40	43
GG-026	0.20		0.20		0.10	0.20	0.10	0.20	170	200	15.0	15.0	170	200	15.0	15.0	170	200	15.0	15.0	45	45	45	45	45	45	45	45
GG-021	0.10		0.10		0.10	0.60	0.10	0.60	200	200	12.6	14.3	200	200	12.6	14.3	200	200	12.6	14.3	38	43	38	43	38	43	38	43
GG-012	0.30		0.60		0.20	0.47	0.20	0.47	509	225	15.0	14.3	509	225	15.0	14.3	509	225	15.0	14.3	45	43	45	43	45	43	45	43
GG-004	0.10		0.13		0.13		0.13		225	225	16.0	16.6	225	225	16.0	16.6	225	225	16.0	16.6	48	50	48	50	48	50	48	50
GC-298	0.20		0.20		0.90		0.90		170	260	15.3	13.6	170	260	15.3	13.6	170	260	15.3	13.6	46	41	46	41	46	41	46	41
GE-005	0.30		0.50		0.20		0.20		200	225	16.0	16.6	200	225	16.0	16.6	200	225	16.0	16.6	47	47	47	47	47	47	47	47
GC-290	0.30		0.25		0.70		0.70		200	200	13.0	14.6	200	200	13.0	14.6	200	200	13.0	14.6	46	44	46	44	46	44	46	44
GG-039	0.39		0.20		0.20	0.30	0.20	0.30	190	200	13.0	13.3	190	200	13.0	13.3	190	200	13.0	13.3	39	40	39	40	39	40	39	40
GA-221	0.20		0.30		0.65	0.20	0.65	0.20	250	250	16.0	14.5	250	250	16.0	14.5	250	250	16.0	14.5	45	47	45	47	45	47	45	47
GG-008	0.70		0.18		0.10	0.30	0.10	0.30	350	180	15.6	16.6	350	180	15.6	16.6	350	180	15.6	16.6	47	50	47	50	47	50	47	50
GA-236	0.40		0.30		0.50	0.30	0.50	0.30	301	300	16.4	12.0	301	300	16.4	12.0	301	300	16.4	12.0	50	36	50	36	50	36	50	36
GC-279	0.24		0.52		0.15		0.15		150	200	15.3	15.6	150	200	15.3	15.6	150	200	15.3	15.6	46	47	46	47	46	47	46	47
GG-002	0.10		0.50		0.14		0.14		225	225	13.0	14.6	225	225	13.0	14.6	225	225	13.0	14.6	39	44	39	44	39	44	39	44
GA-276	0.20		0.30		0.50	0.14	0.50	0.14	275	160	13.6	14.6	275	160	13.6	14.6	275	160	13.6	14.6	41	44	41	44	41	44	41	44
GC-377	0.20		0.10		0.30	0.30	0.30	0.30	190	150	11.3	12.8	190	150	11.3	12.8	190	150	11.3	12.8	34	39	34	39	34	39	34	39
GC-359	0.15		0.30		0.10	0.30	0.10	0.30	200	290	12.0	13.6	200	290	12.0	13.6	200	290	12.0	13.6	36	41	36	41	36	41	36	41
GC-342	0.56		0.40		0.30	0.30	0.30	0.30	150	150	16.0	15.6	150	150	16.0	15.6	150	150	16.0	15.6	48	47	48	47	48	47	48	47
GA-264	0.14		0.12		0.36	0.30	0.36	0.30	180	180	17.0	16.0	180	180	17.0	16.0	180	180	17.0	16.0	52	48	52	48	52	48	52	48
GA-293	0.60		0.40		0.20	0.24	0.20	0.24	195	260	13.6	12.6	195	260	13.6	12.6	195	260	13.6	12.6	41	38	41	38	41	38	41	38
GA-281	0.20		0.20		0.39	0.20	0.39	0.20	200	225	14.3	14.0	200	225	14.3	14.0	200	225	14.3	14.0	43	42	43	42	43	42	43	42
GC-345	0.30		0.20		0.20	0.20	0.20	0.20	170	150	14.0	15.0	170	150	14.0	15.0	170	150	14.0	15.0	42	44	42	44	42	44	42	44
GC-366	0.20		0.10		0.10	0.10	0.10	0.10	190	210	12.0	12.6	190	210	12.0	12.6	190	210	12.0	12.6	36	46	36	46	36	46	36	46
GC-387	0.20		0.42		0.35	0.38	0.35	0.38	215	190	16.0	14.6	215	190	16.0	14.6	215	190	16.0	14.6	48	44	48	44	48	44	48	44
GC-286	0.61		0.20		0.58	0.40	0.20	0.40	280	280	14.3	14.0	280	280	14.3	14.0	280	280	14.3	14.0	50	47	50	47	50	47	50	47
GC-295	0.30		0.20		0.32	0.46	0.32	0.46	350	260	16.6	16.0	350	260	16.6	16.0	350	260	16.6	16.0	42	44	42	44	42	44	42	44
GC-326	0.10		0.20		0.10	0.20	0.10	0.20	250	225	14.0	14.3	250	225	14.0	14.3	250	225	14.0	14.3	42	45	42	45	42	45	42	45
GC-278	0.56		0.30		0.30	0.40	0.30	0.40	190	120	14.0	15.0	190	120	14.0	15.0	190	120	14.0	15.0	42	43	42	43	42	43	42	43
GC-332	0.30		0.20		0.50	0.40	0.50	0.40	180	180	14.0	14.3	180	180	14.0	14.3	180	180	14.0	14.3	43	41	43	41	43	41	43	41
GC-327	0.40		0.30		0.20	0.20	0.20	0.20	325	300	12.6	14.6	325	300	12.6	14.6	325	300	12.6	14.6	38	44	38	44	38	44	38	44
GC-317	0.50		0.30		0.10	0.20	0.10	0.20	150	275	16.0	15.0	150	275	16.0	15.0	150	275	16.0	15.0	48	46	48	46	48	46	48	46
GC-277	0.36		0.32		0.20	0.30	0.20	0.30	509	300	17.0	16.0	509	300	17.0	16.0	509	300	17.0	16.0	52	48	52	48	52	48	52	48
GC-309	0.40		0.40		0.20	0.10	0.20	0.10	150	150	11.3	12.6	150	150	11.3	12.6	150	150	11.3	12.6	34	38	34	38	34	38	34	38
GE-017	0.20		0.10		0.10	0.31	0.10	0.31	228	210	14.4	14.7	228	210	14.4	14.7	228	210	14.4	14.7	43	44	43	44	43	44	43	44

PLACEBO
max 0.90 0.50 0.60 0.50 0.90 0.70
min 0.10 0.10 0.10 0.10 0.10 0.10
mean 0.33 0.27 0.27 0.28 0.31 0.26

ID	0	210	290	9S	0	210	290	9S	0	210	290	9S	0	210	290	9S	0	210	290	9S		
	GB	GB	GB	GB	PMN	PMN	PMN	PMN	LINF	LINF	LINF	LINF	EOS	EOS	EOS	EOS	MONOS	MONOS	MONOS	MONOS		
GC-365	7400	6500			56	58		40	42				0				2				0	
GG-028	9800	6100	5100		61	55	52	45	34	46			4				1				0	
GG-029	4200	5800	5850		50	62	66	36	32	34			18				0				0	
GA-248	6850	7350	9250		59	70	73	25	41	20			0				0				0	
GG-022	6050	7200	6600		59	61	58	38	38	36			1				2				0	
GE-031	8300	10350			44	71		30	30	23			24				2				2	
GE-041	5100	7100			51	66		26	28				11				10				2	
GG-026	4900	11700	13550		44	70	72	30	40	28			14				1				0	
GG-021	8900	7500	9500		64	64	66	34	33	32			1				2				0	
GG-012	10900	6800	7400		73	63	60	33	26	36			0				0				2	
GG-004	7500				56			32	32				12				0				0	
GC-298	8600	5650			62	48		40	30				0				0				5	
GE-005	7900				68			32	32				0				0				0	
GC-290	4300	8250	11100		58	60	65	37	38	32			0				2				0	
GG-009	8400	11900	8500		40	67	70	26	48	22			4				4				2	
GA-221	4900	7750	4500		60	52	42	46	40	52			0				0				3	
GG-008	8850	7200	8300		66	74	66	24	32	31			2				0				1	
GA-236	7800	8600	6450		60	71	60	27	35	38			5				0				0	
GC-279	8750	8900			64	70		30	10				0				0				0	
GG-002	8400	14800			61	67		19	20				18				1				0	
GA-276	7750	5700	8000		64	64	69	36	32	30			2				0				0	
GC-377	6800				66			32	32				1				1				0	
GC-359	5500	5500	6150		57	59	64	41	41	36			2				0				0	
GC-342	6400	6500	11500		56	64	34	34	34	40			8				0				0	
GA-264	8600	7750	6450		60	63	54	35	35	46			3				0				0	
GA-293	6250	4800	5800		70	68	60	26	26	40			4				0				0	
GA-281	5650	7000	5800		57	62	66	42	42	32			0				0				2	
GC-345	5200	6250			64	44		36	36	40			0				0				0	
GC-366	5700	8200			64	59		36	36	40			0				0				0	
GC-387	10300	5600	6450		57	50	58	34	34	46			9				0				2	
GC-286	6900	7600	7600		64	74		34	34	22			0				0				2	
GC-295	8450	4700	6300		68	60	62	27	27	38			3				0				0	
GC-326	7250	6200			59	55		39	39	43			0				2				0	
GC-278	9700	9350			64	63		34	34	32			0				2				0	
GC-332	9100	14500	9200		71	76	67	20	20	21			6				1				0	
GC-327	8200	8650	7600		69	60	58	31	31	40			0				0				0	
GC-317	7250	8700			60	74		40	40	23			0				0				0	
GC-277	7400	10000	7150		70	68	60	28	28	31			0				2				0	
GC-309	5350	6200	7200		52	69	66	44	44	29			0				0				0	
GE-017	14100	7200	5600		69	61	60	30	30	37			0				1				2	
PLACE80																						
max	14100	14500	14800	13550	73	76	74	48	48	46	52	24	16	12	26	10	2	5	4			
min	4200	4700	5650	4500	40	44	48	10	10	21	20	0	0	0	0	0	0	0	0	0	0	
mean	7491	7463	8182	7609	60	63	63	33	33	34	35	4	2	3	2	1	0	1	1			