Persistence: Cysts or trophozoites of *G. lamblia* observed in at least one of the post-treatment stool examinations performed at the Day 7-10 evaluation.

Response criteria definitions were determined on the basis of guidelines published for the evaluation of new anti-infective drugs for the treatment of diarrhea caused by *Giardia lamblia* (Cooperstock et al., 1992).

Adverse events were reviewed at the Day 7-10 follow-up visit. Adverse events were recorded on the appropriate case report forms (CRF), and the severity of each adverse event was graded on a four-point scale: mild, moderate, severe and life-threatening. Where applicable, adverse events were classified as Serious or Unexpected, and the relationship to the study drug was always recorded.

10.1.12 Statistical and Analytic Plans

The study analysis was carried out based upon the protocol and a detailed plan designed prior to locking of the database and breaking the blind.

Data for a modified intent-to-treat population was used for the primary efficacy analysis. The modified intent-to-treat population consisted of all patients randomized to the study excluding:

- patients who do not have *Giardia* trophozoites or cysts in their stool at baseline, and
- patients who have other identified causes of diarrhea at baseline (e.g., pathogenic bacteria, *C. parvum,* or *E. histolytica*).

A secondary analysis of all patients randomized to the study was also planned by the applicant. In addition, in the event that were a significant number of protocol deviations, the applicant planned to analyze a subset of patients who complete the study according to the protocol.

The primary efficacy analysis was defined by the protocol as a comparison of the proportion of patients with a 'well' clinical response for the nitazoxanide tablet group to that of the placebo group. Planned secondary efficacy analyses included:

- comparison of the proportion of patients with a 'well' clinical response rate for nitazoxanide tablets compared to nitazoxanide suspension,
- comparison of the proportion of patients with a 'well' clinical response rate for nitazoxanide suspension compared to placebo,
- comparison by treatment group of the median time from initiation of treatment to passage of last unformed stool,

Clinical Reviewer's Comment: The protocol did not specifically state that investigators should obtain the time from initiation of treatment to the passage of last unformed stool. This analysis was to have been a secondary efficacy analysis; however, due to a lack of data, the analysis was not performed by the applicant. The reviewer feels that an analysis of time to response would be an interesting analysis but not necessary for determining the efficacy of the drug.

- comparison of parasitological response rates for the nitazoxanide tablets and placebo, comparison of the parasitological response rates for the nitazoxanide tablets and suspension,
- comparison of parasitological response rates for the nitazoxanide suspension and placebo,
- intrapatient correlation of parasitological outcome with clinical outcome for each treatment group,
- comparison of potential food effect on efficacy for active treatment groups, and

Clinical Reviewer's Comment: Due to the small number of patients with evaluable data, an analysis of efficacy for subgroups based on food consumption was not conducted by the applicant.

- comparison by treatment group of the results of Day 14-17 stool examinations for clinical responders.

Proportional clinical and parasitological response rates, intrapatient correlation of parasitological outcome with clinical outcome, and the results of stool examinations at Day 14-17 for clinical responders were compared using Fisher's Exact tests (two-sided).

Two-sided 95% confidence intervals were calculated for the differences in the proportional clinical and parasitological response rates using the preferred method described by Newcombe (1998) with correction for continuity. The comparison by treatment group of the median time from the beginning of treatment to the passage of the last unformed stool was to be conducted using Kaplan-Meier survival analysis.

Adverse events were summarized for each treatment group, and the proportions of patients in each group experiencing adverse events were compared using chi-square tests.

10.1.13 Determination of Sample Size

Assuming a clinical response rate of 85% for nitazoxanide suspension and that the expected response rate for the nitazoxanide tablets is equal to that of the nitazoxanide suspension and using a two-group large-sample normal approximation test of proportions with a one-sided 0.025 significance level, a sample size of 54 patients in each group was deemed by the applicant to be sufficiently powerful (82%) to reject the null hypothesis that nitazoxanide tablets and nitazoxanide suspension are not equivalent (the response

rate for nitazoxanide tablets is inferior to that of nitazoxanide suspension by 20% or more) in favor of the alternative hypothesis that the proportions in the two groups are equivalent.

A Fisher's exact test with a 0.05 two-sided significance level had 97% power to detect the difference between an expected response rate of 85% for each active treatment group and an expected response rate of 40% for the placebo group when the sample sizes were 54 for each of the active treatment groups and 27 for the placebo group.

It was not possible to accurately project the number of patients that might be nonevaluable to other identified causes of diarrhea or lack of *Giardia* trophozoites or cysts in their stool at baseline. In order to adjust for this uncertainty, the total number of patients planned for enrollment (135) was increased by one for each patient considered non-evaluable due to lack of *Giardia* trophozoites or cysts in the baseline stool sample or due to other identified causes of diarrhea at baseline.

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10.1.14 Disposition of Patients

One-hundred thirty-five (135) patients were enrolled in the study. One-hundred thirty-three (133) of these completed the study. Two patients discontinued the study prematurely, one due to an adverse event (abdominal pain) and another who failed to return for post-treatment follow-up examinations.

Clinical Reviewer's Comment: The FDA microbiology reviewer was interested in knowing the number of patients screened at each of the two study sites in order to find 135 patients to enroll. The applicant replied that in [redacted] Peru study participants were recruited by nurses who went out into 80 surrounding communities in cooperation with leaders of community-based nutritional programs. Among the communities from which stool samples were collected, the proportion of participants with Giardia observed in a stool sample ranged from 0 to 16%. Patients screened in Peru 4,278, Patients enrolled=90.

Despite the endemicity of Giardia lamblia in Peru, the applicant only enrolled 2% (90/4278) patients screened. More than 95% (4092/2378) of patients screened were not eligible due to lack of cysts or trophozoites observed in a stool sample at screening (see below).

Reasons for not being enrolled in Peru:

- *No Giardia cysts or trophozoites observed in stool sample at screening (N=4,092)*
- *Subjects declined participation in the study prior to enrollment (N=28)*
- *Giardia cysts or trophozoites observed in stool sample at screening, but not at baseline (N=28)*
- *Clinical symptoms did not satisfy inclusion criteria (N=25)*
- *Mixed infections (N=4 Hymenolepis nana, N=1 Strongyloides stercoralis, N=1 Fasciola hepatica + Taenia)*
- *Younger than 12 years of age (N=5)*
- *Enrollment terminated at the study site due to completion of study (N=2)*
- *Concomitant therapy incompatible with study requirements (N=1)*
- *Pregnancy (N=1)*

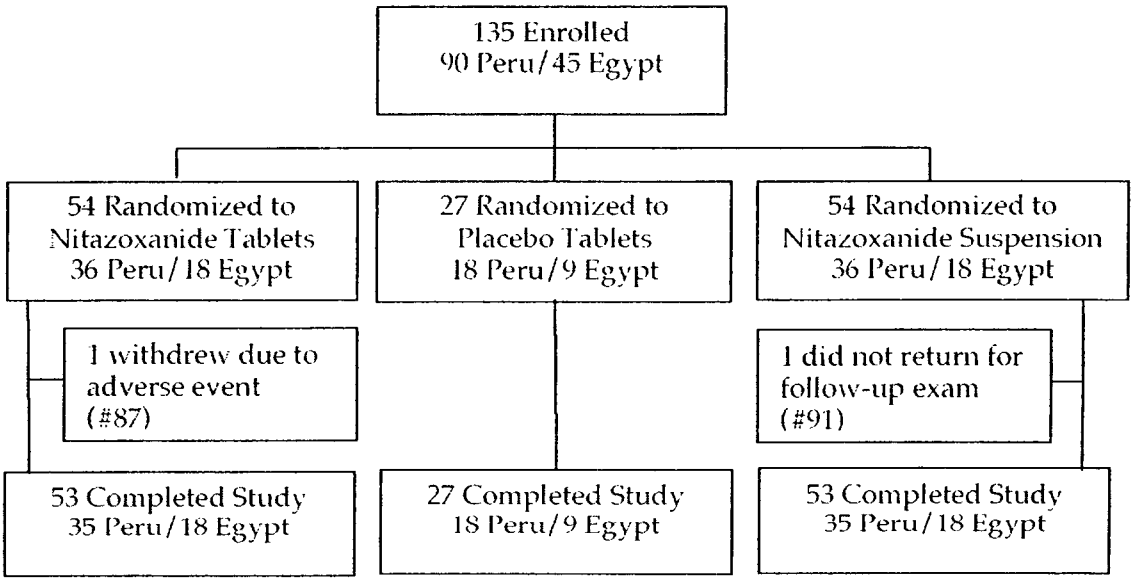
Ir [redacted] Egypt, patients presenting at the outpatient clinic with diarrhea were evaluated in accordance with usual standards of care. Patients screened in Egypt 593, Patients enrolled= 4.

Reasons for not being enrolled in Egypt:

- *No Giardia cysts or trophozoites observed in stool sample at screening (N=523)*
- *Giardia cysts or trophozoites observed in stool sample by microscopic exam but not by immunofluorescence assay (N=10)*
- *Giardia cysts or trophozoites observed in stool sample by immunofluorescence assay but not by microscopic exam (N=5)*
- *Concomitant therapy incompatible with study requirements (N=4)*
- *Subjects declined participation in the study prior to enrollment (N=4)*
- *Mixed infections with other pathogens (N=1 Blastocystis hominis + Hymenolepis nana, N=1 H. nana)*

A flowchart of patient disposition, for those enrolled into the study, is present in Figure 2.

FIGURE 2
Patient Disposition Flowchart



The protocol called for use of a modified intent-to-treat population for the primary efficacy analysis. This population was to consist of all patients randomized excluding

- patients who did not have *Giardia* trophozoites or cysts in their stool at baseline and
- patients who had other identified causes of diarrhea at baseline (e.g., pathogenic bacteria, *Cryptosporidium parvum*, *Entamoeba histolytica*).

No patients were excluded from the modified intent-to-treat population, and therefore, all patients randomized to the study were included in the analysis.

Clinical Reviewer's Comment: Fifteen patients were negative for cysts in the baseline stool sample (i.e., microscopic examination of both unconcentrated and concentrated stool samples were negative and showed zero cysts). All were positive by IFA at baseline (cyst counts ranged from 1 to 3.5). All but two were positive by all three tests at screening (#2 was only positive by IFA at screening; #13 was negative in unconcentrated stool, but positive on the other two tests at screening).
A summary the 15 patients is shown in the table below. All patients were enrolled in Egypt:

Patient Number	*Treatment*	*Number of cysts in concentrated stool at screening*
1	*Nitazoxanide tablet*	*1*
2	*Nitazoxanide suspension*	*3.5*
4	*Nitazoxanide tablet*	*1*
10	*Nitazoxanide tablet*	*3.5*
11	*Nitazoxanide tablet*	*7.5*
12	*Nitazoxanide tablet*	*3.5*
13	*Nitazoxanide suspension*	*1*
14	*Nitazoxanide suspension*	*Not done*
15	*Placebo*	*1*
18	*Placebo*	*1*
19	*Nitazoxanide suspension*	*1*
121	*Nitazoxanide suspension*	*1*
127	*Nitazoxanide suspension*	*1*
135	*Nitazoxanide tablet*	*1*

A sensitivity analysis of the clinical and parasitological response on Day 7 was done by the FDA Statistical and Clinical reviewers excluding these 15 patients (plus Patient #125/ Tablet/Egypt), as per the reason described below (i.e., a total of 16 excluded). See results section.

Three patients (#18 from the placebo group, #19 from the suspension group and #125 from the nitazoxanide tablet group) were enrolled at the site in Egypt with fewer than 3 stools per day at baseline. These patients had more than three stools along with other symptoms of giardiasis at the screening visit. All three patients had *Giardia lamblia* cysts in their stools at screening and at baseline. Patients 18 and 125 had other symptoms of giardiasis and were passing unformed stools at baseline. Subject 19 had no symptoms of giardiasis at baseline.

One patient (#87; 16 year old female) discontinued treatment with nitazoxanide tablets due to abdominal pain after one day of treatment (2 doses).

10.1.15 Demographic and Other Baseline Characteristics

A summary of demographic data and disease-related characteristics is presented in Table 1.

Other notable symptoms at baseline included nausea (27 patients: 9 active tablet, 4 placebo tablet and 14 suspension; p = 0.34) and vomiting (9 patients: 1 active tablet, 2 placebo tablet, 6 suspension; p = 0.15). Five patients also reported blood in their stools (3 active tablet, 2 placebo tablet, 0 suspension; p = 0.16).

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10.1.15 Demographic and Other Baseline Characteristics

A summary of demographic data and disease-related characteristics is presented in Table 1.

Other notable symptoms at baseline included nausea (27 patients: 9 active tablet, 4 placebo tablet and 14 suspension; $p = 0.34$) and vomiting (9 patients: 1 active tablet, 2 placebo tablet, 6 suspension; $p = 0.15$). Five patients also reported blood in their stools (3 active tablet, 2 placebo tablet, 0 suspension; $p = 0.16$).

TABLE 1
Demographic and Disease-Related Characteristics

	All Subjects	Active Tablets	Placebo Tablets	Suspension	P^1
Race:					
Hispanic	90	36	18	36	1.0
Caucasian	45	18	9	18	
Gender:					
Male	91	34	23	34	.09
Female	44	20	4	20	
Age (years):					
Mean	19.82	19.98	18.87	20.13	.85
S.D.	9.64	10.29	7.10	10.19	
Range	12-55	12-55	12-34	12-51	
Weight (kgs):					
Mean	52.81	53.34	53.78	51.80	.82
S.D.	15.33	16.16	16.86	13.87	
Range	25-100	25-100	28-80	25-81	
Stool Frequency					
1-2/day	3	1	1	1	.76
3-4/day	127	51	26	50	
5-10/day	5	2	0	3	
Stool Consistency					
Liquid	26	12	5	9	.48
Soft	107	42	22	43	
Formed	2	0	0	2	
Abdominal Pain/Cramps					
Yes	115	48	43	24	.43
No	20	6	11	3	
Duration of Diarrhea					
Mean	6.17 [2]	5.74 [2]	6.59	6.41	.38
S.D.	3.02	2.50	2.95	3.52	
Range	1-27	1-14	2-18	2-27	
Giardia cyst quantitation[3]					
Median	3.5	3.5	5	3	.54
Range	0-80	0-80	0-38	0-60	

[1] Chi-square test used for comparing proportions, t-test for means, Wilcoxon test for medians.

[2] Excludes one outlier with diarrhea for more than 5 years.

[3] Number of *Giardia* cysts observed per microscopic field (x400 magnification) after concentration of stool. 129 of 135 patients had data reported. Reporting of median was more appropriate than mean due to the nature of the data (e.g., the laboratory in Egypt reported >10 organisms/field as the high end of the range while the laboratory in Peru attempted to make accurate counts as approximations). Some patients from the Egyptian site showed no cysts in their stool at baseline by microscopic examination of concentrated stool, but cysts were observed by immunofluorescence assay.

A more detailed description of the number of *Giardia* cysts in the baseline concentrated stool sample is shown in Table 2.

Clinical Reviewer's Comment: Table 2 was created by the reviewer.

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TABLE 2
Description of Cyst Counts in the Baseline Concentrated Stool Sample by Treatment Group

	Tablet	Placebo	Suspension
N of Patients	51 (3 with missing data excluded)	26 (1 with missing data excluded)	50 (2 with missing data excluded)
Patients with missing data*	#8, 142 and 145 (all from Egypt)	#131 (Egypt)	#32 (Peru) and #141 (Egypt)
Mean number of cysts ± SD	6.2 ± 11.7	6.5 ± 8.1	5.3 ± 9
Range	0 to 80	0 to 38	0 to 60
N of patients with 0 to 1 cyst	11	10	18
N of patients with > 10 cysts	6 (actual number of cysts in these patients: 11, 12, 18, 20, 25 and 80)	5 (actual number of cysts in these patients: 12, 12, 16.5, 17.5, and 38)	5 (actual number of cysts in these patients: 12, 14, 15, 25, and 60)
Patients with zero cysts in concentrated stool	6 patients; all from Egypt; actual number of cysts found by immunofluorescence: 1, 1, 1, 1, 10, and 3.5	2 patients; both from Egypt; actual number of cysts found by immunofluorescence: 1 and 1	7 patients; all from Egypt; actual number of cysts found by immunoflourescence: 1, 1, 1, 1, 1, 3.5 and 3.5,

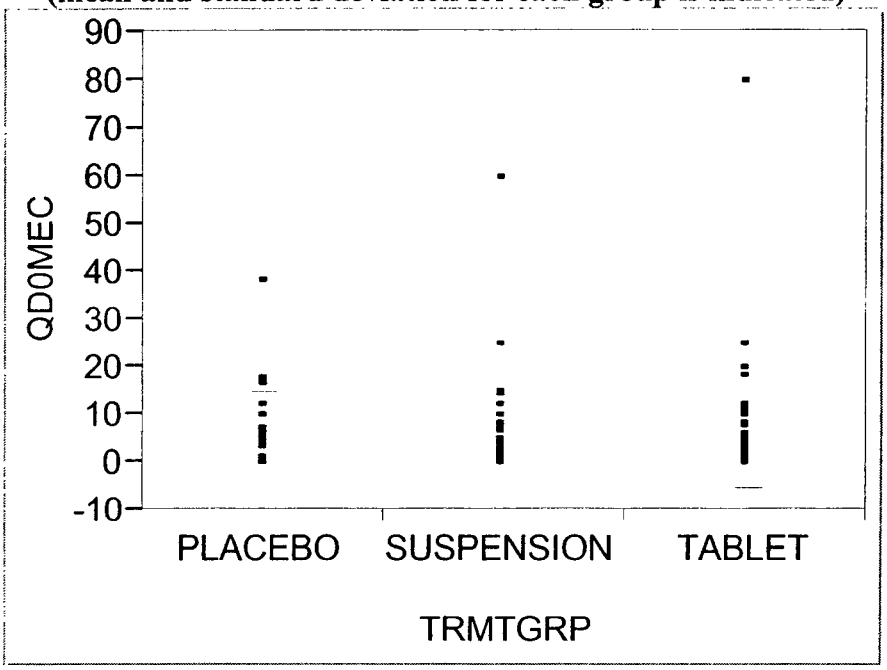
* Description of patients with missing data (i.e., no cyst count on baseline unconcentrated stool):

- Patient #8: no cyst count performed for unconcentrated or concentrated baseline stool samples, but had 7.5 cysts by IFA; positive on all three baseline tests for cysts (unconcentrated and concentrated stool and IFA)
- Patient #32: no cyst count performed for unconcentrated or concentrated baseline stool samples and had 0 cysts by IFA; positive for cysts at baseline in unconcentrated and concentrated stool and IFA was negative
- Patients #131 and 141: no cyst count performed for unconcentrated or concentrated baseline stool samples and had 1 cyst by IFA; positive on all three baseline tests for cysts (unconcentrated and concentrated stool and IFA)
- Patients #142: no cyst count performed for unconcentrated or concentrated baseline stool samples and had 3.5 cysts by IFA; positive on all three baseline tests for cysts (unconcentrated and concentrated stool and IFA)
- Patients #145: no cyst count performed for unconcentrated or concentrated baseline stool samples and had 1 cyst by IFA; positive on all three baseline tests for cysts (unconcentrated and concentrated stool and IFA)

The cyst count (mean ± SD) in the baseline concentrated stool sample by treatment group is shown graphically in Figure 3.

Clinical Reviewer's Comment: Figure 3 was created by the reviewer.

FIGURE 3
Cyst Count on Baseline Concentrated Stool Sample by Treatment Group (mean and standard deviation for each group is indicated)



10.1.16 Assessment of Treatment Compliance

Of the 135 patients enrolled in the study, 132 returned diaries reporting their use of medication (131 patients also returned medication bottles at the Day 7 follow-up visit).

Ninety-six patients indicated that they had taken the study medication with food as instructed. The diaries of 33 patients were not complete enough to determine whether they took their medication with food or not. Three (3) patients clearly did not take at least 4 of their 6 doses with food. Due to the small number of patients with evaluable data, an analysis of efficacy for subgroups based on food consumption was not conducted by the applicant.

Clinical Reviewer's Comment: The relative importance of systemic versus local (i.e., luminal) drug concentrations for antimicrobial activity is unknown. See discussion of food effect and bioavailability of the tablet versus the suspension in Section 8.1 "Dosing and Administration" of this review.

The Reviewer believes that the clinical data obtained in this study are sufficient to conclude efficacy of nitazoxanide tablets and nitazoxanide suspension against Giardia lamblia. The subgroup analyses based on food consumption are not necessary.

10.1.17 Efficacy Results

Two patients (#87 from the nitazoxanide tablet group and #91 from the nitazoxanide suspension group) dropped out of the study. These patients were treated as clinical and parasitological failures.

Clinical Response

The clinical responses recorded at the Day 7-10 visit for the nitazoxanide tablets, nitazoxanide suspension, and the placebo tablets are summarized in Table 3. The proportion of "well" clinical responses in the active treatment group was significantly higher than in the placebo treatment group (p = 0.0002 for tablet versus placebo and p = 0.0006 for suspension versus placebo).

Clinical Reviewer's Comment: Table 3 was modified from the applicant's submission for clarity.

TABLE 3
Clinical Response Rates by Treatment Group on Days 7-10

Response	Nitazoxanide Tablets N=54	Nitazoxanide Suspension N=54	Placebo N=27
Well	46 (85.2%)*	45 (83.3%)**	12 (44.4%)
	95% CI [-13.5%, 17.1%]		
Continuing Illness	8 (14.8%)	9 (16.7%)	15 (55.5%)

* p = 0.0002 (two-sided Fisher's exact test) for nitazoxanide tablets versus placebo (primary comparison)
** p = 0.0006 (two-sided Fisher's exact test) for nitazoxanide suspension versus placebo (secondary comparison)

Clinical Reviewer's Comment: A sensitivity analysis of clinical response excluding 15 patients with zero cysts found in the baseline unconcentrated and concentrated stool sample was performed for each treatment group by the FDA Statistical and Clinical Reviewers. The results are shown here:

Response	*Nitazoxanide Tablets*	*Nitazoxanide Suspension*	*Placebo*
Well	*39/47 (83.0%)**	*38/47 (80.9%)***	*11/25 (44%)*
	95% CI [-14.9, 19.1%]		

** p-value tablet versus placebo = 0.0029*
*** p-value suspension versus placebo = 0.0011*

Clinical Reviewer's Comment: A subset analysis of clinical and parasitological response in patients with less severe disease versus more severe disease (as defined by ≤ 10 cysts and > 10 cysts in the concentrated stool sample at baseline) was performed for each treatment group by the FDA Statistical and Clinical Reviewers. The results are shown here. In the "less severe disease" group, both nitazoxanide tablets and nitazoxanide

suspension are significantly better than placebo in terms of both clinical and parasitological response. In the "more severe disease" group, p-values are not included for the comparison of nitazoxanide to placebo, as the sample size is too small for a meaningful comparison.

Less Severe Disease (i.e., ≤ 10 cysts in Baseline Stool Sample)

Response	*Nitazoxanide Tablets*	*Nitazoxanide Suspension*	*Placebo*
Clinical Response ("Well")	*40/48 (83.3%)**	*42/49 (85.7%)***	*11/22 (50.0%)*
Parasitological Response (Eradication)	*30/48 (62.5%)#*	*25/49 (51.0%)##*	*5/22 (22.7%)*

** p-value tablet versus placebo for clinical response = 0.0078*
*** p-value suspension versus placebo for clinical response = 0.0026*
 # p-value tablet versus placebo for parasitological response = 0.0041
p-value suspension versus placebo for parasitological response = 0.0373

More Severe Disease (i.e., > 10 cysts in Baseline Stool Sample)

Response	*Nitazoxanide Tablets*	*Nitazoxanide Suspension*	*Placebo*
Clinical Response ("Well")	*6/6 (100%)*	*3/5 (60%)*	*1/5 (20%)*
Parasitological Response (Eradication)	*0/6 (0%)*	*1/5 (20%)*	*0/5 (0%)*

Parasitological Response

The parasitological response rates at Day 7-10 for the group receiving nitazoxanide tablets, nitazoxanide suspension, and placebo tablets are summarized in Table 3. The proportion of patients eradicated (i.e., no cysts or trophozoites observed in two stool samples collected between study Days 7 and 10) in the active treatment group was significantly higher than in the placebo treatment group ($p = 0.0019$ for nitazoxanide tablets versus placebo and $p = 0.0146$ for nitazoxanide suspension versus placebo).

Clinical Reviewer's Comment: Tables 4 and 5 were modified from the applicant's submission for clarity.

TABLE 4
Parasitological Response Rates by Treatment Group at Day 7-10

Response	Nitazoxanide Tablets N=54	Nitazoxanide Suspension N=54	Placebo N=27
Eradication	30 (55.5%)*	26 (48.1%)**	5 (18.5%)
	95% CI [-12.4%, 26.4%]		
Persistence	24 (44.4%)	28 (51.9%)	22 (81.5%)

* p = 0.0019 (two-sided Fisher's exact test) for nitazoxanide tablets versus placebo (primary comparison)
** p = 0.0146 (two-sided Fisher's exact test) for nitazoxanide suspension versus placebo (secondary comparison)

A disproportionate number of patients with persistence came from Peru compared to Egypt (see discussion of results by study site).

Clinical Reviewer's Comment: A sensitivity analysis of parasitological response excluding 15 patients with zero cysts found in the baseline unconcentrated and concentrated stool sample was performed for each treatment group by the FDA Statistical and Clinical Reviewers. The results are shown here:

Response	*Nitazoxanide Tablets*	*Nitazoxanide Suspension*	*Placebo*
Well	*23/47 (48.9%)**	*20/47 (42.5%)***	*4/25 (16.0%)*
	95% CI [-13.2%, 25.9%]		

* *p-value tablet versus placebo = 0.0347*
** *p-value suspension versus placebo = 0.0098*

Clinical Reviewer's Comment: Table 6 was created by the reviewer.

TABLE 6
Description of Cyst Counts in the Day 7 Concentrated Stool Samples by Treatment Group

	Tablet	Placebo	Suspension
N	51 (1 patient with missing data excluded)	27 (two patients with only one sample each are included)	53 (1 patient with missing data excluded)
Patients with missing data	#87/Peru	--	#91/Peru
Mean ± SD	Sample #1: 1.8 ± 3.9 Sample #2: 2.0 ± 3.8	Sample #1: 3.0 ± 3.5 Sample #2: 3.3 ± 4.6	Sample #1: 1.3 ± 2.2 Sample #2: 1.8 ± 3.7
Range	Sample #1: 0 to 20 Sample #2: 0 to 15	Sample #1: 0 to 13 Sample #2: 0 to 20	Sample #1: 0 to 8 Sample #2: 0 to 18
N of patients with zero cysts in both samples	34	5 (one patient out of 5 had 0 in one sample and the other was missing)	29
N of patients with > 10 cysts in at least one of two samples	3	1 (#103 from Peru; actual number of cysts was 13 and 20)	3 (#21 from Peru had 1 and 18; #52 from Peru had 8 and 14; and #102 had 7 and 13)

The cyst count (mean ± SD) in the Day 7 concentrated stool samples by treatment group is shown graphically in Figures 4A and 4B.

Clinical Reviewer's Comment: Figures 4A, 4B, 5, and 6 were created by the reviewer.

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FIGURE 4A
Cyst Count in Concentrated Stool Sample #1 at Day 7 by Treatment Group (indicating mean and standard deviation)

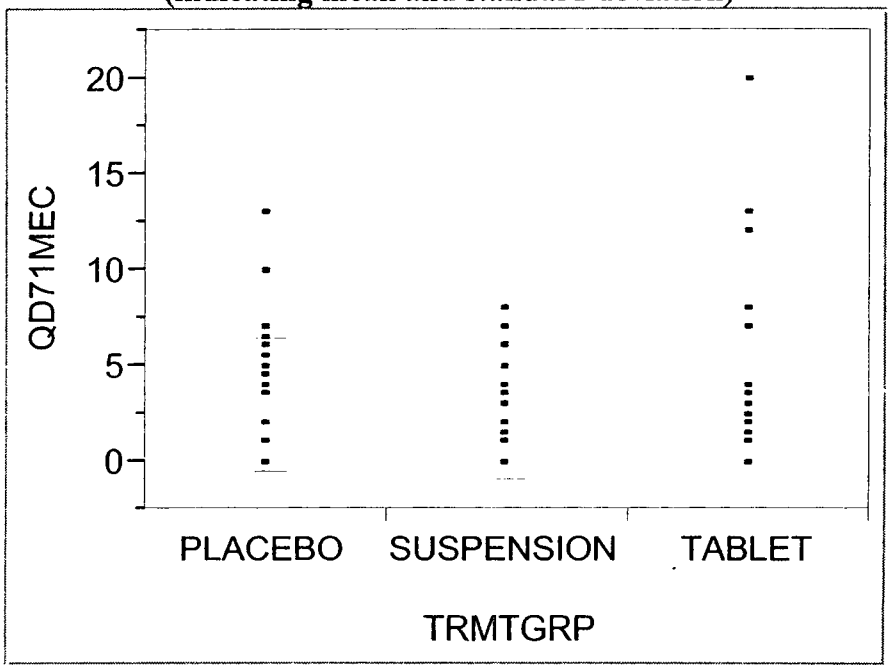
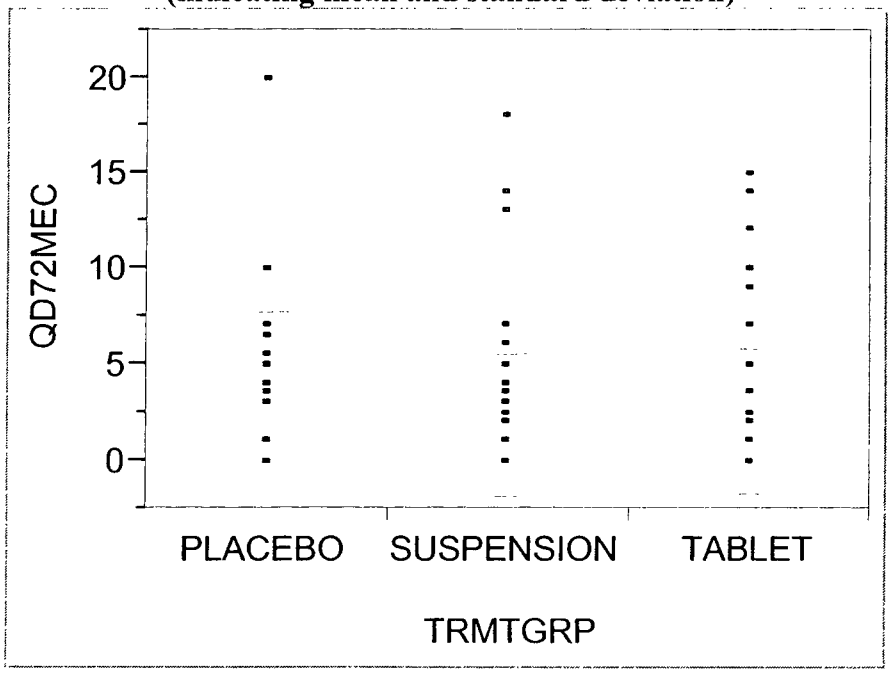
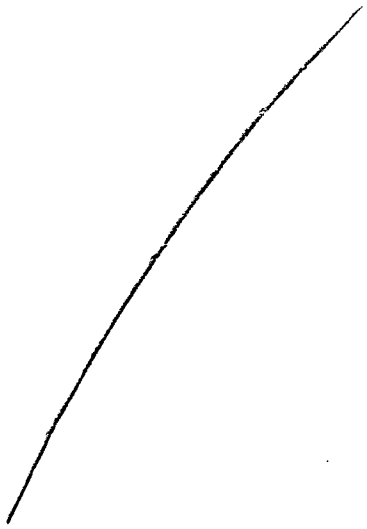


FIGURE 4B
Cyst Count in Concentrated Stool Sample #2 at Day 7 by Treatment Group (indicating mean and standard deviation)



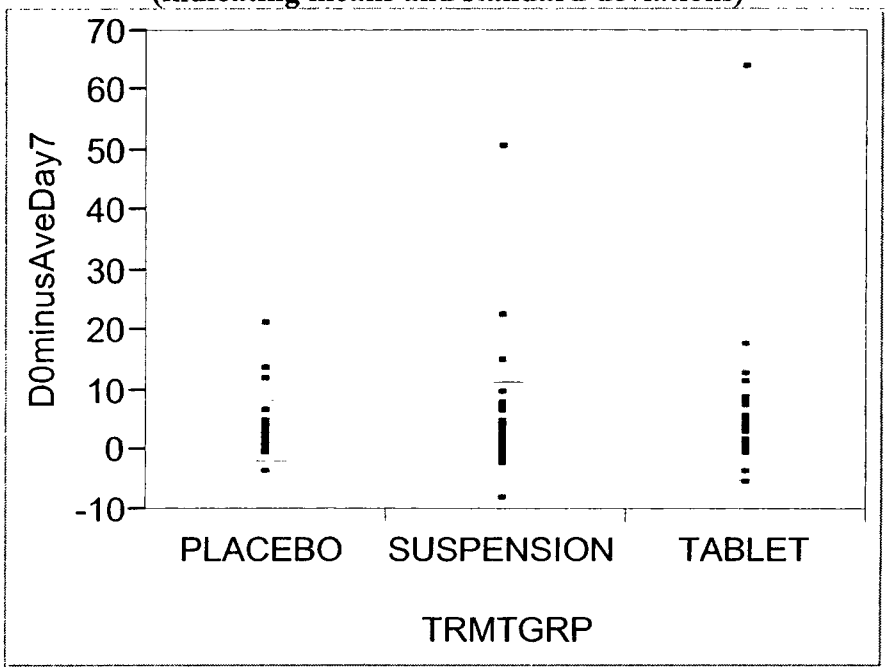
The number of cysts in concentrated stool samples at baseline and then again at Day 7 for each individual patient by treatment group is shown in Figure 5.

FIGURE 5
Individual Cyst Counts in Concentrated Stool Samples at Baseline and Day 7* by Treatment Group



The difference between the cyst counts at baseline and Day 7 (i.e., baseline minus Day 7) in concentrated stool samples for individual patients is shown in Figure 6 for each treatment group. The mean ± SD drop in cysts counts is 4.3 ± 9.4 for the nitazoxanide tablet group, 3.7 ± 7.9 nitazoxanide suspension group, and 3.3 ± 5.2 for the placebo group

FIGURE 6
Individual Patient Reduction in Parasite Count (Baseline minus Day 7*) by Treatment Group
(indicating means and standard deviations)



* cyst count on Day 7 is an average of the count from two samples obtained 24 hours apart between Days 7 and 10

A categorical analysis of the difference in cyst counts at baseline and Day 7 (using the maximum of two concentrated stool samples at Day 7) was conducted by the FDA Statistical Reviewer and is shown in Table 7. Improvement is defined as difference of > 0; worse is defined as a difference of < 0 and no change is a difference equal to 0. The results show that there is no overall difference between the treatment means.

Clinical Reviewer's Comment: Table 7 was created by the FDA statistical reviewer.

TABLE 7
Categorical analysis of the difference between Cyst Counts in Concentrated Stool Samples at Baseline and Day 7 by Treatment Group

	Nitazoxanide Tablet	Nitazoxanide Suspension	Placebo	Overall p-value
Improvement	36/50 (72%)	37/51 (72.6%)	18/26 (69.2%)	.99
No change	9/50 (18%)	8/51 (15.7%)	5/26 (19.2%)	
Worse	5/50 (10%)	6/51 (11.8%)	3/26 (11.5%)	

Correlation of Clinical and Parasitological Response

The intrapatient correlation of clinical and parasitological response rates at Day 7-10 for the nitazoxanide tablet, nitazoxanide suspension, and placebo groups are presented in Table 8.

TABLE 8
Correlation of Clinical and Parasitological Response Rates by Treatment Group at Day 7-10

Response	Nitazoxanide Tablets N=54		Nitazoxanide Suspension N=54		Placebo N=27	
	Well	Continuing Illness	Well	Continuing Illness	Well	Continuing Illness
Eradication	28 (51.9%)	2 (3.7%)	26 (48.1%)	0 (0%)	4 (14.8%)	1 (3.7%)
Persistence	18 (33.3%)	6 (11.1%)	19 (35.2%)	9 (100%)	8 (29.6%)	14 (51.9%)

Table 9 shows the clinical and parasitological response rates and kappa statistic by treatment group. The results show a weak, but positive correlation between the groups, as evidenced by the low, but positive kappa result.

Clinical Reviewer's Comment: Table 9 was created by the FDA Statistical and Clinical reviewers.

TABLE 9
Clinical and Parasitological Response Rates and Correlations

	Nitazoxanide Tablet	Nitazoxanide Suspension	Placebo
Clinical Response (Well)	46/54 (85.2%)	45/54 (83.3%)	12/27 (44.4%)
Parasite Response (Eradication)	30/54 (55.6%)	26/54 (48.2%)	5/27 (18.5%)
Kappa	0.196	0.313	0.283

Clinical Reviewer's Comment: A sensitivity analysis of the correlation between clinical and parasitological response excluding 15 patients with zero cysts found in the baseline unconcentrated and concentrated stool sample was performed for each treatment group by the FDA Statistical and Clinical Reviewers. The results are shown here:

	Nitazoxanide Tablet	*Nitazoxanide Suspension*	*Placebo*
Clinical Response (Well)	*39/47 (83.0%)*	*38/47 (80.9%)*	*11/25 (44.0%)*
Parasite Response (Eradication)	*23/47 (48.9%)*	*20/47 (42.5%)*	*4/25 (16%)*
Kappa	*0.161*	*0.299*	*0.39*

Efficacy at Follow-up (Day 14-17)

The results of stool examinations at Day 14-17 are compared by treatment group for clinical responders (as assessed at Day 7) in Table 10.

TABLE 10
Parasitological Response in Stool in Clinical Responders by Treatment Group at Day 14-17

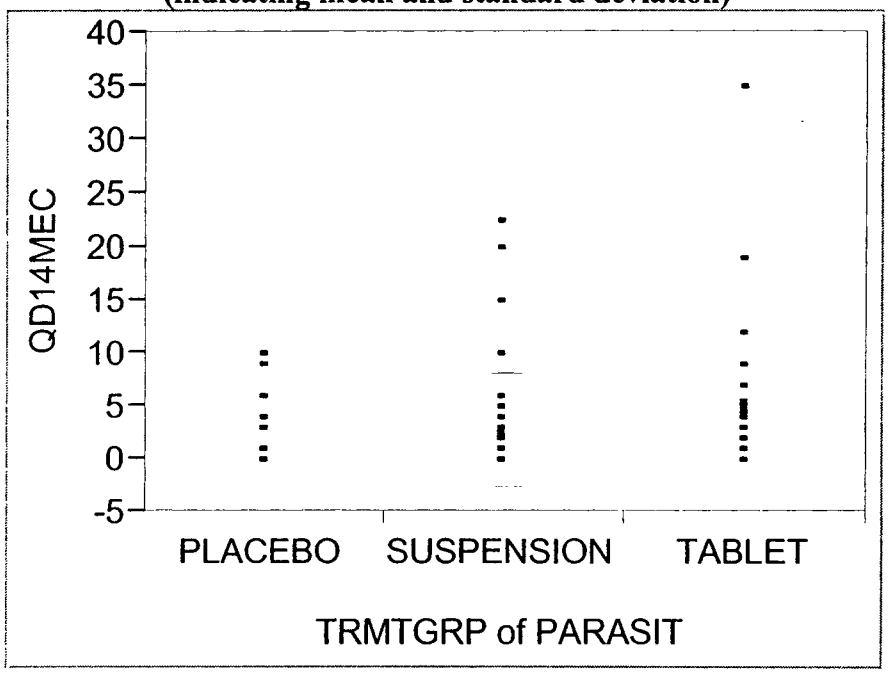
Stool Results	Nitazoxanide Tablets N=45*	Nitazoxanide Suspension N=43*	Placebo N=12
Negative	22 (48.9%)	24 (55.8%)	3 (25.0%)
Positive	23 (51.1%)	19 (44.2%)	9 (75.0%)

*one patient with a clinical response in the nitazoxanide tablet group and two in the nitazoxanide suspension group did not submit a stool sample at Day 14 to 17.
p = 0.1682 (Chi Square test)

The cyst count (mean ± SD) in the Day 14 concentrated stool sample for the clinical responders by treatment group is shown graphically in Figure 7.

Clinical Reviewer's Comment: Figure 7 was created by the reviewer.

FIGURE 7
Cyst Count in Concentrated Stool Sample at Day 14 by Treatment Group (indicating mean and standard deviation)



The mean ± SD change in cyst counts between Day 7 and Day 14 is -1.54 ± 4.7 for the nitazoxanide tablet group, -1.53 ± 4.4 for the nitazoxanide suspension group, and -2.2 ± 6.5 for the placebo group.

In patients who were clinical responders at Day 7, the number of cysts in concentrated stool samples at baseline, Day 7, and Day 14 for each individual patient by treatment group is shown in Figure 8. Although there is a mean drop in the cyst counts between the Day 7-10 and Day 14-17 visits, an individual assessment of cyst counts between all three time points (i.e., baseline, Day 7-10, and Day 14-17) in the concentrated stool samples shows that the drop in counts at Day 7-10, was not sustained and tended to rebound to baseline levels at Day 14-17.

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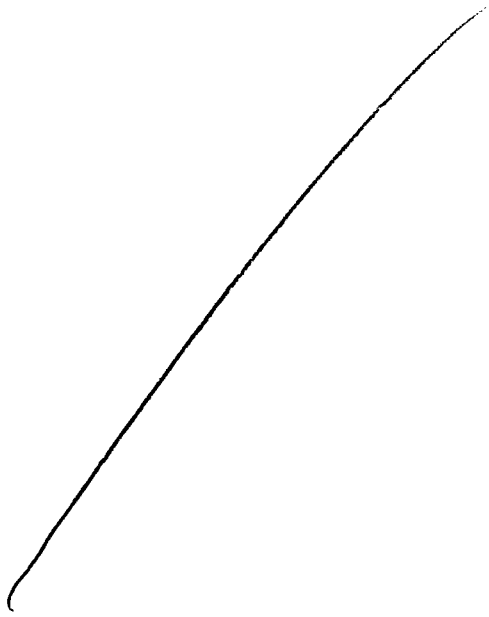
FIGURE 8
Individual Cyst Counts in Concentrated Stool Samples in Clinical Responders (as Assessed at Day 7) at Baseline, Day 7*, and Day 14 by Treatment Group



Clinical Reviewer's Comment: Across the three treatment groups it appears that there is a rebound in the number of cysts in concentrated stool samples between Days 7 and 14. Clinical response, as per the protocol, was assessed at Day 7, but not at Day 14. Concomitant medications were recorded only at the baseline and Day 7 visits. Therefore, based upon the data collected, it is not possible to determine which patients relapsed clinically at Day 14 based upon their symptoms or their need for additional drug therapy (i.e., antimicrobials or anti-diarrheal drugs).

The clinical significance of rebounding cyst counts at follow-up was investigated further by the Reviewer.

Published literature of trials using other antimicrobial agents to treat giardiasis, for the most part, does not address clinical and/or microbiologic response at follow-up.

The IDSA guidelines for evaluating drugs to treat giardiasis (Cooperstock, et al. 1992) recommend evaluating response (clinical and microbiologic) between 48 hours and 7 days following the end of treatment. The guidelines do not discuss follow-up to assess relapse.

Of the patients enrolled in Egypt, there were 7/16 patients in the nitazoxanide tablet group and 7/17 patients in the nitazoxanide suspension group with zero cysts in the

concentrated stool samples at all three sampling time points. This is in contrast to 0/29 patients in the nitazoxanide tablet group and only 1/29 patients in the nitazoxanide suspension group with zero cyst counts at all three time points enrolled in Peru. The applicant acknowledges that in the area of Peru where subjects were recruited for the study, Giardia is known to be hyper-endemic. Therefore, rapid re-infection may not be unexpected; however, this cannot be demonstrated within this study.

Stool samples may become negative for cysts during and following treatment, but the organism may be sequestered in the duodenum and so the patient is never truly eradicated (Gilman et al. 1988).

It should also be noted that the detection of cysts in this study was more qualitative than quantitative due to the microbiologic methods of counting cysts per high power field in one to two stool samples. True quantitative detection of cysts would involve collection of stool over 24 hours and determining the number of cysts per gram of stool.

In summary, the clinical significance of an apparent rebound in cyst counts at follow-up in the current study is unknown.

Efficacy Results by Study Site

This trial enrolled patients at two study sites – one in Peru and one in Egypt. Patients enrolled at the study center in Peru were slightly younger than those enrolled at the center in Egypt. They were Hispanic as opposed to Caucasian, and their weight was less due to their age (more adolescents).

The duration of diarrhea at baseline was also slightly lower at baseline for patients enrolled at the study center in Peru. The median quantitation of *Giardia lamblia* cysts in the stool samples of the patients enrolled at the study center in Peru was also significantly higher than that of the patients enrolled at the study center in Egypt.

The differences in age of the patients by study site may be explained, according to the applicant, by the methods used for recruiting patients to the study. At the study center in Egypt, patients were recruited from patients who visited the outpatient clinic seeking medical attention for diarrheal illness. In the case of the Peruvian study center, many of the patients were recruited by nurses caring for adolescents with diarrhea attending local schools.

The difference in quantitation of *Giardia lamblia* cysts in baseline stool samples could possibly be due, in part, according to the applicant, to small differences in the methods used for concentrating stool prior to counting the cysts. More likely, they believe, the difference truly reflects a higher number of *Giardia* cysts in the stools of the Peruvian patients, since *Giardia* is reportedly hyper-endemic in this region of Peru, which is not the case with the study center in Egypt.

TABLE 11
Demographic and Disease-Related Characteristics by Study Center

	All Subjects	Peru	Egypt	p^1
Race:				
Hispanic	90	90	-	<.0001
Caucasian	45	-	45	
Gender:				
Male	91	65	26	.12
Female	44	25	19	
Age (years):				
Mean	19.82	17.51	24.43	<.0001
S.D.	9.64	7.82	11.26	
Range	12-55	12-54	12-55	
Weight (kgs):				
Mean	52.81	47.83	62.64	<.0001
S.D.	15.33	13.03	14.88	
Range	25-100	27-84	25-100	
Stool Frequency				
1-2/day	3	-	3	.0002
3-4/day	127	90	37	
5-10/day	5	-	5	
Stool Consistency				
Liquid	26	15	11	.48
Soft	107	74	33	
Formed	2	1	1	
Abdominal pain/cramps				
Yes	115	78	37	.28
No	20	12	8	
Duration of Diarrhea				
Mean	6.17 [2]	5.42	7.79 [2]	<.0001
S.D.	3.02	2.10	3.95	
Range	1-27	1-14	3-27	
Giardia cyst quantitation[3]				
Median	3.5	5	1	<.0001[4]
Range	0-80	0.5-80	0-10	

[1] Chi Square or Fisher's Exact test used for comparing proportions, t-test for means.

[2] Excludes one outlier with diarrhea for more than 5 years.

[3] Number of *Giardia* cysts observed per microscopic field (x400 magnification) after concentration of stool. 129 of 135 patients had data reported. Reporting of median was more appropriate than mean due to the nature of the data (e.g., the laboratory in Egypt reported >10 organisms/field as the high end of the range while the laboratory in Peru attempted to make accurate counts as approximations). Some patients from the Egyptian site showed no cysts in their stool at baseline by microscopic examination of concentrated stool, but cysts were observed by immunofluorescence assay.

[4] Wilcoxon test used to compare medians.

A more detailed description of the number of *Giardia* cysts in the baseline concentrated stool sample is shown in Table 12.

Clinical Reviewer's Comment: Table 12 was created by the reviewer.

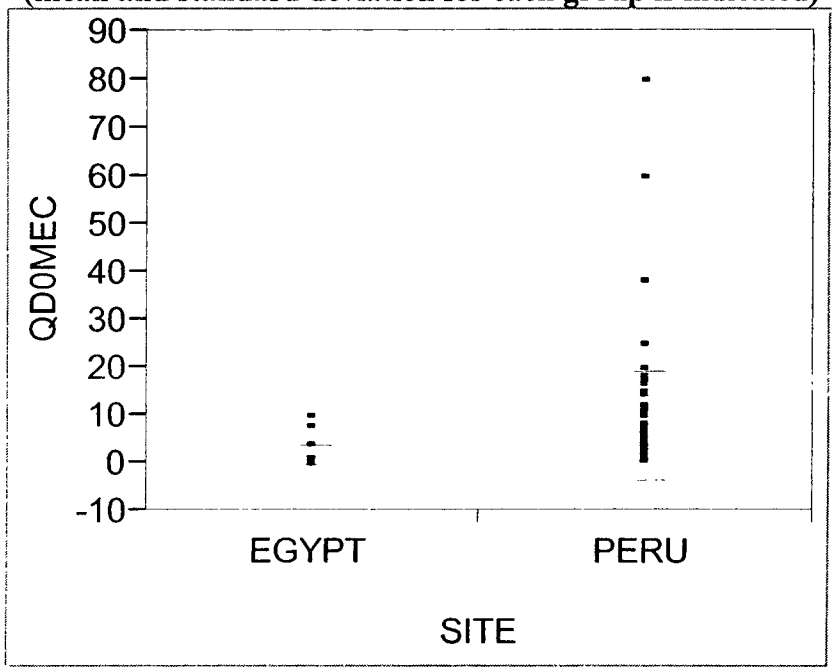
TABLE 12
Description of Cyst Counts in the Baseline Concentrated Stool Sample by Study Site

	Peru	Egypt
N	88 (1 patient with missing data excluded)	40 (5 patients with missing data excluded)
Mean number of cysts ± SD	7.8 ± 11.4	1.6 ± 2.2
Range	0 to 80	0 to 10
N of patients with 0 to 1 cyst	11	28
N of patients with > 10 cysts	16 (actual number of cysts in these patients: 11, 12, 14, 15, 16.5, 17.5, 18, 20, 25, 25, 38, 60, 80)	none

The cyst count (mean ± SD) in the baseline concentrated stool sample by study site is shown graphically in Figure 9.

Clinical Reviewer's Comment: Figure 9 was created by the reviewer.

FIGURE 9
Cyst Count at Baseline in Concentrated Stool Sample by Study Site
(mean and standard deviation for each group is indicated)



Clinical response rates and parasitological response rates at Days 7-10 by study site and treatment group are presented in Tables 13 and 14, respectively.

TABLE 13
Clinical Response Rates ("Well") by Treatment Group and Study Site at Day 7-10

Treatment Group	Peru	Egypt	*p*
Nitazoxanide Tablet	29/36 (81%)	17/18 (94%)	0.24
Nitazoxanide Suspension	29/36 (81%)	16/18 (89%)	0.70
Placebo Tablet	8/18 (50%)	3/9 (33%)	0.68

TABLE 14
Parasitological Response Rates by Treatment Group and Study Site at Day 7-10

Treatment Group	Peru	Egypt	*p*
Nitazoxanide Tablet	13/36 (36%)	17/18 (94%)	< 0.0001
Nitazoxanide Suspension	11/36 (31%)	15/18 (83%)	0.0004
Placebo Tablet	3/18 (17%)	2/9 (22%)	1.0

The cyst count (mean ± SD) in the Day 7 concentrated stool samples by treatment group for Peru and Egypt is shown graphically in Figures 10A and 10B and 11A and 11B, respectively.

Clinical Reviewer's Comment: Figures 10A, 10B, 11A, 11B, 12, 13, 14, and 15 were created by the reviewer.

FIGURE 10A
Cyst Count in Concentrated Stool Sample #1 at Day 7 by Treatment Group
PERU SITE
(indicating mean and standard deviation)

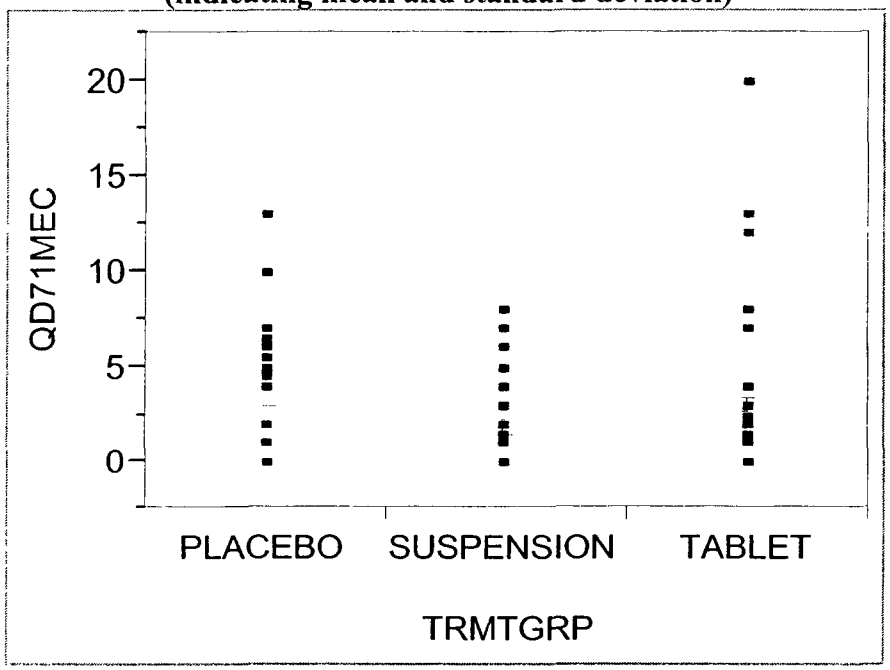


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FIGURE 10B
Cyst Count in Concentrated Stool Sample #2 at Day 7 by Treatment Group
PERU SITE
(indicating mean and standard deviation)

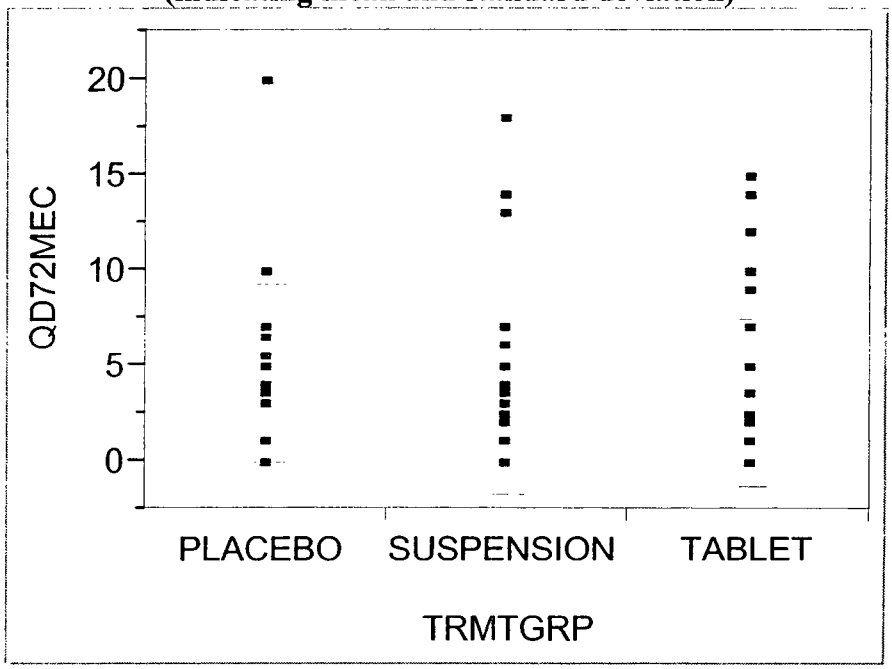


FIGURE 11A
Cyst Count in Concentrated Stool Sample #1 at Day 7 by Treatment Group
EGYPT SITE

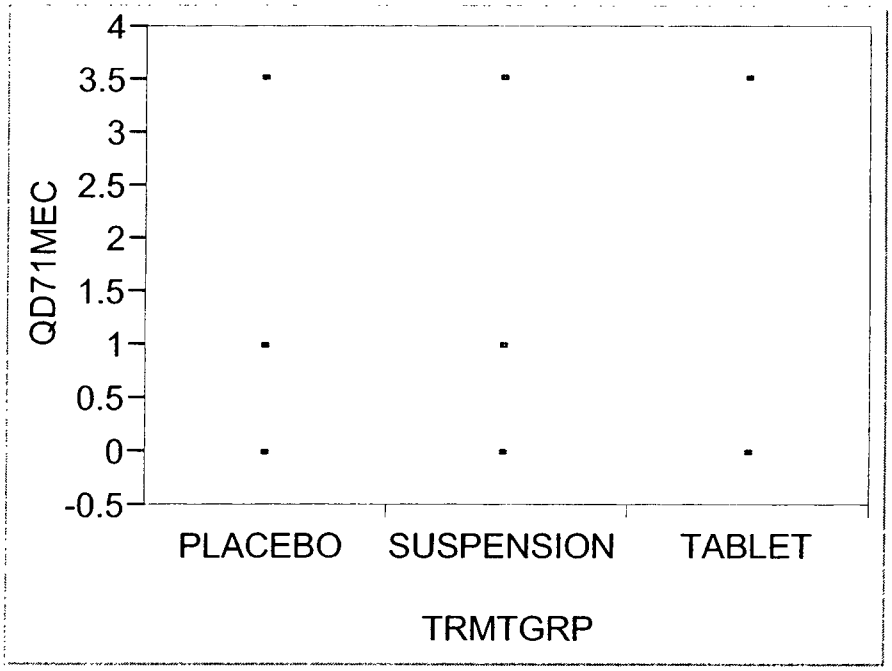
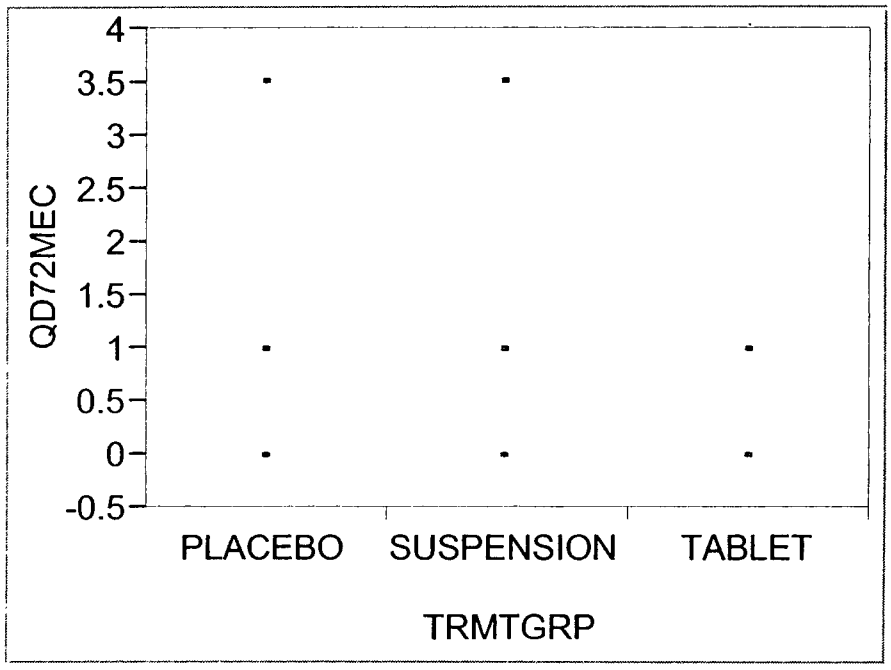


FIGURE 11B
Cyst Count in Concentrated Stool Sample #2 at Day 7 by Treatment Group
EGYPT SITE



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The number of cysts in concentrated stool samples at baseline and then again at Day 7 for each individual patient by treatment group is shown in Figure 12 for Peru and Figure 13 for Egypt.

FIGURE 12
Individual Cyst Counts in Concentrated Stool Samples at Baseline and Day 7* by Treatment Group – PERU SITE

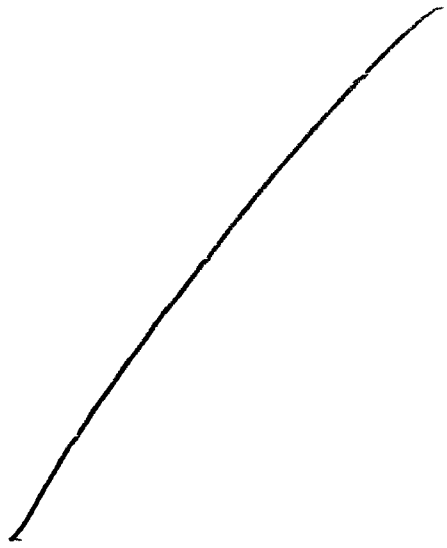
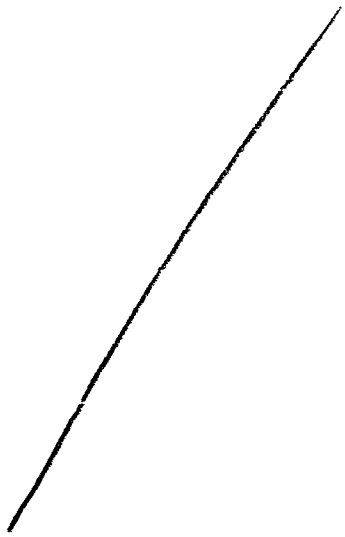
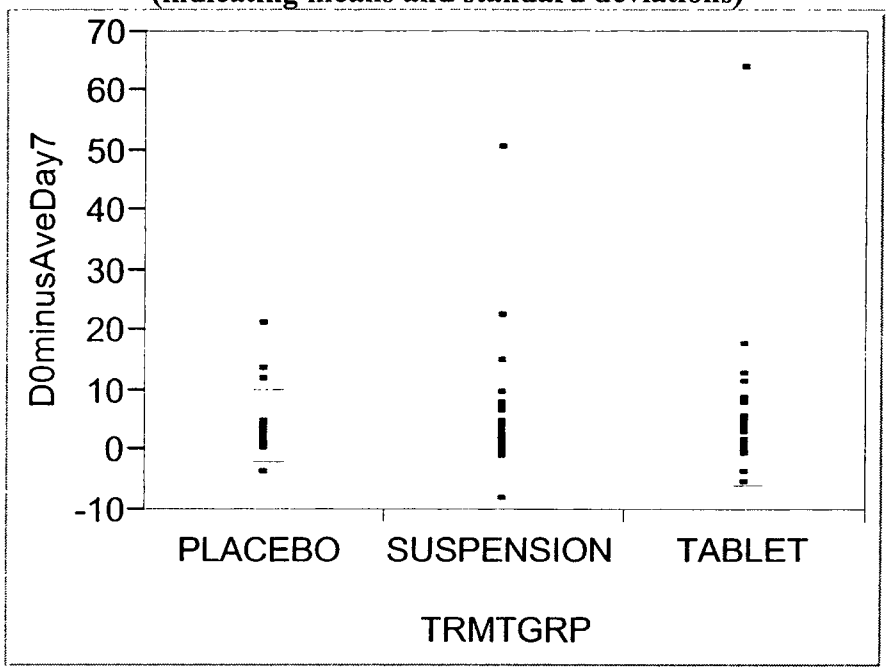


FIGURE 13
Individual Cyst Counts in Concentrated Stool Samples at Baseline and Day 7* by Treatment Group – EGYPT SITE



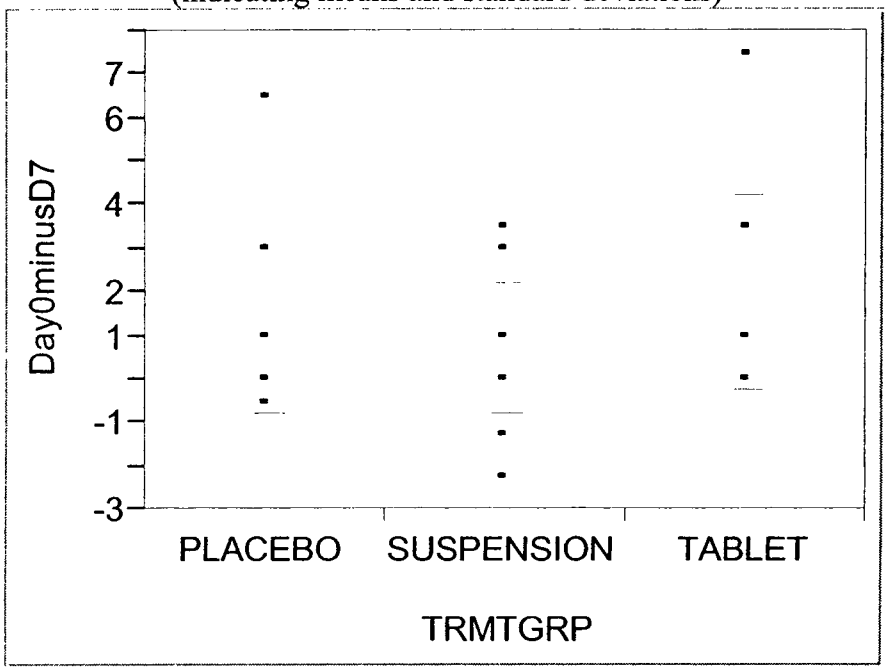
The difference between the cyst counts at baseline and Day 7 (i.e., baseline minus Day 7) in concentrated stool samples for individual patients by treatment group is shown in Figure 14 for Peru and Figure 15 for Egypt.

FIGURE 14
Individual Patient Reduction in Parasite Count (Baseline minus Day 7*) by Treatment Group – PERU SITE
(indicating means and standard deviations)



* cyst count on Day 7 is an average of the count from two samples obtained 24 hours apart between Days 7 and 10

FIGURE 15
Individual Patient Reduction in Parasite Count (Baseline minus Day 7*) by Treatment Group – PERU SITE
(indicating means and standard deviations)



* cyst count on Day 7 is an average of the count from two samples obtained 24 hours apart between Days 7 and 10

A categorical analysis of the difference in cyst counts at baseline and Day 7 (maximum of two concentrated stool samples) was conducted by the FDA statistical reviewer and is shown in Table 15 for Peru and Table 16 for Egypt. Improvement is defined as difference of > 0; worse is defined as a difference of < 0 and no change is a difference equal to 0. The results show that there is no overall difference between the treatment means.

Clinical Reviewer's Comment: Tables 15 and 16 was created by the FDA statistical reviewer.

TABLE 15
Categorical analysis of the difference between Cyst Counts in Concentrated Stool Samples at Baseline and Day 7 by Treatment Group – PERU Site

	Nitazoxanide Tablet	Nitazoxanide Suspension	Placebo	Overall p-value
Improvement	27/35 (77.1%)	28/34 (82.4%)	13/18 (72.2%)	0.79
No change	3/35 (8.6%)	2/34 (5.9%)	3/18 (16.7%)	
Worse	5/35 (14.3%)	4/34 (11.8%)	2/18 (11.1%)	

TABLE 16
Categorical analysis of the difference between Cyst Counts in Concentrated Stool Samples at Baseline and Day 7 by Treatment Group – EGYPT Site

	Tablet	Suspension	Placebo	Overall p-value
Improve	9/15 (60%)	9/17 (52.9%)	5/8 (62.5%)	0.51
No change	6/15 (40%)	6/17 (35.3%)	2/8 (25%)	
Worse	0/15 (0%)	2/17 (11.7%)	1/8 (12.5%)	

The intrapatient correlation of clinical and parasitological response rates by treatment group are presented in Table 17 for the Peru site and in Table 18 for the Egypt site.

The Peru site found higher proportions of patients treated with nitazoxanide tablets or suspension who were clinical responders but were still excreting *Giardia* cysts in stool samples collected four to seven days following treatment ("well/persistence").

Clinical Reviewer's Comment: Tables 17 and 18 were created by the reviewer by merging several of the applicant's tables.

TABLE 17
Intrapatient Correlation of Clinical and Parasitological Response Rates by Treatment Group – PERU Site

Response	Nitazoxanide Tablets* N=36		Nitazoxanide Suspension** N=36		Placebo*** N=18	
	Well	Continuing Illness	Well	Continuing Illness	Well	Continuing Illness
Eradication	12 (33.3%)	1 (2.7%)	11 (30.6%)	0 (0%)	3 (16.7%)	0 (0%)
Persistence	17 (47.2%)	6 (16.7%)	18 (50%)	7 (19.4%)	6 (33.3%)	9 (50%)

*p = 0.38 (two-sided Fisher's exact test)
**p = 0.076 (two-sided Fisher's exact test)
*** p = 0.21 (two-sided Fisher's exact test)

TABLE 18
Intrapatient Correlation of Clinical and Parasitological Response Rates by Treatment Group – EGYPT Site

Response	Nitazoxanide Tablets* N=18		Nitazoxanide Suspension** N=18		Placebo*** N=9	
	Well	Continuing Illness	Well	Continuing Illness	Well	Continuing Illness
Eradication	16 (89%)	1 (6%)	15 (83.3%)	0 (0%)	1 (11.1%)	1 (11.1%)
Persistence	1 (6%)	0 (0%)	1 (5.5%)	2 (11.1%)	2 (22.2%)	5 (55.5%)

*p = 1.0 (two sided Fisher's exact test)
** p = 0.0196 (two-sided Fisher's exact test)
*** p = 1.0 (two-sided Fisher's exact test)

The results of stool examinations at Day 14-17 for clinical responders by study site are compared in Table 19. Clinical responders (as assessed at Day 7) in the nitazoxanide tablets and nitazoxanide suspension treatment groups who were enrolled at the study center in Egypt were more likely to have negative stool examinations for *Giardia* on Day 14 than clinical responders from those treatment groups who were enrolled at the study center in Peru.

Clinical Reviewer's Comment: Table 19 was created by the reviewer by merging the applicant's original tables.

TABLE 19
Parasitological Response in Stool in Clinical Responders by Treatment Group at Day 14-17

Stool Results	Nitazoxanide Tablets[1]		Nitazoxanide Suspension[2]		Placebo[3]	
	Peru N=29	Egypt N=16*	Peru N=27**	Egypt N=16	Peru N=29	Egypt N=3
Negative	6 (20.7%)	16 (100%)	10 (37.0%)	14 (87.5%)	1 (3.4%)	2 (66.7%)
Positive	23 (79.3%)	0 (0%)	17 (63.0%)	2 (12.5%)	8 (27.6%)	1 (33.3%)

*one clinical responder did not submit a stool sample on Day 14-17
** two clinical responders did not submit a stool sample on Day 14-17
[1] p < 0.001 (Fisher's exact test)
[2] p = 0.016 (Fisher's exact test)
[3] p = 0.1273 (Fisher's exact test)

The cyst count (mean ± SD) in the Day 14 concentrated stool sample for the clinical responders by treatment group for Peru and Egypt is shown graphically in Figures 16A and 16B.

Clinical Reviewer's Comment: Figures 16A and 16B were created by the reviewer.

FIGURE 16A
Cyst Count in Concentrated Stool Sample in Clinical Responders at Day 14 by Treatment Group – PERU SITE (indicating mean and standard deviation)

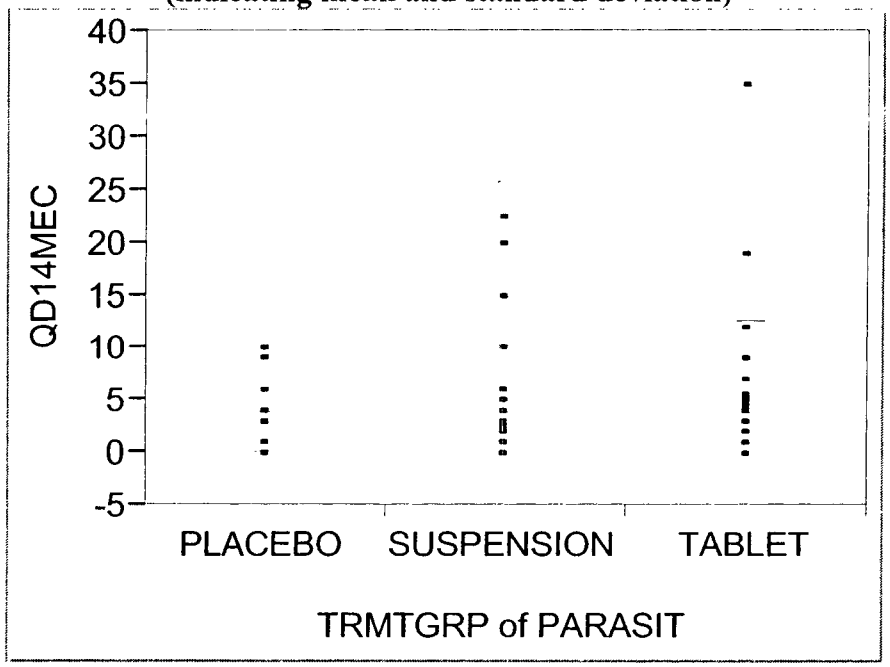


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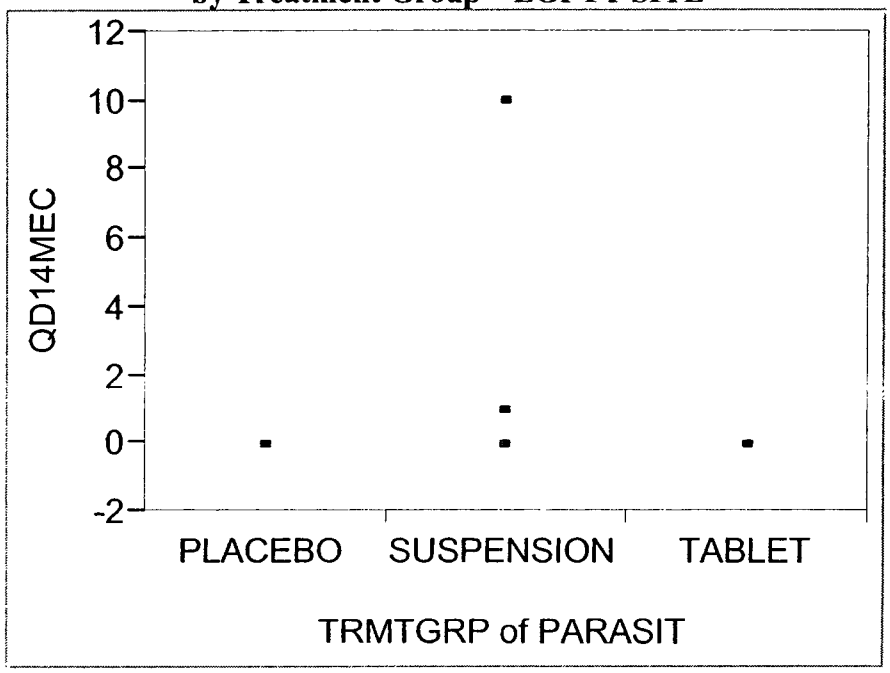
FIGURE 16B
Cyst Count in Concentrated Stool Sample in Clinical Responders at Day 14 by Treatment Group – EGPYT SITE



In patients who were clinical responders (as assessed at Day 7), the number of cysts in concentrated stool samples at baseline, Day 7, and Day 14 for each individual patient by treatment group is shown in Figure 17 for Peru and Figure 18 for Egypt.

Clinical Reviewer's Comment: Of the patients enrolled in Egypt, there were 7/16 patients in the nitazoxanide tablet group and 7/17 patients in the nitazoxanide suspension group with zero cysts in the concentrated stool samples at all three sampling time points. This is in contrast to 0/29 patients in the nitazoxanide tablet group and only 1/29 patients in the nitazoxanide suspension group with zero cyst counts at all three time points in concentrated stool samples who were enrolled in Peru.

FIGURE 17
Individual Cyst Counts in Concentrated Stool Samples in Clinical Responders at Baseline, Day 7*, and Day 14 by Treatment Group – PERU SITE

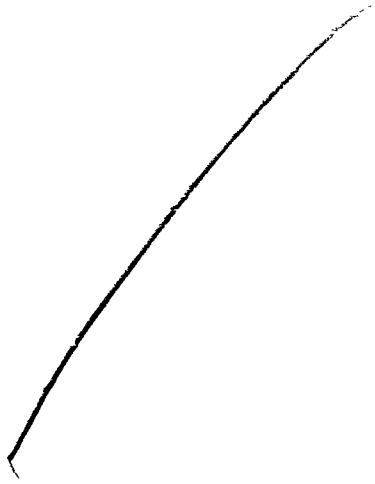


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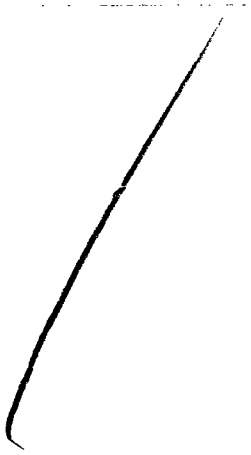
FIGURE 18
Individual Cyst Counts* in Concentrated Stool Samples in Clinical Responders at Baseline, Day 7, and Day 14 by Treatment Group – EGYPT SITE**



While the clinical responses by treatment group were similar for the two study centers, patients enrolled at the center in Peru and treated with nitazoxanide tablets or nitazoxanide suspension were more likely to have *Giardia* cysts in their stools four to seven days after treatment than were patients enrolled at the center in Egypt.

In an attempt to explain the difference, the applicant examined the potential effect of demographic and disease related characteristics of the patient populations. From Table 11 the obvious differences in the patients recruited by the two sites were:

- age
- weight
- duration of diarrhea at baseline
- number of cysts observed in the baseline stool samples.

Therefore, the applicant compared (for each treatment group) age, weight, duration of diarrhea at baseline and number of cysts observed in baseline stool samples for the parasitological responders to that of parasitological failures. Because the number of failures from the Egyptian site was small, only patients from the Peruvian site were evaluated. The results of this evaluation are presented in Table 20.

TABLE 20
Age, Duration of Diarrhea, and Baseline Cyst Quantitation by Parasitological Response for Patients Enrolled at the Peruvian Site

	Parasitological Response		
	Eradication	Persistence	p^1
Nitazoxanide Tablets			
Age (mean years)	16.2	18.3	.4775
Weight (mean kgs)	45.8	48.8	.4985
Duration of diarrhea (mean days)	5.2	5.3	.8307
Cyst quantitation			
Mean	3.7	10.5	.1487
Median	4	5	.0635
Nitazoxanide Suspension			
Age (mean years)	17.1	18.0	.7453
Weight (mean kgs)	52.1	46.7	.2302
Duration of diarrhea (mean days)	5.2	5.5	.5998
Cyst quantitation			
Mean	4.5	8.4	.3169
Median	1	3	.0654
Placebo Tablets			
Age (mean years)	13.0	17.7	.3041
Weight (mean kgs)	39.3	48.7	.3762
Duration of diarrhea (mean days)	4.0	6.1	.0689
Cyst quantitation			
Mean	2.3	9.6	.2065
Median	1	5	.0558

[1] t-tests used to compare means. Wilcoxon test used to compare medians

There is no apparent relationship between age, weight or duration of diarrhea and parasitological response. In each of the three treatment groups, however, higher numbers of cysts observed in the baseline stool sample were associated with the presence of *Giardia* cysts in at least one of the two stool samples collected four to seven days after treatment (i.e., "persistence").

The applicant proposed that the relationship between cyst quantitation in the baseline stool sample and the presence of cysts in stool samples collected four to seven days after treatment suggests that:

- in cases of heavy colonization of the intestinal tract by *Giardia* cysts, some cysts may remain sequestered in the small bowel after treatment; and/or
- patients heavily colonized by *Giardia* at baseline are likely to continue ingesting *Giardia* cysts during treatment and follow-up making it difficult to evaluate parasitological response.

In the area of Peru where patients were recruited for the study, *Giardia* is hyperendemic. In this type of population, the applicant states, re-infection is rapid, and the excretion of cysts discontinues spontaneously over time (Gilman et al. 1988).

Efficacy Results by Age, Race, and Sex

Clinical Reviewer's Comment: Tables 21 through 24 were created by the reviewer.

Age: Clinical and parasitological response rates at Day 7 to 10 for adolescents (≥ 12 to < 18 years) and adults (≥ 18 years) by treatment group are shown in Tables 21A and 21B.

Clinical Reviewer's Comment: In the Reviewer's opinion, differences seen in clinical response and parasitological eradication between adolescent (≥ 12 to < 18 years) and adult (≥ 18 years) patients is not considered clinically meaningful and no adjustments to the adult dosing of nitazoxanide are warranted for adolescents.

TABLE 21A
Clinical Response Rates (%) by Age and Treatment Group on Days 7-10

Response	Nitazoxanide Tablets		Nitazoxanide Suspension		Placebo	
	Adolescents (≥ 12 to < 18 yrs) N=33	Adults (≥ 18 yrs) N=21	Adolescents (≥ 12 to < 18 yrs) N=35	Adults (≥ 18 yrs) N=19	Adolescents (≥ 12 to < 18 yrs) N=15	Adults (≥ 18 yrs) N=12
Well	27 (82%)	19 (90%)	30 (86%)	15 (79%)	8 (53%)	4 (33%)
Continuing Illness	6 (18%)	2 (10%)	5 (14%)	4 (21%)	7 (47%)	8 (67%)

TABLE 21B
Parasitological Response Rates (%) by Age and Treatment Group at Day 7-10

Response	Nitazoxanide Tablets		Nitazoxanide Suspension		Placebo	
	Adolescents (< 18 yrs) N=33	Adults (≥ 18 yrs) N=21	Adolescents (< 18 yrs) N=35	Adults (≥ 18 yrs) N=19	Adolescents (< 18 yrs) N=15	Adults (≥ 18 yrs) N=12
Eradication	17 (52%)	13 (62%)	16 (46%)	10 (53%)	3 (20%)	2 (17%)
Persistence	16 (48%)	8 (38%)	19 (54%)	9 (47%)	12 (80%)	10 (83%)

Race: Patients in Peru were classified as Hispanic and patients in Egypt were classified as Caucasian. Therefore, clinical and parasitological response rates at Day 7 to 10 for Hispanics and Caucasians are the same as by study site, as shown in Tables 13 and 14.

Clinical Reviewer's Comment: In the Reviewer's opinion, any differences seen in clinical response and parasitological eradication between Caucasian and Hispanic patients is not considered clinically meaningful and no adjustments to the dosing of nitazoxanide are warranted based on race.

Sex: Clinical and parasitological response rates at Day 7 to 10 for males and females by treatment group are shown in Tables 22A and 22B.

Clinical Reviewer's Comment: In the Reviewer's opinion, any differences seen in clinical response and parasitological eradication between male and female patients is not considered clinically meaningful and no adjustments to the dosing of nitazoxanide are warranted based on sex.

TABLE 22A
Clinical Response Rates (%) by Sex and Treatment Group on Days 7-10

Response	Nitazoxanide Tablets		Nitazoxanide Suspension		Placebo	
	Male N=34	Female N=20	Male N=34	Female N=20	Male N=23	Female N=4
Well	28 (82%)	18 (90%)	30 (88%)	15 (75%)	10 (43%)	2 (50%)
Continuing Illness	6 (18%)	2 (10%)	4 (12%)	5 (25%)	13 (57%)	2 (50%)

TABLE 22B
Parasitological Response Rates (%) by Sex and Treatment Group at Day 7-10

Response	Nitazoxanide Tablets		Nitazoxanide Suspension		Placebo	
	Male N=34	Female N=20	Male N=34	Female N=20	Male N=23	Female N=4
Eradication	19 (56%)	11 (55%)	18 (53%)	8 (40%)	4 (17%)	1 (25%)
Persistence	15 (44%)	9 (45%)	16 (47%)	12 (60%)	19 (83%)	3 (75%)

10.1.18 Safety Results

Safety Population

- Fifty-four (54) patients were exposed to nitazoxanide 500 mg tablets administered as one 500 mg tablet every 12 hours for 3 days.
- Fifty-four (54) patients were exposed to nitazoxanide suspension administered 500 mg nitazoxanide in 25 ml of suspension every 12 hours for 3 days.
- Twenty-seven (27) patients received one placebo tablet every 12 hours for three days.

Brief Summary of Adverse Events

Sixty-one (61) of the 135 patients reported at least one adverse event. A total of 92 adverse events were reported by these 61 patients, as shown in Table 23. Of the 92 adverse events, 42 occurred in the nitazoxanide tablet group, 40 in the nitazoxanide suspension group, and 10 in the placebo group.

Eighty-five (85) of the 92 adverse events were considered mild. The most common symptoms were abdominal pain, diarrhea, nausea, headache, and asthenia.

All of the adverse events were considered possibly or probably related to treatment except for: appendicitis (n=1), fractured femur (n=1), headache (n=1), pharyngitis (n=1) and flu (n=1) [the last three events all occurred in the same patient].

One adverse event was severe. A patient in the nitazoxanide tablet group experienced abdominal pain and the patient dropped out of the study after taking two doses of study drug. Five (5) adverse events were reported as moderate: abdominal pain (1 - placebo), abdominal pain (1 - nitazoxanide tablet), asthenia (1 - nitazoxanide tablet), diarrhea (1 - nitazoxanide tablet) and fractured femur (1 - nitazoxanide tablet).

TABLE 23
Summary of Adverse Events by Treatment Group

Adverse Event	Active Tablet (n= 54)	Suspension (n= 54)	Placebo Tablet (n= 27)
Body as a whole:			
PAIN ABDO	12 (22%)	14 (26%)	5 (19%)
ASTHENIA	7 (13%)	5 (9%)	1 (4%)
HEADACHE	4 (7%)	5 (9%)	2 (7%)
FLU SYND	1 (2%)	-	-
Digestive:			
NAUSEA	4 (7%)	4 (7%)	-
DIARRHEA	1 (2%)	-	1 (4%)
VOMIT	-	1 (2%)	-
THIRST	1 (2%)	-	-
UG:			
URINE ABNORM	4 (7%)	5 (9%)	-
EDEMA LABIA	1 (2%)	-	-
Nervous:			
DIZZINESS	2 (4%)	2 (4%)	-
SOMNOLENCE	1 (2%)	2 (4%)	-
REFLEXES INC	-	1 (2%)	-
EMOTION LABIL	-	-	1 (4%)
Respiratory:			
PHARYNGITIS	1 (2%)	-	-
RHINITIS	-	1 (2%)	-
SS:			
PAIN EAR	1 (2%)	-	-
EYE DIS	1 (2%)	-	-
MS:			
BONE FRACT SPONTAN	1 (2%)	-	-

Clinical Reviewer's Comment: The term "Urine abnorm" included 9 patients with urine discoloration.

Deaths

There were no deaths reported in this study.

Serious Adverse Events

There was one serious adverse event, a patient (#123) from the nitazoxanide tablet group, who developed appendicitis three days after the end of treatment. The appendicitis (described as PAIN ABDO in Table 14) was considered to be unrelated to treatment.

> #123), a 12 year-old female weighing 25 kg was enrolled at the site in Egypt on August 21, 2003 and completed treatment taking her last dose of medication on August 23, 2003. On she noticed severe right lower abdominal pain that was diagnosed as appendicitis. An appendectomy was performed on the same day, and the patient was discharged from the hospital two days later. The appendicitis was considered unrelated to the study medication.

Discontinuations due to Adverse Events

One patient from the nitazoxanide tablet group dropped out of the study after taking two doses due to abdominal pain that was classified as severe.

Safety Results by Age, Race, and Sex

Clinical Reviewer's Comment: Tables 24-26 were created by the reviewer.

Age: Adverse events in adolescents (≥ 12 to < 18 years) compared to adults (≥ 18 years) are shown in Table 24.

Clinical Reviewer's Comment: In the Reviewer's opinion, any differences seen in adverse event rates between adolescent (≥ 12 to < 18 years) and adult (≥ 18 years) patients treated with nitazoxanide tablets or suspension is not considered clinically meaningful and does not warrant reporting by age in the product labeling.

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TABLE 24
Rates (%) of Adverse Events* by Age and Treatment Group

Adverse Event	Nitazoxanide Tablet		Nitazoxanide Suspension		Placebo	
	Adolescents (≥ 12 to < 18 yrs) N=22	Adults (≥ 18 yrs) N=20	Adolescents (≥ 12 to < 18 yrs) N=26	Adults (≥ 18 yrs) N=14	Adolescents (≥ 12 to < 18 yrs) N=6	Adults (≥ 18 yrs) N=4
ASTHENIA	1 (4.6%)	6 (30.0%)	3 (11.5%)	2 (14.3%)	--	1 (25%)
BONE FRACT	--	--	--	--	--	--
DIARRHEA	1 (4.6%)	--	--	--	--	1 (25%)
DIZZINESS	2 (9.1%)	--	2 (7.7%)	--	--	--
EDEMA LABIA	1 (4.6%)	--	--	--	--	--
EMOTION LABIL	--	--	--	--	1 (16.7%)	--
EYE DIS	1 (5.0%)	--	--	--	--	--
FLU SYN	--	1 (5.0%)	--	--	--	--
HEADACHE	3 (13.6%)	1 (5.0%)	4 (15.4%)	1 (7.1%)	1 (16.7%)	1 (25%)
NAUSEA	2 (9.1%)	2 (10.0%)	2 (7.7%)	2 (14.3%)	--	--
PAIN ABDO	9 (40.9%)	3 (15.0%)	9 (34.6%)	5 (35.7%)	4 (66.7%)	1 (25%)
PAIN EAR	--	1 (5.0%)	--	--	--	--
PHARYNGITIS	--	1 (5.0%)	--	--	--	--
REFLEXES INC	--		1 (3.9%)		--	
RHINITIS	--		1 (3.9%)		--	
SOMNOLENCE	1 (4.5%)	--	1 (3.9%)	1 (7.1%)	--	--
THIRST	--	1 (5.0%)	--	--	--	--
URIN ABNORM	2 (9.1%)	2 (10.0%)	2 (7.7%)	3 (21.4%)	--	--
VOMIT	--	--	1 (3.9%)	--	--	

* numbers reflect events and not patients, a patient may have had more than one event

Race: Adverse events in Egyptian (Caucasian) compared to Peruvian (Hispanic) patients is shown in Table 25.

Clinical Reviewer's Comment: In the Reviewer's opinion, any differences seen in adverse event rates between Caucasian and Hispanic patients treated with nitazoxanide is not considered clinically meaningful and does not warrant reporting by race in the product labeling.

TABLE 25
Rates (%) of Adverse Events* by Race (Caucasian and Hispanic) and Treatment Group

Adverse Event	Nitazoxanide Tablet		Nitazoxanide Suspension		Placebo	
	C (Egypt) N=12	H (Peru) N=30	C (Egypt) N=7	H (Peru) N=33	C (Egypt) N=1	H (Peru) N=9
ASTHENIA	7 (58.3%)	--	5 (71.4%)	--	1 (100%)	--
BONE FRACT	1 (8.3%)	--	--	--	--	--
DIARRHEA	--	1 (3.3%)	--	--	--	1 (11.1%)
DIZZINESS	--	2 (6.7%)	--	2 (6.1%)	--	--
EDEMA LABIA	--	1 (3.3%)	--	--	--	--
EMOTION LABIL	--	--	--	--	--	1 (11.1%)
EYE DIS	--	1 (3.3%)	--	--	--	--
FLU SYN	--	--	--	--	--	--
HEADACHE	--	4 (13.3%)	--	5 (15.2%)	--	2 (22.2%)
NAUSEA	--	4 (13.3%)	--	4 (12.1%)	--	--
PAIN ABDO	2 (16.7%)	10 (33.3%)	--	14 (42.4%)	--	5 (55.5%)
PAIN EAR	--	1 (3.3%)	--	--	--	--
PHARYNGITIS	--	1 (3.3%)	--	--	--	--
REFLEXES INC	--	--	--	1 (3.0%)	--	--
RHINITIS	--	--	--	1 (3.0%)	--	--
SOMNOLENCE	--	1 (3.3%)	1 (14.3%)	1 (3.0%)	--	--
THIRST	--	1 (3.3%)	--	--	--	--
URIN ABNORM	2 (16.7%)	2 (6.7%)	1 (14.3%)	4 (12.1%)	--	--
VOMIT	--	--	--	1b (3.0%)	--	--

* numbers reflect events and not patients, a patient may have had more than one event

Sex: Adverse events in male compared to female patients by treatment group are shown in Table 26.

Clinical Reviewer's Comment: In the Reviewer's opinion, any differences seen in adverse event rates between male and female patients treated with nitazoxanide is not considered clinically meaningful and does not warrant reporting by sex in the product labeling.

TABLE 26
Rates (%) of Adverse Events* by Sex and Treatment Group

Adverse Event	Nitazoxanide Tablet		Nitazoxanide Suspension		Placebo	
	Male N=22	Female N=20	Male N=22	Female N=18	Male N=10	Female N=0
ASTHENIA	5 (22.7%)	2 (10.0%)	1 (4.5%)	4 (22.2%)	1 (10.0%)	--
BONE FRACT	--	1 (5.0%)	--	--	--	--
DIARRHEA	1 (4.5%)	--	--	--	1 (10.0%)	--
DIZZINESS	2 (9.1%)	--	2 (9.1%)	--	--	--
EDEMA LABIA	1 (4.5%)	--	--	--	--	--
EMOTION LABIL	--	--	--	--	1 (10.0%)	--
EYE DIS	--	1 (5.0%)	--	--	--	--
FLU SYN	--	1 (5.0%)	--	--	--	--
HEADACHE	2 (9.1%)	2 (10.0%)	4 (18.2%)	1 (5.5%)	2 (20.0%)	--
NAUSEA	1 (4.5%)	3 (15.0%)	1 (4.5%)	3 (16.7%)	--	--
PAIN ABDO	5 (22.7%)	7 (35.0%)	8 (36.4%)	6 (33.3%)	5 (50.0%)	--
PAIN EAR	1 (4.5%)	--	--	--	--	--
PHARYNGITIS	--	1 (5.0%)	--	--	--	--
REFLEXES INC	--	--	1 (4.5%)	--	--	--
RHINITIS	--	--	--	1 (5.5%)	--	--
SOMNOLENCE	--	1 (5.0%)	1 (4.5%)	1 (5.5%)	--	--
THIRST	--	1 (5.0%)	--	--	--	--
URIN ABNORM	4 (18.2%)	--	3 (13.6%)	2 (11.1%)	--	--
VOMIT	--	--	1 (4.5%)	--	--	--

* numbers reflect events and not patients, a patient may have had more than one event

Laboratory Findings

Laboratory tests not routinely collected.

Vital Signs

No significant findings.

10.1.19 Conclusions

Efficacy: A total of 135 patients were enrolled (54 randomized to nitazoxanide tablets, 54 to nitazoxanide suspension, and 27 to placebo). No patients were excluded from the modified intent-to-treat population, and therefore, all patients randomized to the study were included in the analysis. Two patients (one from the nitazoxanide tablet group and one from the nitazoxanide suspension group) dropped out of the study. These patients were treated as clinical and parasitological failures.

The number of *Giardia* cysts observed per microscopic field after concentration of stool was reported at baseline in 129 of 135 patients. The mean number of cysts was approximately 6 in the nitazoxanide tablet group, 5 in the nitazoxanide suspension group, and 7 in the placebo group. Some patients from the Egyptian site showed no cysts in their stool at baseline by microscopic examination of concentrated stool (6 in the nitazoxanide tablet group, 2 in the nitazoxanide suspension group, and 7 in the placebo group), but cysts were observed by immunofluorescence assay. A sensitivity analysis was performed by the FDA Clinical and Statistical Reviewers excluding these patients, along with an additional patient who was enrolled at the site in Egypt with fewer than 3 stools per day at baseline. The clinical and parasitological response rates were similar whether or not these patients were included in the analysis.

The mean number of cysts in the two concentrated stool samples obtained 24 hours apart between Days 7 and 10 were lower in all three groups (approximately 2 in the nitazoxanide tablet group, 2 in the nitazoxanide suspension group, and 3 in the placebo group). There were 34, 29, and 5 patients with no cysts detected in both stool samples for the nitazoxanide tablet, nitazoxanide suspension, and placebo groups respectively. However, the drop in the number of cysts between the baseline and Day 7-10 samples (mean ± SD) occurred in all three groups and was reported as: 4.3 ± 9.4 for the nitazoxanide tablet group, 3.7 ± 7.9 nitazoxanide suspension group, and 3.3 ± 5.2 for the placebo group. In addition, the number of cysts in stool samples at baseline and Day 7-10 (using the maximum of two concentrated stool samples at Day 7) was also compared in a categorical analysis (i.e., improved, no change, worsened) and the results showed there was no overall difference between the treatment means.

The proportion of "well" clinical responses recorded at the Day 7-10 test of cure visit (i.e., 4 to 7 days following the end of treatment) were: 85% (46/54) for the nitazoxanide tablet group, 83% (45/54) of the nitazoxanide suspension group, and 44% (12/27) for the placebo group. The proportion of "well" clinical responses in the active treatment group was significantly higher than in the placebo treatment group ($p = 0.0002$ for tablet versus placebo), which was the primary statistical comparison. The lower bound of the 95% confidence interval of the treatment difference between nitazoxanide tablets and nitazoxanide suspension was above the pre-specified non-inferiority margin of 15% (i.e., -13.5%, 17.1%), indicating that the clinical response rate to the nitazoxanide tablets was non-inferior to the nitazoxanide suspension.

The proportion of patients eradicated (i.e., no cysts or trophozoites observed in two stool samples collected between study Days 7 and 10) was: 55.5% (30/54) in the nitazoxanide tablet group, 48% (26/54) in the nitazoxanide suspension group, and 18.5% (5/27) in the placebo group. The parasitological response rate in the active treatment group was significantly higher than in the placebo treatment group ($p = 0.0019$ for nitazoxanide tablets versus placebo), which was the primary statistical comparison. The lower bound of the 95% confidence interval of the treatment difference between nitazoxanide tablets and nitazoxanide suspension was above the pre-specified non-inferiority margin of 15%

(i.e., -12.4%, 26.4%), indicating that the parasitological response rate to the nitazoxanide tablets was non-inferior to the nitazoxanide suspension.

The intrapatient correlation of clinical and parasitological response rates at Day 7-10 was calculated using the kappa statistic. The results showed a weak, but positive correlation between the groups (kappa of 0.196 for the nitazoxanide tablet group, 0.313 for the nitazoxanide suspension group, and 0.283 for the placebo group).

The clinical and parasitological response rates, as well as the intrapatient correlation between the two endpoints, were similar whether or not the patients without cysts in the baseline concentrated stool sample were included in the analyses.

Parasitological response was evaluated at a follow-up visit at Day 14-17 (i.e., 11 to 14 days following the end of therapy). Clinical response was not assessed. Of the patients who were clinical responders at Day 7, the following number of patients were had no cysts detected in the concentrated stool sample at Day 14-17: 49% (22/45) in the nitazoxanide tablet group, 56% (24/43) in the nitazoxanide suspension group, and 25% (3/12) in the placebo group. The mean ± SD change in cyst counts between Day 7 and Day 14 was -1.54 ± 4.7 for the nitazoxanide tablet group, - 1.53 ± 4.4 for the nitazoxanide suspension group, and -2.2 ± 6.5 for the placebo group. Although there was a mean drop in the number of cysts between the Day 7-10 and Day 14-17 visits, an assessment of cyst counts in individual patients between all three time points (i.e., baseline, Day 7-10, and Day 14-17) revealed some outlier patients who had an initial drop in the number of cysts between baseline and Day 7-10, but then had a rebound in the number of cysts back to baseline levels at Day 14-17. Therefore, nonsustained parasitological response was observed, mainly at the Peru study site.

The patients enrolled in Peru had a higher baseline cyst count (mean ± SD) combined across all treatment groups (7.8 ± 11.4) than did the patients in Egypt (1.6 ± 2.2).

The proportion of "well" clinical responses recorded at the Day 7-10 test of cure visit were numerically lower in Peru than in Egypt for both the nitazoxanide treatment groups and higher for the placebo group: 81% (29/36) vs. 94% (17/18) for the nitazoxanide tablet group, 81% (29/36) vs. 89% (16/18) for the nitazoxanide suspension group, and 50% (8/18) vs. 33% (3/9) for the placebo group.

The proportion of patients eradicated at Day 7-10 was lower in Peru than in Egypt for all three treatment groups: 36% (13/36) vs. 94% (17/18) in the nitazoxanide tablet group, 31% (11/36) vs. 83% (15/18) in the nitazoxanide suspension group, and 17% (3/18) vs. 22% (2/9) in the placebo group.

The Peru site compared to the Egypt site also found higher proportions of patients treated with nitazoxanide tablets or suspension who were clinical responders but were still excreting *Giardia* cysts in stool samples at Day 7-10 (i.e., clinically well with parasitological persistence): 47% (17-36) vs. 6% (1/18) for the nitazoxanide tablet group,

50% (18-36) vs. 5.5% (1/18) for the nitazoxanide suspension group, and 33% (6/18) vs. 22% (2/9) for the placebo group.

Clinical responders (as assessed at Day 7) in the nitazoxanide tablets and nitazoxanide suspension treatment groups who were enrolled at the study center in Peru were less likely to have negative stool examinations for *Giardia* on Day 14 than clinical responders from those treatment groups who were enrolled at the study center in Egypt: 21% (6/29) vs. 100% (16/16) for the nitazoxanide tablet group, 37% (10/27) vs. 87.5% (14/16) for the nitazoxanide suspension group, and 3% (1/29) vs. 67% (2/3) for the placebo group.

The applicant has proposed that the relationship between cyst quantitation in the baseline stool sample and the presence of cysts in stool samples collected after treatment in Peru suggests that in cases of heavy colonization of the intestinal tract by *Giardia* cysts, some cysts may remain sequestered in the small bowel after treatment; and/or patients heavily colonized by *Giardia* at baseline are likely to continue ingesting *Giardia* cysts during treatment and follow-up making it difficult to evaluate parasitological response.

Differences, if any, seen in the parasitological eradication rates between the following patient groups are not considered clinically meaningful: adolescents (12 to < 18 years) and adults (≥ 18 years); males and females; Caucasians and Hispanics. No adjustments to the dosing of nitazoxanide tablets are warranted based on age, sex or race.

In summary, clinical response at the test of cure visit (Day 7-10) in the nitazoxanide tablet group was significantly higher than in the placebo treatment group and the clinical response rate for nitazoxanide tablets was non-inferior to nitazoxanide suspension. The Clinical Studies section of the label should include clinical results for patients at the Day 7-10 visit. Specific parasitological results should not be included, since there is only a weak correlation between clinical and parasitological response. The prescriber should also be informed that at the follow-up visit (Day 14-17) cyst counts rebounded in many patients. Without a clinical assessment at the follow-up visit it is difficult for an assessment to be made of the significance of this parasitological finding.

Safety: Adverse events in adolescent and adult patients treated with nitazoxanide tablets and suspension were experienced by 61 of the 135 patients in the safety population. A total of 92 adverse events were reported by these 61 patients. Of the 92 adverse events, 42 occurred in the nitazoxanide tablet group, 40 in the nitazoxanide suspension group, and 10 in the placebo group.

The most common adverse events (occurring in at least 2 patients in both the nitazoxanide tablet and nitazoxanide suspension groups were: abdominal pain (22% of patients in the nitazoxanide tablet group and 26% in the nitazoxanide suspension group), asthenia (13% of patients in the tablet group and 9% in the suspension group), headache (7% in the tablet group and 9% in the suspension group), nausea (7% in both the tablet and suspension groups), abnormal urine (7% of the tablet group and 9% in the suspension

group), and dizziness (4% in both the tablet and suspension groups). Abdominal pain was the most common adverse event in the placebo group (19%).

Eighty-five (85) of the 92 adverse events were considered mild. Many of these (i.e., abdominal pain, diarrhea, nausea, headache, and asthenia) potentially could be symptoms of giardiasis.

There were no deaths reported in this study. One adverse event was serious (severe abdominal pain in a patient from the nitazoxanide tablet group). The patient developed appendicitis, which was considered to be unrelated to treatment, and dropped out of the study after taking two doses of study drug.

Differences, if any, seen in adverse events reported for the following patient groups are not considered clinically meaningful: adolescents (12 to < 18 years) and adults (≥ 18 years); males and females; Caucasians and Hispanics. Reporting of adverse events by age, sex, or race is not warranted in the labeling of nitazoxanide tablets.

In summary, nitazoxanide tablets and suspension were associated with mainly mild, gastrointestinal adverse events, the most common being abdominal pain which was also reported in the placebo group and may be related to the underlying disease (i.e., giardiasis) for which the patients were being treated.

10.2 Line-by-line Labeling Review

The approved label for nitazoxanide tablets and oral suspension is included as Appendix 10.4.

10.3 References

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10.4 Final Labeling for Nitazoxanide (Alinia®) Tablets and Oral Suspension (7/9/04)

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