

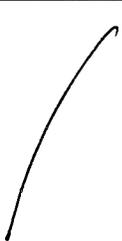
results for patients at the Day 7-10 visit. Specific parasitological results should not be included since there is only a weak correlation between clinical and parasitological response. The prescriber should also be informed that at the follow-up visit (Day 14-17) cyst counts increased in many patients: 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.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The nitazoxanide tablet development program contains safety information from 1628 HIV-uninfected adults and adolescent patients aged 12 years and older who received nitazoxanide tablets in controlled and uncontrolled studies, as shown in Table 3.

TABLE 3
Summary of Controlled and Uncontrolled Studies of Nitazoxanide Tablets in Patients Aged 12 Years and Older (HIV-uninfected)

| Study Number | Indication Studied | Number of Patients | Dosage Regimen |
|---------------|---|--------------------|---|
| RM01-3011 | Diarrhea caused by <i>Giardia lamblia</i> | 54 | 500 mg bid x 3 days |
| RM-NTZ-98-001 | Diarrhea caused by <i>Giardia lamblia</i> or <i>Entamoeba histolytica</i> | 47 | 500 mg bid x 3 days |
| RM-NTZ-98-002 | Diarrhea caused by <i>Cryptosporidium parvum</i> | 25 | 500 mg bid x 3 days |
| CL-NTZ-95-001 | Mixed intestinal parasitic infection | 121 | 500 mg bid x 3 days |
| PRC-94-NTZ03 | Mixed intestinal parasitic infection | 415 | 500 mg bid x 3 days |
| RM-96-401 | Mixed intestinal parasitic infection | 129 | Various doses (500 to 2000 mg qd) and durations (1 to 7 days) |
| RM-NTZ-99-008 |  | 40 | 500 mg bid x 7 days |
| RM-94-NTZ-04 | | 393 | 500 mg bid x 6 or 7 days |
| RM-NTZ-96-001 | | 195 | 500 mg or 100 mg x 7 or 14 days |
| RM-NTZ-95-01 | | 17 | 500 mg bid x 10 days |
| RM-NTZ-99-001 | | 68 | 2000 or 3000 mg x 1 day; and 500 or 1000 mg bid x 3 days |

| Study Number | Indication Studied | Number of Patients | Dosage Regimen |
|---------------|--------------------|--------------------|---|
| RM-NTZ-99-002 | — | 124 | 2000 or 3000 mg x 1 day; and 500 or 1000 mg bid x 3 or 7 days |

There were 54 HIV-negative patients aged 12 years and older who received nitazoxanide suspension as a comparator in controlled clinical trials (i.e., Study RM01-3011). No deaths, drop-outs due to adverse events, or other serious or potentially serious adverse events occurred in these patients.

7.1.1 Deaths

No deaths occurred in patients treated with nitazoxanide tablets. One death was reported in a 38 year old male patient randomized to placebo in Study RM-NTZ-98-001.

Clinical Reviewer's Comment: For more information see Medical Officer's Review for NDA 21-497 dated January 7, 2003, by Rosemary Johann-Liang, M.D.

7.1.2 Other Serious Adverse Events

One serious adverse event (appendicitis requiring hospitalization) occurred in 12 year old female patient enrolled in Study RM01-3011 three days after the end of 3 days of treatment with nitazoxanide tablets. The appendicitis, reported as abdominal pain, was considered to be unrelated to treatment.

7.1.3 Dropouts and Other Significant Adverse Events

Nine patients treated with nitazoxanide tablets and one patient treated with placebo discontinued study medication due to adverse events as shown in Table 4.

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TABLE 4
Discontinuations Due to Adverse Events

| Study number | Patient age/Sex | Nitazoxanide Dose | Adverse event | Duration (days) | Outcome |
|---------------|-----------------|-------------------|--|-----------------|------------|
| RM01-3011 | 16 F | 500 mg BID | Abdominal pain; Study drug discontinued | 3 | Resolved |
| RM-NTZ-98-002 | 30 F | 500 mg BID | Dizziness; Study drug discontinued | Unknown | Resolved |
| RM-NTZ-99-001 | 40 F | 1000 mg BID | Diarrhea; Study drug discontinued | 2 | Resolved |
| RM-NTZ-99-002 | 44 F | 1000 mg BID | Nausea; Study drug discontinued | 1 | Resolved |
| | 48 F | 500 mg BID | Stomach pain; Study drug discontinued | 2 | Resolved |
| | | | Vomiting; Study drug discontinued | 2 | Resolved |
| | 24 F | 1000 mg BID | Stomach pain; Study drug discontinued | 4 | Resolved |
| | 17 F | 500 mg BID | Diarrhea; Study drug discontinued | 2 | Resolved |
| | 24 F | 1000 mg BID | Diarrhea; Study drug discontinued | 2 | Resolved |
| | | | Stomach pain; Study drug discontinued | 7 | Unresolved |

7.1.4 Common Adverse Events

Adverse events reported in patients treated with nitazoxanide tablets (N=1628) or placebo (N=129) are shown in Tables 5 and 6, respectively. The rates of occurrence of the adverse events for nitazoxanide tablets do not appear to be different from those of placebo.

Clinical Reviewer's Comment: Tables 5 through 7 were created by the applicant and submitted to the NDA on June 25, 2004.

TABLE 5
Adverse Events: Patients (Aged 12 Years and Older) Who Received Nitazoxanide
Tablets in Controlled and Uncontrolled Studies (N=1628)

| Body system Adverse event | Patients Reporting AEs | |
|------------------------------|---------------------------|-----|
| | Number | % |
| BODY | | |
| PAIN ABDO | 109 | 6.7 |
| HEADACHE | 51 | 3.1 |
| ASTHENIA | 10 | 0.6 |
| FEVER | 6 | 0.4 |
| PAIN | 5 | 0.3 |
| ALLERG REACT | 3 | 0.2 |
| PAIN PELVIC | 2 | 0.1 |
| FLU SYND | 1 | 0.1 |
| CHILLS | 1 | 0.1 |
| CHILLS FEVER | 1 | 0.1 |
| DIG | | |
| DIARRHEA | 70 | 4.3 |
| NAUSEA | 50 | 3.1 |
| VOMIT | 7 | 0.4 |
| NAUSEA/VOMIT | 3 | 0.2 |
| DYSPEPSIA | 3 | 0.2 |
| NAUSEA VOMIT DIAR | 2 | 0.1 |
| ANOREXIA | 2 | 0.1 |
| FLATUL | 1 | 0.1 |
| CONSTIP | 1 | 0.1 |
| THIRST | 1 | 0.1 |
| DRY MOUTH | 1 | 0.1 |
| NER | | |
| DIZZINESS | 16 | 1.0 |
| SOMNOLENCE | 10 | 0.6 |
| HYPESTHESIA | 1 | 0.1 |
| INSOMNIA | 1 | 0.1 |
| TREMOR | 1 | 0.1 |
| UC | | |
| URIN ABNORM | 13 | 0.8 |
| DYSURIA | 2 | 0.1 |
| METRRORRHAGIA | 1 | 0.1 |
| PAIN KIDNEY | 1 | 0.1 |
| AMENORRHEA | 1 | 0.1 |
| EDEMA LABIA | 1 | 0.1 |

TABLE 5 (continued)
Adverse Events: Patients (Aged 12 Years and Older) Who Received Nitazoxanide Tablets in Controlled and Uncontrolled Studies (N=1628)

| Body system Adverse event | Patients Reporting AEs | |
|------------------------------|------------------------|-----|
| | Number | % |
| MAN SGPT INC | 14 | 0.9 |
| SKIN | | |
| RASH | 3 | 0.2 |
| PRURITUS | 2 | 0.1 |
| RASH VESIC BULL | 1 | 0.1 |
| SS | | |
| EYE DIS | 3 | 0.2 |
| PAIN EAR | 1 | 0.1 |
| RES | | |
| EPISTAXIS | 1 | 0.1 |
| LUNG DIS | 1 | 0.1 |
| PHARYNGITIS | 1 | 0.1 |
| CV | | |
| SYNCOPE | 1 | 0.1 |
| TACHYCARDIA | 1 | 0.1 |
| MS | | |
| MYALGIA | 1 | 0.1 |
| BONE FRACT SPONTAN | 1 | 0.1 |
| MS/NER | | |
| CRAMPS LEG | 1 | 0.1 |
| CV/NER | | |
| HYPERTENS | 1 | 0.1 |

TABLE 6
Adverse Events: Patients (Aged 12 and older) in Placebo Control Groups (N=129)

| Body system Adverse event | Patients Reporting AEs | |
|------------------------------|------------------------|-----|
| | Number | % |
| BODY | | |
| PAIN ABDO | 11 | 8.5 |
| HEADACHE | 3 | 2.3 |
| EDEMA FACE | 1 | 0.8 |
| ASTHENIA | 1 | 0.8 |
| DEATH | 1 | 0.8 |
| DIG | | |
| DIARRHEA | 4 | 3.1 |
| DYSPEPSIA | 1 | 0.8 |
| NER | | |
| DIZZINESS | 2 | 1.6 |
| SOMNOLENCE | 2 | 1.6 |
| EMOTION LABIL | 1 | 0.8 |
| UG | | |
| URIN ABNORM | 1 | 0.8 |
| DYSURIA | 1 | 0.8 |

7.1.5 Laboratory Findings

Laboratory values were not routinely collected in all studies. The values reported for patients with laboratory adverse events are summarized in Table 7. Most of the changes represent only slight deviations from the normal laboratory range.

TABLE 7
Adverse Events Related to Laboratory Abnormalities for Patients (Aged 12 Years and Older) Who Received Nitazoxanide Tablets in Controlled and Uncontrolled Trials

| Study no. | Patient no. | Lab parameter | Normal range | Before treatment | After treatment |
|---------------|-------------|---------------|--------------|------------------|-----------------|
| RM-94-NTZ-04 | AM 008 | SGPT | < 43 | 42 | 45 |
| RM-94-NTZ-04 | AM 011 | SGPT | < 43 | 43 | 46 |
| RM-94-NTZ-04 | SMK 189 | SGPT | < 43 | 42 | 61 |
| RM-94-NTZ-04 | HA 264 | SGPT | < 43 | 42 | 45 |
| RM-94-NTZ-04 | HA 265 | SGPT | < 43 | 42 | 46 |
| RM-94-NTZ-04 | HA 266 | SGPT | < 43 | 40 | 45 |
| RM-94-NTZ-04 | HA 267 | SGPT | < 43 | 40 | 45 |
| RM-94-NTZ-04 | HA 285 | SGPT | < 43 | 30 | 60 |
| RM-94-NTZ-04 | HR 056 | SGPT | < 43 | 42 | 45 |
| RM-94-NTZ-04 | HR 079 | SGPT | < 43 | 40 | 45 |
| RM-94-NTZ-04 | HR 082 | SGPT | < 43 | 40 | 45 |
| RM-94-NTZ-04 | HR 117 | SGPT | < 43 | 42 | 45 |
| RM-NTZ-96-001 | 007 | SGPT | < 43 | 28 | 65 |
| RM-NTZ-96-001 | 235 | SGPT | < 43 | 32 | 100 |

Units: SGPT: IU/L

7.1.6 Vital Signs

No clinically significant findings.

7.2 Safety Conclusions

Nitazoxanide tablets and suspension are associated with mild, gastrointestinal adverse events, the most common being abdominal pain which was also reported, although less frequently, in the placebo group.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The 500 mg dose (twice daily) of nitazoxanide and the 3-day duration of treatment selected for this study were based upon prior clinical studies that had demonstrated the safety and efficacy of nitazoxanide in the treatment of *Giardia lamblia*.

The proposed dosing regimen is one tablet (500 mg nitazoxanide) or 25 mL of suspension (500 mg nitazoxanide) every 12 hours taken with food for 3 days.

In the original submission for the nitazoxanide tablet (NDA 21-497), the presence of food was shown to prolong the rate of appearance of tizoxanide (metabolite of nitazoxanide) in plasma and increase the extent of systemic exposure. Administration of nitazoxanide tablets following a high-fat (48% of kcal as fat) meal compared with the fasted state resulted in a $116 \pm 83\%$ (range 6% to 289%) increase in AUC and $73 \pm 81\%$ (range -26% to 248%) increase in C_{max} . The median T_{max} was greater when nitazoxanide was given with food (3.25 hours versus 2 hours). In summary, administration of nitazoxanide with food results in higher exposure.

Results from the clinical efficacy studies submitted with NDAs 21-497 (nitazoxanide tablet) and 21-498 (nitazoxanide oral suspension), suggest that nitazoxanide oral suspension was effective in treating children (aged 1 to 11 years) with diarrhea when administered as the suspension and taken with food. However, the effectiveness of the tablets administered with food in adolescents and adults (aged ≥ 12 years) was not adequately demonstrated.

The applicant also conducted a bioequivalence study between a 500 mg dose given as suspension or tablet as part of NDA 21-498. The results showed that the bioavailability of the nitazoxanide active metabolite tizoxanide was 41% lower for the suspension formulation compared to the tablet formulation and the bioavailability of tizoxanide glucuronide was 30% lower for the suspension compared to the tablet. The 90% confidence intervals of the test/reference ratios were shifted towards lower values and were outside the acceptable limits of 80% to 125%.

From the pharmacokinetic studies, it can be concluded that food increases the absorption of tizoxanide from the suspension and that the suspension is less bioavailable than the tablets. An increased systemic exposure to tizoxanide with the tablets (taken with or without food) compared to the suspension may result in a decreased efficacy, as concluded from the clinical efficacy studies. Thus, in the Approvable letter for NDA 21-497, the relative contribution of local (i.e., the gastrointestinal tract) versus systemic activity was recommended for further study. The applicant was asked to characterize "the contribution of food-effect (fed-state versus fasting-state) on the clinical efficacy" of the tablets and suspension in adults.

Clinical Reviewer's Comment: The pharmacokinetic results quoted here came from the Clinical Pharmacology/Biopharmaceutics Review by Dakshina Chilukuri, Ph.D. filed with the original submission of NDA 21-497. See also the Approvable letter for NDA 21-497 in Section 2.5 "Pre-Submission Regulatory Activity" of this review.

In the current NDA submission, the applicant submitted a bioavailability study evaluating the rate and extent of absorption of a 500 mg dose of nitazoxanide suspension given in the fed (standard FDA high-fat meal) versus fasted state. The results showed that the AUC of tizoxanide and tizoxanide glucuronide were increased by 39% and 49%, respectively, in the presence of food. The resulting 90% confidence interval of the AUC test/reference ratio was shifted up and fell outside the acceptable limits of 80% to 125%. The peak plasma concentrations of both tizoxanide and tizoxanide glucuronide were relatively unchanged and the 90% confidence intervals of the C_{max} test/reference ratio were within the acceptable limits of 0.8-1.25. In summary, administration of nitazoxanide suspension with food results in higher exposure, in terms of AUC but not C_{max} .

In Study RM01-3011 the applicant compared the efficacy of nitazoxanide tablets to the nitazoxanide suspension in adult and adolescent patients aged 12 years and older and was able to show that there was no significant effect of dosage form on clinical or parasitological efficacy, as determined by a lower bound of the 95% confidence interval of the treatment difference lying above -15%.

In Study RM01-3011 the applicant was unable to characterize the contribution of food-effect on clinical efficacy due to incomplete reporting of meals in the patients' study diaries. However, since the clinical efficacy of the tablets was comparable to the suspension when administered with food in adults, it can be concluded that an increase in the systemic exposure to tizoxanide does not adversely affect the efficacy of the tablets, although the relative contribution of systemic versus local antimicrobial activity is still unclear.

8.2 Drug-Drug Interactions

Tizoxanide is highly bound to plasma protein (>99.9%). Therefore, caution should be used when administering nitazoxanide concurrently with other highly plasma protein-bound drugs with narrow therapeutic indices (e.g., warfarin), as competition for binding sites may occur. *In vitro* metabolism studies have demonstrated that tizoxanide has no significant inhibitory effect on cytochrome P450 enzymes. Although no drug-drug interaction studies have been conducted *in vivo*, it is expected that no significant interaction would occur when nitazoxanide is co-administered with drugs that either are metabolized by or inhibit cytochrome P450 enzymes.

8.3 Special Populations

8.3.1 Efficacy in Special Populations

Clinical and parasitological response rates observed in Study RM01-3011 by sex (males compared to females) and race (Caucasians compared to Hispanics), and can be found in the Review of Study RM01-3011 (Section 10.1 of this document). Differences, if any, seen in the response rates are not considered clinically meaningful. No adjustments to the adult dosing of nitazoxanide tablets or suspension in adolescents are warranted based on sex or race.

8.3.2 Safety in Special Populations

Concentrations of nitazoxanide are not detectable in plasma, although the metabolite tizoxanide is detectable in plasma following oral administration of nitazoxanide and subsequently undergoes glucuronidation in the liver. Nitazoxanide tablets and suspension have not been studied in patients with compromised renal or hepatic function; however, it is not anticipated that patients with hepatic or renal disease will experience drug toxicity, since most of the drug stays intraluminally within the gastrointestinal tract.

There are no adequate and well-controlled studies in pregnant women.

It is not known whether nitazoxanide is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when nitazoxanide is administered to a nursing woman.

An evaluation of the safety of nitazoxanide tablets by sex and race (Caucasians and Hispanics) in controlled and uncontrolled trials is reported below. The safety data are collected from efficacy trials of various bacterial and parasitic infections. The dosage of nitazoxanide tablets, as well as the duration of treatment, varied across trials (see Table 3 in the Section 7.1 of this document, "Methods and Findings").

| |
|---|
| <p><i>Clinical Reviewer's Comment: Tables 8 through 15 were created by the applicant and submitted to the NDA on June 25, 2004.</i></p> |
|---|

Males and Females: Adverse events in HIV-uninfected patients who received nitazoxanide tablets or placebo in controlled and uncontrolled studies are shown in Tables 8 and 9 for male and Tables 10 and 11 for female patients, respectively.

TABLE 8
Adverse Events: HIV- Uninfected Patients Who Received Nitazoxanide Tablets in
Controlled and Uncontrolled Studies
Males Only (N=849)

| Body system Adverse event | Patients Reporting AEs | |
|------------------------------|------------------------|-----|
| | Number | % |
| BODY | | |
| PAIN ABDO | 34 | 4.0 |
| HEADACHE | 10 | 1.2 |
| ASTHENIA | 5 | 0.6 |
| FEVER | 3 | 0.4 |
| PAIN | 1 | 0.1 |
| CHILLS | 1 | 0.1 |
| DIG | | |
| DIARRHEA | 11 | 1.3 |
| NAUSEA | 11 | 1.3 |
| DYSPEPSIA | 2 | 0.2 |
| VOMIT | 1 | 0.1 |
| NAUSEA VOMIT DIAR | 1 | 0.1 |
| UG | | |
| URIN ABNORM | 6 | 0.7 |
| EDEMA LABIA | 1 | 0.1 |
| MAN | | |
| SGPT INC | 6 | 0.7 |
| NER | | |
| DIZZINESS | 2 | 0.2 |
| SOMNOLENCE | 2 | 0.2 |
| SS | | |
| EYE DIS | 1 | 0.1 |
| PAIN EAR | 1 | 0.1 |
| RES | | |
| EPISTAXIS | 1 | 0.1 |
| LUNG DIS | 1 | 0.1 |

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TABLE 9
Adverse Events: HIV- Uninfected Patients (Ages 12 Years and Older) in Placebo
Control Groups
Males Only (N=69)

| Body system Adverse event | Patients Reporting AEs | |
|------------------------------|---------------------------|------|
| | Number | % |
| BODY | | |
| PAIN ABDO | 9 | 13.0 |
| HEADACHE | 3 | 4.3 |
| ASTHENIA | 1 | 1.4 |
| DEATH | 1 | 1.4 |
| DIG | | |
| DIARRHEA | 2 | 2.9 |
| DYSPEPSIA | 1 | 1.4 |
| NER | | |
| DIZZINESS | 2 | 2.9 |
| SOMNOLENCE | 1 | 1.4 |
| EMOTION LABIL | 1 | 1.4 |
| UC | | |
| URIN ABNORM | 1 | 1.4 |
| DYSURIA | 1 | 1.4 |

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TABLE 10
Adverse Events: HIV-Uninfected Patients Who Received Nitazoxanide Tablets in
Controlled and Uncontrolled Studies
Females Only (N=779)

| Body system Adverse event | Patients Reporting AEs | |
|------------------------------|------------------------|-----|
| | Number | % |
| BODY | | |
| PAIN ABDO | 75 | 9.6 |
| HEADACHE | 41 | 5.3 |
| ASTHENIA | 5 | 0.6 |
| PAIN | 4 | 0.5 |
| FEVER | 3 | 0.4 |
| ALLERG REACT | 3 | 0.4 |
| PAIN PELVIC | 2 | 0.3 |
| FLU SYND | 1 | 0.1 |
| CHILLS FEVER | 1 | 0.1 |
| DIG | | |
| DIARRHEA | 59 | 7.6 |
| NAUSEA | 39 | 5.0 |
| VOMIT | 6 | 0.8 |
| NAUSEA/VOMIT | 3 | 0.4 |
| ANOREXIA | 2 | 0.3 |
| DYSPEPSIA | 1 | 0.1 |
| NAUSEA VOMIT DIAR | 1 | 0.1 |
| FLATUL | 1 | 0.1 |
| CONSTIP | 1 | 0.1 |
| THIRST | 1 | 0.1 |
| DRY MOUTH | 1 | 0.1 |
| NER | | |
| DIZZINESS | 14 | 1.8 |
| SOMNOLENCE | 8 | 1.0 |
| HYPESTHESIA | 1 | 0.1 |
| INSOMNIA | 1 | 0.1 |
| TREMOR | 1 | 0.1 |
| UC | | |
| URIN ABNORM | 7 | 0.9 |
| DYSURIA | 2 | 0.3 |
| METRRORRHAGIA | 1 | 0.1 |
| PAIN KIDNEY | 1 | 0.1 |
| AMENORRHEA | 1 | 0.1 |

TABLE 10 (continued)
Adverse Events: HIV-Uninfected Patients Who Received Nitazoxanide Tablets in
Controlled and Uncontrolled Studies
Females Only (N=779)

| Body system Adverse event | Patients Reporting AEs | |
|------------------------------|---------------------------|-----|
| | Number | % |
| MAN SGPT INC | 8 | 1.0 |
| SKIN | | |
| RASH | 3 | 0.4 |
| PRURITUS | 2 | 0.3 |
| RASH VESIC BULL | 1 | 0.1 |
| SS | | |
| EYE DIS | 2 | 0.3 |
| CV | | |
| SYNCOPE | 1 | 0.1 |
| TACHYCARDIA | 1 | 0.1 |
| MS | | |
| MYALGIA | 1 | 0.1 |
| BONE FRACT SPONTAN | 1 | 0.1 |
| RES | | |
| PHARYNGITIS | 1 | 0.1 |
| MS/NER | | |
| CRAMPS LEG | 1 | 0.1 |
| CV/NER | | |
| HYPERTENS | 1 | 0.1 |

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TABLE 11
Adverse Events: HIV- Uninfected Patients (Ages 12 Years and Older) in Placebo Control Groups
Females Only (N=60)

| Body system Adverse event | Patients Reporting AEs | |
|------------------------------|------------------------|-----|
| | Number | % |
| BODY | | |
| PAIN ABDO | 2 | 3.3 |
| EDEMA FACE | 1 | 1.7 |
| DIG | | |
| DIARRHEA | 2 | 3.3 |
| NER | | |
| SOMNOLENCE | 1 | 1.7 |

Caucasians and Hispanics: Adverse events in HIV-uninfected patients who received nitazoxanide tablets or placebo in controlled and uncontrolled studies are shown in Tables 12 and 13 for Caucasian patients and Tables 14 and 15 for Hispanic patients, respectively.

TABLE 12
Adverse Events: HIV-Uninfected Patients Who Received Nitazoxanide Tablets in Controlled and Uncontrolled Studies
Caucasian Only (N=1,086)

| Body system Adverse event | Patients Reporting AEs | |
|------------------------------|------------------------|-----|
| | Number | % |
| BODY | | |
| PAIN ABDO | 34 | 3.1 |
| ASTHENIA | 8 | 0.7 |
| HEADACHE | 7 | 0.6 |
| FEVER | 1 | 0.1 |
| DIG | | |
| NAUSEA | 16 | 1.7 |
| DIARRHEA | 11 | 1.0 |
| DYSPEPSIA | 2 | 0.2 |
| VOMIT | 1 | 0.1 |
| ANOREXIA | 1 | 0.1 |
| CONSTIP | 1 | 0.1 |
| DRY MOUTH | 1 | 0.1 |
| MAN | | |
| SGPT INC | 14 | 1.3 |
| NER | | |
| DIZZINESS | 8 | 0.7 |
| SOMNOLENCE | 3 | 0.3 |
| UG | | |
| URIN ABNORM | 6 | 0.6 |
| DYSURIA | 2 | 0.2 |
| MS | | |
| BONE FRACT SPONTAN | 1 | 0.1 |

TABLE 13
Adverse Events: HIV- Uninfected Patients (Ages 12 Years and Older) in Placebo
Control Groups
Caucasian Only (N=79)

| Body system Adverse event | Patients Reporting AEs | |
|------------------------------|---------------------------|-----|
| | Number | % |
| BODY | | |
| PAIN ABDO | 2 | 2.5 |
| EDEMA FACE | 1 | 1.3 |
| ASTHENIA | 1 | 1.3 |
| DEATH | 1 | 1.3 |
| DIG | | |
| DIARRHEA | 1 | 1.3 |
| DYSPEPSIA | 1 | 1.3 |
| NER | | |
| DIZZINESS | 2 | 2.5 |
| SOMNOLENCE | 2 | 2.5 |
| UG | | |
| URIN ABNORM | 1 | 1.3 |
| DYSURIA | 1 | 1.3 |

TABLE 14
Adverse Events: HIV-Uninfected Patients Who Received Nitazoxanide Tablets in
Controlled and Uncontrolled Studies
Hispanic Only (N=512)

| Body system Adverse event | Patients Reporting AEs | |
|------------------------------|------------------------|------|
| | Number | % |
| BODY | | |
| PAIN ABDO | 72 | 14.1 |
| HEADACHE | 44 | 8.6 |
| FEVER | 5 | 1.0 |
| PAIN | 5 | 1.0 |
| ALLERG REACT | 3 | 0.6 |
| ASTHENIA | 2 | 0.4 |
| PAIN PELVIC | 2 | 0.4 |
| FLU SYND | 1 | 0.2 |
| CHILLS | 1 | 0.2 |
| CHILLS FEVER | 1 | 0.2 |
| DIG | | |
| DIARRHEA | 59 | 11.5 |
| NAUSEA | 30 | 5.9 |
| VOMIT | 6 | 1.2 |
| NAUSEA/VOMIT | 3 | 0.6 |
| NAUSEA VOMIT DIAR | 2 | 0.4 |
| DYSPEPSIA | 1 | 0.2 |
| ANOREXIA | 1 | 0.2 |
| FLATUL | 1 | 0.2 |
| THIRST | 1 | 0.2 |
| NER | | |
| DIZZINESS | 8 | 1.6 |
| SOMNOLENCE | 7 | 1.4 |
| HYPESTHESIA | 1 | 0.2 |
| INSOMNIA | 1 | 0.2 |
| TREMOR | 1 | 0.2 |
| UG | | |
| URIN ABNORM | 6 | 1.2 |
| METRORRHAGIA | 1 | 0.2 |
| PAIN KIDNEY | 1 | 0.2 |
| AMENORRHEA | 1 | 0.2 |
| EDEMA LABIA | 1 | 0.2 |

TABLE 14 (continued)
Adverse Events: HIV- Uninfected Patients Who Received Nitazoxanide Tablets in
Controlled and Uncontrolled Studies
Hispanic Only (N=512)

| Body system Adverse event | Patients Reporting AEs | |
|------------------------------|------------------------|-----|
| | Number | % |
| SKIN | | |
| RASH | 2 | 0.4 |
| PRURITUS | 2 | 0.4 |
| RASH VESIC BULL | 1 | 0.2 |
| SS | | |
| EYE DIS | 3 | 0.6 |
| PAIN EAR | 1 | 0.2 |
| RES | | |
| EPISTAXIS | 1 | 0.2 |
| LUNG DIS | 1 | 0.2 |
| PHARYNGITIS | 1 | 0.2 |
| CV | | |
| TACHYCARDIA | 1 | 0.2 |
| MS | | |
| MYALGIA | 1 | 0.2 |
| MS/NER | | |
| CRAMPS LEG | 1 | 0.2 |
| CV/NER | | |
| HYPERTENS | 1 | 0.2 |

TABLE 15
Adverse Events: HIV- Uninfected Patients (Ages 12 Years and Older) in Placebo
Control Groups
Hispanic Only (N=50)

| Body system Adverse event | Patients Reporting AEs | |
|------------------------------|------------------------|------|
| | Number | % |
| BODY | | |
| PAIN ABDO | 9 | 18.0 |
| HEADACHE | 3 | 6.0 |
| DIG | | |
| DIARRHEA | 3 | 6.0 |
| NER | | |
| EMOTION LABIL | 1 | 2.0 |

In the Reviewer's opinion, any differences seen in adverse event rates between male and female patients or Caucasian and Hispanic patients treated with nitazoxanide tablets are not considered clinically meaningful and do not warrant reporting by sex or race in the product labeling.

8.4 Pediatrics

Children (aged 1 to 11 years):

Nitazoxanide suspension has previously been shown to be safe and effective for the treatment of diarrhea caused by *Cryptosporidium parvum* and *Giardia lamblia* in children aged 1 to 11 years. NDA 21-498 for this indication was approved by the FDA on November 22, 2002. See the approved labeling for specific information on efficacy and safety of nitazoxanide suspension in this age group.

Nitazoxanide tablets have not been evaluated for safety and efficacy in children less than 12 years of age.

Adolescents (aged 12 years and older):

Nitazoxanide tablets and suspension were evaluated for safety and efficacy in adolescent patients aged 12 to 17 years for the treatment of diarrhea caused by *Giardia lamblia* in Study RM01-3011. Clinical and parasitological response rates at Day 7-10 for adolescents and adults by treatment group did not reveal any clinically meaningful difference. Similarly, adverse events in adolescents and adults by treatment group were evaluated and no clinically meaningful differences were observed. (See Review of Study RM01-3011 in Section 10.1 of this document).

Nitazoxanide tablets have been evaluated for safety in 197 adolescent patients aged 12 to 17 years and 35 corresponding patients receiving placebo, including patients enrolled in Study RM01-3011. Tables 17 and 18 list the incidence of adverse events in for nitazoxanide tablets and placebo, respectively, in adolescent patients. For comparison, adverse events from 1431 patients \geq 18 years treated with nitazoxanide tablets and 94 corresponding patients receiving placebo are shown in Tables 19 and 20, respectively. Adverse events are similar between nitazoxanide tablets and placebo in both adolescents and adults.

| |
|--|
| <p><i>Clinical Reviewer's Comment: Tables 16 through 19 were created by the applicant and submitted to the NDA on June 25, 2004.</i></p> |
|--|

TABLE 16
Adverse Events: Patients Treated with Nitazoxanide Tablets
Aged 12 through 17 Years (N=197)

| Body system Adverse event | Patients Reporting AEs | |
|------------------------------|------------------------|------|
| | Number | % |
| BODY | | |
| PAIN ABDO | 29 | 14.7 |
| HEADACHE | 13 | 6.6 |
| FEVER | 3 | 1.5 |
| ASTHENIA | 2 | 1.0 |
| PAIN | 1 | 0.5 |
| CHILLS | 1 | 0.5 |
| DIG | | |
| DIARRHEA | 9 | 4.6 |
| NAUSEA | 7 | 3.6 |
| NAUSEA VOMIT DIAR | 1 | 0.5 |
| NER | | |
| DIZZINESS | 5 | 2.5 |
| SOMNOLENCE | 1 | 0.5 |
| UG | | |
| URIN ABNORM | 2 | 1.0 |
| DYSURIA | 1 | 0.5 |
| EDEMA LABIA | 1 | 0.5 |
| SS | | |
| EYE DIS | 2 | 1.0 |

TABLE 17
Adverse Events: Patients in Placebo Control Groups
Aged 12 through 17 Years (N=35)

| Body system Adverse event | Patients Reporting AEs | |
|------------------------------|------------------------|------|
| | Number | % |
| BODY | | |
| PAIN ABDO | 6 | 17.1 |
| HEADACHE | 2 | 5.7 |
| NER | | |
| SOMNOLENCE | 1 | 2.9 |
| EMOTION LABIL | 1 | 2.9 |

TABLE 18
Adverse Events: Patients Treated with Nitazoxanide Tablets
Aged 18 Years and Older (N=1,431)

| Body system Adverse event | Patients Reporting AEs | |
|------------------------------|------------------------|-----|
| | Number | % |
| BODY | | |
| PAIN ABDO | 80 | 5.6 |
| HEADACHE | 38 | 2.7 |
| ASTHENIA | 8 | 0.6 |
| PAIN | 4 | 0.3 |
| FEVER | 3 | 0.2 |
| ALLERG REACT | 3 | 0.2 |
| PAIN PELVIC | 2 | 0.1 |
| FLU SYND | 1 | 0.1 |
| CHILLS FEVER | 1 | 0.1 |
| DIG | | |
| DIARRHEA | 61 | 4.3 |
| NAUSEA | 43 | 3.0 |
| VOMIT | 7 | 0.5 |
| NAUSEA/VOMIT | 3 | 0.2 |
| DYSPEPSIA | 3 | 0.2 |
| ANOREXIA | 2 | 0.1 |
| NAUSEA VOMIT DIAR | 1 | 0.1 |
| FLATUL | 1 | 0.1 |
| CONSTIP | 1 | 0.1 |
| THIRST | 1 | 0.1 |
| DRY MOUTH | 1 | 0.1 |
| NER | | |
| DIZZINESS | 11 | 0.8 |
| SOMNOLENCE | 9 | 0.6 |
| HYPESTHESIA | 1 | 0.1 |
| INSOMNIA | 1 | 0.1 |
| TREMOR | 1 | 0.1 |
| UG | | |
| URIN ABNORM | 11 | 0.8 |
| DYSURIA | 1 | 0.1 |
| METRRORRHAGIA | 1 | 0.1 |
| PAIN KIDNEY | 1 | 0.1 |
| AMENORRHEA | 1 | 0.1 |

TABLE 18 (continued)
Adverse Events: Patients Treated with Nitazoxanide Tablets
Aged 18 Years and Older (N=1,431)

| Body system Adverse event | Patients Reporting AEs | |
|------------------------------|------------------------|-----|
| | Number | % |
| MAN | | |
| SGPT INC | 14 | 1.0 |
| SKIN | | |
| RASH | 3 | 0.2 |
| PRURITUS | 2 | 0.1 |
| RASH VESIC BULL | 1 | 0.1 |
| RES | | |
| EPISTAXIS | 1 | 0.1 |
| LUNG DIS | 1 | 0.1 |
| PHARYNGITIS | 1 | 0.1 |
| SS | | |
| EYE DIS | 1 | 0.1 |
| PAIN EAR | 1 | 0.1 |
| CV | | |
| SYNCOPE | 1 | 0.1 |
| TACHYCARDIA | 1 | 0.1 |
| MS | | |
| MYALGIA | 1 | 0.1 |
| BONE FRACT SPONTAN | 1 | 0.1 |
| MS/NER | | |
| CRAMPS LEG | 1 | 0.1 |
| CV/NER | | |
| HYPERTENS | 1 | 0.1 |

TABLE 19
Adverse Events: Patients in Placebo Control Groups
Aged 18 Years and Older (N=94)

| Body system Adverse event | Patients Reporting AEs | |
|------------------------------|------------------------|-----|
| | Number | % |
| BODY | | |
| PAIN ABDO | 5 | 5.3 |
| HEADACHE | 1 | 1.1 |
| EDEMA FACE | 1 | 1.1 |
| ASTHENIA | 1 | 1.1 |
| DEATH | 1 | 1.1 |
| DIG | | |
| DIARRHEA | 4 | 4.3 |
| DYSPEPSIA | 1 | 1.1 |
| NER | | |
| DIZZINESS | 2 | 2.1 |
| SOMNOLENCE | 1 | 1.1 |
| UG | | |
| URIN ABNORM | 1 | 1.1 |
| DYSURIA | 1 | 1.1 |

In summary, the efficacy and adverse event profile of nitazoxanide tablets and suspension in adolescent patients aged 12 years and older are similar to adults. Therefore, no

adjustments to the adult dosing of nitazoxanide tablets or suspension in adolescents are warranted based on efficacy. Reporting of adverse events for adolescents separate from adults in the product labeling is also not warranted. Children less than 12 years of age should be dosed with the suspension formulation of nitazoxanide and adverse events for children should be reported separately from adults and adolescents.

8.5 Advisory Committee Meeting

Not applicable.

8.6 Literature Review

The applicant was asked by the Division on January 28, 2004 to provide additional information to support their request for approval of nitazoxanide in adult immunocompetent patients with *Cryptosporidium parvum*. The requested information was stated as follows:

1. Please submit information on the pathophysiology of infection with *Cryptosporidium parvum* as compared to *Giardia lamblia*; specifically, please address the clinical and microbiological basis to support the premise that efficacy for the treatment of Giardiasis is predictive of clinical success in the treatment of cryptosporidiosis.
2. Please submit information comparing the pathophysiology of infection with *Cryptosporidium parvum* in adults to that in children. Specifically, please justify the premise that response in children is predictive of response in adults. Your response should address the epidemiology of disease in adults and children, as well as other factors that would predict response may be either similar or different between adults or children. In this context, please also address previous information showing lack of efficacy for nitazoxanide in immunocompromised adults.

The applicant submitted a response on April 23, 2004. A summary of that response is provided here. A complete listing of the cited references can be found in Section 10.3 of this document.

1. Pathophysiology of *C. parvum* infection compared to *Giardia* infection

Cryptosporidium and *Giardia* are ingested as oocyst and cysts, respectively and excyst upon exposure to the low pH and contents of the stomach and proximal small intestine. *Cryptosporidium* excysts as sporozoites; *Giardia* excysts as trophozoites. Both sporozoites and trophozoites adhere to small intestine epithelial cells. *Giardia* trophozoites do not penetrate the cells whereas *Cryptosporidium* sporozoites do resulting in parasitophorous vacuoles where the sporozoite changes to a trophozoite. Both *Giardia* and *Cryptosporidium* trophozoites reside in the small intestine where they replicate and/or reproduce. Finally, encystation occurs in the terminal ileum and the oocysts of *Cryptosporidium* and cysts of *Giardia* are excreted in the feces (Farthing, 1999; Hart, 1999).

There are many pathophysiological similarities between *Cryptosporidium parvum* and *Giardia lamblia* infection. Histologic findings in the small intestine include atrophic changes of villi, crypt hyperplasia, epithelial damage, infiltration of the lamina propria by plasma cells, lymphocytes, neutrophils and in the case of *C. parvum*, macrophages (Ungar, 2000; Hill, 2000).

The mechanism by which these organisms cause diarrhea has not been completely elucidated. *In vitro* studies have shown that attachment of *C. parvum* sporozoites to the apical surface of epithelial cells appears to activate secondary signal pathways in the host cell that alter cell function (Clark, 1999; McCole et al., 2000; Chen et al., 2001; Forney et al., 1999). In directly infected biliary cells, *C. parvum* has been shown to directly activate the nuclear factor- κ B (NF- κ B) system (Chen et al., 2001) causing the release of cytokines and chemokines that play a critical role in the pathogenesis and inflammation associated with cryptosporidiosis (McDonald et al., 2000; Laurent et al., 1997; Laurent et al., 1998). In biliary infection, *C. parvum* has also been shown to induce epithelial cell apoptosis in nearby, uninfected cells that appears to be associated with the Fas receptor-Fas ligand death pathway (Chen et al., 1999). Therefore, as suggested by Chen et al., 2002, it appears that *C. parvum* has the capacity to invade epithelial cells and induce survival signals (e.g., NF- κ B) in the infected cells allowing the organism to propagate, while simultaneously triggering alterations (e.g., apoptosis) in nearby uninfected cells. *Giardia* has also been shown to induce enterocyte apoptosis in the small intestinal epithelial barrier (Chin et al., 2002).

In vitro and animal studies have demonstrated the effects of *C. parvum* and *G. lamblia* on host intestinal ion transport and glucose absorption that lead to diarrhea. Two studies using piglet ileal mucosa and the other using human jejunum suggest that *C. parvum* affects intestinal ion transport. Sodium chloride transport was disrupted in the piglet model; ion transport and sodium-glucose absorption was disrupted in an adult immunosuppressed mouse model (Tilley & Upton, 1997; Tzipori, 1998; Guarino et al., 1995; Moore et al., 1995). Similarly, an experiment in gerbils infected with *G. lamblia* showed that glucose stimulated sodium ion absorption was decreased in the jejunum (Buret et al., 1992). Experiments in gerbils, rats and neonatal rats infected with *Giardia* resulted in impairment of H₂O, sodium and chlorine ions absorption in response to glucose (Cevallos et al., 1995). Other studies in brush border membrane vesicles from infected mice have provided further evidence that there is impairment of glucose and amino acid transport due to *Giardia* (Samra et al., 1987).

Despite the uncertainty of the complete mechanism of pathogenesis of these protozoa, the available information suggests that these organisms attach to intestinal cells resulting in the damage to the microvilli and subsequent triggering of secondary signal pathways that lead to disruption of ion transport and absorption, as well as inducing host cell apoptosis.

Host immune responses to *Cryptosporidium* and *Giardia* infections involve both humoral and cell mediated responses. Immunologic studies in humans have determined that specific anti-*Giardia* antibodies (IgG, IgM and IgA), and anti-*Cryptosporidia* antibodies (IgG and IgM) or fecal or salivary IgA, can be detected during the course of infection and persist for varied lengths of time (Farthing, 1990; Heyworth, 1992; Ungar et al., 1990; Ungar et al., 1989; Ungar et al., 1988; Riggs, 1997; Cozon et al., 1994; Flanigan, 1994; Benhamou et al., 1995). Heyworth (1992) has suggested that an intestinal antitrophozoite antibody blocks adherence of trophozoites to intestinal epithelium with subsequent removal of trophozoites from the intestine by peristalsis. Similarly, *C. parvum* infection can be prevented or interrupted by antibodies that bind to *Cryptosporidium* life cycle stages present in the lumen (Heyworth 1992). In animals and humans, T-cells have also been shown to be important immunologic mediators of *Giardia* and *Cryptosporidium* infection (Roberts-Thomsom & Michell, 1978; Stevens et al., 1978; Riggs, 1997; Chen et al., 1993; Urban et al., 1996; Flanigan et al., 1992; Crowe et al., 1991; Crabb 1998). Animals and patients with a variety of immune deficiencies, T-cell abnormalities and diffuse or selective B-cell deficiencies have been shown to develop chronic and more severe disease than immunocompetent hosts (Farthing, 2000; Manabe, 1998; Blanshard et al., 1992; Clifford et al., 1990; Jacyna et al., 1990;

Theodos, 1998; Webster, 1980; Ungar et al., 1990; Ungar et al., 1991; Mead et al., 1991; Mead et al., 1994; Riggs, 1997; Chen et al., 1993).

The role of an antiprotozoal agent in treating *Giardiasis* and cryptosporidiosis is to help the immune system fight off the infection by killing organisms, thereby reducing the duration of illness and possibly preventing chronic disease. When the immune system is not functioning properly, the role of the antiprotozoal agent becomes much more important.

Based upon the information presented above related to the pathophysiology of infection by *Cryptosporidium* and *Giardia*, it is reasonable to conclude that the efficacy of nitazoxanide tablets in treating *Giardiasis* is predictive of clinical success in treating cryptosporidiosis. This premise is supported by:

Microbiology data:

1. Nitazoxanide has shown activity *in vitro* against trophozoites of *Giardia* and sporozoites of *Cryptosporidium*, the stage of the life cycle that attaches itself to small intestine epithelial cells (see NDA 21-497).
2. Nitazoxanide has also shown activity against each of these organisms in animal models (NDA 21-497).

Clinical data:

1. Pediatric outpatients with diarrhea caused by *Cryptosporidium* respond to a three day course of nitazoxanide suspension in a manner that is quite similar to the response of pediatric patients with diarrhea caused by *Giardia*. In adequate and well-controlled clinical studies of nitazoxanide suspension in pediatric patients using the same response definitions, clinical response rates of 88% and 85% were observed for patients with cryptosporidiosis and *Giardiasis*, respectively (studies RM-NTZ-98-002 and RM-NTZ-99-010 in NDA 21-497).
2. The clinical and parasitological responses of non-immunodeficient adults with diarrhea caused by *Cryptosporidium parvum* strongly suggest clinical efficacy in treating diarrhea caused by *Cryptosporidium parvum* in this patient population (see study RM-NTZ-98-002, also in NDA 21-497).

2. Pathophysiology of *C. parvum* infection in adults compared to that in children

The pathophysiology of infection with *Cryptosporidium parvum* was discussed above. Both adults and children are susceptible to *Cryptosporidium* infection. Disease is caused when oocysts are ingested by adults or children. The most common ways that *Cryptosporidium* is transmitted are by person-to-person contact, ingestion of contaminated food or water, or contact with infected animals. Information on whether individuals can experience more than one attack of cryptosporidiosis or if immunity can be acquired is limited. In a study of 19 healthy immunocompetent adults, patients were re-infected with *Cryptosporidium parvum* one year after initial exposure. Fewer subjects shed oocysts after the second exposure (3 of 19; 16%) than the first exposure (12/19; 63%), and the mean number of unformed stools passed was lower after exposure (11.25 versus 8.62) (Okhuysen et al., 1998).

There is no suggestion in the medical literature or from our experience in studying nitazoxanide in adults and children with cryptosporidiosis that there is any difference in the pathophysiology of *Cryptosporidium* in adults as compared to children. Conversely, cryptosporidiosis has been reported in the public literature in both genders in individuals of all ages. During the Milwaukee outbreak in 1993 that was estimated to affect 403,000 people, the average age of 285 people surveyed who had laboratory-confirmed cryptosporidiosis was 41 years (range, 2 months to 93 years) (MacKenzie et al., 1994). Only 48 (17%) of these 285 people were immunocompromised. Young children, particularly those younger than 2 years, may be more susceptible to infection,

perhaps reflecting increased fecal-oral transmission in this age group, a lack of protective immunity from prior exposure, or relative immunologic immaturity (Ungar, 2000).

In randomized double-blind placebo controlled studies (studies RM02-3007 and RM02-3008), we demonstrated that severely malnourished *HIV-negative* pediatric inpatients with diarrhea caused by *C. parvum* respond to a three-day course of treatment with nitazoxanide suspension while severely malnourished pediatric inpatients with acquired immune deficiency syndrome (AIDS) did not respond to the same short course of treatment. Based on these studies, we were able to distinguish the activity of nitazoxanide in an immunocompromised population as compared to an immunodeficient population.

This distinction was discussed with FDA during the course of finalizing the label for Alinia® (nitazoxanide) for Oral Suspension.

The distinction noted in pediatric patients based on immune status is absolutely consistent with the findings of each of 5 clinical studies in adults with cryptosporidiosis. Study RM-NTZ-98-002 in nonimmunodeficient adults with diarrhea caused by *C. parvum* strongly suggested clinical efficacy following a short three-day course of treatment.

It is worthwhile to note that successful treatment of *Giardiasis* in AIDS patients with very low CD4 counts is also reported to require longer courses of treatment with nitazoxanide (Abboud et al, 2001).

Considering all of the above, we conclude that the clinical effectiveness of nitazoxanide in treating nonimmunodeficient pediatric patients with diarrhea caused by *Cryptosporidium parvum* is predictive of clinical effectiveness in non-immunodeficient adults.

8.7 Other Relevant Materials

None.

9 OVERALL ASSESSMENT

9.1 Conclusions on Available Data

Nitazoxanide (Alinia®) tablets and oral suspension are safe and effective for the treatment of diarrhea caused by *Giardia lamblia* in adults and adolescent patients 12 years of age and older. Nitazoxanide tablets and oral suspension are recommended for approval for this indication. Safety and effectiveness of nitazoxanide tablets have not been established in patients with immunodeficiency.

Insufficient data are contained within this submission to provide evidence of the safety and efficacy of nitazoxanide (Alinia®) tablets for the treatment of diarrhea caused by *Cryptosporidium parvum* in adults and adolescent patients 12 years of age and older.

9.2 Recommendation on Regulatory Action

Nitazoxanide (Alinia®) tablets, as a treatment regimen of one 500 mg tablet taken twice daily for 3 days, should be approved for the treatment of diarrhea caused by *Giardia lamblia* in adults and adolescent patients aged 12 years and older. In addition, nitazoxanide oral suspension, as a treatment regimen of 500 mg (25 mL) taken twice daily for 3 days, should also be approved for the treatment of diarrhea caused by *Giardia lamblia* in adults and adolescent patients aged 12 years and older.

Nitazoxanide (Alinia®) tablets should not be approved for the treatment of diarrhea caused by *Cryptosporidium parvum* in adults and adolescent patients 12 years of age and older.

9.3 Recommendation on Post-Marketing Actions

There are no recommendations for risk management activity or required Phase 4 studies at this time. The applicant has indicated that they plan to study parasitological and clinical response at 2 weeks following the end of treatment with nitazoxanide compared to another FDA-approved drug for *Giardia lamblia*.

9.3.1 Risk Management Activity

None.

9.3.2 Required Phase 4 Commitments

None.

9.3.3 Other Phase 4 Requests

None.

9.4 Labeling Review

The label for nitazoxanide oral suspension in pediatrics aged 1 to 11 years (approved previously) and nitazoxanide tablets in adults and adolescents aged 12 years and older (the subject of this submission) were merged in order to help prescribers find all the pertinent information for nitazoxanide in one place, rather than having two separate labels.

A summary of the important changes made to the combined label are discussed below:

2 Page(s) Withheld

 Trade Secret / Confidential

✓ Draft Labeling

 Deliberative Process

10 APPENDIX

10.1 Review of Individual Study Report – Protocol RM01-3011

Multicenter, Double-Blind, Placebo-Controlled Study of Nitazoxanide Tablets in the Treatment of Giardiasis in Adults and Adolescents

All of the tables in this review are a reproduction of the applicant's original tables in the NDA submission, except where noted otherwise.

Study Dates: February 2003 to November 2003
Date of Final Report: January 9, 2004

10.1.1 Ethical Conduct of the Study

Prior to initiation of the study, the study protocol and informed consent was approved by the Medical Ethics Review Board of the Consejo Regional XVII Cajamarca Colegio Médico del Peru for the site in Cajamarca, Peru and by the ethical committee of the Benha University Hospital of the University of Zagazig for the site in Benha, Egypt.

Both study medications are approved for marketing in Peru, nitazoxanide as Colufase® and metronidazole as Flagyl®.

The study was performed in accordance with the guidelines set by the World Medical Assembly (Declaration of Helsinki, last amendment in Edinburgh, Scotland, 2000).

10.1.2 Study Objectives

The primary objective of the study was to demonstrate the efficacy of nitazoxanide tablets in the treatment of diarrhea caused by *Giardia lamblia* in non-immunodeficient adults and adolescents.

The secondary objective of the study was to demonstrate non-inferiority of nitazoxanide tablets compared to nitazoxanide suspension in the treatment of diarrhea caused by *Giardia lamblia* (delta of 20%).

10.1.3 Study Design

The study was a multicenter, placebo-controlled study evaluating the efficacy and safety of nitazoxanide tablets and suspension in the treatment of diarrhea caused by *Giardia lamblia*. A total of 135 evaluable patients (≥ 12 years) were to be selected according to the study inclusion and exclusion criteria.

Patients presenting to the hospital with diarrhea were offered the opportunity to participate in the study. The patient was informed of the nature of the study and signed consent was obtained prior to participation in the study.

10.1.4 Microbiologic Procedures

During a screening evaluation, fecal samples from adults and adolescents with diarrhea were subjected to microscopic examination (concentrated and unconcentrated stool) for the detection of cysts of *Giardia lamblia* and for the identification of other parasites. If *Strongyloides stercoralis* was suspected, a Baermann concentration test was carried out.

Stool samples were also subjected to either an immunofluorescence assay () or an enzyme immunoassay () for the detection of *G. lamblia* and *C. parvum*. Patients were considered positive for cysts of *G. lamblia* if any of the three tests for *G. lamblia* were positive. If a patient was not positive for cysts of *G. lamblia* at baseline, he/she was excluded from the analysis of efficacy.

Clinical Reviewer's Comment: The applicant noted that the () test was recalled from the market and therefore not used in this study. Only the () assay was used.

Stool samples were also cultured to eliminate bacterial causes of diarrhea such as salmonellosis and shigellosis. Patients enrolled with bacterial causes of diarrhea were excluded from the analysis of clinical efficacy.

Patients were evaluated again 7 to 10 days after the start of therapy with collection of two stool samples at least 24 hours apart between Day 7 and Day 10. Stool samples were subjected to examination for cysts of *G. lamblia* using microscopic examination (concentrated and unconcentrated stool), and immunofluorescence assay. If the immunofluorescence assay was not able to be performed, the microscopic examination was relied upon as the sole determination of parasitological response. Patients were considered positive for cysts of *G. lamblia* if any of these three tests were positive.

10.1.5 Inclusion Criteria

- Age \geq 12 years.
- Patients with diarrhea (\geq 3 bowel movements/day) with one or more enteric symptoms such as abdominal pain or cramps, nausea, vomiting, tenesmus or malabsorption.
- *G. lamblia* cysts detected in a stool specimen obtained 7 days before enrollment

10.1.6 Exclusion Criteria

- Patients with identified causes of diarrhea other than *G. lamblia* (e.g., pathogenic bacteria, *Cryptosporidium parvum*, *Entamoeba histolytica*).
- Use within 2 weeks of enrollment of any drug or therapy with antiprotozoal activity including 5-nitroimidazoles such as metronidazole, tinidazole, ornidazole, secnidazole, hydroxyquinoline derivatives, trimethoprim-sulfamethoxazole (trimethoprim-sulfamethoxazole may be used within 2 weeks of enrollment, but may not be used concomitantly during therapy) and acetamide analogues such as diloxanide, paromomycin and nitazoxanide.
- Females who are pregnant, suspected of being pregnant or breast feeding [urine pregnancy tests are required for all women of childbearing potential or who are two years or less post-menopausal].
- Serious systemic disorders incompatible with the study.
- History or hypersensitivity to nitazoxanide.
- Patients in whom the possibility of receiving a placebo and not being able to receive immediately an effective treatment will be incompatible with the severity of the patient's illness according to the Investigator's judgment.
- Patients known or suspected of having AIDS.
- Patients with known immune deficiencies (e.g., cancer chemotherapy patients, patients with hypogammaglobulinemia).

10.1.7 Removal of Patients

Patients may have been removed from the study by the Investigator for any of the following reasons:

- Medical conditions that require study discontinuation.
- Intercurrent illness which would, in the judgment of the Investigator in consultation with the medical monitor, tend to affect the assessment of clinical and mental status to a significant degree.
- Noncompliance with the protocol.
- Patient desire to discontinue participation.

10.1.8 Treatments Administered/Treatment Compliance

Study medications were dispensed during the baseline evaluation. The dose regimens were:

- Group 1: One nitazoxanide 500 mg tablet with food each morning and evening for 3 consecutive days.
- Group 2: 25 mL of nitazoxanide (100 mg/5 mL) suspension with food each morning and evening for 3 consecutive days.

Group 3: One placebo tablet with food each morning and evening for 3 consecutive days.

Patients were instructed to take the study medication with food.

Patient compliance with the protocol was recorded in the case report form at the Day 7-10 evaluation. Patients were required to return any unused study medication.

At the time of dispensing the medication, each patient was given a diary for recording administration of the medication, adverse events and information related to the number of stools per day and their consistency.

The study medications were provided by The Romark Institute for Medical Research. The active formulations for this study were a tablet (batch 97E07 manufactured by _____ containing 500 mg of nitazoxanide plus standard excipients and a strawberry-flavored suspension containing 100 mg/5 mL of nitazoxanide after reconstitution (batch 26726 manufactured by _____). The placebo tablets (batch 99I21 manufactured by _____) had the same appearance and inactive ingredients as the active tablets.

The study medication was packaged and labeled by the Sponsor except that the powder for suspension was packaged in bottles by the manufacturer, _____. The tablets (verum and placebo) were packaged for each patient in an HDPE bottle, each bottle containing six 500 mg nitazoxanide tablets or six placebo tablets according to the treatment regimen. The suspension was packaged for each patient in three small brown glass bottles, each bottle containing 20.4 grams of powder for reconstitution as 60 mL of 100 mg/5 mL nitazoxanide suspension. The bottles were stored at room temperature.

10.1.9 Study Visits

During the baseline visit, the following procedures were carried out:

- confirmation that the patient satisfies all inclusion/exclusion criteria;
- complete medical history;
- physical examination, including body weight;
- urine pregnancy test for all women of child-bearing potential or who were two years or less post-menopausal;
- evaluation of clinical symptoms;
- review concomitant medications; and
- collection of a stool sample to confirm the presence of *G. lamblia* cysts.

Patients were evaluated 7 to 10 days after the start of therapy. Examinations included:

- brief physical examination including body weight;

- review of patient diary and evaluation of clinical symptoms;
- review of adverse events/side effects;
- review of compliance and collection of any unused medications; and
- collection of two stool samples at least 24 hours apart between Day 7 and Day 10.

After they had completed the protocol, and based upon the Investigator's judgment, patients with an unsatisfactory clinical response at the Day 7-10 evaluation were offered a standard course of metronidazole.

All clinical responders at the Day 7-10 evaluation were to return between Days 14 and 17 and submit one fecal sample for examination for *G. lamblia* cysts or trophozoites.

At the time of each return visit, the patients were questioned regarding the occurrence and nature of any adverse events. Any subject affected was examined by the Investigator as deemed necessary to ascertain the course of the event and any residual effects. All patients were instructed to contact the Investigator, Investigator's assistants, or clinical personnel should the subject have any serious adverse experiences.

FIGURE 1
Study Design and Schedule of Assessments

| Study Procedure | Study Day | | | |
|--|---------------------------------------|--------------|-------------------------------------|---|
| | Pre-Study/ Screening Evaluation | Baseline (0) | Day 7-10 Follow-up Evaluation | Day 14-17 Confirmation Evaluation |
| Signed informed consent | X | | | |
| Stool sample for parasitological exam | X | X | X* | X |
| Urine pregnancy test | | X | | |
| Review of clinical symptoms | | X | X | |
| Review of inclusion/exclusion criteria | | X | | |
| Complete medical history | | X | | |
| Physical examination | | X | X | |
| Record concomitant medications | | X | X | |
| Instruct patient on taking study medication/completing patient diary | | X | | |
| Record concomitant medications | | X | X | |
| Collection of any unused study medication | | | X | |
| Collect patient diary | | | X | |
| Review/record AEs | | | X | |
| Review/record compliance | | | X | |

* At the day 7-10 evaluation, 2 stool samples were collected at least 24 hours apart

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10.1.10 *Prior and Concomitant Therapy*

The use within 2 weeks of enrollment of any drug or therapy with antiprotozoal activity including 5-nitroimidazoles such as metronidazole, tinidazole, ornidazole, secnidazole, hydroxyquinoline derivatives, trimethoprim-sulfamethoxazole and acetamide analogues such as diloxanide, paromomycin and nitazoxanide was prohibited. Trimethoprim-sulfamethoxazole could be used within 2 weeks of enrollment, but not concomitantly during therapy.

10.1.11 *Efficacy and Safety Variables and Assessments*

The primary endpoint used to determine efficacy was the clinical response, resolution of clinical symptoms associated with giardiasis.

The secondary endpoints used to determine efficacy were:

- eradication of cysts of *Giardia lamblia* from post-treatment stool samples, and
- time from beginning of treatment to passage of last unformed stool.

On Day 7-10, patients were assessed for clinical and parasitological improvement.

The criteria for evaluating clinical response were:

Well: The patient experienced no symptoms, passed no watery stools and no more than two soft stools, and had no hematochezia within the past 24 hours or the patient experienced no symptoms and passed no unformed stools (i.e., passed either no stools or only formed stools) within the past 24 hours.

Continuing illness: The passage of any number of watery stools, the passage of more than two soft stools per 24 hours, or the documentation of hematochezia or enteric symptoms plus the passage of any number of soft or watery stools during the past 48 hours.

Clinical treatment failure: Clinical deterioration or worsening of symptoms after at least 24 hours of treatment resulting in the patient being removed from the study.

Two fecal samples obtained for each patient between Days 7 and 10 were subjected to parasitological examination. The parasitological response criteria were:

Eradication: No cysts or trophozoites of *G. lamblia* observed in either of the 2 post-treatment parasitological examinations.

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,
- inpatient 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, inpatient 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 Cajamarca, 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)*

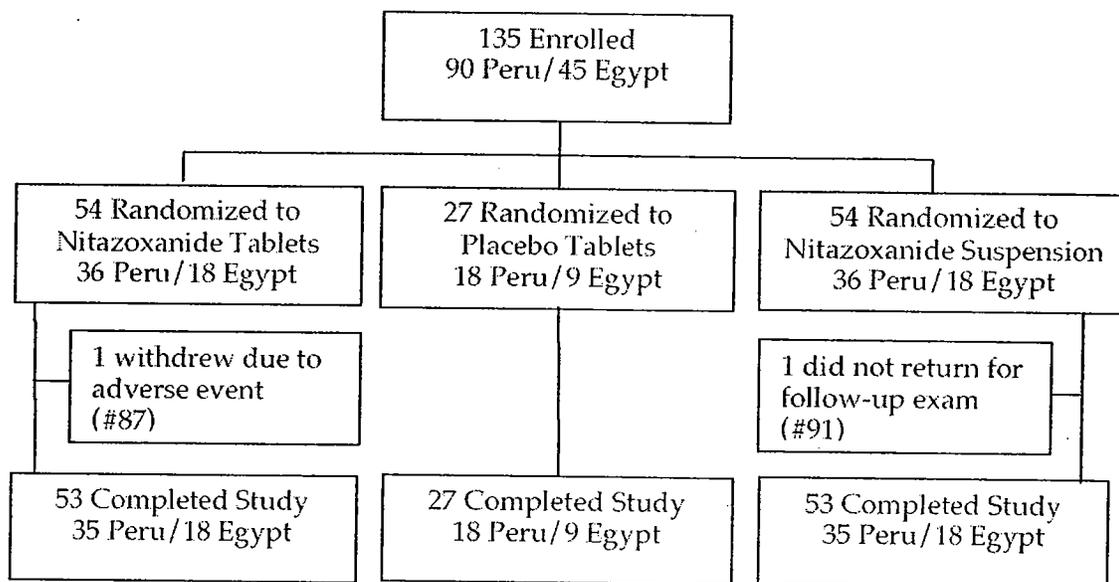
In Benha, Egypt, patients presenting at the outpatient clinic with diarrhea were evaluated in accordance with usual standards of care. Patients screened in Egypt 593, Patients enrolled= 4.

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:

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

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; $p = 0.16$).

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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 | |
| <i>Giardia</i> 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 \pm SD | 6.2 \pm 11.7 | 6.5 \pm 8.1 | 5.3 \pm 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 immunofluorescence: 1, 1, 1, 1, 1, 3.5 and 3.5, |

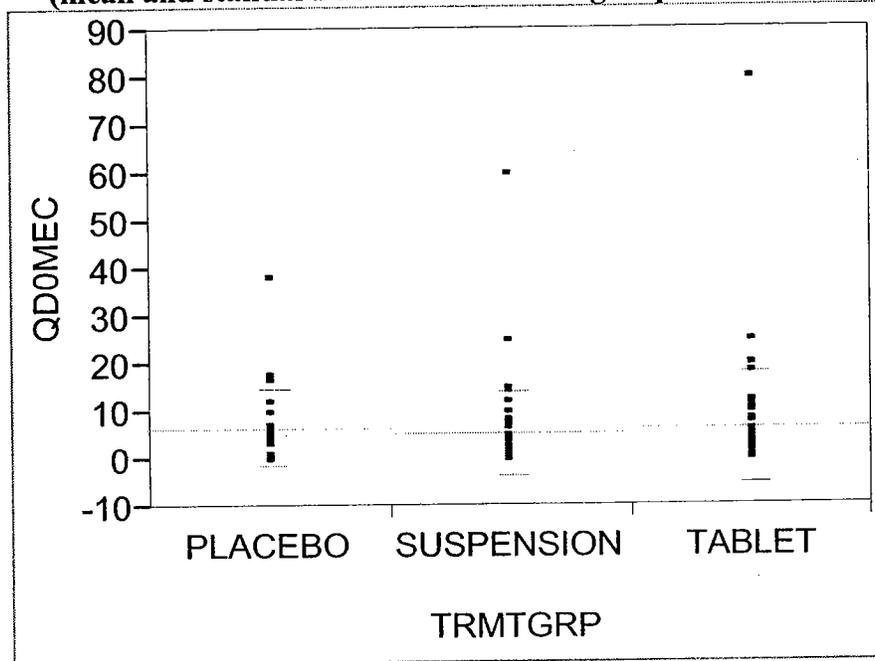
* Description of patients with missing data (i.e., no cyst count on baseline unconcentrated stool):

- 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 \pm 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

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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 \pm SD | Sample #1: 1.8 \pm 3.9 Sample #2: 2.0 \pm 3.8 | Sample #1: 3.0 \pm 3.5 Sample #2: 3.3 \pm 4.6 | Sample #1: 1.3 \pm 2.2 Sample #2: 1.8 \pm 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 \pm 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.

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

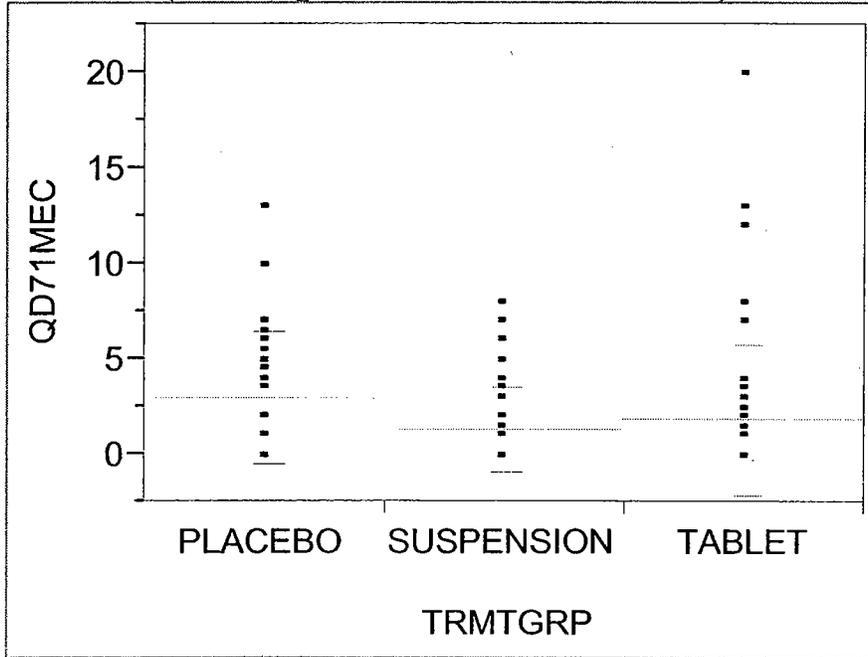
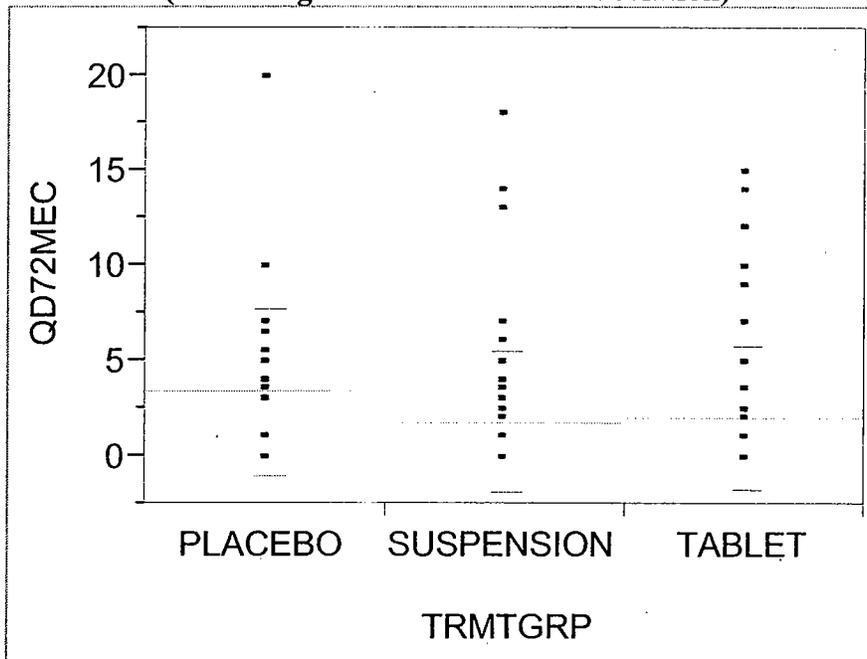
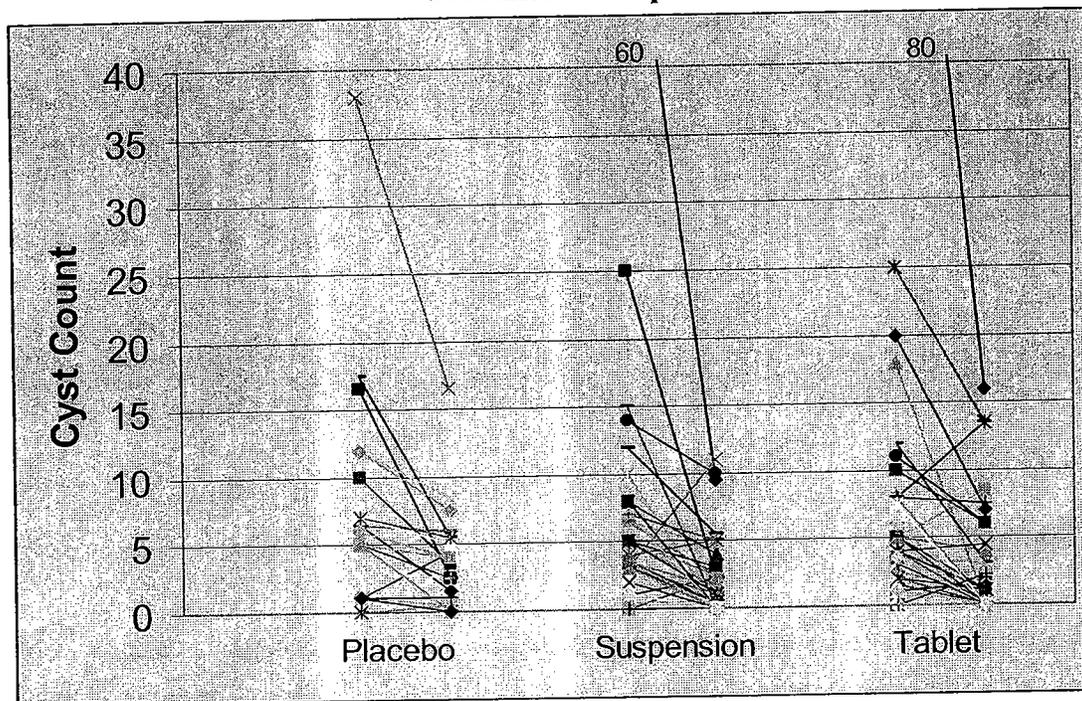


FIGURE 4B
Cyst Count in Concentrated Stool Sample #2 at Day 7 by Treatment Group
(indicating mean and standard deviation)



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.

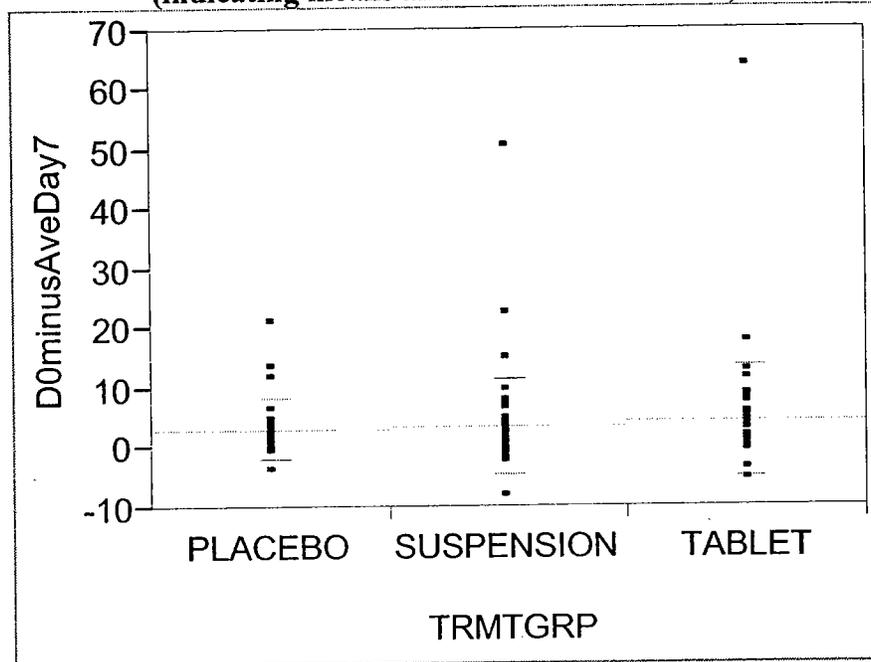
FIGURE 5
Individual Cyst Counts in Concentrated Stool Samples at Baseline and Day 7* by Treatment Group



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

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 \pm 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 inpatient 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

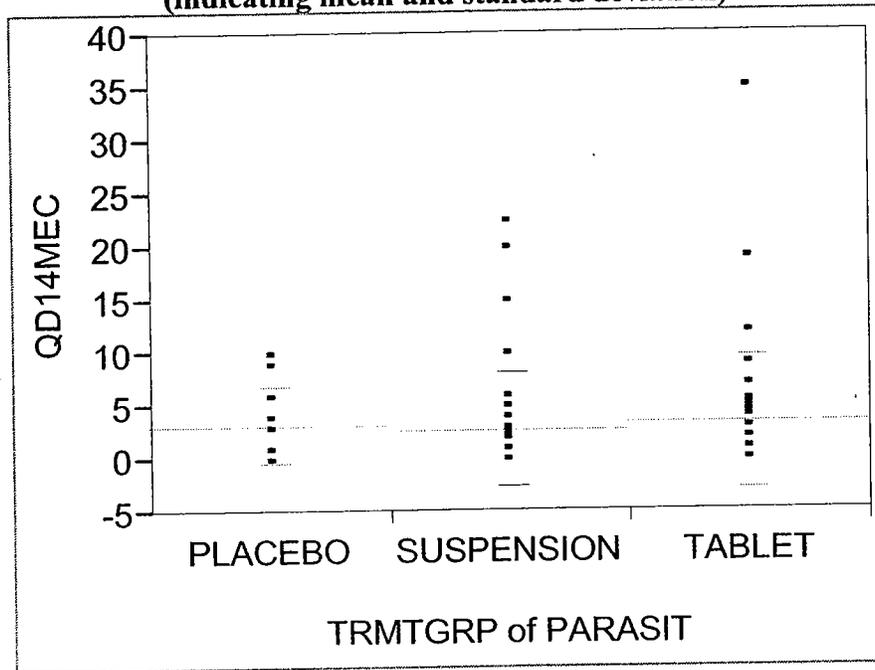
| Stool Results | Nitazoxanide Tablets N=45* | Nitazoxanide Suspension N=43* | Placebo N=12 |
|---------------|-------------------------------|----------------------------------|-----------------|
| Negative | 22 (48.9%) | 24 (55.8%) | 3 (25.0%) |
| Positive | 23 (51.1%) | 19 (44.2%) | 9 (75.0%) |

*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 \pm 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.

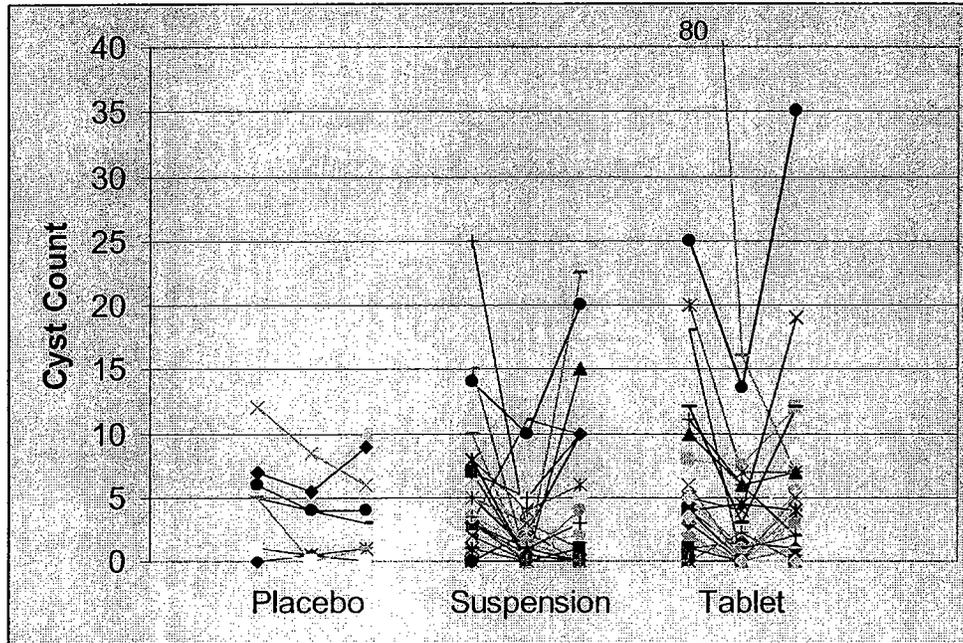
FIGURE 7
Cyst Count in Concentrated Stool Sample at Day 14 by Treatment Group
(indicating mean and standard deviation)



The mean \pm 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.

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



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

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 | |
| <i>Giardia</i> cyst quantitation³ | | | | |
| 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.

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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.

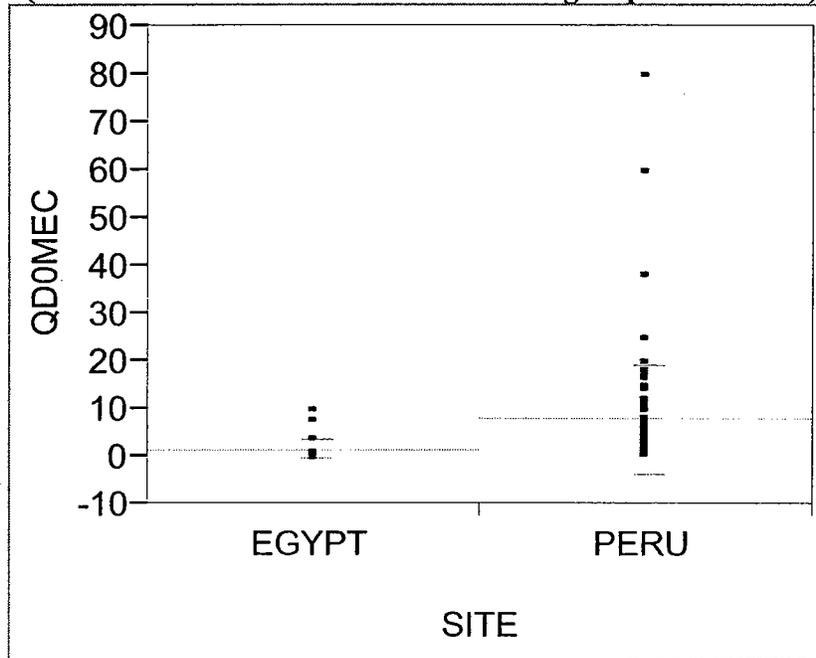
TABLE 12
Description of Cyst Counts in the Baseline Concentrated Stool Sample by Study Site

| | Peru | Egypt |
|--------------------------------|--|---|
| N | 88 (1 patient with missing data excluded) | 40 (5 patients with missing data excluded) |
| Mean number of cysts \pm SD | 7.8 \pm 11.4 | 1.6 \pm 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 \pm 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 | <i>p</i> |
|-------------------------|-------------|-------------|----------|
| 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 |

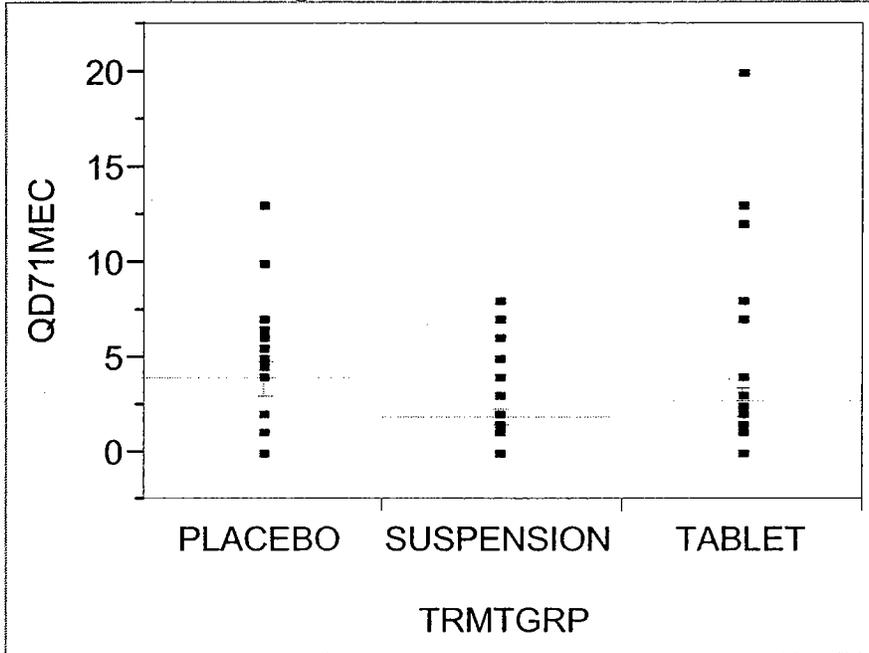
TABLE 14
Parasitological Response Rates by Treatment Group and Study Site at Day 7-10

| Treatment Group | Peru | Egypt | <i>p</i> |
|-------------------------|-------------|-------------|----------|
| 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 \pm 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)

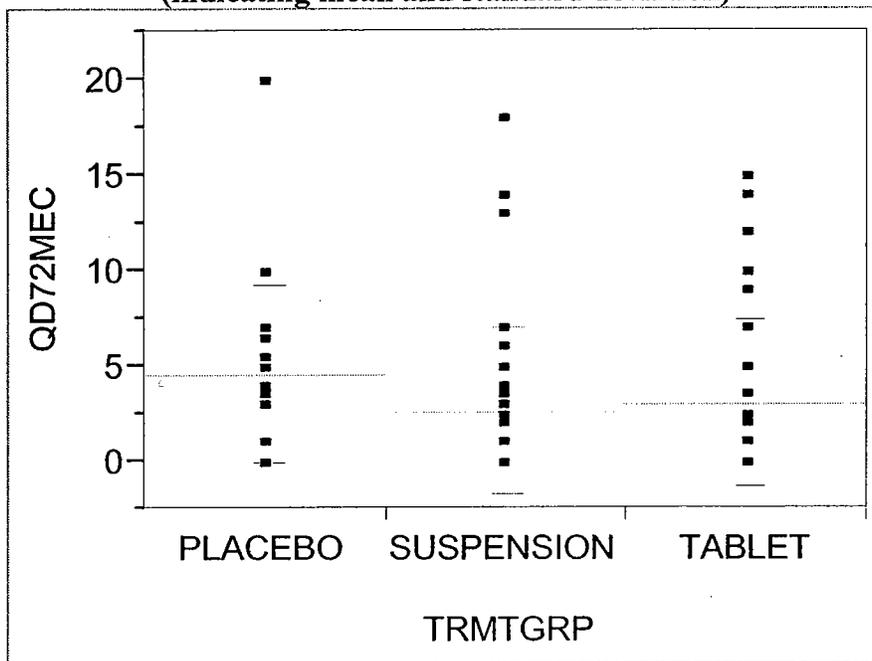


FIGURE 11A
Cyst Count in Concentrated Stool Sample #1 at Day 7 by Treatment Group
EGYPT SITE

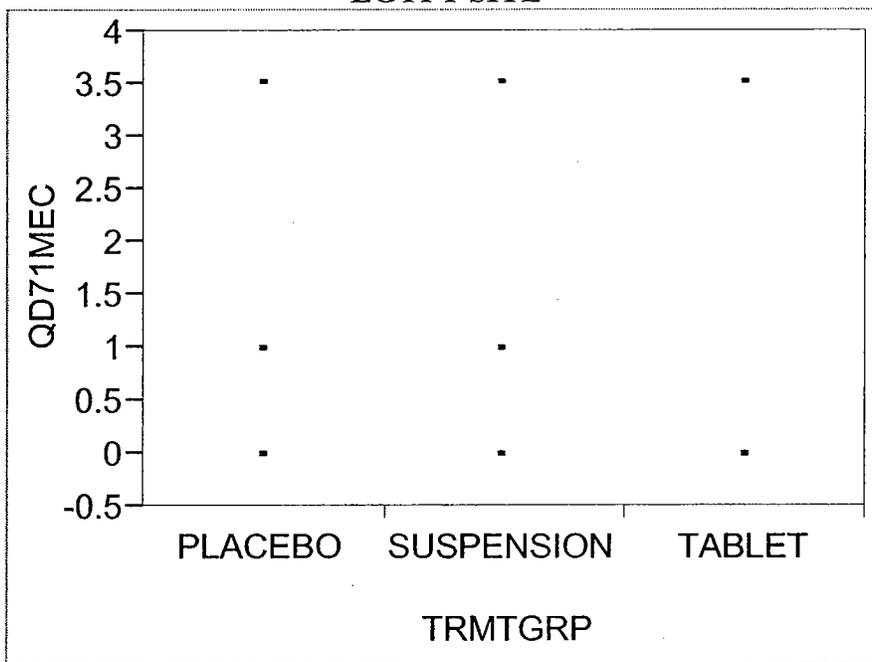
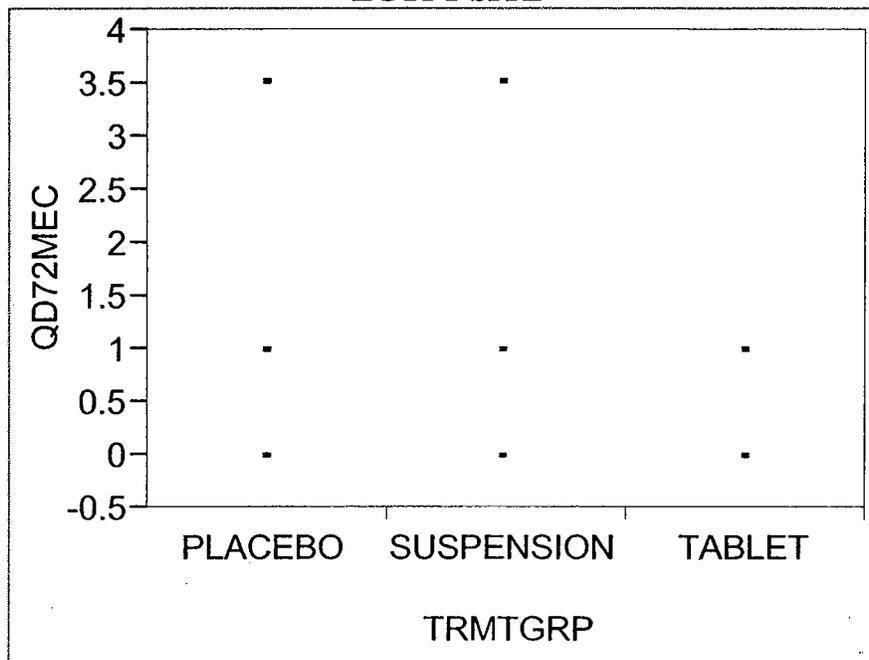


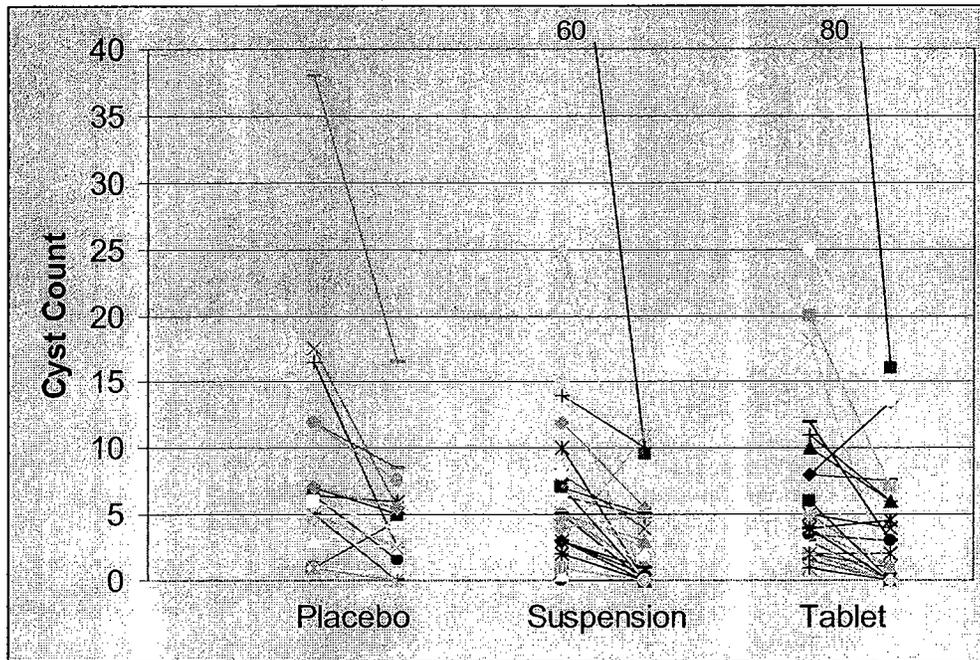
FIGURE 11B
Cyst Count in Concentrated Stool Sample #2 at Day 7 by Treatment Group
EGYPT SITE



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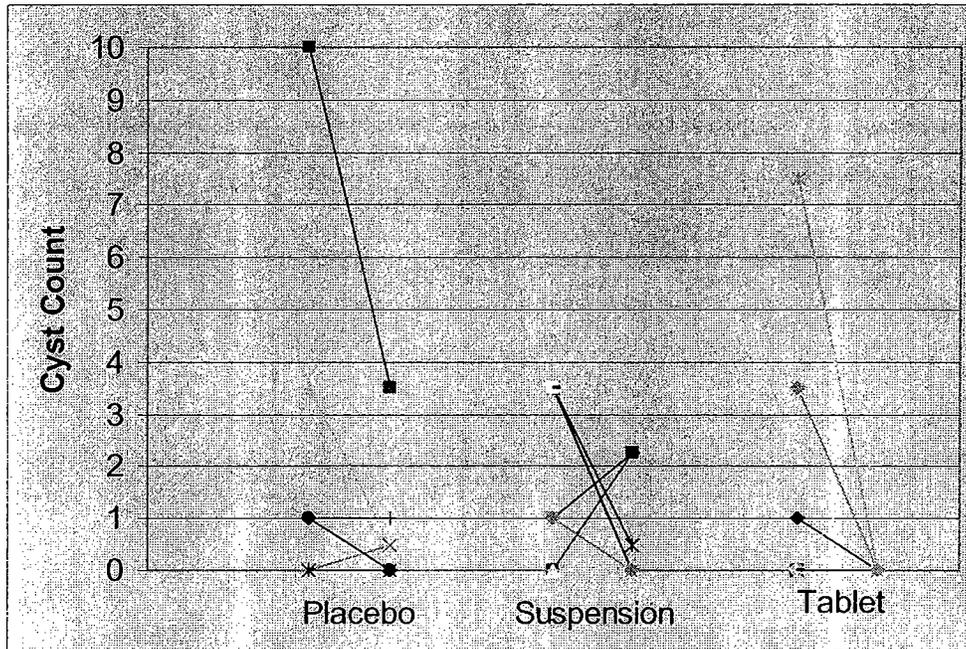
The number of cysts in concentrated stool samples at baseline and then again at Day 7 for each individual patient by treatment group is shown in Figure 12 for Peru and Figure 13 for Egypt.

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



*cyst count on Day 7 is the average from two samples obtained at least 24 hours apart between Days 7 to 10

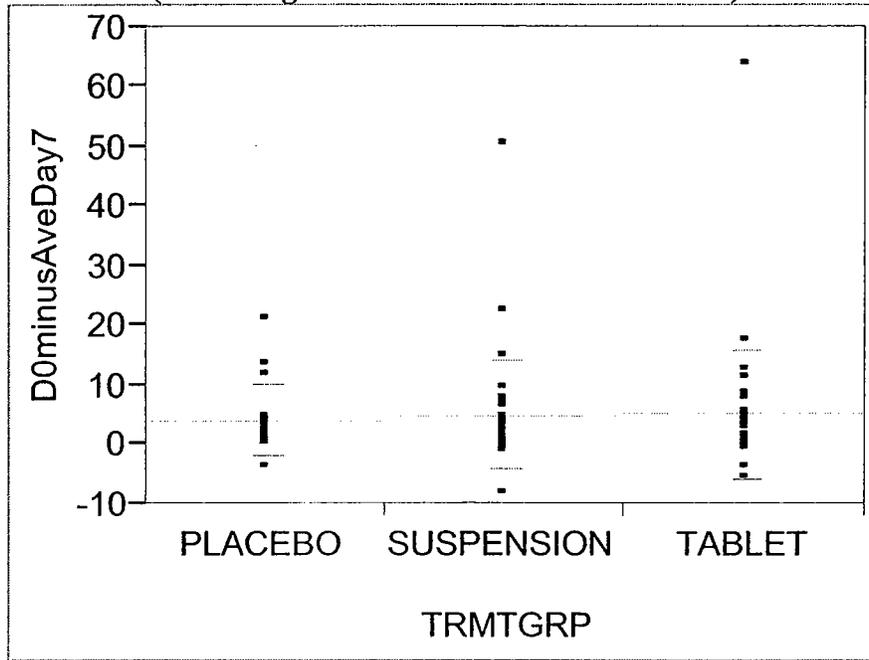
FIGURE 13
Individual Cyst Counts in Concentrated Stool Samples at Baseline and Day 7*
by Treatment Group – EGYPT SITE



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.

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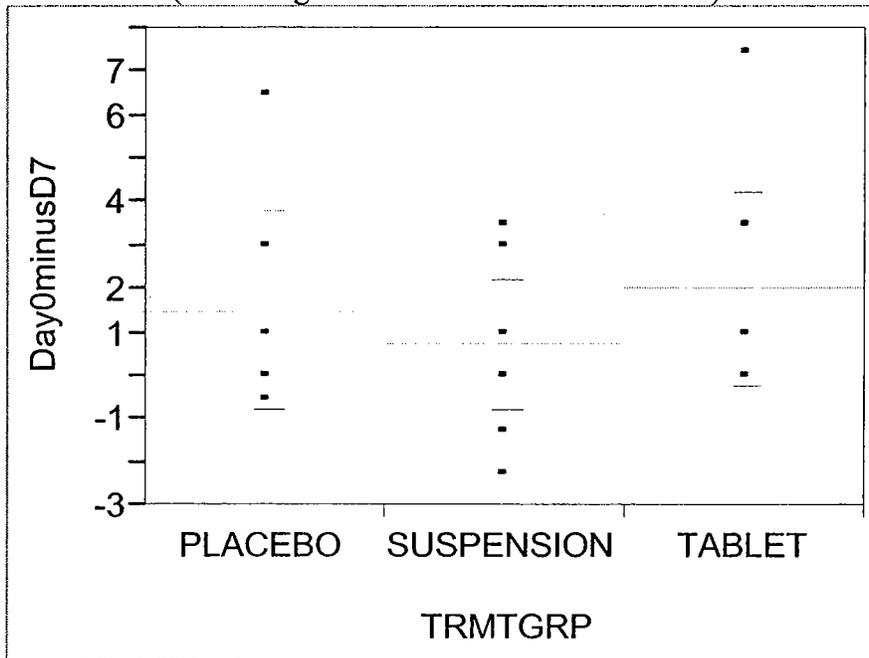
FIGURE 14
Individual Patient Reduction in Parasite Count (Baseline minus Day 7*) by
Treatment Group – PERU SITE
(indicating means and standard deviations)



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

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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 inpatient 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
Inpatient 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
Inpatient 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)

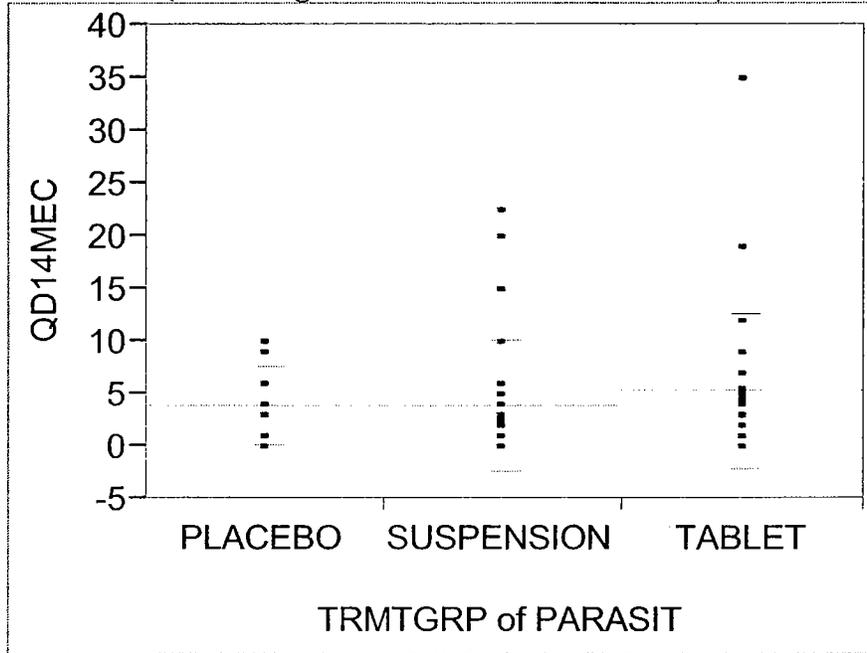
² p = 0.016 (Fisher's exact test)

³ p = 0.1273 (Fisher's exact test)

The cyst count (mean \pm 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.

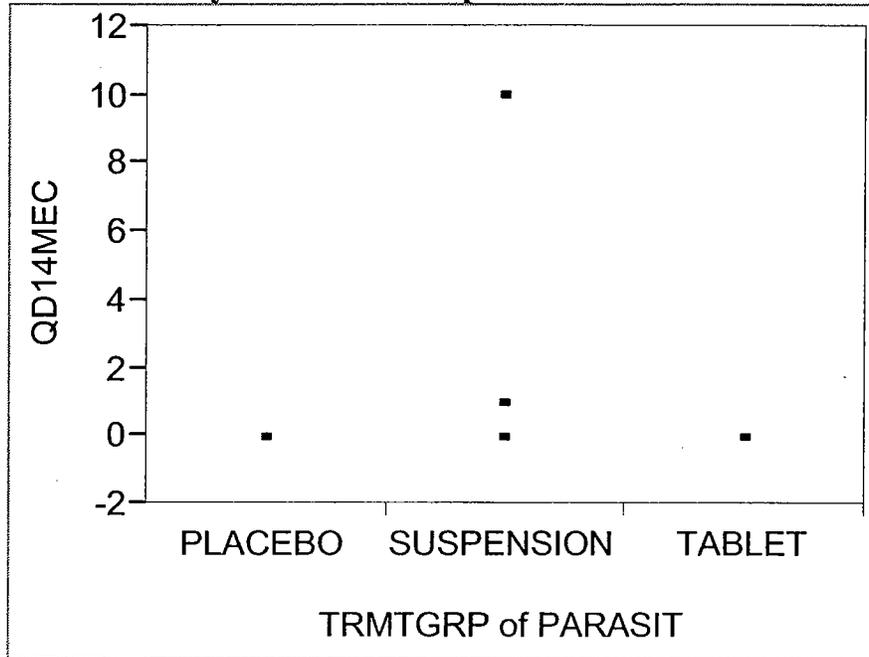
Clinical Reviewer's Comment: Figures 16A and 16B were created by the reviewer.

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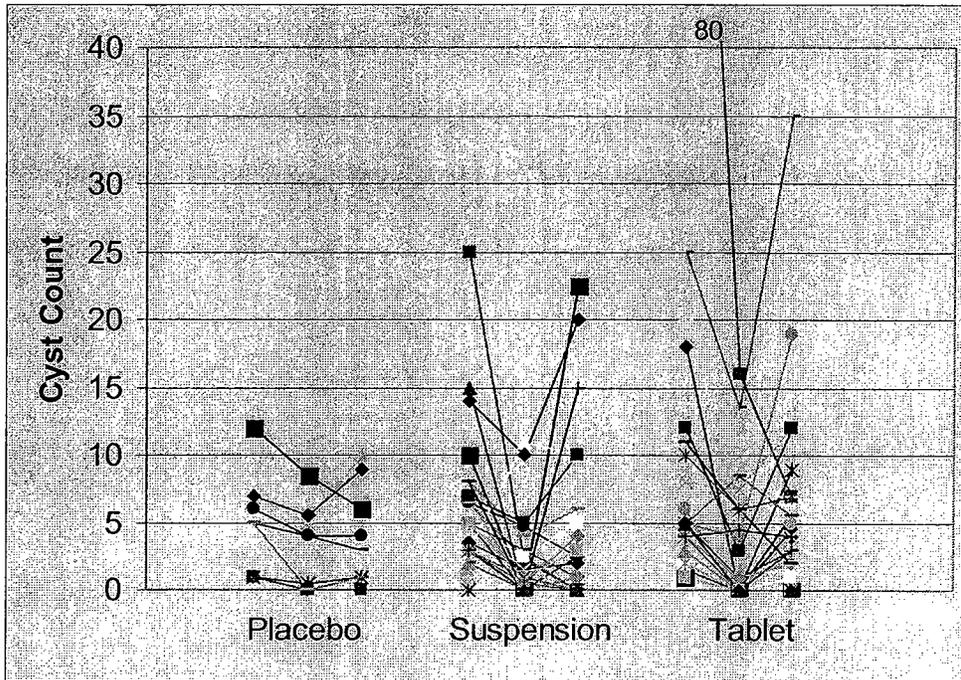
FIGURE 16B
Cyst Count in Concentrated Stool Sample in Clinical Responders at Day 14
by Treatment Group – EGPYT SITE



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.

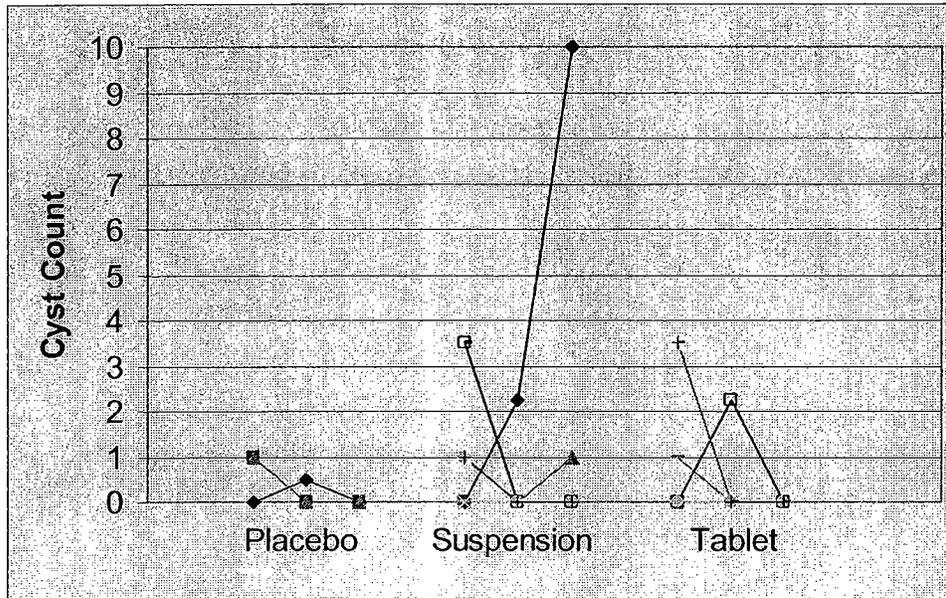
FIGURE 17
Individual Cyst Counts in Concentrated Stool Samples in Clinical Responders at
Baseline, Day 7*, and Day 14 by Treatment Group – PERU SITE



*cyst count on Day 7 is the average from two samples obtained at least 24 hours apart between Days 7 to 10

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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**



* patients with negative cyst counts at all three time points are not represented in this figure.

** cyst count on Day 7 is the average from two samples obtained at least 24 hours apart between Days 7 to 10

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 | | <i>p</i> ¹ |
|----------------------------------|--------------------------|-------------|-----------------------|
| | Eradication | Persistence | |
| 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) |
|-------------------------|--------------------------|-----------------------|---------------------------|
| <i>Body as a whole:</i> | | | |
| 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%) | - | - |
| <i>Digestive:</i> | | | |
| NAUSEA | 4 (7%) | 4 (7%) | - |
| DIARRHEA | 1 (2%) | - | 1 (4%) |
| VOMIT | - | 1 (2%) | - |
| THIRST | 1 (2%) | - | - |
| <i>UG:</i> | | | |
| URINE ABNORM | 4 (7%) | 5 (9%) | - |
| EDEMA LABIA | 1 (2%) | - | - |
| <i>Nervous:</i> | | | |
| DIZZINESS | 2 (4%) | 2 (4%) | - |
| SOMNOLENCE | 1 (2%) | 2 (4%) | - |
| REFLEXES INC | - | 1 (2%) | - |
| EMOTION LABIL | - | - | 1 (4%) |
| <i>Respiratory:</i> | | | |
| PHARYNGITIS | 1 (2%) | - | - |
| RHINITIS | - | 1 (2%) | - |
| <i>SS:</i> | | | |
| PAIN EAR | 1 (2%) | - | - |
| EYE DIS | 1 (2%) | - | - |
| <i>MS:</i> | | | |
| BONE FRACT | 1 (2%) | - | - |
| SPONTAN | - | - | - |

Best Possible Copy

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 _____ after her last dose of study medication, 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

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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 \pm 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 inpatient 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 inpatient 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 \pm 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 \pm 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 (\geq 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 (\geq 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.

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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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DIVISION DIRECTOR REVIEW

Applicant: Romark Laboratories, L.C.
Tampa, Florida

Drugs: NDA 21-497, Alinia™ (nitazoxanide oral tablets) 500 mg
NDA 21-498, Alinia™ (nitazoxanide for oral suspension) 100 mg/5 mL

Date of Submission: May 29, 2002 (User Fee due date November 29, 2002)

Proposed Indications:

- Treatment of diarrhea caused by *Cryptosporidium parvum* in patients without acquired immunodeficiency syndrome (non-AIDS patients).
- Treatment of diarrhea caused by *Giardia lamblia* in non-AIDS patients.

Proposed Age Groups and Dosage Regimens:

- Age 12 years and above: 500 mg Tablets PO every twelve hours for 3 days
- Age 4-11 years: 10 mL (200 mg nitazoxanide) every 12 hours for 3 days
- Age 1-3 years: 5 mL (100 mg nitazoxanide) every 12 hours for 3 days

Purpose of Memorandum:

The purpose of this memorandum is to provide a brief summary of the Division's recommendations on these applications, including the scientific and regulatory issues surrounding the approval of nitazoxanide for oral suspension; and the deficiencies with the tablet formulation.

Background:

Nitazoxanide was first submitted to the Agency as IND 48,620 on August 10, 1995, and on December 26, 1997, the NDA 20-871 for oral tablets was submitted for the proposed treatment of diarrhea caused by *Cryptosporidium parvum* in HIV positive patients. This application was taken to advisory committee, the committee voted that the studies did not show efficacy of the product in the proposed indication.

On August 31, 1999, IND 58,895 was submitted to the Agency to evaluate nitazoxanide for oral suspension in children.

The applicant obtained orphan drug designation for "treatment of cryptosporidium" on June 1, 2001 and for "intestinal giardiasis" on February 14, 2002.

On May 29, 2002, Romark submitted NDA's 21-497 and 21-498 and requested approval for treatment of diarrhea caused by *Cryptosporidium parvum* and *Giardia lamblia* in immunocompetent patients. One study in pediatric patients with AIDS was also submitted. Because the applications contained studies that showed superiority of nitazoxanide over placebo for *C. parvum*, an infection for which there is no currently-approved therapy, the applications were granted priority reviews.

Nitazoxanide is approved for marketing in multiple Central and South American countries. A reported — courses of therapy have been sold in Latin America.

Evaluation of Efficacy:

The applications contained results from 5 controlled clinical studies

| | |
|---------------|--|
| RM-NTZ-98-002 | A double-blind placebo-controlled study in adults and children with diarrhea caused by <i>C. parvum</i> (n=50 adults and n=49 children in Egypt) |
| RM02-3007 | A double-blind placebo-controlled study in HIV-seronegative children with diarrhea caused by <i>C. parvum</i> (n=50 children in Zambia) |
| RM02-3008 | A double-blind placebo-controlled study in HIV-seropositive children with diarrhea caused by <i>C. parvum</i> (n=50 children in Zambia) |
| RM-NTZ-98-001 | A double-blind placebo-controlled study in adults with diarrhea caused by <i>G. lamblia</i> or <i>E. histolytica</i> (n=93 adults in Egypt) |
| RM-NTZ-99-010 | A single-blind metronidazole-controlled study in children with diarrhea caused by <i>G. lamblia</i> (n=110 children in Peru) |

The following factors were among those evaluated:

- Clinical outcome - clinical response from ≥ 3 unformed stools to no unformed stools by 7 ± 2 days after completing therapy, clinical response by patient
- Microbiological outcome - outcome in patients with *C. parvum* or *G. lamblia* as single pathogen, microbiology response by patient, culture at 7 ± 2 days and 10 ± 2 days after completing therapy
- Intra-patient clinical and microbiological correlation
- Safety

The results of the comparative clinical trials that evaluated the efficacy of NTZ in the treatment of these intestinal infections are provided in the tables below.

Results of Clinical Studies of *CRYPTOSPORIDIUM PARVUM*

| Study & Site | Population | NTZ | Placebo | P value |
|--------------|--|-------------|------------|---------|
| 98-002 Egypt | HIV(-) pediatric patients (MOR p 38) | | | |
| | Clinical | 21/24 (88%) | 9/24 (38%) | .0004 |
| | Parasitological | 18/24 (75%) | 6/25 (24%) | .0001 |
| | OTLUS* | 3.5 days | > 6 days | .0001 |
| 3007 Zambia | HIV(-) pediatric patients (MOR p 41) | | | |
| | Clinical | 14/25 (56%) | 5/22 (23%) | .037 |
| | Parasitological | 13/25 (52%) | 3/22 (14%) | .007 |
| 3008 Zambia | HIV(+) pediatric patients treated for 3 days (MOR p 44) | | | |
| | Clinical | 2/25 (8%) | 6/24 (25%) | .14 |
| | Parasitological | 4/25 (16%) | 5/25 (20%) | 1.0 |
| | Mortality | 5/25 (20%) | 4/24 (17%) | 1.0 |
| 98-002 Egypt | HIV (-) adult patients with single pathogen (MOR p36) | | | |
| | Clinical | 15/21 (71%) | 9/21 (43%) | .118 |
| | Parasitological | 12/21 (57%) | 6/21 (29%) | .118 |

*OTLUS – onset of therapy to time of last unformed stool

Results of Clinical Studies of *GIARDIA LAMBLIA*

| Study & Site | Population | NTZ | Control | Statistic |
|--|---|-------------|---------------|------------|
| 99-010 Peru -ITT -Per protocol | Pediatric patients , sole pathogen (MOR p52) | | | |
| | | Suspension | Metronidazole | 95% C.I. |
| | Clinical | 47/55 (85%) | 44/55 (80%) | -9%, +20% |
| | Microbiology | 39/55 (71%) | 41/55 (75%) | -20%, +13% |
| | Clinical | 43/48 (90%) | 39/47 (83%) | -8%, +21% |
| | Microbiology | 39/47 (83%) | 37/46 (80%) | -15%, +17% |
| 98-001 Egypt | Adult patients, sole pathogen (MOR p 49) | | | |
| | | Tablet | Placebo | P value |
| | Clinical | 8/8 (100%) | 3/10 (30%) | < .02 |
| | Microbiology | 6/8 (75%) | 0/10 (0%) | < .008 |

The adult study serves as corroborative data for the pediatric study.

Results of Safety Analyses

| | | NTZ | Control |
|-----------------------|--------------------|--------------|--------------|
| Adverse Events | Overall | 40/194 (21%) | 44/199 (22%) |
| By age group | Adult patients | 14/72 (19%) | 11/70 (16%) |
| | Pediatric patients | 26/122 (21%) | 33/129 (26%) |
| Severe adverse events | Pediatric patients | 7/122 (6%) | 10/129 (8%) |
| Deaths | Pediatric patients | 7/122 (6%) | 10/129 (8%) |

Severe adverse events and deaths were reported in patients who were HIV positive (study 3008) or in patients on the placebo arm of the studies.

For the overall NTZ program, the applicant indicated that 2,789 patients had been exposed to NTZ, including 2,453 who received at least 3 days of treatment. Safety data has been evaluated from 910 pediatric patients studied in comparative and non-comparative studies for a range of parasitic gastrointestinal infections. Including the pediatric patients studied in the controlled trials summarized above, there were a total of 133 children 1-2 years old, 525 children 4-11 years old and 252 children 12-19 years old enrolled in these trials. Among 2,349 HIV negative patients, there were no serious adverse events reported and no drug-related adverse effects on hematology, chemistry or urinalysis. The adverse events in the NTZ treated patients did not differ significantly from those patients receiving placebo.

Recommendations for Regulatory Action [excepts from Dr. Rosemary Johann-Liang's Medical Officer Review]

- NDA 21-497 (nitazoxanide tablets) should receive an APPROVABLE action. Although NTZ treatment effect for diarrhea due to *C. parvum* or *G. lamblia* is suggested from studies RM-NTZ-98-002 and RM-NTZ-98-001, substantial evidence of efficacy has not yet been shown through these trials. Statistical endpoints were not met for non-AIDS adult population for the treatment of *C. parvum* diarrhea, and the number of non-AIDS adult patients with *G. lamblia* as sole pathogens for study were too small to provide substantial evidence at this time. The applicant will need to demonstrate substantial efficacy in this population with adequate number of patients having the sole pathogen under study. It is further recommended that in future efficacy studies to garner this indication, the contribution of formulation-effect (the tablet and suspension formulations should be compared to each other and to placebo) as well as food-effect (fed-state versus fasting-state) be elucidated.
- NDA 21-498 (nitazoxanide oral suspension) should receive an APPROVAL action for the treatment of diarrhea due to *C. parvum* and *G. lamblia*. Clinical efficacy and safety of the product were adequately demonstrated for children 1 year to less than 12 years of age. Two adequate and well-controlled studies demonstrating that nitazoxanide oral suspension was superior to placebo were submitted for *C. parvum*. One adequate and well-controlled study was submitted demonstrating efficacy in *G. lamblia*; the results of these study were corroborated by evidence of superiority of

nitazoxanide tablets compared to placebo in a limited number of adults treated with diarrhea where *G. lamblia* was the sole pathogen. However, neither rigorous microbiological data nor substantial evidence of the correlation between clinical and microbiological endpoints was shown at this time to warrant the indication “eradication of oocysts or cysts”.

- The proposed trade name, , was unacceptable (see DMETS and DDMAC consults) and the company has chosen Alinia. This name was considered acceptable by the consultants.

Summary and Recommendations:

The Applicant has submitted two NDA’s requesting approval of the indications listed above. Specifically, nitazoxanide for oral suspension has been evaluated in pediatric patients between the ages of 1 and 11 years, inclusive, while the oral tablet formulation has been evaluated in adult patients (ages > 12). The review team’s recommendations are that the data for the oral suspension are adequate to recommend approval for this use (see package insert for oral suspension), while the information on the oral tablet is at present inadequate for approval. The latter, while inadequate for approval, are encouraging and do support further investigation of the tablet formulation (outlined in the approvable letter).

As presented in more detail above, the data are adequate to support the approval of the oral suspension in the treatment of the two indications in pediatric patients 1 through 11 years in age who are HIV negative and who do not have an immunodeficiency. The question was raised whether these pediatric data can be extrapolated to adults so that the oral suspension could be approved for treatment of adult patients, or even that a dose could be determined for the tablet formulation. De facto, this would be a reverse application of the pediatric rule; in this case, the proposal would be that pediatric data would be used to extrapolate efficacy to adults [See 21 CFR 201.57 (f) (9) *Pediatric Use*]. While this approach may be considered from the regulatory standpoint, there are several scientific questions that are unanswered and therefore preclude using or relying on this approach in this case. These are summarized below:

- The pediatric patients in clinical trials received the oral suspension at 100 mg BID for patients 1-2 years of age and 200 mg BID for patients > 2-11 years of age. The correct dose of oral suspension in adults is unknown, and cannot be derived from pediatrics because of the following unanswered issues.
 - The tablet is not bioequivalent to the oral suspension. The oral suspension formulation is less bioavailable compared to the tablet, therefore the oral suspension provides relatively lower systemic levels and higher gastrointestinal luminal levels compared to the tablet. Both *C. parvum* and *G. lamblia* are pathogens found in the gastrointestinal lumen. It is unknown whether the systemic drug levels or the luminal drug levels are more important for efficacy, therefore it is not possible to determine a therapeutically bioequivalent dose.

- There is a food effect demonstrated on the tablet formulation in adults; food enhances absorption. This further confounds determining the appropriate dose in adults.
- While the pathophysiology of the infections may be comparable in adults and children, it is not clear that children and adults are equally susceptible to the infection. Thus, even if they were given the “same” doses based on pharmacokinetic calculations of systemic exposure or luminal exposure, it is not known that these would have comparable efficacy because of the host differences. Related to this issue is the finding that, the 3 day regimen was shown to be effective in HIV negative pediatric patients with *C. parvum*, but was NOT effective when tested in HIV positive patients with AIDS infected with *C. parvum*. Thus, differences in host factors need to be considered.
- The safety profile of the tablet formulation in non-HIV infected adult patients is also quite limited, although this should not be considered a major deficiency, because a large safety database is available from HIV infected adults and did not show a safety signal. Animal data and pediatric patient safety data are also encouraging. However, further studies in adults with the tablet formulation to address the efficacy deficiencies will provide more safety data.

In summary, while the data on the oral tablet and evidence of limited efficacy in adults is encouraging, the current data do not support approval of the tablet formulation or of the adult population. On note, the applicant has not requested that we consider approval based on extrapolation from pediatric patient and oral suspension data, and continues plans to develop the tablet formulation in adults.

In the approval letter for the oral suspension, the applicant has been asked to further characterize the pharmacokinetic profile of the oral suspension, and to monitor patient use of the product, specifically whether off label use and long-term use may occur.

In the approvable letter for the tablets, the applicant has been asked to further evaluate the efficacy of NTZ in adults with *C. parvum* as a single pathogen, and *G. lamblia* as a single pathogen in adequate and well-controlled studies. Specifically, the applicant has been asked in these studies to address the microbiological response in each patient and correlate this with the clinical response in that patient. A request was made to consider evaluating the efficacy of the tablet as well as the oral suspension in adults.

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