parasitological response. The kappa values show very poor correlation in the placebo arm but a better correlation in the NTZ arm.

However, as it has been summarized in the microbiology review (see above under Microbiology section and complete discussion in Dr. Suvarna's Microbiological Review) that the parasitological assessment in this study was sub-optimal. For C. *parvum*, oocysts are shed intermittently and the optimum number of negative stool samples to confirm the absence of protozoa has not been determined. What is generally recommended is that 3 or more stool samples be examined within 5 days for clinical evaluation of new drugs. The stool samples should be concentrated and the examination of the concentrated stool samples should be performed by 2 or more methods (staining, immunofluorescence assays, EIA). The parasitological examination in this study was mainly by microscopic examination of stools using the Ziehl Neelson acid-fast stained smears with one drop of stool sample. Moreover, only 9 patients had confirmation by — immunoassay.

Table 8: FDA Analysis - Crypto Study 98-002 (Children ITT)

Grp	Trt	N	Clinical Response		Parasite Response		Kappa	$\bar{C}P + C\bar{P}$
			% Well	p-value	% E	p-value		
Ch	P	25	36.0	.0003	20.0	.0002	.039 (.188)	7+3=10
	NTZ	24	87.5		75.0		.333 (.223)	4+1=5
Ch F	P	9	55.6	.0211	22.2	.03	-.047 (.262)	4+1=5
	NTZ	12	100		75.0		N/A	3+0=3
Ch M	P	16	25.0	.02	18.8	.0061	.091 (.262)	3+2=5
	NTZ	12	75.0		75.0		.556 (.278)	1+1=2

Ch-F: female children; Ch-M: male children; P: placebo; C: clinical response of Well ; $\bar{P}$: parasitological response of persistent; $\bar{C}$: clinical response of Continuing Illness; P: parasitological response of eradicated; numbers in ( ) denote standard deviation around the Kappa coefficients

As discussed under the efficacy summary of adult subjects, the other main problem with this study was that out of the 100 total patients, 21 patients had other parasites besides *C. parvum* isolated at the screening visit. Thirteen children (4 in placebo arm and 9 in NTZ arm) and 8 adults (4 in placebo arm and 4 in NTZ arm) made up those 21 patients. The sensitivity analyses excluding

these patients from the ITT population was performed by the team statistician and the following shows the numbers for the patients taking the suspension formulation.

Table 9: FDA Analysis – Children with *C. parvum* as sole pathogen at screening, Efficacy response and Kappa coefficients

Age group	Trt N	Clinical Resp % Well p	Parasite Resp % E p	Kappa Coefficient
Children < 12 yrs	P 21 NTZ 15	28.6 86.7 (.0008)	19.1 73.3 (.0019)	-.037 (.204) +.189 (.270)

MO COMMENT: *When patients with only C. parvum at screening were included in the analysis of clinical and parasitological response, there is still statistical significance for both primary endpoints. However, the kappa coefficients remain poor and inconsistent. This poor correlation coupled with the less then optimal microbiological methodology (as described above) does not suggest a complete understanding and linkage of clinical and microbiological responses in this disease.*

Two other placebo-controlled trials conducted in children with cryptosporidial diarrhea (studies RM02-3007 and RM02-3008) were presented as pivotal studies for this application.

Study 3007 was a randomized, double-blind, placebo-controlled clinical trial of nitazoxanide 100 mg/ 5 ML suspension in HIV-seronegative children with diarrhea caused by *Cryptosporidium parvum*. The study was conducted at the Department of Pediatrics and Child Heath, University Teaching Hospital of Lusaka, Zambia between November 2000 and July 2001. The goal of this study was to see if NTZ treatment effect would be shown in malnourished HIV-seronegative African children.

To be eligible for inclusion in the study, children must have reported diarrhea at baseline (> 3 unformed stools per day), and oocysts of *C. parvum* must have been identified in a stool sample collected within 7 days prior to enrollment. A second stool examination was conducted on the day of enrollment to confirm the presence of *C. parvum*.

MO COMMENT: *This is different from Study 002, which had no confirmatory stool examination on the day of enrollment*

The study was designed to enroll 50 children. The sample size was calculated to provide 80% power to detect a difference between an 85% response rate for the nitazoxanide treatment group and an expected 40% response rate for the placebo group using a two-sided alpha of 0.05. The primary endpoint of the

study was the clinical response of the children with parasitological response and time from initiation of treatment to passage of last unformed stool being analyzed as secondary endpoints.

Fifty children between the ages of 12 and 35 months were enrolled in the study. All except two of the children were malnourished based on weight for age z-scores with 68% considered moderately to severely underweight. Each child was hospitalized for the duration of the study, and upon enrollment was administered 5 mL of nitazoxanide suspension or a matching placebo suspension twice daily for three days and was provided complete supportive therapy including oral rehydration therapy, intravenous fluids, antibiotics, multiple micronutrients (including vitamin A and zinc), and nutritional support with a skimmed milk-based feed.

Data from 47 children were analyzed. According to the protocol, three children, all randomized to the placebo group, were excluded from the analyses because they had no oocysts in their stool at baseline.

> ***MO COMMENT:*** *Again, these three patients are a problem because if you leave all three included in the analysis (all three are in the placebo arm), there is no statistical difference between the two treatment arms. Remember that in the other cryptosporidium study (Study 98-002), only screening stool examination was used and thus these three patients would have been included in the analysis.*

The applicant's analysis was presented in their Table 3-3 which summarizes study 3007 response data by treatment group.

Table 10: Applicant's Efficacy Summary; Study 3007

	Nitazoxanide	Placebo	P[a]
Clinical response[b]	14/25 (56%)	5/22 (22%)	0.037
Parasitological resp[c]	13/25 (52%)	3/22 (14%)	0.007
Mortality rate[d]	0/25 (0%)	4/22 (18%)	0.041

[a]Fisher's exact test, two-sided; [b]no. "well"/ total; [c]no. with two negative stool exams / total; [d]no. of deaths / total

The applicant stated that this study demonstrated significant improvements in efficacy for clinical response (primary endpoint) and parasitological response (a secondary endpoint). Because four children died during the study, a comparison of mortality rates was also conducted. This analysis showed a significantly higher mortality rate for the placebo group than for the group treated with nitazoxanide. The applicant goes on to state that the analysis of median time from initiation of treatment to passage of last unformed stool (the other secondary endpoint) did not show a significant difference because a number of the children who satisfied the definition of "well clinical response" were still passing soft (unformed) stools at the day 7 follow-up examination. The applicant

stated that in retrospect, this endpoint was probably not appropriate for a population of very young malnourished children.

In the FDA's sensitivity analysis, the first item was to look at the correlation between the above (Applicant's Table 3-3) clinical and parasitological response rates using the Kappa Statistic.

Table 11: FDA Analysis – Efficacy Response with Kappa Statistic; Study 3007

	Nitazoxanide	Placebo	P[a]
Clinical response[b]	14/25 (56%)	5/22 (22%)	0.037
Parasitological resp[c]	13/25 (52%)	3/22 (14%)	0.007
Kappa Coefficient	.096 (.225)	.116 (.198)	

As was seen in study 002, the correlation between the two response rates for treatment of *C. parvum* are again poor. The Kappa Coefficients for both arms are again close to 0.

Another analysis was done (for consistency) by including in the analysis all patients who *had C. parvum* at the screening visit. This was what the Applicant had done for Study 98-002. Hence, the three patients that were excluded by the Applicant in their ITT analysis were included in the following analysis. When this is done, the statistical significance between the two groups no longer exist.

Table 12: FDA Analysis - Include all children with *C. parvum* at screening

	Nitazoxanide	Placebo	P[a]
Clinical response	14/25 (56%)	8/25 (32%)	0.1536
Parasitological resp	13/25 (52%)	5/25 (25%)	0.0792

In order to increase the numbers of patients for comparison for this age group, the next FDA analysis took **studies 98002 and 3007 and pooled the results.** Here, the children with mixed infections and children who did not take the medication at all were excluded. Again, all children in both studies who had *C. parvum* isolated at the screening visit were included. This resulted in n=46 children for the placebo arm and n=39 children in the nitazoxanide arm.

Table 13: FDA Analysis – Pooled Efficacy Results with *C. parvum* as sole pathogen at screening; Studies 98002 and 3007

	Nitazoxanide	Placebo	P[a]
Clinical response[b]	26/39 (66.7 %)	14/46 (30.4 %)	0.0011
Parasitological resp[c]	23/39 (59 %)	10/46 (21.7 %)	0.0007
Kappa Coefficient	.218	.182	

Therefore in pooling the results obtained from children <12 years old and primarily malnourished with *C. parvum* as the sole pathogen at the screening visit from Egypt and Zambia, clear treatment effect of nitazoxanide over placebo was shown.

The statistical reviewer's subgroup analysis among these children are shown next. This shows that for certain subgroups such as being male and being African, the necessary p-values were not met. This is probably due to the small number of patients at the level of subgroups analysis. What stands out is that, consistently down the columns, it can be seen that the percentage of responders in the NTZ arm are always greater than the placebo, and as just mentioned, the overall response data is shown to be favorable for nitazoxanide in this population.

Table 14: FDA Analysis – Subgroup Efficacy Analyses with Kappa Statistics from Pooled Efficacy Results with *C. parvum* as sole pathogen at screening; Studies 98002 and 3007

Grp	Trt	N	Clinical Response		Parasite Response		Kappa	$C\bar{P} + \bar{C}P$
			% Well	p-value	% E	p-value		
All Data	P	46	30.4	.0011	21.7	.0007	.218	9+5=14
	NTZ	39	66.7		59.0		.182	9+6=15
<4	P	34	29.4	.0131	23.5	.0231	.398	5+3=8
	NTZ	31	61.3		51.6		.025	9+6=15
4-11	P	12	33.3	.0281	16.7	.0045	-.286	4+2=6
	NTZ	8	87.5		87.5		1.0	0+0=0
Female	P	15	33.3	.0032	13.3	.0032	.118	4+1=5
	NTZ	16	87.5		68.8		.130	4+1=5
Male	P	31	29.0	.0994	25.8	.0861	.271	5+4=9
	NTZ	23	52.2		52.2		.129	5+5=10
African 3007	P	25	32	.1536	24	.0792	.409	4+2=6
	NTZ	24	54.2		50		.083	6+5=11
Cauca-sion 98002	P	21	28.6	.0008	19.1	.0019	-.037	5=3=8
	NTZ	15	86.7		73.3		.189	3+1=4

P: placebo; C: clinical response of Well ; $\bar{P}$: parasitological response of persistent; $\bar{C}$: clinical response of Continuing Illness; P: parasitological response of eradicated; numbers in ( ) denote standard deviation around the Kappa coefficients.

The controlled study for *C. parvum* diarrhea that the applicant has directed us to was **Study No. RM02-3008**. According to the applicant, at the same time that study 3007 was being conducted in HIV-seronegative children in Zambia, an identical double-blind placebo-controlled study was conducted in Zambian children who were HIV-seropositive. The clinical and parasitological response rates and the mortality rates for this study are presented below in applicant's Table 3-4. This summary shows that for HIV seropositive children, there was no treatment effect of 3 day NTZ therapy over placebo.

Table 15: Applicant's Efficacy Summary; Study 3008

	Nitazoxanide	Placebo	P[a]
Clinical response[b]	2/25 (8%)	6/24 (25%)	0.14
Parasitological resp[c]	4/25 (16%)	5/25 (20%)	1.0
Mortality rate[d]	5/25 (20%)	4/24 (17%)	1.0

[a]Fisher's exact test, two-sided; [b]no. "well"/ total; [c]no. with two negative stool exams / total; [d]no. of deaths / total

The applicant compared the demographic and disease-related characteristics of the children enrolled in this study 3008 with those of the children enrolled in study 3007. Aside from their HIV status, the children in 3008 were more severely malnourished than the HIV seronegative cohort with lower weight for age Z-scores ($p<0.0001$, t-test), they reported a longer duration of diarrhea at the time of enrollment ($P=0.0073$, t-test), and they had lower CD4 counts ($P<0.0001$, t-test).

The following is Applicant's Table 3-5; RM02-3008: Comparison of important disease-related characteristics of HIV-seropositive children compared to HIV-seronegative children.

Table 16: Applicant's Summary Comparison of Characteristics of patients from Studies 3007 (HIV seronegative) and 3008 (HIV seropositive)

	HIV seronegative Study RM02-3007		HIV seropositive Study RM02-3008	
	NTZ	Placebo	NTZ	Placebo
Malnutrition status[a]				
Severely underweight	11 (44%)	11 (50%)	21 (84%)	17 (71%)
Moderate underweight	6 (24%)	6 (27%)	3 (12%)	4 (17%)
Mild underweight	7 (28%)	4 (18%)	-	3 (12%)
Not underweight	1 (4%)	1 (5%)	1 (4%)	-
CD4 count				
Mean:	1548	1452	619	621
SD:	508	503	446	632
Range:				

	HIV seronegative Study RM02-3007		HIV seropositive Study RM02-3008	
	NTZ	Placebo	NTZ	Placebo
Duration of diarrhea (days)				
Mean:	24.48	15.29	44.0	55.0
SD:	20.05	11.46	62.83	77.85
Median:	18	9	29	25
Range:				
[a]Based on weight for age z-scores: Z< -3.0 = severe underweight; Z<-2.0 = moderate underweight; Z < -1.0 = mild underweight				

***MO COMMENT**: The following information on Z scores was provided by the Applicant upon request, and clarified the system used to characterize nutritional state of the patients enrolled in both Zambian studies.*

The weight-for-age z-scores were calculated using the methodology described on the internet site for the National Center for Health Statistics:
www.cdc.gov/nchs/about/major/nhanes/growthcharts/datafiles.htm

The growth chart used for these calculations was the weight-for-age chart for children from birth to 36 months of age (also found at the above-referenced website).
The formula used to calculate the weight-for-age z-scores was: ***Z= ((X/M)L - 1)/(L*S)***
where Z= weight-for-age z-score
X= weight of the child (from the case report form)
M= median weight (from the NCHS growth chart)
L= power in the Box-Cox transformation (from the NCHS growth chart)
S= generalized coefficient of variation (from the NCHS growth chart)

For this third study of *C. parvum* diarrhea, the Applicant concluded that while this study did not support the efficacy of a three-day course of nitazoxanide in this population, it is important in that it clearly demonstrates a non-effective dose in children with acquired immune deficiency syndrome. Data from children who failed the initial treatment and were treated with a second three-day course of nitazoxanide in an uncontrolled phase of this study suggested that a longer duration of treatment would be effective in treating diarrhea caused by *C. parvum* in this population.

***MO COMMENT**: Therefore, while clinical treatment effect of a 3 day course of NTZ was apparent over placebo in mainly malnourished but HIV seronegative children, children who were HIV seropositive (with AIDS) and more malnourished did not statistically exhibit clinical benefit from 3 day therapy of NTZ over placebo.*

Efficacy Conclusions for C. parvum Treatment in Children

For seeking the indication for treatment of diarrhea caused by *C. parvum* with a 3-day therapy of NTZ oral suspension in HIV sero-negative children (ages 1 to 11), the applicant has provided data from two studies (Egyptian study 98-002 and Zambian study 3007). The third study (Zambian study 3008) was a study in HIV sero-positive children where treatment effect of 3-day NTZ therapy over placebo was not demonstrated. It is important to point out that the population of children from the Zambian studies was mainly malnourished children. When the two studies (98-002 and 3007) are pooled for children with *C. parvum* in the stool at the screening visit (children with mixed infections and children who did not take medication were excluded), 39 children in the NTZ arm and 46 children in the placebo arm constituted the comparison groups. For children, both clinical response (66.7% NTZ vs. 30.4% placebo; p=.0011) and parasitological response (59% NTZ vs. 21.7% placebo; p=.0007) rates are statistically significant. However, there was inconsistent correlation between clinical and micro endpoints across treatment subgroups with kappa statistic values for the overall comparison (ks = .182 for NTZ group and ks = .218 for the placebo group). Hence, although the numbers are small, efficacy has been demonstrated in terms of clinical endpoint (treatment of diarrhea caused by *C. parvum* in children; NDA 21-498). Microbiological endpoint has not been adequately addressed since the parasitological assessments (parasitological assessment by the acid-fast stain method with one drop of stool sample and confirmed by immunofluorescent assay method in only 9 patients) were less than optimal and the correlation with clinical response is poor.

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Diarrhea caused by Giardia Lamblia in Children: NDA 21-498

Efficacy of NTZ for G. lamblia diarrhea (clinical and microbiological claims) in patients taking the 100 mg/ 5 mL Oral Suspension (Children 2-11 years)

Efficacy evidence of NTZ for G. lamblia diarrhea in children taking the oral suspension came from one active-controlled study.

Study RM-NTZ-99-010 was conducted to demonstrate non-inferiority of a three day course of nitazoxanide suspension compared to a five day course of metronidazole suspension in treating diarrhea caused by Giardia lamblia in children. The study was conducted in Cajamarca, Peru between January and March, 2000. The study was a randomized, single-blind, controlled study with the parasitologist being blinded as to the treatment group assignment. The study was designed with reference to published guidelines for evaluation of new drugs for treatment of diarrhea caused by G. lamblia [Cooperstock et al. Evaluation of New Anti-Infective Drugs for the Treatment of Diarrhea Caused by Giardia lamblia. *Clinical Infectious Diseases 1992; 15 (suppl 1): S244-8*]. Children from 2 to 11 years of age with acute or chronic diarrhea and cysts of *G. lamblia* in a stool sample within 7 days prior to inclusion were eligible for enrollment in the study. Diarrhea was defined as > 3 unformed stools per day or unformed stools without increased stool frequency for more than 4 weeks. Unformed stools could be either soft (taking the shape of the container) or watery (can be poured or soaks into a diaper). Children with positive enzyme immunoassay of fecal samples for Entamoeba histolytica or Cryptosporidium parvum, children using any drug with antiprotozoal activity within 2 weeks of enrollment, and children known to have or suspected of having AIDS were excluded from the study.

> ***MO COMMENT**: NDA 21-498 is for age range 1-11 years although for this giardia study, children were enrolled down to 2 years only. Nevertheless, since the pathophysiology of the giardia disease and pharmacokinetic parameters are similar in 1 and 2 year olds, and since data is available in 1 year olds from Cryptosporidiosis studies, it is reasonable to keep the 1 – 11 years as the treatment age range.*

The children received 5 mL (ages 2-3) or 10 mL (ages 4-11) of nitazoxanide 100 mg/5 mL suspension twice daily for 3 days or 5 mL of a 125 mg/5 mL (ages 2-5) or 250 mg/5 mL (ages 6-11) metronidazole suspension twice daily for 5 consecutive days. Patients were instructed to take their mediation with food.

The Applicant chose the control drug to be metronidazole because it is the most widely used product in the world for treating giardiasis. It is not approved for treating giardiasis in the United States. The guidelines used to design this trial suggest that quinacrine, furazolidone or metronidazole may be used as a control drug and that the cure rates for quinacrine (85-95%) and metronidazole (80-95%)

should be expected to be higher than that of furazolidone (70-80%). The formulation of metronidazole used in the study was a 125 mg or 150 mg/5ML suspension depending on the age of the children.

> ***MO COMMENT:*** *The Applicant was asked to submit a translated package insert of metronidazole from Peru. The review of the translated package insert showed that Giardiasis is listed under the INDICATIONS section. The product (Flagyl®) was manufactured by Rhone-Poulenc Rhorer. The treatment regimens used were the approved regimens for use of the Flagyl® suspension in foreign countries. In consultation with the FDA NTZ team, it was determined that this active comparator was acceptable given that it was an approved regimen for use in Peru. It is also important to point out that the recommended dosing for Flagyl® is a 3 times a day frequency. The Applicant used a 2 times a day regimen in this study. However, given that the efficacy rate for metronidazole arm resulted in an efficacy rate that is expected (in the 80% range), this dosing was acceptable.*

The primary endpoint of the study was the clinical response of the patients at the day 7 follow-up visit with parasitological response being evaluated as a secondary endpoint. The sample size (55 patients per treatment group) was calculated to provide 80% power to detect a difference of 20% in the response rates of the two treatment groups (consistent with the published guidelines).

Data was analyzed for an intent-to-treat population (primary analysis) and for a per-protocol population which excluded one child in the metronidazole treatment group that did not return for the day 7 follow-up examination and 14 children (7 from each group) who reported missing at least one dose of study medication.

One hundred and ten (110) children were enrolled in the study. The clinical and parasitological responses by treatment group are presented in Table 4-3. The primary efficacy analysis was conducted on an intent-to-treat basis using data from all patients enrolled. A secondary analysis was conducted for a "per-protocol" population that excluded patients who failed to take all of the study medication or return for follow-up evaluation.

Table 22: Applicant's Efficacy Summary; Study 99-010

	Nitazoxanide	Metronidazole	Diff.	95% CI
Intent-to-Treat				
Clinical response	47/55 85%	44/55 80%	+5.4%	-8.9%, +19.7%
Age 4-11	34/41 83%	35/44 80%		
Age 2-3	13/14 93%	9/11 82%		
Parasitological resp	39/55 71%	41/55 75%	-3.6%	-20.1%, +12.6%
Age 4-11	30/41 73%	32/44 73%		
Age 2-3	9/14 64%	9/11 82%		

	Nitazoxanide	Metronidazole	Diff.	95% CI
Per-Protocol				
Clinical response	43/48 90%	39/47 83%	+6.6%	-7.7% +21.0%
Age 4-11	31/35 89%	31/37 84%		
Age 2-3	12/13 92%	8/10 80%		
Parasitological resp	39/47 83%	37/46 80%	+0.8%	-15.1%, +16.9%
Age 4-11	30/35 86%	29/37 78%		
Age 2-3	9/12 75%	8/9 89%		

***MO COMMENT**: Although non-inferiority for both clinical response and parasitological response is shown when the data is analyzed for the per-protocol population, only clinical response in the Intent-to-treat analysis met the set lower bound of the non-inferiority margin. The parasitological response rate for nitazoxanide just missed the pre-set lower bound of the margin.*

Since, this is the only study (and it is active-controlled, single-blinded, 55 patients total in the nitazoxanide arm) that the Applicant has submitted for this indication in this age group using the suspension formulation, this statistically lacking result cannot be compensated enough by the clinical evidence to support the claim of parasitological response.

Moreover, as was discussed under the seeking of parasitological claim for C. parvum diarrhea, the microbiological and laboratory assessments in this study were less than optimal. The following is a table from the team's microbiologist, D. Suvarna's review. For the G. lamblia studies, she pointed out that what is usually recommended is examination of 3 or more stool samples AND staining of the smear are recommended.

In the case of study 010, only direct microscopy of concentrated and unconcentrated stool samples were performed with no attempt at quantification. There was no immunoassay done to confirm and contrast the results.

***Giardia* studies**	**Parasitological examination methods**	
— (n =100; 22 with Giardiasis)	Direct microscopic examination of unconcentrated and concentrated stool	— immunoassay (16 patients)
RM-99-010 (children) (n =110)	Direct microscopic examination of unconcentrated and concentrated stool- **NO quantitative results**	

However, this is the only study of the 5 studies submitted by the Applicant where the Kappa Statistic is consistent and relevant. The following table is from the Team's Statistician, Dr. Zalkikar's presentation on this study 010 that shows the analysis of the ITT population.

Table 23: FDA Analysis – Efficacy Responses with Kappa Statistic; Study 010

Age	Trt	N	Clinical Resp	95% CI	Parasite Resp	95% CI	Kappa (s.d.)
			% Well		% E		
<4	MET	11	81.82	(-15.44,37.52)	81.82	(-51.43,16.37)	.389 (.353)
	NTZ	14	92.86		64.29		.243 (.209)
4-11	MET	44	79.55	(-13.19,19.95)	72.73	(-18.46,19.34)	.192 (.161)
	NTZ	41	82.93		73.17		.298 (.168)
Pooled	MET	55	80.00	(-8.64,19.54)	74.55	(-20.3, 13.0)	.227 (.147)
	NTZ	55	85.45		70.91		.276 (.139)

MO COMMENT: *Clinical response is statistically comparable between the two arms but the parasitological response misses the lower bound of the confidence interval. Kappa coefficients are consistent across treatment arms.*

Efficacy Conclusions for G. lamblia Treatment in Children

For seeking the indication for treatment of diarrhea caused by *G. lamblia* with a 3-day therapy of NTZ oral suspension in HIV sero-negative children (ages 1 to 11), the applicant provided data from a single-center study (Study in Peru 99-010). This was an active-controlled study with metronidazole as the comparator and *G. lamblia* as the sole baseline pathogen. The ITT population consisted of 110 patients with 55 in the NTZ group and 55 in the metronidazole group. It should be noted that children enrolled were actually 2 – 11 years in this study. The clinical response in children treated with NTZ (85.5% NTZ vs. 80% placebo; CI –8.64, 19.54) was shown to be non-inferior to that of metronidazole (an approved drug for treatment of giardiasis in Peru). However, for parasitological response (70.9% NTZ vs. 74.6% placebo; CI –20.3, 13), the rate for NTZ just missed the lower bound of the –20% CI. The correlation between clinical and microbiological endpoints (by kappa statistic) were slightly better and consistent across subgroups in this study in comparison to the previous 4 studies with ITT kappa coefficients at (+.227 for NTZ group and +.276 for the metronidazole group). Hence, although the numbers are small, efficacy has been demonstrated in terms of clinical endpoint (treatment of diarrhea caused by *G. lamblia* in children who are HIV negative). NDA 21-498 is for age range 1-11 years although for this giardia study, children were enrolled down to 2 years only. Nevertheless, since the pathophysiology of the giardia disease and pharmacokinetic parameters are similar in 1 and 2 year olds, and since data is available in 1 year olds from Cryptosporidiosis studies, the age range to be treated can remain as 1 – 11 years. The parasitological endpoint (

) was not met statistically in this study.

Integrated Efficacy Summary Conclusions

Guidelines for the development of anti-infective drugs for treatment of diarrhea including diarrhea caused by *Giardia lamblia* were published in Clinical Infectious Diseases 1992; 15 (Suppl 1): S244-8. There are no guidelines for development of anti-infective drugs for treatment of diarrhea caused by *C. parvum*.

The following is a summary table of efficacy for these two NDA applications. On top are relevant excerpts taken from the above guideline since this is the document that the Applicant has relied on to conduct the clinical trials of the current NDAs under review. The 5 pivotal trials are then listed under the corresponding items.

MO COMMENT: To reiterate, substantial evidence of efficacy for nitazoxanide was shown for treatment of C. parvum and G. lamblia diarrhea (clinical response only) in pediatric patients ages 1- 11 years (NDA 21-498).

Table 24: Efficacy Assessment and Response Summary

Study	Minimal Diag Criteria	Inclu/ Exclu Criteria	Pre	Day 0	Tx	Clinical Assess Day	Clinical Assess Resp	Parasit Assess Day	Parasit Assess Resp	KAPPA Clin/micro correlate?
IDSA Guideline For study of Giardia	Diarrhea: Passage of ≥3 unformed stools/d Must have *G. lamblia* as sole pathogen	Adults must also have enteric symptom Exclude if presence of an additional intestinal pathogen	-48 hours to 0 hour Do clinical. Lab. and stool exam	Start Tx Do clinical. Lab. and stool exam	Maintain diary Median time from tx to passage of last unformed stool	48 hours to 7 days after tx finishes	Well: first 24 hrs with only 2 soft stools or first 48 hrs w/no unformed stools *Cont* Illness: Failure	At least 48 hours after the last dose of med	At least two stool samples Eradicate Persistent	
Egypt Crypto Adults Kids	Multiple Pathogens	Not all w/symp	Stool exam w/in 7d	No stool exam	3 days tx Adults 3 v 6d NS Kids 3.5 v 6d (p=.0001)	7 ± 2 d	Adults ITT or by Crypt (NS) Kids 88 v 38% (p=.0004)	7± 2 d 10 ± 2 d	Adults ITT or by Crypt (NS) Kids 75 v 24% (p=.0001)	Kids .333 (NTZ)
Zambia HIV- Kids	Crypto only	Malnour sick	Stool exam w/in 7d	Stool exam Excluded in ITT if neg	Poor diary	7 ± 2 d	56% v 22% (P=.037)	7 ± 2 d 10 ± 2 d	52 v 14% (P=.007)	.096 (NTZ)
Zambia HIV+ Kids	Crypto only	AIDS sick	Stool exam w/n 7d	Stool exam	Poor diary	7 ± 2 d	No effect over placebo	7 ± 2 d 10 ± 2 d	No effect over placebo	
Peru ActiveC Kids	Giardia only	Single pathogen study	Stool exam w/in 7d	Stool exam	3d v 5d tx 4d v 4d st	7 ± 2 d	85 v 80% (-.10, .21)	7 ± 2 d 10 ± 2 d	71 v 75% (-.21, .13)	NTZ: .276 MTN .227

Integrated Review of Safety

Summary of Safety Data from the 5 Pivotal Studies constituting [redacted] NDA 21-498
(includes both adults who took **Tablets** and children who took the Suspension)

Table 25: Integrated Safety Summary of the Five Pivotal Studies

Study	Exposure # to NTZ	AE	Which arm (see next table)	Analysis of AE	Serious AE	Death	Labs
98-002	25 adults 24 children	26 total; 24 pts (11kids; 13adults) 25 AEs mild 1 AE moderate: dizziness (NTZ)	12 AE for NTZ 14 AE for placebo OR NTZ: 12AE/11pts PLA:14AE/13pts	No diff compared to placebo	none	none	None done
02-3007	25 children (total of 47 treatments due to re-tx)	15 total by 8 pts 3 mild (vomiting) 1 mod (tetany) 11 severe	2 AE for NTZ 13 AE for placebo OR NTZ; 2 AE/2 pts PLA: 13 AE/6 pts	P<.0001 For AE P=.018 For #pts	11 AEs from 4 pts PLA	4 all "not related" (Placebo)	No diff Bet Day 0 and 7
02-3008	25 children (total of 55 treatments due to re-tx)	18 Total by 14 pts 1 mild (anemia) 17 severe	8 AE for NTZ 10 AE for placebo OR NTZ: 8AE/ 7pts PLA: 10 AE 7pts	No diff Compared to placebo	17 AEs from 13 pts	13 death 7 placebo 6 NTZ "not related" (Placebo)	No diff Bet Day 0 and 7
[redacted]	47 adults	16 total by 13 pts 10 AEs mild 5 AEs mod (dizziness, nausea) 1 AE severe	11 AEs for NTZ 5 AEs for placebo OR NTZ; 11AE/ 7 pts PLA: 5 AE/ 5 pts	No diff Compared to placebo	1 due to status asthmaticus	1 due to status asthmaticus "not related"	None done
99-010	48 children 13 (2-3 yrs) 35 (4-11 y)	28 total by 25 pts all mild	14 AEs for NTZ 14 AEs for MTN OR NTZ:14 AE/13pts MTN: 14 AE/13pts	No diff compared to MTN	none	none	None done
In Total	72 adults 122 children [redacted] Control 70 adults 129 children	103 AEs total NTZ + Control 26 adults with AE 58 kids with AE	47 AE total NTZ 56 AE total Cont OR NTZ: 14 adultsAE 26 kidsAE Cont: 11 adultsAE 33 kids AE	4 studies no diff 1 study with diff	1 adult 28 AEs from 17 kids	18 death total 12 placebo 6 NTZ	2 no diff 3 none done

PLA: placebo; MTN: metronidazole

Major safety issues were not associated with the use of NTZ for 3 days in the 5 studies submitted to the two NDAs. In total, there were 47 adverse events across the 5 studies for the NTZ arms and 56 adverse events in the control arms with the most common adverse event being abdominal pain (13 events in NTZ arm, 12 events in the control arm). The overall adverse event rates across the 5

studies pooled were 21% overall for NTZ and 22% for control. There were no differences in the rate or character of adverse events between the NTZ treated arms and control arms for 4 of the 5 studies. In study 3007 (Zambian study in HIV sero-negative malnourished children), adverse events in the NTZ-treated arm (including death) were significantly less (2 AE for NTZ, 13 AE for placebo: p<.0001) in comparison to the placebo arm. There were 18 deaths in all, across the 5 studies (6 in the NTZ arm and 12 in the placebo arm). All 6 of the deaths in the NTZ arm were form study 3008 (Zambian study in HIV sero-negative children) and the deaths were deemed "not related" to treatment. The following table lists the cumulative numbers for each adverse event identified throughout the five pivotal studies.

Table 27: Cumulative Adverse Event /By Event Counts Over The Five Studies (— 21-498)

Adverse Event	Nitazoxanide	Placebo/Metronidazole
Body as a Whole		
Fever	-	1
Sepsis	3	9
Death	-	5
Refeeding Syndrome	-	2
Digestive System		
Abdominal pain	13	12
Anorexia	2	1
Dry Mouth	1	0
Diarrhea	2	5
Nausea	1	-
Vomiting	1	2
Constipation	1	0
Dyspepsia	2	2
CNS System		
Headache	1	4
Dizziness	1	3
Drowsiness	4	2
Cardiovascular System		
Heart Failure	-	2
Viral myocarditis	1	-
Urogenital System		
Urine discoloration	5	1
Dysuria	1	1
Miscellaneous		
Facial edema	0	1
Anemia	-	2
Pneumonia	2	-
Tetany	-	1
Metabolic Acidosis	2	-

MO COMMENT: *There does not appear to be any major safety issues identified with this new molecular entity given orally for 3 days across the 5 pivotal studies that the Applicant has submitted to both NDA applications. Since only NDA 21-498 (the Suspension formulation for*

pediatric patients ages 1 – 11 years) is being recommended for approval at this time, it would be important to see if there are any specific safety issues related to the drug ingested in children and/or the drug in suspension formulation. (next section)

APPEARS THIS WAY
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ON ORIGINAL

Summary of Safety Data from the 4 Pivotal Studies constituting NDA 21-498
(includes only children who took the Suspension)

Adverse Events

Only study —— was an adult/adolescent only study. Study 98-002 had children, adolescents and adults while the 3 remaining studies were children only studies (See Table 25 above). The following table compares the adverse event incidences (cumulative of the 4 studies, causality mainly "not-related" or "possibly-related").

Table 26: Adverse Events Incidence for Children 1-11 years; NDA 21-498

Studies	NTZ Suspension	Control
98-002 Egypt	4 AEs in 4 pts	7 AEs (placebo) in 7 pts
02-3007 Zambia	2 AEs in 2 pts	13 (placebo) in 6 pts
02-3008 Zambia	8 AEs in 7 pts	10 (placebo) in 7 pts
—— Egypt	---	---
99-010 Peru	14 AEs in 13 pts	14 (metronidazole) in 13 pts
Total AE patients Over Total # in Study	26 /122	33 /129
AE Incidence	**21%**	**26%**

***MO COMMENT**: Looking at just the children who took the suspension formulation (NDA 21-498) does not change the overall Adverse Event characteristics. NTZ was well tolerated when compared to the controls. The adverse events were comparable between the study drug and controls for studies 98-002, 02-3008, and 99-010. It is the study from Zambia (02-3007) in HIV seronegative malnourished children that showed the imbalance in favor of the NTZ arm (p<.0001). The higher adverse event number in the placebo arm comes from the four children who died on study (all in the placebo arm; see section below under Deaths).*

Severe Adverse Events

All the adverse events reported from children receiving the nitazoxanide in studies 98-002, 02-3007, and 99-010 were recorded as "mild'. There were 11 severe AEs from study 02-3007 but all were from the 4 patients who died during study in the placebo arm. There were 17 severe AEs from 13 patients reported from study 02-3008. The following is a breakdown of the severe AEs by treatment arm.

Table 27: Severe Adverse Events Incidence for Children 1-11 years; NDA 21-498

Studies	NTZ Suspension	Control
98-002 Egypt	none	none
02-3007 Zambia	none	11 Severe AEs* from 4 pts sepsis n=4 death n=4 heart failure n=1 refeeding syn. n=1 diarrhea n=1 *all from the 4 patients who died
02-3008 Zambia	8 severe AEs from 7 pts sepsis n=3 pneumonia n=2 acidosis n=2 myocarditis n=1	9 severe AEs from 6 pts sepsis n=5 anemia n=1 refeeding syn n=1 heart failure n=1 diarrhea n=1
—— Egypt	---	---
99-010 Peru	none	none
Total AE patients Over Total # in Study	7 /122	10 /129
AE Incidence	**5.7%**	**7.8%**

Deaths on study

There were no deaths reported for children who were HIV negative receiving nitazoxanide for 3 days. In Study 02-3007, there were 4 deaths in young malnourished HIV seronegative children in the placebo arm with the probable cause of death as "sepsis, not-related" to study. No cultures or autopsy results were available to verify the cause of death. In the HIV seropositive children study, there were 13 deaths in total out of 50 children enrolled. Six deaths were in the NTZ arm and 7 in the placebo arm. The following is a breakdown of all deaths in studies involving children 1-11 years old.

Table 28: Deaths During Study for Children 1-11 years; NDA 21-498

Studies	NTZ Suspension	Control
98-002 Egypt	none	none
02-3007 Zambia	none	4 deaths Probable cause of death: sepsis with malnutrition n=2 sepsis with diarrhea n=1 sepsis with refeeding syn n=1
02-3008 Zambia	7 deaths Probable cause of death: sepsis n=3 pneumonia n=2 acidosis n=1 myocarditis n=1	6 deaths Probable cause of death: sepsis n=5 diarrhea n=1
—— Egypt	---	---
99-010 Peru	none	none

Studies	NTZ Suspension	Control
Total AE patients Over Total # in Study	7 /122	10 /129
AE Incidence	**5.7%**	**7.8%**

Laboratory Monitoring

There were no blood tests performed in the Egypt and Peru studies. Only the two Zambian studies (02-3007 and 02-3008) had laboratory monitoring performed. The tests reported were for hematology (Hgb, Hct, RBC, MCHC, MCH, MCV, WBC, neutrophils, lymphs, monos, eosinos, basos, platelets); blood chemistry (SGOT, SGPT, GGT, ALP, creatinine, glucose, sodium, potassium); urinalysis (protein, blood, glucose, ketones, pH, specific gravity, bilirubin). These laboratory tests were performed at baseline and then repeated at day 7-10 follow-up visit. No laboratory adverse events were reported. There were no treatment related changes detected in laboratory parameters. There were a large number of clinically significant laboratory abnormalities, primarily anemia, elevated white cell counts and elevated liver function tests, which existed at baseline and which were attributable to the children's malnutrition and poor health.

> ***MO COMMENT**: No additional or different safety issues were identified when just children 1-11 years (who received the suspension formulation of nitazoxanide) of age were analyzed. For the population that is being granted approval for the treatment of diarrhea due to C. parvum or G. lamblia (children ages 1 – 11 years who are HIV negative) with 3 day therapy of nitazoxanide, there were no severe adverse events or deaths in the submitted studies. The incidence of adverse events (all recorded as "mild" in the NTZ arm) were comparable to the adverse events in the control arm.*
>
> *The reasons for the discrepancy in the 3007 study in the number of deaths (0 in the NTZ arm and 4 in the placebo arm) were explored in great detail. There were no baseline characteristics or concomitant treatment differences between the two arms that could explain the discrepancy.*
>
> *Laboratory monitoring was sparse. Only the two studies from Zambia had laboratory testing performed which included hematology, liver function tests, and chemistry. However, serum bilirubin and albumin levels were not part of the panel. There were many clinically significant laboratory abnormalities in these sick populations of malnourished children, but a pattern of abnormal association with nitazoxanide administration was not evident.*

Safety Database of the All Children ages 1- 11 years in the Nitazoxanide Clinical Program

Narratives of Significant Adverse Events

There were only three adverse events that were classified as serious and probably related to nitazoxanide. All three were from one child with AIDS-related cryptosporidiosis.

Study no.: UMD-95-009A
Patient no. 135

Events
Diarrhea - Probably Related
Vomit - Probably Related
SGOT Inc- Probably Related

Narrative
9 year old female. Treatment was initiated on 2/10/96 at a dose of 9.5 mg/kg b.i.d. TPN was also initiated at the same time as nitazoxanide. Baseline laboratory results indicated elevated AST (316, normal range 16-46) and ALT (73, normal range 10-35). On 2/16/96, AST was 749 and ALT was 295. The patient was admitted to the hospital on 2/17/96 due to the elevated liver function tests and increased diarrhea and vomiting, and the study medication was permanently discontinued on that date. On the date of discontinuation, AST had dropped to 632 with ALT of 342. On 2/20/96, AST was 244, and ALT was 205. The investigator noted that TPN could not be ruled out as a possible cause of the elevated liver function tests. Transitory elevations of transaminases are common with the initiation of TPN. The patient was hospitalized on March 12, 1996 with frequent diarrhea and vomiting related to cryptosporidiosis, was discharged on hospice care and died on 4/6/96.

> ***MO COMMENT**: Given the history of this patient, the Applicant did not consider any of these events to be related to use of nitazoxanide. This conclusion is acceptable.*

Most commonly reported event: "PAIN ABDO"

In controlled studies, there were no significant differences in the frequency of reporting of abdominal pain between the nitazoxanide and control groups.

Adverse Reactions from HIV negative Children (n=613)

In controlled and uncontrolled clinical studies of 613 pediatric patients who received nitazoxanide suspension, the most frequent adverse events reported regardless of causality assessment were: abdominal pain (7.8%), diarrhea (2.1%), vomiting (1.1%) and headache (1.1%). These were typically mild and transient in nature. In placebo-controlled clinical trials, the rates of occurrence of these events did not differ significantly from those of the placebo. None of the 613 pediatric patients discontinued therapy because of adverse events.

Adverse events occurring in less than 1% of the patients participating in clinical trials are listed below:
Digestive System: nausea, anorexia, flatulence, appetite increase, enlarged salivary glands.
Body as a Whole: fever, infection, malaise.
Metabolic & Nutrition: increased creatinine, increased SGPT.
Skin: pruritus, sweat.
Special Senses: eye discoloration.
Respiratory System: rhinitis.
Nervous System: dizziness.
Urogenital System: discolored urine.

Significant AE: none
Death: none

> ***MO COMMENT***: *In this database of over 600 children ages 1-11 years who are HIV negative, nitazoxanide given orally in suspension formulation for 3 days appears to have a benign safety profile.*

Applicant's Safety Tables

The following 5 tables were selected from the September 23, 2002 submission by the Applicant as part of the presentation of the safety database for pediatric patients ages 1-11 years upon request from the FDA. These selected tables were taken directly from the Applicant's submission and shown here. In order of appearance, they are as follows:

- Nitazoxanide Exposure for Children Ages 1 through 11
- Controlled Studies in Children ages 1 through 11 (Non-AIDS patients)
- Uncontrolled Studies in Children ages 1 through 11 (Non-AIDS patients)
- Adverse Events for All Children Ages 1 through 11
- Adverse Events for All Children Ages 1 through 11 in Controlled Studies

Table 6: Nitazoxanide Exposure for Children Ages 1 through 11

	All Children	Number of Patients Exposed to Nitazoxanide							
		<3 d	3 d	>3 d-1 wk	>1 wk-2 wk	>2 wk-1 m	>1 m-3 m	3 m-6 m	> 6 m
Entire population	658	49	492	107	6	1	1	1	1
By sex:									
Male	337	30	253	49	4	-	1	-	-
Female	321	19	239	58	2	1	-	1	1
By AIDS status:									
Non-AIDS patients	613	48	470	94	1	-	-	-	-
AIDS patients	45	1	22	13	5	1	1	1	1
By age:									
1 yr-1 yr 11 m	54	1	33	17	3	-	-	-	-
2 yrs - 2 yrs 11 m	55	2	44	8	1	-	-	-	-
3 yrs - 3 yrs 11 m	24	4	20	-	-	-	-	-	-
4 yrs - 4 yrs 11 m	27	5	20	1	1	-	-	-	-
5 yrs - 5 yrs 11 m	35	6	24	3	-	-	-	1	1
6 yrs - 6 yrs 11 m	60	2	49	8	-	1	-	-	-
7 yrs - 7 yrs 11 m	71	5	50	16	-	-	-	-	-
8 yrs - 8 yrs 11 m	82	4	64	12	1		1		
9 yrs - 9 yrs 11 m	70	5	49	16	-	-	-	-	-
10 yrs-10 yrs 11m	101	9	75	17	-	-	-	-	-
11 yrs-11yrs 11 m	79	6	64	9	-	-	-	-	-
By Dose:									
Ages 12-47 months									
100 mg q.d.	6	6	-	-	-	-	-	-	-
100 mg b.i.d.	127	1	97	25	4	-	-	-	-
Ages 4 - 11 years									
160 mg q.d.	6	6	-	-	-	-	-	-	-
200 mg q.d.	5	5	-	-	-	-	-	-	-
1000 mg q.d.	7	-	7	-	-	-	-	-	-
2000mg q.d.	6	6	-	-	-	-	-	-	-
200 mg b.i.d.	443	25	359	54	2	1	-	1	1
400 mg b.i.d.	1	-	-	-	-	-	1	-	-
500 mg b.i.d.	52	28	24	-	-	-	-	-	-
1000 mg b.i.d.	5	-	5	-	-	-	-	-	-

Abbreviations: d= day, wk= week, m= month, yrs= years, q.d.= once per day, b.i.d.= every 12 hours

For list of studies contributing patients, a description of the studies and the number of patients contributed, please refer to Tables 1 through 5.

Reconciliation of children enrolled in studies (see Tables 1 - 5) to total children exposed

Total children ages 1 through 11 enrolled in studies listed in Tables 1 through 5	885
Less patients randomized to control groups	245
Less patients enrolled in nitazoxanide treatment groups but not exposed (1 from each of studies RM-NTZ-99-017, RM-NTZ-98-002 and RM-96.401)	3
Add children randomized to receive placebo who were subsequently re-treated with nitazoxanide (8 from RM02-3007, 13 from RM02-3008)	21
Total children ages 1 through 11 exposed to nitazoxanide	658

Table 2 CONTROLLED STUDIES IN CHILDREN AGES 1 THROUGH 11 (NON-AIDS PATIENTS)

Protocol no.	Principal Investigator	Design	Indication studied	Age, sex, race	No. subjects enrolled	Dose	Frequency	Duration	Status	CRFs Available	Full report
RM-NTZ-98-002	Samir M. Kabil, MD	Double blind, placebo-controlled	Diarrhea caused by *Cryptosporidium parvum*	1-11 yrs 29 M/21F 50 C	12 13 25 50 total	100 mg 200 mg Placebo	b.i.d. b.i.d. b.i.d.	3 days 3 days 3 days	Completed	Yes	
RM-NTZ-99-010	Juan Jave Ortiz, MD	Randomized, single-blind, active-controlled	Diarrhea caused by *Giardia lamblia*	2-11 yrs. 54 M/56 F 110 H	41 14 26 29 110 total	200 mg 100 mg MTZ 250mg MTZ 125 mg	b.i.d. b.i.d. b.i.d. b.i.d.	3 days 3 days 5 days 5 days	Completed	Yes	
RM02-3007	M. Paul Kelly, MD	Randomized, double-blind, placebo-controlled	Diarrhea caused by *Cryptosporidium parvum*	12-35 months 34 M/16 F 50 B	25 25 50 total	100 mg Placebo	b.i.d. b.i.d.	3 days 3 days	Completed	Yes	
RM-NTZ-99-015	Juan Jave Ortiz, MD	Randomized, single-blind, active-controlled	Enteric helminth infection	3-11 yrs. 32 M/38 F 70 H	1 34 35 70 total	100 mg 200 mg ALB 400 mg	b.i.d. b.i.d. q.d.	3 days 3 days 1 day	Completed	Yes	
RM-NTZ-99-017	Juan Jave Ortiz, MD	Randomized, single-blind, active-controlled	Enteric helminth infection	2-11 yrs. 20 M/20 F 40 H	1 19 20 40 total	100 mg 200 mg ALB 400	b.i.d. b.i.d. q.d.	3 days 3 days 1 day	Completed	Yes	
RM-NTZ-99-019	Juan Jave Ortiz, MD	Randomized, single-blind, active-controlled	Enteric helminth infection	4-11 yrs. 49 M/51 F 100 H	50 50 100 total	200 mg PZQ 25 mg/kg	b.i.d. q.d.	3 days 1 day	Completed	Yes	
RM-NTZ-99-014	Juan Jave Ortiz, MD	Double-blind, placebo-controlled	Fascioliasis	2-11 yrs. 21 M/29 F 50H	1 39 10 50 total	100 mg 200 mg Placebo	b.i.d. b.i.d. b.i.d.	7 days 7 days 7 days	Completed	Yes	

Table 3 CONTROLLED STUDIES IN CHILDREN AGES 1 THROUGH 11 WITH AIDS

Protocol no.	Principal Investigator	Design	Indication studied	Age, sex, race	No. subjects enrolled	Dose	Frequency	Duration	Status	CRFs Available	Full report
RM02-3008	M. Paul Kelly, MD	Randomized, double-blind, placebo-controlled	Diarrhea caused by *Cryptosporidium parvum*	1-7 yrs. 27 M/23 F 50 B	24 1 25 50 total	100 mg 200 mg Placebo	b.i.d. b.i.d. b.i.d.	3 days 3 days 3 days	Completed	Yes	NDA

M = Male, F = Female
C = Caucasian, B = Black, H = Hispanic, A = Asian, O = Other
yrs= years, q.d.= once per day, b.i.d.= every 12 hours, MTZ= metronidazole, ALB= albendazole, PZQ= praziquantel

Table 4 UNCONTROLLED STUDIES IN CHILDREN AGES 1 THROUGH 11 (NON-AIDS PATIENTS)

Protocol no.	Principal Investigator	Design	Indication studied	Age, sex, race	No. subjects enrolled	Dose	Frequency	Duration	Status	CRFs Available	Full report
CL-NTZ-95-001	Raul Romero Cabello, MD	Phase III, open-label	Intestinal parasitic infection	5-11 yrs. 53 M/72 F 125 H	125 total	200 mg	b.i.d.	3 days	Completed	Yes	NDA
PRC-94-NTZ-03	H. Abaza, MD; . .	Phase III, open-label	Intestinal parasitic infection	1-11 yrs. 74 M/57F 131 C	30 101 131 total	100 mg 200 mg	b.i.d. b.i.d.	3 days 3 days	Completed	Yes	
RM-94-NTZ-04	H. Abaza, MD; .	Phase II/III, dose-range, open-label	Fasciolinsis	5-11 yrs. 5 M/9 F 14 C	14 total	200 mg	b.i.d.	6 or 7 days	Completed	Yes	
RM-96.401	David Botero, MD	Phase II, dose-range, open-label	Intestinal parasitic infection	6-11 yrs. 35 M/36 F 71 H	6 7 25 5 28 71 total	2000 mg 1000 mg 500 mg 1000 mg 500 mg	q.d. q.d. b.i.d. b.i.d. b.i.d.	1 day 3 days 3 days 3 days 7 days	Completed	Yes	

Table 5 UNCONTROLLED STUDIES IN CHILDREN AGES 1 THROUGH 11 WITH AIDS

Protocol no.	Principal Investigator	Design	Indication studied	Age, sex, race	No. subjects enrolled	Dose	Frequency	Duration	Status	CRFs Available	Full report
UMD-95-009 A	Multiple	Open-label, compassionate use	Diarrhea caused by *Cryptosporidium parvum*	4-9 yrs. 4 F 2 B/2 H	4 total	200 mg	b.i.d.	Not limited	Completed	Yes	NDA
UMD-95-009 B	Multiple	Randomized, open-label, compassionate use	Diarrhea caused by *Cryptosporidium parvum*	5-8 yrs. 2 M/1 F 1 C/2 B	2 1 3 total	200 mg 400 mg	b.i.d. b.i.d.	Not limited	Completed	Yes	

M = Male, F = Female
C = Caucasian, B = Black, H = Hispanic, A = Asian, O = Other
yrs= years, q.d.= once per day, b.i.d.= every 12 hours

Table 7: Adverse Events for All Children Ages 1 through 11 Exposed to Nitazoxanide (N=658)

Body system / Adverse event	Patients Reporting AEs		Severity and Relationship to Use of the Drug																			
			Mild				Moderate				Severe				Life-threatening				Not Recorded*			
	Number	%	N	U	P	PR	N	U	P	PR	N	U	P	PR	N	U	P	PR	N	U	P	PR
BODY																						
PAIN ABDO	48	7.3	1	1	23	7	-	-	2	-	-	-	-	-	-	-	-	-	-	-	14	-
HEADACHE	7	1.1	2	-	1	3	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-
HIV SYND	3	0.4	-	-	-	-	-	-	-	-	1	-	-	-	2	-	-	-	-	-	-	-
SEPSIS	3	0.4	-	-	-	-	-	-	-	-	3	-	-	-	-	-	-	-	-	-	-	-
FEVER	2	0.3	-	-	-	1	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-
INFECT	1	0.2	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
MALAISE	1	0.2	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
DIG																						
DIARRHEA	14	2.1	-	-	4	2	-	-	-	-	-	-	-	1	-	-	-	-	-	-	7	-
VOMIT	8	1.2	1	-	2	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	4	-
NAUSEA	5	0.8	-	-	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3	-
PANCREATITIS	3	0.4	-	-	-	-	-	-	1	-	2	-	-	-	-	-	-	-	-	-	-	-
ANOREXIA	2	0.5	-	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
FLATUL	2	0.5	-	-	-	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
APPETITE INC	1	0.2	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
NAUSEA VOMIT DIAR	1	0.2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-
SALIV GLAND ENLARGE	1	0.2	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
MAN																						
ACIDOSIS	2	0.3	-	-	-	-	-	-	-	-	2	-	-	-	-	-	-	-	-	-	-	-
SGOT INC	1	0.2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-
SGPT INC	1	0.2	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
CREATININE INC	1	0.2	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
RES																						
PNEUMONIA	2	0.3	-	-	-	-	-	-	-	-	2	-	-	-	-	-	-	-	-	-	-	-
RHINITIS	1	0.2	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
SKIN																						
PRURITUS	1	0.2	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
SWEAT	1	0.2	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
NER																						
DIZZINESS	1	0.2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-
CV																						
MYOCARDITIS	1	0.2	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-
SS																						
EYE DIS	2	0.3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	-
UG																						
URIN ABNORM	1	0.2	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Relationship to use of the drug: N= not related, U=unlikely related, P= possibly related, PR= probably related

* Severity not specifically recorded in case report forms for these adverse events from studies PRC-94-NTZ-03 and RM-96.401. Sponsor believes these to be mild.

Table 8: Adverse Events for All Children Ages 1 though 11 in Controlled Studies

Body System Adverse Event	Nitazoxanide (N=294)		All Controls (N=245)		Placebo (N=85)		Metronidazole (N=55)		Anthelmintics (N=105)	
	No. with AEs	%	No. with AEs	%	No. with AEs	%	No. with AEs	%	No. with AEs	%
BODY										
PAIN ABDO	31	10.5	13	5.3	2	2.4	8	14.5	3	2.9
HEADACHE	7	2.4	7	2.9	1	1.2	4	7.3	2	1.9
SEPSIS	3	1.0	9	3.7	9	10.6	-	-	-	-
FEVER	1	0.3	1	0.4	-	-	1	1.8	-	-
DEATH	-	-	4	1.6	4	4.7	-	-	-	-
PERINATAL DIS	-	-	2	0.8	2	2.4	-	-	-	-
PAIN	-	-	1	0.4	1	1.2	-	-	-	-
INFECT	1	0.3	-	-	-	-	-	-	-	-
MALAISE	1	0.3	-	-	-	-	-	-	-	-
DIG										
DIARRHEA	4	1.4	6	2.4	4	4.7	-	-	2	1.9
VOMIT	3	1.0	3	1.2	1	1.2	1	1.8	1	1.0
ANOREXIA	2	0.7	1	0.4	1	1.2	-	-	-	-
NAUSEA	2	0.7	2	0.8	-	-	-	-	2	1.9
APPETITE INC	1	0.3	-	-	-	-	-	-	-	-
SALIV GLAND ENLARGE	1	0.3	1	0.4	-	-	-	-	1	1.0
DYSPEPSIA	-	-	1	0.4	1	1.2	-	-	-	-
RES										
PNEUMONIA	2	0.7	-	-	-	-	-	-	-	-
RHINITIS	1	0.3	-	-	-	-	-	-	-	-
COUGH INC	-	-	2	0.8	-	-	-	-	2	1.9
PHARYNGITIS	-	-	1	0.4	-	-	-	-	1	1.0
SKIN										
PRURITUS	1	0.3	-	-	-	-	-	-	-	-
SWEAT	1	0.3	-	-	-	-	-	-	-	-
MAN										
ACIDOSIS	2	0.7	-	-	-	-	-	-	-	-
CV										
MYOCARDITIS	1	0.3	-	-	-	-	-	-	-	-
HEART FAIL	-	-	2	0.8	2	2.4	-	-	-	-
UG										
URIN ABNORM	1	0.3	-	-	-	-	-	-	-	-
HAL										
ANEMIA	-	-	2	0.8	2	2.4	-	-	-	-
MS										
TETANY	-	-	1	0.4	1	1.2	-	-	-	-
NER										
DIZZINESS	-	-	1	0.4	1	1.2	-	-	-	-

See Tables 9-1 through 9-5 for details on severity and relationship of Adverse Events to use of study medication.

Safety Database for the Overall Nitazoxanide Clinical Program

For the overall NTZ clinical program (32 studies in total), the applicant listed the total number of NTZ exposure at 2,789 patients with 2,453 receiving at least 3 days of treatment. Among the 2,349 patients who did not have AIDS, no serious adverse events have been reported, and no drug-related adverse effects on hematology, clinical chemistry or urinalysis laboratory parameters were detected. The frequency and nature of adverse events reported by patients receiving nitazoxanide in double-blind placebo-controlled studies did not differ significantly from those of patients receiving the placebo.

Adverse experience in Clinical Studies; Overall Program

	Non-AIDS patients on NTZ	AIDS patients on NTZ
Most Common AE	Abdominal pain 6.7% Diarrhea 3.7% Headache 2.5% Nausea 2.4% (Mild, no different in rate from placebo)	Vomiting 19.1% Abdominal pain 10.9% Death 8.9% Discoloration sclera 8.9% Pneumonia 5.5% Discoloration of urine 5.2% (mainly serious in nature)
Serious AE	None reported	Many including death
Kids 1-11 years Deaths, Drop-outs Due to AE and Other **Serious** or Potentially Serious AE NTZ EXPOSURE CHART GIVES 658 children	None on NTZ 11 on Placebo	10 on NTZ 2 on placebo

The rates of occurrence of adverse events in AIDS patients treated with nitazoxanide during the course of double-blind placebo-controlled studies were, as a rule, not significantly different from the rates observed in patients treated with the placebo. As exceptions, in this population, treatment with nitazoxanide was associated with a significant increase in the rate of occurrence of yellow discoloration of the sclera and urine (both mild and transient in nature).: Treatment with nitazoxanide was also associated with a significant reduction in the rate of reporting diarrhea as an adverse event.

Controlled Studies in AIDS patients

INCREASE AE on NTZ	DECREASE AE on NTZ
Significant increase in the rate of occurrence of yellow discoloration of the sclera and urine (both mild and transient in nature) Eye discoloration NTZ: 32/193 (16.6%) Placebo: 0/149 (0%) Urine discoloration NTZ: 20/193 (10.4%) Placebo: 0/149 (0%)	Significant reduction in the rate of reporting diarrhea as an adverse event Diarrhea NTZ: 10/193 (5.2%) Placebo: 17/149 (11.4%)

Clinical Laboratory Evaluations: Overall Program Summary

Non-AIDS patients	Controlled Studies in AIDS pts	Uncontrolled Studies in AIDS pts
N=1928 (uncontrolled patients) and N=363 (controlled patients) in total had laboratory evaluations. One case of creatinine increase, 9 cases of anemia, 15 cases of increases in SGPT, 2 cases of leukocytosis, all of which were mild except for one case of anemia that was considered moderate. Most of the changes represent only slight deviations from the normal laboratory range and within 2X upper range of normal.	N=195 laboratory evaluations in total. One severe electrolyte abnormality considered not related to the drug, 3 mild to moderate cases of anemia (2 anemia in placebo control) and 2 cases of hematuria (1 in placebo).	N = 286 laboratory evaluations in total. 5 cases of liver func abnormalities, 9 cases of increased alkaline phosphatase, 7 cases of bilirubinemia, 5 cases of increased AGOT, 5 cases of increased SGPT, 5 cases of increased amylase, I case of increased creatinine, 1 case of hypercalcemia, 1 case of hyperglycemia, 1 case of hypoglycemia, 1 case of hypoproteinemia, 1 case of hypovolemia, 15 cases of anemia, 5 cases of thrombocytopenia, 5 cases of leukopenia, 4 cases of eosinophilia, 3 cases of hypochromatic anemia, 2 cases of pancytopenia, 1 case of iron deficiency anemia, 1 case of monocytosis, and 4 cases of hematuria.

The applicant also presented an analysis where laboratory values for all subjects exposed to nitazoxanide in phase II and III clinical trials, who had lab data before and after treatment, but excluding patients with AIDS, was pooled, and changes in values from baseline were compared using a matched pairs t-test. This analysis did not reveal any significant changes in laboratory values except for red blood cells (slight increase), white blood cells (slight decrease), hematocrit (slight decrease), eosinophils (slight decrease), SGOT (slight decrease) and SGPT (slight decrease).

> ***MO COMMENT:*** *Since the laboratory monitoring from the 5 studies submitted to the NDAs being reviewed was limited, the overall program's laboratory evaluation assessments were helpful in reinforcing the conclusion that nitazoxanide appears safe especially in non-AIDS patients without major adverse event or laboratory abnormality experiences.*

Integrated Safety Summary Conclusions

One-hundred twenty-two pediatric patients ages 1-11 years (verses 129 control patients) comprised the safety database for NDA 21-498 (nitazoxanide for oral suspension). For this population that is being granted approval for the treatment of diarrhea due to C. parvum or G. lamblia (children ages 1-11 years who are HIV negative) with 3 day therapy of nitazoxanide, there were no severe adverse events or death in the submitted studies. NTZ was well tolerated when compared to the controls. The incidence of adverse events (all recorded as

"mild" on the NTZ arm) were comparable to the adverse events in the control arm.

In the overall clinical program, the safety of nitazoxanide has been evaluated in 2,789 patients during the course of clinical studies. The population exposed to nitazoxanide during clinical studies includes 910 children (133 aged 1 to 3 years, 525 aged 4 to 11 years and 252 aged 12 to 19 years). The population included 1623 males and 1166 females, and it included subjects representing three races (1515 Caucasian, 971 Hispanic, 273 black).

In double-blind placebo-controlled studies of the three-day treatment regimen in non-AIDS patients, adverse experiences reported by patients receiving nitazoxanide did not differ significantly from those reported by patients on placebo. No serious adverse events have been reported for the 2,170 non-AIDS patients exposed to nitazoxanide during the course of clinical studies. Evaluations of clinical laboratory data in more than 1,600 patients suggest that nitazoxanide has no significant effect on hematology, clinical chemistry, or urinalysis parameters.

> ***MO COMMENT:*** *It appears that based on the totality of data available for assessment of the safety of nitazoxanide, the proposed 3-day course of treatment with nitazoxanide is safe for use in humans. For the population that is being recommended for approval for the treatment of diarrhea due to C. parvum or G. lamblia (children ages 1-11 years who are HIV negative) with a 3 day therapy with nitazoxanide suspension, no additional or different safety issues were identified. Nitazoxanide shows a favorable safety profile.*

SUMMARY AND RISK / BENEFIT ANALYSIS

In summary then, the Applicant has shown evidence of safety through the two NDAs (— 21-498) that nitazoxanide given to non-AIDS patients for 3 days orally. Substantial evidence of efficacy has been shown for NDA 21-498 (pediatric patients 1 – 11 years of age administered the suspension formulation),

Before the final recommendations for regulatory action on — NDA 21-498 can be made, it is important to consider the evidence/lack of evidence regarding efficacy and safety of the new drug from the risk / benefit balance perspective. In regards to safety, there does not appear to be any major or irreversible risk associated with 3-day course of oral nitazoxanide therapy in non-AIDS patients. What then might be the possible benefits? What population of patients would most benefit from this potential therapy? The Applicant has stated the following regarding how this drug therapy will fulfill the current unmet medical needs.

"*Cryptosporidium parvum* and *Giardia lamblia* are each causes of persistent diarrhea in humans. *C. parvum* has been reported to cause malnutrition, impaired growth and death in children in developing countries. *C. parvum* is also associated with wasting and death in adults with immune disorders such as AIDS in the United States. *G. lamblia* has been reported to cause impaired growth in children in developing countries. The prevalence of *C. parvum* and *G. lamblia* in the United States is currently low. However, with increasing travel and immigration, the prevalence of diarrhea caused by these organisms may increase. At present, there is no drug approved for treating diarrhea caused by *C. parvum* in the United States. There is only one drug, furazolidone, approved for treating diarrhea caused by *G. lamblia* (this drug is no longer manufactured however). Metronidazole is not approved for treating giardiasis in the United States, but is commonly used for this indication. Metronidazole is not available as a pediatric formulation, and while not recognized as prevalent, metronidazole resistance has been reported for *G. lamblia*."

Thus, for non-AIDS patients, it is the population of children ("*C. parvum* has been reported to cause malnutrition, impaired growth and death in children in developing countries; *G. lamblia* has been reported to cause impaired growth in children in developing countries; metronidazole is not available as a pediatric formulation") who would most benefit from a potential new treatment of the two parasitic infections. There were no additional safety issues specifically raised concerning the use of nitazoxanide in the pediatric non-AIDS population.

Another factor to be considered in the risk/benefit balance is that *C. parvum* is now classified as an emerging pathogen by the Center for Disease Prevention and Control (CDC) and listed under Category 2, water safety threats, in the critical biological agent categories for public health preparedness. Since there are no currently approved treatment for *C. parvum* infections, the approval and availability of safe and effective treatment will be of benefit to public health preparedness.

REGULATORY RECOMMENDATIONS:

Recommendations for Regulatory Action

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REGULATORY RECOMMENDATIONS: NDA 21-498

Recommendations for Regulatory Action

- It is recommended that the regulatory action for NDA 21-498 (NTZ oral suspension) be an APPROVAL action for the treatment of clinical disease only. Efficacy and safety of NTZ treatment for diarrhea due to *C. parvum* and *G. lamblia* were adequately demonstrated for children 1 years to less than 12 years of age. However, neither vigorous microbiological assessments/data nor substantial evidence of the correlation between clinical and microbiological endpoints was shown at this time to warrant the granting of the indication

Recommendations for Phase IV Commitments

- Food-effect pK studies with the suspension formulation: The drug is recommended by the Applicant to be administered with food. However, the bioequivalence data when viewed together with the food-effect data and the efficacy data indicate that the drug should not be administered with food. This is to achieve high local concentrations in the gastrointestinal tract where the site of action resides.
- In vitro drug interaction studies with tizoxanide and tizoxanide glucuronide (the major moieties found in plasma): Nitazoxanide showed potential to inhibit cytochrome P450 2C9. However, since only tizoxanide and tizoxanide glucuronide can be determined in the systemic circulation, the clinical relevance of this study is not clear. It is recommended that the applicant repeat the in vitro drug-drug interaction studies with the active metabolites of nitazoxanide

- In vitro absorption studies with tizoxanide: It is recommended that the applicant investigate in vitro transfer of tizoxanide across the digestive epithelium. This is because it is not known to what extent conversion of nitazoxanide to tizoxanide occurs prior to absorption through the intestinal wall.
- Tracking the actual use of nitazoxanide suspension after approval: A well-defined plan/execution/tracking of drug dispension that would ensure usage consistent with labeled indications are recommended. The FDA's Office of Drug Safety concurred with the review team's assessment that nitazoxanide is safe for short term use, but raised concerns regarding the following possible circumstances 1) Off-label use 2) Duration of use (repeat and prolonged dosing) 3) Use in children with different characteristics than those studied

Recommendations for Labeling

- *Clinical Pharmacology* section (please see Biopharmaceutics review for specific recommendations): The pK specifics (including the absorption Table) should be data from pediatric patients 1 – 11 years of age
  Pediatric patients less than 1 years of age should be included under special populations as a population without clinical information.
- *Microbiology* section (please see Microbiology review for specific recommendations): Wording regarding the mechanism of action has to be consistent with the data that was actually presented. Substantial evidence of *in vitro* activity coupled with causing similar clinical symptomatology (as the parasites with clinical evidence of effectiveness) is needed at a minimum to be listed under the activity *in vitro* section.
- *Indications and Usage* section: Suggested wording for this section would be the following. "Nitazoxanide for Oral Suspension is indicated for the treatment of diarrhea caused by *Cryptosporidium parvum* and *Giardia lamblia* in pediatric patients 1- 11 years of age. Safety and effectiveness of Nitazoxanide Oral Suspension has not been established in patients who are HIV positive or patients with immunodeficiency. Safety and effectiveness of Nitazoxanide Oral Suspension in pediatric patients less than one year of age, pediatric patients > 11 yeas of age, and adults have not been studied".
- *Human Dose Equivalents* (please see Pharmacology/Toxicology review for the specific recommendations): The human dose equivalents given under fertility and under pregnancy/reproduction sections should be based on the 11 year old weight (the high end of the 1-11 years age range being approved under this label)
- Under the *Precautions*, the following additions are suggested to clarify for the prescriber which populations the drug is not to be used.

Pediatric Patients < 1 year of age and > 11 years of age
Safety and effectiveness of Nitazoxanide for Oral Suspension in pediatric patients less than one year of age and > 11 years of age have not been studied.
Adult and Geriatric Patients
Safety and Effectiveness of Nitazoxanide for Oral Suspension in adult and geriatric patients has not been studied.
Patients with Immunodeficiency (all ages)

DRAFT

- The Adverse Events section should list AE data from the safety database of 1 – 11 year old pediatric patients who were HIV negative (n=613).
- Clinical Studies Section should be included with information from pediatric patient (1-11 years of age) data for clinical response (studies 98-002 and 3007 for *C. parvum* and study 99-010 for *G. lamblia*)

Recommendation for Trade Name

- DDMAC and DMETS are not recommending the use of the trade name "Cryptaz" at this time because 1) it is specific only for the indication for treatment of cryptosporidium (and *G. lamblia* infection treatment is also being approved) 2) safety issues in confusing this name with other drugs already on market (especially Ceftaz).
- DDMAC and DMETS have found the alternative candidate name "Alinia" to be acceptable. This name "Alinia" is therefore recommended as the trade name for the nitazoxanide suspension.

/S/

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