CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204684Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION
ADDENDUM

CLINICAL STUDIES

NDA/BLA #:	204684
Supplement #:	0006
Drug Name:	Impavido® (miltefosine)
Indication(s):	Treatment of visceral, cutaneous and mucosal leishmaniasis
Applicant:	Paladin Therapeutics Inc.
Date(s):	Submission date: April 19, 2013
	PDUFA due date with 3 month extension: March 19, 2014
Review Priority:	Priority review
Biometrics Division:	DB IV
Statistical Reviewer:	Lan Zeng, M.S.
Concurring Reviewers:	Karen Higgins, Sc.D., Statistics Team Leader
	Dionne Price, Ph.D., Acting Division Director
Medical Division:	Division of Anti-Infective Products
Clinical Team:	Hala Shamsuddin , M.D., Medical Reviewer
	Thomas Smith, M.D., Medical Team Leader
Project Manager:	Gregory DiBernardo

TABLE OF CONTENTS

1 Purpose of Addendum

The purpose of this addendum is to report results of additional analyses results which were not presented in the review referenced on the cover page.

2 Final Cure in Study 3154

As noted in Section 3.2.1.1.3 of the original review for Study 3154, there were 2 miltefosine patients (2-071 and 3-042) not initially cured at the end of treatment and were coded as final cure in the submitted datasets. In the original review, these 2 subjects were conservatively counted as treatment failure which gave a final cure rate of 89.6% in the miltefosine group and 94.9% in the amphotericin B (AMB) group for the ITT analysis. For the PP analysis, the final cure rates were 91.7% in the miltefosine group and 97.9% in the AMB group, respectively.

As per medical officer, these 2 patients would be considered as final cure since neither of them met the criteria of lack of cure, which was defined as fever, Hb < 10 if woman and 11.5 if man, platelets < 100k, WBC < 3500, and spleen that had not regressed by more than 30%. Considering these 2 subjects as final cure and as shown in Table 1, the final cure rate is 90.3% in the miltefosine group and 94.9% in the AMB group for the ITT analysis. The difference is 4.6% with the exact 95% upper confidence bound being 9.8%, which is within the FDA determined NI margin of 10%. Note Patient 2-071 is excluded from the PP analysis because of premature discontinuation of treatment. The PP analysis gives the difference of 5.8% with 95% upper confidence limit of 10.2%. The revised final cure rate does not alter the conclusion that miltefosine is non-inferior to amphotericin B in the ITT and PP population for the primary endpoint of final cure. Note that results from the sponsor's analysis are reported in the labeling.

Table 1 Final Cure Rate at 6-month Follow Up in Study 3154

Population	AMB	MLT	AMB – MLT Difference (95% Exact CI)[a]	P-value[b]
Sponsor's Analysis				
ITT	96/99 (97.0%)	282/299 (94.3%)	2.7% (-3.0, 6.8)%	0.3242
PP	94/94 (100.0%)	279/287 (97.2%)	2.8% (-1.0, 5.5)%	0.0963
Worst Case Scenario	99/99 (100.0%)	282/299 (94.3%)	5.7% (2.1, 9.0)%	0.0112
FDA's Analysis				
ITT	94/99 (94.9%)	270/299 (90.3%)	4.6% (-2.0, 9.8)%	0.1499
PP	92/94 (97.9%)	266/289 (92.0%)	5.8% (0.3, 10.2)%	0.0418

AMB= amphotericin B; MLT=miltefosine

[a]Confidence interval based on the standardized statistic and inverting two 1-sided tests

[b]Boschloo's test

3 Miltefosine Dose Effect

Study 3154 for Visceral Leishmaniasis (VL)

As discussed in Section 4.1.1.2 of the original review for Study 3154, there was no significant relationship between miltefosine daily dosage per kg body weight and final cure rate although there was a trend toward lower final cures in subjects who received less than 2.5 mg/kg miltefosine dose. Among the 299 patients treated with miltefosine, 28 received 50 mg per day due to body weight <25 kg and all were cured. The other 271 patients received 100 mg per day and 254/271 (93.7%) were cured. A logistic regression based on these 271 patients is conducted to test the effect of baseline body weight on final cure. There is no significant relationship between baseline weight and final cure at 6 months follow up (P-value=0.2057).

Studies 3168 and Z020 for of Cutaneous Leishmaniasis (CL)

As discussed in Section 4.2.1.2 of the original review for Study 3168, there was no apparent relationship between miltefosine daily dosage per kg body weight and definitive cure although definitive cure rate was lower in subjects who received a miltefosine dose less than 2.5 mg/kg/day. In Study Z020, the definitive cure was defined as 100% re-epithelializaton and loss of induration of all initial lesions at 2-months and at 6 months, no new lesions, residual lesions with parasites or ≥ 50% enlargement of a lesion prior to 6 months. The original review did not report the definite cure rate with respect to miltefosine dosage (mg/kg) in Study Z020. The following table provides definite cure rate of cutaneous leishmaniasis by miltefoine dosage (mg/kg) for different geographic regions. Note that *L. braziliensis* is epidemiologically most prevalent in Guatemala and Bahia, Brazil while the most epidemiologically prevalent spieces is *L. guyanensis* in Manaus, Brazil and *L. panamensis* in Columbia, respectively.

Table 2 Definite Cure Rates by Miltefosine Dose and Study Site

MLT Dose (mg/kg)	Study 3168 Columbia	Study 3168 Guatemala	Study Z020a Manaus, Brazil	Study Z020b Bahia, Brazil	All
1.4 -< 2	2/4 (50%)	0/1 (0.0%)	4/10 (40%)	2/2 (100%)	8/17 (47.1%)
2- <2.5	18/25 (72%)	7/14 (50%)	13/18 (72.2%)	6/9 (66.7%)	44/66 (66.7%)
2.5-< 3	16/16 (100%)	11/22 (50%)	8/10 (80%)	21/24(87.5%)	56/72 (77.8%)
≥ 3	4/4 (100%)	1/3 (33.3%)	2/2 (100%)	5/5 (100%)	12/14 (85.7%)
Total	40/49 (81.6%)	19/40 (47.5%)	27/40 (67.5%)	34/40 (85%)	120/169 (71.0%)

A total of 169 patients were treated by miltefosine for cutaneous leishmaniasis; 15 received 100 mg per day due to body weight <45 kg and 13/15 were definite cure. The other 154 patients received 150 mg per day and 107/154 (69.5%) were definite cure. A logistic regression is conducted on these 154 patients to test the effects of baseline weight and geographic region on definite cure. There is no interaction between weight and region. There is significant relationship between baseline weight and definite cure (P-value=0.0112). Patients with lower weights had a significantly higher chance to

achieve definite cure at the end of 6-month follow up. However, it is not clear if this is due to the fact that these patients weighed less or received higher dose on a mg/kg basis.

4 Addtional Analysis of Study Z020

As discussed in the original review, Study Z020 was split into two studies, Z020a and Z020b, both of which were randomized, open-label, comparative trials that enrolled children 2-11 years of age and adults ≥ 12 years of age. A total of 180 patients (90 in each site) were enrolled as per protocol. The original plan as stated in the protocol appeared to be for the study to be analyzed as a whole, combining the two sites and the two age populations. However, there were two articles written for the two different sites and the information by site is informative given the different species at the two sites. Hence data were analyzed and presented in the original review separately for each part of the study and for adults/adolescents only with the knowledge that there was no adjustment for multiplicity.

Analyses of efficacy data for pediatric patients separately and for Study Z020 as a whole are included in this addendum (Table 3 and Table 4).

Table 3 Cure Rates in Pediatric Patients in Study Z020

	Study Z020a		Study Z020b	
Patient Status	**MEG**	**MLT**	**MEG**	**MLT**
At 2 months after end of therapy	N=10	N=20	N=10	N=20
missing visit	1	5	0	0
Failure	2	4	0	4
Initial cure	7 (70.0%)	11 (55.0%)	10 (100.0%)	16 (80.0%)
At 6 months after end of therapy	N=10	N=20	N=10	N=20
Lost to Follow up (LTFU)	2	2	1	2
Failure	2	4	0	5
Definitive cure	6 (60.0%)	14 (70.0%)	9 (90.0%)	13 (65.0%)
Analysis of Definitive Cure Rate				
mITT analysis				
Definite cure	6 (60.0%)	14 (70.0%)	9 (90.0%)	13 (65.0%)
Difference (MLT – MEG)	-	10.0%	-	-25.0%
(95% Exact CI)[a]		(-25.7, 47.7)%		(-52.0, 12.3)%
P-value[b]	-	0.6538		0.1766

MEG=Glucantime; MLT=miltefosine

[b]Confidence interval based on the standardized statistic and inverting two 1-sided tests

[a]Boschloo's test

Study Z020a

At 2 months after completing therapy, 7 (70%) of the 10 Glucantime-treated pediatric patients and 11 (55.0%) of the 20 miltefosine-treated pediatric patients were initially cured in Study Z020a. There were 6 patients who missed the 2-month exam, 1 in the Glucantime (MEG) group and 5 in the miltefosine (MLT) group.

At 6-month post treatment, there were 4 pediatric patients (2 MEG; 2 MLT) who were lost to follow up and did not come to 6-month visit. There were 6 pediatric patients (2 MEG; 4 MLT) who clinically failed. If patients who were lost to follow up were considered as failures in the mITT analysis, the definitive cure rate was 70.0% for the miltefosine group and 60.0% for the Glucantime group. There was no statistical difference between the cure rates for the two treatment groups (P-value=0.6538). The 95% confidence interval for the difference in cure rates was (-25.7, 47.7)% .

Study Z020b

At 2 months after completing therapy, 10 (50.0%) of the 10 Glucantime-treated pediatric patients and 16 (80.0%) of the 20 miltefosine-treated pediatric patients were initially cured. All patients had the 2-month exam.

At 6-month post treatment, there were 3 pediatric patients (1 MEG; 2 MLT) who were lost to follow up and did not come to 6-month visit. There were 5 pediatric patients (0 MEG; 5 MLT) who clinically failed. If patients who were lost to follow up were considered as failures in the mITT analysis, the definitive cure rate was 65% for the miltefosine group and 90% for the Glucantime group, respectively. There was no statistical difference between the cure rates for the two treatment groups (P-value=0.1766). The 95% confidence interval for the difference in cure rates was (-52.0, 12.3)% . Note that miltefosine is not statistical superior to Glucantime in pediatric patients as observed in the adult/adolescent patients where miltefosine treatment led to a 40% increase in definite cure rate (P-value=0.0018)

Study Z020

Results from the analysis of Study Z020 as a whole considering age and site as subgroups are presented in Table 4. When all subjects were analyzed together, miltefosine appeared to be similarly efficacious as Glucantime. The definitive cure rate for miltefosine was 73.3% of 120 patients and for Glucantime was 60% of 60 patients with a difference (95% CI) of 13.3% (-1.4, 28.4)%. Of note that miltefosine efficacy in terms of definite cure rate is different in pediatric patients than that in the adult/adolescent population. For adult/adolescent patients, miltefosine treatment led to similar or significantly higher cure rates at 6 months post therapy. The improvement in definite cure rate is 7.5% in Manaus, Brazil and 40% in Bahia, Brazil. For pediatric patients, however, an opposite relationship was observed in the two study sites. Miltefosine treatment corresponded to a 10% efficacy improvement in Manaus, Brazil but 25% decrement in definite cure in Bahia, Brazil. Furthermore, an analysis of Study Z020 as a whole with adjustment for study site and age did not find miltefosine to be statistical superior to Glucantime in definite cure rates (P-value=0.0694).

Table 4 Definitive Cure Rate at 6 Months by Site and Age Group in Study Z020

ITT Population	MEG	MLT	MLT - MEG Difference (95% Exact CI)	P-value[a]
All subjects	36/60 (60.0%)	88/120 (73.3%)	13.3% (-1.4, 28.4)%	0.076
Site				
Manaus (20a)	18/30 (60.0%)	41/60 (68.3%)	8.3% (-12.5, 30.1)%	0.4534
Bahia (20b)	18/30 (60.0%)	47/60 (78.3%)	18.3% (-2.4, 39.3)%	0.0869
Age				
Pediatrics	15/20 (75.0%)	27/40 (67.5%)	-7.5% (-30.4, 18.7)%	0.5973
Adults	21/40 (52.5%)	61/80 (76.3%)	23.8% (5.2, 41.9)%	0.0121
Site and Age				
Manaus (20a) pediatrics	6/10 (60.0%)	14/20 (70.0%)	10% (-25.7, 47.7)%	0.6538
Manaus (20a) adults	12/20 (60.0%)	27/40 (67.5%)	7.5% (-17.9, 34.6)%	0.6147
Bahia (20b) pediatrics	9/10 (90.0%)	13/20 (65.0%)	-25% (-52.0, 12.3)%	0.1766
Bahia (20b) adults	9/20 (45.0%)	34/40 (85.0%)	40.0% (8.6, 63.5)%	0.0018

[a]Boschloo's test

As noted in the original review, there was no pre-specified plan for the analysis of Study Z020 or a justified non-inferiority margin for comparison of miltefosine against Glucantime. Although the results in adult/adolescents were supportive of the effect of miltefosine in the treatment of cutaneous leishmaniasis, findings in the pediatric patients were not as strong, especially in the area of Bahia, Brazil where miltefosine therapy resulted in 65% cure rate compared to 90% in patients treated by Glucantime. Again, the study was open label and used small block sizes leading to a potential concern over the randomization of the study. Therefore, interpretation of statistical analysis should be viewed with caution.

5 Labeling

In Section 14 clinical trial of the label, efficacy of miltefosine for the treatment of visceral leishmaniasis is reported from Study 3154 as follows:

Table 5: Efficacy of IMPAVIDO in Visceral Leishmaniasis in Patients ≥12 years of Age in India

	IMPAVIDO N = 299	**Amphotericin B Deoxycholate N = 99**
End of therapy		
Initial Cure	293 (98%)	97 (98%)
6 months after therapy		
Final Cure*	282 (94%)	96 (97%)
Treatment Failure	9 (3%)	0 (0)
Not Assessable	8 (3%)	3 (3%)

* The 95% exact confidence interval for the difference (IV Amphotericin – IMPAVIDO) in final cure is (-3.0%, 6.8%).

For the treatment of cutaneous leishmaniasis, results from Study 3168 are reported below. Note that in the original review the difference between groups was 36.8% with the exact 95% CI of (18.5, 52.4), which was computed based on the standardized statistic and inverting two 1-sided tests . Given the sample size, it is appropriate to use the normal approximation to the binomial for calculating both p-value and 95% CI as it was used in the label.

Table 6: Efficacy of IMPAVIDO Compared to Placebo in the Treatment of Cutaneous Leishmaniasis in Colombia and Guatemala

	IMPAVIDO	**Placebo**
Definite Cure*	59/89 (66%)	13/44 (30%)
Colombia	40/49 (82%)	9/24 (38%)
Guatemala	19/40 (48%)	4/20 (20%)

* The difference (95% CI) between groups is 36.8% (20.1%, 53.4%) with P-value<0.0001.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LAN ZENG
02/18/2014

KAREN M HIGGINS
02/19/2014
I concur.

DIONNE L PRICE
02/19/2014
concur

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	204684
Supplement #:	0006
Drug Name:	Impavido® (miltefosine)
Indication(s):	Treatment of visceral, cutaneous and mucosal leishmaniasis
Applicant:	Paladin Therapeutics Inc.
Date(s):	Submission date: April 19, 2013
	PDUFA due date: December 18, 2013
Review Priority:	Priority review, 6 month
Biometrics Division:	DB IV
Statistical Reviewer:	Lan Zeng, M.S.
Concurring Reviewers:	Karen Higgins, Sc.D., Statistics Team Leader
	Dionne Price, Ph.D., Acting Division Director
Medical Division:	Division of Anti-Infective Products
Clinical Team:	Hala Shamsuddin , M.D., Medical Reviewer
	Thomas Smith, M.D., Medical Team Leader
Project Manager:	Gregory DiBernardo

Keywords: non-inferiority (NI) margin, open-label, randomization

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY

This New Drug Application (NDA) submission contains six clinical studies submitted by Paladin Therapeutics to evaluate the efficacy and safety of miltefosine (MLT) for the treatment of visceral leishmaniasis (VL), mucosal leishmaniasis (ML), and cutaneous leishmaniasis (CL) in adolescents and adults ≥12 years weighing ≥30 kg. Two of these studies, Study 3154 and Study 3168, were pivotal trials to support the VL and CL indications, respectively. The remaining 4 studies provided supportive evidence, one for VL (Z025), two for CL (Soto and Z020), and one for ML (Z022). Miltefosine was administered at a target dose of 2.5 mg/kg/day for 28 consecutive days in all 6 trials.

For the VL indication, Study 3154 was a randomized, open-label, active controlled, multicenter, Phase 3 trial conducted in Bihar, India which compared oral miltefosine with amphotericin B intravenously given at a total dose of 15 mg/kg every other day over 30 days. A total of 400 patients aged ≥12 years were enrolled and randomized, with 398 exposed to at least one dose of study medication (299 on miltefosine and 99 on amphotericin B). At 6 month after the end of therapy, 282 (94.3%) of the 299 miltefosine-treated patients were cured compared to 96 (97%) of 99 patients treated with amphotericin B. Miltefosine was considered non-inferior to amphotericin B with the upper bound of the 95% confidence limit for the difference, 6.8%, less than the FDA defined non-inferiority margin of 10%. Several sensitivity analyses were performed by this reviewer to account for patients with protocol violations or without initial cure, and gender disparity or inconsistent aspiration among study centers. The results were supportive of the results of the primary analysis. Non-inferiority of miltefosine as compared to amphotericin B can hence be concluded.

As a supportive trial for the VL indication, Study Z025 conducted in Ethiopia was a randomized, open label comparison of oral miltefosine to sodium stibogluconate (SSG) 20 mg/kg/day intramuscularly for 30 days. A total of 580 male patients aged 15 years or up were enrolled and randomized; all exposed to at least one dose of study medication (290 on miltefosine and 290 on SSG). This study also enrolled a substantial number of HIV-infected subjects. However, due to lack of patient level data, this review was only based on the sponsor's study report and the publication[2] by *Ritmeijer et al (2006)*. At 6 months after end of treatment, the final cure rate was 174/290 (60.0%) for the miltefosine group and 189/290 (65.2%) for the SSG group. The final cure rates for miltefosine compared to SSG were lower in HIV positive patients (46% vs 56.8%) and more comparable in HIV negative patients (75.6% vs 77.4%). At 6 months the SSG group had a higher rate of mortality compared to the miltefosine group, mainly driven by the subset of subjects with unknown HIV status. However, throughout the study miltefosine subjects were more likely to experience failure, either as initial failure at the end of therapy or relapse at 6 months after completion of therapy, which implies possibly that the fewer deaths seen with miltefosine were not necessarily due to increased efficacy of miltefosine. The overall assessment of the study is complicated by a large amount of missing data, the lack of patient level data, and by

the re-treatment of subjects who had initial failure, especially in the miltefosine group. However, this study is supportive of the results seen in study 3154.

For the CL indication, the primary evidence of efficacy comes from Study 3168, a randomized, placebo-controlled, double-blind trial conducted in two centers, Colombia where *L.v. panamensis* was epidemiologically the predominant pathogen and Guatemala where *L. v. braziliensis* and *L. m. mexicana* were endemic. Patients were randomized in a 2:1 ratio to receive either miltefosine 50 mg or matching placebo capsules orally for 28 days with a target dose of 2.5 mg/kg per day. In total 133 patients aged ≥12 years entered the study; all received at least one dose of study medication (89 on miltefosine and 44 on placebo). At 6 months after treatment completion, 59 (66.3%) miltefosine-treated patients and 13 (29.6%) placebo-treated patients achieved definite cure. There was a significant improvement of 36.8% in definite cure in the miltefosine group over the placebo group ($p < 0.0001$). The superiority of miltefosine over placebo is robust to various sensitivity analyses and subgroup analyses by age group, gender, center, or prior diagnosis. Miltefosine cure rate was 81.6% (versus 37.5% in placebo) in Colombia and 47.5% (versus 20% in placebo) in Guatemala. Miltefosine was superior to placebo in terms of definite cure at 6 months after end of treatment, although its efficacy was more evident in Colombia than in Guatemala. However, it is of concern that this pivotal trial may not have been completely blinded and that the pre-generated randomization list might not have been fully complied with at one study site.

Study Soto and Study Z020 were submitted as supportive trials for the CL indication.

Study Soto was an open label active comparator trial in patients aged ≥ 12 years that compared oral miltefosine versus intramuscular administration of meglumine antimoniate (MEG) 20 mg /kg/day for 20 days in Bolivia where *L. braziliensis* was epidemiologically the predominant pathogen for CL. This active controlled trial did not include a justified non-inferiority margin to allow for a conclusion regarding the efficacy of miltefosine. Additionally, it is not clear if the study used an appropriate method of randomization. There were unexplained procedure changes during study conduct and it was unclear why the study was stopped early. Forty subjects included in the miltefosine group had a definitive cure rate at 6-month follow up of 80% as reported by the sponsor. Miltefosine efficacy for CL in Bolivia cannot be adequately determined from Study Soto.

Study Z020 was a randomized, active controlled, open-label clinical trial comparing miltefosine versus intramuscular administration of meglumine antimoniate (Glucantime, MEG) 20 mg /kg/day given for 20 days. There were two parts to this study which the sponsor reported separately, Z020a conducted in Manaus, Brazil, where *L.(V.) guyanensis* was epidemiologically the predominant pathogen, and Z020b conducted in Bahia, Brazil where *L.(V.) braziliensis* was endemic. The study enrolled both children aged 2-11 years and adolescent/adults age 12-65 years. Patients were randomized in 2:1 allocation between miltefosine and Glucantime within each center and separately for pediatric and adolescent/adult patients. In contrast to other studies submitted for this NDA review, parasitologic speciation of the infecting leishmania organisms was obtained in every subject

and confirmed the epidemiologic prevalence. This active controlled trial did not include a justified non-inferiority margin. This review evaluated data from the adolescent/adult patients. At 6 months after the end of therapy, in Manaus, the definitive cure rate was 67.5% (27/40) for miltefosine and 60% (12/20) for Glucantime (P-value = 0.6147). The 95% confidence interval for the difference in cure rates was (-17.9, 34.6)%. In Bahia, the definitive cure rate for miltefosine was 85% (34/40) and for Glucantime was 45% (9/20) (P-value = 0.0018). The 95% confidence interval for the difference in cure rates was (8.6, 63.5)%. The results were consistent with respect to various sensitivity analyses and are supportive of miltefosine efficacy against *L.(V.) guyanensis* or *L.(V.) braziliensis*. Though supportive, these results should be interpreted with caution since they are essentially subgroup analyses of the whole Z020 study and there was a lack of pre-specified type I error control.

For the ML indication, Study Z022 was a single-arm, single-center trial that followed a cohort of 79 patients for 12 months. The study found a decrease in disease severity during the trial and the cure rate at 12 months post treatment was 62%. Interpretation of the results is very limited due to lack of comparator.

In conclusion, this review found miltefosine to be effective in the treatment of VL based on one pivotal and one supportive study and in the treatment of CL with one pivotal and one supportive study. The effect of miltefosine in the treatment of mucosal leishmaniasis is unclear due to lack of comparative studies; however, data from one uncontrolled trial is available. We defer to the clinical reviewers as to how much of the efficacy from VL and CL can support the ML indication. While adequate efficacy has been demonstrated for VL and CL, the overall results were not as strong as they could have been due to various issues associated with the study conduct and analysis.

2 INTRODUCTION

2.1 Overview

Miltefosine is an alkyllysophospholipid analogue drug for the treatment of visceral leishmaniasis and cutaneous leishmaniasis and has been marketed in 14 countries including Germany, India, Colombia, Guatemala, Honduras, and Eucador. The sponsor, Paladin Therapeutics, submitted NDA 204684 on April 19, 2013 seeking approval for the treatment of visceral leishmaniasis (VL) caused by *L. donovani* and for the treatment of mucosal (ML) and cutaneous leishmaniasis (CL) caused by members of the subgenus *Viannia* (*L.v. braziliensis, L.v. guyanenesis, L.v. panamensis*) in adults and adolescents ≥12 years weighing ≥30 kg. The target regimen is 2.5 mg/kg/day for 28 consecutive days. The FDA granted miltefosine orphan designation in October 2006 and Fast Track Designation in May 2010. The NDA was granted a priority review with a goal date of December 19, 2013.

In support of the VL indication, one pivotal trial (Study 3154) and one supportive trial (Study Z025) were submitted for review. Study 3154 was a randomized, open-label, active controlled, multicenter, Phase 3 trial in India which compared oral miltefosine use for 28 days with amphotericin B intravenously given at a total dose of 15 mg/kg every other day over 30 days. Study Z025 conducted in Ethiopia was a randomized, open label comparison of oral miltefosine to sodium stibogluconate 20 mg/kg/day intramuscularly for 30 days.

In support of the CL indication, data from one pivotal trial (Study 3168) and 2 supportive studies (Study Soto and Study Z020) were submitted. Study 3168 was a randomized, placebo-controlled, double-blinded trial conducted in two centers, one in Colombia where *L.v. panamensis* was epidemiologically the predominant pathogen and one in Guatemala where *L. v. braziliensis* and *L. m. mexicana* were endemic. Patients received either miltefosine 50 mg or matching placebo capsules orally for 28 days with a target dose of 2.5 mg/kg per day. Study Soto was an open label, active comparator trial of oral miltefosine versus intramuscular administration of meglumine antimoniate (Glucantime) 20 mg /kg/day for 20 days in Bolivia. Study Z020 was a randomized, active comparator-controlled, open-label clinical trial to evaluate the efficacy and safety of miltefosine versus intramuscular administration of Glucantime 20 mg /kg/day given for 20 days. There were two parts to this study, Z020a conducted in Manaus, Brazil, where *L.(V.) guyanensis* was epidemiologically the predominant pathogen, and Z020b conducted in Bahia, Brazil where *L.(V.) braziliensis* was endemic.

To extend the indication from CL to ML, one study (Study Z022) was submitted. Study Z022 was an uncontrolled single-center Phase 2 trial of miltefosine in Bolivia. Patients were administered miltefosine at a target dose of 2.5 mg/kg/day for 28 days and were followed up to 12 months after the end of therapy.

Together the above 6 studies form the core of this statistical review.

2.2 Data Sources

Data sets for this New Drug Application for miltefosine Capsules, NDA 204684, were initially submitted in the original NDA submission (SN000) on September 27, 2012. The full electronic path according to the CDER EDR naming convention was as follows:

\\Cdsesub1\evsprod\NDA204684\0000\m5\datasets

A preliminary data evaluation found that the application was not sufficiently complete and problems such as missing important datasets or erroneous key parameters did not permit a substantive review. A refuse to file (RTF) letter was issued to the sponsor on November 26, 2012 under 21 CFR 314.101(d). On January 8, 2013, a meeting was held between the sponsor and the Agency during which it was agreed that the sponsor would amend the NDA previously submitted with information requested in the RTF letter including response to non-RTF comments and some additional CMC revisions. Consequently, the resubmission of the NDA occurred on April 19, 2013 and the re-submitted datasets were located at:

\\Cdsesub1\evsprod\NDA204684\0006\m5\datasets

Additional datasets in response to the Agency's information request dated May 31, 2013 were submitted on June 7, 2013:

\\Cdsesub1\evsprod\NDA204684\0007\m5\datasets

The electronic datasets re-submitted on April 19, 2013 and June 7, 2013 generally represented the data described in the study report.

APPEARS THIS WAY ON ORIGINAL

3 STATISTICAL EVALUATION

As proposed by the sponsor, miltefosine is indicated in adolescents and adults >12 years of age weighing >30 kg (66 lbs) for treatment of:

- Visceral leishmaniasis due to *Leishmania donovani*
- Cutaneous leishmaniasis due to members of the *Leishmania viannia (v)* subgenus (*L.v. braziliensis, L.v. guyanenesis, L.v. panamensis*)
- Mucosal leishmaniasis due to *L.v. braziliensis, L.v. guyanenesis, and L.v. panamensis*

This review will discuss the results from studies for the 3 indications, visceral leishmaniasis, cutaneous leishmaniasis and mucosal leishmaniasis, separately, in Sections 3.2.1, 3.2.2, and 3.2.3.

3.1 Data and Analysis Quality

The re-submitted data generally followed FDA guidance and were ready to be reviewed. However, there were various issues with data quality and integrity. None of the 6 studies submitted to this NDA were conducted under an IND. All but one study (3168) were open-labeled which could contain serious biases. Additionally, it is not clear if 3168 was fully blinded or merely used treatment masking with codes "A" and "B." There was a lack of prospective statistical analysis plans in most studies and no justified non-inferiority margin for some active controlled trials. In many studies, the efficacy endpoints, analytical populations, and analysis methods were defined post hoc or changed from those in the original protocol or literature if available. Although randomization lists were provided for most studies, there was no randomization date in the submitted datasets. Given the very limited information on randomization algorithm, it is unclear if the submitted randomization lists were actually used in the study and impossible to verify the randomized treatment assignment. A detailed discussion of these issues can be found in the sections on the individual studies in Section 3 and in Section 5.1 of this review.

There were a few occasions that some extra effort was needed to process the data. For instance, in Study 3154, the submitted final efficacy data did not match the definition of primary efficacy endpoint. There were 2 patients who should have been coded as failure according to the definition of final cure. Instead, they were coded as final cure. This reviewer had to manually change them to treatment failure. In Study Z022, the definition of mucosal severity score was given but the score was not provided in the dataset. This reviewer had to compute this composite score using algorithm specified in the study report.

The overall data and analysis quality of this NDA is poor. Tremendous amount of time and effort were spent in the review of this NDA.

3.2 Evaluation of Efficacy

3.2.1 Studies for Visceral Leishmaniasis (VL)

Two studies have been submitted to evaluate the efficacy and safety of miltefosine on visceral leishmaniasis (VL), including one pivotal study (Study 3154) and 1 supportive study (Study Z025).

Study 3154 contains the primary information on the efficacy of miltefosine for the treatment of visceral leishmaniasis. The title of study 3154 is: "Clinical trial to assess efficacy and safety of orally administered miltefosine in patients with visceral leishmaniasis (VL)."

Study Z025 contains supportive information on the efficacy of miltefosine for the treatment of visceral leishmaniasis. The title of study Z025 is: "A Comparison of Miltefosine and Sodium Stibogluconate for Treatment of Visceral Leishmaniasis in an Ethiopian Population."

3.2.1.1 Study 3154

3.2.1.1.1 Objectives and Study Design (Study 3154)

Study 3154 was a randomized, open-label, active controlled, multicenter, Phase 3 trial comparing oral miltefosine (MLT) with intravenous amphotericin B (AMP), the standard of care for treating patients with visceral leishmaniasis (VL). The primary objective was to show that miltefosine was not or only moderately inferior to amphotericin B in terms of final cure rates. The trial was conducted in 3 medical centers in Bihar, India between 1999 and 2000.

Comment*: Note that the trial was open-label and bias or expectations of the observers might influence the measurement taken. Potential problems associated with an open-label design, such as imbalance in randomization or disproportional withdrawal between the two groups, will be examined in this review.*

Eligible patients aged 12 years or older with visceral leishmaniasis were centrally registered and randomly assigned at each site to miltefosine or amphotericin therapy in a 3:1 ratio. Patients randomized to the miltefosine group received miltefosine capsule orally for 28 days according to their body weight (2.5 mg per kilogram per day). Patients weighing more than 25 kg received 100 mg daily while those weighing 25 kg or less received 50 mg each morning. Patients randomized to the amphotericin B group were administered amphotericin B intravenously at a total dose of 15 mg/kg every other day over 30 days for a total of 15 infusions. All patients were hospitalized during treatment. Patients were monitored weekly during therapy, at the end of therapy (on Day 28 for patients receiving miltefosine and on

Day 30 for those receiving amphotericin), and 6 months after the completion of therapy. Splenic or bone marrow aspirate was done at screening assessment and on Day 28 (MLT group) or Day 30 (AMB group) end of treatment. In patients with an aspirate score=1 at end of treatment, another aspirate was evaluated 4 weeks after end of treatment. In patients with clinical signs and/or symptoms attributable to visceral leishmaniasis during follow up, a parasitological examination was to be performed to decide whether visceral leishmaniasis (spleen or bone marrow aspirate score > 0) or another disease (negative parasitology to be confirmed by appropriate test) was the cause.

Comment*: The protocol stated that a randomization list was established per study center and patients were numbered for each study center separately. A trial publication[1] (Sundar et al., 2002) indicated that permuted blocks of 4 patients each were used for randomization. The actual randomization list was provided in Appendix A of the study report. Note that it is not ideal for an open-label study to use permuted block randomization with small block size and within center.*

The primary efficacy endpoint of this study was the rate of patients with final cure 6 months after end of treatment. Final cure was defined as initial cure followed by 6 months follow up without relapse and absence of clinical signs or symptoms attributable to visceral leishmaniasis. Initial cure was defined as eradication of parasites at the end of treatment or within 4 weeks thereafter if re-assessment of spleen or bone marrow parasitology occurred. A patient was considered treatment failure if

- spleen or bone marrow aspirate score > 1 at end of treatment (no adequate response to therapy), or
- spleen or bone marrow aspirate score > 0 at re-assessment 4 weeks after end of treatment, or
- spleen or bone marrow aspirate score > 0 anytime following the 4 weeks after end of treatment (relapse) until 6 months follow up

Secondary endpoints of this trial included the assessment of initial (parasitological) cure and clinical response at end of treatment, as well as the characterization of the safety of the proposed miltefosine schedule.

There were 3 analysis populations defined in the clinical protocol. The intention-to-treat (ITT) population would include all randomized patients exposed to study medication. The per-protocol (PP) population would be a subset of the ITT population diminished by major protocol violators. The safety population would include all patients having received at least one dose of the trial medication and who were not lost to follow-up before the first control examination would be included in the analysis of safety data. The study report written by the sponsor stated the 3 analysis populations as follows:

- Intention-to-treat (ITT): All subjects who were exposed to randomized trial medication.
- Per protocol (PP): A subset of the ITT population, including only subjects who were treated as planned and follow-up for at least 6 months after end of treatment or until treatment failure.

- Safety: All subjects who were exposed to randomized trial medication and in whom minimum follow-up information on tolerability was available.

Comment*: Failure to take study medication is not a good reason to be excluded from the ITT analysis in an open label study. Please see Section 3.2.1.1.2 for handling of non-treated patients in the current study.*

Comment*: For the PP analysis, the sponsor excluded patients who died during the study (until treatment failure). Please see Section 3.2.1.1.3 for additional analysis by this reviewer which did not exclude deaths.*

The primary analysis was done for the ITT population in which patients who were lost to follow up before assessment of final cure were handled as non-responders (no final cure) in both treatment groups. Two sensitivity analyses were performed by the sponsor: the analysis of the PP population and the investigation of a "worst case scenario' by defining drop-outs as non-responders for miltefosine and as responders for the amphotericin B group. According to the sponsor, the confirmatory analysis calculated a center adjusted 97.5%-upper confidence bound for the absolute difference of response rate (AMB – MLT). Non-inferiority was concluded if this upper confidence limit was ≤15%. Additionally, a confidence bound without center adjustment was calculated. The FDA considered a 10% margin statistically justified and more clinically acceptable.

Comment*: A non-inferiority margin of 15% for the absolute difference of response rates in favor of amphotericin B was originally considered by the sponsor as acceptable. The Agency defined an acceptable non-inferiority margin of 10% in a communication with the sponsor dated March 20, 2012 (Appendix 1) as follows:*

> *"For Study 3154, our analysis estimates the pseudo-placebo response rate at 47.1% (38.14%, 56.03%), and the response rate to amphotericin B at 97.8% (96.14%, 99.52%). M1 is therefore conservatively estimated at 40.11%. Although a margin of 15% could be supported, a margin of 10% is more appropriate for this potentially fatal disease.*
>
> *Furthermore, we noticed that two studies were randomized, open-label trials comparing Amphotericin B with Sb [Sodium Stibogluconate] in Bihar, India (Mishra 1994 and Thakur 2004). The treatment difference and associated exact 95% confidence intervals are 37.5% (22.7%, 54.2%) in the Mishra 1994 Study and 53.4% (40.0%, 66.4%) in the Thakur 2004 Study. They both individually support a 15% margin. Again, a margin of 10% is more appropriate for this potentially fatal disease."*

According to the protocol, the sample size calculation was based on the final cure rates using the restricted maximum likelihood method. An allocation ratio of 3:1 in favor of miltefosine was chosen in order to gain more experience with miltefosine. The significance level for the 1-sided non-inferiority test was 0.025, the required power was 80%, and the

non-inferiority margin used by the sponsor was 15%. Assuming that the expected final cure rates ranged from 88% to 92% for miltefosine and 94% to 98% for amphotericin B, there were 25 different combinations for the total sample size varied between 132 and 692 and was not greater than 400 in 21 of the combinations. Hence 400 patients (300 MLT, 100 AMB) were to be recruited.

3.2.1.1.2 Patient Disposition, Demographics and Baseline Characteristics (Study 3154)

A total of 400 patients were enrolled and randomized, with 398 exposed to at least one dose of study medication. Table 1 provides a brief overview of patient disposition.

Table 1 Number of subjects and disposition

	AMB	MLT	Total
Number randomized	99	301	400
No. who did not receive drug	1	1	2
No. with randomization error	1 [a1)]	-	1
Number treated with drug	99	299	398
Number completed treatment (Day 28)	96	290	386
Discontinued treatment prematurely	3 [b1)]	9 [b2)]	12
Number evaluated at the end of treatment	97	294	391
Not evaluated at completion of therapy	2 [c1)]	5 [c2)]	7
Number evaluated at follow-up visit (6 months)	96	291	387
Not evaluated at 6-month follow up visit	3 [d1)]	8 [d2)]	11
Number with major protocol violations	5	12	17
Randomization error	1 [a1)]	0	1
Premature discontinuation of treatment	3 [b1)]	9 [b2)]	12
Loss to follow up	1 [e1)]	3 [e2)]	4
Patients in efficacy analyses			
Intent to treat	99	299	398
Per protocol	94	287	381
Patients in safety analyses	99	299	398

AMB= amphotericin B; MLT=miltefosine

a1) Patient 3-060

b1) Patient 1-137, 2-021, 3-104 b2) Patient 1-086, 1-116, 2-043, 2-048, 2-069, 2-071, 2-092, 3-012, 3-038

c1) Patient 1-137, 2-021 c2) Patient 1-086, 2-048, 2-071, 2-092, 3-038

d1) Patient 1-137, 2-021, 3-052 d2) Patient 1-086, 2-043, 2-048, 2-092, 3-030, 3-038, 3-069, 3-092

e1) Patient 3-052 e2) Patient 3-030, 3-069, 3-092

Comment*: There were 2 patients who were randomized but did not receive any drug. Given the open-label design, they should have been included in the analysis since the very reason for them not taking drug could be due to the knowledge of treatment assignment. However, due to lack of information and since they were only 2 out of the 400 patients and one on each treatment arm, no additional investigation was conducted in this matter.*

Note that Patient 3-060 should have received MLT according to the randomization list but due to an error during the centralized randomization procedure the investigator was falsely instructed to administer AMB. This patient was a final cure and, therefore, inclusion of this subject in the AMB arm does not bias the results in favor of MLT. Given the 3:1

randomization to MLT or AMB, the proportions of subjects who discontinued treatment prematurely, who were not evaluated at completion of therapy, and who were not evaluable at the 6 month follow-up visit, were all balanced between the treatment arms.

There were 12 patients who discontinued the study treatment prematurely, 3 in the AMB and 9 in the MLT group. Note that one MLT patient (3-038) died after being treated with MLT for 11 days due to pyogenic meningitis. Five of the 12 patients who discontinued the study treatment prematurely were still in the study and were evaluated at 6 month after the end of therapy. Seven subjects who discontinued the study treatment prematurely and 4 additional patients (1 AMB: 3-052; 3 MLT: 3-030, 3-069, 3-092) who discontinued the study prematurely were not evaluated at the planned 6 months follow-up period after end of treatment. Three of these patients were lost to follow up and one MLT patient (3-030) died about 2 weeks after the end of treatment. These 11 patients were considered as failures in the primary efficacy analysis. Given the 3:1 randomization ratio, the proportions of patients not evaluated at 6 months follow-up were similar (3.0% versus 2.7%) between the two arms.

Comment*: Note there were 2 deaths in this study, both from the MLT arm. See Section 3.3.1.1 for analysis of these subjects.*

Comment*: Note that the percentages of patients who discontinued treatment (3%) or were lost to follow up (1%) were comparable between the 2 arms. This showed that potential problems attributable to the open-label nature of this design might be less of a concern.*

Miltefosine capsules were given for 28 days at a dose of 100 mg/day in patients with a body weight of at least 25 kg and at a dose of 50 mg/day in patients with a lower body weight. The treatment duration was 28 days in 290 patients (97.0%) as planned. In the remaining 9 patients (3.0%), who discontinued therapy prematurely, the treatment duration was between 3 and 22 days.

Comment*: The following table shows miltefosine patients' body weight according to medication dosage. The mean weight was 40.5 kg for patients receiving 100 mg/day MLT and 19.7 kg for those receiving 50 mg/day MIL. Thus the mean miltefosine dosage was 2.46 mg/kg/day in patients with body weight ≥25 kg and 2.54 mg/kg/day in those with lower body weight. The effect of body weight and/or medication dosage on final cure is discussed more in Section 4.1.1.2.*

	MLT 100mg/day (N=271)	**MLT 50 mg/day** (N=28)
Weight (kg)		
Mean ± SD	40.5 ± 8.3	19.7 ± 2.2
Median	40.0	20.0
Range	25 – 67	15 - 23

MLT=miltefosine

Amphotericin B was administered intravenously in a dose of 1 mg/kg body weight every-other-day for a period of 30 days. The absolute daily dose of Amphotericin B was between

14 and 64 mg. The median daily dose was 40 mg. The treatment duration was 30 days in 96 of the 99 patients (97.0%). Three patients (3.0%), who discontinued therapy prematurely, were treated for 6, 8, or 20 days.

In total, 17 patients were excluded from the PP population efficacy analysis because of premature discontinuation of treatment (12 patients) or follow-up (4 patients), or randomization error (1 patient). Patient 3-060, who was randomized to miltefosine but treated with Amphotericin B, was excluded from the PP population but analyzed as treated in the ITT and safety analyses.

***Comment**: Note that we do not agree that the 2 deaths were excluded from the sponsor's per protocol (PP) analysis. Please see FDA PP analysis in Section 3.2.1.1.3 for details.*

Selected demographic characteristics and baseline covariates were compared between treatment groups (Table 2), which are similar except for gender. Approximately one-third of the patients were 12 to 18 years of age. The median parasitological score was 1.92 in both groups. In the miltefosine group, 271 (90.6%) patients had a body weight of 25 kg or higher and received the drug at a dosage of 100 mg/day while the remaining 28 patients were treated at 50 mg/day due to their lower body weight. In total, 113 (28.4%) patients had previously been treated for leishmaniasis, mainly with pentavalent antimonial drugs; 85 of these were allocated to miltefosine and 28 to AMB treatment. There was a clear imbalance in gender distribution where 70.6% of patients in the MLT group were males compared to that of 58.6% in the AMB group (2-sided Fisher test P-value = 0.035).

APPEARS THIS WAY ON ORIGINAL

Table 2 Demographics and Baseline Characteristics in Study 3154

	AMB (N=99)	MLT (N=299)	Total (N=398)
Center			
1 (Kala-azar Research Centre)	36 (36.4%)	109 (36.5%)	145 (36.4%)
2 (Banaras Hindu University)	36 (36.4%)	108 (36.1%)	144 (36.2%)
3 (Balaji Utlhan Sanastan)	27 (27.3%)	82 (27.4%)	109 (27.4%)
Gender (N, %)			P=0.035
Male	58 (58.6%)	211 (70.6%)	269 (67.6%)
Female	41 (41.4%)	88 (29.4%)	129 (32.4%)
Age (year)			
Mean ± SD	26.3 ± 12.0	26.5 ± 12.7	26.5 ± 12.5
Median	25.0	25.0	25.0
Range	12 – 60	12 – 64	12 – 64
<18 years	31 (31.3%)	102 (34.1%)	133 (33.4%)
≥18 years	68 (68.7%)	197 (65.9%)	265 (66.6%)
Weight (kg)			
Mean ± SD	38.3 ± 12.1	38.6 ± 10.0	38.5 ± 10.6
Median	40.0	40.0	40.0
Range	14 – 64	15 – 67	14 – 67
<25 kg	16 (16.2%)	28 (9.4%)	44 (11.1%)
≥ 25 kg	83 (83.8%)	271 (90.6%)	354 (88.9%)
Previously treated			
Previously treated	28 (28.3%)	85 (28.4%)	113 (28.4%)
Newly diagnosed	71 (71.7%)	214 (71.6%)	285 (71.6%)
Parasitologic Score			
Mean ± SD	1.92 ± 1.1	1.92 ± 1.0	1.92 ± 1.0
Median	2.0	2.0	2.0
Range	1.0 – 5.0	1.0 – 5.0	1.0 – 5.0

AMB= amphotericin B; MLT=miltefosine

Comment*: Note that females seemed to be preferentially enrolled in the AMB arm. The gender mismatch was most obvious in study Site 1, to a lesser extent in Site 3, but not in study Site 2. In Site 1, the male to female ratio was 4.2 (88/21) in the MLT arm versus 1.8 (23/13) in the AMB arm. In Site 2, the male to female ratio was 1.6 (66/42) in the MLT arm and 1.4 (21/15) in the AMB arm, respectively. In Site 3, the male to female ratio was 2.3 (57/25) in MLT arm versus 1.1 (14/13) in the AMB arm. The potential impact of this gender imbalance on final cure is further investigated in Section 4.1.1.1. Note that there did not appear to be a treatment by gender interaction on cure; however, this does lead to some possible concern over how the study was conducted. For instance, a trial publication[1] (Sundar et al., 2002)[1] indicated that permuted blocks of 4 patients each were used for randomization. The small block size in this open-label study might have allowed the investigator to easily figure out the next treatment and compromised the integrity of the randomization, potentially allowing the investigator to enroll more female patients onto the AMB arm.*

As discussed above, the protocol planned that in patients with clinical signs and/or symptoms attributable to visceral leishmaniasis during follow up, a parasitological

examination was to be performed to decide whether visceral leishmaniasis (spleen or bone marrow aspirate score > 0) or another disease (negative parasitology to be confirmed by appropriate test) was the cause. In practice however, splenic aspiration did not occur on all subjects with clinical signs or symptoms. There were 100 patients with signs and symptoms at 6-month follow up. These subjects were fairly evenly distributed among the 3 sites (Site 1: 27/145 (18.6%); Site 2: 37/144 (25.7%); Site 3: 38/109 (34.9%)). However, there was a large disparity with respect to number of aspirations conducted at the different sites. Among the 27 patients who underwent a spleenic aspiration, 23 (85%) were at Site 1, 2 (5.7%) were at Site 2 and 2 (5.3%) at Site 3, respectively. This indicates substantial inconsistency among 3 sites in following up patients with residual signs and symptoms at 6 months; the majority of subjects (25/27, 92.6%) who had signs and symptoms at 6 months at Site 1 were assessed, but only a small portion of subjects at Site 2 (2/35, 5.7%) and Site 3 (2/38, 5.2%) were assessed.

***Comment**: This large disparity with respect to number of aspirations performed at different sites is another concern regarding the conduct of this study. While the majority of subjects who had signs and symptoms at 6 months at Site 1 were assessed, only a small portion of subjects at Site 2 and Site 3 were assessed. Please see Section 3.2.1.1.3 for details of an additional analysis conducted by FDA to assess the impact of this issue.*

3.2.1.1.3 Efficacy Results (Study 3154)

The primary efficacy parameter of Study 3154 was the rate of patients with final cure 6 months after end of treatment. Table 3 summarizes the final cure rates at 6 months after the end of treatment. For the ITT population, of the 299 patients who started oral treatment with miltefosine, 282 were verified to be cured which is a 94.3% cure rate for miltefosine-treated patients compared to a 97% (96/99) cure rate in patients treated with amphotericin B. The difference in cure rate is 2.7% with 95% confidence interval of (-3.0%, 6.8%) in the ITT analysis. The upper 95% confidence bound of 6.8% is within the sponsor pre-defined limit of 15% and the FDA pre-defined limit of 10%. Non-inferiority of miltefosine with respect to amphotericin B can hence be concluded with the sponsor's ITT analysis.

Table 3 Final Cure Rate at 6-month Follow Up in Study 3154

Population	AMB	MLT	AMB – MLT Difference (95% CI)	P-value[a]
Sponsor's Analysis				
ITT	96/99 (97.0%)	282/299 (94.3%)	2.7% (-3.0, 6.8)%	0.3242
PP	94/94 (100.0%)	279/287 (97.2%)	2.8% (1.0, 5.5)%	0.0963
Worst Case Scenario	99/99 (100.0%)	282/299 (94.3%)	5.7% (2.1, 9.0)%	0.0112
FDA's Analysis				
ITT	94/99 (94.9%)	268/299 (89.6%)	5.3% (-1.4, 10.6)%	0.1084
PP	92/94 (97.9%)	265/289 (91.7%)	6.2% (0.6, 10.6)%	0.0339

AMB= amphotericin B; MLT=miltefosine

[a]Boschloo's test

***Comment**: Note Patient 3-060 received AMB instead of MLT per randomization and was analyzed as treated in all analyses in Table 3. If this patient were included in the MLT group in the Sponsor's ITT analysis, the final cure rate would be 95/98 (96.9%) in AMB and 283/300 (94.3%) in MLT which does not change the above results.*

Table 3 also contains two alternative analyses conducted by the sponsor in order to test the sensitivity of the primary endpoint, final cure rate, to the definition of the relevant study population and the handling of drop-outs. The first alternative analysis conducted by the sponsor compared the treatments for the Per Protocol (PP) population, where the final cure rate was 100% in the AMB group and 97.2% in the MLT group. The second alternative analysis conducted by the sponsor was based on the ITT population in a "worst case scenario" where drop-outs in the MLT group were defined as non-responders while drop-outs in the control group were assumed to be responders. In this "worst case scenario" the final cure rate was 100% in patients treated with AMB compared to 94.3% in those treated with MLT. The difference was 5.7% with 95% confidence interval of (2.1%, 9.0%). The upper 95% confidence bound of the difference in final cure rates was 5.5% in the PP analysis and 9.0% in the "worst case scenario" analysis, both of which are below the FDA prescribed margin of 10% for the upper limit of the 95% confidence interval.

The two FDA alternative analyses attempt to address the large disparity with respect to number of aspirations conducted at different sites. Because of this inconsistency, the FDA medical officer evaluated the clinical data for these subjects, blinded as to which subject should have undergone an aspirate. Based on clinical judgment, 14 additional subjects (2 AMB; 12 MLT) were identified as having sufficient signs and symptoms of leishmaniasis but without an aspirate to be able to rule our leishmaniasis. In the FDA analysis these subjects are conservatively considered as treatment failures/relapse. Please refer to the FDA medical officer's review for details. Furthermore, as noted below there were 2 miltefosine patients (2-071 and 3-042) who were not initially cured at the end of treatment but were coded as final cure in the submitted datasets. In accordance with the final cure definition, these 2 subjects should be counted as treatment failure at the 6 month follow up visit. Considering these additional subjects as failures gives a final cure rate of 89.6% in the miltefosine group and 94.9% in the AMB group for the ITT analysis. The difference was 5.3% with 95% upper confidence bound being 10.6%. Note that this is just outside of the FDA determined NI margin of 10%. The FDA Per Protocol (PP) analysis considered these additional failures and included the 2 deaths as treatment failures. This analysis gives the difference of 6.2% with 95% upper confidence limit of 10.6%.

The following section presents data details on the efficacy of miltefosine as compared with that of amphotericin B at completion of therapy and 6 months post end of therapy (Table 4).

Table 4 Efficacy of Miltefosine as Compared with that of Amphotericin B in Study 3154

	Amphotericin B (N=99)	Miltefosine (N=299)	Total (N=398)
At completion of therapy			
Not assessed	2 [a1)]	5 [a2)]	7
Spleen/bone marrow aspiration score=1	0	1 [b2)]	1
Initial cure	97 (98.0%)	293 (98.0%)	390 (98.0%)
At 6 month post end of therapy			
Not assessed	3 [c1)]	8 [c2)]	11
Treatment failure	0	9 [d2)]	9
Final cure	96 (97.0%)	282 (94.3%)	378 (95.0%)

AMB= amphotericin B; MLT=miltefosine

a1) Patient 1-137, 2-021 a2) Patient 1-086, 2-048, 2-071, 2-092, 3-038
b2) Patient 3-042

c1) Patient 1-137, 2-021, 3-052 c2) Patient 1-086, 2-043, 2-048, 2-092, 3-030, 3-038, 3-069, 3-092
d2) Patient 1-014,1-053,1-061, 1-096, 1-116, 1-130, 1-141, 3-013, 3-064

At the end of treatment, 7 patients (AMP: 1-137, 2-021; MLT: 1-086, 2-048, 2-071, 2-092, 3-038) who discontinued treatment prematurely were not evaluated for initial cure. Splenic aspirates were obtained from 391 patients, out of which 385 were initially cured with no amastigotes in the parasitologic aspirate. The remaining 6 patients (MLT: 2-016, 3-042, 3-066, 3-072, 3-107; AMB: 2-058) had a parasitological score 1 at this visit (1-10 amastigotes per 1000 fields). Five of these patients were re-tested 4 weeks later and were without parasitological findings at that time. One patient (3-042) was not re-tested but was followed-up as planned and coded in the dataset as final cure at 6 month visit. Overall at the end of therapy or within 4 weeks thereafter, in the MLT group, 293 of 299 patients (98.0%) were initially cured, 5 patients were not assessable and one patient was falsely not re-tested. In the AMB group 97 of 99 (98.0%) patients had an initial cure, 2 patients were not assessable. Note Patient 3-038 died after being treated MLT for 11 days due to pyogenic meningitis.

Comment*: We disagree with the sponsor about the final status of 2 miltefosine patients (2-071 and 3-042). According to the definition, final cure was initial cure followed by 6 months follow up without relapse and absence of clinical signs and symptoms. These 2 patients were not initially cured at the end of treatment and should be considered as failure instead of final cure as coded in the submitted dataset.*

At the 6-month follow up visit, 11 patients could not be assessed for final cure, including 7 (2 AMB: 1-137, 2-021; 5 MLT: 1-086, 2-043, 2-048, 2-092, 3-038) who discontinued treatment and 4 (AMP: 3-052; MLT: 3-069, 3-092, 3-030) who had initial cure at the completion of therapy but discontinued follow up prematurely. Among the 387 patients who were evaluated at 6-month follow up visit, 96 were in the AMB group and 291 were in the MLT group. A total of 100 patients (12AMB; 88 MLT) had symptoms that were potentially indicative of leishmaniasis. In 76 of these 100 patients, causes other than

leishmaniasis were identified by the sponsor. The remaining 24 patients in whom relapse of leishmaniasis could not be ruled out clinically were all in the MLT group. Splenic aspirations was performed in 27 patients and 9 patients of these patients, all treated by MLT, tested positive for leishmaniasis. Thus, there were 9 patients in the MLT group and no patients in the AMB group with a relapse of visceral leishmaniasis after therapy. Considering the 11 non-assessable patients also as treatment failures, the final cure rate is 97% in the AMB group and 94.3% in the MLT group, respectively.

3.2.1.1.4 Efficacy Conclusions (Study 3154)

Similar final cure rates from VL were achieved after oral use of miltefosine (target of 2.5 mg/kg/day generally achieved by 100 mg/kg/day for 28 days) and after intravenous use of amphotericin B (1 mg/kg every other day for 30 days), 94.3% vs. 97.0%, respectively, when all randomized patients who received at least one dose of study medication were analyzed (ITT Analysis). The difference was not statistically different and the upper bound of the 95% confidence interval for the difference in final cure rates at 6 months post-treatment follow up is 6.8%, less than the FDA defined non-inferiority margin of 10%. The results were robust when only patients without major protocol deviation were analyzed (PP Analysis), or when drop-outs in the MLT group were defined as non-responders while drop-outs in the control group were assumed to be responders ("Worst Case Scenario" Analysis).

Two FDA alternative analyses, which included 16 additional patients (14 per clinical judgment and 2 per final cure definition) as treatment failures, estimated the final cure rate conservatively at 89.6% in the miltefosine group and 94.9% in the amphotericin B group (ITT Analysis). The difference was 5.3% with 95% confidence interval of (-1.4, 10.6)%. The final cure rates by the PP Analysis were 91.7% for miltefosine and 97.9% for amphotericin B with a difference of 6.2% and 95% CI of (0.6, 10.6)%. We believe these results are supportive and conclude that miltefosine is effective in the treatment of VL.

3.2.1.2 Study Z025

Study Z025 contains supportive information on the efficacy of miltefosine for the treatment of visceral leishmaniasis. The title of study Z025 is: "A Comparison of Miltefosine and Sodium Stibogluconate for Treatment of Visceral Leishmaniasis in an Ethiopian Population".

According to the sponsor, a total of 580 patients were randomized to the study but the sponsor received data for 50 patients only. This included data for 49 patients who died, 15 in the miltefosine group and 34 in the SSG group. Data was provided for one additional subject (Patient ID 174) who did not complete treatment. Since patient level data is not available for the majority of subjects, no data analysis was conducted by this reviewer. This study also enrolled a substantial number of HIV-infected subjects. However, the HIV status for individual subjects was not given to the sponsor and was not available for review. This

review will use information provided by the sponsor in its study report and a literature publication[2] by *Ritmeijer et al-2006*.

***Comment**: Due to lack of information on patient level data, results below are solely based upon the sponsor's study report and/or the reference article.*

3.2.1.2.1 Objectives and Study Design (Study Z025)

Study Z025 was a randomized, open label comparison of oral miltefosine to standard of care sodium stibogluconate (SSG) in the treatment of Ethiopian visceral leishmaniasis (VL). The primary objective was to determine the efficacy of miltefosine compared with that of sodium stibogluconate (SSG), the active comparator, in VL patients. The trial was conducted between 2003 and 2005 in the Tigray region in Ethiopia where *L. donovani* was common.

Since more than 80% of patients treated in the Tigray region were adult men and due to concerns about female reproductive toxicity, Study Z025 only enrolled male patients aged ≥15 years with parasitologically and/or serologically confirmed VL. Eligible patients were randomized in 1:1 allocation between miltefosine and SSG. Patients randomized to the miltefosine group received miltefosine 100mg orally for 28 days. Patients randomized to the SSG group were administered SSG 20 mg/kg/day intramuscularly for 30 days. Because of the different routes of administration, the study was unblinded. Patients were hospitalized during the treatment. Baseline assessments included demographics, history of leishmaniasis, signs of visceral disease, immunological or parasitological confirmation of disease, and hemoglobin determination. Human immunodeficiency virus (HIV) serology was performed on many of the patients. Patients were monitored for tolerance and clinical signs daily during therapy, at the end of therapy and 6 months after the completion of therapy.

***Comment**: Note that the trial was open-labeled and bias or expectations of the observers might influence the measurement taken. The study report stated that measurement bias was minimized by training and supervision. The microscopist was blinded to the treatment group of the slides being evaluated.*

***Comment:** The randomization list provided in the study report showed that permuted blocks of size 4 were used in randomization. Note the protocol indicated there were 2 study sites, Mycadra and Humera, but it is unclear if the randomization was stratified by site. If it was, given the open-label design, the investigator would have been able to tell the treatment assignment many subjects prior to enrollment.*

According to the protocol, the main outcome of analysis was the final cure rate at the 6-month follow-up visit. The study report stated that the primary efficacy endpoint of this study was final cure rate at 6 months after completion of treatment in the Per Protocol (PP) population (see below). Patients with final cure were those who exhibited initial cure (clinically improved at the end of therapy and without parasites if they were investigated at

this time) followed by final cure at 6 months follow-up (clinically improved at this time and without parasites if investigated).

***Comment**: Note that final cure rate as the main outcome was defined in the original protocol but the PP population as analysis base was added post-hoc by the sponsor. See below for discussion.*

Secondary outcomes defined in the protocol included initial cure rate, side effects, intercurrent events, and relapse. The study report stated that the secondary efficacy endpoint was initial cure rate in the Intent-to-Treat (ITT) population (see below). Initial cure was defined as clinically cured (alive and with fever clearance, diminution of spleen size, increased hemoglobin, or weight gain at the end of therapy), and without parasites at the end of therapy if parasite aspiration was performed. The study report also defined post-hoc efficacy endpoints which were death rates at the end of therapy and at 6 months follow-up in the ITT population.

***Comment**: Note that initial cure rate as one secondary outcome was defined in the original protocol but the ITT population as analysis base was added post-hoc by the sponsor.*

Neither the original protocol nor the article contained explicit discussion about analysis population. According to the protocol, HIV seropositive, seronegative, and status-unknown patients were to be analyzed separately. The protocol described sample size calculation based on difference in cure rates between 2 treatments in the HIV-negative patients and implied that primary analysis would be in the HIV-negative population. The article stated that data were analyzed on an intent-to-treat basis. The study report defined 3 analysis populations post-hoc as follows:

- Intention-to-treat (ITT): Included all randomized subjects.
- Per protocol (PP): Included all ITT subjects who were not lost to follow-up.
- Safety: All subjects which received any administration of miltefosine or SSG.

***Comment**: None of above 3 analysis populations was previously specified in the protocol. Instead, they were defined in the Statistical Analysis Plan dated April 15, 2011 and the final study report dated June 13, 2012, years after the study was completed.*

Section 9.5.6 of the study report stated that "Because of the high rate of lost-to-follow-up, and in accord with the United States Food and Drug Administration (US FDA) communication of March 30, 2012 , the population for which final cure was determined was the per protocol population (the population that was randomized and was available for evaluation at 6 months)." The study report stated that efficacy outcomes were compared between groups by uncorrected chi-square test. The 95% confidence interval for the difference between the proportions of cured patients in the two treatment groups will be subjected to a non-inferiority analysis. For the non-inferiority analysis, the upper limit of the 95% confidence interval of the difference between the two groups was specified at 10%.

***Comment**: We disagree with the sponsor's choice of per protocol population for the determination of the primary efficacy endpoint. Instead, we consider the primary analysis to be based on the Intent-to-treat (ITT) population. As communicated to the sponsor in a correspondence dated March 30, 2012, the use of a PP analysis was to support the NI margin estimated for the ITT population:*

> *"Our analyses estimate the initial and final cure rates for Sb in East Africa in the ITT population at 93.5% (91.28%, 95.67%) and 77.9% (67.00%, 88.81%) respectively. The final cure rate in the per-protocol (PP) population is estimated at 93.2% (91.44%, 94.94%). For the ITT population, using the final cure estimates, M1 is conservatively estimated at 10.97%. Because most of these studies were conducted under field conditions where 6 months follow up may prove to be a challenge, we also considered the treatment effect for initial cure in the ITT population (35.7%) and the treatment effect for final cure in the PP population (35.4%). These can also be used to help support an NI margin justification for initial and final cure. Although based on these two analyses 15% NI margins could be supported for initial and final cure, margins of 10% are more appropriate for this potentially fatal disease."*

***Comment**: The sponsor had proposed to use a 10-15% non-inferiority (NI) margin to be used to establish the efficacy of miltefosine for approval (IND 105430, SDN20, February 14, 2012). Based on statistical analyses of literature results, the FDA has advised the sponsor that a non-inferiority margin of 10% would be more appropriate for this fatal disease. Please see Appendix for communication date March 30, 2012 regarding the justification of non-inferiority margins.*

The protocol stated that patients who did not respond clinically or parasitologically to miltefosine treatment or who showed severe symptoms possibly caused by miltefosine would receive treatment with SSG 20 mg/kg per day for 30 days. Patients who did not respond to SSG treatment or who developed intolerable SSG toxicity were treated ex-protocol with amphotericin B deoxycholate. The study investigator would analyze mortality and toxicity data on an ongoing basis and decided whether or not early termination of the trials was needed.

***Comment**: One problem with an open label study that occurred with this trial is that investigators analyze the data on an ongoing basis, instead of leaving the monitoring of the study to an independent DSMB. Note that we cannot be confident that any alterations to the conduct of the trial were made in an unbiased way.*

***Comment**: The protocol allowed miltefosine patients who failed initial treatment to receive SSG but did not specify how these patients would be analyzed. This could cause problem if they were considered as a final cure at 6 month after completion of therapy, as their cure should not be attributed to miltefosine. See Section 3.2.1.2.2 for more discussion.*

The sample size assumed that an important (and clinically unacceptable) clinical difference in the two drugs was 10%. A 10% difference in cure rate between 2 treatments would lead to reject the less-effective treatment. Since SSG has a cure rate of approximately 95% in

HIV-negative patients, an 85% cure rate was set for miltefosine in HIV-negative patients. With $\alpha = .05$ and power = 80%, a sample size of 141 HIV- negative patients per treatment group was calculated. It was anticipated that about 30% of patients would be HIV-positive, about 20% of patients would decline HIV testing, and about 15% of patients would loss to follow-up. Thus, the initial sample size was 290 patients per treatment group.

3.2.1.2.2 Patient Disposition, Demographics and Baseline Characteristics (Study Z025)

A total of 580 patients were enrolled, randomized, and exposed to at least one dose of study medication. Table 5 provides a brief overview of patient disposition. By the end of treatment, 256 patients were initially cured in the miltefosine group. Six miltefosine-treated patients had died and 23 had failed therapy, with the rest of the subjects being lost to follow-up (4) or having discontinued therapy (1). In comparison, there were 254 initial cures in the SSG group, 28 patients died, 2 failed therapy, and 6 subjects were lost to follow-up. Although initial cure was similar, SSG recipients were more likely to die by the end of initial treatment, while miltefosine subjects were more likely to experience initial failure.

By 6 months follow-up, 174 (60%) of the 290 patients originally treated with miltefosine were cured, 17 (5.9%) died, 30 (10%) relapsed, and 69 (24%) lost to follow-up. Of the 290 patients originally treated with SSG, 189 (65%) were cured, 34 (12%) died, 7 (2%) relapsed, and 60 (21%) lost to follow-up. Again, there were more deaths in the SSG group but more relapses in the miltefosine group at 6-month follow up. Note that in this presentation of the data from the study report, it is not clear how those subjects who were initial failures were accounted for at the 6 month follow-up visit.

Table 5 Number of subjects and disposition (Study Z025)

	SSG	MLT	Total
No. Randomized	290	290	580
No. Treated with drug	290	290	580
Status at the end of treatment			
Discontinuation	0	1	1
Lost to follow up	6	4	10
Death	28	6	34
Initial failure	2	23	25
Initial cure	254	256	510
Status at 6-month follow-up			
Lost to follow up	60	69	129
Death	34	17*	51
Relapse	7	30	37
Final cure	189	174	363

SSG=sodium stibogluconate; MLT=miltefosine

* The publication stated that 17 patients died, but the sponsor's data consisted of 15 deaths (6 during therapy and 9 post therapy).

According to the publication[2] by *Ritmeijer et al* (2006), the initial cure rate by the end of therapy was 256/290 (88.3%) for miltefosine patients and 254/290 (87.6%) for SSG patients. All patients who experienced initial treatment failure (23 in the miltefosine group and 2 in the SSG group) were immediately re-treated with 30 days of SSG treatment. Consequently 17 of the 23 initial miltefosine failures and 1 of the 2 initial SSG failures were cured after re-treatment with SSG.

***Comment**: The study report provided no information about whether or not the 18 re-treated subjects (17 miltefosine and 1 SSG) contributed to the final cure rate. Therefore, interpretation of the final cure rate is confounded by re-treatment of subjects who had initial failure, especially in the miltefosine group.*

A total of 415 patients were examined at the 6-month visit, 213 in the miltefosine group and 202 in the SSG arm. The number of patients cured at 6-month follow up was 174 in the miltefosine arm and 189 in the SSG arm. Thus the final cure rate at 6-month follow up was 174/290 (60%) for miltefosine and 189/290 (65.2%) for SSG. Later 30 of the 174 miltefosine patients experienced relapse compared to 7 of the 189 SSG patients. These relapsed patients were again re-treated as per protocol.

Demographic and baseline characteristic data for all patients are given in Table 6. The values of these entrance characteristics were similar for the miltefosine and SSG groups. All patients were male by protocol, had a mean age of 29 years, and were sick for a mean of 2.6 to 2.8 months. Patients had on average a large spleen (9.3 - 9.5 cm below the left costal margin) and were anemic (hemoglobin = 9.1 - 9.2 g/dL). In addition, the mean body mass index was 17.3 - 17.4 indicative of malnutrition. Approximately 65% of enrolled subjects underwent voluntary HIV testing, and about 30% were infected. A higher percentage of miltefosine subjects were HIV infected (22% vs. 15%), while a higher percentage of SSG subjects were HIV status unknown (38% vs. 33%).

Table 6 Demographics and Baseline Characteristics (Study Z025)

	SSG (N=290)	**MLT (N=290)**
Age (years) Mean ± SD	29 ± 9.6	29 ± 9.9
Body Mass Index Mean ± SD	17.4 ± 1.8	17.3 ± 2.1
Hemoglobin (g/dL) Mean ± SD	9.1 ± 2.3	9.2 ± 2.3
Spleen size (cm) Mean ± SD	9.5 ± 5.7	9.3 ± 5.6
Duration of illness (month) Mean ± SD	2.6 ± 2.1	2.8 ± 2.1
Unable to walk unaided (%)	28/290 (9.7%)	32/290 (11.5%)
HIV serostatus (%)		
Positive	44/290 (15%)	63/290 (22%)
Negative	137/290 (47%)	131/290 (46%)
Unknown	109/290 (38%)	96/290 (33%)

SSG=sodium stibogluconate; MLT=miltefosine

All treatments were taken under supervision or were administered by study personnel. Patients in the miltefosine group received 100 mg per day as they all weighed at least 25 kg. SSG-treated patients were administered drug on a mg/kg basis, thus all patients received 20 mg Sb/kg/day.

3.2.1.2.3 Efficacy Results (Study Z025)

Table 7 presents the analysis results for initial cure rate at the end of initial treatment and final cure rate at the 6-month follow up visit. The sponsor analyzed the initial cure rate in the ITT population and final cure rate in the PP population. For completeness, three additional analyses were conducted by this reviewer based on either the ITT or PP population. Note that at 6 months after treatment completion, there was a large portion of patients lost to follow up, 60 (21%) in the SSG arm and 69 (24%) in the miltefosine arm. These patients were included as failures in the ITT population but excluded from PP population.

APPEARS THIS WAY ON ORIGINAL

Table 7 Initial and Final Cure Rates in Study Z025

Population	SSG	MLT	SSG – MLT Difference (95% CI)	P-value[a]
Initial Cure Rate (at the end of treatment)				
ITT (Sponsor's analysis#1)	254/290 (87.6%)	256/290 (88.3%)	-0.7% (-6.1, 4.7)%	0.8315
Reason for failure:				
Initial failure	2 (0.7%)	23 (7.9%)		
Death	28 (9.6%)	6 (2.1%)		
Discontinued	0 (0.0%)	1 (0.3%)		
Defaulted	6 (2.1%)	4 (1.4%)		
PP (FDA analysis#1)	254/284 (89.4%)	256/285 (89.8%)	-0.4% (-5.5, 4.7)%	0.9287
Reason for failure:				
Initial failure	2 (0.7%)	23 (8.1)		
Death	28 (9.9%)	6 (2.1%)		
Final Cure Rate[c] (at 6-months follow up)				
ITT (FDA analysis#2)	189/290 (65.2%)	174/290 (60.0%)	5.2% (-2.8, 13.1)%	0.2039
Reason for failure:				
Relapse	7 (2.4%)	30 (10.3%)		
Death	34 (11.7%)	17 (5.9%)		
Defaulted	60 (20.7%)	69 (23.8%)		
PP (Sponsor's analysis#2)	189/230 (82.2%)	174/219 (79.5%)	2.7% (-4.6, 10.1)%	0.4961
Reason for failure:				
Relapse	7 (3.0%)	30 (13.7%)		
Death	34 (14.8%)	15 (6.8%)		
PP (FDA analysis#3)[b]	189/230 (82.2%)	174/221 (78.7%)	3.4% (-3.9, 10.9)%	0.3740
Reason for failure:				
Relapse	7 (3.0%)	30 (13.6%)		
Death	34 (14.8%)	17 (7.7%)		

SSG=sodium stibogluconate; MLT=miltefosine

Source of patient numbers by category: Figure 1 of study report.

[a]Boschloo's test

[b] The article reported 17 MLT deaths (as compared to 15 in the study report) leading to 221 patients evaluated at 6-month follow-up visit.

[c] Though final cure rate, as defined, required that subjects have an initial cure, the study report does not list initial cure as one of the reasons for failure at 6 months. It is unknown how the 2 and 23 subjects who were initial failures are captured in the final cure results. They could have been considered as cures, relapses, or defaulted.

For the initial cure rate at the end of treatment in the intent to treat population (Sponsor's analysis #1), the results in the miltefosine and SSG group appear similar, 88.3% for miltefosine and 87.6% for SSG. The difference was -0.7% with 95% CI for the difference in cure rates being (-6.1, 4.7)%. Also reported are the results for the per protocol population where missing data were excluded (FDA analysis #1). There were very few subjects with missing data at this early time point and the results are very close to those of the intent to treat population. Both of these analyses have an upper bound of the 95% CI of 4.7% which is within the 10% NI margin. However, though the overall initial cure rates are similar, as can be seen from Table 7, the reasons for failure were very different between the two arms.

Most of the miltefosine subjects who failed were failure of treatment while most of the SSG subjects who were failures had died.

For the results of final cure, in the ITT analysis (FDA analysis #2), the final cure rate was 174/290 (60.0%) for the miltefosine group and 189/290 (65.2%) for the SSG group. The difference between the two groups was 5.2% with the upper limit of the 95% CI being 13.1%. In the PP analysis (Sponsor's analysis #2), the sponsor reported the final cure rates of 79.5% in the miltefosine group and 82.2% in the SSG group with the difference being 2.7% and 95% CI of (-4.6, 10.1)%. The large difference between these two analyses of final cure is due to the large number of subjects with missing data by the time of the assessment of the final cure which were all excluded from the PP analysis. FDA analysis #3 is reported in the table, as well, and it accounts for an additional two subjects who are listed to have died in the article. Note the study reported 15 miltefosine deaths as compared to 17 in the article which led to either 219 (Sponsor's analysis #2) or 221 (FDA analysis #3) patients in the PP population. The results of the three analyses of final cure were similar in that the final cure rates in SSG recipients were higher (although not statistically significant) than miltefosine patients and none of the upper 95% CI bounds of the difference was less than the non-inferiority margin of 10%. Similar to the results of initial cure, for final cure the failure rate on the miltefosine arm was driven by treatment failures (relapses) while the failure rate on the SSG arm was driven by deaths. Of note, it is not clear based on the study report how subjects with an initial failure were included in the analysis of final cure. According to the definition of final cure, these subjects should have been considered a failure for final cure as well; however, based on the study report, it is not clear if that happened.

Table 8 shows the final cure rates by HIV serostatus in the ITT population using information from the article[2] by Ritmeijer et al (2006). For HIV infected patients, the final cure was 46% in the MLT group which was lower than that of 56.8% in the SSG group, though not statistically significantly lower. The difference was 10.8% and the upper limit of the 95% confidence interval was 29.6%, much greater than the non-inferiority margin of 10%. For HIV negative patients, 99/131 (75.6%) of the miltefosine patients were cured compared to 106/137 (77.4%) of the SSG patients. The difference was 1.8% with 95% CI (-8.5, 12.2)%, the upper limit of which was greater than the margin of 10%. For patients with unknown HIV status, the final cure rates were 47.9% in the miltefosine arm and 53.2% in the SSG arm, respectively. None of the upper limits of 95% CIs for the difference met the 10% NI margin and miltefosine was less efficacious in HIV infected subjects as compared to non-HIV infected patients. Though the details of the protocol are vague, the analysis of HIV negative patients appears to have been the planned analysis in the study protocol.

Table 8 Final Cure Rates at 6-month follow up by HIV Status (Study Z025)

	SSG	MLT	SSG – MLT Difference (95% CI)	P-value[a]
All subjects	189/290 (65.2%)	174/290 (60.0%)	5.2% (-2.8, 13.1)%	0.2039
HIV Status				
HIV infected	25/44 (56.8%)	29/63 (46.0%)	10.8% (-8.7, 29.6)%	0.2805
Non-HIV infected	106/137 (77.4%)	99/131 (75.6%)	1.8% (-8.5, 12.2)%	0.7630
HIV Status Unknown	58/109 (53.2%)	46/96 (47.9%)	5.3% (-8.5, 18.9)%	0.4589

SSG=sodium stibogluconate; MLT=miltefosine

[a]Boschloo's test

Mortality data submitted by the sponsor is shown in Table 9. At the end of therapy, there were 28 deaths in the SSG group versus 6 deaths in the miltefosine group (P-value = 0.0001). There were additional 15 deaths (6 in the SSG group and 9 in the MLT group) during follow up period. At the end of 6-month follow up, the total number of deaths was 34 in the SSG group compared with 15 in the miltefosine group. This difference was also statistically significant (P-value=.005).

Table 9 Mortality in Study Z025 (per data submitted by the sponsor)

	SSG (N=290)	MLT (N=290)	All Subjects (N=580)	P-value
By the End of Therapy				
Death rate, n(%)	28 (9.7%)	6 (2.1%)	34 (5.9%)	0.0001[a]
Time to death				0.022[b]
Mean ± SD	16.7±6.67	8.83±6.55	15.3±7.22	
Median	15.0	7.0	14.0	
Range	8.0 – 28.0	2.0 – 19.0	2.0 – 28.0	
By 6 Months follow up				
Death rate, n(%)	34 (11.7%)	15 (5.2%)	49 (8.4%)	0.005[a]
Time to death	No data	No data	No data	
Mean ± SD				
Median				
Range				

SSG=sodium stibogluconate; MLT=miltefosine

[a]Boschloo's test

[a] Kruskal Wallis test

Comment*: Note again that data submitted by the sponsor contained a total of 15 deaths in the miltefosine group instead of the 17 as reported in the publication[2] by Ritmeijer et al (2006). Note that the p-value for this comparison is 0.013.*

***Comment**: The study report showed the day of death for the 34 patients who died during therapy. However, the day of death was not recorded for 6 SSG patients and 9 miltefosine patients who had died between the end of therapy and the 6 month follow up.*

Table 10 presents the death rates by HIV serostatus in the ITT population according to the article[2] by *Ritmeijer et al* (2006). For HIV infected patients, the death rates were similar between the 2 groups. For HIV negative patients, the death rate was 0.8% in the MLT which was lower than that of 4.4% in the SSG group (P-value=0.0769). For patients with unknown HIV status, the death rates were 8.3% in the miltefosine arm and 21.1% in the SSG arm, respectively. The difference was 12.8% which was statistically significant (P-value=0.0105). Overall mortality at 6 months was significantly lower in the miltefosine group as compared to the SSG group (5.9% vs 11.7%, P-value=0.0125).

Table 10 Death Rates at 6-month follow up by HIV Status (Study Z025)

	SSG	MLT	SSG – MLT Difference (95% CI)	P-value[a]
All subjects	34/290 (11.7%)	17/290 (5.9%)	5.9% (1.2, 10.7)%	0.0125
HIV Status				
HIV infected	5/44 (11.4%)	7/63 (11.1%)	0.3% (-12.4, 14.5)%	0.9879
Non-HIV infected	6/137 (4.4%)	1/131 (0.8%)	3.6% (-0.3, 8.6)%	0.0769
HIV Status Unknown	23/109 (21.1%)	8/96 (8.3%)	12.8% (2.7, 22.6%)	0.0105

SSG=sodium stibogluconate; MLT=miltefosine
[a]Boschloo's test

3.2.1.2.4 Efficacy Conclusions (Study Z025)

Based on our assessment of the study report and the publication[2] by *Ritmeijer et al (2006),* miltefosine efficacy was similar to SSG in terms of initial cure rate at the end of treatment. However, though the overall initial cure rates are similar, the reasons for failure were very different between the two arms. Most of the miltefosine subjects who failed were failure of treatment while most of the SSG subjects who were failures had died.

The final cure rate at the 6-month follow up was lower at 60% for miltefosine and 65.2% for SSG when all patients were analyzed due to the large amount of missing data. While the 5.2% difference between groups was not statistically significant, the upper limit of 95% confidence interval was 13.1% which did not meet the non-inferiority margin of 10%. The assessment of the final cure rate is complicated by a large amount of missing data, the variable reasons for failure between the two arms, and by the re-treatment of subjects who had initial failure, especially in the miltefosine group. The final cure rates for miltefosine compared to SSG were lower in HIV positive patients (46% vs 56.8%) and more comparable in HIV negative patients (75.6% vs 77.4%).

At 6 months the SSG group had a higher rate of mortality compared to the miltefosine group, mainly driven by the subset of subjects with unknown HIV status. For patients with unknown HIV status, the death rates were 8.3% in the miltefosine arm and 21.1% in the

SSG arm (P-value=0.0105), respectively. However, throughout the study miltefosine subjects were more likely to experience initial failure at the end of therapy or relapse at 6 months after completion of therapy which implies possibly that the fewer deaths seen with miltefosine were not necessarily due to increased efficacy of miltefosine.

Results are not validated by this reviewer due to lack of patient level data.

APPEARS THIS WAY ON ORIGINAL

3.2.2 Studies for Cutaneous Leishmaniasis (CL)

Four studies have been submitted to evaluate the efficacy and safety of miltefosine on CL, including one pivotal study (Study 3168) and 2 supportive studies (Study Soto and Study Z020).

3.2.2.1 Study 3168

Study 3168 contains the primary information on the efficacy of miltefosine for the treatment of cutaneous leishmaniasis. The title of study 3168 is: "Clinical trial to assess efficacy and safety of orally administered miltefosine in patients with cutaneous leishmaniasis (CL)."

3.2.2.1.1 Objectives and Study Design (Study 3168)

Study 3168 was conducted as a randomized, placebo-controlled, double-blind multicenter trial to assess the efficacy and safety of oral miltefosine in patients with cutaneous leishmaniasis (CL). The primary objective was to demonstrate that miltefosine is superior to placebo in cutaneous leishmaniasis when assessed 2 weeks and 6 months after end of treatment. The trial was conducted from 2000 to 2002 in 2 different regions, Colombia where *L.v. panamensis* was common and Guatemala where *L. v. braziliensis* and *L. m. mexicana* were endemic.

The study population included male and female patients aged older than 12 years, who had newly diagnosed or resistant/relapsing CL without mucosal involvement, parasitologically confirmed, presenting with at least one skin ulcer or inflammatory induration with positive parasitology (minimum area: 50 mm^2). Eligible patients were randomized by center in a 2:1 ratio to receive either miltefosine 50 mg or matching placebo capsules orally for 28 days with a target dose of ~2.5 mg/kg per day. Patients weighing ≥45 kg were administered 3 capsules per day and patients weighing < 45 kg were given 2 capsules per day, all under the observation of study staff.

Comment*: The study report provided the randomization scheme in Appendix A 6.1 which indicated a permuted blocks of size 3 was used and the list had "TG Letter" of "A" or "B". It appears that treatment was masked as "A" and "B" which essentially allowed the study investigator to separate 2 groups of patients. It is highly likely that this study was not fully blinded.*

Comment*: It is questionable if the randomization list was fully complied with. There was no randomization date in the submitted database. When using the date of first medication exposure as a surrogate for randomization date, it appears that in the Colombia site, subjects were not given ID numbers according to the order in the randomization list. The*

first ID numbers used were 21 to 33 in July of 2000. It was only beginning 04/22/2001 that the ID numbers were in order, 1 through 20 and 40 through 70. Though it is unclear why the randomization list started at 21 instead of 1, there did not appear to be a pattern that selected out ID numbers for miltefosine or placebo. For the Guatemala site, the ID numbers were in order of medication start date.

Patients were observed for lesion size and appearance, laboratory and vital parameters, and adverse events weekly during treatment, at end of treatment, and at 2 weeks, 2 and 6 months after end of treatment. A lesion was defined as a treatment failure if it enlarged by 50% or was positive for parasites 2 weeks to 6 months after the end of therapy, relapsed (enlarged) after previously diminishing in size, or did not completely reepithelialize by 6 months after the end of therapy. Appearance of a new lesion from which leishmania could be demonstrated was also considered a failure. Cure was defined as complete healing of all lesions by 6 months after the end of therapy. For a patient to be cured, no lesion could enlarge by 50%, be parasite positive, relapse, or heal incompletely, and no new leishmania-positive lesion could appear.

Clinical responses at 2 weeks after end of treatment were defined as follows:

- Apparent cure: Complete epithelialization of all ulcers, and complete disappearance of inflammatory induration from all lesions.
- Partial cure: Incomplete epithelialization or incomplete regression of inflammatory induration of any lesion, and not more than 50% enlargement of previously documented lesions, and no parasites (if tested for), and no new lesions.
- Failure: Lack of achieving partial cure, defined as 50% enlargement of the total lesion area, or presence of parasites, or new lesion.
- Not assessable: Not seen at this time period.

At 6 months follow-up, clinical responses were classified as below:

- Definitive Cure: Complete epithelialization of all ulcers, and complete disappearance of inflammatory induration from all lesions, and no positive parasitology between 2 weeks and the 6 month follow up, and no new lesions between 2 weeks and 6 months, and not 50% enlargement of lesion between 2 weeks and 6 months.
- Failure: Not achieve Definitive cure.
- Not assessable: Not seen at this time period.

The primary efficacy endpoint of Study 3168 was rate of patients with apparent cure or partial cure at 2 weeks followed by definitive cure at 6 months (current definition). Patients who failed at either 2 weeks or 6 months were considered as clinical failures. Patients classified as failure at 2 weeks were also classified as failure at 6 month visit.

Comment*: According to the sponsor, in the trial protocol the primary endpoint was initially defined as the rate of patients with apparent cure (2 weeks after end of treatment) and definite cure (after relapse-free 6 months follow up). An inspection of the data under blinded condition revealed a considerable number of cases with a status of partial cure 2 weeks after end of treatment but a definite cure after 6 months follow up. As the main*

treatment intention was the achievement of long term cures, the delayed completion of the full treatment effect was considered to be of minor clinical relevance. The primary endpoint was hence changed to capture all cases with at least partial cure (2 weeks after end of treatment) and definite cure (after relapse-free 6 months follow up). The decision to extend the definition of response was made under blinded conditions and is stated to be documented in the SAP. Note that the statistical analysis plan (SAP) was not submitted with this NDA. Per Section 4.2 of the study report, the SAP was finalized on 4/3/2003 while the database lock and unblinding occurred on 4/11/2003. However, as discussed earlier, it is not clear if this study was fully blinded as subjects might have been labeled with masked terms such as "A" and "B". Because this study might not have been fully blinded, it is possible that the decision to change the primary endpoint was based on knowledge of the study results. For this reason, we will assess the study using both the revised as well as the original definition of definite cure.

Three analysis populations were defined in the protocol as follows:

- Analysis of safety (Safety): All patients who applied the trial medication at least once and who were not lost to follow up after the baseline visit were evaluated.
- Intention to treat (ITT): All randomized and exposed patients.
- Per protocol (PP): All patients who fulfilled the selection criteria and who received the scheduled trial medication on at least 90% of the planned treatment days and who were assessed at least for apparent cure. Patients who dropped out early due to lack of efficacy will not be excluded from the PP population.

The primary analysis was based on the ITT population to test the differences between miltefosine and placebo with respect to the rate of patients with at least partial cure at 2 weeks after end of treatment and definite cure after relapse-free 6 months follow up. The analysis of the PP population serves as a sensitivity analysis. A two-sided Cochran-Mantel-Haenszel (CMH) test stratified by center was performed for the null hypothesis of no treatment difference between miltefosine and placebo. According to the protocol, assuming a significance level of 0.05 and statistical power of 80%, the sample size was between 81 and 111 if the cure rate was at least 30% higher with miltefosine than with placebo which varied between 20% and 60%. To account for possible drop outs, 132 patients, i.e., 88 for miltefosine and 44 for placebo, were to be recruited into this study.

3.2.2.1.2 Patient Disposition, Demographics and Baseline Characteristics (Study 3168)

A total of 133 patients entered the study, with disposition as shown in Table 11.

Table 11 Number of subjects and disposition (Stud 3168)

	PLA	MLT	Total
No. Randomized	44	89	133
No. Treated with drug	44	89	133
No. Received ≥90% Medication (Treated ≥ 25 days)	42	87	129
Treated < 25 days	2 [a1)]	2 [a2)]	4
No. Evaluated at 2 weeks post end of therapy	43	85	128
Not evaluated at 2 weeks post end of therapy	1 [b1)]	4 [b2)]	5
No. Evaluated at follow-up visit (6 months)	43	84	127
Not evaluated at 6 months follow up	1 [b1)]	5 [c2)]	6
No. with major protocol violations	2	4	6
Treated < 25 days	2 [a1)]	2 [a2)]	4
Treated ≥ 25 days but not assessable at 2 weeks and 6 months	0	1 [d2)]	1
Treated ≥ 25 days but loss to follow up <2 weeks post end of therapy	0	1 [e2)]	1
Patients in efficacy analyses			
Intent to treat	44	89	133
Per protocol	42	85	127
Patients in safety analyses	44	89	133

PLA=placebo; MLT=miltefosine

a1) Patient 2-12, 2-23

a2) Patient 2-16, 2-31

b1) Patient 2-12

b2) Patient 1-15, 1-77, 2-16, 2-31

c2) Patient 1-15, 1-39, 1-76, 1-77, 2-16

d2) Patient 1-15

e2) Patient 1-77

There were 4 patients (2 PLA: 2-12, 2-23; 2 MLT: 2-16, 2-31) who were treated for less than 25 days, i.e. received less than 90% of the planned study medication. One patient (MLT: 1-15) discontinued treatment and study procedures after 26 days but had no evaluation of response at either 2 weeks or 6 months after the end of treatment. Another patient (MLT: 1-77) was lost to follow up after completion of treatment but before evaluation of response, which the protocol required 2 weeks after end of treatment. These 6 patients (2 PLA, 4 MLT) were excluded from the Per Protocol (PP) analysis of efficacy. Note there were 2 patients (1-39, 1-76) who completed 28 days of miltefosine treatment, had apparent cure at 2 weeks post end of therapy and not assessable at 6 months follow up were included as treatment failures in both the ITT and PP analyses.

Table 12 summarizes the data on demographics and baseline characteristics of the patients, which reveals no major differences between the two groups. On average, patients were in the third decade of life and weighed about 60 kg. Approximately 90% of patients were males, 86.4% enrolled in the placebo group and 91% in the miltefosine group. Leishmaniasis was newly diagnosed in 34/44 (77.3%) placebo patients and in 77/89 (86.5%) miltefosine patients. The difference in proportions of newly diagnosed patients did not constitute a major imbalance between the two arms.

Table 12 Demographics and Baseline Characteristics in Study 3168

	PLA (N=44)	MLT (N=89)	Total (N=133)
Center			
Colombia	24 (54.5%)	49 (55.1%)	73 (54.9%)
Guatemala	20 (45.5%)	40 (44.9%)	60 (45.1%)
Gender (N, %)			
Male	38 (86.4%)	81 (91.0%)	119 (89.5%)
Female	6 (13.6%)	8 (9.0%)	14 (10.5%)
Age (year)			
Mean ± SD	26.1 ± 12.6	24.9 ± 9.8	25.3 ± 10.8
Median	22.5	22.0	22.0
Range	12 – 63	12 – 55	12 – 63
Children (≤18)	14 (31.8%)	19 (21.3%)	33 (24.8%)
Adults (>18)	30 (68.2%)	70 (78.7%)	100 (75.2%)
Race			
white	31 (70.5%)	63 (70.8%)	94 (70.7%)
Black or African American	2 (4.5%)	9 (10.1%)	11 (8.3%)
American Indian or Alaska native	11 (25.0%)	17 (19.1%)	28 (21.0%)
Ethnicity			
Hispanic or Latino	32 (72.7%)	64 (71.9%)	96 (72.2%)
Not reported	12 (27.3%)	25 (28.1%)	37 (27.8%)
Weight (kg)			
Mean ± SD	58.4 ± 11.3	59.5 ± 11.0	59.1 ± 11.1
Median	59.5	60.0	60.0
Range	33 – 82	29 – 84	29 – 84
< 45 Kg	6 (13.6%)	9 (10.1%)	15 (11.3%)
≥45 Kg	38 (86.4%)	80 (89.9%)	118 (88.7%)
Diagnosis of CL			
Previously treated	10 (22.7%)	12 (13.5%)	22 (16.5%)
Newly diagnosed	34 (77.3%)	77 (86.5%)	111 (83.5%)

PLA=placebo; MLT=miltefosine

Patients with a body weight ≥ 45 kg received a daily dose of 150 mg (3x50 mg) miltefosine or matching placebo, patients with a body weight < 45 kg received a daily dose of 100 mg (2x50 mg). The treatment duration was 28 days in all patients except 6 patients (2 PLA: 2-12, 2-23; 4 MLT: 1-15, 1-59, 2-16, 2-31) who discontinued the study treatment prematurely with a treatment duration between 21 and 27 days. Note Patient 1-59 discontinued treatment after 27 days, had partial cure at 2 weeks after completion of therapy, and eventually had definite cure.

Comment*: The following table shows body weight for miltefosine patients by medication dosage. The mean weight was 36.4 kg for patients receiving 100 mg/day MLT and 62.1 kg for those receiving 150 mg/day MIL. Thus the mean miltefosine dosage was 2.75 mg/kg/day in patients with body weight <45 kg and 2.42 mg/kg/day in those with body weight ≥45 kg.*

The effect of body weight and/or medication dosage on final cure is further discussed in Section 4.2.1.2.

	MLT 100mg (N=9)	**MLT 150 mg** (N=80)
Weight (kg)		
Mean ± SD	36.4 ± 5.0	62.1 ± 8.0
Median	35.0	62.0
Range	29 - 44	47 - 84

MLT=miltefosine

3.2.2.1.3 Efficacy Results (Study 3168)

Table 13 presents the results of primary efficacy analysis under both the current and original definition for the definite cure at 6-month follow up. In the ITT analysis of patients overall, 59 (66.3%) miltefosine-treated patients and 13 (29.6%) placebo-treated patients achieved definite cure on the basis of clinical and parasitological responses after 6 months of follow-up. There was a significant improvement of 36.8% in definite cure in the miltefosine group over the placebo group ($p < 0.0001$). When the PP population was analyzed, the rate of definite cure was 69.4% in the miltefosine group and 31.0% in the placebo group ($p < 0.0001$), respectively. When the rates of definite cure based on original definition were considered, significant improvement still exists for the miltefosine treatment over placebo (P-value <0.0001) for both ITT and PP analyses.

Table 13 Definite cure rate at 6-month follow up in Study 3168

Population	**PLA**	**MLT**	**MLT – PLA Difference (95% CI)**	**P-value[a]**
Current definition				
ITT	13/44 (29.6%)	59/89 (66.3%)	36.8% (18.5, 52.4)	<0.0001
PP	13/42 (31.0%)	59/85 (69.4%)	38.5% (19.9, 54.5)	<0.0001
Original definition				
ITT	7/44 (15.9%)	48/89 (53.9%)	38.0% (20.6, 52.2)	<0.0001
PP	7/42 (16.7%)	48/85 (56.5%)	39.8% (21.6, 54.4)	<0.0001

PLA=placebo; MLT=miltefosine

[a]Boschloo's test

***Comment**: As indicated in Section 3.2.2.1.1, the primary efficacy endpoint was originally defined as the rate of patients with apparent cure at 2 weeks after end of treatment and definite cure after relapse-free 6 months follow up. It was later changed to rate of patients with apparent or partial cure at 2 weeks after end of treatment and definite cure after relapse-free 6 months follow up. There were 6 failures after an initial partial response, in 2 cases after use of MLT and in 4 cases after placebo. A total of 17 patients (11 MLT, 6 PLA) eventually achieved a definite cure after an initial partial response. These patients would be considered as not achieving the primary efficacy endpoint at 6 months under the original definition.*

Table 14 shows data details on efficacy of miltefosine as compared with that of placebo at 2 weeks and 6 months after end of therapy.

Table 14 Efficacy of Miltefosine as Compared with that of Placebo in Study 3168

	PLA (N=44)	MLT (N=89)	Total (N=133)
At 2 weeks after end of therapy			
Not assessed	1 [a1)]	4 [a2)]	5
Clinical failure	26	16	42
Partial cure	10 (22.7%)	13 (14.6%)	23 (17.3%)
Apparent cure	7 (15.9%)	56 (62.9%)	63 (47.4%)
At 6 months after end of therapy			
Not assessed	1 [b1)]	5 [b2)]	6
Clinical failure	30	25	55
Definite cure	13 (29.6%)	59 (66.3%)	72 (54.1%)

PLA=placebo; MLT=miltefosine

a1) Patient 2-12 a2) Patient 1-15, 1-77, 2-16, 2-31

b1) Patient 2-12 b2) Patient 1-15, 1-39, 1-76, 1-77, 2-16

Status of cure was assessed 2 weeks after end of treatment for 128 patients, excluding 4 patients (1PLA: 2-12; 3 MLT: 1-15, 2-16, 2-31) who discontinued treatment prematurely and 1 patient (MLT: 1-77) who was lost to follow up 3 days after completion of therapy. In the placebo group, 10 (23.3%) patients were assessed as partial cure and 7 (16.3%) patients had apparent cure at 2 weeks follow up. The remaining 26 placebo patients were assessed as clinical failures, including Patient 2-23 who discontinued treatment prematurely after 23 days on study medication. In the miltefosine group, the number and rates of clinical failure, partial and apparent cure were 16 (18.0%), 13 (14.6%) and 56 (62.9%), respectively.

Comment*: Below is a summary of apparent or partial cure rates at 2 weeks after the end of treatment results for both ITT and PP population. The apparent or partial cure rate observed for miltefosine was considerably greater than the apparent or partial cure rate observed for placebo.*

Apparent or partial cure rate at 2 weeks after end of treatment in Study 3168

Population	PLA	MLT	MLT – PLA Difference (95% CI)	P-value[a]
ITT	17/44 (38.6%)	69/89 (77.5%)	38.9% (20.9, 55.0)%	<0.0001
PP	17/42 (40.5%)	69/85 (81.2%)	40.7% (24.7, 58.4)%	<0.0001

PLA=placebo; MLT=miltefosine

[a]Boschloo's test

At the 6-month follow up visit, 72 patients had definite cure, 55 patients were clinical failures and 6 patients could not be assessed, including 3 patients (1 PLA: 2-12; 2 MLT: 1-15, 2-16) who discontinued treatment, 1 patient (MLT: 1-77) who completed 28 days of therapy but discontinued follow up prematurely, and 2 patients (MLT: 1-39, 1-76) who had

apparent cure at 2 weeks but were not evaluated at 6 months follow up. In the miltefosine group, 48 of the 56 patients who had an apparent cure and 11 of the 13 patients who had partial cure respectively 2 weeks after end of treatment were evaluated as definitive cure at 6 months follow up. The remaining 6 patients (1-18, 1-36, 2-27, 2-32, 2-44, 2-52) with apparent cure and 2 patients (1-57, 2-21) with partial cure respectively 2 weeks after end of treatment relapsed (clinical failure) in the subsequent observation period. There were an additional 17 patients for a total of 25 who were clinical failures at 6 months follow up, one (2-31) discontinued treatment after 21 days on miltefosine and was not assessable at 2 weeks post therapy and the other 16 were clinical failures at 2 weeks after end of treatment. In the placebo group, all of the 7 patients with apparent cure at 2 weeks were definite cure at 6 month evaluation while 4 (1-42, 2-03, 2-06, 2-33) of the 13 patients with partial cure relapsed and the other 6 were assessed as definite cure at 6 months. An additional 26 patients in the placebo group were clinical failures at 2 weeks and at 6 months as well. Overall, a total of 30 in the MLT group and 31 patients in the placebo group had symptoms showing clinical failure or relapse or not assessable.

3.2.2.1.4 Efficacy Conclusions (Study 3168)

Miltefosine was effective in the treatment of patients with CL with a definite cure rate of 66.3% (ITT) compared with a placebo cure rate of 29.6% at 6 months after the end of therapy. The 36.8% improvement in definite cure was statistically significant (P-value <0.001). If subjects who did not have apparent cure at 2 weeks after end of treatment were considered as treatment failures at final 6 months follow up, the cure rates were 53.9% in the miltefosine group and 15.9% in the placebo group (P<0.001). The results are robust whether the intent-to-treat or per protocol population was used for analysis.

However, there are concerns that this pivotal trial may not have been completely blinded and treatment allocation in the Colombia site was probably not in accordance with the randomization list. Some caution is needed in interpreting findings from the study.

APPEARS THIS WAY ON ORIGINAL

3.2.2.2 Study Soto

Study Soto was initiated after low response to miltefosine was observed in cutaneous leishmaniasis patients in Guatemala (Study 3168), where the infecting species were *L. braziliensis* and *L. mexicana*. It was designed to directly evaluate the relative efficacy of miltefosine to antimony in Bolivia, where *L. braziliensis* was epidemiologically the predominant pathogen for CL. A single group trial (Study Z022) had been performed to test the effectiveness of miltefosine on mucosal leishmaniasis (ML) in Bolivia. Study Soto was conducted at the same Bolivian site as the mucosal trial but employed a randomized comparative design for CL patients. Because the mucosal leishmaniasis protocol (study Z022) preceded this CL protocol chronologically, the CL protocol was conducted as an Amendment to the preceding mucosal leishmaniasis protocol (Amendment #03 to the Z022 protocol). The title of Amendment #03 was: "Oral Miltefosine for the Treatment of Mucosal Leishmaniasis in Bolivia – Inclusion of subject groups with cutaneous leishamaniasis to the Protocol".

Note there was no standalone protocol for Study Soto. The study was completed and published (Soto et al., 2008)[4] before the current sponsor of the development of this product was identified. The sponsor obtained the case report forms from the principal investigator, created the statistical analysis plan, and wrote the study report for this NDA submission.

3.2.2.2.1 Objectives and Study Design (Study Soto)

Study Soto was a randomized, open label, active comparator trial of oral miltefosine versus standard therapy with intramuscular pentavalent antimony in the treatment of cutaneous leishmaniasis (CL) in Bolivia. The primary objective was to determine the efficacy and safety of miltefosine compared to that of Glucantime (MEG) for CL treatment. The main criteria for inclusion were age > 12 years, a skin ulcer confirmed to be caused by *Leishmania* by visualization of parasites in lesion material by Giemsa staining, without mucosal disease, without anti-leishmanial therapy for at least 2 months, without significant concomitant disease by history, physical examination, or laboratory tests. Patients who met entrance criteria were randomized in 2:1 allocation between miltefosine and Glucantime. Patients randomized to the miltefosine group received miltefosine at a target dose of 2.5 mg/kg/day orally for 28 days. Patients randomized to the Glucantime group were administered 20 mg /kg/day antimony intramuscularly for 20 days. Because of the difference in route of administration, treatment was open-label. The study was conducted from 2005 to 2007 in Bolivia where *L. braziliensis* was endemic.

Comment*: This open label study was conducted in a single center and was highly likely not randomized. See discussion below.*

***Comment**: According to the study report, species identification was not performed in Study Soto. Prior epidemiology in this region of Bolivia suggested that L. braziliensis was prevalent.*

Tolerance was evaluated daily during therapy by patient evaluation for subjective adverse events (AEs). At the end of therapy, screening laboratory tests were repeated. Efficacy was evaluated by parasitological evaluation of cutaneous lesions and measuring the size of lesions at baseline, at the end of therapy, and at 1, 3 and 6 months after the end of therapy. The area of the lesion was computed by multiplying lesion length x lesion width.

According to the study report Section 9.7, several procedural changes occurred during the conduct of the study. For instance, the entrance characteristics of age was changed from ">2 yrs" to ">12 yrs". The follow up periods was changed from "2 weeks / 2 months / 6 months" to "1 month / 3 months / 6 months".

***Comment**: Note there were no relevant information as to when and why the above change occurred. It is unclear how it might affect the study results.*

The study protocol (Amendment #03) contained very limited information about data analysis, which only stated that the rates (proportions) of cure, fail and indeterminate results in the miltefosine group would be compared with the rates in the group of Glucantime by chi-square test. There was no clear definition of efficacy endpoint, analysis population, or analysis methods. Information presented below in this regard is provided by the sponsor post-hoc in its study report.

According to the study report, the primary efficacy variable was clinical cure defined as complete re-epithelialization of all lesion ulcers on a patient at 6 months after the end of therapy. Clinical responses were defined as follows:

- Cure: 100% re-epithelializaton of all initial lesions
- Failure: Increase in lesion size at the end of therapy or at 1 month after therapy by 50% in comparison with the initial measurements, less than 50% decrease in size at 3 months after therapy in comparison with the initial measurements, lack of 100% decrease in size at 6 months after therapy; relapse; appearance of new lesions
- Lost to Follow-up: Did not come to final study evaluation

Subjects who do not achieve clinical cure at 6 months after the end of therapy will be classified as lost to follow up (there was evidence of clinical improvement or cure but the final follow up disease assessment was not performed) or clinical failure (for as long as the subject was followed during the study, the area of the lesions did not improve or cure as described above).

There were 2 analytic populations:

- Modified Intention-to-treat (mITT Population): included all subjects who received any administration of miltefosine or Glucantime.

- Safety Population: included all subjects who received any administration of investigational product.

As the primary efficacy analysis, the cure rates were compared by a two-sided Fisher's Exact Test for the mITT analysis set. Subjects who did not come to the final 6 month follow up were considered failures to achieve cure for the mITT analysis. A total of 80 subjects were planned in the protocol, 54 in the miltefosine group and 26 in the Glucantime group. The number of subjects and subject allocation (2 MLT: 1 MEG) was chosen based on resource constraints and the desire to provide more subjects for the experimental (miltefosine) group. There was no formal statistical hypothesis.

Comment*: While the study protocol (Amendment #03) defined evaluation criteria (cure, partial healing, improvement, and failure) and efficacy responses (clinical cure, clinical improvement, no clinical change, and clinical worsening), there were no specific plan on data analysis. The statistical methods with consideration on efficacy endpoints, analysis population, missing data handling were created by the sponsor post hoc, years after the study was completed and results published.*

3.2.2.2.2 Patient Disposition, Demographics and Baseline Characteristics (Study Soto)

According to the study report, the original randomization scheme allotted 54 subjects to miltefosine and 26 subjects to Glucantime. Some numbers on the original randomization list as provided in Appendix 16.1.7 were not used. The final number of subjects was 40 that received miltefosine and 18 that received Glucantime. No relevant information was given as to why the study was stopped early.

A close evaluation of the data revealed that Study Soto was highly likely non-randomized. The reasons are:

- Appendix 16.2.1, Table 17 showed 6 patients had received prior leishanmaiss treatment. It is interesting that the 3 patients (Patients 43, 45, 74) previously treated with miltefosine were randomized to Glucantime and that the 3 previously treated Glucantime (Patient ID 20, 31, 46) were randomized to miltefosine.
- Appendix 16.1.7 provided master randomization list for Study Soto. For the miltefosine subjects, the last 11 numbers at the end of randomization list were not used as expected. For the Glucantime subjects, however, 2 ID numbers (65, 74) among the last 9 at the end of randomization list (59, 62, 65, 69, 72, 74, 77, 78, and 80) were used. It is strange that ID number 65 and 74 was used while the preceding numbers (59, 62 before 65 and 69, 72 before 74) were not used.
- There was no randomization date in the submitted database. When using the date of first medication exposure as a surrogate for randomization date, it appears that subjects were not given ID numbers according to the order in the randomization list. The following patterns were noticed when subjects were sorted by date of first medication exposure:

- The first 10 subjects (IDs 1, 2, 4, 5, 8, 9, 10, 12, 13, 15) all received miltefosine. The sponsor stated that patient ID 10 was randomized to Glucantime but received miltefosine instead. These patients started treatment during 11/12/05 to 11/16/05. The three other Glucantime ID numbers, 3, 6, and 11 were skipped. These Glucantime subjects, 3, 6, and 11, received medication after 11/16/2005. The study report stated that records are missing for miltefosine ID number 7 and miltefosine ID number 14 was misdiagnosed and never treated.
- The 25th to 29th subjects were given ID numbers 28, 29, 30, 31, 33, respectively, and started their miltefosine on 01/28/2006. ID 32 was given to a Glucantime subject who started medication on 03/07/2006.
- The 35th to 40th subjects were given ID numbers 39, 40, 41, 42, 44, and 46, respectively, and initiated treatment between 4/8/20006 and 4/27/2006. ID 43 and 45 were given to Glucantime subjects, who received treatment on 5/25/2006 and 6/21/2006.
- The 46th to 50th subject were given ID numbers 51, 52, 54, 55, and 57, respectively, and started their miltefosine between 5/25/2006 and 6/16/2006. ID numbers 53 and 56 were given to Glucantime subjects who were treated on 7/1/2006 and 8/15/2006.

Comment*: Because of the above findings and the lack of randomization date data, the actual use of randomization in Study Soto is questionable. It is very likely that the study was not randomized. Interpretation of results from this study is thus limited.*

Table 15 shows subject disposition for Study Soto. Drug was not discontinued for any subject. One subject (Soto-10) randomized to Glucantime but administered miltefosine was analyzed with the miltefosine group by the sponsor. In the miltefosine group, 38/40 (95%) completed the study and 2 subjects were lost to follow up. Patient ID 29 was lost after the 3-month visit and the date of final clinical evaluation was missing in the dataset for Patient ID 24. In the Glucantime group, 14/18 (77.8%) completed the study and 4 subjects were lost to follow-up. Patient ID 18 was lost after completing treatment and the date of final clinical evaluation was missing in the dataset for Patient ID 56, 65, and 74. Of note these 3 patients were the last three to be treated with a treatment start date of 8/15/2006, 8/19/2006 and 10/21/2006. It is quite likely the case that the data on these 3 patients were lost not due to their own inability to return to follow-up but instead due to the ending of the trial. For this reason, it does not seem appropriate to impute these missing values as failures. The sponsor states that 3 additional subjects (Patient ID 14, 17, and 58), all treated by miltefosine, and did not have records available. The sponsor did not consider these subjects as lost to follow-up and were not included as failures in the sponsor's analysis. Note that patient status at the end of treatment, at 1 month after treatment, or at 3 months after treatment was not included in the submitted datasets, but were included in the article written on this study *(Soto et al., 2008)*[4].

Table 15 Number of subjects and disposition in Study Soto

	MEG	MLT	Total
No. Treated with drug	18	40	58
No. Completed treatment	18	40	58
No. Evaluated at the end of treatment	No data	No data	No data
No. Evaluate at 1 month after treatment	No data	No data	No data
No. Evaluate at 3 month after treatment	No data	No data	No data
No. Evaluate at 6 month after treatment	14	38	52
lost to follow up	4*	2	6
records lost	0	3	3
Patients in efficacy analyses			
Modified Intent to treat (mITT)	18	40	58
Patients in safety analyses			
safety	18	40	58

MEG=Glucantime; MLT=miltefosine

* Including 3 patients (Patient ID 56, 65, 74) likely due to the ending of the trial

Demographic parameters did not vary substantially between the treatment groups (Table 16). The mean age was 28 years. Of the treated subjects, 77% were male and 95% were of the Aymara and Quechua ethnicities. Patient's mean age was 27.7 years and mean weight was 57.7 kg. There were 6 adolescent subjects (12 to 17 years of age) in the Glucantime and 7 in the miltefosine group. Thirty-four (59%) of the 58 patients had one lesion and no subject had more than 3 lesions. Of the 40 miltefosine-treated patients, 62.5% had a single lesion while 50% of those treated with Glucantime had a single lesion. Baseline lesion area ranged from 4 mm^2 to 3172 mm^2. Mean and median lesion areas for the 60 lesions on the 40 miltefosine subjects were slightly larger than the 30 lesions on the 18 Glucantime subjects. The total lesion area per patient was on average 464.1 mm^2 in the miltefosine group and 388.8 mm^2 in the Glucantime group, which were not statistically different.

APPEARS THIS WAY ON ORIGINAL

Table 16 Demographics and Baseline Characteristics in Study Soto

	MEG (N=18)	MLT (N=40)	Total (N=58)
Gender (N, %)			
Male	14 (77.8%)	31 (77.5%)	45 (77.6%)
Female	4 (22.2%)	9 (22.5%)	13 (22.4%)
Age (year)			
Mean ± SD	25.1 ± 13.4	28.9 ±11.6	27.7 ± 12.2
Median	20.5	26.5	25.5
Range	12 - 51	12 - 57	12 - 57
12 - <18 years	6 (33.3%)	7 (17.5%)	13 (22.4%)
≥18 years	12 (66.7%)	33 (82.5%)	45 (77.6%)
Ethnicity			
Caucasian	1 (5.6%)	0 (0%)	1 (1.7%)
Moseten	2 (11.1%)	0 (0%)	2 (3.4%)
Aymara	11 (61.1%)	25 (62.5%)	36 (62.1%)
Quechua	4 (22.2%)	15 (37.5%)	19 (32.8%)
Weight (kg)			
Mean ± SD	57.0± 11.0	58.0 ± 8.2	57.7 ± 9.1
Median	58.8	59	59.0
Range	38 – 79.5	39 - 78	38.0 – 79.5
<45 Kg	2 (11.1%)	3 (7.5%)	5 (8.6%)
≥45 Kg	16 (88.9%)	37 (92.5%)	53 (91.4%)
Number (%) of Subjects with			
1 lesion	9 (50%)	25 (62.5%)	34 (58.6%)
2 lesions	6 (33.3%)	10 (25.0%)	16 (27.6%)
3 lesions	3 (16.7%)	5 (12.5%)	8 (13.8%)
Total Number of Lesions	N=30	N=60	N=90
Lesion Area (mm^2)			
Mean ± SD	233.3± 255.4	309.4 ± 454.7	284.0 ± 399.5
Median	150	178	168.5
Range	4- 900	10 - 3172	4 - 3172
Total Lesion Area (mm2) per patient	N=18	N=40	N=58
Mean ± SD	388.8± 398.2	464.1 ± 562.9	440.7 ± 515.1
Median	294.5	239.5	257.5
Range	4- 1525	24 - 3172	4 - 3172

MEG=Glucantime; MLT=miltefosine

All subjects took miltefosine or Glucantime for the prescribed number of days (28 or 20, respectively), except for one Glucantime-treated subject (Patient Soto-03) who received 22 rather than 20 days of therapy. Miltefosine treatment was with 50 mg capsules, with a maximum of 3 capsules a day, treatment was 50 mg (1 capsule), 100 mg (2 capsules) or 150 mg (3 capsules) a day, whichever was closer to the target of 2.5 mg/kg/day. Three miltefosine patients received 100mg per day while 37 were administered 150 mg per day. The average dose of miltefosine was 146.3 mg per day and the mean dose of Glucantime was 3 mL per day.

3.2.2.2.3 Efficacy Results (Study Soto)

Table 17 presents clinical responses in Study Soto at 6 months after the end of therapy. Clinical cure was defined as 100% re-epithelialization of all initial lesions. Of note there was an imbalance in number of failure and lost to follow up between the two arms. In the Glucantime group, the sponsor reported that 22.2% of patients were lost compared to 5.5% who were failures. In contrast, 5% miltefosine patients were lost as compared to 15% who were failures. Several sensitivity analyses were performed by this reviewer to examine how clinical cure rates might be affected by this large disparity.

When patients lost to follow up (LTFU) were considered as failure in both groups (Scenario #1, mITT population as defined in the study report), 80.0% of the miltefosine group compared to 72.2% of the Glucantime group was cured at 6 months. This difference was 7.8% favoring miltefosine although not statistically significant. When patients actually evaluated at 6 months visit were considered (i.e., excluding those lost to follow-up) (Scenario #2), the cure rate was 84.2% with miltefosine treatment and 92.9% with Glucantime use, which was in favor of Glucantime treatment despite no statistical difference. When patients lost to follow up were included as cure in both groups (Scenario #3), the cure rate was 85% with miltefosine treatment and 94.4% with Glucantime use, which again was in favor of Glucantime treatment despite no statistical difference. Scenario #3 essentially compared the two groups with respect to failure rate, which was further evaluated by subgroups in Section 4.2.2. The results of cure rates are heavily driven by the way of how missing data (lost to follow up) are handled. The sponsor's study report only stated cure rates from Scenario #1, 80% for miltefosine subjects and 72.2% for Glucantime subjects. In fact, miltefosine cure rate can be 7.8% higher than Glucantime (Scenario #1) or 14.4% lower than Glucantime (Scenario #4) depending how patients lost to follow up are analyzed. No definite conclusion regarding clinical cure rate can be drawn from this study.

Table 17 Clinical responses at 6-month follow up in Study Soto

	MEG (N=18)	MLT (N=40)	MEG – MLT Difference (95% CI)	P-value[a]
Patient Status				
Lost to follow up (LTFU)	4 (22.2%)	2 (5.0%)		
Failure	1 (5.5%)	6 (15.0%)		
Cure	13 (72.2%)	32 (80.0%)		
Analysis of Cure Rate				
Scenario #1: Including LTFU as failure in both MEG and MLT	13/18 (72.2%)	32/40 (80.0%)	-7.8% (-34.8, 15.3)%	0.8185
Scenario #2: Excluding LTFU	13/14 (92.9%)	32/38 (84.2%)	8.6% (-18.6, 26.8)%	0.5861
Scenario #3: Including LTFU as cure in both MEG and MLT	17/18 (94.4%)	34/40 (85.0%)	9.4% (-13.3, 25.8)%	0.3722
Scenario #4: Including LTFU as cure in MEG and failure in MLT	17/18 (94.4%)	32/40 (80.0%)	14.4% (-8.2, 31.2)%	0.1748

MEG=Glucantime; MLT=miltefosine

[a]Boschloo's test

***Comment**: The study report showed that among the 6 subjects who failed miltefosine, 4 never cured and 2 relapsed. The study reports also discusses those subjects lost to follow-up on the Glucantime arm; 3 of the 4 Glucantime subjects who were lost to follow up were apparent cures at their 3 months visit. Note that this information cannot be verified by this reviewer as the submitted dataset only contains efficacy information from the 6-month visit.*

As stated above, we believe that 3 Glucantime patients (Patient ID 56, 65, 74) listed as being lost to follow-up by the sponsor likely had data missing due to the stopping of the trial and should not be considered as true lost to follow-up and 3 MLT patients (Patient ID 7, 17, 58) whose records were missing should also be considered in the assessment of the trial if the 3 Glucantime subjects are included. Table 18 considers this information in the scenarios and different analyses.

Table 18 Clinical responses at 6-month follow up in Study Soto

	MEG (N=18)	MLT (N=43)	MEG – MLT Difference (95% CI)	P-value[a]
Patient Status				
Lost to follow up (LTFU)	1 (5.6%)	2 (4.7%)		
Lost records[b]	3 (16.7%)	3 (7.0%)		
Failure	1 (5.5%)	6 (13.9%		
Cure	13 (72.2%)	32 (74.4%)		
Analysis of Cure Rate				
Scenario #5: Including LTFU as failure and excluding lost records[b]	13/15 (86.7%)	32/40 (80.0%)	6.7 % (-21.4. 26.3)%	0.8993
Scenario#6: Including LTFU and lost records as failure	13/18 (72.2%)	32/43 (74.4%)	-2.2% (-29.4, 20.8)%	0.9916

MEG=Glucantime; MLT=miltefosine

[a]Boschloo's test

[b]3 MEG patients changed from LTFU to lost records; 3 MLT patients whose records were lost are included

***Comment**: Although Study Soto was not a non-inferiority trial by design, it is interesting to note that the upper 95% confidence limit for cure rate difference between groups was likely between 9.6% and 31.2% depending on how patients lost to follow up were counted. We would need evidence that the comparator Glucantime was more effective than placebo by a margin of at least approximately 30% in order to comfortably conclude that miltefosine was superior to placebo. Given the results from the placebo controlled trial previously discussed, this is quite possible. However, the sponsor did not provide a discussion of the non-inferiority assessment of miltefosine compared to Glucantime.*

Table 19 shows detailed efficacy results by post treatment evaluation time point. As efficacy data before the 6 month visit was not submitted by the sponsor, results prior to the 6-month visit were taken from the Soto article[4]. The article presented cure rates for patients evaluated at each time point. Cure rates presented by this reviewer in Table 19 were calculated out of all patients in each group, considering patients lost to follow up as failures. There was no statistical difference in cure rates between treatment groups at any of the time points. At the end of therapy, 15 (34.1%) miltefosine patients were cured while 9 (50%) Glucantime

patients were cured. By 1 month after the end of therapy, 31 (70.5%) patients in the miltefosine group were cured, compared with 16 (88.9%) in the Glucantime group. The cure rate was 88.6% for miltefosine patients and 83.3% for Glucantime patients at 3 months, and 81.8% for miltefosine patients and 83.3% for Glucantime patients at 6 months post treatment. Based on this information it appears that response to miltefosine was slower than Glucantime. Results of a FDA analysis (Scenario #1) based on the submitted data are included for comparison purpose. The data submitted to the FDA are much more supportive of miltefosine than the results in the article.

Table 19 Efficacy of Miltefosine as Compared with that of Glucantime in Study Soto

	MEG	MLT	MEG – MLT Difference (95% CI)	P-value[a]
Article by Soto				
At the end of treatment	N=18	N=44		
cure	9 (50.0%)	15 (34.1%)	15.9% (-11.9, 42.2)%	0.2872
failure	0	0		
lost	1	0		
unknown	8	29		
At 1 month after treatment	N=18	N=44		
cure	16 (88.9%)	31 (70.5%)	18.4% (-7.1, 37.4)%	0.1293
failure	0	0		
lost	2	0		
unknown	0	13		
At 3 months after treatment	N=18	N=44		
cure	15 (83.3%)	39 (88.6%)	-5.3% (-30.6, 12.9)%	0.8606
failure	1	4		
lost	2	1		
unknown	0	0		
At 6 months after treatment	N=18	N=44		
cure	15 (83.3%)	36 (81.8%)	1.5% (-23.8, 20.9)%	1.0
failure	1	5		
lost	2	3		
FDA Analysis (Scenario #1)				
At 6 months after treatment	N=18	N=40		
cure	13 (72.2%)	32 (80.0%)	-7.8% (-34.8, 15.3)%	0.8185
failure	1 (5.5%)	6 (15.0%)		
lost	4 (22.2%)	2 (5.0%)		

MEG=Glucantime; MLT=miltefosine
[a]Boschloo's Test

Comment: *The article had 44 subjects in the miltefosine group as compared to 40 miltefosine subjects in the study report. According to the study report, 1 miltefosine subject (Patient ID 14) never received drug due to misdiagnosis and 3 miltefosine subjects (Patient ID's 7, 17, and 58) had records missing. It is unclear if these 4 specific subjects were included in the article.*

Table 20 is similar to Table 19 but excluded patients lost to follow up in calculating cure rates as was done in the article. These results are more in favor of SSG and at 1 month after

the end of therapy, the difference in cure rate was statistically significant (P-value=0.0179) with 70.5% of patients in the miltefosine group were cured compared to 100% of patients in the Glucantime group. By 3 months, the cure rates were no longer statistically different between the two treatments. This confirms the analysis above that it appeared that response to miltefosine was slower than Glucantime.

Table 20 Efficacy of Miltefosine as Compared with that of Glucantime in Study Soto

	MEG	MLT	MEG – MLT Difference (95% CI)	P-value[a]
Article by Soto				
At the end of treatment	N=17	N=44		
cure	9 (52.9%)	15 (34.1%)	18.9% (-9.6, 45.35)%	0.2193
failure	0	0		
lost	1	0		
At 1 month after treatment	N=16	N=44		
cure	16 (100%)	31 (70.5%)	29.6% (7.6, 45.7)%	0.0179
failure	0	0		
lost	2	0		
At 3 months after treatment	N=16	N=43		
cure	15 (93.8%)	39 (90.7%)	3.1% (-21.1, 17.9)%	0.9279
failure	1	4		
lost	2	1		
At 6 months after treatment	N=16	N=41		
cure	15 (93.8%)	36 (87.8%)	5.9% (-18.5, 21.9)%	0.6173
failure	1	5		
lost	2	3		
FDA Analysis (Scenario #2)				
At 6 months after treatment	N=14	N=38		
cure	13 (92.9%)	32 (84.2%)	8.6% (-18.6, 26.8)%	0.5861
failure	1	6		
lost	4	2		

MEG=Glucantime; MLT=miltefosine

[a]Boschloo's test

3.2.2.2.4 Efficacy Conclusions (Study Soto)

Miltefosine efficacy for *cutaneous leishmaniasis* in Bolivia cannot be adequately determined from Study Soto. It is not clear to us if this study randomized subjects to treatment. There were unexplained procedure changes during study conduct and it was unclear why the study was stopped early. The interpretation of the results is highly dependent on how subjects who were lost to follow-up are analyzed. There is concern that some Glucantime subjects were not followed due to their being the final three of the study. However, this study does give some evidence based on the article that subjects treated with miltefosine take longer to cure than subjects treated with Glucantime.

3.2.2.3 Study Z020

According to the study publications[5,6] (articles by Talhari et al., 2010 and Machado et al., 2011), Study Z020 was conducted following the observation that miltefosine-induced cure rate for leishmaniasis varied among the species of Leishmania causing disease and also between the same species acquired from different endemic areas. The study was designed to evaluate the efficacy and safety of miltefosine versus meglumine antimoniate (Glucantime) for the treatment of CL. There were two parts to this study, Z020a conducted in Manaus, Brazil, where *L.(V.) guyanensis* was epidemiologically the predominant pathogen, and Z020b conducted in endemic rural area in Bahia, Brazil where *L.(V.) braziliensis* was endemic. In contrast to the other studies submitted for the NDA review, parasitologic speciation of the infecting Leishmania organisms was obtained in every subject.

The sponsor refers to the two parts of Z020 as two separate studies. The title of Study Z020a is **"**Efficacy and Safety of Miltefosine Compared to Parenteral Antimony in the Treatment of Cutaneous Leishmaniasis Caused by *Leishmania (Viannia) guyanensis* in Manaus, Brazil: A Randomized Controlled Clinical Trial". The title of Study Z020b is: "Clinical Study to Assess the Efficacy and Safety of Oral Miltefosine in Brazilian Patients with Cutaneous Leishmaniasis Compared to Glucantime Standard Therapy as Active Control".

We view Z020a and Z020b as two parts of the same study. They are reviewed together here since these two studies were performed at the same time, used the same protocol, and case report forms, contained one pooled planned sample size, and were coordinated by the same coordinator. However, because there were separate articles for these two studies, presumably before the sponsor of the NDA got involved and the leishmania species was different, results below are presented separately for each study.

Each sub-study enrolled both children 2-11 years of age and adolescent/adults 12 years of age and older. This review will focus on the adolescent and adults 12 years of age and older as the indication sought by the applicant is for adult subjects only.

Comment*: Note for the pediatric patients, there is no obvious concern regarding the results in pediatrics. The sponsor's study report stated that in Study Z020a, the definitive cure rate at 6 months was 14/20 (70%) in the miltefosine group and 6/10 (60%) in the Glucantime group. In Study Z020b, the definitive cure rate at 6 months was 13/20 (65%) in the miltefosine group and 9/10 (90%) in the Glucantime group.*

3.2.2.3.1 Objectives and Study Design (Study Z020)

According to the study protocol, the objective of Study Z020 was to assess if the therapeutic activity and the safety of oral miltefosine in Brazilian patients with cutaneous leishmaniasis was similar to that observed in previous studies conducted in patients from Colombia and

Guatemala and to what extent the activity varied with leishmania species. The study reports stated that the specific objectives were to determine the efficacy and tolerance of miltefosine compared to Glucantime.

Study Z020 was a randomized, active comparator-controlled, open-label clinical trial to assess the efficacy and safety of oral miltefosine in patients with CL due to *L. guyanensis (Study Z020a)* or *L. braziliensis* (Study Z020b) in Brazil. Patients who met entrance criteria were randomized in 2:1 allocation between miltefosine and Glucantime. Adolescent/adult patients aged 12-65 yrs were randomized separately from pediatric patients aged 2-11 yrs. Patients randomized to the miltefosine (MLT) group received miltefosine (available in either 10 mg or 50 mg per capsule) at a target dose of 2.5 mg/kg/day orally for 28 days. Patients randomized to the Glucantime (MEG) group were administered 20 mg /kg/day antimony intramuscularly for 20 days. Because miltefosine was an oral medication and Glucantime was a parenteral medication, neither patients nor medical staff was blinded to study treatment. This study was conducted from 2007 to 2009 in Brazil.

Comment*: The protocol stated that treatment allocation was according to the randomization list generated by the institute of Biostatistics. No information regarding randomization procedure was provided. From the randomization scheme and code listed in Appendix 16.1.7 of the study report, it appeared that the randomization was stratified by sub-study and age and used a permuted block of size 3. Given the open-label nature of the design, the small block size would allow the investigator to easily know many patients' treatment assignment prior to enrollment. This is a concern as investigators might enroll patients in a particular order to enable certain patients to receive certain study medication, thereby eliminating the randomization. Since no randomization date was provided in the datasets and medication start dates varied, we cannot verify if the submitted randomization lists were actually complied with.*

Subjective tolerance and laboratory parameters were evaluated weekly during therapy and at the end of therapy. Efficacy was evaluated by measuring the lesion ulceration and surrounding inflammation at the beginning of therapy, the end of therapy, and at 2 weeks, 1, 2, 4, 6 months post therapy. Leishmania speciation was performed for every patient.

The protocol classified response criteria as follows: apparent cure, definitive cure, partial cure, and lack of clinical success. The primary efficacy endpoint was definitive cure defined as complete epithelializaton of all ulcers by the end of 6 months of the follow-up period. The study report stated that the definition of definitive cure in the protocol was incomplete, since it did not incorporate some of the criteria that would otherwise define a subject as a treatment failure. Thus the primary efficacy endpoint, definitive cure, was restated in the study report as 100% re-epithelializaton and loss of induration of all initial lesions at 2-months and at 6 months, no new lesions, residual lesions with parasites or $\geq$ 50% enlargement of a lesion prior to 6 months. Apparent cure was defined as complete re-epithelializaton of all ulcers at the 2 month follow-up. Failure was defined as the lack of either apparent cure at 2 months or lack of definitive cure at 6 months. In addition, other reasons for failure were residual lesions with presence of parasites in a Giemsa stained

imprint, or appearance of any new lesions, or ≥ 50% enlargement of previously documented lesions at any time prior to 6 months.

Comment*: Please note that the FDA medical officer has agreed with this newly defined primary efficacy endpoint.*

Comment*: While apparent cure was defined in the protocol and study report, the variable for the 2-month outcome in the submitted dataset was named "Initial cure". The term of initial cure will be used in this review.*

The protocol defined 3 analysis populations including Per Protocol, intention-to-treat, and safety analysis populations. It also stated that the primary analysis would be based on the intention to treat population. The definition of the intention to treat population excludes those lost to follow-up after baseline, an exclusion that we would not typically agree with. However, the sponsor redefined the analysis populations to the following, which do not exclude those subjects lost to follow-up:

- Modified Intention-to-treat (mITT Population): included all subjects who were exposed to study medication.
- Safety Population: included all subjects who had a least one dose of miltefosine or Glucantime for which case report form data were provided.

Note that we would not agree with the exclusion of subjects from the primary analysis population due to not receiving drug given that this is an open label study where knowledge of treatment assignment might influence the choice of the patient to receive medication. However, as discussed below, no subject was randomized and not treated.

The cure rates were compared by a two-sided Fisher's Exact Test for the mITT analysis set. Subjects who did not meet the criteria for cure or who did not come to the final 6 month follow up were considered failures in the mITT analysis.

There was no formal hypothesis stated in the protocol. The protocol for Z020 included a brief discussion of the sample size which was planned to be 180 total (Z020a and Z020b, adults and pediatrics). The sample size appears to have been chosen based on a desired precision of an estimate of miltefosine cure rate if the observed proportion cured with miltefosine was at least 89%. For Study Z020a, the initially planned number of subjects was 45 pediatric patients (age range: 2 to 11 years) and 45 adolescent/adult patients (age range: 12 to 65 years) in Study Z020a. The sample size was changed to 30 pediatric patients and 60 adolescent/adult patients according to protocol amendment #2. The publication[5] (*Talhari et al-2011*) stated that sample size was calculated based on an expected 30% difference between groups (cure rate of 50% for meglumine and 80% for miltefosine), 95% confidence interval and a power of 80%. For Study Z020b, there was no change in sample size: 30 pediatric patients and 60 adolescent/adult patients. The publication[6] (*Machado et al-2010*) of Study Z020b stated that sample size was calculated based on an absolute difference as large as 25% in cure rates between the two treatment groups with a statistical significance of 0.05 and a power of 80%.

The following section will report trial results for the adolescent and adult patient population.

***Comment**: It appears that the original plan was for the study to be analyzed as a whole, combining the two sites and the two age populations. However, there were two articles written for the two different sites and the information by sites is very informative given the different species at the two sites. Note that the results by age group (as given in the review) and by site, may be considered as subgroup analyses. Therefore, interpretation of statistical analysis, most importantly the protection of type I error control, should be viewed with caution.*

3.2.2.3.2 Patient Disposition, Demographics and Baseline Characteristics (Study Z020)

Table 21 shows disposition for adolescent/adult patients in Studies Z020a and Z020b.

Table 21 Number of subjects and disposition in Study Z020

	Study Z020a			Study Z020b		
	MEG	**MLT**	**Total**	**MEG**	**MLT**	**Total**
No. Randomized	20	40	60	20	40	60
No. Treated with drug	20	40	60	20	40	60
No. Completed Treatment	20	37	57	16	35	51
Treatment stopped early	0	3[a]	3	4[b]	5[c]	9
No. Evaluated at 2 month after treatment	18	36	54	19	39	58
Missing visit	2	4	6	1	1	2
No. Evaluated at 6 month after treatment	19	36	55	16	39	55
Early withdrew	1	4	5	4	1	5
Patients in efficacy analysis						
Modified Intent to treat (mITT)	20	40	60	20	40	60
Patients in safety analysis						
safety	20	40	60	20	40	60

MEG=Glucantime; MLT=miltefosine

[a]Patients 048, 049 and 056 were treated with miltefosine for 10, 12, and 14 days, respectively.

[b]Patients 132, 158, 162, and 164 were treated with Glucantime for 14 days.

[c]Patients 159, 160, 161, 163 and 165 were treated with miltefosine for 14 days.

<u>Study Z020a</u>

A total of 60 patients were enrolled in Study Z020a, 20 in the Glucantime group and 40 in the miltefosine group. Of the 20 Glucantime-treated patients, 2 missed the 2-month visit and 1 withdrew prior to the 6-month exam. The number of patients who completed the study and were evaluated at 6 months after treatment completion was 19 in the Glucantime group. Of the 40 miltefosine-treated patients, 4 missed the 2-month visit and 4 were early withdrawal before the end of the study. The number of patients who completed the study and were evaluated at 6 months after treatment completion was 36 in the miltefosine group. All 60 patients received at least one dose of study drug and constituted the mITT population for efficacy analysis.

All patients in the Glucantime group were administered Glucantime intramuscularly for 20 days. In the miltefosine group, all but 3 patients received miltefosine orally for 28 days. Patient 048 was lost after 10 days on miltefosine and Patient 049 was removed from the study after 12 days of therapy due to intercurrent malaria infection. Patient 056 was recorded as having received only 14 days of dosing but completed the study.

Except for Patients 056 and 069 who were treated with 100 mg per day, all adolescent/adult patients treated with miltefosine received three 50 mg tablets per day (total daily dose 150 mg) during the study. The mean miltefosine dose was 2.3 mg/kg/day ranging from 1.4 to 3.1 mg/kg/day.

Study Z020b

A total of 60 patients were enrolled in Study Z020b, 20 in the Glucantime group and 40 in the miltefosine group. Of the 20 Glucantime-treated patients, 1 missed the 2-month visit and 4 withdrew prior to the 6-month exam. The number of patients who completed the study and were evaluated at 6 months after treatment completion was 16 in the Glucantime group. Of the 40 miltefosine-treated patients, 1 missed the 2-month visit and 1 withdrew before the end of the study. The number of patients completed the study and evaluated at 6 months after treatment completion was 39 in the miltefosine group. All 60 patients received at least one dose of study drug and constituted the mITT population for efficacy analysis.

Comment*: Note the large and imbalanced number of patients who withdrew prior to the study end, 4/20 (20%) in the Glucantime arm and 1/40 (2.5%) in the miltefosine arm. The impact of early withdrawal on efficacy outcome is explored in Section 3.2.2.3.3.*

Nine patients were treated with study medication for 14 days instead of 20 (for Glucantime patients) or 28 days (for miltefosine patients). In the Glucantime group, 4 patients (Patient 132, 158, 162, and 164) were recorded as having taken the first 2 weeks of therapy but none during the third week. In the miltefosine group, 5 patients (Patients 159, 160, 161, 163, and 165) were recorded as having taken the first 2 weeks of therapy but not the third week.

Except for 4 patients (Patients 135, 157, 163, and 166) who were treated with 100 mg per day, all adolescent/adult patients treated with miltefosine received three 50 mg tablets per day which was equivalent to total daily dose of 150 mg. The mean miltefosine dose was 2.6 mg/kg/day with a range of 1.9 to 3.3 mg/kg/day.

Summary statistics for gender, age, weight, and baseline lesion for all patients are shown in Table 22.

Table 22 Demographics and Baseline Characteristics in Study Z020

	Study Z020a			Study Z020b		
	MEG (N=20)	**MLT** (N=40)	**Total (N=60)**	**MEG** (N=20)	**MLT** (N=40)	**Total (N=60)**
Gender (N, %)						
Female	3 (15.0%)	8 (20.0%)	11 (18.3%)	9 (45.0)	9 (22.5)	18 (30.0)
Male	17 (85.0%)	32 (80.0%)	49 (81.7%)	11 (55.0)	31 (77.5)	42 (70.0)
Age (year)						
Mean ± SD	30.6 ± 14.6	30.9 ± 13.5	30.8 ± 13.7	29.5 ± 13.4	29.4 ±14.2	29.4 ± 13.8
Median	24.5	29	28	28	24	25.5
Range	14 - 57	12 - 61	12 - 61	13 - 65	12 - 59	12 - 65
<18 years	2 (10.0%)	8 (20.0%)	10 (16.7%)	4 (20.0%)	6 (15.0%)	10 (16.7%)
≥18 years	18 (90.0%)	32 (80.0%)	50 (83.3%)	16 (80.0%)	34 (85.0%)	50 (83.3%)
Weight (kg)						
Mean ± SD	64.8 ± 11.3	66.3 ± 13.5	65.8 ± 12.7	60.6 ± 11.8	56.3 ± 10.2	57.7 ± 10.8
Median	64	64	64	59.5	56.5	58.0
Range	43 - 84	42 - 104	42 -104	38 - 89	35 - 80	35 - 89
<45 Kg	1 (5.0%)	2 (5.0%)	3 (5.0%)	2 (10.0%)	4 (10.0%)	6 (10.0%)
≥45 Kg	19 (95.0%)	38 (95.0%)	57 (95.0%)	18 (90.0%)	36 (90.0%)	54 (90.0%)
Number (%) of Subjects with						
1 lesion	8 (40.0)	19 (47.5)	27 (45.0)	19 (95.0)	29 (72.5)	48 (80.0)
2 lesions	4 (20.0)	4 (10.0)	8 (13.3)	0 (0.0%)	7 (17.5)	7 (11.7)
3 lesions	3 (15.0)	8 (20.0)	11 (18.3)	1 (5.0)	4 (10.0)	5 (8.3)
4 lesions	3 (15.0)	7 (17.5)	10 (16.7)	-	-	-
5 lesions	2 (10.0)	2 (5.0)	4 (6.7)	-	-	-
Total Number of Lesions per subject						
Mean ± SD	2.35 ± 1.42	2.23 ± 1.35	2.27 ± 1.36	1.10 ± 0.45	1.38 ± 0.67	1.28 ± 0.61
Median	2	2	2	1.0	1.0	1.0
Range	1-5	1-5	1-5	1.0 - 3.0	1.0 - 3.0	1.0 - 3.0
Spieces (%)						
L. braziliensis	1 (5.0)	1 (2.5)	2 (3.3)	20 (100%)	40 (100%)	60 (100%)
L. guyanensis	19 (95.0)	39 (97.5)	58 (96.7)	-	-	-

MEG=Glucantime; MLT=miltefosine

In Study Z020a, most (81.7%) of adolescent/adults were male; the mean age was 30.8 years; the mean weight was 65.8 kg and the range was 42-104 kg. There were 1 to 5 lesions per subject and 45% (27/60) of patients had a single lesion. Leishmania speciation was obtained in all patients and *L. guyanensis* was identified in 58 (96.7%) patients. There was no significant difference in these characteristics between the two study groups.

In Study Z020b, the majority (70%) of adolescents/adult subjects was male; the mean age was 29.4 years; the mean weight was 57.7 kg and ranged between 35 and 89 kg. There were 1 to 3 lesions per subject and 80% (48/60) of subjects had a single lesion. In the two treatment groups, 77-80% of adolescent/adult subjects were parasitologically-positive by either culture or PCR. *L. braziliensis,* identified in 41 biopsy samples by PCR, was the only species found. There was no significant difference in these characteristics between the two study groups. However, the miltefosine group tended to have more males than females and had more subjects with multiple lesions compared to the Glucantime group.

3.2.2.3.3 Efficacy Results (Study Z020)

Table 23 presents initial cure at 2 months after end of therapy and definitive cure rates at 6 months after end of therapy for the two treatment groups.

Table 23 Cure Rates in Study Z020

	Study Z020a		Study Z020b	
Patient Status	**MEG**	**MLT**	**MEG**	**MLT**
At 2 months after end of therapy	N=20	N=40	N=20	N=40
missing visit	2	4	1	1
Failure	4	7	6	4
Initial cure	14 (70.0%)	29 (72.5%)	13 (65.0%)	35 (87.5%)
At 6 months after end of therapy	N=20	N=40	N=20	N=40
Lost to Follow up (LTFU)	1	4	4	1
Failure	7	9	7	5
Definitive cure	12 (60.0%)	27 (67.5%)	9 (45.0%)	34 (85.0%)
Analysis of Definitive Cure Rate				
mITT analysis				
Definite cure	12/20 (60.0%)	27/40 (67.5%)	9/20 (45.0%)	34/40 (85.0%)
Difference (MLT – MEG)	-	7.5%	-	40.0%
(95% CI)		(-17.9, 34.6)%		(8.6, 63.5)%
P-value	-	0.6147	-	0.0018
Sensitivity analysis #1				
Definite cure	12/19 (63.2%)	27/36 (75.0%)	9/16 (56.3%)	34/39 (87.2%)
Difference (MLT – MEG)	-	11.8%	-	30.9%
(95% CI)		(-13.9, 39.2)%		(2.4, 58.3)%
P-value	-	0.41	-	0.0235
Sensitivity analysis #2				
Definite cure	13/20 (65.0%)	31/40 (77.5%)	13/20 (65.0%)	35/40 (87.5%)
Difference (MLT – MEG)	-	12.5%	-	22.5%
(95% CI)		(-11.6, 38.5)%		(0.0, 47.3)%
P-value	-	0.3694	-	0.0504

MEG=Glucantime; MLT=miltefosine
[a]Boschloo's test
Sensitivity analysis #1: Excluding LTFU
Sensitivity analysis #2: Including LTFU as cure in both MEG and MLT

Study Z020a

At 2 months after completing therapy, 14 (70%) of the 20 Glucantime-treated patients and 29 (72.5%) of the 40 miltefosine-treated patients were initially cured. There were 6 patients who missed the 2-month exam, 2 in the Glucantime group and 4 in the miltefosine group.

At 6-month post treatment, there were 5 patients (1 MEG; 4 MLT) who were lost to follow up and did not come to 6-month visit. There were 16 patients (7 MEG; 9 MLT) who clinically failed. If patients who were lost to follow up were considered as failures in the mITT analysis, the definitive cure rate was 67.5% for the miltefosine group and 60.0% for the Glucantime group. There was no statistical difference between the cure rates for the two treatment groups (P-value=0.6147). The 95% confidence interval for the difference in cure rates was (-17.9, 34.6)%.

In order to assess the impact of subjects who withdrew early from the study for reasons other than clinical failure, this reviewer performed 2 sensitivity analyses. Sensitivity Analysis #1 excluded patients who were lost to follow up and the definitive cure rates were based on patients actually evaluated at 6-months. When the 5 early dropouts were excluded from the analysis, 12 (63.2%) of the 19 Glucantime-treated patients had definitive cure and 27 (75.0%) of the 36 miltefosine-treated patients had definitive cure (P-value=0.41). Sensitivity Analysis #2 included patients who were lost to follow up in the analysis and assumed them cured at 6-month visit. The corresponding cure rates were 65% for Glucantime and 77.5% for miltefosine (P-value=0.3694). There was no statistical difference between the two treatment groups in terms of definitive cure at 6-month after the end of therapy although the cure rate appeared to be slightly higher in the miltefosine group.

Comment*: Although this study was not a non-inferiority trial by design, it is interesting to note that the lower 95% confidence limit for cure rate difference between groups was approximately 18%. We would need evidence that the comparator Glucantime was more effective than placebo by a margin of at least approximately this much in order to comfortably conclude that miltefosine was superior to placebo. Given the results from the placebo controlled trial previously discussed, this is quite possible. However, the sponsor did not provide a discussion of the non-inferiority assessment of miltefosine compared to Glucantime.*

Study Z020b

At 2 months after completing therapy, 13 (65.0%) of the 20 Glucantime-treated patients and 35 (87.5%) of the 40 miltefosine-treated patients were initially cured. There were 2 patients who missed the 2-month exam, 1 in each treatment group.

At 6-month post treatment, there were 5 patients (4 MEG; 1 MLT) who were lost to follow up and did not come to 6-month visit. There were 12 patients (7 MEG; 5 MLT) who clinically failed. If patients who were lost to follow up were considered as failures in the mITT analysis, the definitive cure rate was 85% for the miltefosine group and 45% for the

Glucantime group, which was statistically significantly different (P-value=0.0018). The 95% confidence interval for the difference in cure rates was (8.6, 63.5)%.

In order to assess the impact of subjects who withdrew early from the study for reasons other than clinical failure, this reviewer performed 2 sensitivity analyses. Sensitivity Analysis #1 excluded patients who were lost to follow up and the definitive cure rates were based on patients actually evaluated at 6-months. When the 5 early dropouts were excluded from the analysis, 9 (56.3%) of the 16 Glucantime-treated patients had definitive cure and 34 (87.2%) of the 39 miltefosine-treated patients had definitive cure (P-value=0.0235). Sensitivity Analysis #2 included patients who were lost to follow up in the analysis and assumed them cured at 6-month visit. The corresponding cure rates were 65% for Glucantime and 87.5% for miltefosine (P-value=0.0504). The miltefosine-treated subjects had a significantly better outcome than those treated with Glucantime in terms of definitive cure at 6 months follow up.

***Comment**: Given that the results of miltefosine compared to Glucantime were superior, it is not necessary to determine a valid non-inferiority margin in order to interpret the results. However, we do note that as discussed above, the analysis of the adults from the Z020b site can be considered a subgroup analysis, in which control of multiplicity had not been pre-specified or taken into account in the analysis. These results though supportive of the effect of miltefosine should be considered with some caution.*

3.2.2.3.4 Efficacy Conclusions (Study Z020)

Miltefosine efficacy for the treatment of *cutaneous leishmaniasis* had been studied in Study Z020 which was split in two parts, Z020a in Manaus, Brazil where *L.(V.) guyanensis* was epidemiologically the predominant pathogen and Z020b in Bahia, Brazil where *L.(V.) braziliensis* was endemic. Miltefosine was compared to Glucantime with respect to definitive cure rate at 6 months after completion of therapy for adolescent/adult patients who were at least 12 years old. In Study Z020a, miltefosine appeared to be similarly efficacious as Glucantime. The definitive cure rate for miltefosine was 67.5% of 40 patients and for Glucantime was 60% of 20 patients (95% CI of the difference of (-17.9, 34.6)%. In Study Z020b, miltefosine was superior to Glucantime. The definitive cure rate for miltefosine was 85% of 40 patients and for Glucantime was 45% of 20 patients (P-value = 0.0018). The results were consistent when patients who withdrew prematurely from the study were considered as failures in the analysis, or were excluded from the analysis, or were included in the analysis as cured. Though these results are supportive of the effect of miltefosine in the treatment of cutaneous leishmaniasis, some caution should be considered given that these results are essentially subgroup analyses of the whole Z020 study with a lack of pre-specified type I error control for multiplicity, there was no pre-specified NI margin, and the study was open label and used small block sizes leading to a potential concern over the randomization of the study.

***Comment**: Note that in an analysis of Z020 as a whole, stratified by age and site, miltefosine was not found to be statistical superior to Glucantime (Exact CMH test p value = 0.09).*

3.2.3 Studies for Mucosal Leishmaniasis (ML)

3.2.3.1 Study Z022

Study Z022 was originally designed as a Phase 2, randomized, equivalency study of oral miltefosine versus standard therapy with pentavalent antimony (Glucantime) in the treatment of Mucosal Leishmaniasis (ML). The trial was amended when the study team became aware that pentavalent antimony had been rejected as ineffective for ML at this site. The study was conceptually modified to compare oral miltefosine with intravenous amphotericin B. When the efficacy of oral miltefosine became apparent in initial patients, however, additional patients refused to be entered into an amphotericin B arm. Therefore, the final study design became an evaluation of 1 cohort of 79 patients who received miltefosine. The protocol was not formally amended during the study. The title of Study Z022 is "Treatment of Bolivian Mucosal Leishmaniasis with Miltefosine".

3.2.3.1.1 Objectives and Study Design (Study Z022)

According to the study protocol, the intention of this study was to evaluate if miltefosine, 2.5mg/kg/day by 28 days, compared favorably with Glucantime, 20 mg/kg/day by 28 days, in the treatment of the mucosal leishmaniasis in Bolivia. Because of the change in treatment groups (i.e. elimination of the randomized comparison to pentavalent antimony), the study became a single-group, open-label, single-center Phase 2 trial of miltefosine in patients with ML. The objectives were changed to evaluate the effectiveness of miltefosine by examining lesions for signs of healing and tolerance to miltefosine by recording AEs that occurred during the treatment of patients with ML.

Patients who met the inclusion criteria were administered miltefosine at a target dose of 2.5 mg/kg/day for 28 days with meals. All treatment was observed by study staff. Tolerance was determined twice a week during therapy by evaluating AEs. At the end of therapy, screening laboratory tests were repeated. Patients were evaluated at the beginning of therapy, the end of therapy, and at 2 weeks and 2, 6, 9, and 12 months after the end of therapy. This trial was conducted from 2004 to 2006 at Hospital Local in Palos Blancos, Bolivia.

***Comment**: Note the 2-week visit was added (not in the protocol) to increase follow up.*

The protocol classified efficacy responses as: clinical cure, clinical improvement, without clinical changes, clinical worsening, parasitological cure, and parasitological fault. According to the article[7] by Soto et al. 2007 that reported the results of this study, the

protocol-defined outcomes were clinical cure (>90% loss of presenting signs), clinical improvement (50%-90% loss of presenting signs), no clinical change (25% worsening to 49% improvement in presenting signs), and clinically worse (>25% worsening of presenting signs or relapse after initial improvement).

There were 5 anatomic sites involved: nasal skin, nasal mucosa, palate, pharynx, and larynx. Each lesion was to be individually used for efficacy analysis. Because of the complexity of analyzing data from each of 5 anatomic sites from each of 6 time points for 79 patients, the sponsor retrospectively created a composite endpoint, the "mucosal severity score" (ML severity score), which consisted of the sum of the grades for all lesion sites. This ML severity score was specified as the primary efficacy endpoint in the study report.

At any assessment time point, the ML severity score was computed by adding a severity score (0 =none, 1 = mild, 2 = moderate, 3 = severe) for each of 4 pathological signs (erythema, edema, infiltration, and erosion) for each of the 5 disease sites (nasal skin, nasal mucosa, palate, pharynx, and larynx). For example, at any time point, the maximum mucosal severity score for a subject who presents with lesions involving the nasal skin, nasal mucosa, palate, pharynx, and larynx patient is 60: 3 points for each of 4 pathological signs at each of the 5 sites. Larger scores appropriately reflected an increased severity of involvement for any sign, increased number of signs of involvement at any site, and increased number of disease sites.

Comment*: Note the protocol stated that erythema, edema, scabs, and perforation would be the signs to be evaluated. Clinical consideration led the investigator to construct ML severity score using erythema, edema, infiltration, and erosion as final signs.*

Comment*: Limited information is available regarding the ML severity score. It seems that each site and each sign is equally weighted in the scoring system. We do not know whether the ML severity score has been previously used or validated and what kind of properties it has.*

The study report stated that efficacy was based on the extent of lesion healing by using the change in the ML severity score at 12 months compared with the baseline score. Efficacy responses at 12 months post treatment were defined below.

Response	Change in ML Severity Score Compared with Baseline
cured	≥ 90% improvement
improved	50 to < 90% improvement
not changed	25% worsening to < 50% improvement
worsened	< 25% worsening
presumptive failure	discontinued follow-up because cure at 12 months was unlike

Comment*: It is unclear if these cut points were fully explored as being meaningful to a patient.*

The study report defined 3 analysis datasets:

- Safety analysis set: included all subjects who had a least one oral dose of miltefosine. The analysis of all safety variables was based on this population.
- Modified intention-to-treat (mITT) set: included all subjects who were exposed to study medication and for whom at least one follow-up documentation of any efficacy data was available.
- Per-protocol (PPS) set: included all subjects who fulfilled the selection criteria and who received the scheduled trial medication on at least 90% of the planned treatment days and who were assessed after 12 months.

Comment*: We disagree with the above definition of mITT set which required subjects to have at least one follow-up documentation of any efficacy data. Please note that all subjects were actually included in the mITT analysis.*

According to the study report, ML severity scores and efficacy responses were calculated for the mITT and PPS sets. Subjects who did not come to the final 12-month follow-up visit were considered failures to achieve cure for the mITT analysis. In addition, ML severity scores and efficacy responses were calculated for subgroups of the mITT and PPS with just proximal disease and subjects with distal disease. Subjects with proximal disease include those lesions that affect nasal skin, nasal mucosa, and lips, but without any evidence of distal disease. Subjects with distal disease include those subjects that have distal disease with or without proximal disease. Distal disease includes lesions involving the palate, pharynx, larynx, uvula, and epiglottis.

Sample size of Study Z022 was determined as described in the original protocol when the miltefosine group (75 patients) was to be compared with the Glucantime group (25 patients). After the study was changed, the original miltefosine group size was retained, ultimately resulting in 79 patients treated.

3.2.3.1.2 Patient Disposition, Demographics and Baseline Characteristics (Study Z022)

Table 24 shows subject disposition in Study Z022. All 79 patients received at least 1 dose of drug. Three patients were not evaluable at 12 months post treatment, including 1 patient (No. 106) who was not seen at 12 months, 1 patient (No. 31) who had paracoccidiomycosis instead of leishmaniasis but was misdiagnosed at entry, and 1 patient (No. 43) who died of intercurrent disease during therapy. All patients except Patient No. 043 took miltefosine for the prescribed number of days. All subjects were included in the mITT analysis. The 3 non-evaluable subjects were excluded from the PP analysis.

Table 24 Number of subjects and disposition in Study Z022

	N
No. Treated with drug	79
No. Completed treatment	78[a]
No. Evaluable	76
lost to follow up	1[b]
Wrong diagnosis	1[c]
death	1[a]
Patients in efficacy analyses	
Modified Intent to treat (mITT)	79
Per-protocol (PP)	76
Patients in safety analyses	
safety	79

[a]Patient 043 died during therapy
[b]Patient 106 was not seen at 12 months
[c]Patient 031 was misdiagnosed

Table 25 presents demographics and baseline characteristics of the 79 patients. The mean age was 39 years with a range between 12 and 79 years of age. There were a greater proportion of males (73%) than females (27%). The race was mostly mestizo (mixed European and Native American Indian ancestry) (92%), followed by Native Indian (5%), Black (1%), and Unknown (1%). Baseline weight record was not known for Patient 043 and the average weight for 78 patients was 58 kg.

The average number of clinical sites involved was 1.8 and the ML severity score at study entry was 9.4, ranging from 1 to 38. About half of the patients had distal disease which involved nasal skin and/or nasal mucosa. Cultures were taken from only a few patients and all parasites were identified as *L braziliensis.*

APPEARS THIS WAY ON ORIGINAL

Table 25 Demographics and Baseline Characteristics in Study Z022

Characteristic	Result (N=79*)
Gender (n, %)	
Male	58 (73.4%)
Female	21 (26.6%)
Race (n, %)	
Black	1 (1.3%)
Mestizo	73 (92.4%)
Native Indian	4 (5.1%)
Unknown	1 (1.3%)
Ethnicity (n, %)	
Moseten	2 (2.5%)
White/Aymara	68 (86.1%)
White/Quechua	5 (6.3%)
Unknown	4 (5.1%)
Age (year)	
Mean ± SD	39.4 ± 16.5
Median	38
Range	12 - 79
12-<18 years	4 (5.1%)
>=18 years	75 (94.9%)
Weight (kg)[a]	
Mean ± SD	58.0 ± 9.0
Median	58
Range	35 - 85
< 45 kg	1 (1.3%)
≥ 45 kg	77 (94.4%
unknown	1 (1.3%)
Number of clinical sites involved	
Mean ± SD	1.8 ± 0.9
Median	2
Range	1-5
ML severity score before treatment	
Mean ± SD	9.4 ± 7.4
Median	6
Range	1-38
Disease type	
distal	39 (49.4%)
proximal	40 (50.6%)

*unless otherwise noticed.
[a]N=78 since 1 patient (No. 043) had no body weight record

3.2.3.1.3 Efficacy Results (Study Z022)

Table 26 summarizes the clinical response rates at the 12-month exam for both the mITT and PP populations. For the mITT population: 49 (62.0%) patients were cured, 16 (20.3%)

improved, 6 (7.6%) showed no change and 1 (1.3%) worsened. In addition, 4 patients were presumptive failures. Three of these 4 patients (No. 73, 74, and 115) did not return for 12-month follow-up, but the investigator was informed by other parties that the patients had failed. The fourth patient (No. 79) had a severity score prior to 12 months that was 30% larger than at entrance and was judged by the investigator to have failed at that time.

Table 26 Clincial Responses at 12-month after treatment in Study Z022

Clinical Response	mITT (N=79)	PP (N=76)
Cured	49 (62.0%)	49 (64.5%)
Improved	16 (20.3%)	16 (21.1%)
No Change	6 (7.6%)	6 (7.9%)
Worsened	1 (1.3%)	1 (1.3%)
Presumptive Failure	4 (5.1%)	4 (5.3%)
Not Evaluable	3 (3.8%)	-

Of the 49 subjects defined by the sponsor as cured using the ML severity score, all 49 obtained a complete cure, meaning a complete resolution of each of the 4 pathological signs for each of the disease sites affected. This is important in that the complete cure rate is 62% which is not reliant on the ML severity scores, whose properties are unknown.

Table 27 shows the response rates for patients by disease type at study entry. The cure rates at 12-month follow up were 56.4% and 67.5% in patients with distal and proximal disease, respectively.

Table 27 Clinical response by body weight and disease status in Study Z022

	N	Cured	Improved	No Change	Worsened	Presumptive Failure	Not Evaluable
All subjects	79	49 (62.0%)	16 (20.3%)	6 (7.6%)	1 (1.3%)	4 (5.1%)	3 (3.8%)
Disease Type							
Distal	39	22 (56.4%)	12 (30.8%)	3 (7.7%)	0 (0.0%)	2 (5.1%)	0 (0.0%)
Proximal	40	27 (67.5%)	4 (10.0%)	3 (7.5%)	1 (2.5%)	2 (5.0%)	3 (7.5%)

Table 28 provides summary values of the ML severity score at all time points for the mITT population. Mean ML severity scores steadily decreased from nearly 10 to approximately 2 over the 13 months of the trial. The mean ML severity score at the 12-month exam was 1.79 with a range of 0 to 26.

Table 28 Summary ML Severity Scores during the course of Study Z022

	N	Mean	SD	Median	Min	Max
Before treatment	78	9.44	7.44	6	1	38
After end of treatment						
2 weeks	78	5.15	6.14	2	0	31
2 months	77	3.83	4.73	2	0	20
6 months	76	2.18	3.88	0	0	17
9 months	75	1.64	3.38	0	0	16
12 months	73	1.79	3.98	0	0	26

3.2.3.1.4 Efficacy Conclusions (Study Z022)

In Study Z022, a cohort of 79 patients with mucosal leishmaniasis caused by *L braziliensis* in Bolivia was treated by miltefosine and followed for 12 months after completing therapy. The rate of complete cure at 12 months post treatment was 62%. Due to the nature of single-center single-arm open-label design, interpretation of results from this study is limited.

3.3 Evaluation of Safety

This section provides a brief summary of safety data on miltefosine. For detailed safety information, please refer to the FDA medical officer's review.

3.3.1 Studies for Visceral Leishmaniasis (VL)

3.3.1.1 Study 3154

A total of 169 (42.5%) subjects reported at least one adverse event (AE) in Study 3154, 125 (41.8%) in miltefosine and 44 (44.4%) in the amphotericin B group. Treatment emergent AEs were reported in 106 patients (35.5%) after use of miltefosine and in 39 patients (39.4%) after use of amphotericin B. There were 6 miltefosine subjects (2.0%) and 1 amphotericin B subject (1.0%) that developed at least one serious adverse event (SAE). Eight miltefosine subjects (2.7%) and 3 amphotericin B subjects (3.0%) developed an AE that led to drug discontinuation. These included the subjects with SAEs. Two deaths occurred during the study, both in the miltefosine arm. The first death (Patient 3-038) was a 13 year old male patient who became drowsy on Day 11 of miltefosine treatment and died 2 days later due to meningitis. The second death (Patient 3-030) was a 15 year female who had finished miltefosine course.

Among the 197 AEs reported for the miltefosine group, 159 (80.7%) had standard toxicity grade of 1, 21 (10.7%) were graded 2, 10 (5.1%) were graded 3, and 7 (3.6%) were graded 4. According to the study report, the most commonly reported adverse reactions in miltefosine patients were nausea and vomiting, affecting about 37.8% and 20.4% of the miltefosine treated patients respectively. The corresponding incidence rates in the amphotericin B group were 20.2% and 6.1%, respectively. Anorexia was also reported as most frequent, affecting 11% of miltefosine patients and 13.1% amphotericin B patients, respectively.

Among the 79 AEs reported for the amphotericin B group, 57 (72.5%) had standard toxicity grade of 1, 15 (18.9%) were graded 2, 4 (5.1%) were graded 3, and 3 (3.8%) were graded 4. The most commonly reported adverse reactions were rigors, affecting 90.1% of patients in

the amphotericin B group. In addition, thrombocytopenia, headache, hypokalemia, and fever were reported.

3.3.1.2 Study Z025

A few adverse events including gastrointestinal symptoms (vomiting and diarrhea), respiratory symptoms (pneumonia), and bleeding were recorded in Study Z025. Specifically, the incidence of vomiting was higher in the miltefosine group than that in the SSG group, 159/290 (54%) versus 93/290 (32%). The incidences of other AEs were equal or slightly lower in miltefosine-treated patients compared to those of SSG-treated patients, 51% versus 53% for diarrhea, 27% versus 33% for pneumonia, and 22% versus 22% for bleeding. There was one significant AE. Patient No.174 discontinued treatment with miltefosine due to presumed "allergy" 21 days after entering the study.

Deaths were evaluated as an efficacy endpoint in this study and summary statistics for deaths in each group are discussed in Section 3.2.1.2.3 above. Almost all patients who died during therapy received drug up to the day of death. All the 15 patients who died after therapy essentially completed the targeted treatment period of 28 days for miltefosine and 30 days for SSG. There were no SAEs according to the study report.

3.3.2 Studies for Cutaneous Leishmaniasis (CL)

3.3.2.1 Study 3168

A total of 376 adverse event (AE) records were included in the submitted dataset, 276 on miltefosine subjects and 100 on placebo subjects. Among the 276 AEs reported for the miltefosine group, 238 (86%) had standard toxicity grade of 1, 18 (6.5%) were graded 2, and 20 (7.2%) had no severity recorded. Placebo patients reported 100 AEs, 74 (74%) were graded 1, 9 (9%) were graded 2, and 17 (17%) had no severity recorded. According to the study report, the most commonly reported adverse reactions in miltefosine patients were nausea and vomiting, affecting about one third of the miltefosine treated patients (36% and 31.5%, respectively). The corresponding incidence rates in the placebo group were lower (9.1% and 4.5%, respectively). Motion sickness and headache were the most frequently observed adverse events for both groups. The incidence rate during miltefosine use was slightly higher than placebo (motion sickness: 29.2% vs. 22.7%; headache: 27% vs. 20.5%). Additionally, there were a few other nonspecific symptoms reported in miltefosine treated patients but not in the placebo group. These included dizziness (4.5%), pruritus (4.5% each), somnolence (3.4%), and malaise (2.2%).

Miltefosine treatment was discontinued prematurely in one patient (Pat 1/59) at day 27 due to motion sickness and headache. There was no serious adverse event or death reported for Study 3168.

3.3.2.2 Study Soto

A total of 48 (83%) subjects reported at least one AE in Study Soto, 34 in miltefosine and 14 in Glucantime group. Most (60% and 71% in the two groups, Glucantime and miltefosine, respectively) of the AEs in both treatment groups were mild. There was one severe AE, lower abdominal pain in one subject (Patient ID 44) treated with miltefosine.

There were 97 AEs in the miltefosine group, 69 (71.1%) were mild, 3 (3.1%) were moderate, 1 (1.0%) were severe and 24 (24.8%) had no severity recorded. The most commonly reported AEs involved gastrointestinal tract such as nausea (47.5% of subjects), vomiting (37.5% of subjects), and diarrhea (15.0% of subjects). Besides gastrointestinal disorders, headache, decreased appetite, and somnolence were the other most commonly reported AEs in 27.5%, 15%, and 10% of subjects, respectively.

There were 37 AEs in the Glucantime group, 22 (59.5%) were mild, 5 (13.5%) were moderate, and 10 (27.0%) had no severity recorded. AEs due to Glucantime typically involve the musculoskeletal system. Arthralgias and myalgia were reported by 42.9% and 14.3% of subjects who received Glucantime, respectively. Injection site pain was also commonly reported, 35.7% of subjects. Headache was reported in 50% of subjects receiving Glucantime, of which 21.4% of subjects reported moderate headache.

Comment*: Please note that according to the article[4] by Soto et al., miltefosine patients were queried daily during therapy for vomiting, diarrhea, nausea, anorexia, abdominal pain, headache, and motion sickness. Glucantime patients were queried daily for diarrhea, headache, arthraglgia, and local pain. Because of the possible different practice, the reporting of adverse events might somewhat be biased.*

There were no deaths, other severe adverse events, or other significant adverse events.

3.3.2.3 Study Z020

Study Z020a

In Study Z020a in adolescent/adult patients, 31 (77.5%) of the 40 miltefosine-treated subjects and 10 (50.0%) of the 20 Glucantime-treated subjects reported at least one AE. All AEs were mild to moderate except 3 in the miltefosine group (1 instance of abdominal pain, 1 instance of back pain and 1 instance of urticaria).

Miltefosine side effects typically involve the gastrointestinal system. Of the 40 adolescent/adults, diarrhea, vomiting, nausea, and abdominal pain were reported by 4 (10%), 16 (40%), 8 (20%), and 5 (12.5%) subjects respectively. One report of abdominal pain was severe in intensity. There were 4 cases of mild testicular pain in adolescent/adults that each lasted for 1, 1, 1, and 6 days. AEs due to Glucantime typically involve the musculoskeletal system. For the 20 adolescent/adult subjects, there were 2 (10%) cases of mild and 5 (25%) cases of moderate arthralgias.

There were no deaths, other severe adverse events, or other significant adverse events in Study Z020a.

Study Z020b

In Study Z020b in adolescent/adult patients, at least one AE was reported in 100% of subjects. The majority of AEs were mild in both groups (71.2% miltefosine and 63.6% Glucantime). Moderate AEs were reported in 65% of miltefosine-treated subjects and in 80% of Glucantime-treated subjects. A few AEs were severe: 1 of 257 in the miltefosine group and 3 of 118 in the Glucantime group. Each of these severe AEs was reported in different subjects.

Miltefosine side effects typically involve the gastrointestinal system. Of the 40 adolescent/adults, diarrhea, vomiting, abdominal pain, and nausea were reported by 8, 18, 7, and 4 subjects respectively, with 1 episode each of diarrhea and vomiting being severe.

Glucantime side effects typically involve the musculoskeletal system. For all Glucantime subjects, there were 11, 1 and 5 cases of mild to moderate arthralgia/back pain/myalgia, 14 of which were attributable to drug.

There were no deaths, other severe adverse events, or other significant adverse events.

3.3.3 Studies for Mucosal Leishmaniasis (ML)

3.3.3.1 Study Z022

Seventy-four (94%) of the 79 patients experienced at least one adverse event (AE). There were 258 AEs in total, 244 AEs (94.6%) were grade 1, 14 AEs (5.4%) were grade 2, and no AE was grade 3 or higher. Main adverse events noted in at least 2% of subjects included abdominal pain, dysphagia, gastritis, nausea, malaise, non-cardiac chest pain, pyrexia, decreased appetite, arthralgias, back pain, dizziness, headache, and pruritis. There was 1 subject who discontinued the drug due to an AE and 1 subject who died. There was no other severe adverse event and no other significant adverse event.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Studies for Visceral Leishmaniasis (VL)

4.1.1 Study 3154

4.1.1.1 Gender, Race, Age, and Geographic Region (Study 3154)

Subgroup analysis by race is not applicable in Study 3154 since all patients were classified as Asians with the exceptions of 2 Nepalese patients. An analysis of the final cure rates by subgroups of age, gender, and center was performed for Study 3154 (Table 29).

Table 29 Final cure at 6 months by age, gender, or center in Study 3154

ITT Population	AMB	MLT	AMB – MLT Difference (95% CI)	P-value[a]
All subjects	96/99 (97.0%)	282/299 (94.3%)	2.7% (-3.0, 6.8)%	0.3242
Age				
12-18 years	30/31 (96.8%)	100/102 (98.0%)	-1.3% (-14.3, 4.9)%	0.9873
>=18 years	66/68 (97.1%)	182/197 (92.4%)	4.7% (-2.7, 10.1)%	0.1755
Gender				
Male	56/58 (96.6%)	199/211 (94.3%)	2.2% (-6.2, 7.4)%	0.7192
Female	40/41 (97.6%)	83/88 (94.3%)	3.2% (-7.1, 11.0)%	0.5213
Center				
Site 1	35/36 (97.2%)	101/109 (92.7%)	4.5% (-7.1, 12.0)%	0.4405
Site 2	35/36 (97.2%)	105/108 (97.2%)	0.0% (-11.3, 6.0)%	1.0
Site 3	26/27 (96.3%)	76/82 (92.7%)	3.6% (-11.6, 12.8)%	0.6527
Center and Gender				
Site 1 Male	23/23 (100%)	80/88 (90.9%)	9.1% (5.4, 17.6)%	0.1358
Site 1 Female	12/13 (92.3%)	21/21 (100%)	-7.7% (-36.0, 9.9)%	0.2092
Site 2 Male	20/21 (95.2%)	65/66 (98.5%)	-3.3% (-21.1, 5.1)%	0.4548
Site 2 Female	15/15 (100%)	40/42 (95.2%)	4.8% (-16.6, 16.6)%	0.5878
Site 3 Male	13/14 (92.9%)	54/57 (94.7%)	-1.9% (-27.1, 10.5)%	1.0
Site 3 Female	13/13 (100%)	22/25 (88.0%)	12% (-14.1, 31.2)%	0.2442

AMB= amphotericin B; MLT=miltefosine

[a]Boschloo's Test

Of a total of 133 patients aged 12 to 18 years old, 102 of them were treated by miltefosine and had a final cure rate of 98% compared to 96.8% in those treated with amphotericin B. In the 265 patients who were 18 years old or up, the final cure rate was 92.4% in the miltefosine group and 97.1% in the amphotericin B group. The difference in final clinical cure rates between treatment groups was not statistically significant in either age category. The upper 95% confidence bound for the difference was 4.9% in adolescents and 10.1% in patients aged 18 or above, respectively.

As noted in Section 3.2.1.1.2, there was a clear imbalance in gender distribution since 70.6% of patients in the miltefosine group were males compared to that of 58.6% in the amphotericin B group (2-sided Fisher test P-value = 0.035). Table 29 shows that in the miltefosine group, the proportion of male and female patients with clinical cure was 94.3% for both genders. In the amphotericin B group, the final cure rate was 96.6% for males and 97.6% for females. Despite the fact that males seemed to be preferentially enrolled in the miltefosine arm, there was no statistical difference between amphotericin B and miltefosine in terms of final cure for either male or female patients. The upper 95% confidence bound for the difference was 7.4% in males and 11.0% in female patients, respectively.

The 398 patients exposed to study medication were recruited in 3 centers with the sample sizes being 145, 144, and 109, respectively. The results for each of the 3 centers are provided in Table 29. The differences in final cure rates between amphotericin B and miltefosine treatments were 4.5%, 0.0%, and 3.6% for centers 1, 2, and 3, respectively. The corresponding upper 95% confidence bound for the difference was 12.0%, 6.0%, and 12.8% in centers 1, 2, and 3, respectively.

A further analysis was conducted to investigate center and gender together with respect to final cure. As discussed in Section 3.2.1.1.2, the gender mismatch was most obvious in study Site 1 (M/F 4.2 in MLT; 1.8 in AMB), to a lesser extent in Site 3 (M/F 2.3 in MLT; 1.8 in AMB), but not in study Site 2 (M/F1.6 in MLT; 1.4 in AMB). Table 29presents the final cure rates at 6-month post treatment by center and gender. While male patients in Site 1 seemed to have higher final cure rate with amphotericin B treatment, the final cure rate was higher with miltefosine in females at Site 1. In both Site 2 and 3, miltefosine treatment corresponded to slightly higher final cure rates in males and slightly lower cure rates in females. None of these differences was statistically significant and there was no apparent relationship among center, gender, and final clinical cure.

Overall, analyses of the final cure rates by subgroups of age, gender, and center showed generally consistent results as those when all randomized patients were analyzed.

4.1.1.2 Other Special/Subgroup Populations (Study 3154)

Study 3154 allowed for the inclusion of newly diagnosed (not pretreated) as well as patients previously treated for their disease. Table 30 shows the final cure rate in relation to prior treatment. There was no apparent difference in the cure rate depending on the history of the disease in relation to prior therapy. In the miltefosine group, 80 of the pretreated patients (94.1%) had a final cure diagnosed 6 months after end of treatment with miltefosine. This final cure rate was the same in the subgroup of newly diagnosed patients (94.4%) and in all miltefosine-treated patients (94.3%). In the amphotericin B reference group, 26 of 28 pre-treated patients (92.9%) and 70 of 71 newly diagnosed patients (98.6%) were finally cured after use of amphotericin B.

Table 30 Final cure at 6 months by prior therapy or body weight in Study 3154

ITT Population	AMB	MLT	AMB – MLT Difference (95% CI)	P-value[a]
All subjects	96/99 (97.0%)	282/299 (94.3%)	2.7% (-3.0, 6.9)%	0.3242
Diagnosis of VL				
Previously treated	26/28 (92.9%)	80/85 (94.1%)	-1.3% (-17.2, 8.4)%	0.9914
Newly diagnosed	70/71 (98.6%)	202/214 (94.4%)	4.2% (-2.0, 8.7)%	0.1401
Body Weight				
< 25 kg	16/16 (100%)	28/28 (100%)	NA	NA
≥ 25 kg	80/83 (96.4%)	254/271 (93.7%)	2.7% (-4.0, 7.3)	0.3783

AMB= amphotericin B; MLT=miltefosine

[a]Boschloo's Test

The protocol of Study 3154 defined the target dose of miltefosine to be 2.5 mg/kg/day. The great majority of patients allocated to miltefosine, 271 of 299 patients received miltefosine at a dosage of 100 mg/day while a lower dosage of 50 mg/day was used in of the remaining 28 patients with a body weight below 25 kg. Table 30 displays the final clinical cure rates by body weight. For patients whose body weight was lower than 25 kg, the final cure rates were 100% following either amphotericin B or miltefosine (50 mg/day) treatment. In patients with body weight at least 25 kg, the final cure rates were 96.4% in the amphotericin B arm and 93.7% in the miltefosine (100 mg/day) arm with no statistical significant difference between these 2 arms.

In the miltefosine group, as stated above, dosage varied based on body weight of < or >= 25 kg, in order to achieve an approximately 2.5 mg/kg dosage. The mg/kg dosage ranges from 1.5 mg/kg to 4.0 mg/kg among all the subjects in the miltefosine group. A logistic regression was conducted to see if there was a relationship between mg/kg dose and definitive cure. There was no apparent relationship between miltefosine daily dosage per kg body weight and final cure rate (P-value=0.1231). However, as shown in the table below, there is a trend toward lower final cures in subjects who received less than 2.5 mg/kg miltefosine dose.

MLT Dose (mg/kg)	Final Cure
1.5 -< 2	24/26 (92.3%)
2- <2.5	96/104 (92.3%)
2.5-< 3	114/121 (94.2%)
3-3.9	39/39 (100%)
≥ 4	9/9 (100%)
Total	282/299 (94.3%)

MLT=miltefosine

4.1.2 Study Z025

4.1.2.1 Gender, Race, Age, and Geographic Region (Study Z025)

Since Study Z025 only enrolled male patients, subgroup analysis by gender is not applicable. The study was conducted in Humera Hospital and Mycadra Health Center in Ethiopia. The study report does not contain any information on subgroup analysis based on center, race, or age. No relevant information was submitted for review.

4.1.2.2 Other Special/Subgroup Populations (Study Z025)

As stated by the sponsor, HIV seropositive, seronegative, and status-unknown patients were to be analyzed separately according to the clinical protocol. Based on information from the article[2] by *Ritmeijer et al (2006),* final cure rates at 6-month follow up were calculated respectively for HIV-infected, Non-HIV infected, and HIV status unknown patients. Please see Section 3.2.1.2.3 for details.

4.2 Studies for Cutaneuous Leishmaniasis (CL)

4.2.1 Study 3168

4.2.1.1 Gender, Race, Age, and Geographic Region (Study 3168)

Table 31 summarizes definite cure by subgroups of race, age, gender, and center was performed for Study 3168.

APPEARS THIS WAY ON ORIGINAL

Table 31 Definite cure at 6 months by race, age, gender, and center in Study 3168

ITT Population	PLA	MLT	MLT - PLA Difference (95% CI)	P-value[a]
All subjects	13/44 (29.6%)	59/89 (66.3%)	36.8% (18.5, 52.4) %	<0.0001
Race				
White	11/31 (35.5%)	43/63 (68.3%)	32.8% (10.2, 52.0)%	0.0039
Black or African American	0/2 (0.0%)	8/9 (88.9%)	88.9% (3.7, 99.7)%	0.0375
American Indian or Alaska Native	2/11 (18.2%)	8/17 (47.1%)	28.9% (-10.4, 59.4)%	0.167
Age				
12-<18 years	6/14 (42.9%)	15/19 (78.9%)	36.1% (0.8, 65.4)%	0.0441
>=18 years	7/30 (23.3%)	44/70 (62.9%)	39.5% (18.0, 56.9)%	<0.001
Gender				
Male	9/38 (23.7%)	53/81 (65.4%)	41.8% (22.5, 57.5) %	<0.001
Female	4/6 (66.7%)	6/8 (75.0%)	8.3% (-43.9, 57.5) %	0.8565
Center				
Colombia	9/24 (37.5%)	40/49 (81.6%)	44.1% (18.9, 64.8) %	<0.001
Guatemala	4/20 (20.0%)	19/40 (47.5%)	27.5% (0.8, 49.1) %	0.0434
Center and Gender				
Colombia Male	5/18 (27.8%)	34/42 (80.9%)	53.2% (21.8, 74.4)%	<0.001
Colombia Female	4/6 (66.7%)	6/7 (85.7%)	19.1% (-32.0, 66.4)%	0.5825
Guatemala Male	4/20 (20.0%)	19/39 (48.7%)	28.7% (1.5, 50.6)%	0.0364
Guatemala Female	0/0	0/1	NA	NA

PLA=placebo; MLT=miltefosine
[a]Boschloo's Test

In Study 3168, 94 (70.7%) patients were white, 63 were treated by miltefosine and 31 by placebo. There was significant improvement in definite cure, 68.3% in the miltefosine group versus 35.5% in the placebo group, which was consistent with the results when all subjects were analyzed. The difference in definite cure rates was 88.9% for black or African American patients and 28.9% for American Indian or Alaska Native patients. However, interpretation is limited due to the small number of subjects in these race categories.

A total of 33 patients aged 12 to 18 years old, 19 of them were treated by MLT and had a definite cure rate of 78.9% compared to 42.9% in those treated with placebo (P-value=0.0441). In the 100 patients who were 18 years old or up, the definite cure rate was 62.9% in the MLT group and 23.3% in the placebo group (P-value<0.001).

As shown in Table 31, there were only 14 female patients in Study 3168 and the proportion of females was low compared to males, 10% versus 90%. In male patients, the 6-month definite cure rate were 53/81 (65.4%) after miltefosine treatment and 9/38 (23.7%) after placebo treatment, respectively. In females, the corresponding cure rates were 4/6 (66.7%) and 6/8 (75.0%), which were not statistically different. Note that only the Colombia site recruited a relevant number of female patients (13 females vs 60 males), while in Guatemala all patients but one were males (1 female vs 59 males).

The 133 patients exposed to study medication were recruited in 2 centers (Colombia and Guatemala) with the sample size being 73 and 60 respectively. Definite cure rates by center are provided in Table 31 which shows about 2.2-fold higher cure rate of miltefosine-treated patients compared to placebo in both centers. In Colombia, 40 (81.6%) miltefosine recipients and 9 (37.5%) placebo recipients were cured. In Guatemala, 19 (47.5%) miltefosine recipients and 4 (20.0%) placebo recipients were cured. Of note both the placebo and miltefosine cure rates in Guatemala were less than those in Colombia, with 20% versus 37.5% in placebo group and 47.5% versus 81.6% in patients treated miltefosine. In Colombia the difference in definite cure between placebo and miltefosine was 44.1% with 95% confidence interval of (18.9%, 64.8%) (P-value <0.001). At Guatemala, the difference was 27.5% with 95% CI (0.8%, 49.19%) (P-value=0.0434).

According to the study report, the leishmania speciation was different between the two study centers, which might attribute to the lower response in both study arms in Guatemala compared to Colombia. In Colombia, cultures of 7 baseline lesion aspirates were speciated by monoclonal antibody binding. All 7 parasites were *L. v. pana*mensis. In Guatemala, 46 of the 60 infecting parasites were speciated by PCR. A total of 63% of speciated parasites were *L. v. braziliensis,* and 37% of speciated parasites were *L. m. mexicana.* The rate of cure of *L. v. braziliensis* was low (33%), compared with the rate of cure of *L. m. mexicana* (60%). Note the submitted NDA does not contain patient level data on parasitologic speciation of the infecting *Leishmania* organism.

4.2.1.2 Other Special/Subgroup Populations (Study 3168)

Study 3168 allowed for the inclusion of newly diagnosed (not pretreated) as well as patients previously treated for their disease. Table 32 shows the definite cure rate in relation to prior treatment. In newly diagnosed patients, miltefosine showed significant improvement in the cure rate over placebo, 68.8% versus 32.4%. However, the efficacy of miltefosine was not statistically significant in patients who had been previously treated. Of the 22 pre-treated patients, 6 patients eventually had proven failure or relapse after treatment with miltefosine and 8 did not achieve definite cure after treatment with placebo. This corresponded to a cure rate of 50% (6/12) in miltefosine arm and 20% (2/10) in placebo arm, a 30% improvement despite of lack of significance probably due to limited number of subjects.

Table 32 Definite cure at 6 months by prior treatment and body weight in Study 3168

ITT Population	PLA	MLT	MLT - PLA Difference (95% CI)	P-value[a]
All subjects	13/44 (29.6%)	59/89(66.3%)	36.8% (18.5, 52.4) %	<0.0001
Diagnosis of CL				
Newly diagnosed	11/34 (32.4%)	53/77 (68.8%)	36.5% (15.7, 54.2)%	0.0006
Previously treated	2/10 (20.0%)	6/12 (50.0%)	30.0% (-12.5, 66.3)%	0.1738
Body Weight				
< 45 kg	3/6 (50.0%)	9/9 (100%)	50% (5.2, 88.2)%	0.0282
≥ 45 kg	10/38 (26.3%)	50/80 (62.5%)	36.2% (16.8, 52.6)%	<0.001

PLA=placebo; MLT=miltefosine
[a]Boschloo's Test

To achieve the miltefosine target dose of 2.5 mg/kg/day, 118 patients weighing ≥45 kg were administered 3 capsules per day and the other 15 patients weighing < 45 kg were given 2 capsules per day. Table 32 displays the definite cure rates at 6 month after the end of therapy by body weight. For patients with body weight lower than 45 kg, the definite cure rates were 100% after miltefosine use and 50% after placebo. In patients with body weight at least 45 kg, the definite cure rates were 62.5% in the MLT arm and 26.3% in the placebo arm. The difference was 36.2% (P-value<0.001), consistent with the findings when all subjects were included in the analysis.

In the miltefosine group, as stated above, dosage varied based on body weight of < or >= 45 kg, in order to achieve an approximately 2.5 mg/kg dosage. The mg/kg dosage ranges from 1.8 mg/kg to 3.4 mg/kg among all the subjects in the miltefosine group. A logistic regression was conducted to see if there was a relationship between mg/kg dose and definitive cure. There was no apparent relationship between miltefosine daily dosage per kg body weight and definitive cure (P-value=0.4643). However, as shown in table below, definitive cure rate was lower in subjects who received a miltefosine dose less than 2.5 mg/kg/day.

MLT Dose (mg/kg)	Definitive Cure
1.8 -< 2	2/5 (40.0%)
2- <2.5	25/39 (64.1%)
2.5-< 3	27/38 (71.1%)
≥ 3	5/7 (71.4%)
Total	59/89 (66.3%)

MLT=miltefosine

4.2.2 Study Soto

As discussed in Section 3.2.2.2.3, there was a large disparity in number of failures and lost to follow up in the two study arms, which affected the calculation of clinical cure rate at 6 months after the end of therapy. Since there was concern with subjects not being followed equally on the two arms, rates of lost to follow-up are questionable. In order to better

explore the efficacy of miltefosine, un-confounded with lost to follow-up, failure rate at 6 month follow up was computed and employed for the purpose of subgroup analysis. The results of failure rates were consistent in that failure rate in miltefosine subjects were higher as compared to that in Glucantime subjects although the differences were not statistically significant.

4.2.2.1 Gender, Race, Age, and Geographic Region (Study Soto)

Subgroup analysis by center is not applicable as there is only a single center in Study Soto.

As shown in Table 33, a total of 13 patients were aged 12 to 18 years old, 7 of them were treated by miltefosine and had a failure rate of 28.6% compared to 16.7% in those treated with Glucantime. In the 45 patients who were 18 years old or up, the failure rate was 12.1% in the miltefosine group and 0% in the Glucantime group. There were only 13 female patients in Study Soto and the proportion of females was low compared to males, 22.4% versus 77.8%. In male patients, the 6-month failure rates were 6/31 (19.4%) after miltefosine treatment and 1/14 (7.1%) after Glucantime use, respectively. In females, the corresponding cure rates were 0/9 (0.0%) and 0/4 (0.0%). Consistent with the overall population results, miltefosine treatment had higher failure rate than Glucantime at 6 month after the end of therapy, though not statistically significantly higher.

Table 33 Failure rate at 6 months by age and gender in Study Soto

mITT Population	MEG	MLT	MEG - MLT Difference (95% CI)	P-value[a]
All subjects	1/18 (5.5%)	6/40 (15.0%)	-9.4% (-13.3, 25.8)%	0.3722
Age				
12-<18 years	1/6 (16.7%)	2/7 (28.6%)	-11.9% (-59.4, 40.2)%	0.7644
>=18 years	0/12 (0.0%)	4/33 (12.1%)	-12.1% (-28.7, 14.5)%	0.2558
Gender				
Male	1/14 (7.1%)	6/31 (19.4%)	-12.2% (-31.9, 15.9)%	0.3592
Female	0/4 (0.0%)	0/9 (0.0%)	NA	NA

MEG=Glucantime; MLT=miltefosine
[a]Boschloo's Test

4.2.2.2 Other Special/Subgroup Populations (Study Soto)

Higher failure rates in miltefosine subjects were also observed when patients were analyzed by baseline body weight or number of lesions. Table 34 displays the failure rates at 6 month after the end of therapy by body weight. Although there were only a few patients with body weight lower than 45 kg, their failure rates were 33.3% after miltefosine use and 0.0% after Glucantime. In patients with body weight at least 45 kg, the failure rates were 13.5% in the MLT arm and 6.3% in the Glucantime arm. The difference was 7.3%, consistent with the findings when all subjects were included in the analysis.

A total of 34 patients had a single lesion at baseline, 25 of them were treated by miltefosine and had a failure rate of 16% compared to 11.1% in those treated with Glucantime. In the 16 patients who had 2 lesions at baseline, the failure rate was 10% in the miltefosine group and 0% in the Glucantime group. The failure rate was 20% in the miltefosine group and 0% in the Glucantime group for those patients with 3 lesions at baseline. There was no statistically significant difference between treatment groups.

Table 34 Failure rate at 6 months by body weight and number of lesions in Study Soto

ITT Population	MEG	MLT	MEG - MLT Difference (95% CI)	P-value[a]
All subjects	1/18 (5.5%)	6/40 (15.0%)	-9.4% (-13.3, 25.8)%	0.3722
Body Weight				
< 45 kg	0/2 (0.0%)	1/3 (33.3%)	-33.3% (-90.6, 60.4)%	0.6676
≥ 45 kg	1/16 (6.3%)	5/37 (13.5%)	-7.3% (-24.1, 17.6)%	0.5541
Number of Lesions				
1	1/9 (11.1%)	4/25 (16%)	-4.9% (-28.7, 32.7)%	0.9414
2 or 3	0/9 (0.0%)	2/15 (13.3%)	-13.3% (-40.9, 20.0)%	0.3709

MEG=Glucantime; MLT=miltefosine
[a]Boschloo's test

To achieve the miltefosine target dose of 2.5 mg/kg/day, 37 patients weighing ≥45 kg were administered 3 capsules (150mg) per day and the other 3 patients weighing < 45 kg were given 2 capsules (100mg) per day. In the miltefosine group, the average body weight was 58kg (range 39-78kg) and the mean dosage was 2.6 mg/kg/day. There was no apparent relationship between miltefosine daily dosage per kg body weight and definitive cure according to a logistic regression model (P-value=0.3597).

4.2.3 Study Z020

4.2.3.1 Gender, Race, Age, and Geographic Region (Study Z020)

While Study Z020 was essentially one whole study with 2 centers, results from each center were reported separately as Study Z020a and Study Z020b. There was no information on race in the submitted datasets or study report. Thus subgroup analysis by center or race for each of Study Z020a or Study Z020b is not applicable.

Study Z020a

Table 35 shows the primary efficacy outcome by patient's age and gender for Study Z020a. In the adolescent age (<18 years) group, 1 of 2 Glucantime subjects (50%) versus 6 of 8 miltefosine subjects (75%) were cured. For adult patients, the cure rate was 61.1% for the Glucantime group and 65.6% for the miltefosine group. There was no statistical difference between the cure rates for the two treatment groups in either age category. There were 11 female and 49 male adolescent/adult patients in Study Z020a. In female patients, the 6-month definite cure rate were 7/8 (87.5%) after miltefosine treatment and 0/3 (0.0%) after Glucantime treatment (P-value=0.0145), respectively. In males, the corresponding cure rates were 20/32 (62.5%) and 12/17 (70.6%); however, the difference was not statistically significant. Except for male patients, miltefosine treatment had higher definitive cure rate than Glucantime at 6 month after the end of therapy.

Table 35 Definitive Cure Rate at 6 months by age and gender in Study Z020a

ITT Population	MEG	MLT	MLT - MEG Difference (95% CI)	P-value[a]
All subjects	12/20 (60.0%)	27/40 (67.5%)	7.5% (-17.9, 34.6)%	0.6147
Age				
<18years	1/2 (50.0%)	6/8 (75.0%)	25.0% (-43.6, 84.2)%	0.7393
>=18 years	11/18 (61.1%)	21/32 (65.6%)	4.5% (-23.1, 33.1)%	0.7767
Gender				
Female	0/3 (0.0%)	7/8 (87.5%)	87.5% (15.8, 99.7)%	0.0145
Male	12/17 (70.6%)	20/32 (62.5%)	-8.1% (-34.4, 22.1)%	0.6576

MEG=Glucantime; MLT=miltefosine

[a]Boschloo's test

Study Z020b

Table 36 shows the primary efficacy outcome by patient's age and gender for Study Z020b. In adult patients, there was a statistical significant improvement in definitive cure rate in response to miltefosine treatment. Twenty-eight (82.4%) of the 34 miltefosine patients achieved definitive cure compared to 43.8% (7/16) Glucantime patients (P-value = 0.0107) at 6 months after the end of therapy. Cure rates in adolescent subjects were 100% for miltefosine and 50% for Glucantime (P-value =0.099). There were 18 female and 42 male patients in Study Z020b. In male patients, the 6-month definite cure rate were 28/31 (90.3%) after miltefosine treatment and 6/11 (54.5%) after Glucantime treatment (P-value=0.018), respectively. In females, the corresponding cure rates were 6/9 (66.7%) and 3/9 (33.3%), respectively. Consistent with the overall population results, miltefosine treatment led to higher definitive cure rate than Glucantime at 6 month after the end of therapy.

Table 36 Definitive Cure Rate at 6 months by age and gender in Study Z020b

ITT Population	MEG	MLT	MLT - MEG Difference (95% CI)	P-value[a]
All subjects	9/20 (45.0%)	34/40 (85.0%)	40.0% (8.6, 63.5)%	0.0018
Age				
<18years	2/4 (50.0%)	6/6 (100.0%)	50.0% (-8.7, 93.2)%	0.099
>=18 years	7/16 (43.8%)	28/34 (82.4%)	38.6% (6.9, 64.9)%	0.0107
Gender				
Female	3/9 (33.3%)	6/9 (66.7%)	33.3% (-18.1, 73.3)%	0.2384
Male	6/11 (54.5%)	28/31 (90.3%)	35.8% (4.9, 66.5)%	0.018

MEG=Glucantime; MLT=miltefosine

[a]Boschloo's test

4.2.3.2 Other Special/Subgroup Populations (Study Z020)

Study Z020a was conducted in region of Brazil where CL was mainly due to *L. guyanensis.* PCR-speciation showed that of the 60 lesions from adolescent/adult patients tested, all but 2 (Patient 046, 083) were due to *L. guyanensis*. At the 6 month follow up, Patient 046 treated with miltefosine had definitive cure and Patient 083 treated with MEG was evaluated as failure. No subgroup analysis by leishmaniasis species was performed.

Study Z020b was conducted in region of Brazil where CL was mainly due to *L.braziliensis.* According to the study report, that in 41 biopsy samples by PCR, *L.braziliensis* was the only species found. Therefore, no subgroup analysis by leishmaniasis species was performed.

Study Z020a

The target dose of miltefosine oral therapy was 2.5 mg/kg/day. Patients were administered with 2 or 3 capsules of 50 mg miltefosine each day according to their body weights. As shown in Table 37 for Study Z020a, there were only 3 patients with body weight lower than 45 kg, 1 in the Glucantime group and 2 in the miltefosine group. In patients with body weight at least 45 kg, the definitive cure rate was higher in the miltefosine group, 68.4% in the MLT arm versus 57.9% in the Glucantime arm but the difference was not statistically significant.

In the miltefosine group, the average body weight was 66.3kg (range 42-104kg) and the mean dosage was 2.3 mg/kg/day. Twenty-seven of the 40 patients were cured when assessed at 6 month follow up. A logistic regression model was utilized to analyze the relationship between daily MLT dosage on a mg/kg basis and definite cure rate. There appears to be a positive relationship between miltefosine daily dosage per kg body weight and definitive cure (P-value=0.0205). Those who have received higher daily miltefosine dose on a mg/kg basis had a significantly higher chance to achieve definite cure at the end of 6 month follow up.

Table 37 Definite cure at 6 months by body weight and treatment duration in Study Z020a

ITT Population	MEG	MLT	MLT - MEG Difference (95% CI)	P-value[a]
All subjects	12/20 (60.0%)	27/40 (67.5%)	7.5% (-17.9, 34.6)%	0.6147
Body Weight				
< 45 kg	1/1 (100.0%)	1/2 (50.0%)	-50.0% (-98.7, 76.9)%	0.7698
≥ 45 kg	11/19 (57.9%)	26/38 (68.4%)	10.5% (-15.8, 38.1)%	0.4623
Number of lesions				
Single	5/8 (62.5%)	14/19 (73.7%)	11.2% (-26.0, 51.9)%	0.6232
multiple	7/12 (58.3%)	13/21 (61.9%)	3.6% (-30.8, 38.7)%	0.8932

MEG=Glucantime; MLT=miltefosine
[a]Boschloo's test

As stated earlier, nearly half (27/60, 45%) of the patients in Study Z020a had single lesion at study entry. Table 37 shows that 19 of the 27 patients with single lesion were treated by miltefosine and had a definitive cure rate of 73.7% compared to 62.5% in those treated with Glucantime. In the 33 patients who had 2 or more lesions at baseline, the definitive cure rate was 61.9% in the miltefosine group and 58.3% in the Glucantime group. There was no statistically significant difference between treatment groups.

Study Z020b

Table 38 shows the definite cure rate at 6 months after the end of therapy by patient's body weight in Study Z020b. For patients with body weight lower than 45 kg, their definite cure rates were 75% after miltefosine use and 50% after Glucantime use. In patients with body weight at least 45 kg, the definite cure rates were generally higher in the miltefosine group, 86.1% in the miltefosine arm versus 44.4% in the Glucantime arm (P-value=0.0018).

In the miltefosine group, the average body weight was 56.3 (range 35-80kg) and the mean dosage was 2.5 mg/kg/day. Thirty-four of the 40 patients were cured when assessed at 6 month follow up. A logistic regression model was utilized to analyze the relationship between daily miltefosine dosage on a mg/kg basis and definite cure rate. There was no apparent relationship between miltefosine daily dosage per kg body weight and definitive cure (P-value=0.5685).

Table 38 Definite cure at 6 months by body weight and treatment duration in Study Z020b

ITT Population	MEG	MLT	MLT - MEG Difference (95% CI)	P-value[a]
All subjects	9/20 (45.0%)	34/40 (85.0%)	40.0% (8.6, 63.5)%	0.0018
Body Weight				
< 45 kg	1/2 (50.0%)	3/4 (75.0%)	25% (-56.9, 89)%	0.815
≥ 45 kg	8/18 (44.4%)	31/36 (86.1%)	41.7% (9.6, 65.9%)	0.0018
Number of lesions				
Single	9/19 (47.4%)	23/29 (79.3%)	31.9% (3.7, 57.8)%	0.0264
Multiple	0/1 (0.0%)	11/11 (100%)	100% (-2.0, 100.0)%	0.064

MEG=Glucantime; MLT=miltefosine

[a]Boschloo's test

As stated earlier, the majority (48/60, 80%) of patients in Study Z020b had single lesion at study entry. Table 38 shows that 29 of the 48 patients with single lesion were treated by miltefosine and had a definitive cure rate of 79.3% compared to 47.4% in those treated with Glucantime (P-value=0.0264). In the 12 patients who had 2 or more lesions at baseline, the definitive cure rate was 11/11 (100%) in the miltefosine group and 0/1 (0.0%) in the Glucantime group.

4.3 Studies for Mucosal Leishmaniasis (ML)

4.3.1 Study Z022

4.3.1.1 Gender, Race, Age, and Geographic Region (Study Z022)

Subgroup analysis by center is not applicable as there is only a single center in Study Z022.

As shown in Table 39, there were only 4 patients who were less than 18 years old. At 12-months after end of therapy, 1 was cured, 2 improved, and 1 had condition worsened. In patients aged 18 and up, the cure rate was 64%. There were 21 female patients in Study Z022 and the proportion of females was low compared to males, 26.6% versus 73.4%. In male patients, the 12-month cure rate was 33/58 (56.9%). In females, the corresponding cure rates were 16/21 (76.2%), which was slightly higher than males. However, interpretation of the results is limited due to the nature of single-arm study design without a comparator.

Table 39 Clinical response by Age and Sex in Study Z022

	N	Cured	Improved	No Change	Worsened	Presumptive Failure	Not Evaluable
All subjects	79	49 (62.0%)	16 (20.3%)	6 (7.6%)	1 (1.3%)	4 (5.1%)	3 (3.8%)
Age							
12-<18 years	4	1 (25.0%)	2 (50.0%)	0 (0.0%)	1 (25.0%)	0 (0.0%)	0 (0.0%)
>=18 years	75	48 (64.0%)	14 (18.7%)	6 (8.0%)	0 (0.0%)0	4 (5.3%)	3 (4.0%)
Gender							
Male	58	33 (56.9%)	15 (25.9%)	5 (8.6%)	0 (0.0%)	3 (5.2%)	2 (3.5%)
Female	21	16 (76.2%)	1 (4.8%)	1 (4.8%)	1 (4.8%)	1 (4.8%)	1 (4.8%)

4.3.1.2 Other Special/Subgroup Populations (Study Z022)

Table 40 shows the response rates for patients by body weight and disease status or type at study entry. There was only 1 patient with a body weight less than 45 kg. As reported in Section 3.2.3.1.3, the cure rate of distal patients was 56.4%, whereas the cure rate of patients with proximal disease was 67.5%. Again, interpretation of the results is limited due to the nature of single-arm study design without a comparator.

Table 40 Clinical response by body weight and disease status in Study Z022

	N	Cured	Improved	No Change	Worsened	Presumptive Failure	Not Evaluable
All subjects	79	49 (62.0%)	16 (20.3%)	6 (7.6%)	1 (1.3%)	4 (5.1%)	3 (3.8%)
Body Weight							
< 45 kg	1	1(100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
≥ 45 kg	77	48 (62.3%)	16 (20.8%)	6 (7.8%)	1 (1.3%)	4 (5.2%)	2 (2.6%)

5 SUMMARY AND CONCLUSIONS

This NDA submission contained 6 studies which evaluated the efficacy and safety of miltefosine for the treatment of visceral, cutaneous, and mucosal leishmaniasis. Miltefosine capsules were given orally at target of 2.5 mg/kg/day for 28 days in all studies.

5.1 Statistical Issues

The following issues identified during the review are common among the submitted studies.

- Except for Study 3168, all of the studies submitted to support the efficacy and safety of miltefosine were of open-label design which may introduce serious bias and impact study integrity. Additionally, Study 3168 which was reported to be blinded appears to have been merely masked using terms “A” and “B”. Bias or expectations of the observers can not only influence the measurement taken but also affect study conduct. For example in Study Z025, the study investigator would analyze mortality

and toxicity data on an ongoing basis and there was no assurance that any alterations to the conduct of the trial were made in an unbiased way. In Study 3154, a few non-treated subjects were excluded from the sponsor's analysis. It should be noted that the very reason for a subject not taking medication may be because of the knowledge of treatment assignment.

- Although the randomization lists were provided for the studies, there was no randomization date in the submitted datasets. It is unclear if the submitted randomization lists were actually used in the study. In many studies the order given in the randomization lists did not appear to have been followed. Furthermore, there was very limited information on the randomization algorithm. It appears from the randomization list that a permuted block of a small size, 3 or 4, were used in most cases. Given the nature of open-label design, it is possible that investigators might enroll patients in a particular order to enable certain patients to receive certain study medication, thereby eliminating the randomization.

- Many analyses included in the sponsor's study reports were performed post hoc. None of the 6 studies was conducted under an IND. All studies were completed and published before the current sponsor of the development of miltefosine was identified. The sponsor obtained study documents such as case report forms, protocols, datasets in most cases, and published articles from the investigators. The sponsor then created statistical analysis plans and clinical study reports submitted to this NDA. In many studies, the efficacy endpoints, analytical populations, and analysis methods were defined post hoc or changed from those in the original protocol or literature if available. For example, the protocol of Study Z025 contained no explicit discussion about analysis populations. The publication of Study Z025 stated that data were analyzed on an intent-to-treat basis. The sponsor defined 3 analysis populations (Intent-to-treat, Per protocol, and Safety) post-hoc and chose the Per Protocol population for the analysis of primary efficacy endpoint, which the FDA disagreed.

- The submitted datasets often do not contain outcomes measured prior to final evaluation. In Study Soto, although clinical responses were evaluated at the end of therapy and at 1, 3, and 6 months afterwards, only data at the 6-month visit were submitted. Our evaluation of early miltefosine efficacy has to rely on the published article[4] on this study (*Soto et al. 2008*). In Study Z020, the study report showed patient's status at 2, 4, or 6 months after the end of treatment but the submitted datasets included no information at 4 months visit.

5.1.1 Studies for Visceral Leishmaniasis (VL)

In support of the VL indication, one pivotal study (Study 3154) and one supportive study (Study Z025) were submitted. Study 3154 was conducted in 1999-2000 in India and Study

Z025 was conducted in 2003-2005 in Ethiopia. In both countries, *L. donovani* is epidemiologically the causative species.

Study 3154

Study 3154 was a randomized, open-label, non-inferiority trial comparing miltefosine to amphotericin B intravenously at a total dose of 15 mg/kg every other day over 30 days in the treatment of VL. Patients aged ≥12 years were randomized in 3:1 to receive miltefosine or amphotericin B. All were hospitalized during treatment and followed up to 6 months after the completion of therapy. The primary efficacy endpoint was the rate of patients with final cure defined as initial cure followed by 6 months follow up without relapse and absence of clinical signs or symptoms attributable to visceral leishmaniasis.

Main issues encountered during the review of Study 3154 are as follows:

- The protocol specified non-inferiority (NI) margin was 15% for the absolute difference of response rates in favor of amphotericin B. However, the FDA considered a margin of 10% more acceptable based on the severity of the disease (See Appendix 1 – NI margin justification).
- There was a gender imbalance between treatment groups as more males were enrolled in the miltefosine arm. The gender mismatch was most noted at Site 1 (M/F ratio 4.2 in the miltefosine arm and 1.8 in the amphotericin arm), and to a lesser extent at Site 3 (M/F ratio 2.3 in the miltefosine arm and 1.1 in the amphotericin arm), but not at study Site 2 (M/F ratio 1.6 in the miltefosine arm and 1.4 in the amphotericin arm). A subgroup analysis was conducted to investigate gender and site together with respect to final cure and no interaction was found between gender and cure.
- There existed substantial inconsistency between the 3 sites in following up residual signs and symptoms at 6 months. The majority (85%) of subjects (85%) with VL signs and symptoms at 6 months at Site 1 were further evaluated with a marrow or splenic aspirate, but only 5.7% at Site 2 and 5.3% at Site 3 respectively were further evaluated. Alternative analysis was performed by the FDA which conservatively considered 14 additional subjects (12 in the miltefosine arm and 2 in the amphotericin arm) as treatment failures/relapse.
- There were 2 patients in the miltefosine group (2-071 and 3-042) who were not initially cured at the end of treatment but were coded in the submitted dataset as final cure at 6 month follow up. They were considered as treatment failures by this reviewer according to the definition of final cure. Additionally, this reviewer disagreed with the sponsor on exclusion of 2 deaths from the PP analysis and instead included them as failures in the FDA PP analysis.

Z025

Z025 was a randomized, open-label study comparing miltefosine to standard of care sodium stibogluconate (SSG) IM 20 mg/kg daily for 30 days. Only male subjects aged 15 years or up were enrolled and the randomization ratio was 1 miltefosine: 1 SSG. This study also enrolled a substantial number of HIV-infected subjects. Patients were hospitalized during the treatment and were monitored till 6 months after the completion of therapy. The protocol stated that the main outcome of analysis was the final cure rate at the 6-month follow-up visit.

Below are some major issues with Study Z025:

- The sponsor did not have patient level data for the majority of patients in Study Z025. The study enrolled 580 patients but only 50 patients' data were available to the sponsor. The sponsor's study report and this NDA review both used the published article that reported the findings of this study.
- The sponsor defined the analysis population post hoc, choosing Per Protocol (PP) population for the analysis of final cure and Intent-to-treat (ITT) population for the analysis of initial cure at the end of therapy. We disagree with the sponsor's choice of PP population for the determination of the primary efficacy endpoint. Instead, we consider the primary analysis to be based on the ITT population. As communicated to the sponsor in a correspondence dated 3/30/2013, the use of a PP analysis was to support the NI margin estimated for the ITT population. Although a 15% NI margins could be supported for initial and final cure, margins of 10% are more appropriate for this potentially fatal disease (See Section 6.1 for the non-inferiority margin justification).
- Patients who failed initial treatment (23 in the miltefosine group and 2 in the SSG group) were immediately re-treated by SSG treatment. Consequently 17 of the 23 initial miltefosine failures and 1 of the 2 initial SSG failures were cured after re-treatment with SSG. There was no information about how many of the re-treated subjects contributed to the final cure rate. Therefore, interpretation of the final cure rate is confounded by re-treatment of subjects who had initial failure, especially in the miltefosine group.
- There were very few subjects with missing data at end of treatment when initial cures were examined. However, by the time final cures were assessed, there were a large number of subjects with missing data which complicated the assessment of the final cure rate.
- The protocol described sample size calculation based on HIV-negative patients and specified a separate analysis of cure rates by HIV status. Given that the primary analysis might have been in the HIV-negative patients as implied in the protocol, this reviewer analyzed final cure rates and death rates with respect to HIV status using information from study publication[2] by *Ritmeijer et al-2006.*
- The study report defined death as a post hoc efficacy endpoint but we viewed it more likely a safety problem. At 6 months the SSG group had a higher rate of mortality compared to the miltefosine group, mainly driven by the subset of subjects with unknown HIV status. However, throughout the study miltefosine subjects were

more likely to experience failure, either as initial failure at the end of therapy or relapse at 6 months after completion of therapy, which implies possibly that the fewer deaths seen with miltefosine were not necessarily due to increased efficacy of miltefosine but instead due to safety concerns with the comparator.

5.1.2 Studies for Cutaneous Leishmaniasis (CL)

In support of the CL indication, data from one pivotal trial (Study 3168) and 2 supportive studies (Study Soto and Study Z020) were submitted. Study 3168 was conducted in 2000-2002 at two centers, Colombia where *L.v. panamensis* was common and Guatemala where *L. v. braziliensis* and *L. m. mexicana* were endemic. Study Soto was conducted from 2005 to 2007 in Bolivia, where *L. braziliensis* was epidemiologically the predominant pathogen. Study Z020 was split into two parts, Z020a and Z020b. Study Z020a was conducted in 2007-2008 in Manaus, Brazil, where *L.(V.) guyanensis* was epidemiologically the predominant pathogen and Study Z020b was conducted in 2007-2009 in Bahia, Brazil where *L.(V.) braziliensis* was endemic.

Study 3168

Study 3168 was a randomized, placebo-controlled, double-blinded multicenter trial to assess the efficacy and safety of oral miltefosine in patients with cutaneous leishmaniasis (CL). Patients aged ≥12 years were randomized in a 2:1 ratio to receive either miltefosine 50 mg or matching placebo capsules orally for 28 days with a target dose of ~2.5 mg/kg per day. The primary efficacy endpoint was rate of patients with apparent cure or partial cure at 2 weeks followed by definitive cure at 6 months after end of treatment.

Below are some main issues encountered during the review of Study 3168:

- There is a possibility that this study was not completely blinded. The study report provided the randomization scheme in Appendix A 6.1 which indicated a permuted blocks of size 3 was used and the list had "TG Letter" of "A" or "B". The treatment was masked as "A" or "B", which essentially allowed the study investigator to separate 2 groups of patients.
- There was a change in the definition of primary efficacy endpoint during the trial process. The primary endpoint was initially defined as the rate of patients with apparent cure at 2 weeks after end of treatment and definite cure after relapse-free 6 months follow up. It was later changed to the rate of patients with partial or apparent cure at 2 weeks after end of treatment and definite cure after relapse-free 6 months follow up. The sponsor stated that the change was made under blinded conditions. However, since the treatments were marked with "A" or "B", it is possible that the decision to change the primary endpoint was based on knowledge of the study results. Alternative analyses were conducted by the FDA using the original definition of the primary efficacy endpoint.

- It is questionable if the randomization list was fully complied with. There was no randomization date in the submitted database. When using the date of first medication exposure as a surrogate for randomization date, it appears that the ID numbers were in order of medication start date for patients in the Guatemala site. In the Colombia site, however, subjects were not given ID numbers according to the order in the randomization list. The first ID numbers used were 22 and 23 on 07/01/2000, then 21, 24, 25, 26 on 07/03/2000, then 27 on 07/10/2000, then 28, 29, 30 on 07/11/2000, etc. It was only beginning 04/22/2001 that the ID numbers were in order, 1 through 20 and 40 through 70. Interestingly the Colombia site also enrolled 13 female patients as compared to 1 female patient in Guatemala and both the placebo and miltefosine cure rates in Colombia were higher than those in Guatemala.

Study Soto

Study Soto was a randomized, open label, active comparator trial of oral miltefosine versus the standard therapy Glucantime (MEG). Subjects ≥ 12 years of age were assigned to receive either miltefosine or Glucantime IM for 20 mg/kg/day for 20 days in a 2:1 ratio. The primary efficacy endpoint was definite cure, defined as complete re-epithelialization of all lesions at 6 months after end of treatment. There was no formal statistical hypothesis.

There are several issues with Study Soto:

- There was no standalone protocol for Study Soto. The trial was conducted as an amendment to the preceding mucosal leishmaniasis protocol (Protocol Z022 Amendment #03), which contained very limited information about data analysis. There was no clear definition of efficacy endpoint, analysis population, or analysis methods. The statistical methods with consideration on efficacy endpoints, analysis population, missing data handling were created by the sponsor post hoc, years after the study was completed and results published. The sponsor did not propose or justify a non-inferiority margin to allow for adequate interpretation of the study.
- Study Soto was highly likely not randomized. Three patients previously treated with miltefosine were assigned to Glucantime and another 3 previously treated Glucantime were assigned to miltefosine. Some numbers on the master randomization list submitted by the sponsor were not used as expected. There was no randomization date in the submitted database. When using the date of first medication exposure as a surrogate for randomization date, it appears that subjects were not given ID numbers according to the order in the randomization list. Therefore, the actual use of randomization in Study Soto is questionable and interpretation of results is very limited.
- The conduct of Study Soto is in question. There were unexplained changes during the trial and undocumented exclusion of subjects in study reporting. The study was apparently stopped prior to reaching the full planned enrollment. It appeared that 3 Glucantime-treated subjects who were listed as lost to follow-up and imputed as failures in the primary analysis were likely not followed due to the closing of the

study. There were 3 miltefosine-treated subjects whose information, including case report forms, were lost were not included in the study report or datasets.

- There was an imbalance in number of failure and lost to follow up between the two arms. In Glucantime group, the sponsor reported that 22.2% of patients were lost compared to 5.5% who were failures. In contrast, 5% miltefosine patients were lost as compared to 15% were failures. Several sensitivity analyses were performed by this reviewer to examine the impact on clinical cure rates by this large disparity.

Study Z020

Study Z020 was split into two studies, Z020a and Z020b, both of which were randomized, open-label, comparative trials that enrolled children 2-11 years of age and adults ≥ 12 years of age. Subjects were randomized 2:1 to either miltefosine or Glucantime intramuscally IM at 20 mg/kg/day for 21 days. The primary endpoint was definite cure, defined as complete re-epithelialization of all initial ulcers at 2 months and at 6 months and no new lesions and no residual lesions with parasites or ≥ 50% enlargement of a lesion prior to 6 months. There was no statistical hypothesis. In contrast to the other studies submitted for this NDA review, parasitologic speciation of the infecting leishmania organisms was obtained in every subject.

The following are main statistical issues with Study Z020:

- There was no pre-specified plan to analyze Study Z020 as one whole study with 2 parts or two separate studies. Study Z020 was initially planned as a controlled, open, randomized, two-center study with a total of 180 patients (90 in each site) as per protocol. The original plan appeared to be for the study to be analyzed as a whole, combining the two sites and the two age populations. However, there were two articles written for the two different sites and the information by site is very informative given the different species at the two sites. Hence data were analyzed and presented in this review separately for each study with the knowledge that the results by age group and by site, may be considered as subgroup analyses. Therefore, interpretation of statistical analysis, most importantly the protection of type I error control, should be viewed with caution.
- This active controlled trial did not include a justified non-inferiority margin to allow for a conclusion regarding the efficacy of miltefosine. Although the results in Study Z020b were statistically significant, an analysis of Z020 as a whole with stratification by age and site, did not find miltefosine to be statistical superior to Glucantime (P-value = 0.09).

5.1.3 Studies for Mucosal Leishmaniasis (ML)

For the ML indication, one single arm study, Study Z022, was submitted. The study was conducted in 2004-2006 in Bolivia, where *L. braziliensis* is epidemiologically the predominant pathogen. It was originally planned as a Phase 2, randomized, comparative study of oral miltefosine versus standard therapy with pentavalent antimony. The trial was amended due to the inability to enroll patients into the comparator arm. The final study

design became an evaluation of 1 cohort of 79 patients who received miltefosine. Subjects ≥18 years were treated with miltefosine for 28 days and followed for 12 months post the end of therapy. The primary efficacy endpoint was cure at 12 months, defined as ≥ 90% improvement in mucosal severity score at 12 months compared to baseline. The mucosal severity score consisted of the sum of severity grades for each of erythema, edema, infiltration and erosion at each of five anatomic sites (nasal skin, nasal mucosa, palate, pharynx, and larynx).

The main issue with Study Z022 was lack of a comparator arm, thus interpretation regarding miltefosine effect is very limited. Furthermore, there is not much information about the composite variable, mucosal severity score. It seems that each site and each sign is equally weighted in the scoring system. We do not know whether the mucosal severity score has been previously used or validated and what kind of properties it has.

5.2 Collective Evidence

This section summarizes the collective evidence regarding the efficacy of miltefosine. With regard to safety, the most commonly reported adverse events involved gastrointestinal tract such as nausea or vomiting, and diarrhea. Please refer to the medical officer's review for safety information

5.2.1 Studies for Visceral Leishmaniasis (VL)

The efficacy of miltefosine in the treatment of VL is supported by one pivotal study (Study 3154) in India and one supportive trial (Study Z025) in Ethiopia.

Miltefosine was found to be effective based on non-inferior results were seen compared to amphotericin B in pivotal Study 3154. Similar final cure rates from VL were achieved after oral use of miltefosine (target of 2.5 mg/kg/day generally achieved by 100 mg/kg/day for 28 days) and after intravenous use of amphotericin B (1 mg/kg every other day for 30 days), 94.3% vs. 97.0%, respectively. Two FDA alternative analyses, which included 16 additional patients (14 per clinical judgment and 2 per final cure definition) as treatment failures, gave supportive results for the efficacy of miltefosine.

Study Z025 was supportive of the results of the 3154 but our conclusions differ from the sponsor. Based on our assessment of the study report and the publication[2] by *Ritmeijer et al (2006),* miltefosine efficacy was similar to SSG in terms of initial cure rate at the end of treatment. However, though the overall initial cure rates are similar, the reasons for failure were very different between the two arms. Most of the miltefosine subjects who failed were failure of treatment while most of the SSG subjects who were failures had died. At 6 months the SSG group had a higher rate of mortality compared to the miltefosine group, mainly driven by the subset of subjects with unknown HIV status. For patients with unknown HIV status, the death rates were 8.3% in the miltefosine arm and 21.1% in the SSG arm (P-value=0.0105), respectively. However, throughout the study miltefosine

subjects were more likely to experience initial failure at the end of therapy or relapse at 6 months after completion of therapy which implies possibly that the fewer deaths seen with miltefosine were not necessarily due to increased efficacy of miltefosine. Complete review of this study was not possible due to the lack of patient level data.

Overall, miltefosine has been shown as effective to treat VL in terms of final cure at 6 months post therapy and there is a trend toward lower final cures in subjects who received less than 2.5 mg/kg miltefosine dose.

5.2.2 Studies for Cutaneous Leishmaniasis (CL)

One confirmatory trial (Study 3168) and two supportive studies (Study Soto and Study Z020) were submitted. Except for Study Soto which cannot be considered as a randomized trial, the other two studies involved 4 geographic regions and 4 different leishmaniasis species. The efficacy of miltefosine in the treatment of CL is demonstrated in Study 3168 and Z020. Results from Study 3168 and Z020 also showed that miltefosine-induced cure rate for leishmaniasis varied among the species of leishmaniasis causing disease and also between the same species acquired from different endemic areas.

Miltefosine was effective in the treatment of patients with CL with a definite cure rate of 66.3% (ITT) compared with a placebo cure rate of 29.6% at 6 months after the end of therapy. The 36.8% improvement in definite cure was statistically significant (P-value <0.001). The results are considered robust with respect to missing data and slight deviations from the definition of the primary endpoint. There were two centers in Study 3168. Miltefosine cure rate was 81.6% (versus 37.5% in placebo) in Columbia where *L.v. panamensis* was epidemiologically the predominant pathogen and 47.5% (versus 20% in placebo) in Guatemala where *L. v. braziliensis* and *L. m. mexicana* were endemic. The variability in cure rates may be due to different leishmaniasis species. There are concerns regarding the study conduct in terms of blinding. However, the robust results eliminate some of the concern.

The supportive study Z020 was useful in that unlike the other studies parasitologic speciation of the infecting Leishmania organisms was obtained in every subject. Study Z020 which was split in two parts, Z020a in Manaus, Brazil where *L.(V.) guyanensis* was the predominant pathogen and Z020b in Bahia, Brazil where *L.(V.) braziliensis* was the predominant pathogen. Miltefosine was compared to Glucantime with respect to definitive cure rate at 6 months after completion of therapy for pediatric patients and for adolescent/adult patients who were at least 12 years old. The sponsor reports the results separately for the two sites. We also report the results separately due to the different organisms at the different sites. Additionally, we focus on the results in adolescents and adults. Note however, that these analyses constitute subgroups analyses without a pre-specified control for multiplicity. In Study Z020a, miltefosine appeared to be similarly efficacious as Glucantime. The definitive cure rate for miltefosine was 67.5% of 40 patients and for Glucantime was 60% of 20 patients (95% CI of the difference of (-17.9, 34.6)%. In Study Z020b, miltefosine was superior to Glucantime. The definitive cure rate for

miltefosine was 85% of 40 patients and for Glucantime was 45% of 20 patients (P-value = 0.0018). Though these results are supportive of the effect of miltefosine in the treatment of cutaneous leishmaniasis, some caution should be considered given that these results are essentially subgroup analyses of the whole Z020 study with a lack of pre-specified type I error control for multiplicity, there was no pre-specified NI margin, and the study was open label and used small block sizes leading to a potential concern over the randomization of the study.

5.2.3 Studies for Mucosal Leishmaniasis (ML)

Study Z022 was submitted to extend the CL indication to ML. This uncontrolled single-center study followed 79 patients who were treated with miltefosine. The rate of complete cure at 12 months post treatment was 62%. Due to the nature of single-center single-arm open-label design, interpretation of results from this study is limited.

5.3 Conclusions and Recommendations

This NDA submission contains 6 studies which evaluated the efficacy and safety of miltefosine for the treatment of visceral, cutaneous, and mucosal leishmaniasis. Miltefosine capsules were given orally at target of 2.5 mg/kg/day for 28 days in all studies.

This review found miltefosine to be effective in the treatment of VL based on one pivotal and one supportive study and in the treatment of CL with one pivotal and one supportive study. The effect of miltefosine in the treatment of mucosal leishmaniasis is unclear due to lack of comparative studies; however, data from one uncontrolled trial is available. We defer to the clinical reviewers as to how much of the efficacy from VL and CL can support the ML indication. While adequate efficacy has been demonstrated for VL and CL, the overall results were not as strong as they could have been due to various issues associated with the study conduct and analysis.

6 APPENDIX

6.1 FDA Advice Letter (Mar 30, 2012) regarding the Justification of Non-Inferiority Margins

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

COMMUNICATION SHEET

DATE: March 30, 2012

To: Jonathan D. Berman, M.D., Ph.D. Vice President for Clinical Affairs	**From:** Gregory F. DiBernardo Regulatory Project Manager
Company: Paladin Labs, Inc. c/o Fast-Track Drugs and Biologics LLC	Division of Anti-Infective Products (DAIP)
Fax number: Communication sent via E-mail	**Fax number:** (301) 796-9881
Phone number: (301) 922-2097 E-mail: jberman@fasttrackresearch.com	**Phone number:** (301) 796-4063

Subject: IND 105430

Total no. of pages including cover: 4

Comments: FDA comments on your February 14, 2012, submission to IND 105430

Confirm receipt of this communication at: gregory.dibernardo@fda.hhs.gov

Document to be mailed: ☐ **YES** ☑ **NO**

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-1400. Thank you.

IND 105430

Dear Dr. Berman,

Please refer to your Investigational New Drug Application (IND) 105430 submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for the investigation of Impavido (miltefosine) for visceral leishmaniasis, mucosal leishmaniasis, and cutaneous leishmaniasis.

We have the following comments on your February 14, 2012 IND submission:

We reviewed the literature you submitted to justify the non-inferiority margin to be used in the evaluation of miltefosine in the treatment of visceral leishmaniasis (VL). We agree that there are no data that can be used to determine the placebo effect using the primary endpoint of final cure at 6 months. We also agree to the use of the response rate to Sodium Stibogluconate (Sb) for the treatment of VL in Bihar, India, as the "pseudo-placebo" rate, and that this rate can be extrapolated to Study Z025 conducted in Africa.

In addition to the literature you provided, we identified the following *additional* articles:

1. For the determination of the response rate to Sb in Bihar, India:

    a. Thakur CP., et al. Do the diminishing efficacy and increasing toxicity of sodium stibogluconate in the treatment of visceral leishmaniasis in Bihar, India, justify its continued use as a first line drug? An observational study of 80 cases. Ann Trop Med Parasitology 1998;92:561-569
    b. Jha TK., et al. Randomized controlled trial of aminosidine (paromomycin) vs. sodium stibogluconate for treating visceral leishmaniasis in North Bihar, India. BMJ 1998;316:1200-1204
    c. Thakur CP., et al. A prospective randomized, comparative, open-label trial of the safety and efficacy of paromomycin plus sodium stibogluconate versus sodium stibogluconate alone for the treatment of visceral leishmaniasis. Transactions of the Royal society of Tropical Medicine and Hygiene 2000;94:429-431
    d. Thakur CP., Narayan S. A comparative evaluation of amphotericin B and sodium antimony gluconate as first line drugs in the treatment of Indian visceral leishmaniasis. Annals Tropical Medicine and Parasitology 2004;98:129-138

2. For the determination of the response rate to amphotericin B in Bihar, India:

    a. Mishra M., et al. Amphotericin versus pentamidine in antimony-unresponsive kala-azar. Lancet 1992;340:1256
    b. Mishra M., et al. Amphotericin versus sodium stibogluconate in the first line treatment of Indian kala-azar. Lancet 1994;344:1599-1600
    c. Thakur CP., Narayan S. A comparative evaluation of amphotericin B and sodium antimony gluconate as first line drugs in the treatment of Indian visceral leishmaniasis. Annals Tropical Medicine and Parasitology 2004;98:129-138
    d. Das V., et al. A controlled, randomized nonblinded clinical trial to assess the efficacy of amphotericin B deoxycholate as compared to pentamidine for the treatment of unresponsive visceral leishmaniasis cases in Bihar, India. Therapeutics and Clinical Risk Management 2009;5:117-124

e. Sundar S., et al. Single dose liposomal amphotericin B for visceral leishmaniasis in India. NEJM 2010;362:504-512
f. Sundar S., et al. Comparison of short course multi-drug treatment with standard therapy for visceral leishmaniasis in India: an open-label, non-inferiority, randomized controlled trial. Lancet 2011;377:477-486

3. For the determination of the response rate to Sb in East Africa:

a. Zijlstra E., et al. The treatment of kala-azar in Sudan with sodium stibogluconate: a randomized trial of three dosage regimens. Transactions of the Royal Society of Tropical Medicine and Hygiene 1993;87:307-309
b. Seaman J., et al. Epidemic visceral leishmaniasis in Sudan: A randomized trial of aminosidine plus sodium stibogluconate versus sodium stibogluconate alone. JID 1993;168:715-720
c. Veeken H., et al. A randomized comparison of branded sodium stibogluconate and generic sodium stibogluconate for the treatment of visceral leishmaniasis under field conditions in Sudan. Tropical Medicine and International Health 2000;5:312-317

Because of the unequal study population sizes, we used a weighted analysis described by DerSimonian and Laird to estimate the pooled rate and individual confidence intervals. Additionally, instead of computing a difference and its associated confidence interval as if the two rates were from one randomized trial, we utilized a more conservative approach as given in the Non-inferiority Clinical Trial Guidance (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM202140.pdf), where a conservative estimate from "placebo" (i.e., the upper confidence limit) is compared to a conservative estimate from the active control for the NI study (i.e., the lower confidence limit). Finally, it does not seem necessary to us to limit the studies to those conducted prior to your Study 3154 or Study Z025.

For Study 3154, our analysis estimates the pseudo-placebo response rate at 47.1% (38.14%, 56.03%), and the response rate to amphotericin B at 97.8% (96.14%, 99.52%). M1 is therefore conservatively estimated at 40.11%. Although a margin of 15% could be supported, a margin of 10% is more appropriate for this potentially fatal disease.

Furthermore, we noticed that two studies were randomized, open-label trials comparing Amphotericin B with Sb in Bihar, India (Mishra 1994 and Thakur 2004). The treatment difference and associated exact 95% confidence intervals are 37.5% (22.7%, 54.2%) in the Mishra 1994 Study and 53.4% (40.0%, 66.4%) in the Thakur 2004 Study. They both individually support a 15% margin. Again, a margin of 10% is more appropriate for this potentially fatal disease.

For Study Z025, we extrapolated the pseudo-placebo rates from studies conducted in India; these are 48.2% (40.80%, 55.60%) for initial cure defined as absence of parasites and improvement of clinical symptoms at the end of treatment and 47.1% (38.14%, 56.03%) for final cure defined as no clinical and parasitological relapse in the 6 months of follow up. Our analyses estimate the initial and final cure rates for Sb in East Africa in the ITT population at 93.5% (91.28%, 95.67%)

and 77.9% (67.00%, 88.81%) respectively. The final cure rate in the per-protocol (PP) population is estimated at 93.2% (91.44%, 94.94%). For the ITT population, using the final cure estimates, M1 is conservatively estimated at 10.97%. Because most of these studies were conducted under field conditions where 6 months follow up may prove to be a challenge, we also considered the treatment effect for initial cure in the ITT population (35.7%) and the treatment effect for final cure in the PP population (35.4%). These can also be used to help support an NI margin justification for initial and final cure. Although based on these two analyses 15% NI margins could be supported for initial and final cure, margins of 10% are more appropriate for this potentially fatal disease.

Reference: DerSimonian, R., Laird, N. (1986), "Meta-Analysis in Clinical Trials," *Controlled Clinical Trials*. 7, 177-188.

If you have any questions regarding this communication, please contact Gregory DiBernardo, Regulatory Project Manger, at (301) 796-4063.

6.2 References

1. Sundar S., et al. ORAL MILTEFOSINE FOR INDIAN VISCERAL LEISHMANIASIS. The New England Journal of Medicine 2002; 347: 1739-1746.
2. Ritmeijer K., et al. A Comparison of Miltefosine and Sodium Stibogluconate for Treatment of Visceral Leishmaniasis in an Ethiopian Population with High Prevalence of HIV Infection. Clinical Infectious Diseases 2006; 43:357–364
3. Soto J., et al. Miltefosine for New World Cutaneous Leishmaniasis. Clinical Infectious Diseases 2004; 38: 1266-1272
4. Soto J., et al. Short Report: Efficacy of Miltefosine for Bolivian Cutaneous Leishmaniasis. *Am. J. Trop. Med. Hyg.,* 78(2), 2008, pp. 210–211
5. Talhari AC., et al. Randomized Controlled Clinical Trial to Access Efficacy and Safety of Miltefosine in the Treatment of Cutaneous Leishmaniasis Caused by *Leishmania* (*Viannia*) *guyanensis* in Manaus, Brazil. *Am. J. Trop. Med. Hyg.,* 84(2), 2011, pp. 255–260
6. Machado PR., et al. Miltefosine in the Treatment of Cutaneous Leishmaniasis Caused by Leishmania braziliensis in Brazil: A Randomized and Controlled Trial. PLoS Negl Trop Dis 4(12): e912.
7. Soto J., et al. Treatment of Bolivian Mucosal Leishmaniasis with Miltefosine. Clinical Infectious Diseases 2007; 44:350–356

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LAN ZENG
09/27/2013

KAREN M HIGGINS
09/27/2013
I concur.

DIONNE L PRICE
09/30/2013
concur with overall conclusions

STATISTICS FILING CHECKLIST FOR A NEW NDA 204684

NDA Number: 204684 **Applicant: Paladin Therapeutics, Inc.** **Stamp Date: April 19, 2013**

Drug Name: Impavido (miltefosine) **NDA Type: NME (1)**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	x			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	x			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	x			Gender analysis added in this resubmission
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	x			Further clarification required. See Page 3.

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ___Yes_____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	x			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	x			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			x	
Appropriate references for novel statistical methodology (if present) are included.	x			
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	x			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	x			

STATISTICS FILING CHECKLIST FOR A NEW NDA 204684

List of studies to be reviewed under NDA204684

Study	Design	Primary Efficacy Endpoint	Dosage Regimen	# Subjects	Applicant's Main Efficacy Results	
					Cure Rate	P-value
Visceral leishmaniasis						
3154	Open, parallel group	Final cure at 6 months after the end of treatment	miltefosine x28 days	299	282/299 (94.3%)	97.5% CI upper bound =6.2% NI margin=15%
			amphotericin B (AMP) x 30 days	99	96/99 (97.0%)	
Z025*	Open, parallel group	Cure rate at 6 months	miltefosine x28 days	290	174/219 (79.5%)	0.464
			Stibogluconate (SSG) x 20 days	290	189/230 (82.2%)	
Cutaneous leishmaniasis						
3168	Double-blind, parallel group	Definite cure at 6 months after the end of treatment	miltefosine x28 days	89	59/89 (66.3%)	<0.0001
			Placebo x 28 days	44	13/44 (29.6%)	
Soto 2008	Open, parallel group	Clinical cure (100% re-epithelialization of all lesion ulcers on a subject) at 6 months after the end of treatment	miltefosine target 2.5 mg/kg/day x 28 days	44	32/40 (80.0%)	0.83
			meglumine antimonate 20 mg/kg/day x 20 days	18	13/18 (72.2%)	
Z020a	Open, parallel group	Definite cure at 6 months after the end of treatment	miltefosine target 2.5 mg/kg/day x 28 days	60	41/60 (68.3%)	0.485
			meglumine antimonate 15-20 mg/kg/day x 20 days	30	18/30 (60.0%)	
Z020b	Open, parallel group	Definite cure at 6 months after the end of treatment	miltefosine target 2.5 mg/kg/day x 28 days	60	47/60 (78.3%)	0.083
			meglumine antimonate 20 mg/kg/day x 20 days	30	18/30 (60.0%)	
Mucosal leishmaniasis						
Z022	Open, 1-cohort	ML severity score	miltefosine target 2.5 mg/kg/day x 28 days	79	Cure rate 49/79 (62.0%)	

* Individual patient data available for only 50 subjects with severe adverse events or death.

Additionally, the sponsor submitted reports for 2 uncontrolled studies in CL (3092 and z027) and 9 uncontrolled studies in VL (0033, 3089, 3091, 3109, 3127, 3206, z013, z013b, and z019). These studies will not be reviewed due to their uncontrolled nature.

List of issues requiring further clarification from the sponsor

1. There exists discrepancy in treatment identification between study report and datasets provided for Study Z025. For instance, Subjects 494, 381, 395, 409, 027, 430, 509 and 569 received miltefosine according to the study report (Table 37) but SSG according to their datasets. The study report (Table 37) shows that Subjects 092, 272, 390, 398, 423, 460, 504, 205 and 536 received SSG but the datasets indicates their group assignment were miltefosine. Please clarify.

2. Some important variables are not clearly labeled. For instance, according to the study 3154 report (Section 6.1), Subject 3/060 was randomized to the miltefosine group but received AmpB. However, planned treatment for this patient is recorded as AmpB in "dm.xpt" (ARM and ARMCD labeled as "Description of Planned treatment"). According to the Soto study report (Section 10.2), Subject 10 was randomized to Glucantime but received miltefosine. However, the planned treatment for this subject was recorded as miltefosine in "adsl.xpt" (TRTA labeled as "Planned Treatment"). Please clarify.

3. The length of some variables is not consistently defined. For example, the length of USUBJID (unique subject ID) variable in the analysis datasets is different from that in the tabulation datasets in Studies 3154, 3168 and Soto. In Study 3154, USUBJID length=10 in analysis datasets but length=11 in tabulation datasets. In Study Soto, USUBJID length=7 in analysis datasets but length=10 in tabulation datasets. In Study 3168, USUBJID length=10 in analysis datasets but length=9 in tabulation datasets. Please clarify. Additionally for Study 3168, please confirm if, for example, Subject 3168-1/067 in the analysis datasets is the same as Subject 3168-1/67 in the tabulation datasets.

4. For Studies Z020a and Z020b, the length and width of ulcerated or induration lesion are provided in the datasets while the study report summarizes the lesion area. There is no specification on how ulcerated or induration lesion area is computed. Please clarify.

5. Some variables are not available in the datasets. For instance, while Study 3168 report Table 5.2.1 shows summary statistics for Performance status (Karnofsky), this parameter is not provided in Study 3168 datasets ('vs.xpt' has BMI instead).

STATISTICS FILING CHECKLIST FOR A NEW NDA 204684

Lan Zeng

Reviewing Statistician Date

Karen Higgins

Supervisor/Team Leader Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LAN ZENG
06/03/2013

KAREN M HIGGINS
06/03/2013

STATISTICS FILING CHECKLIST FOR A NEW NDA 204684

NDA Number: 204684 | **Applicant: Paladin Therapeutics, Inc.** | **Stamp Date: September 27, 2012**

Drug Name: Impavido (miltefosine) | **NDA Type: NME (1)**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	x			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	x			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).		x		See Page 3 attached
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).				See Pages 4,5,6 attached

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ___No_____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.				
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.				
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.				
Appropriate references for novel statistical methodology (if present) are included.				
Safety data organized to permit analyses across clinical trials in the NDA/BLA.				
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.				

STATISTICS FILING CHECKLIST FOR A NEW NDA 204684

Lan Zeng

Reviewing Statistician Date

Karen Higgins

Supervisor/Team Leader Date

STATISTICS FILING CHECKLIST FOR A NEW NDA 204684

Indication/ Study		Design	Dosage Regimen	# Subjects per Study Report	#Subjects in Datasets	Data Reviewable?
VL	3154	Open, parallel group	miltefosine x28 days	299	400	No
			amphotericin B (AMP) x 30 days	99		
	Z025	Open, parallel group	miltefosine x28 days	290	50	No
			Stibogluconate (SSG) x 20 days	290		
CL	3168	Double-blind, parallel group	miltefosine x28 days	89	133	No
			Placebo x 28 days	44		
	Soto 2008	Open, parallel group	miltefosine target 2.5 mg/kg/day x 28 days	44	58	Yes, but require extra data manipulation
			meglumine antimonate 20 mg/kg/day x 20 days	18		
	Z020a	Open, parallel group	miltefosine target 2.5 mg/kg/day x 28 days	60	90	No
			meglumine antimonate 15-20 mg/kg/day x 20 days	30		
	Z020b	Open, parallel group	miltefosine target 2.5 mg/kg/day x 28 days	60	90	No
			meglumine antimonate 20 mg/kg/day x 20 days	30		
ML	Z022	Open, 1-cohort	miltefosine target 2.5 mg/kg/day x 28 days	79	79	Not checked

Statistical Deficiencies/Issues

Efficacy was NOT investigated for important subgroups such as gender in any of the 6 studies conducted for VL and CL. In Study 3154, there is a clear imbalance in gender distribution as 211/299 (70.6%) of the miltefosine-treated patients versus 58/99 (58.6%) of the amphotericin B-treated patients were males (P-value=0.035). In Study Z020b, 44/60 (74.6%) patients in the miltefosine group were males compared to 53.3% in the active control group (P-value=0.043). None of these studies was analyzed with respect to gender distribution.

Dataset Deficiencies

1. Some important datasets are not submitted. For example, according to the cover letter dated 11/12/2012, "*the ADaM dataset for study 3154 contains two xpt files, one for clinical response data (study 3154 adcr.xpt) and one for the parasitological methods, clinical response, and parasitological response (study 3154 adcrp.xpt)*." However, the two datasets submitted on 11/12/2012, namely "adcr.xpt" and "adcrp.xpt", appear to be identical. If the cover letter is correct, then one dataset has not been submitted.

2. Some key parameters are missing or erroneous in the datasets. For example,

   1) There is no variable in the datasets indicating if the actual treatment a subject received is the same as planned. Treatment assignment for some subjects is not consistent across datasets. For example, in Study 3154, Subject 3154-3060 had TRT=1 (miltefosine) in "rando.xpt", TRT=2 (amphotericin B) in "rando-c.xpt", TRT=2 (amphotericin B) in "response.xpt", and TRTA='amphotericin B' in "adcr.xpt". All of these variables are labeled as "Actual Treatment".

   2) Start and stop date of study treatment are not provided for most studies. Treatment duration is not available for Study soto.

   3) Treatment durations are not consistent for several subjects in Study Z020a, Z020b and 3168. For example, conflicting values of treatment duration are shown for the following subjects:

Study	Subject	TRTDUR	Treatment Duration
Z020a	048	10, 28	???
	049	12, 28	???
	056, 058, 060, 062, 064, 065	14, 28	
Z020b	103, 105, 132, 158, 159, 160, 161, 162, 163, 164	14, 28	???
3168	159	27, 28	???

   4) There is no information about apparent cure (secondary efficacy endpoint) in the datasets for Studies Z020a and Z020b. The study reports defined apparent cure as complete re-epithelialization of all ulcers at the 2 month follow-up. However, the submitted datasets only contain response information at the 6 month follow-up.

   5) Subject IDs in the datasets do not correlate with those in the study report. For example, in Study 3154 report, subjects are referred as Pat 1/137, Pat 1/116, Pat 3/38, and Pat 2/92, etc. However, in the datasets USUBJID is denoted as 3154-1001, 3154-1100, etc.

Dataset Deficiencies (Cont.)

3. Visit days in the datasets are confusing as many of them do not correlate with the timing of assessments per the protocol or with the days designated in the "tv.xpt" dataset. For example, in Study 3168

	Visit
Time schedule as per the protocol	Screening (Day 0), During treatment (Day 1, 7, 14, 21, 28=EOT) Post treatment (Day 42=2 weeks after EOT, 88=2 months after EOT, 182=6 months after EOT)
"Define.pdf"	0=Screening, 1=Day 1, 7= Day 7, 14= Day 14, 21=Day 21, 28=Day 28, 50=3 months after EOT 70=6 months after EOT or at relapse
Actual Data	
response.xpt	**55**, 70
ae.xpt	**37, 40**
final.xpt	50, **60**
labor.xpt	0, 28, **60**, 70
Sperm.xpt	0, **55**, 70
vital.xpt	0, 7, 14, 21, 28, **60**, 70

4. The "define.pdf" file does not provide adequate documentation about the datasets.

1) There are no definitions for many key fields. For example,

Study	**Dataset**	**Variable**	**Label**	**Type**	**Codelist on "define.pdf"**	**Actual Data Value**	**Actual Data Meaning**
3154	pop.xpt	DISCON	Discontinuation	Num		0,1,2,3	**???**
	final-t.xpt	ALIVE	Patient alive	Num		1,2,3	**???**
3168	pop.xpt	DISCON	Discontinuation	Num		0	**???**
	Response.xpt	RESP_P1	Parasitological response (off treatment)	Num	1=yes; 2=no	1,2,3,4	**???**
Z025	alldata.xpt	CURETEST	Test of cure	Char		Ln neg, na, neg, spleen neg	**???**
	alldata.xpt	PRE_RX	Pretreated with antileishmanial	Num		1,2	**???**
	alldata.xpt	DAT	Direct Agglutination Test	Char	1=positive; ND=not done	7,8,9,10,11	**???**
	alldata.xpt	ASPIR	Splenic aspirate test for Leish	Char	p=positive; n=negative; ND=not done	1,2,3,4,5,6	**???**

Dataset Deficiencies (Cont.)

2) For the analysis datasets in Study 3154, the "define.pdf" does not correlate with the dataset "adcr.xpt". The following variables are specified in the "define.pdf" but don't appear in the dataset "adcr.xpt": TRT, EXAM, RESPONSE, and EXDAYS. Dataset "adcr.xpt" contains the following variables which are not included in the "define.pdf": CLINRESP, PARARESP, SEQ, TRTA, and TRTDUR.

3) For the tabulation datasets in Study 3168, the "define.pdf" has the following explanation about RESP_FIN in "response.xpt": "*At 3 months, 1=apparent cure, 2=partial cure, 3=clinical failure, 4=not assessable; at six month follow up, 1=definite cure, 2=clinical failure, 3=other*". However, there is no variable indicating 3 month time point in dataset "response.xpt".

4) For the tabulation datasets in Study 3154, the "define.pdf" indicates "*One record per subject*" for datasets "ecg.xpt" and "final-t.xpt". However, there are multiple records per subject in these datasets (a total of 1967 records in "ecg.xpt" and 935 records in "final-t.xpt").

The following comments, while not refuse to file issues, should be addressed in your response to this letter. Otherwise they may cause difficulties in navigating your datasets:

- Datasets for Study Z020a and Study Z020b are combined. Please submit data for different studies under separate directories.

- Coded variables are used in SAS datasets but no formats are provided. Please submit a format.xpt file for the ease of reading your data.

- Many parameters (SEX, USUBJID) are defined as character variables with length of 200 in Study Soto. This could lead to truncation problems in data programming.

- Some key parameters are defined as character variables in one dataset and numeric variables in another. For example, in Study Soto, SITEID is defined as numeric in "adsl.xpt" but character in "dm.xpt".

- Some key parameters have different variable lengths in different datasets. For example, in Study Soto, USUBJID has length of 30 in "adsl.xpt" and 200 in "dm.xpt".

- Some variables are not clearly labeled. For example, in Study Soto, DOMAIN in "dc.xpt" is labeled as "then delete".

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LAN ZENG
11/26/2012

KAREN M HIGGINS
11/26/2012