CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204684Orig1s000

MEDICAL REVIEW(S)

Clinical Investigator Financial Disclosure
Review Template

Application Number: 204684
Submission Date(s): September 27, 2012 and April 19, 2013
Applicant: Paladin Therapeutics, Inc.
Product: IMPAVIDO (miltefosine)
Reviewer: Hala Shamsuddin, M.D.
Date of Review: February 24, 2014

Covered Clinical Study (Name and/or Number):
Study 3154
Study 3168
Study Z020a and b
Study SOTO
Study Z022
Dutch PK study

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from applicant)
Total number of investigators identified: Six (6)		
Number of investigators who are sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): Six (6)		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: None Significant payments of other sorts: None Proprietary interest in the product tested held by investigator: None Significant equity interest held by investigator in sponsor of covered study: None		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes X	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes X	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) None		
Is an attachment provided with the	NA	No ☐ (Request explanation

reason:		from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*. Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

Reviewer's Comments

The financial disclosure statement from the sponsor was submitted with the original NDA on September 27, 2012. The NDA was resubmitted on April 19, 2013 after refuse to file was issued. No new clinical studies were conducted in the interim between the original submission and re-submission.

Certification was submitted that the sponsor had not entered into any financial arrangements with any of the clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21CFR 54.2(a). Certification was provided that none of the listed investigator disclosed a proprietary interest in the product or significant equity in the sponsor as defined in 21 CFR 54.2(b) and (c), and that no listed investigator received significant payments of other sorts 21CFR (f).

The applicant for NDA 204684 has adequately disclosed financial interests/arrangements with the clinical investigators.

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/s/

HALA H SHAMSUDDIN
03/04/2014

Clinical Review

NDA	204684 SDN 006
Type of Review	Priority
Submit Date	April 19, 2012
Received Date	April 19, 2013
PDUFA Goal Date	December 19, 2013
Office/ Division	Office of Antimicrobial Products (OAP) Division of Anti-Infective Products (DAIP)
Reviewer	Hala Shamsuddin MD
Team Leader	Thomas Smith MD
Product Established Name	Miltefosine
Trade Name	Impavido®
Therapeutic Class	Anti-Parasitic, Anti-Protozoal
Sponsor	Paladin Therapeutics
Formulation	Oral Capsule 50 mg
Dosing Regimen	50 mg twice or three times a day (Target Dose 2.5mg/kg/day)
Indications	• Treatment of Visceral Leishmaniasis caused by *L. donovani* • Treatment of Mucosal Leishmaniasis • Treatment of Cutaneous Leishmaniasis caused by *L. braziliensis, L. guyanensis* and *L. panamensis*
Intended Population	Individuals ≥12 Years of Age

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Recommendations/Risk Benefit Assessment

Recommendation on Regulatory Action

The recommendation is to approve miltefosine for the treatment of

- Visceral leishmaniasis acquired in geographic areas where epidemiologically *L. donovani* is the prevalent species
- Cutaneous leishmaniasis acquired in geographic areas where members of the *Leishmania* subgenus *Viannia* (*L. v. braziliensis, L.v. guyanensis and L.v. panamensis*) are the prevalent species
- Mucosal leishmaniasis due to members of the *Leishmania* subgenus *Viannia*

Risk Benefit Assessment

The benefits of miltefosine outweigh the risks for each of the sought indications: VL, CL and ML.

Visceral Leishmaniasis Due to *L. donovani*

Visceral leishmaniasis is a fatal disease if untreated. The main therapies include pentavalent antimony preparations, amphotericin or liposomal amphotericin, and paromomycin, all of which are administered parenterally. Pentavalent antimony preparations are not recommended for use in the Indian subcontinent due to resistance, and the cost of liposomal amphotericin may be prohibitive in the areas of the world where it is needed. Paromomycin is not available in the United States. All these treatments have significant toxicities, including infusion reactions, renal impairment and hematologic toxicity (amphotericin), cardiac, musculoskeletal, hepatic and pancreatic toxicities (antimony), and renal and auditory toxicity (paromomycin).

In contrast, miltefosine is administered orally. In the pivotal VL trial in India, oral miltefosine was non-inferior to IV amphotericin B, both given for one month, in the treatment of VL. Cure at 6 months exceeded 90%, and mortality was < 1%. In Phase 4 and published trials in India, Bangladesh and Nepal, final cure in the evaluable population under actual conditions of use was also high and mortality <1%. In the supportive trial in Ethiopia in a population with high HIV prevalence, mortality was lower in the miltefosine arm compared to pentavalent antimony. Clinical cure in HIV negative patients was similarly high in Ethiopia and India.

Miltefosine was overall well tolerated. Main AEs included vomiting and diarrhea. In the Indian Phase 3 trial, approximately 3% of subjects in either treatment arm discontinued treatment due to an AE. Serious AEs and AEs leading to drug discontinuation that were assessed as related or possibly related to miltefosine included rash, Stevens-Johnson syndrome, thrombocytopenia with melena, jaundice and CTCAE Grade 4 diarrhea. Elevations of Cr above baseline were less frequently encountered and milder compared to

amphotericin B. Elevations of transaminases did not lead to discontinuation of the drug and were reversible. No subject discontinued miltefosine due to renal impairment or hepatic enzyme elevation, and one subject (0.3%) discontinued miltefosine due to isolated hyperbilirubinemia.

Cutaneous Leishmaniasis Due to Members of the Subgenus *L. Viannia*

Miltefosine was superior to placebo for the primary endpoint of complete healing of CL lesions in Colombia and Guatemala at 6 months. Miltefosine also resulted in more rapid resolution compared to placebo. Despite limitations of the active-controlled studies, orally administered miltefosine and intravenous or intramuscular pentavalent antimony preparations resulted in similar cure rates in Bolivia and Brazil. Adverse events mainly include nausea, vomiting, diarrhea, headache and dizziness. Elevations in creatinine above baseline were mild and reversible. Elevations of hepatic enzymes were also mild and reversible. In CL trials, no subject discontinued therapy due to hepatic or renal impairment.

Mucosal Leishmaniasis Due to Members of the Subgenus *L. Viannia*

ML occurs in patients who have or have had New World CL, mainly due to *Leishmania* organisms in the subgenus *Viannia*. The disease is relentlessly progressive with destruction of nasal and pharyngeal structures. Miltefosine resulted in complete healing in approximately 60% of Bolivian subjects, higher than the historical amphotericin cure rate at the same study center and comparable to pentavalent antimony cure rates in Peru. The Bolivian study site had indicated that, in their experience, pentavalent antimony preparations were not effective.

Miltefosine is embryotoxic and teratogenic in animals at doses lower than the human therapeutic dose. The recommendation is to contraindicate the drug in pregnancy women for all indications.

Recommendations for Post-market Risk Evaluation and Mitigation Strategies

A Risk Evaluation and Mitigation Strategy (REMS) is not required beyond labeling and a Medication Guide to mitigate the reproductive risks associated with miltefosine exposure in men and women.

Miltefosine is embryotoxic and teratogenic in animals at doses lower than the therapeutic human dose. The German product labeling contraindicates Impavido during pregnancy, and it is recommended that the US product labeling recommend the same. Miltefosine has a terminal half-life of approximately 30 days, and a woman may become pregnant during or soon after the end of therapy, thus potentially extending the risk to the fetus beyond the duration of therapy. Mandating a negative pregnancy test prior to dispensing

the drug will only partially mitigate the risk to the fetus. The number of women expected to use the drug in the United States is expected to be very low (less than 10/year), and the number of pregnant women requiring the drug is expected to be even lower. Most physicians will seek expert help in managing leishmaniasis, making an education plan for physicians or patients not feasible.

Labeling will include a boxed warning regarding use in pregnancy and the need for effective contraception in women of reproductive potential. Labeling will also include this information in the Warnings sections and a description of the animal reproductive findings in the Non-Clinical Toxicology section and in the Use in Special Populations section. Labeling will also include a warning regarding possible adverse effects of miltefosine on male and female fertility during therapy and the uncertainty regarding long term effects on fertility. A Medication Guide will be also dispensed with every prescription.

The other toxicities associated with miltefosine exposure are nausea, vomiting, diarrhea, headache, dizziness and pruritus, impairment of kidney and hepatic function, and possibly thrombocytopenia. These risks can be managed by describing the adverse events and recommending monitoring of hematologic, renal and hepatic functions during therapy in the product labeling.

Recommendations for Post-market Requirements and Commitments

CMC recommended two postmarketing commitments to develop an appropriate method for release and stability testing of the drug product and drug substance, and to perform (b) (4) testing.

Four postmarketing requirements are recommended to be conducted in the target population: a dedicated QT study to evaluate the effects of miltefosine on the QT interval, a study to evaluate the effect of miltefosine on spermatogenesis, collection of data regarding pregnancy outcomes in women who become pregnant while taking miltefosine or during 5 months after end of miltefosine therapy and an observational study to collect data regarding efficacy and adverse reactions in patients with leishmaniasis who weigh more than 75 kg.

Executive Summary

Leishmaniasis

Leishmania organisms are intracellular protozoan parasites that are transmitted to a mammalian host by the bite of the female phlebotomine sandfly. The genus is divided into two subgenera, *Leishmania* and *Viannia*. *Leishmania* subgenus includes *L. donovani, L. chagasi/infantum, L. tropica, L. major, L. aethiopica, L. mexicana and L. amazonensis*.

The subgenus *Viannia* includes *L. braziliensis, L. peruviana, L. guyanensis and L. panamensis*. Traditionally, *Leishmania* infections that occur in Asia, Africa, Europe and the Middle East are designated Old World, while infections that occur in the Americas are designated New World.

The main clinical syndromes are cutaneous leishmaniasis (CL), mucosal leishmaniasis (ML) and visceral leishmaniasis (VL).

CL usually presents as one or more skin ulcers at the site of the sandfly bite. In most cases, the ulcer spontaneously resolves within several months, leaving a scar. The goals of therapy are to accelerate healing, decrease morbidity and decrease relapse. For New World CL, the goals also include decreasing the risk of local and mucosal dissemination. There are no FDA approved drugs for the treatment of CL. Topical therapies that have been used include paromomycin and intralesional antimony, and thermotherapy. Systemic therapies include IM or IV pentavalent antimony preparations (sodium stibogluconate and meglumine), IV amphotericin B, or an oral azole (ketoconazole, fluconazole).

ML occurs in 1-10% of patients with New World CL, and results from dissemination of the infecting parasite from the skin to the naso-oropharyngeal mucosa. ML is progressive, with eventual destruction of nasal and pharyngeal structures. Death may occur due to complicating aspiration pneumonia. There are no FDA approved drugs for the treatment of ML. Therapies that have been used include pentavalent antimony preparations and amphotericin B.

Visceral leishmaniasis is the result of systemic infection and is progressive over months or years. The term kala-azar refers to the most severe form of VL. Classic manifestations include fever, hepatomegaly, prominent splenomegaly, and bone marrow involvement with pancytopenia. VL is fatal if untreated. Liposomal amphotericin B (AmBisome) was FDA approved in 1997 for the treatment of VL on the basis of literature reports of uncontrolled studies in Mediterranean patients infected with *L. chagasi/infantum*. Other therapies used include amphotericin B deoxycholate, pentavalent antimony preparations and paromomycin. Antimonials are not recommended for use in the Indian subcontinent because of resistance.

HIV co-infection adversely affects the course of VL, resulting in higher mortality and multiple relapses after treatment.

Miltefosine

The sponsor is seeking FDA approval for the treatment of VL caused by *L. donovani* and for the treatment of ML and CL caused by members of the subgenus *Viannia*.

Miltefosine is an alkyllysophospholipid analogue with *in vitro* activity against *Leishmania* species. *Leishmania* organisms transport miltefosine via translocation machinery located at the parasite's plasma membrane. Once internalized, miltefosine inhibits mitochondrial function through inhibition of cytochrome C oxidase, and

phospholipid and sterol synthesis through inhibition of phospholipase C, resulting in apoptotic-like cell death. Intrinsic or acquired resistance may be due to reduced levels of the translocation machinery proteins.

Miltefosine is orally administered. The half-life in Indian VL patients receiving doses 50-150 mg/day was 150-200 hours and steady state was not reached on Day 23. The terminal half-life in Dutch soldiers with CL was 31 days. Miltefosine is cleaved by phospholipase D to choline which is incorporated into tissues and hexadecanol which is oxidized to palmitic acid. Miltefosine is not a substrate, an inhibitor or an inducer of CYP 450 enzymes. Drug interaction studies have not been conducted.

Main toxicities noted in rats include hyperplasia of tubular and transitional renal epithelium, necrosis of testicular tubules, increases in liver transaminases and bilirubin, and reversible dose and duration dependent retinal atrophy. The retinal changes were not noted in dogs. In mice, rats and rabbits, miltefosine was fetotoxic and teratogenic. Malformed fetuses showed misshapen cerebral structures, misshapen eyes and hemo- or hydrocephalus. Miltefosine had no effect on hERG channel, and no cardiovascular effects were noted in dogs or pigs. IV miltefosine is hemolytic, but hematologic effects of orally administered miltefosine were not noted.

Miltefosine is registered in Germany as a topical drug to treat cutaneous cancers. As an oral agent, it is registered in Germany, several countries in South America and the Indian subcontinent for the treatment of VL and CL. Miltefosine was included in the WHO essential medicines list as an anti-leishmaniasis medicine in March 2011.

Summary of Efficacy

VL Caused by *L. donovani*

For the VL indication, the sponsor submitted one pivotal study and one supportive study.

The pivotal study, Study 3154, was a randomized, open label, non-inferiority design comparative study conducted in 1999-2000 at 3 study sites in India where epidemiologically *L. donovani* is known to be the infecting pathogen. Subjects ≥ 12 years of age with clinical signs and symptoms compatible with VL parasitologically confirmed by spleen aspirate were randomized in a 3:1 ratio to receive oral miltefosine 50 mg twice a day if weight ≥ 25 kg or once a day if weight < 25 kg for 28 days or IV amphotericin B deoxycholate 1 mg/kg every other day for 15 doses. All subjects were hospitalized for the duration of therapy. Pregnant women were excluded, as were subjects with severe pancytopenia, renal or hepatic impairment or co-infection with TB, malaria or HIV.

Treatment response was classified as Initial Cure, Final Cure, Relapse or Failure. Initial Cure was defined as absence of parasites at the end of therapy (parasite score 0 on spleen or bone marrow aspirates). Subjects with parasite density of 1 at EOT were re-assessed 1 month later, and designated as initial cure if the score was 0 or treatment failure if the score was > 0.

Treatment failure was defined as spleen or marrow aspirate score > 1 at EOT or score > 0 any time one month after EOT.

Final Cure was defined as Initial Cure plus no relapse and absence of clinical signs and symptoms attributable to leishmaniasis during the 6 months follow up. Absence of clinical signs and symptoms attributable to VL was defined as

1- Loss of fever that is attributed to VL and
2- Spleen size at least 30% smaller than at pre-treatment (only applicable if spleen size was > 1 cm below the costal margin at pre-treatment). If palpable spleen was ≤ 1 cm at pre-treatment, it must not be > 1 cm when clinical response is assessed, and
3- Hemoglobin ≥ 10.0 g/dl for female subjects or ≥ 11.5 g/dl for male subjects (or at EOT, residual decrement from the lower limit of normal < 10% of the decrement at baseline), and
4- Platelets ≥ 100,000/ul (or at EOT, residual decrement from the lower limit of normal < 30% of the decrement at baseline), and
5- Leukocytes ≥ 3500/ul (or at EOT, residual decrement from the lower limit of normal < 30% of the decrement at baseline)

Subjects who had experienced initial cure but who did not have absence of clinical signs and symptoms of VL at the 6 months follow up visit were to undergo a repeat spleen or marrow aspirate. Those with a positive aspirate were classified as relapse.

The primary efficacy endpoint was Final Cure. Sample size was calculated based on one-sided alpha 0.025, power 0.80 and NI margin of 15%, assuming final cure rates of 88 to 92% for miltefosine of and 94 to 98% for amphotericin. Although the study's pre-specified NI margin of 15% could be statistically supported, the FDA considered a margin of 10% more acceptable based on the severity of the disease.

299 subjects received miltefosine and 99 subjects received amphotericin B. At baseline, the study arms were matched for age, weight, BMI, performance status, prior VL therapy, parasite density and duration of VL symptoms. A statistically significant higher percentage of males were randomized to miltefosine (p 0.035), raising some concerns regarding the randomization process. The gender imbalance between the treatment arms was most noted at study site 1 (M/F ratio 4.2 in the miltefosine arm and 1.8 in the amphotericin arm), and to a lesser extent at study 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). Approximately a third of enrolled subjects had received prior antimony therapy and approximately a third were 12 to 17 years of age.

98% of subjects in each treatment arm experienced initial cure.

Table 1: Initial Cure – Study 3154

	MLT N = 299	AMB N = 99

Initial Cure	293 (98.0%)	97 (98.0%)
Parasitology score 0 at EOT	289 (96.7%)	96 (97.0%)
Parasitology score 1 at EOT	5 (1.7%)	1 (1.0%)

At 6 months, 88 miltefosine subjects (29.4%) and 12 (12.1%) amphotericin subjects did not have absence of signs and symptoms as defined by the protocol. The investigators attributed these signs and symptoms to alternative diagnoses in 73 subjects, most commonly malnutrition. The remaining 27 subjects underwent a marrow or spleen aspirate, all in the miltefosine arm. Nine subjects were positive for *Leishmania* amastigotes. Two additional subjects who had absence of signs or symptoms as defined by the protocol also underwent an aspirate, and both were negative. The final cure according to the sponsor's analysis was 94.3% in the miltefosine arm vs. 97.0% in the amphotericin arm. The difference was 2.7% (-1.62%, 6.93%), indicating that miltefosine is non-inferior to amphotericin.

Table 2: Final Cure – Study 3154 – Sponsor Analysis

	MLT N = 299	AMB N = 99	Difference AMB-MLT	P Value
ITT				
Final Cure 95% CI	282 (94.3%) 91.1%, 96.7%	96 (97.0%) 91.4%, 99.4%	2.7% (-1.62%, 6.93%)	0.43
Relapse	9 (3.0%)	0		
Deaths	2 (0.7%)	0		
Not-assessable	6 (2.0%)	3 (3.0%)		
PP				
	MLT N = 287	AMB N = 94	Difference AMB-MLT	P Value
Final Cure	279 (97.2%)	94 (100%)	2.8% (0.88, 4.69%)	0.21

Of the 100 subjects without absence of signs and symptoms at 6 months, 27 were at study site 1, 35 at study site 2, and 38 at study site 3. However, of the 27 subjects who underwent an aspirate at 6 months for parasitologic confirmation of cure or relapse, 23 were at site 1 (23/27, 85%), two were at site 2 (2/35, 5.7%) and two at site 3 (2/38, 5.3%). Because of this significant inconsistency between the sites in following up residual signs and symptoms suggestive of VL at 6 months, the FDA reviewer evaluated the clinical data for the 100 subjects, blinded as to which subject underwent a follow up aspirate. The reviewer identified 27 subjects who warranted further evaluation: the 9 subjects who had a positive aspirate, 4 of the subjects who had a negative aspirate, and an additional 14 subjects, 12 miltefosine recipients and 2 amphotericin recipients. If these 14 subjects are conservatively considered failures, the final cure is conservatively estimated at 90.3% in the miltefosine arm and 94.9% in the amphotericin arm. The difference is 4.6% (-2.0%, 9.8%). The conclusion that miltefosine is non-inferior to amphotericin B holds.

Subjects who received less than 2-2.5 mg/day had a numerically lower cure rate.

Table 3: Miltefosine Final Cure Rate – Study 3154 – Sponsor Cure Rates

Miltefosine Dose mg/kg	Final Cure	Relapse

1.7 -< 2	24/26 (92.3%)	1/26 (3.8%)
2- <2.5	96/104 (92.3%)	6/104 (5.8%)
2.5-< 3	114/121 (94.2%)	2/121 (1.7%)
3-3.9	39/39 (100%)	0
≥ 4	9/9 (100%)	0
Total	282/299 (94.3%)	9/299 (3.0%)

Table 4: Miltefosine Final Cure Rate – Study 3154 – Reviewer Cure Rates

Miltefosine Dose mg/kg	Final Cure	Relapse
1.7- < 2	22/26 (84.6%)	3/26 (11.5%)
2- <2.5	92/104 (88.5%)	10/104 (9.6%)
2.5-< 3	109/121 (90.1%)	7/121 (5.8%)
3-3.9	38/39 (97.4%)	1 (2.6%)
≥ 4	9/9 (100%)	0
Total	270/299 (90.3%)	21/299 (7.0%)

The supportive study for the VL indication was Study Z025, conducted in 2003-2005 by Medicins Sans Frontieres in a semi-nomadic population in Ethiopia, where epidemiologically *L. donovani* is known to be the infecting species. The sponsor did not have the primary efficacy data for this study. The sponsor's study report and our analyses both used the published article that reported the findings of this study.

Z025 was a randomized, open-label study comparing oral miltefosine 100 mg daily for 28 days to IM sodium stibogluconate (SSG) 20 mg/kg daily for 30 days. Only male subjects at least 15 years of age were enrolled, because birth control in women could not be assured. Subjects with fever > 2 weeks duration and evidence of splenomegaly or lymphadenopathy and wasting and a negative malaria smear were eligible. VL was diagnosed by a high *Leishmania* direct agglutination test (DAT) titer. Subjects with an indeterminate titer and subjects previously treated for VL underwent spleen or lymph node aspirate for parasitologic diagnosis. Spleen or lymph node aspirates were performed at end of therapy. Subjects who did not respond clinically or parasitologically to miltefosine were re-treated with SSG. Subjects who did not respond to SSG or were intolerant of SSG were re-treated with another SSG course or with amphotericin B. The primary endpoint was final cure, defined as initial cure and no symptoms of relapse at 6 months. Initial cure was defined as a negative aspirate at EOT with clinical improvement, or if an aspirate could not be performed, as clinical cure. The FDA had recommended a non-inferiority margin of 10% for final cure. The sponsor proposed a post-hoc primary endpoint of mortality by the end of therapy.

290 subjects received miltefosine and 290 subjects received SSG. Subjects were matched as to age, BMI, Hb, and spleen size and performance status. Subjects were asked to volunteer for HIV serology testing, typically 2-3 weeks after providing consent to be in the study. 65% of enrolled subjects underwent voluntary HIV testing, and approximately 30% were infected. A higher percentage of miltefosine subjects were HIV infected, while a higher percentage of SSG subjects were HIV status unknown. The most likely explanation for this imbalance was that HIV testing was requested at 2-3 weeks after initiation of therapy, and a higher percentage of SSG subjects had died by then.

Approximately 88% experienced initial cure at end of therapy in each arm. Although initial cure was similar, SSG recipients were significantly more likely to die by EOT, while miltefosine subjects were significantly more likely to experience initial failure. Published data from East Africa indicates that SSG therapy in HIV negative VL patients remains highly effective. The relatively high mortality in the SSG arm in this study is therefore unlikely to be due to resistance/ineffective therapy.

23 miltefosine subjects who experienced initial failure were re-treated with SSG, while 2 SSG subjects who experienced initial failure were re-treated with amphotericin B. The disposition flow diagram in the published article indicated that these subjects were not excluded from calculation of final cure, and it was unclear how many contributed to the final cure rate. Approximately 20% of subjects were lost to follow up in each arm. At 6 months, a higher percentage of miltefosine subjects relapsed. Final cure in the ITT population was 60% for miltefosine and 65.2% for SSG. The difference (MLT-SSG) was -5.2% (-13.0, 2.7). In the PP population, final cures were 79.5% for miltefosine and 82.2% for SSG. The difference was 2.7% (-4.6%, -10.0%). However, not excluding subjects who had initial failure and who received re-treatment from the final analysis confounds the interpretation of final cure, especially in the miltefosine arm.

For the sponsor-proposed post-hoc primary endpoint of death by EOT, miltefosine was superior to SSG. However, the open label trial design may introduce biases in treatment assignment which could not be examined because of the lack of access to primary patient level data introduces uncertainty. The conclusion of miltefosine superiority to SSG was therefore not accepted.

The high SSG initial mortality mainly occurred in HIV status unknown subjects, and the high miltefosine initial failure and relapse after therapy occurred mainly in the HIV infected group. Among HIV negative subjects, ITT final cure was 76% vs. 77% and PP final cure was 93% and 94% for miltefosine and SSG respectively.

Table 5: Miltefosine Efficacy - VL – Study Z025

	MLT N = 290	SSG N = 290	P value
Initial Cure at EOT	256 (88.3%)	254 (87.6%)	0.9
Died During Therapy	6 (2.1%)	28 (9.7%)	0.0001
Initial Failure	23 (7.9%)	2 (0.7%)	< 0.0001
Initial cure at end of re-treatment	273 (94.1%)	255 (87.9%)	
Followed at 6 months	213 (73.5%)	202 (69.7%)	
Final Cure 95% CI	174 (60.0%) (54.1%, 65.7%)	189 (65.2%) (59.4%, 70.6%)	0.23
Died During Follow up	11 (3.8%)	6 (2.1%)	
Total Deaths	17 (5.9%)	34 (11.7%)	0.0001
Relapse	30 (10.3%)	7 (2.4%)	0.019

In addition to these trials, the study report summaries for dose ranging studies conducted in India and for two Phase 4 studies conducted in India and Nepal were submitted.

The dose ranging trials indicated that doses lower than 2.5 mg/kg/day were less effective than higher doses, and that durations of less than 4 weeks were less effective than longer durations. Doses higher than 2.5 mg/kg/day were poorly tolerated due to vomiting and renal and hepatic toxicities.

The Phase 4 trial in India (Z013) enrolled 1132 patients, 428 children (age 2-11) and 704 adults. Initial cure was 93.2% and initial failure 0.6%. Final cure at 6 months in the ITT population was 82% and in the PP population 98.6%. Relapse occurred in approximately 4% and mortality was 0.3%.

The Phase 4 trial in Nepal (Z013b) enrolled 125 subjects, 33 below the age of 12. Initial cure was 97% and final cure at 6 months was 84% in the ITT population and 90% in the PP population. Approximately 10% of subjects relapsed. Mortality was 1.6%.
In addition to the above studies, three published studies evaluated miltefosine in the treatment of VL. All three studies were reported in the literature 10 years after Study 3154 was conducted or reported. These studies were conducted in India, Nepal and Bangladesh.

The study in India was conducted at one of the study sites that participated in Study 3154 (site 2) and reported on the efficacy of miltefosine after a decade of use. The study design was the same as Study 3154. 567 patients were enrolled and given the drug under daily observation. Initial cure was approximately 98%. 7% of subjects relapsed. Final cure in the ITT population was 90.3%. Mortality was < 1%. In comparison, the final miltefosine cure rate in Study 3154 overall was 94% and at that study site 97%. The authors expressed concern that the lower final cure rate and higher relapse rate compared to Study 3154 may be indicative of the emergence of resistance. Culture and susceptibility data were not reported.

The study in Nepal enrolled 120 VL patients. Initial cure in the ITT population was 96%. 10.8% relapsed within 6 months, and a similar percentage relapsed in the subsequent 6 months. The ITT and PP cure rates at 6 months were 83% and 86% respectively. Mortality at 6 months was <1%. DNA fingerprinting indicated that relapses were not due to reinfection. Miltefosine exposure and miltefosine IC_{50} pre and post therapy were similar in the cured and failed patients. The increased incidence of relapse beyond 6 months and higher relapse rates compared to Study 3154, as well as the occurrence of late relapses are, however, all concerning for the emergence of resistance.

The study in Bangladesh enrolled 977 patients. Initial cure in the ITT population was 88%. Mortality was < 1%. 95 subjects did not have absence of signs or symptoms, 73 of whom had isolated anemia. If all these subjects are considered relapses, the relapse rate was 10%, and the final cure was 72% in the ITT population and 85% in the PP population. Final cure rate would be higher if one third of subjects with isolated anemia are considered relapses.

The following table summarizes the results of the Phase 4 and published trials.

Table 6: Effectiveness of Miltefosine in Post-Marketing Studies - VL

Effectiveness in Post-Marketing Studies	Z013 N = 1132	Z013b N = 125	Rahman et al. N = 977	Sundar et al. N = 567	Rijal et al. N = 120	Study 3154 N = 299
Country	India	Nepal	Bangladesh	India	Nepal	India
Initial Cure - ITT	1055 (93.2%)	121 (96.8%)	865 (88.5%)	553 (97.5%)	115 (95.8%)	293 (98.0%)
Final Cure - ITT	927 (81.9%)	105 (84%)	701 (71.8%)	512 (90.3%)	99 (82.5%)	282 (94.3%)
Final Cure - PP	927/971 (95.5%)	105/117 (89.7%)	701/820 (85%)	512/553 (92.6%)	99/115 (86.1%)	282/287 (98.3%)
Not assessable	158 (14.0%)	8 (6.4%)	121 (12.4%)	11 (1.9%)	7 (5.8%)	6 (2.0%)
6 month Relapse	44 (3.9%)	12 (9.6%)	95* (9.7%)	39 (7.2%)	13 (10.8%)	9 (3.0%)
6 month Mortality	3 (0.3%)	2 (1.6%)	6 (0.6%)	5 (0.9%)	1 (0.8%)	2 (0.7%)

*Assumes that all subjects with residual anemia are not cured.

A study from India reported that ED_{90} of *Leishmania* amastigotes from Bihar, where miltefosine use is extensive, was statistically significantly higher than ED_{90} from Uttar Pradesh, where miltefosine use is not extensive. ED_{50} values were not statistically significantly different. Another study from India reported that the mean miltefosine post-therapy IC_{50} were significantly higher in VL patients who relapsed compared to VL patients who were cured.

CL Due to Members of the Subgenus *Viannia*

For the CL indication, the sponsor submitted one pivotal study (Study 3168) and two supportive studies (Study Soto, and Study Z020).

Study 3168 was a randomized, placebo-controlled study conducted in Colombia and Guatemala in 2000-2002. Subjects ≥ 12 years of age with parasitologically confirmed CL lesions and without underlying medical conditions or laboratory abnormalities were enrolled. Clinical response was classified as apparent cure, partial cure, definite cure or failure.

Apparent cure was defined as complete epithelialization of all lesions at 2 weeks after EOT.

Partial cure was defined as incomplete epithelialization or incomplete regression of induration of any lesion, no > 50% enlargement of previously documented lesions, and no appearance of new lesions at 2 weeks. If parasitology was not done 2 weeks after EOT, the evaluation of partial cure was based on clinical parameters only.

Definite cure was defined as complete epithelialization of all ulcers and complete disappearance of inflammatory induration from all lesions and no positive parasitology

between 2 weeks and the 6 months follow up and no new lesions between 2 weeks and 6 months follow up and no 50% enlargement of lesions between 2 weeks and 6 months.

Failure at 2 weeks was defined as lack of achieving apparent or partial cure.

The primary endpoint was apparent or partial cure at 2 weeks followed by definite cure at 6 months. Subjects classified as failure at 2 weeks were also classified as failure at 6 months.

89 subjects received miltefosine and 44 subjects received placebo. The treatment groups were matched as to age, gender, weight, BMI, history of previous CL treatment, number and size of lesions. Miltefosine was superior to placebo for definite cure (66.3% vs. 29.6%, p value <0.0001). The treatment difference was 36.7% (95% CI 20.1%, 53.4%). Cure rate in each treatment arm was higher in Colombia compared to Guatemala, but miltefosine was superior to placebo at each country/study site.

Table 7: Definite Cure by Study Center/Country –Study 3168

	Placebo	Miltefosine	Difference	P value
ITT				
Colombia	9/24 (37.5%)	40/49 (81.6%)	44.1%	0.0002
Guatemala	4/20 (20.0%)	19/40 (47.5%)	27.5%	0.0406
Total	13/44 (29.6%)	59/89 (66.3%)	36.7% 95% (CI 20.1, 53.7)	< 0.0001
PP				
Colombia	9/24 (37.5%)	40/47 (85.1%)	47.6%	< 0.0001
Guatemala	4/18 (22.2%)	19/38 (50.0%)	27.8%	< 0.0505
Total	13/42 (31.0%)	59/85 (69.4%)	38.4% 95% CI (21.4, 55.5)%	< 0.0001

Cure rates were higher in Colombia in both treatment arms. A possible explanation may be related to differences in the prevalent epidemiologic species in each country. Epidemiologically, *L. panamensis* and *L. braziliensis* respectively cause approximately 54% and 30% of CL lesions in Colombia, while *L. braziliensis* causes approximately 75% of CL lesions in Guatemala. *L. braziliensis* causes more protracted disease compared to other species: spontaneous resolution at 6 months of CL lesions caused by *L. braziliensis* is 6-8% compared to 30-38% for *L. panamensis* or to 68% for *L. mexicana*. *L. braziliensis* may also be intrinsically less susceptible to miltefosine because it may not fully express the translocation proteins required to internalize the drug. Of note, parasitology or susceptibility profile data were not submitted for review, but the results of this study were reported in the literature. The published article stated that 76% of Guatemalan subjects had a species identified. Of these, two thirds were *L. braziliensis* and one third was *L. mexicana*. In contrast, only 10% of Colombian subjects had a species identified, all *L. panamensis*. The placebo cure rate for the subjects known to be infected with *L. braziliensis* was approximately 8%, similar to what is reported in the literature, and placebo cure for subjects known to be infected with *L. mexicana* was 33%. The corresponding cure rates for miltefosine subjects known to be infected with *L. braziliensis* and *L. mexicana* were 31% and 64% respectively.

Study Soto was an investigator-initiated, open-label comparative study conducted in 2005-2007 in Bolivia where *L. braziliensis* is epidemiologically expected to be the predominant species. Concerns regarding the randomization process were raised in this review based on timing of enrollment and initiation of treatment. In addition, part of the randomization list was not used and the study was closed prior to reaching the full planned enrollment without explanation. There was no pre-specified statistical hypothesis of superiority or non-inferiority.

Subjects ≥ 12 years of age were assigned 2:1 to receive oral miltefosine 2.5 mg/kg/day for 28 days or IM meglumine for 20mg/kg/d for 20 days. The primary efficacy endpoint was definite cure, defined as complete re-epithelialization of all lesions at 6 months after EOT. A lesion was defined as failure if it did not completely re-epithelialize at 6 months after EOT, or if the lesion enlarged by 50% at EOT or 1 month after EOT, if the lesion area did not diminish by 50% at 3 months after EOT, or the lesion relapsed.

43 subjects received miltefosine (40 included in the sponsor's analysis – 3 records were missing) and 18 subjects received meglumine. The sponsor imputed three meglumine subjects who were lost to follow up as failure. However, these subjects were likely not followed due to closure of the study and therefore were not included in our analysis. Definite cure occurred in 32/40 miltefosine subjects (80%), and 13/15 subjects who received meglumine (86.7%). The 95% CI for meglumine – miltefosine difference was -21.4%, 26.3%.

Study Z020 was conducted in 2007-2009 and was split into two studies, Z020a and Z020b. Study Z020a was conducted in an area of Brazil where *L. guyanensis* is epidemiologically the predominant pathogen and Z020b was conducted in an area of Brazil where *L. braziliensis* is epidemiologically the predominant pathogen. Both studies were randomized, open-label, comparative trials that enrolled children 2-11 years of age and adults ≥ 12 years of age. Subjects with parasitologically confirmed CL received either miltefosine at a target dose of 2.5 mg/kg/day for 28 days or meglumine IM at 20 mg/kg/day for 21 days. The primary endpoint was definite cure, defined as complete re-epithelialization 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 pre-specified statistical hypothesis.

In each study, 40 adults and 20 children received miltefosine and 20 adults and 10 children received meglumine. Because the applicant is limiting the indication to subjects ≥ 12 years of age, results will focus on this age group. There was an imbalance in the number of withdrawals across arms without further information provided as to the reasons for these withdrawals. Miltefosine appeared superior to meglumine in Study Z020b; however, considering Z020 as one study and considering the results in the entire enrolled population, this finding of superiority was not substantiated.

Table 8: Miltefosine Efficacy – Study Z020 – Subjects ≥12 years of Age

	Miltefosine	Meglumine	Difference

			MEG –MLT 95% CI
Z020a			
Definite Cure - ITT	27/40 (67.5%)	12/20 (60.0%)	-7.5% (-34.6,17.9)%
Z020b			
Definite Cure - ITT	34/40 (85.0%)	9/20 (45.0%)	-40% (-63.5,-8.6)%
Z020			
Definite Cure - ITT	61/80 (76.3%)	21/40 (52.5%)	-23.8% (-41.9,-5.2)%

Table 9: Miltefosine Efficacy – Z020 – All Subjects

Definite Cure - ITT	Miltefosine	Meglumine	Difference MEG –MLT 95% CI
< 12 years of age	27/40 (67.5%)	15/20 (75.0%)	7.5% (-18.7, 30.4)%
≥ 12 years of age	61/80 (76.3%)	21/40 (52.5%)	-23.8% (-41.9, -5.2)%
All Subjects	88/120 (73.3%)	36/60 (60.0%)	-13.3% (-28,4,1.4)%

In contrast to the other studies submitted for the NDA review, parasitologic speciation of the infecting *Leishmania* organisms was obtained in every subject in Study Z020. As epidemiologically expected, 99% of isolates in Study Z020a were *L. guyanensis,* and 100% of isolates in Study Z020b were *L. braziliensis*.

As already mentioned, *L. braziliensis* epidemiologically accounts for 90% of isolates in Bolivia (Study Soto) and 75% of isolates in Guatemala (Study 3168) Despite the limitations of Studies Z020b and Study Soto, definite cure in these studies was higher than definite cure in Guatemala, even after accounting for the earlier timepoint of assessment of failure in Study 3168. In addition, the cure rate in Guatemalan subjects with documented *L. braziliensis* infection was 31.2% (published article). Regional variation in the sensitivity of *L. braziliensis* to miltefosine cannot be excluded.

Table 10: Miltefosine Efficacy by Geographic Region – CL Subjects ≥ 12 years of Age

	Miltefosine Definite Cure
Guatemala* (3168)	19/40 (47.5%)
Bolivia (Soto) *	32/40 (80.0%)
Bahia, Brazil* (Z020b)	34/40 (85.0%)
Colombia	40/49 (81.6%)
Manaus, Brazil (Z020a)	27/40 (67.5%)

**L. braziliensis* epidemiologically most prevalent

In each study and in all studies combined, miltefosine subjects who received less than 2 mg/kg/day had a lower cure rate compared to subjects who received higher doses.

Table 11: Effect of Miltefosine Dose – Studies 3168, Z020 and Soto – Subjects ≥ 12 years of Age

Miltefosine mg/kg Dose	Definite Cure
1.4 - < 2	9/18 (50.0%)
2-2.4	56/81 (69.1%)

2.5-2.9	71/90 (78.9%)
3-3.9	16/20 (80.0%)
Total	152/209 (72.7%)

ML Due to Members of the Subgenus *Viannia*

For the ML indication, the sponsor submitted one single arm study, Study Z022, conducted in 2004-2006 in Bolivia, where *L. braziliensis* is epidemiologically the predominant pathogen. A comparative study was planned, but the study site refused randomization to a comparator antimonial treatment arm because in their experience antimonials were ineffective. Subjects refused randomization to an IV amphotericin comparative arm because miltefosine is orally administered.

79 adult subjects received a target miltefosine dose of 2.5 mg/kg/day (150 mg/day) for 28 days. 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 five anatomic sites (nasal skin, nasal mucosa, palate, pharynx, and larynx).

49/79 subjects (62%) were cured, with a severity score of 0 at 12 months, indicating complete healing. Because this was a single arm study, published reports regarding the effectiveness of other ML therapies were retrieved. The published article that reported this study also reported clinical response of 19 historical control subjects who received amphotericin B at the same study site. The baseline mean severity score in these subjects was comparable to the baseline mean score in miltefosine subjects (mean score 10). Of the 19 amphotericin subjects, 3 discontinued the drug due to an adverse event and 2 were lost to follow up. 7 of the 14 evaluable subjects were cured (50.0%). The cure rate in the ITT population was 7/19 (36.8%). Published reports from Peru indicated a 12 month cure rate of 45-60 % for ITT patients treated with pentavalent antimony and studies from Brazil reported 12 month cure rates of 80-100% of patients treated with pentavalent antimony, and 57% of patients treated with amphotericin B.

Table 12: Cure Rate – Study Z022 – ITT and PP

	ITT 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%)	0

Mean miltefosine mg/kg dose was similar among subjects who were cured compared to subjects who were not. Subjects who received dose less than 2mg/kg/day had a lower cure rate, but the number of subjects who received this dose is small.

Table 13: Effect of Miltefosine Dose – Study Z022

Miltefosine mg/kg	Cured
< 2	2/4 (50.0%)
2-2.4	15/19 (79.0%)
2.5-2.9	26/38 (68.4%)
3-3.9	5/16 (31.2%)
≥4	1/1 (100%)

Summary of Safety

In all studies, the main adverse events that occurred more frequently in miltefosine recipients were vomiting and diarrhea, which were noted at all clinical dose ranges.

Table 14: Summary of AE – Studies 3154, 3168, Z020, Soto, VL and CL Dose Ranging Studies

	Miltefosine N = 587	Miltefosine N = 321	Amphotericin N = 99	Meglumine N = 58	Placebo N = 44
Study	3154, 3168, Soto, Z020, Z022	Dose Ranging VL and CL	3154	Soto Z020	3168
Death	3 (0.5%)	2 (0.6%)	0	0	0
SAE	7 (1.2%)	2 (0.6%)	1 (1.0%)	0	0
AE leading to drug discontinuation	9 (1.5%)	13 (4.0%)	3 (3.0%)	0	0
Vomiting	328 (55.6%)	128 (39.9%)	20 (20.2%)	0	0
Diarrhea	87 (14.8%)	85 (26.5%)	6 (6.1%)	3 (5.2%)	2 (4.5%)
Transaminases > 3x ULN	60 (10.2%)	46 (14.3%)	11 (11.1%)	2 (3.4%)	0
Cr elevation > 1.5x baseline	79 (13.5%)	20 (6.2%)	40 (40.4%)	3 (5.1%)	2 (4.5%)

Visceral Leishmaniasis

The frequency of AEs for Phase 1, 2 and 3 studies conducted in India are summarized.

Table 15: Summary of AE – Phase 1 and 2 Indian Studies and Study 3154

	MLT			AMB N = 99
	Phase 1&2 N = 249	3154 N = 299	Total N = 548	
Subjects with at least one AE	-	125 (41.8%)	-	44 (44.5%)
Subjects with SAE	2 (0.8%)	6 (2.0%)	8 (1.5%)	1 (1.0%)
AE that led to drug discontinuation	13 (5.2%)	8 (2.7%)	21 (3.8%)	3 (3.0%)
Death	2 (0.8%)	2 (0.7%)	3 (0.6%)	0

In Study 3154, nausea, vomiting and diarrhea were noted more frequently in the miltefosine arm, whereas 90% of amphotericin subjects experienced amphotericin infusion reaction (fever and rigors) and received therapeutic and preventive treatments

for such reactions. The frequency of vomiting increased as mg/kg miltefosine dosage increased.

Table 16: Effect of Miltefosine mg/kg Dose on Frequency of Elicited AEs of Diarrhea and Vomiting – Study 3154

	Miltefosine mg/kg				AMB
	1.4-< 2 N = 26	2-<3 N = 225	≥3 N = 48	Total N = 299	N = 99
Diarrhea	3 (11.5%)	52 (23.1%)	6 (12.5%)	61 (20.4%)	6 (6.1%)
Vomiting	6 (23.1%)	85 (37.8%)	22 (45.8%)	113 (37.8%)	20 (20.2%)

Table 17: Spontaneously Reported AE occurring in ≥ 2% of Subjects – Study 3154

MedDRA v. 12.0 System Organ Class Preferred Term	MLT N = 299	AMB N = 99
Blood and Lymphatic Disorders		
Thrombocytopenia	2 (0.7%)	2 (2.0%)
Gastrointestinal Disorders		
Diarrhea	9 (3.0%)	2 (2.0%)
Vomiting	3 (1.0%)	7 (7.1%)
General Disorders and Administration Site Conditions		
Asthenia	19 (6.3%)	4 (4.0%)
Pyrexia	28 (9.3%)	11 (11.1%)
Rigors	10 (3.3%)	1 (1.0%)
Metabolism and Nutrition Disorders		
Anorexia	69 (23.1%)	22 (22.2%)
Nervous System Disorders		
Headache	4 (1.4%)	2 (2.0%)
Respiratory and Thoracic Disorders		
Cough	8 (2.7%)	2 (2.0%)
Dyspnea	2 (0.7%)	2 (2.0%)

Table 18: Elicited AEs – Study 3154

	MLT N = 299	AMB N = 99
Temperature ≥ 100^{o} F	254 (84.9%)	84 (84.8%)
Investigator-assessed as related to study drug	0	72 (72.7%)
Associated with rigors	1 (0.3%)	68 (68.7%)
Rigors	1 (0.3%)	90 (90.1%)
Vomiting	113 (37.8%)	20 (20.2%)
Diarrhea	61 (20.4%)	6 (6.1%)

The deaths in Phase 1 and 2 studies were due to grade 4 diarrhea and renal and cardiac failure in one (assessed as possibly related to miltefosine – subject received 6 mg/kg/day), and pulmonary infection in another (assessed as unrelated). The two deaths in Study 3154 both occurred in the miltefosine arm and were both assessed as unlikely to be due to miltefosine. The first death occurred in a 13 year old male subject who became

drowsy on Day 11 of miltefosine treatment after complaining of earache for 4 days. Physical exam and CSF evaluation were compatible with acute bacterial meningitis due to a Gram negative organism sensitive only to ciprofloxacin. He died 2 days later. The second death was a 15 year female who had finished miltefosine course with fever resolution but persistent splenomegaly and severe anemia (Hb 3.9). Spleen aspirate was negative for *Leishmania* but positive for *P. vivax*. She was treated with chloroquine, followed by primaquine. She died three weeks after finishing the primaquine course (2 months after discontinuation of miltefosine). Her death was assessed as unlikely due to miltefosine.

Six miltefosine subjects and one amphotericin subject developed at least one SAE in Study 3154. Serious AEs that occurred in the miltefosine arm included the bacterial meningitis and malaria with fatal outcomes. The other SAEs included hemiplegia, hemiparesis, convulsions, Stevens-Johnson syndrome, melena and thrombocytopenia. SAEs in the amphotericin arm included renal impairment and nystagmus. Stevens-Johnson syndrome occurred on day 6 in a 12 year old male who received 2.8 mg/kg/day dose and was assessed as related to miltefosine. Melena with thrombocytopenia were assessed as possibly related to miltefosine and the other AEs as unrelated.

Eight miltefosine subjects and 3 amphotericin subjects developed an AE that led to drug discontinuation in Study 3154. These included the subjects with SAEs. The additional miltefosine subjects had skin rash and arthritis, CTC grade 4 diarrhea and grade 4 jaundice, all assessed as drug related. The additional amphotericin subjects had dyspnea and thrombocytopenia.

Mean Cr increased from 0.9 to 1.1 among amphotericin recipients at EOT, but remained stable at 0.9 in the miltefosine arm in Study 3154. Mean Cr was similar in both arms at 6 months follow up. Absolute Cr values were between 2 and 5.5 in 6 subjects in each arm at EOT (2% vs. 6% in the miltefosine and amphotericin arms respectively), and did not exceed 2.1 at follow up in any subject. All amphotericin subjects experienced some degree of Cr elevation above baseline at EOT, compared to approximately 50% of miltefosine subjects. Cr elevations >1.5x baseline (CTCAE grade 2) occurred in approximately 10% of miltefosine subjects at EOT, compared to 40% of amphotericin subjects. In the miltefosine arm, a higher percentage of CTCAE grade 2 elevations occurred in subjects who received a dose > 2 mg/kg/day, but grade1 elevations were not dose dependent. No miltefosine subject discontinued therapy due to renal impairment.

Table 19: Effect of Miltefosine Dose on Cr – Study 3154

	Miltefosine Dose mg/kg			
	1.4-< 2 N = 26	2-<3 N = 225	≥3 N = 48	Total N = 299
Cr 1-<1.5x baseline	12 (46.2%)	90 (40.0%)	18 (37.5%)	120 (40.1%)
Cr 1.5-<3x baseline	1 (3.8%)	20 (8.9%)	4 (8.3%)	25 (8.4%)
Cr ≥ 3x baseline	0	4 (1.8%)	0	4 (1.3%)

In Study 3154, mean transaminase values, mean alkaline phosphatase and mean bilirubin remained stable in each arm during therapy. Approximately 3% and 17% of miltefosine recipients had ALT or AST > 3x ULN (CTCAE grade 2) at EOT, compared to 1% and 9% in the amphotericin arm. One miltefosine subject discontinued therapy due to isolated hyperbilirubinemia.
In the Phase 1 and 2 studies, several subjects discontinued therapy due to grade 3 elevations in liver enzymes.

In Study 3154, hemoglobin increased more slowly during therapy in amphotericin recipients and a higher proportion of amphotericin subjects had Hb decrease of at least 2 grams at EOT, probably reflecting amphotericin hematologic toxicity and/or hemo-dilution due to IV hydration that is usually administered with amphotericin infusions. A higher percentage of miltefosine subjects had thrombocytopenia at EOT (platelets < 75k in 13% vs. 10%) and 6 month follow up (2% vs. 1%). The higher frequency at follow up is probably explained by the higher incidence of relapse, but the possibility that the higher frequency at EOT may be due to miltefosine cannot be ruled out.

The AE profile reported in the published VL trials was similar to the pre-marketing studies. Mortality was <1% except one study that had mortality of 1.6%. Deaths were either due to complications of VL, volume depletion with renal impairment or sepsis. Two subjects died suddenly. Less than 1% of subjects discontinued therapy, usually due to vomiting, diarrhea, or impaired liver or renal function.

Cutaneous Leishmaniasis

In CL studies, main adverse events that were noted more frequently in miltefosine recipients included nausea, vomiting, diarrhea, headache, dizziness, somnolence, pruritus, decreased appetite and pyrexia. Motion sickness was coded only at the Colombia site of Study 3168, and thus erroneously appears as more frequent in the placebo recipients. These subjects were coded as having nausea and dizziness as well. One subject discontinued treatment due to AE (motion sickness) and there were no serious adverse events or deaths.

Table 20: Adverse Events Occurring in ≥ 2% of Subjects ≥ 12 years of Age in Studies 3168, Soto and Z020

MedDRA v. 12.0 System Organ Class Preferred Term	Miltefosine N = 209	Meglumine N = 58	Placebo N = 44
Blood and Lymphatics			
Lymphadenopathy	4 (1.9%)	2 (3.4%)	0
Ear and Labyrinth			
Motion Sickness	26 (12.4%)	0	10 (22.7%)
Gastrointestinal			
Abdominal Pain	19 (9.1%)	3 (5.2%)	4 (9.1%)
Diarrhea	25 (12.0%)	3 (5.2%)	2 (4.5%)
Dyspepsia	12 (5.7%)	2 (3.4%)	3 (6.8%)
Nausea	82 (39.2%)	3 (5.2%)	5 (11.4%)
Vomiting	43 (20.6%)	0	0

General/Administration Site			
Application site	0	6 (10.3%)	0
Asthenia	8 (3.8%)	4 (6.9%)	0
Malaise	4 (1.9%)	1 (1.7%)	1 (2.3%)
Pain at lesion	18 (8.6%)	5 (8.6%)	0
Pyrexia	27 (12.9%)	6 (10.3%)	2 (4.5%)
Infections and Infestations			
Lymphangitis	7 (3.3%)	0	0
Lesion Infection	3 (1.4%)	2 (3.4%)	0
Parasitic	4 (1.9%)	0	1 (2.3%)
Metabolism and Nutrition			
Decreased appetite	13 (6.2%)	4 (5.8%)	0
Musculoskeletal			
Arthralgia	7 (3.3%)	23 (39.7%)	1 (2.3%)
Back pain	6 (2.9%)	1 (1.7%)	0
Myalgia	2 (1.0%)	7 (12.1%)	2 (4.5%)
Nervous System			
Dizziness	19 (9.1%)	4 (6.9%)	0
Headache	63 (30.1%)	20 (34.5%)	10 (22.7%)
Somnolence	5 (2.4%)	0	0
Skin and Subcutaneous Tissue			
Pruritus	11 (5.3%)	0	0
Rash	3 (1.4%)	2 (3.4%)	

The frequency of vomiting increased as mg/kg miltefosine dosage increased.

Table 21: GI AE by Dose – Subjects ≥ 12 years of Age – Studies 3168, Soto and Z020

Miltefosine mg/kg dose	1.4-<2.3 N = 58	2.3-<3 N = 131	≥3 N = 20	Total N = 209
Diarrhea	6 (10.3%)	18 (13.7%)	1 (5.0%)	25 (12.0%)
Nausea	26 (44.8%)	50 (38.2%)	6 (30.0%)	82 (39.2%)
Vomiting	8 (13.8%)	37 (28.2%)	8 (40.0%)	53 (25.4%)

In all studies except Z020b, mean Cr increased in the miltefosine arm and remained stable in the comparator arm at EOT. Absolute Cr values were < 2. Some degree of Cr elevation above baseline was noted at EOT in approximately 65% of miltefosine subjects enrolled in all CL studies combined compared to approximately 35% of meglumine subjects and 50% of placebo subjects. However, a greater percentage of miltefosine subjects had CTCAE grade 2 elevations. The percentage of miltefosine subjects with grade 2 elevations above baseline was higher at doses greater than 2.2 mg/kg/day, but grade 1 increases were not dose dependent.

A similar proportion of miltefosine, meglumine and placebo subjects had elevations of liver enzymes at EOT. No hematologic toxicities were noted.

Table 22: Summary of Lab Abnormalities at EOT in Subjects ≥ 12 years of Age – Studies 3168, Soto and Z020

EOT	Miltefosine	Meglumine	Placebo

	N = 209	N = 58	N = 44
Cr			
Cr >1-<1.5x baseline	99 (47.4%)	17 (29.3%)	24 (45.5%)
Cr 1.5-<3x baseline	36 (17.2%)	3 (5.1%)	2 (4.5%)
Cr 3-<6x baseline	2 (1.0%)	0	0
ALT			
ALT >1-3x ULN	13 (7.7%)	4 (6.9%)	2 (4.5%)
ALT >3-5x ULN	0	1 (1.7%)	0
AST			
AST > 1-3x ULN	7 (4.1%)	5 (8.6%)	1 (2.3%)
AST >3-5x ULN	0	1 (1.7%)	0
Alkaline Phosphatase			
AP >1-2.5x ULN	18 (10.7%)	3 (5.1%)	7 (15.9%)
AP >2.5-5x ULN	0	0	0
Total Bilirubin			
Bilirubin ≥1.5 mg/dL	1 (0.5%)	0	2 (4.5%)

Table 23: Effect of Miltefosine Dose on Cr at EOT in Subjects ≥ 12 years of Age – Studies 3168, Soto and Z020

	Miltefosine			
EOT	1.4-2.2 N = 58	2.3-<3 N = 131	≥ 3 N = 20	Total N =209
Cr >1-<1.5x baseline	32 (55.2%)	62 (47.3%)	5 (25.0%)	99 (47.4%)
Cr ≥ 1.5-< 3 x baseline	7 (12.1%)	25 (19.1%)	4 (20.0%)	36 (17.7%)
Cr ≥ 3-6x baseline	1 (1.7%)	1 (0.8%)	0	2 (1.0%)
Total	40 (69.0%)	88 (67.2%)	9 (45.0%)	137 (65.6%)

Periodic Safety Reports (PSURs) were submitted to the German regulatory authorities. Approximately 90,000-100,000 patients were exposed to miltefosine. The AEs included in the PSURs that have not already been mentioned include several reports of decreased ejaculate volume and scrotal pain in men, agranulocytosis in one subject also receiving a fluoroquinolone, epistaxis and gingival bleeding. Three cases of thrombocytopenia during miltefosine therapy were reported in HIV positive patients co-infected with VL. The German product labeling was updated in 2008 to include thrombocytopenia as an adverse event.

Ophthalmic Effects

Retinal degeneration that was dose and duration dependent was noted in the 8 week and 52 week rat toxicity studies, but was not noted in the dog toxicity studies. This was related to effects of the drug on retinal pigment epithelial cells and with sufficient duration of dosing at a dose of 21.5 mg/kg, the effects were not fully reversible.

Ophthalmologic evaluation in 25 cancer patients who received oral miltefosine in Germany in 1992 concluded that miltefosine may induce electrophysiologically

detectable changes in the retinal pigment epithelium of the human eye without associated impairment of visual acuity or changes the electroretinogram.

All Phase 2 VL studies and Study 3154 in India included weekly visual assessment (total 548 subjects). Study 3168 in CL patients also included visual assessments. One subject was reported as having an unspecified "abnormal fundoscopy" in one eye that resolved at 6 months and one subject was reported as having "central retinosis". Visual findings were otherwise unremarkable, and no visual symptoms were reported in any of the pre or post marketing studies or in PSURs.

Reproductive Effects

In animal toxicology studies, miltefosine was associated with testicular atrophy and reduced fertility in male rats, follicular atresia in female dogs, and embryotoxicity and/or teratogenicity in pregnant female rats and rabbits.

Assessment of Male Fertility

Spermiograms were obtained at screening, 2 weeks and 6 months in 15 men who participated in the CL study, Study 3168 (11 miltefosine recipients and 4 placebo recipients). There were large variations in sperm counts and motility. The results were judged by the sponsor as not significant.

220 male subjects who previously participated in Phase 2 VL studies and in Study 3154 in India and who had a female sexual partner were retrospectively tracked and queried regarding reproductive performance. These included 197 miltefosine recipients and 23 amphotericin recipients. Assessments were done 11-57 months after miltefosine therapy. 69% of miltefosine male recipients (136/197) had proven fertility documented by at least one delivery or ongoing pregnancy. 58% (56/96) of the subset of male subjects who were enrolled in Study 3154 had proven fertility compared to 52% (12/23) of amphotericin recipients.

Post treatment spermiograms were also obtained in 12 miltefosine subjects enrolled in 3154. In ten, the findings were normal. One man had oligospermia but had generated two pregnancies since the end of treatment with miltefosine. The other man was 35 years old and had not generated progeny at any age. The oligospermia in this patient was documented 3 years after end of miltefosine treatment.

The Division of Bone, Reproductive and Urology Products (DBRUP) considered these evaluations limited and recommended one of the following: a primate study pre-marketing, a randomized, placebo-controlled study in healthy male volunteers to assess the effects of miltefosine on sex hormones and spermatogenesis (possibly enrolling men who are planning to undergo elective sterilization), or major warnings in the product labeling, with a requirement to conduct a postmarketing study to evaluate the effects of miltefosine on human spermatogenesis and male sex hormones in the target population.

A primate study is unlikely to fully resolve the issue of adverse effects on human male fertility. The need to administer the drug for at 28 days to reach steady state and toxicities associated with miltefosine preclude conducting a study in healthy volunteers. In fact, a thorough QT study had been waived because of this reason. A post-marketing study in the target population is recommended. The design of such a study will be further discussed with the sponsor and with DBRUP. In the meantime, it is recommended that the product labeling and the medication guide include warnings regarding potential adverse effect of miltefosine on male fertility.

Reproductive Toxicity in Women

Miltefosine German labeling contraindicates the drug in pregnant women and recommends birth control during therapy and for 3 months post therapy in women of childbearing potential.

A total of 143 women at least 12 years of age were enrolled in the premarketing clinical trials (3168, Soto, Z020, Z022 and 3154). All were required to use some form of birth control for the duration of treatment and for 2-3 months post therapy. No pregnancies were reported. Only 3 pregnancies have been reported in the sponsored Phase 4 studies, without congenital abnormalities. As already mentioned, approximately 100, 000 miltefosine prescriptions have been dispensed as of November 2011. Based on the male/female ratio of subjects enrolled in clinical trials, it is estimated that at least 20,000 women have received the drug, and it is expected that more than 3 pregnancies would have occurred, even if optimal birth control is used. It is likely that pregnancies are under-reported.

DBRUP recommended that the product labeling include a warning regarding risks to the fetus during pregnancy and the need for birth control during therapy and (b) (4) months post therapy. In addition, DBRUP recommended a voluntary post-marketing pregnancy and birth registry and a study to evaluate drug interactions between miltefosine and oral contraceptives. However, clinical pharmacology did not believe that such a drug interaction study was necessary because miltefosine is not an inducer or an inhibitor of CYP enzymes.

Pediatric and Maternal Health Staff were consulted regarding designation of pregnancy category to miltefosine. There are no human data, but the animal data indicate embryo and fetal lethality and teratogenicity at doses lower than the therapeutic human doses. Because VL is fatal if untreated and can result in vertical transmission to the fetus, and because ML results in serious morbidity, PMHS recommended pregnancy category (b) (4) for these indications. On the other hand, although CL in pregnancy may result in atypical lesions, and has been associated with preterm labor in one study, vertical transmission is not thought to occur and there are topical treatment options. For CL, pregnancy category (b) (4) was recommended.

However, because miltefosine was originally developed as an anti-neoplastic drug and is cytotoxic, a pregnancy category D would be more appropriate based on mechanism of action. In addition, the number of pregnant women requiring the drug for the treatment of

leishmaniasis is expected to be very small, and the international product labeling contraindicates the drug in all forms of leishmaniasis. For these reasons, a pregnancy category D is recommended for all indications, and it is recommended that miltefosine be contraindicated during pregnancy.

A boxed warning regarding use in pregnancy and the need for effective birth control in women of reproductive potential is recommended.

Cardiac Safety

The effects of miltefosine on the QT interval have not been rigorously evaluated. A thorough QT study was waived because the need for lengthy exposures to achieve steady state and the toxicities of miltefosine precluded conducting such a study in healthy volunteers, and ethical considerations precluded conducting a placebo-controlled QT study in patients with leishmaniasis. A dedicated QT study is recommended as a post-marketing requirement.

Introduction and Regulatory Background

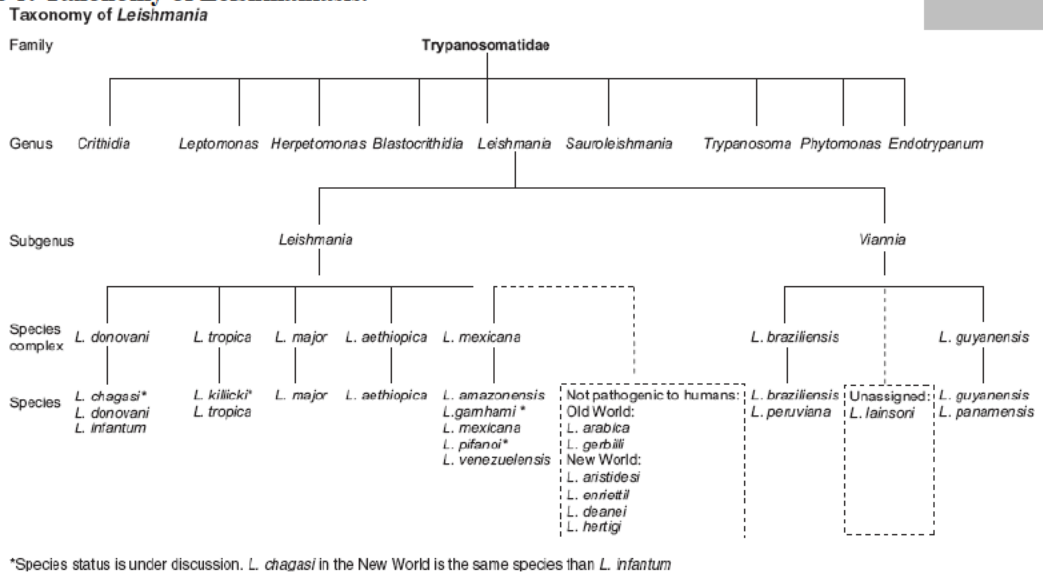
Leishmaniasis

Leishmania species are intracellular protozoan parasites that are transmitted to a mammalian host by the bite of the female phlebotomine sandfly. The flagellated promastigote is phagocytized by the host's macrophages and transforms within the phagolysosome into non-flagellated amastigote. The amastigotes replicate leading to rupture of the infected cell and infection of other reticuloendothelial cells. When a sandfly bites an infected host, the ingested amastigotes transform back to promastigotes thus completing the life cycle.

The genus *Leishmania* is classified in two sub-genera: *Leishmania* and *Viannia*. Taxonomy[1] of *Leishmania* is shown in Figure 1.

[1] Control of the leishmaniases: Report of a meeting of the WHO Expert Committee on the Control of Leishmaniasis, Geneva, 22-26 March 2010, accessed at http://www.who.int/leishmaniasis/en/

Figure 1: Taxonomy of Leishmaniasis.



*Species status is under discussion. *L. chagasi* in the New World is the same species than *L. infantum*

Leishmania infections that occur in Asia, Africa, Europe and the Middle East are designated Old World, while infections that occur in the Americas are designated New World.

The clinical outcome of *Leishmania* infection depends on the host's immune response and the characteristics of the infecting *Leishmania* species. In general, the main clinical syndromes are cutaneous leishmaniasis (CL), mucosal leishmaniasis (ML) and visceral leishmaniasis (VL).

Approximately 0.7-1.2 million new CL cases occur annually world-wide[2]. Approximately 75% of the world's CL cases occur in ten countries: Iran, Syria, Algeria, Ethiopia, North Sudan, Afghanistan, Costa Rica, Brazil, Colombia and Peru. In the United States, CL may be seen in returning travelers following exposure in endemic regions, and in American soldiers serving in Iraq, Afghanistan or South America. CL usually presents as one or more skin ulcers at the site of the sandfly bite on exposed areas of the skin. The ulcer spontaneously heals within a period of several months in most cases, leaving a scar. In the New World, the causative species are classified in the subgenus *Viannia* (*L. braziliensis, L. guyanensis, L. panamensis, L. peruviana*), or in the subgenus *Leishmania* (*L. amazonensis and L. mexicana*). In the Old World, the causative agents are in the subgenus *Leishmania* (*L. major, L. tropica, L. aethiopica, L. infantum and L. donovani*). Diagnosis can be confirmed by visualizing the amastigotes on scrapings from the ulcer. Detection of kinetoplast DNA by PCR is used for species identification. Serologic tests are not helpful.

[2] World Health Organization survey 2007 to 2010 to update the epidemiology of leishmaniasis, accessed at http://www.who.int/leishmaniasis/resources/Leishmaniasis_worldwide_epidemiological_and_drug_access_update.pdf

Mucosal Leishmaniasis occurs in 1-10% of patients with New World CL. It results from dissemination of the infecting parasites from the skin to the naso-oropharyngeal mucosa. 90% of ML cases occur in three countries: Bolivia, Brazil and Peru. Mucosal infection can manifest concurrently with the cutaneous lesions or several years later. Initial manifestations are persistent nasal symptoms with erythema and edema of the nasal mucosa, followed by progressive, ulcerative destruction of the naso-oropharyngeal mucosa and cartilage and bones of the nose and pharynx, leading to mutilation of the face. The disease can be fatal due to complicating aspiration pneumonia. The species that cause ML are organisms in the subgenus *Viannia* (*L. braziliensis*, *L. panamensis* and *L. guyanensis*) and *L. amazonensis* from the subgenus *Leishmania*. Clinical diagnosis is based on clinical findings in an endemic area and scar of previous CL, and confirmed by visualizing the amastigotes from snip biopsies or tissue scraping. However, ML is associated with very low parasite burden, leading to low yield of histopathologic diagnosis.

Visceral Leishmaniasis is the result of systemic infection. The WHO estimates that approximately 400,000 new cases of VL occur annually world-wide, and 90% of all cases of VL occur in six countries: India, Bangladesh, Sudan, South Sudan, Ethiopia and Brazil. VL may occur as an opportunistic infection in HIV positive persons in areas of the world where the two diseases coexist.

VL progresses over months or years and encompasses a broad range of clinical severity. The term kala-azar (Hindi for black sickness) refers to the most severe form of the disease, late stage VL. The classic manifestations of severe disease include cachexia, fever, hepatomegaly, prominent splenomegaly, and bone marrow involvement with resultant pancytopenia. Renal involvement is common and secondary bacterial infections can occur. VL is fatal if untreated.

The *Leishmania* species that cause VL are *L. donovani* in the Indian subcontinent, Asia, and Africa, and *L. infantum*/*L. chagasi* in the Mediterranean region, southwest and central Asia, and South America. Diagnosis is clinical, and is confirmed by demonstrating amastigotes in aspirates from the spleen, bone marrow, lymph nodes, or liver. Detection of kinetoplast DNA by PCR is used for species identification. High titer anti-*Leishmania* antibodies are usually present. Serologic tests that do not require a laboratory and can be done under field conditions include the direct agglutination test of promastigotes (DAT) and immunochromatographic detection of a cloned recombinant K39 antigen by dipstick.

The clinical syndromes and geographic distribution of *Leishmania* are summarized.

Table 24: *Leishmania* species that cause disease in humans

Species	Clinical Syndrome	Main Geographic Distribution
Subgenus *Leishmania*		
L. donovani complex *L. donovani* *L. infantum sensu stricto*	VL	 China, Indian subcontinent China, Middle East

L. chagasi sensu stricto		Central and South America
L. mexicana complex *L. mexicana* *L. amazonensis*	CL	Mexico, Central and South America Panama and South America
L. tropica	CL	Central Asia, Indian subcontinent, Middle East, North Africa
L. major	CL	Central Asia, Indian subcontinent, Middle East, North Africa, Ethiopia
L. aethiopica	CL	Ethiopia, Kenya, Sudan
Subgenus *Viannia*		
L. (V.) braziliensis	CL, ML	Central and South America
L. (V.) guyanensis	CL, ML	South America
L. (V.) panamensis	CL, ML	Central America, Venezuela, Colombia, Peru
L. (V.) peruviana	CL	Peru

Modified from Herwaldt, B: Harrison's Principles and Practice of Internal Medicine, 2008
VL: Visceral Leishmaniasis
CL: Cutaneous Leishmaniasis
ML: Mucosal Leishmaniasis

Product Information

Miltefosine (hexadecylphosphocholine) is an alkyllysophospholipid analogue that was originally developed as an anti-neoplastic drug, but was ineffective for that indication when given systemically. It is registered in Germany as a topical drug to treat cutaneous cancers. As an oral agent, it is registered in Germany, Argentina, Colombia, Bolivia, Guatemala, Ecuador, Honduras, Peru, Paraguay, Mexico, Nepal, India, Pakistan and Bangladesh for the treatment of VL and CL. In March 2011, miltefosine was included in the WHO essential medicines list as an anti-leishmaniasis medicine[3].

Tables of Currently Available Treatments for Proposed Indications

Therapy is indicated for all cases of VL. For the treatment of VL caused by *L. donovani* in Bangladesh, Bhutan, India and Nepal, the WHO currently recommends[1] (in order of preference) liposomal amphotericin, liposomal amphotericin 5 mg/kg single dose in combination with either oral miltefosine daily for 7 days or IM paromomycin for 10 days, or miltefosine plus paromomycin, or amphotericin B deoxycholate for 15-20 doses, or a pentavalent antimonial.

For the treatment of VL caused by *L. donovani* in East Africa (Ethiopia, Eritrea, Kenya, Somalia, Sudan and Uganda) and Yemen, the WHO recommends (in order of preference) a combination of pentavalent antimonial plus paromomycin, pentavalent antimonial, liposomal amphotericin, amphotericin, or miltefosine.

For the treatment of VL caused by *L. infantum* in the Mediterranean basin, Middle East, Central Asia and South America, the WHO recommends (in order of preference) liposomal amphotericin, pentavalent antimonial, or amphotericin.

[3] http://whqlibdoc.who.int/hq/2011/a95053_eng.pdf

In the United States, liposomal amphotericin (AmBisome®) is the only FDA-approved treatment for VL. AmBisome approval was based on review of literature reports of uncontrolled studies conducted in Mediterranean patients with VL due to *L. infantum/chagasi*. The recommended dose is administered intravenously over several weeks. Because of cost, this drug is not available in the areas of the world where it is needed, and amphotericin B deoxycholate administered IV over 15 to 30 days is used instead. Amphotericin preparations are associated with infusion-related and hematologic and renal toxicities.

Therapy is indicated for all cases of ML. There are no FDA approved therapies in the United States for this indication. The WHO recommends (not ranked in the order of preference) pentavalent antimonial alone or with pentoxifylline, amphotericin or liposomal amphotericin. Miltefosine can be used for ML in Bolivia.

Because CL lesions heal spontaneously, the treatment decision for CL must take host and parasite factors into consideration, including lesion location(s), size and number, and parasite tissue tropism (i.e., likelihood of dissemination). The goals of therapy for CL, when used, are to accelerate healing, decrease morbidity, decrease the risk of local and mucosal dissemination, and decrease relapse.

There are no FDA approved drug therapies for CL in the United States. A device, ThermoMed, is cleared in the US for the treatment of CL. The rationale is that *Leishmania* organisms do not survive temperatures greater than 39-41^{o}C after cumulative exposure of at least 20 hours. The main adverse events associated with the device include skin blistering at the site of the device application with secondary bacterial infection and hypopigmentation. The device is not practical to use for larger lesions, in patients with multiple lesions or in patients with lesions on the face. In those patients with lesions caused by *Leishmania* species associated with mucosal disease, the device may not prevent mucosal involvement. In addition, the device cannot be autoclaved, raising concerns about proper infection control.

For the treatment of CL in the Old World, the WHO currently recommends (not in order of preference) topical paromomycin, intralesional antimonial, or thermotherapy, or systemic therapy with fluconazole, pentavalent antimonial IM or IV with or without pentoxifylline. For the treatment of CL in the New World, the WHO recommends topical therapy with paromomycin or intralesional antimonial, or systemic therapy with ketoconazole or miltefosine (*L. mexicana*), pentamidine or pentavalent antimonial or miltefosine (*L. guyanensis* and *L. panamensis*), pentavalent antimonial or amphotericin or liposomal amphotericin for *L. braziliensis*, and pentavalent antimonial for *L. amazonensis*, *L. peruviana*, and *L. venezuelensis*.

Pentavalent antimony preparations (Sb^{V}) have been the main therapy for all forms of leishmaniasis in many areas of the world for decades, but are not marketed in the US. Pentavalent antimony preparations include sodium stibogluconate (SSG or Pentostam) and meglumine (Glucantime). SSG is available in the United States through INDs held by

the CDC and the US Army. They are administered parenterally (IM or IV) for 21-30 days, but can also be given intra-lesionally for CL. Pentavalent antimonials are associated with significant toxicities including GI, musculoskeletal, pancreatic, cardiac and hepatic toxicity. In a report of 96 US military personnel with VL or CL treated with SSG, arthralgias and myalgias occurred in 60%, abdominal pain in approximately 30%, nausea/vomiting in 30%, headache in 23%, ECG changes in 21%, elevated pancreatic enzymes in 96% and elevated AST/ALT in 60% of patients[4].

In addition, pentavalent antimony preparations are increasingly ineffective in some geographic areas due to resistance. In Bihar state, India, where up to 45% of the world cases of VL occur, 60 - 80% of infections are resistant to pentavalent antimony. In South America, increasing dosages are required to achieve cure.

IV paromomycin, an aminoglycoside, is not available in the US but is licensed in India for the treatment of VL, with comparable efficacy to amphotericin B. Similar to other aminoglycosides, main toxicities of paromomycin are renal, auditory and vestibular.

IV or IM pentamidine has been used to treat VL and is available in the US, but it is associated with low efficacy and a number of toxicities including hypotension, myocarditis, renal toxicity and hypo- and hyperglycemia.

Local treatments that have been used for CL include 15% paromomycin/12% methylbenzethonium ointment and lesion infiltration with pentavalent antimony. Off-label systemic treatments include the azole antifungals fluconazole, ketoconazole and itraconazole.

Table 25: Currently Available Treatments for Leishmaniasis

Drug	FDA Approved Leishmaniasis Indication	Available in US	Comments
AmBisome® (liposomal amphotericin B)	VL	Marketed	Polyene antifungal FDA approved for VL in 1997. Approval was based on literature reports of uncontrolled studies in Mediterranean patients infected with *L. chagasi/infantum* Administered intravenously over 3 weeks for immunocompetent patients and over 6 weeks for immunocompromised patients Hematologic, renal and infusion-

[4] Aronson NE., et al. Safety and efficacy of IV sodium stibogluconate in the treatment of leishmaniasis: recent US military experience. CID 1998;27:1257-64

			related toxicities Expensive – cost is prohibitive in geographic areas of need
Amphotericin B deoxycholate	No	Marketed	Polyene antifungal Intravenous, every other day for 30 days Hematologic, renal and infusion related toxicities
Pentavalent Antimony Preparations: Sodium Stibogluconate (SSG, Pentostam) and Meglumine (Glucantime)	No	IM SSG is available in the US under IND held by the CDC (IND # 84831) IV SSG is available in the US under IND held by the US army (IND # 14150) Meglumine is not available in the US	Antimony preparations have been the mainstay of treatment for all clinical forms of leishmaniasis for decades Administered IM or IV for 21-30 days, may also be given as intra-lesion injections for CL Associated GI, musculoskeletal, hepatic, pancreatic and cardiac toxicities
Paromomycin	No	Topical preparation (plus gentamicin) available in the US under IND 050098 held by the US army for the treatment of CL IV preparation is not available in the US, but is licensed in India for the treatment of VL	Aminoglycoside Pre-IND submitted in 2004 for IM preparation, IND not subsequently submitted Toxicities are similar to other aminoglycosides: renal and auditory/vestibular
Fluconazole Ketoconazole Itraconazole	No	Marketed	Azole antifungal drugs Hepatic toxicity and numerous drug Interactions
Pentamidine	No	Marketed	IM or IV Not highly effective Hyper-and hypoglycemia, myocarditis and renal toxicity
ThermoMed Thermotherapy	FDA-cleared device for CL	Marketed	Device, locally applied to skin lesion Local irritation and burns

			Infection control issues May not be appropriate for large or multiple lesions or lesions on the face

Availability of Proposed Active Ingredient in the United States

Miltefosine is not marketed in the United States, but is available for the treatment of ML and potentially disseminated CL under an IND held by Paladin Therapeutics (IND 105,430) and for the treatment of infections caused by free living amebae (*Naeglaria*, *Balamuthia* and *Acanthamoeba*) under an IND held by the CDC (IND 118,459). It is also available to treat all forms of leishmaniasis, infections caused by free living amebae and infections caused by *Scedosporium* under single patient IND.

Summary of Pre-Submission Regulatory Activity Related to Submission

Miltefosine was granted orphan designation on October 10, 2006.

The sponsor submitted pre-IND 105,430 for the treatment of CL and ML on May 8, 2009. In a pre-IND meeting on July 29, 2009, the Division of Special Pathogens and Transplant Products (DSPTP, currently Division of Anti-Infective Products/DAIP) advised the sponsor to also consider seeking the indication for the treatment of VL.

On October 8, 2009, the sponsor submitted an outline of proposed clinical studies that could be used to support an NDA seeking approval for miltefosine for the treatment of CL, ML and VL. Briefly, the sponsor proposed using Study 3154 (open randomized non-inferiority trial comparing oral miltefosine to IV amphotericin deoxycholate in the treatment of VL in adults in India) and Study 3206 (open non-comparative trial of miltefosine in the treatment of VL in children 2 to 12 years of age in India) to support seeking the VL indication. Study Z022 (single arm study of miltefosine in the treatment of ML in Bolivia) was proposed to support seeking the indication for ML, and Study 3168 (randomized, double-blind, placebo-controlled study of miltefosine in the treatment of CL conducted in Colombia and Guatemala) was proposed to support seeking the indication for CL.

In a letter dated April 13, 2010, DSPTP advised the sponsor that Studies 3154 and 3168 could be used to support seeking the indications of VL and CL respectively. DSPTP advised inclusion of an additional study in support of seeking each of the VL and CL indications, and suggested that Study Z025 (miltefosine compared to SSG in the treatment of VL in Ethiopia) and either Study Z020a or Z020b (miltefosine compared to meglumine for the treatment of CL in Brazil) could be potentially considered. For ML, the Division indicated that the sponsor could justify the use of a single uncontrolled trial by discussing the clinical spectrum of leishmaniasis and the effectiveness of miltefosine in CL and VL.

On March 8, 2010, the sponsor submitted IND 105,430 as a treatment IND with an open-label protocol for the treatment of ML and potentially disseminated CL.

Because of the unmet medical need for the treatment of CL and ML, and the need for alternative therapies for the treatment of VL, miltefosine was granted Fast Track Designation for the treatment of CL, ML, and VL on May 21, 2010.

The sponsor submitted NDA 204684 on September 27, 2012 for the treatment of VL, ML and CL and also requested Priority Review. A Refuse to File letter was communicated to the sponsor on November 26, 2012. The reason for RTF was that significant deficiencies in the submitted datasets did not allow a meaningful review of safety and efficacy of the drug. On January 8, 2013, the sponsor met with the FDA to discuss the format and content of the datasets for this submission. The NDA was re-submitted on April 19, 2013.

In this resubmission, the sponsor re-iterated the request for priority review, and also requested the Tropical Diseases Priority Review Voucher. Priority review request was granted because miltefosine may provide a significant improvement over other therapies for VL and may offer safe and effective drug therapy for CL and ML where no satisfactory alternatives exist. (Please refer to the priority review determination filed in DARRTS). Because miltefosine is a new molecular entity, qualifies for priority review, is intended for the treatment of a listed tropical disease, and the NDA is submitted under section 505(b)(1) of the FD&C act, the sponsor is eligible to be granted the Tropical Diseases Priority Review Voucher if approved.

Other Relevant Background Information

On January 28, 2010, the QT-IRT reviewer agreed to waive Thorough QT (TQT) study because the need for lengthy exposures to achieve steady state and the teratogenic effects of miltefosine precluded conducting such a study in healthy volunteers, and ethical considerations precluded conducting a placebo-controlled QT study in patients with leishmaniasis. QT-IRT recommended that the sponsor perform a dedicated QT study to characterize the QT effect following miltefosine administration but deferred the timing of such a study to the review division. Based on the available non-clinical and clinical safety information, DSPTP determined that a dedicated QT study could be conducted as a post-marketing requirement (Please refer to QT-IRT reviews and DSPTP review filed in DARRTS).

Ethics and Compliance with Good Clinical Practices

Submission Quality and Integrity

The NDA was submitted electronically using eCTD format.

Compliance with Good Clinical Practices

All submitted clinical trials were conducted in accordance with the national drug laws of the countries where the studies were conducted, the Declaration of Helsinki regarding the treatment of human subjects in a study and with Good Clinical Practice.

All submitted clinical trials were approved by an Independent Ethics Committees (IEC) relevant to the centers involved. An IRB-approved written informed consent was obtained from all participating subjects or legal guardians.

The protocols, informed consents, Case Report Forms, study conduct and study reports were subject to an internal audit. Audit Certificates and quality assurance statements were provided for the clinical studies used to support this application.

In lieu of inspecting the clinical sites, some of which were closed in the interim, the FDA's Office of Scientific Investigation inspected certified copies of the original source data for one of the clinical sites for the pivotal VL study 3154 (India) and one of the sites for the pivotal CL study 3168 (Guatemala) that were held at Paladin's headquarters in Montreal, Canada. No data integrity issues were identified, and the inspection was classified as NAI (no action indicated).

Financial Disclosures

A financial disclosure statement for all trial investigators was included in the original NDA submission.

Significant Efficacy/Safety Issues Related to Other Review Disciplines

Chemistry, Manufacturing and Controls

Miltefosine is the international non-proprietary name of the drug substance hexadecylphosphocholine. It is a structural analog of alkyl(lyso)phospholipids.

The chemical formula is $C_{21}H_{46}N0_4P$, and the molecular weight is 407.6. The chemical structure is shown in Figure 2.

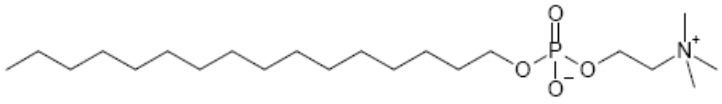


Figure 2: Chemical structure of miltefosine

Miltefosine is a white (b) (4) that is soluble in water. The proposed commercial product is a red hard gelatin capsule containing 50 mg of miltefosine and the following excipients: Colloidal Silicon Dioxide NF, Microcrystalline Cellulose NF (b) (4) Lactose

Monohydrate NF, Talc NF and Magnesium Stearate NF. The capsule shell consists of Gelatin NF, Titanium Dioxide USP, Ferric Oxide NF Red and Purified Water USP. The product is stable at 25C/60% RH for up to 48 months.

Major deficiencies related to analytic procedures of the drug substance and the impurities were identified. The sponsor submitted amendments to address the CMC deficiencies late in the NDA review cycle. These amendments resulted in extension of the PDUFA goal date by 3 months, and were under review at the time of filing this clinical review.

Clinical Microbiology

In vitro Activity

In vitro, miltefosine is active against the extracellular promastigotes and the intracellular amastigotes of a variety of *Leishmania* species, but there is considerable variability in the sensitivity of different *Leishmania* species to miltefosine, with *L. donovani* generally considered the most susceptible and *L. braziliensis* and *L. major* the least susceptible. The ED_{50} of various species as reported in the submission is shown in Table 24.

Table 26: *In Vitro* Activity of Miltefosine Against Various *Leishmania* Species – Submission

Species	Promastigote ED_{50} µM	Amastigote* ED_{50} µM
L. donovani	0.5-1	3.3-11.3
L. mexicana	2.4-12.7	6.8-10.1
L. panamensis	1.3-3.7	10.6
L. major	4.8-13	31.6-37.2
L. tropica	0.6-1.7	5.8-10.2
L. aethiopica	1.1-2.76	2.6-4.9

*Mouse peritoneal macrophage assay

Activity in Animal Models

In BALB/c mouse model of *L. donovani* systemic infection, the ED_{50} was 13.8 mg/kg/d administered subcutaneously for 5 days.

In a T cell deficient and macrophage deficient mouse model of *L. donovani* systemic infection, ED_{50} was 25 mg/kg/d administered orally for 5 days. In a mouse model of cutaneous infection, 10 applications of 6% topical miltefosine applied daily over two weeks cured *L. mexicana* infection, but failed to cure *L major* infection.

Mechanism of Action

Miltefosine is internalized into *Leishmania* via specific protein translocation machinery located at the plasma membrane of the parasite. Once internalized, miltefosine inhibits mitochondrial function by inhibiting cytochrome C oxidase, and interferes with phosphatidylinositol biosynthesis, resulting in apoptotic-like cell death.

Mechanism of Resistance

Resistance to miltefosine may be due to reduced levels of the translocation machinery resulting in decreased miltefosine uptake into the cell.

Reviewer's comments
The VL trials in this submission were in areas where *L. donovani* is the prevalent species. The CL trials enrolled subjects in areas *L. mexicana, L. panamensis, L.amazonensis, L. braziliensis and L. guyanensis* are prevalent. The ED_{50} of miltefosine against some of these species was not included in the submission. The *in vitro* activity as reported in the literature is summarized[5].

Table 27: *In Vitro* Activity of Miltefosine Against Some *Leishmania* Species – Literature

Species	Country	Amastigote ED_{50} ug/ml*
L. donovani	Nepal	0.04 - 8.7
L. braziliensis	Peru	8.4 - >30
L. guyanensis	Peru	1.9 - >30
L. mexicana	Peru	30
L. lainsoni	Peru	1.9-3.4

*Mouse peritoneal macrophage assay

As the above tables indicate, there is considerable variability in the sensitivity of different *Leishmania* species to miltefosine.

As mentioned under the mechanism of action section, *Leishmania* organisms internalize miltefosine via specific protein translocation machinery present at the plasma membrane. This translocation machinery is composed of at least two proteins, LdMT (P type ATPase involved in phospholipid translocation) and its beta subunit LbRos3. In one study, *L. braziliensis* strains from Brazil and Peru were found to express LbRos3 to a lower extent than *L. donovani* strains, resulting in a reduced ability to internalize the drug[6]. *L. braziliensis* may potentially be intrinsically less susceptible to miltefosine because its ability to internalize miltefosine is reduced.

Leishmania species may develop resistance to miltefosine after *in vitro* exposure to sub-inhibitory concentrations. In one study, *in vitro*, exposure of *L. donovani* promastigotes to concentrations of 40 µM (around 16.3 µg/ml) increased the ED_{50} of miltefosine up to 15-

[5] Yardley V, et al. The sensitivity of clinical isolates of Leishmania from Peru and Nepal to miltefosine. Am, J Trop Med Hyg 2005; 73:272-275

[6] Sanchez-Canete MP, et al. Low plasma membrane expression of the miltefosine transport complex renders *L. braziliensis* refractory to the drug. Antimicrob Agents Chemother 2009;53:1305-1313

fold compared to wild type organisms. The resistant parasites demonstrated reduced drug uptake, and possessed a mutation in the alleles coding for LdMT transporter[7].

Because miltefosine has a long half-life, *Leishmania* organisms that persist after treatment may continue to be exposed to sub-inhibitory concentrations for several weeks after discontinuation of therapy, thus raising the potential for development of resistance. Miltefosine is extensively used in Bihar, India as a first line medication to treat VL as a part of the Indian Kala-Azar Elimination Program. The susceptibility to miltefosine of 16 clinical isolates of *L. donovani* obtained from Bihar, India was compared to 12 clinical isolates obtained from a non-endemic area in India (eastern Uttar Pradesh) where miltefosine use is not extensive[8]. The amastigote ED_{90} was statistically significantly higher in the endemic area (mean 17.5+/-2.4 versus mean 13.7+/-3.6, p = 0.005), but the $ED_{50,}$ though numerically higher, was not statistically significantly different (mean 7.1 +/-1.6 in the endemic area versus mean 5.7+/-2.2 in the non-endemic area, p = 0.08).

In another study, the *in vitro* susceptibility of *L. donovani* to miltefosine was determined pre-and post-therapy in VL and PKDL (post kala-azar dermal leishmaniasis) patients[9]. Organisms were cultured from spleen aspirates in VL patients and skin specimens in PKDL patients pre-therapy and at the conclusion of therapy and subjects were followed for 1 year. *Leishmania* could be cultured from spleen aspirates obtained post therapy in a substantial proportion of VL patients who had a negative microscopic examination at EOT and who went on to experience cure at one year. In VL patients who were cured, the mean IC_{50} of post-therapy isolates compared to pre-therapy isolates was comparable (p > 0.05), but the post-therapy IC_{50} was significantly higher in patients with VL who relapsed (4.72 +/- 1.99 vs. 2.43 +/- 1.44 uM, p = 0.04). In patients with PKDL, post therapy IC_{50} was significantly higher compared to pre-therapy (p = 0.03). Point mutations in the miltefosine transporter LdMT and its beta subunit LdRos3 were not present in the clinical isolates, and mRNA expression profile of these genes was comparable between pre- and post-treatment isolates.

The first study indicates that the miltefosine inhibitory concentrations increase after extensive use, and the second study indicates that inhibitory concentrations increase in VL subjects who relapse. Because VL in India is anthroponotic, this may have implications for spread of resistance.

Non-Clinical Toxicology

[7] Seifert K et al. characterization of L. donovani promastigotes resistant to hexadecylphophocholine (miltefosine). Int. J. Antimicrob. Agents 2003;22:380-387
[8] Prajapati VK et al. In vitro antileishmanial drug susceptibility of clinical isolates from patients with Indian visceral leishmaniasis – status of newly introduced drugs. Am J Trop Med Hyg 2012;87:655-657
[9] Bhandari V et al. Drug susceptibility in Leishmania isolates following miltefosine therapy in cases of visceral leishmaniasis and post kala-azar dermal leishmaniasis. PLoS Neglected Tropical Diseases 2012;6:e1657

Toxicities in rats included reversible dose- and duration-dependent retinal atrophy, hyperplasia of tubular and transitional renal epithelium with increased BUN and Cr, mucosal hyperplasia in the small intestines, prostate atrophy and necrosis of testicular tubules and increases in liver transaminases and bilirubin. The ocular changes were thought to be due to changes in retinal pigment epithelial cells and not to direct neurotoxic effects on neuronal structures of the retina.

NOAEL was 4.6 mg/kg in adult rats administered miltefosine orally for 52 weeks. Tumors were noted in the group that received the high dose of 21.5 mg/kg/d (lethal dose, Cmax 83.1 ug/mL). The tumors were mainly of the uterine and testicular tissues.

NOAEL was 3.16 mg/kg/d in dogs administered oral miltefosine for 13 weeks (Cmax 40.6 ug/mL). Noted toxicities included prostate atrophy, hyperemia of intestinal mucosa, alveolar histiocytosis, and pigment accumulation in kupffer cells of the liver.

Carcinogenicity

Miltefosine was not mutagenic in six of seven mutagenic assays. Carcinogenicity studies were not performed but tumors were noted in the 52-weeks toxicity studies in rats in the group that received the high dose of 21.5 mg/kg/d (lethal dose). The tumors were mainly of the uterine and testicular tissues.

Reproductive Toxicity

In male rats, atrophy of seminiferous tubules atrophy and impaired fertility were noted at a dose of 8.25 mg/kg/day. The testicular changes were reversible within 10 weeks after discontinuation of the drug. Testicular atrophy and prostate atrophy were also noted in some dogs.

In female dogs, there was a dose dependent increase of atretic follicles in the ovaries. The changes were reversible within six weeks after discontinuation of the drug.

Miltefosine was embryotoxic and teratogenic in mice, rats and rabbits. The NOAEL for fetotoxicity was 2.15 mg/kg/day in mice, 1.3 mg/kg/day in rats, and 2.4 mg/kg/day for rabbits. All malformed fetuses showed misshapen cerebral structures, misshapen eyes, and hemo-or hydrocephalus.

Cardiovascular Toxicity

Miltefosine did not affect hERG channel at concentrations up to 3 µM (equivalent to1.22 ug/mL). Higher doses could not be tested because the test system was disturbed by the cytotoxic effects of the drug.

There was no effect on heart rate or ventricular contractility in domestic pigs administered up to 200 mg/kg. However, marked decreases in blood pressure and cardiac output were noted at doses of 50-200 mg/kg.

Other Organ Systems

Miltefosine did not have significant CNS toxicity in mice, pulmonary toxicity in pigs or myelotoxicity in all the animal species tested.

Miltefosine did not promote Th1 response or activate natural killer cells, cytotoxic spleen cells, phagocytic activity of macrophages or humoral antibody response in mice, but could possibly up-regulate TNF alpha-receptors.

Reviewer's Comments
Miltefosine was teratogenic and embryotoxic in mice, rats and rabbits at exposures below those resulting from the proposed clinical dose of 2.5 mg/kg/day. Pregnant women should be advised not to receive the drug and women of childbearing age should be advised to use effective contraception. The current product foreign labeling recommends that women of childbearing age should use effective contraception during therapy and for at least 3 months after stopping the drug. Miltefosine has a long half-life. In Indian patients with VL, the half-life is 150-200 hours, and PK data from Dutch patients with CL indicate that the first elimination half-life is 7.05 days and the terminal half-life is 30.9 days[10]. Birth control for (b) (4 months after stopping the drug is more appropriate.

Clinical Pharmacology

In adult Indian patients with VL, steady state was not achieved at 23 days.

Table 28: Mean (%CV) PK Parameters for Oral Miltefosine in Adult Patients with VL

	On Day 23			After last dose
	C_{max} (µg/mL)	T_{max}[a] (hr)	AUC_{tau}[b] (µg·hr/mL)	$t_{1/2}$ (hr)
50 mg/d (6 wks) (Group 1, N=9)	23.5 (30.8)	8 (2 - 24)	445 (28.1)	166.7 (34)
50 mg/d (1 wk) / 100 mg/d (3 wks) (Group 2, N=10)	39.2 (47.6)	5 (2-12)	378 (37.4)	199.8 (65.4)
100 mg/d (4 wks) (Group 3, N=10)	66.2 (28.5)	7 (2-12)	636 (26.7)	154 (31.1)
100 mg/d (1 wk) / 150 mg/d (3 wks) (Group 4, N=10)	75.9 (17.6)	4 (2-8)	486 (18.1)	202.8 (28.9)

[a]: Median (range)
[b]: AUC from time 0 h to 24 h, 12 h, 12 h, and 8 h for Groups 1, 2, 3, and 4, respectively

In Dutch soldiers with CL who received doses of 50 mg three times a day (approximately 1.76 mg/kg/d), miltefosine PK during multiple dosing was best described by a 2-compartment, with first-order absorption, population model. The $t_{1/2\alpha}$ was 6.75 days from bootstrapping. C_{max} and AUC_{tau} were 37 µg/mL and 295 µg·hr/mL, respectively, based on

[10] Dorlo T et al. Pharmacokinetics of miltefosine in Old World cutaneous leishmaniasis patients. Antimicrob Agents Chemother 2008;52:2855-2860

simulated plasma concentrations after the last dosing on day 27. The apparent terminal $t_{1/2}$ was approximately 30 days.

Absorption

Bioavailability in rats and dogs was 82% and 94% respectively. The half-life was 84 hours in rats and 159 hours in dogs. In both species, C_{max} and AUC showed dose proportionality with no gender differences.

Bioavailability studies were not conducted in humans because IV miltefosine is hemolytic. PK studies were also not conducted in healthy human subjects because the drug was initially developed as an anticancer drug, then later for the treatment of VL, a life-threatening condition.

Distribution

In rats, miltefosine is widely distributed with higher accumulation in the kidney, seminal vesicles, liver, spleen, and optic nerve (in decreasing order) and slow elimination from the brain. The slow elimination from the brain is thought to be due to metabolism of miltefosine to choline which is then incorporated into phosphatidylcholine in the brain

Placental transfer and excretion in milk were not investigated, but placental transfer can be assumed as the drug is teratogenic and fetotoxic.

Protein binding is 97.5% in humans. 97% of the protein binding is to albumin and 3% is to LDL.

Metabolism

Miltefosine is cleaved by phospholipase D to choline and hexadecanol. Less than 0.2% is excreted unchanged in urine or feces. Choline is incorporated into tissues, whereas hexadecanol enters the intermediary lipid metabolism and is oxidized to palmitic acid. Patients with Sjogren-Larsson syndrome (a recessively inherited disease that manifests in infancy with major dermatological and neurological signs) are unable to oxidize hexadecanol, and the European product labeling contraindicates miltefosine in these patients.

No oxidative metabolism of miltefosine was observed with any of the reconstituted cytochrome P450 (CYP) monooxygenase systems, comprising the following CYP enzymes: 1A1, 1A2, 1B1, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, 3A4, 3A5, 3A7, 4A1.

Excretion

The urinary excretion of the unchanged drug on Day 23 after repeated oral administration of miltefosine to adult patients was below 0.2% of the daily dose.

Drug-Drug Interactions

Miltefosine is not a substrate, inhibitor, or inducer of CYP450 enzymes. Drug interaction studies have not been conducted.

Reviewer's Comments
Drug-drug interaction studies were not performed. Because miltefosine is not a substrate of P450 isoenzymes, and is not an inducer or a significant inhibitor of these enzymes, it is not expected to have significant drug interactions with drugs that are metabolized or are inducers or inhibitors of the cytochrome P450 isoenzymes. For these reasons, the clinical pharmacology reviewer considered a drug interaction study to evaluate the interaction of miltefosine with oral contraceptives to be unnecessary.

PK studies in patients with renal or hepatic impairment, or in elderly patients, were not performed.

Sources of Clinical Data

The sponsor submitted study reports and datasets for Studies 3168, Soto, Z020a and b in support of CL indication, Study Z022 in support of the ML indication and Study 3154 in support of the VL indication. For Study Z025, a study report based on the published article with analysis regarding the deaths that occurred during the study was submitted. Study reports were submitted for the other studies listed.

Table 29: Table of Studies/Clinical Trials

Study	Country & Study Population	*Leishmania spp*.*	Trial Design	N RX Arms	Primary Endpoint
Visceral Leishmaniasis					
3154	India Age ≥ 12 years	*L. donovani*	Open-label Randomized Active-control NI margin 15%	299 miltefosine 99 Amphotericin B	Final Cure: No parasites at EOT plus no s/s of VL at 6 months
Z025	Ethiopia Males Age ≥ 15 years	*L. donovani*	Open-label Randomized Active-control	290 miltefosine 290 SSG	Final Cure: No parasites or no clinical s/s at EOT plus no s/s of VL at 6 months
Z033	India Males Age ≥ 14 years	*L. donovani*	Dose-Ranging Sequential group	30	Final Cure
3089	India Age ≥ 14 years	*L. donovani*	Dose-ranging Parallel group	45	Final Cure

3091	India Age 2-11	*L. donovani*	Dose-Ranging Sequential group	30	Final Cure
3109	India Age ≥ 12 years	*L. donovani*	Dose-Ranging Sequential group	120	Final Cure
3127	India Age ≥ 12 years	*L. donovani*	Dose Ranging Parallel Group	54	Final Cure
3206	India Age 2-11 years	*L. donovani*	Single arm	80	Final Cure
Z013	India Age ≥ 12 years	*L. donovani*	Post-marketing Efficacy and Safety	1132	Final Cure
Z013b	Nepal Age ≥ 12 years	*L. donovani*	Post-marketing Efficacy and Safety	125	Final Cure
Z019	Brazil Age 2-11 years Age ≥ 12	*L. chagasi*	Single Arm Exploratory	42	Final Cure
Mucosal Leishmaniasis					
Z022	Bolivia Age ≥ 12	*L. braziliensis*	Single arm	79 miltefosine	At least 90% decrease in the mucosal severity score at 12 months
Cutaneous Leishmaniasis					
3168	Colombia Guatemala Age ≥ 12 years	*L. panamensis* *L. braziliensis* *L. mexicana*	Double-blind Randomized Placebo-controlled	89 miltefosine 44 placebo	Definite Cure = Apparent or Partial Cure at 2 weeks after EOT plus resolution of all lesions at 6 months
Soto	Bolivia Age ≥ 12 years	*L. braziliensis*	Open label Randomized Active control	40 miltefosine 18 meglumine	Definite cure: resolution of all lesions at 6 months
Z020a	Brazil 2 -11 years ≥ 12 years	*L. guyanensis*	Open label Randomized Active control	60 miltefosine 30 meglumine	Definite cure: resolution of all lesions at 6 months
Z020b	Brazil 2 -11 years ≥ 12 years	*L. braziliensis*	Open label Randomized Active control	60 miltefosine 30 meglumine	Definite cure: resolution of all lesions at 6 months
3092	Colombia Age > 16 years	*L. panamensis* *L. amazonensis*	Dose Escalating Sequential Group	72	Complete epithelialization at 3 months
Z026	Afghanistan Age > 10 years	*L. tropica or L. major*	Open Label Randomized	147 miltefosine	Definite cure: resolution of all

			Active control	71 IM SSG 126 intra-lesion SSG	lesions at 6 months
Other Studies					
Z027	Venezuela Disseminated CL	*L. amazonensis*	Single arm	16	Improvement in lesion size at day 45
Z005	Studies 033, 3089, 3109, 3127 and 3154		Reproductive Safety	289	
CSR1	Compassionate use			45 (39 HIV co-infected patients)	
CSR2	Cancer patients		Ophthalmologic assessment	25	
CSR3	Cancer patients		Ophthalmologic assessment	25	

*Epidemiologic Prevalence

Discussion of Individual Studies/Clinical Trials

Cutaneous Leishmaniasis Due to Members of the Subgenus Viannia

In support of the CL indication, the sponsor submitted study reports and datasets for Study 3168, Study Soto and Studies Z020a and Z020b. The results of all these studies have been published in medical journals. The sponsor also submitted study reports for Study 3092 (dose ranging study), Study Z027 (single arm treatment of patients with disseminated cutaneous leishmaniasis DCL), and Study Z026 (miltefosine compared to systemic and intralesional SSG).

Study 3168

The study was conducted between June 25, 2000 and December 15, 2002 at two study centers, one in Colombia and one in Guatemala[11]. The study protocols and informed consent were reviewed by Independent Ethics Committees relevant to each study center. The study was monitored by (b) (4), a CRO (contract research organization), based in Colombia.

Study Design

This was a randomized, placebo-controlled, double-blind study. Males and females ≥ 12 years of age with parasitologically confirmed CL in at least one lesion of at least 50mm^2

[11] Soto J. et al. Miltefosine for New World cutaneous leishmaniasis: placebo-controlled multicenter study. Clin Infect Dis 2004; 38:1266-72

area and without mucosal involvement were randomized in 2:1 ratio to receive oral miltefosine or matching placebo for 28 days. Subjects with ≥ 45 kg body weight received miltefosine 50 mg or matching placebo three times a day, while subjects < 45 kg body weight received miltefosine 50 mg or matching placebo twice a day.

Subjects with platelet count <100 x 10^9/L, leukocyte count <3 x 10^9/L, hemoglobin <10 g/100 mL, AST, ALT or alkaline phosphatase >2 x ULN, bilirubin >1.5 x ULN, Cr or BUN >1.5 x ULN, and subjects with any non-compensated or uncontrolled medical condition (such as active tuberculosis, malignant disease, severe malaria, HIV, or other major infectious diseases) were excluded. Pregnant or lactating women and women unable to comply with contraception during therapy and for 2 months after EOT were excluded. Subjects receiving, or having received anti-leishmaniasis drugs within the past 4 weeks were also excluded.

Skin samples (slit skin smear, skin aspirate or biopsy) for *Leishmania* stain, culture and PCR were obtained at baseline, and if lesions had not healed, at 2 weeks, 2 months and 6 months after EOT. Photographs of the lesions were obtained at baseline, at 2 weeks, 2 months and 6 months after EOT. CBC, liver and kidney lab parameters were obtained at baseline, weekly while on treatment and at 2 weeks, 2 months and 6 months after EOT. Ophthalmology exam was obtained at baseline, at EOT and 6 months after EOT. Spermiograms were scheduled at baseline, 2 weeks and 6 months after EOT. However, the center in Guatemala did not participate in evaluating the effects of miltefosine on sperm counts due to religious and cultural reasons. Because of the same reasons, study enrollment in the center in Colombia was slow.

Definitions of clinical response were as follows:
At 2 weeks follow up after EOT:

- Apparent cure was defined as complete epithelialization of all ulcers and complete disappearance of inflammatory induration from all lesions.
- Partial cure was defined as incomplete epithelialization or incomplete regression of inflammatory induration of any lesion, no ≥ 50% enlargement of previously documented lesions, and absence of parasites, and no appearance of new lesions. If parasitology was not done 2 weeks after EOT, the evaluation of partial cure was based on clinical parameters only.
- Failure was defined as lack of achieving partial response (i.e., residual lesions with presence of parasites or appearance of new lesions or ≥ 50% enlargement of previously documented lesions.

At 6 months after EOT:

- Definite cure was defined as complete epithelialization of all ulcers and complete disappearance of inflammatory induration from all lesions. In addition, no new lesions, no positive parasitology and no > 50% enlargement of existing lesions should have occurred in the period 2 weeks and 6 months post-therapy.
- Failure was defined as lack of definite cure

Subjects classified as failure at the 2 weeks were also classified as failure at 6 months. Subjects not cured at two months after EOT received rescue treatment with parenteral pentavalent antimony.

The primary endpoint was initially specified as apparent cure and definite cure. Because many subjects were noted to experience partial cure at 2 weeks after EOT but definite cure at 6 months, the primary endpoint was changed to apparent or partial cure at 2 weeks followed by definite cure at 6 months. This change in the primary endpoint was made while the study was still blinded.

Assuming a placebo rate of 20-60%, power 80% and alpha 0.05, a sample size of 81 to 111 was calculated. Accounting for drop outs and 2:1 randomization in favor of miltefosine, 88 subjects were to be enrolled to receive miltefosine and 44 to receive placebo.

The intent-to-treat population (ITT) included all subjects who received at least one dose of trial medication. The per-protocol (PP) population included all ITT subjects who received the trial medication for at least 90% of the planned treatment days and who were assessed for apparent cure (2 weeks after EOT). Subjects who dropped out earlier due to lack of efficacy were not excluded from the PP. The safety population included all subjects who received at least one dose of trial medication and who were not lost to follow up after baseline visit.

Protocol Amendments

There were 5 protocol amendments. 4 pertained to clarification of study procedures and sample collection, and one pertained to evaluation of the potential effects of miltefosine on male fertility.

Disposition

133 subjects were randomized, 44 to receive placebo and 89 to receive miltefosine. Two placebo subjects and 4 miltefosine subjects did not complete the study.

Table 30: Subject Disposition – Study 3168

	Placebo	Miltefosine
Enrolled	44	89
ITT Population	44	89
Excluded From PP	2 (4.5%)	4 (4.5%)
Lost to follow up	1	2
Lost study medication	1	0
Due to non-compliance	0	1
Due to lack of tolerability	0	1
PP Population	42	85
Safety Population	44	89

Demographics and Other Characteristics

Table 31: Subject Characteristics – Study 3168

	Placebo N = 44	Miltefosine N = 89
Male	38 (86.4%)	81 (91.0%)
Age (years)		
Mean (SD)	26.1 (12.6)	24.9 (9.8)
Range	12-63	12-55
Age < 18 years	14 (31.8%)	19 (21.3%)
Weight (kg)		
Mean (SD)	58.4 (11.3)	59.5 (11.0)
Range	33-82	29-84
BMI		
Mean (SD)	22.0 (3.0)	22.1 (2.9)
Range	16-29.8	14.6-35
Ethnicity		
Hispanic	32 (72.7%)	64 (71.9%)
History of ophthalmic disease*	10 (22.7%)	12 (13.5%)
Previous treatment for CL	10 (22.7%)	14 (15.7%)
Diagnosis of CL		
New	34 (77.3%)	77 (86.5%)
Unresponsive to prior therapy	3 (6.8%)	5 (5.6%)
Relapse	7 (15.9%)	7 (7.9%)
More than one lesion	16 (33.4%)	35 (29.3%)
Lesion Infiltration size (mm^2)		
Mean (SD)	854 (747)	603 (704)
Median	779	480
Range	36-4800	48-11360

*Ophthalmic diagnoses at baseline included amblyopia, decreased visual acuity, burning sensation and foreign body sensation

Reviewer's Comments
13/14 females were enrolled in Colombia, 7 received miltefosine and 6 received placebo. The reasons for the relative lack of female enrollment in Guatemala are not known. The one female enrolled in Guatemala received miltefosine.

Lesions were on average larger in the placebo group. Subjects were otherwise matched for age, weight, BMI, ethnicity, number of lesions and prior treatment for CL.

Efficacy Evaluation

Primary Efficacy Endpoint

The primary efficacy endpoint was apparent or partial cure 2 weeks after end of therapy and definite cure at 6 months after end of therapy.

Table 32: Primary Endpoint – Partial and Apparent Cure at 2 weeks Followed by Definite Cure at 6 Months - ITT – Study 3168

	Placebo	Miltefosine	Difference	P value

	N = 44	N = 89	MLT-PLA 95% CI	
Definite Cure - ITT	13/44 (29.6%)	59/89 (66.3%)	36.7% (20.1, 53.4)	< 0.0001
Definite Cure - PP	13/42 (31.0%)	59/85 (69.4%)	38.4% (21.4, 55.5)	< 0.0001

Reviewer's Comments
Miltefosine was superior to placebo in the treatment of CL for the endpoint of apparent and partial cure at 2 weeks plus definite cure at 6 months. As noted in the study design description, the original protocol specified endpoint was apparent cure at 2 weeks plus definite cure at 6 months. Re-analysis of the data using the original definition does not alter the conclusion of superiority.

Table 33: Definite Cure at 6 months – Original Protocol-Specified Endpoint – Study 3168

	Placebo N = 44	*Miltefosine N = 89*	*MIL-PLA Difference 95% CI*	*P value*
Definite Cure - ITT	*7/44 (15.9%)*	*48/89 (53.9%)*	*38.0% (23.1, 52.9)*	*< 0.0001*
Definite Cure - PP	*7/42 (16.7%)*	*48/85 (56.5%)*	*39.8% (24.4, 55.2)*	*< 0.0001*

The difference in cure between miltefosine and placebo was similar in subjects older or younger than 18 years of age and was comparable to the overall population. There were no subjects 65 years of age or older.

Table 34: Definite Cure by Age – ITT - Study 3168

	Placebo N = 44	*Miltefosine N = 89*	*Miltefosine-Placebo Difference*
<18 years	*6/14 (42.9%)*	*15/19 (84.2%)*	*41.3%*
≥18 years	*7/30 (23.3%)*	*44/70 (65.7%)*	*42.4%*
Total	*13/44 (29.6%)*	*59/89 (66.3%)*	*36.7%*

No gender differences in the natural course of CL are described in the literature. In this study, the placebo response in females was higher compared to the placebo response in males, and miltefosine was not significantly superior to placebo. However, the number of females enrolled is small. In addition, all but one of the 14 females enrolled in this study were in Colombia, where the placebo response was higher compared to Guatemala (see discussion of response by study center results below).

Table 35: Definite Cure by Gender – ITT - Study 3168

	Placebo N = 44	*Miltefosine N = 89*	*Difference*	*P Value*
Men	*9/38 (23.7%)*	*53/81 (65.4%)*	*41.8%*	*< 0.0001*

			(24.7, 58.8)	
Women	*4/6 (66.7%)*	*6/8 (75.0%)*	*8.3% (-39.9, 56.5)*	*1.0*
Total	*13/44 (29.6%)*	*59/89 (66.3%)*	*36.7%*	*< 0.0001*

Definite cure was not affected by ethnicity, BMI or receipt of prior anti-Leishmania therapy.

The mean miltefosine dose was 2.5 mg/kg/d (SD 0.33) and the median dose and range were 2.5 and 1.8-3.4 mg/kg/d respectively. The mean miltefosine dose was similar in subjects who were cured compared to subjects who failed. Miltefosine per kg dose ranged from 1.8-3.4 mg/kg. Definite cure was lower in miltefosine subjects who received less than 2 mg/kg/day compared to miltefosine subjects who received higher doses.

Table 36: Definite Cure by Ethnicity - ITT – Study 3168

	Placebo N = 44	*Miltefosine N = 89*	*Difference*
Hispanic	*11/32 (34.4%)*	*43/64 (67.2%)*	*32.8%*
Other	*2/12 (16.6%)*	*16/25 (64.0%)*	*47.4%*
Total	*13/44 (29.6%)*	*59/89 (66.3%)*	*36.7%*

Table 37: Definite Cure by BMI- ITT – Study 3168

	Placebo N = 44	*Miltefosine N = 89*	*Difference*
BMI < 25	*10/37(27.0%)*	*51/79 (64.6%)*	*37.6%*
BMI ≥ 25	*3/7 (42.9%)*	*8/10 (80.0%)*	*37.1%*
Total	*13/44 (29.6%)*	*59/89 (66.3%)*	*36.7%*

Table 38: Definite Cure by Receipt of Prior Treatment for CL – ITT – Study 3168

	Placebo N = 44	*Miltefosine N = 89*	*Difference*
Prior treatment	*2/10 (20.0%)*	*6/12 (50.0%)*	*30.0%*
No prior treatment	*11/34 (32.4%)*	*53/77 (68.8%)*	*36.4%*
Total	*13/44 (29.6%)*	*59/89 (66.3%)*	*36.7%*

Table 39: Definite Cure by Miltefosine Dose – Study 3168

Miltefosine Dose Per Kg	*Definite Cure*
< 2	*2/5 (40%)*
2-2.4	*24/39 (61.5%)*
2.5-2.9	*29/38 (76.3%)*
3-3.9	*4/7 (57.1%)*
Total	*59/89 (66.3%)*

Table 40: Mean Miltefosine Dose – Cured vs. Failed – Study 3168

Miltefosine Dose	*Definite Cure*	*Failed*
Mean (SD)	*2.48 (0.32)*	*2.49 (0.34)*
Median (Range)	*2.5 (1.9-3.2)*	*2.5 (1.8-3.1)*

Miltefosine was also superior to placebo at each treatment center. However, definite cure in both the placebo group and the miltefosine group was lower in Guatemala compared to Colombia with a smaller treatment effect.

Table 41: Definite Cure by Study Center/Country –Study 3168

	Placebo	Miltefosine	Miltefosine-Placebo Difference	P value
ITT				
Colombia	9/24 (37.5%)	40/49 (81.6%)	44.1%	0.0002
Guatemala	4/20 (20.0%)	19/40 (47.5%)	27.5%	0.0406
Total	13/44 (29.6%)	59/89 (66.3%)	36.7%	< 0.0001
PP				
Colombia	9/24 (37.5%)	40/47 (85.1%)	47.6%	< 0.0001
Guatemala	4/18 (22.2%)	19/38 (50.0%)	27.8%	< 0.0505
Total	13/42 (31.0%)	59/85 (69.4%)	38.4%	< 0.0001

Lower miltefosine exposure may result in lower cure rates: In a dose finding study[12], subjects who received 0.75-1.5 mg/kg/day had lower responses compared to subjects who received approximately 2.3 mg/kg/day. In Study 3168, the mean BMI, mean weight and mean dose were similar among Colombian and Guatemalan subjects. Dosage/exposure and/or weight differences do not explain the difference in response at the study sites in the miltefosine arm.

Epidemiologic studies indicate that the Leishmania species causing CL are different in Colombia and Guatemala. An epidemiologic study of Leishmania species distribution in Colombia identified 7 different species. L. panamensis was the most frequent etiologic agent of CL, representing approximately 54%, followed by L. braziliensis at approximately 30%[13]. In contrast, 73% of CL lesions in Guatemala were caused by L. braziliensis and the rest were caused by L. mexicana[14].

L. braziliensis causes more protracted disease compared to other New World Leishmania species. In the above cited study of CL in Guatemala, only 6% of lesions caused by L. braziliensis were cured at 6 months, compared to 68% of lesions caused by L. mexicana. Another study in Guatemala reported a 6 months placebo cure rate of 0 for L.

[12] Soto J et al. Treatment of American cutaneous leishmaniasis with miltefosine, an oral agent. CID 2001;33:e57-e61
[13] Corredor A et al. Distribution and etiology of leishmaniasis in Colombia. Am J Trop Med Hyg 1990;42:206-214
[14] Herwaldt B, Arana B, Navin T. The natural history of CL in Guatemala. JID 1992; 165:518-527

braziliensis[15]*. Other studies from Colombia reported 30 – 38% placebo cure rates at 6 months for lesions caused by L. panamensis*[16,17,18]*.*

Information regarding speciation of Leishmania isolates in this study was included in the study report as a citation of the published article: "In Colombia, cultures of 7 baseline lesion aspirates from this trial were speciated by monoclonal antibody binding; all 7 were infected by L. (v) panamensis. In Guatemala, 46 of the 60 infecting parasites were speciated by PCR; 63% were L. (v) braziliensis and 37% L. m. mexicana".

Cure rates by species as reported in the journal article are shown in the table below.

Table 42: Definite Cure by Infecting *Leishmania* Species in Guatemalan patients - Study 3168

	Miltefosine N = 40			Placebo N = 20		
L. species	*L. braziliensis* N=16	*L. mexicana* N=14	Unknown N=10	*L. braziliensis* N=13	*L. mexicana* N=3	Unknown N=4
Cured	5 (31.2%)	9 (64.3%)	6 (60.0%)	1 (7.7%)	1 (33.3%)	2 (50.0%)
Failed	10 (62.5%)	5 (35.7%)	3 (30.0%)	11 (84.6%	2 (66.7%)	2 (50.0%)
Un-evaluable	1 (6.25%)	0	1 (10.0%)	1 (7.7%)	0	0

As the table indicates, the placebo cure rate for lesions caused by L. braziliensis was lower compared to the placebo cure rate for lesions caused by other infecting species. The 7.7% placebo cure rate for L. braziliensis was similar to what is reported in the literature. Differences in the natural history of the epidemiologically prevalent species in Colombia and Guatemala may therefore account for the lower placebo cure rate in Guatemala.

The table also indicates that miltefosine cure rates for lesions caused by L. braziliensis were also lower compared to the miltefosine cure rates for lesions caused by L. mexicana or other species. L. braziliensis may be intrinsically less susceptible to miltefosine compared to other species because it may be less able to internalize miltefosine (see microbiology section). The lower miltefosine cure rate in Guatemala may therefore also be possibly explained by differences in the infecting species. However, the lower placebo cure rate and lower miltefosine cure rate for L. braziliensis result in a similar treatment difference compared to L. mexicana (23.5% for braziliensis and 31% for mexicana).

[15] Navin T, Arana B, et al. Placebo-controlled clinical trial of meglumine antimonite vs. localized heat in the treatment of cutaneous leishmaniasis in Guatemala. Am J Trop Med Hyg 1990;42:43-50
[16] Soto J, Berman J. Treatment of New World cutaneous leishmaniasis with miltefosine Trans R Soc Trop Med Hyg 2006; 100 (S1): S34-40
[17] Hendrickx EP et al. Lack of efficacy of mefloquine in the treatment of New World cutaneous leishmaniasis in Colombia, Am J Trop Med Hyg 1998;59:889-92
[18] Velez I et al. Inefficacy of allopurinol as monotherapy for Colombian cutaneous leishmaniasis. A randomized controlled trial. Ann Int Med 1997;126:232-6

Of note, 46/60 (76.7%) subjects in Guatemala had a species identified, while 7/73 (9.6%) subjects in Colombia had an identification. The reasons for this significant difference in efforts to obtain a culture at the two study sites are not clear.

Secondary Efficacy Endpoints

A higher percentage of miltefosine subjects achieved apparent cure at 2 weeks, indicating faster healing time compared to placebo. Similar to definite cure, the percentage of subjects who achieved apparent cure in the miltefosine arm was higher in Colombia compared to Guatemala.

Table 43: Clinical Response Categories 2 Weeks after EOT – ITT - Study 3168

	Placebo N = 44	Miltefosine N = 89
Apparent cure	7/44 (15.9%)	56/89 (62.9%)
Colombia	3/24 (12.5%)	39/49 (79.8%)
Guatemala	4/20 (20.0%)	17/40 (42.5%)
Partial cure	10/44 (22.7%)	13/89 (14.6%)
Colombia	7/24 (29.2%)	6/49 (12.2%)
Guatemala	3/20 (15.0%)	7/40 (17.5%)
Clinical failure	26/44 (59.1%)	16/89 (18.0%)
Colombia	14/24 (58.3%)	2/49 (4.1%)
Guatemala	12/20 (60.0%)	14/40 (35.0%)
Not assessable	0	1/89 (1.1%)
Colombia	0	0
Guatemala	0	1/40 (2.5%)
Missing Data	1/44 (2.3%)	3/89 (3.4%)
Colombia	0	2/49 (4.1%)
Guatemala	1/20 (5.0%)	1/40 (2.5%)

Safety Evaluation

Extent of Exposure

Two miltefosine subjects were lost to follow up. An additional two subjects discontinued prematurely, one due to intolerability after receiving 27 days and one due to non-compliance on day 21. Treatment duration was 28 days in all remaining miltefosine subjects. In the placebo arm, one subject was lost to follow up and one subject lost study medication.

The mean miltefosine dose was 2.5 mg/kg/d (SD 0.33) and the mean duration was 27.9 days. The median dose and range were 2.5 and 1.8-3.4 mg/kg/d respectively.

Concomitant Medications

22/89 (24.7%) miltefosine subjects received at least one concomitant medication, mainly acetaminophen, anti-parasitic and antibacterial drugs.

7/44 (15.9%) of placebo subjects received at least one concomitant medication, mainly NSAIDs, anti-parasitic and antibacterial drugs.

Treatment Emergent Adverse Reactions

65 (73.0%) subjects in the miltefosine arm experienced at least one AE, compared to 23 (52.3%) subjects in the placebo arm. There were no serious adverse events. One subject in the miltefosine arm discontinued therapy on day 27 due to motion sickness. There were no deaths. All AE tables presented were derived from the submitted AE dataset.

Table 44: Summary of AE – Study 3168

	Placebo N = 44	Miltefosine N = 89
N of subjects who experienced at least one AE	23 (52.3%)	65 (73.0%)
N of subjects who experienced a serious AE	0	0
N of subjects who discontinued treatment due to AE	0	1 (1.1%)

Table 45: Treatment Emergent AE – Study 3168

MedDRA v. 12.0 System Organ Class/Preferred Term	Placebo N = 44	Miltefosine N = 89
Ear and Labyrinth	11 (25.0%)	26 (22.9%)
Motion sickness	10* (22.7%)	26* (29.2%)
Ear pain	1 (2.3%)	0
Gastrointestinal Disorders	13 (29.6%)	42 (47.2%)
Abdominal pain	4 (9.1%)	10 (11.2%)
Diarrhea	2 (4.5%	7 (7.9%)
Dyspepsia	3 (6.8%)	5 (5.6%)
Dysphagia	0	1 (1.1%)
Flatulence	0	2 (2.2%)
Nausea	5 (11.4%)	32 (35.9%)
Vomiting	0	4 (4.5%)
General Disorders	3 (6.8%)	8 (9.0%)
Chest pain	1 (2.3%)	0
Pyrexia	2 (4.5%)	5 (5.6%)
Malaise	1 (2.3%)	3 (3.4%)
Rigors	1 (2.3%)	1 (1.1%)
Pain	0	2 (2.2%)
Infections and Infestations	4 (9.1%)	12 (13.5%)
Bacterial Infection	0	4 (4.5%)
Localized abscess	1 (2.3%)	1 (1.1%)
Parasitic infection	1 (2.3%)	3 (3.4%)
URI	2 (4.5%)	2 (2.2%)
Urinary Tract Infection	0	2 (2.2%)
Musculoskeletal and Connective Tissue	3 (6.8%)	3 (3.4%)
Arthralgias	1 (2.3%)	2 (2.2%)
Myalgia	2 (4.5%)	1 (1.1%)

Nervous System Disorders	10 (22.7%)	28 (31.5%)
Headache	10 (22.7%)	25 (28.1%)
Dizziness	0	4 (4.5%)
Psychiatric Disorders	0	3 (3.4%)
Somnolence	0	3 (3.4%)
Respiratory/Thoracic Disorders	1 (2.3%)	6 (6.7%)
Pharyngitis	1 (2.3%)	4 (4.5%)
Influenza	0	1 (1.1%)
Cough	0	1 (1.1%)
Skin and SC Disorders	1 (2.3%)	4 (4.5%)
Cellulitis	1 (2.3%)	0
Pruritus	0	4 (4.5%)
Vascular Disorders	0	1 (1.1%)
Peripheral Edema	0	0

*all Colombia center

Reviewer's Comments
The AEs that occurred more frequently among miltefosine recipients included abdominal pain, nausea, vomiting, diarrhea, headache, dizziness, somnolence, motion sickness, pruritus, pharyngitis and bacterial infection (of the CL site). Of note, all the subjects who had motion sickness were in Colombia. This may indicate inconsistencies in reporting and coding adverse events between the two study centers. The same subjects coded as experiencing motion sickness were also coded as experiencing headache and nausea individually.

The frequency of GI adverse events among miltefosine recipients was not dose dependent.

Table 46: Effect of Miltefosine Dose on GI Adverse Events – Study 3168

	Miltefosine Dose mg/kg			
	1.4-2.2 N = 24	*2.3-<3 N = 58*	*≥ 3 N = 7*	*Total N = 89*
Diarrhea	*0*	*7 (12.1%)*	*0*	*7 (7.9%)*
Nausea	*12 (50.0%)*	*20 (34.5%)*	*0*	*32 (35.9%)*
Vomiting	*0*	*4 (6.9%)*	*0*	*4 (4.5%)*

Ophthalmologic Assessment

Visual acuity, fundoscopy, color vision and perimetry were tested at baseline, during therapy, at EOT and at 6 months follow up. One miltefosine subject was noted as having abnormal fundoscopy in the right eye on day 28 that resolved at 6 months. The abnormality was not specified. All other abnormal visual findings noted during therapy or at 6 months follow up were present at screening. No visual symptoms were reported in any subject.

Reproductive Toxicity Assessment

Spermiograms were at screening, 2 weeks and 6 months in 15 men, 4 in the placebo arm and 11 in the miltefosine arm. There was considerable variability of sperm counts and motility in both treatment arms, rendering the study inconclusive regarding the effects of miltefosine on spermatogenesis.

Renal Toxicity

The overall mean Cr at EOT did not change in the placebo group (0.82) but increased in the miltefosine group from 0.87 to 0.99. The highest absolute Cr value was 1.5.

Table 47: Mean Cr Changes EOT – Study 3168

	Placebo N = 44	*Miltefosine N = 89*
Cr at baseline		
Mean (SD)	*0.82 (0.21)*	*0.87 (0.22)*
Range	*0.3-1.3*	*0.4-1.4*
Cr at EOT		
Mean	*0.82 (0.18)*	*0.99 (0.19)*
Range	*0.5-1.4*	*0.63-1.5*

At EOT, 70.7% of miltefosine recipients and 50% of placebo recipients had some degree of Cr elevation compared to baseline (CTCAE grade 1and 2). The percentage of subjects with Cr elevations above baseline was similar at 3 months (35.9% vs. 34 %).

Table 48: Cr Changes – Study 3168

Cr Increase	*Placebo N = 44*	*Miltefosine N = 89*
EOT		
Cr >1-<1.5x baseline	*24 (45.5%)*	*51 (57.3%)*
Cr ≥ 1.5-< 3x baseline	*2 (4.5%)*	*11 (12.3%)*
Cr ≥ 3-6x baseline	*0*	*1 (1.1%)*
3 Months Post Therapy		
Cr >1-<1.5x baseline	*13 (29.5%)*	*27 (30.3%)*
Cr ≥ 1.5-< 3x baseline	*2 (4.5%)*	*5 (5.6%)*
Cr ≥ 3-6x baseline	*0*	*0*
6 months Post Therapy		
Cr >1-<1.5x baseline	*8 (18.2%)*	*21 (23.6%)*
Cr ≥ 1.5-< 3x baseline	*2 (4.5%)*	*3 (3.4%)*
Cr ≥ 3-6x baseline	*0*	*0*

Grade 2 CTC Cr changes occurred more frequently in miltefosine subjects who received doses higher than 2.3 mg/kg, but Grade 1 changes were not dose dependent.

Table 49: Effect of Dose on Cr – 3168

	Miltefosine Dose mg/kg

EOT	*1.4-2.2 N = 24*	*2.3-<3 N = 58*	*≥ 3 N = 7*	*Total N =89*
Cr >1-<1.5x baseline	*14 (58.3%)*	*34 (58.6%)*	*3 (42.9%)*	*51 (57.3%)*
Cr ≥ 1.5-< 3 x baseline	*2 (8.3%)*	*8 (13.8%)*	*1 (14.3%)*	*11 (12.3%)*
Cr ≥ 3-6x baseline	*0*	*1 (1.7%)*	*0*	*1 (1.1%)*

Hepatic Toxicity

A similar percentage of subjects had increases in ALT, AST, alkaline phosphatase or bilirubin above ULN at EOT. All changes were CTCAE grade 1. No subject in either arm had elevation of ALT or AST > 3x ULN at any time during therapy or follow up.

Table 50: Changes in Transaminases – Study 3168

EOT	*Placebo N = 44*	*Miltefosine N = 89*
ALT > 1-3x ULN	*2 (4.5%)*	*4 (4.5%)*
ALT >3-5x ULN	*0*	*0*
AST >1-3x ULN	*1 (2.3%)*	*2 (2.2%)*
AST >3-5x ULN	*0*	*0*
AP >1-2.5x ULN	*7 (15.9%)*	*13 (14.6%)*
AP >2.5-5x ULN	*0*	*0*
Bilirubin ≥1.5 mg/dL	*2 (4.5%)*	*1 (1.1%)*

At EOT, mean ALT was similar (24.8 +/-15.6 in the placebo arm vs. 25.9 +/-11.7 in the miltefosine arm. The highest absolute value was 94 in both arms.

Hematologic

There were no significant changes in Hb, WBC or platelet count during therapy or at EOT in the miltefosine arm. One placebo subject had a platelet count 100,000 (CTCAE grade 1) on days 7, 14, 21 and 28 of therapy.

Study Conclusions

Miltefosine was superior to placebo in the treatment of CL in the overall study population and at each of the two study centers (Colombia and Guatemala) for the primary endpoint of apparent or partial cure at 2 weeks followed by definite cure at 6 months. Apparent cure at 2 weeks after EOT were also significantly higher in the miltefosine treated subjects, indicating a faster time to healing.

Treatment effect was not affected by age, ethnicity, BMI, or prior treatment with antimony. In women, miltefosine cure rate was similar to placebo. However, the number of women enrolled was small, and almost all of the women enrolled in the study (13 of 14) were enrolled in Colombia, where the cure rates were higher in both study arms compared to Guatemala. The reasons for the lack of enrollment of women in the Guatemala study center are not clear.

Definite cure was lower in Guatemala compared to Colombia in both study arms. A possible explanation for this geographic difference in response may be related to differences in the prevalent *Leishmania* species in each country. Epidemiologically, *L. braziliensis* accounts for approximately 75% of CL lesions in Guatemala and for approximately 30% of CL lesions in Colombia. *L. braziliensis* causes more protracted disease with lower placebo cure rates compared to disease caused by other *Leishmania* species (placebo cure rate approximately 6-7% for *L. braziliensis* compared to 38-68% for other New World species). The higher prevalence of *L. braziliensis* likely accounts for the lower placebo cure rate in Guatemala. The higher prevalence of *L. braziliensis* in Guatemala may also explain the lower miltefosine cure rate in that study center. *L. braziliensis* may be intrinsically less susceptible to miltefosine compared to other species due to its reduced ability to internalize the drug.

Parasitology data were not included in the submitted datasets but were obtained from the published article describing this study. Significantly more subjects had an organism isolated in Guatemala compared to Colombia (77% vs. 10%). The reasons for this significant difference in efforts to identify an organism between the two clinical centers are not clear. The isolated species were consistent with the epidemiologically prevalent species for each country. The placebo response rates for *L. braziliensis* and *L. mexicana* (in Guatemala) and *L. panamensis* (in Colombia) were also consistent to what is reported in the literature.

There were no serious adverse events and no deaths. The main adverse events that occurred more frequently in miltefosine recipients were nausea, vomiting, diarrhea, dizziness, headache, somnolence, pruritus and motion sickness. One subject discontinued therapy due to motion sickness. The AE term motion sickness was only used in Colombia. The same subjects coded as experiencing motion sickness were also coded as experiencing nausea and headache.

A higher percentage of miltefosine subjects experienced CTCAE grade 1 and 2 elevations of Cr above baseline at the end of therapy. Mean Cr among miltefosine recipients was also higher at the EOT compared to placebo recipients. The highest absolute Cr value at any time was 1.5. The percentage of subjects with Cr elevations above baseline was similar at 3 months follow up. CTCAE grade 2 Cr elevations were more frequent at higher miltefosine doses, but grade 1 changes were not dose dependent. A similar percentage of subjects had ALT, AST or alkaline phosphatase elevations above ULN, and all were CTCAE grade 1. There were no hematologic toxicities. One subject was noted to have an unspecified abnormal fundoscopic exam in one eye at the end of therapy that resolved at 6 months. No visual symptoms were reported. Spermiograms performed in 11 miltefosine subjects and 4 placebo subjects showed considerable variability precluding conclusions regarding effects on spermatogenesis. All women of childbearing age were required to use contraception and no pregnancies were reported.

Study SOTO

The study was conducted between November 15, 2005 and March 11, 2007 at a single center in Bolivia (Palos Blancos hospital center)[19]. The study was completed and published prior to the NDA sponsor (Paladin) involvement. Paladin obtained the CRFs from the study PI and a data management and statistical analysis plans were created to analyze the submitted data.

Study Design

This study was investigator-initiated, and was described as an open label, randomized trial comparing oral miltefosine to intramuscular meglumine (Glucantime – pentavalent antimony) in the treatment of CL in Bolivia.

Subjects ≥ 12 years of age with parasitologically confirmed CL by touch preparation of skin tissue and no mucosal involvement were randomized in 2:1 ratio to receive miltefosine 2.5 mg/kg/d for 28 days or IM meglumine 20 mg/kg/d for 20 days. The primary efficacy endpoint was definite cure, defined as complete re-epithelialization of all lesions at 6 months after EOT. A lesion was defined as failure if it did not completely re-epithelialize at 6 months after EOT, or if the lesion enlarged by 50% at EOT or 1 month after EOT, if the lesion area did not diminish by 50% at 3 months after EOT, or the lesion relapsed. For a subject to be cured, all lesions had to be cured.

Subjects who had received prior leishmaniasis therapy could be enrolled if that treatment was at least 2 months prior to enrollment. Subjects with "clinically significant abnormalities" on physical exam or with "clinically significant lab abnormalities" in hematology, transaminases or Cr were excluded. Pregnant and lactating women and women unable to comply with contraception were excluded. Lesion size, parasitology (for non-healed lesions) and labs were re-evaluated at EOT, and 1, 3 and 6 months post therapy. Species identification of the *Leishmania* species visualized on ulcer scrapings was not performed because prior epidemiology in this region of Bolivia indicated that *L. braziliensis* was the prevalent species.

The submitted study report states that there was no pre-specified statistical hypothesis, and that sample size was chosen based on resource constraints.

The ITT and the safety populations included all subjects who received any dose of study drug. The study report did not define a per-protocol population.

Reviewer's Comments
An English translation of the original protocol was provided in the submission and states that assuming a rate of cure of 55% for meglumine, a sample of 100 patients will have "an acceptable" power to detect miltefosine equivalence at 20-30%.

[19] Soto J et al. Efficacy of miltefosine for Bolivian cutaneous leishmaniasis. Am J Trop Med Hyg 2008;78:210-211

Disposition

54 subjects were randomized to receive oral miltefosine and 26 to receive IM meglumine. 11 subjects at the end of the randomization list for miltefosine were not used, and 7 subjects at the end of the randomization list for meglumine were not used. One subject assigned to miltefosine was misdiagnosed and never received drug. Records were missing for 3 additional subjects assigned to miltefosine. One subject assigned to meglumine mistakenly received miltefosine, and was analyzed with the miltefosine group. The final number of subjects analyzed in the miltefosine arm was 40. The final number of subjects analyzed in the meglumine arm was 18.

4 meglumine subjects were lost to follow up and two miltefosine subjects were lost to follow up.

Table 51: Subject Disposition – Study Soto

	Miltefosine	Meglumine
Randomized	54	26
Did not receive drug	11	7
Misdiagnosed and did not receive drug	1	0
Missing Records	3	0
Mistakenly received the other drug	0	1
Included in ITT Analysis	40	18
Completed all visits	38	14
Lost to follow up	2	4

Reviewer's comments

The datasets submitted for this study did not include a tabulation of subject disposition, and did not include the 3 miltefosine subjects whose records were missing. The subject who was assigned to meglumine (Subject Soto-10) but mistakenly received miltefosine was listed with the meglumine group in the demography dataset but with miltefosine in the clinical response analysis, exposure and individual subject line listing datasets. This subject was analyzed with the miltefosine group in the study report data, and will be analyzed with the miltefosine group in this review.

22% and 27% of subjects randomized to miltefosine or meglumine respectively did not receive drug. Of the subjects who received drug, A higher percentage of meglumine subjects were lost to follow up (2/40, 5% vs. 4/18, 22%).

There are concerns whether the study was properly randomized, based on the timing of treatment initiation in relation to the time of randomization. The study was stopped early, and 3 of the meglumine subjects who were lost to follow up were probably not followed because the study closed. The sponsor imputed these subjects as failure. There was no information as to why the study was stopped early.

Demographics and Other Subject Characteristics

Table 52: Subject Characteristics – Study Soto

	Miltefosine N = 40	Meglumine N = 18
Gender		
Male	31 (77.5%)	14 (77.8%)
Female	9 (22.7%)	4 (22.2%)
Age (years)		
Mean (SD)	28.9 (11.6)	25.1 (13.4)
Range	12-57	12-51
Age < 18 years	7 (17.5%)	6 (33.3%)
Ethnicity		
Caucasian	0	1 (5.6%)
Moseten	0	2 (11.1%)
Aymara	25 (62.5%)	11 (61.1%)
Quechua	15 (37.5%)	4 (22.2%)
Weight (kg)		
Mean (SD)	58.0 (8.2)	57.0 (11.0)
Range	39-78	38-80
Lesion area mm^2		
Mean (SD)	309.4 (454.7)	233.3 (255.4)
Median	178	150
Range	10-3172	4-900
Subjects with 1 lesion	25 (62.5%)	9 (50.0%)
Subjects with 2 lesions	10 (25.0%)	6 (33.3%)
Subjects with 3 lesions	5 (12.5%)	3 (16.7%)
Total n of lesions	60	30

Reviewer's Comments
Overall, subjects were matched for age, gender, weight, ethnicity and number of lesions. Lesion size was larger in the miltefosine arm.

Efficacy Evaluation

Primary Endpoint

The primary endpoint was definite cure at 6 months.

Table 53: Definite Cure – Study Report – Study Soto

	Miltefosine N = 40	Meglumine N = 18	Difference MLT-MEG
Definite Cure (%) 95% CI	32 (80.0%) 64.3%, 90.9%	13 (72.2%) 49.1%, 87.5%	+7.8%
Failure	6 (15.0%)	1 (5.5%)	+9.5%
Lost to follow up	2 (5.0%)	4 (22.2%)	-17.2%

Reviewer's Comments
The published article reports slightly different results that what was submitted. In the article, 44 subjects received miltefosine and 18 received meglumine. At 6 months after

therapy 36 miltefosine recipients achieved cure compared to 15 meglumine recipients (81.8% vs. 83.3%).

As mentioned, 3 miltefosine records were missing, and 3 of the meglumine subjects lost to follow up and imputed as failure were probably not followed because the study had closed. The 3 miltefosine subjects were removed from the analysis. Similarly removing the 3 meglumine subjects from the analysis yields a meglumine cure rate 13/15 (86.7%). The difference (MLT-MEG) is -6.7%, 95% CI (-26.3%, 21.4%).

The difference in treatment response was not affected by gender or ethnicity. Miltefosine cure was lower in subjects 12-17 years of age, but the number of subjects enrolled in this age group was low. The mg/kg miltefosine dose ranged between 1.9-3.8 mg/kg. The mean miltefosine dose was similar in subjects who experienced a cure compared to subjects who failed. Only one subject received a dose < 2 mg; no conclusions could be reached regarding dose-response.

Table 54: Miltefosine Efficacy – Modified Cure Rate

	Miltefosine N = 40	Meglumine N = 15	Difference MLT-MEG	95% CI
Definite Cure (%) 95% CI	32 (80.0%) 64.3%, 90.9%	13 (86.7%) 49.1%, 87.5%	-6.7%	(-26.3, 21.4)
Failure	6 (15.0%)	1 (6.7%)	+8.3%	
Lost to follow up	2 (5.0%)	1 (6.7%)	-1.7%	

Table 55: Definite Cure by Age – Study Soto

	Miltefosine N = 40	*Meglumine N = 18*	*MLT - MEG*
Age < 18 years	*4/7 (57.1%)*	*4/6 (66.7%)*	*-9.6%*
Age ≥18 years	*28/33 (84.8%)*	*9/12 (75.0%)*	*+ 9.8%*
Total	*32 (80.0%)*	*13 (72.2%)*	*+7.8%*

Table 56: Definite Cure by Ethnicity – Study Soto

	Miltefosine N = 40	*Meglumine N = 18*	*MLT - MEG*
Aymara	*19/25 (76.0%)*	*8/11 (72.7%)*	*+3.3%*
Quechua	*13/15 (86.7%)*	*3/4 (75.0%)*	*+11.7%*
Caucasian	-	*1/1 (100%)*	-
Moseten	-	*1/2 (50.0%)*	-
Total	*32 (80.0%)*	*13 (72.2%)*	*+7.8%*

Table 57: Definite Cure by Gender – Study Soto

	Miltefosine N = 40	*Meglumine N = 18*	*MLT-MEG*
Male	*23/31 (74.2%)*	*9/14 (64.3%)*	*+9.9%*
Female	*9/9 (100%)*	*4/4 (100%)*	*0*
Total	*32 (80.0%)*	*13 (72.2%)*	*+ 7.8%*

Table 58: Effect of Miltefosine Dose – Study Soto

Miltefosine Dose Per Kg	*Definite Cure*
< 2	*1/1 (100%)*
2-2.4	*13/18 (72.2%)*
2.5-2.9	*13/15 (86.7%)*
3-3.9	*5/6 (83.3%)*
Total	*32/40 (80.0%)*

Table 59: Mean Miltefosine Dose – Study Soto

Miltefosine Dose mg/kg/d	*Cured N = 32*	*Failed N = 6*
Mean (SD)	*2.54 (SD 0.36)*	*2.69 (SD 0.58)*
Median (Range)	*2.52 (1.92-3.8)*	*2.48 (2.3-3.8)*

Epidemiologic studies indicate that L. braziliensis causes at least 85% of CL lesions in Bolivia[20,21,22]. In this study, the overall definite cure at 6 months for subjects who received miltefosine was 74-80%. In comparison, miltefosine cure rates in all Guatemalan subjects and Guatemalan subjects with documented L. braziliensis in Study 3168 were approximately 43% and 31% respectively. The sponsor does not provide possible explanations for this difference in response in the two countries.

In Study 3168, the primary endpoint was apparent or partial cure at 2 weeks after EOT and definite cure at 6 months. Failure was defined similarly in both studies for lesion size but timed at 2 weeks in Study 3168 and at 3 months in this study. Both studies required complete epithelialization of all lesions by 6 months. Cure rates for Study 3168 were re-analyzed using Soto criteria. Four additional Guatemalan miltefosine subjects and one Guatemalan placebo subject would be classified as cure, while no failed subjects from Colombia in either treatment arm would be reclassified as cure. Using Soto criteria, the cure in Guatemala would be at 19+4/40 = 57.5%. This is lower than the lower limit of the 95% CI for cure in Study Soto. Geographic differences in miltefosine susceptibility for L. braziliensis cannot be ruled out.

Safety Evaluation

Extent of Exposure

All miltefosine subjects received the drug for 28 days. The mean miltefosine dose was 2.6 mg/kg/day (SD 0.38) and the median was 2.5 mg/kg/day (range 1.9-3.8).

[20] Garcia A et al. Leishmaniasis in Bolivia: Comprehensive review and current status. Am J Trop Med Hyg 2009;80:704-711
[21] Davies C et al. The epidemiology and control of leishmaniasis in Andean countries. Cad. Saúde Pública, Rio de Janeiro, 2000;16:925-950
[22] http://www.who.int/leishmaniasis/resources/BOLIVIA.pdf

One meglumine subject received the drug for 22 days instead of 20 days. All other subjects received 20 days.

Concomitant Treatments

4 miltefosine subjects and 2 meglumine subjects received concomitant treatment with Depo Provera.

Treatment Emergent Adverse Reactions

14/18 (77.8%) meglumine subjects experienced at least one AE. AEs were not coded by seriousness but by severity. No meglumine subject experienced a severe AE, and no meglumine subject discontinued the drug due to an AE.

34/40 (85.0%) miltefosine subjects experienced at least one AE. One subject experienced a severe AE (lower abdominal pain) that resolved without specific therapy. No miltefosine subject discontinued the drug due to an AE.

There were no deaths.

Table 60: Treatment Emergent AE - Soto

MedDRA v. 12.0 System Organ Class/Preferred Term	Miltefosine N = 40	Meglumine N = 18
Subjects with at least one AE	34 (85.0%)	14 (77.8%)
Gastrointestinal	25 (52.5%)	1 (5.5%)
Abdominal Pain	1 (2.5%)	0
Abdominal Pain Lower	1 (2.5%)	0
Diarrhea	6 (15.0%)	1 (5.5%)
Nausea	19 (47.5%)	0
Vomiting	15 (37.5%)	0
General/Administration Site	4 (10.0%)	7 (38.9%)
Asthenia	1 (2.5%)	1 (5.5%)
Fatigue	1 (2.5%)	0
Injection site pain	0	5 (27.8%)
Malaise	1 (2.5%)	1 (5.5%)
Pyrexia	2 (5.0%)	0
Infections and Infestations	3 (7.5%)	0
Pharyngitis	2 (5.0%)	0
Nematodiasis	1 (2.5%)	
Metabolism	7 (17.5%)	1 (5.5%)
Decreased appetite	7 (17.5%)	1 (5.5%)
Musculoskeletal	1 (2.5%)	7 (38.9%)
Arthralgia	0	6 (33.3%)
Back pain	1 (2.5%)	0
Myalgia	0	2 (11.1%)
Nervous System	15 (37.5%)	7 (38.9%)

Dizziness	1 (2.5%)	0
Headache	11 (27.5%)	7 (38.9%)
Somnolence	4 (10.0%)	0
Respiratory/Thoracic	1 (2.5%)	0
Epistaxis	1 (2.5%)	
Skin/Subcutaneous	1 (2.5%)	0
Pruritus	1 (2.5%)	

Reviewer's Comments
AEs noted more frequently in the meglumine arm included injection site pain, headache, arthralgias and myalgia. AEs noted more frequently in miltefosine recipients included nausea, vomiting, diarrhea, dizziness, somnolence, decreased appetite, pyrexia and pruritus. GI adverse events in the miltefosine arm were not dose dependent.

Table 61: GI AE by Dose – Study Soto

	Miltefosine Dose mg/kg			
	1.4-2.2 N = 8	*2.3-<3 N = 26*	*≥ 3 N = 6*	*Total N = 40*
Diarrhea	*1 (12.5%)*	*4 (15.4%)*	*1 (16.7%)*	*6 (15.0%)*
Nausea	*3 (37.5%)*	*13 (50.0%)*	*3 (50.0%)*	*19 (47.5%)*
Vomiting	*1 (12.5%)*	*9 (34.6%)*	*5 (83.3%)*	*15 (37.5%)*

Renal Toxicity

Mean Cr in miltefosine subjects increased from 0.9 at baseline to 1.1 at EOT but remained stable in meglumine subjects. Absolute Cr values were all < 1.6.

At EOT, a similar percentage of miltefosine and meglumine subjects had CTCAE grade 1 elevations in Cr above baseline. A higher percentage of miltefosine subjects had grade 2 elevations.

Table 62: Cr Changes – Study Soto

	Miltefosine N = 40	*Meglumine N = 18*
Cr > 1-<1.5x baseline	*12 (30.0%)*	*6 (33.3%)*
Cr ≥ 1.5-< 3 x baseline	*13 (32.5%)*	*3 (16.7%)*
Cr at baseline		
Mean (SD)	*0.9 (0.2)*	*0.9 (0.3)*
Range	*0.5-1.3*	*0.5-1.1*
Cr at EOT		
Mean (SD)	*1.1 (0.3)*	*0.9 (0.3)*
Range	*0.5-1.6*	*0.4-1.5*

Grade 2 Cr increase above baseline occurred more frequently in miltefosine subjects who received doses greater than 2.3 mg/kg/day, but grade 1 increases were not dose dependent.

Table 63: Effect of Dose on Cr – Study Soto

	Miltefosine Dose mg/kg			
EOT	*1.4-2.2 N = 8*	*2.3-<3 N = 26*	*≥ 3 N = 6*	*Total N = 40*
Cr > 1-<1.5x baseline	*5 (62.5%)*	*6 (23.1%)*	*1 (16.7%)*	*12 (30.0%)*
Cr ≥ 1.5-< 3 x baseline	*1 (12.5%)*	*9 (34.6%)*	*3 (50.0%)*	*13 (32.5%)*

Hepatic Toxicity

No subject had an elevation of ALT above baseline or above ULN at EOT.
AST, bilirubin or AP were not reported.

Hematologic Toxicity

There were no significant changes in Hb, WBC or platelets in either arm during therapy.

Study Conclusions

The study did not have a pre-specified statistical hypothesis of non-inferiority or superiority. The study was closed early for unclear reasons, and we have concerns regarding randomization. Approximately 80% of subjects in each arm were cured.

Parasitologic identification of the infecting *Leishmania* species was not done. Epidemiologically, *L. braziliensis* is the prevalent species in Bolivia, accounting for least 85% of CL lesions. A higher percentage of miltefosine subjects experienced definite cure in this study compared to Guatemalan subjects in Study 3168 where *L. braziliensis* was also expected to be the prevalent species (74%-80% in this study vs. 42.5% in Guatemala and 31% in Guatemalan subjects with documented *L. braziliensis* in Study 3168). However, in Study 3168, failure at 2 weeks after EOT was classified as failure at 6 months, while Study Soto classified cure at 3 months as failure at 6 months. If Study Soto criteria were used in Study 3168, definite cure in Guatemalan subjects increases to 57.5%. This raises the possibility of geographic differences in *L. braziliensis* susceptibility to miltefosine. I was unable to identify literature that explored geographic differences in susceptibility of *L. braziliensis* to miltefosine.

Main adverse reactions noted more frequently in miltefosine subjects included abdominal pain, nausea, vomiting, diarrhea, decreased appetite, pyrexia, headache, dizziness, somnolence and pruritus. Main AEs noted more frequently in meglumine subjects included injection site pain and musculoskeletal symptoms.

A similar percentage of subjects in each arm had CTCAE grade 1 Cr elevations above baseline, but a higher percentage of miltefosine subjects had grade 2 elevations during therapy. Cr changes were not reported post therapy. The percentage of subjects with Grade 2 Cr elevations increased with increasing mg/kg miltefosine dose, but grade 1 changes were not dose dependent. There were no significant changes in ALT or hematologic parameters.

Study Z020

This study was split in two parts, Z020a and Z020b, both conducted in Brazil. Z020a was conducted in an area where *L. guyanensis* is epidemiologically known to be the predominant pathogen[23] and Z020b was conducted in an area where *L. braziliensis* is epidemiologically known to be the predominant pathogen[24]. The study compared miltefosine to meglumine. A placebo controlled trial was thought to be unethical by the primary investigators because in their experience CL in Brazil has a low placebo cure rate.

Study Z020a

This study was conducted between March 8, 2007 and August 11, 2008 at a single center in Brazil (Dermatology clinic at the Universidade Estadual do Amazonas, Manaus, Brazil). The study protocol was reviewed by the IRB of the Fundacao de Medicina Tropical – Amazonas, and by the Brazilian National Council of Ethics on Research. All subjects or guardians provided written informed consent.

Study Design

This was a randomized, open-label, active control study. Subjects 2 to 65 year of age with recent (less than 3 months) new diagnosis of CL, no history of prior therapy for leishmaniasis, at least one typical ulcerated lesion, and at most 5 lesions, with diameter between 1 and 5 cm and visible *Leishmania* in Giemsa smear of lesion aspiration, biopsy, or smear, and speciation by PCR were randomized in a 2:1 ratio to receive miltefosine orally for 28 days or meglumine (Glucantime) intravenously, or if poor IV access, intramuscularly for 20 days.

Meglumine was administered at 20 mg Sb^V/kg/day up to a maximum daily dose of 1,215 mg. Miltefosine target dose was 2.5 mg/kg/day.

Table 64: Miltefosine Dose - Studies Z020a and Z020b

Body weight	Daily miltefosine dose
9-14 kg	30 mg (2.14-3.3 mg/kg)
15-29 kg	50 mg (1.72-3.3 mg/kg)
30-45 kg	100 mg (2.2-3.3 mg/kg)
> 46 kg	150 mg

Subjects with AST or ALT or alkaline phosphatase > 3 x ULN, total bilirubin > 2 x ULN, serum BUN or Cr > 1.5 times ULN, evidence of serious underlying systemic disease, receiving beta-blocker therapy or anti-arrhythmic drugs, with positive HIV serology, unable to swallow capsules, with severe protein or calorie malnutrition or who have any

[23] Chrusciak-Talhari A 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. 2011;84: 255–260

[24] Machado RR et al. Miltefosine in the treatment of cutaneous leishmaniasis caused by *L. braziliensis* in Brazil: a randomized controlled trial. PLoS Negl Trop Dis 2010;4:e912

de-compensated or non-controlled condition such as active TB, malignancy, serious malaria, HIV infection, Hansen's disease, systemic fungal infection, hepatitis B or C, were excluded. Women of childbearing potential who did not agree to use effective contraception during the treatment period and for 2 additional months after the end of the study and pregnant or breast feeding women were also excluded. Subjects who had received prior *Leishmania* therapy were excluded.

Lesions were evaluated clinically and by photography once weekly during therapy, and at 2 weeks, 1 month, 2 months, 4 months and 6 months after therapy. *Leishmania* stain and culture were obtained at screening and if the lesion had not healed at any of the follow up visits (2 weeks, 1 month, 2 months, 4 months and 6 months after EOT). ECG, hematology and chemistry labs were obtained at baseline, weekly during therapy and at 2 weeks and one month post therapy. Vital signs were obtained at each visit.

The protocol-specified primary endpoint was definite cure, defined as complete re-epithelialization of all ulcers at the 6 months follow up visit. The secondary endpoints were apparent cure and partial cure. Apparent cure was defined as complete re-epithelialization of all ulcers by 2 months after EOT. Partial cure was defined as incomplete re-epithelialization of one or more lesions and an increase of no more than 50% in previously treated lesions and absence of parasites and no new lesions at 2 months after EOT.

For the study report, the endpoints were re-defined. The primary endpoint was Definite Cure, defined as complete re-epithelialization all initial ulcers at 2 months and at 6 months and no new lesions and no residual lesions with parasites or $\geq$ 50% enlargement of a lesion prior to 6 months. If data were missing at 2 months but the 6 months data met the criteria of cure, then the subject was classified as being cured. Subjects lost to follow up for whom a confirmation of cure could not be determined were considered failures. Apparent cure was defined as complete re-epithelialization of all ulcers at 2 months and was a secondary endpoint. Failure was defined as lack of meeting the criteria for cure.

The ITT and safety populations included all subjects who were exposed to at least one dose of medication. The protocol did not define a PP population. Descriptive statistics were used. There was no pre-specified statistical hypothesis. The protocol did not specify the assumptions/estimates of the cure rates used to calculate sample size.

Reviewer's Comments
The endpoints for this study and studies Soto and 3168 are slightly different. In Study 3168, apparent and partial cures were defined at 2 weeks after EOT, and a failure at that time was carried forward. In study Soto, failure at 3 months was carried forward. In this study, apparent and partial cures were defined at 2 months after EOT, and although failure at 2 months was classified as failure at 6 months, subjects with missing data at 2 months but complete healing at 6 months were not classified as failure.

The study report and the study protocol both state that this study was descriptive and there were no pre-specified estimates for cure rates that were used to calculate sample

size. However, the publication states that sample size was calculated based an assumed cure rate of 50% for meglumine, 80% for miltefosine, an expected 30% difference between the treatment arms, and power of 80%.

Protocol Amendments and Violations

There were two protocol amendments, both pertaining to exploratory analyses.

One subject in the miltefosine arm was removed from the protocol due to malaria infection and was classified as failure. Another miltefosine subject received rescue therapy for unclear reasons and was also classified a failure.

Disposition

90 subjects were randomized, 60 to receive miltefosine and 30 to receive meglumine. Subjects < 12 years of age were classified as pediatric.

Table 65: Subject Disposition - Study Z020a

	Miltefosine			Meglumine		
	Adult ≥ 12 yrs	Pediatric < 12 yrs	Total	Adult ≥ 12 yrs	Pediatric < 12 yrs	Total
Randomized	40	20	60	20	10	30
Early Withdrawal	4	6	10 (16.7%)	3	4	7 (23.3%)

Reviewer's Comments
The above table was derived from the submitted disposition dataset, which did not provide time of withdrawal (during therapy or during follow up period) or reasons for early withdrawal.

A higher percentage of subjects withdrew in the meglumine arm.

Demography and Other Subject Characteristics

Table 66: Subject Characteristics - Study Z020a

	Miltefosine			Meglumine		
	Adult N = 40	Ped N = 20*	Total N = 60	Adult N = 20	Ped N = 10	Total N = 30
Male	32 (80.0%)	13 (68.4%)	45 (76.3%)	17 (85.0%)	6 (60.0%)	23 (76.7%)
Female	8 (20.0%)	6 (31.6%)	14 (23.7%)	3 (15.0%)	4 (40.0%)	7 (23.3%)
Mean Age –yrs (SD)	30.9 (13.5)	7.95 (2.5)	23.2 (15.5)	30.6 (14.6)	7.2 (2.4)	22.8 (16.4)
Age 12-17 years	8 (20.0%)	-	8 (13.3%)	2 (10.0%)	-	2 (6.7%)
Age ≥ 18	32 (80.0%)	-	32 (53.3%)	18 (90.0%)	-	18 (60.0%)
Mean Weight- kg (SD)	66.3	28.5	53.7	64.8	26.4	52.0

	(13.5)	(10.5)	(21.9)	(11.3)	(11.1)	(21.5)
Subjects with one lesion	19 (47.5%)	13 (65.0%)	32 (53.3%)	8 (40%)	7 (70.0%)	15 (50%)
Subjects with two lesions	4 (10.0%)	5 (25.0%)	9 (15%)	4 (20.0%)	2 (20.0%)	6 (20%)
Subjects with 3 lesions	8 (20.0%)	1 (5.0%)	9 (15%)	3 (15.0%)	1 (10.0%)	4 (13.3%)
Subjects with 4 lesions	7 (17.5%)	1 (5.0%)	8 (13.3%)	3 (15.0%)	0	3 (10%)
Subjects with 5 lesions	2 (5.0%)	0	2 (3.3%)	2 (10.0%)	0	2 (6.7%)
Mean N of lesions per subject (SD)	2.2 (1.3)	1.5 (0.8)	1.98 (1.24)	2.3 (1.4)	1.4 (0.7)	2.0 (1.3)
Mean Ulcer area per lesion (SD)	191 (200)	157 (130)	182 (185)	242 (236)	248 (234)	243 (234)
Mean Ulcer area per subject (SD) – mm^2	425 (364)	235 (162)	362 (322)	569 (425)	347 (235)	495 (384)
Mean Induration area per lesion (SD)- mm^2	342 (422)	211 (107)	309 (373)	294 (259)	368 (298)	311 (268)
Mean Induration area per subject (SD)- mm^2	760 (655)	317 (163)	613 (580)	692 (456)	515 (343)	633 (424)

* The gender of one subject was not recorded

Reviewer's Comments
There were no significant differences at baseline between the adult subjects in each arm or between the pediatric subjects in each arm.

Microscopy of lesion scrapings was positive at screening in all subjects except one adult subject who received miltefosine in whom microscopy was not performed but culture grew *L. guyanensis*. Species identification was by PCR. Overall, 86/90 isolates (95.6%) were identified as *L. guyanensis*.

Table 67: Parasitology – Study Z020a

	Miltefosine N = 60	Meglumine N = 30
L. guyanensis	58 (96.7%)	28 (93.3%)
L. braziliensis	1 (3.3%)	2 (6.7%)
L. lainsoni	1 (3.3%)	0

Efficacy Evaluation

Primary Endpoint

The primary endpoint was Definite Cure at 6 months.

Table 68: Definite Cure – ITT - Study Z020a

	Miltefosine			Meglumine		
	≥ 12 yrs N = 40	< 12 yrs N = 20	Total N = 60	≥ 12 yrs N = 20	< 12 yrs N = 10	Total N = 30
Definite Cure	27 (67.5%)	14 (70.0%)	41 (68.3%)	12 (60.0%)	6 (60.0%)	18 (60.0%)

Failure	13 (32.5%)	6 (30.0%)	19 (31.7%)	8 (40.0%)	4 (40.0%)	12 (40.0%)

Reviewer's Comments
Definite cure was similar in the two study arms in the overall population and in the adult and pediatric populations. Cure was also similar in adolescent subjects.
In subjects ≥12 years of age, meglumine – miltefosine difference was -7.5%, 95% CI (-34.6, 17.9).

Table 69: Definite Cure by Age – ITT – Study Z020a

Age (Years)	*Miltefosine N = 60*	*Meglumine N = 30*	*Difference MLT-MEG*
2-11	*14/20 (70.0%)*	*6/10 (60.0%)*	*10.0%*
12-17	*6/8 (75.0%)*	*1/2 (50.0%)*	*25.0%*
≥ 18	*21/32 (65.6%)*	*11/18 (61.1%)*	*4.5%*
Total	*41/60 (68.3%)*	*18/30 (60.0%)*	*8.3%*

Definite cure was lower in females who received meglumine compared to females who received miltefosine or to males who received either treatment but the number of female subjects in the meglumine arm is small.

Table 70: Definite Cure by Gender – ITT - Study Z020a

	Miltefosine N = 60	*Meglumine N = 30*	*Difference MLT-MEG*
Male	*30/45 (66.7%)*	*16/23 (69.6%)*	*-2.9%*
Female	*11/14 (78.6%)*	*2/7 (28.6%)*	*50.0%*
Gender Not reported	*0/1*	*0*	*-*

The majority of subjects in each arm had L. guyanensis at baseline. The one miltefosine subject who had L. braziliensis was cured.

Table 71: Definite Cure by *Leishmania* Species – ITT- Study Z020a

	Miltefosine			*Meglumine*		
	≥ 12 years N = 40	*< 12 years N = 20*	*Total N = 60*	*≥ 12 years N = 20*	*< 12 years N = 10*	*Total N = 30*
L. guyanensis	*26/39 (66.7%)*	*13/19 (68.4%)*	*39/58 (67.2%)*	*12/19 (63.2%)*	*5/9 (55.6%)*	*17/28 (60.7%)*
L. braziliensis	*1/1 (100%)*	*0*	*1/1 (100%)*	*0/1 (100%)*	*1/1 (100%)*	*1/2 (50.0%)*
L. lainsoni	*0*	*1/1 (100%)*	*1/1 (100%)*	*0*	*0*	*0*

Mean miltefosine dose was higher in subjects who were cured compared to subjects who failed (mean dose 2.53 vs. 2.2 mg/kg/day). The mg/kg dose ranged between 1.4-3.4 mg/kg/day. Subjects who received less than 2 mg/kg per day had a lower cure rate.

Table 72: Mean Miltefosine Dose – Study Z020a

	Miltefosine Cured	*Miltefosine Failed*

Dose/kg/day	*≥ 12 years*	*< 12 years*	*Total*	*≥ 12 years*	*< 12 years*	*Total*
Mean Dose (SD)	*2.4 (0.35)*	*2.8 (0.49)*	*2.53 (0.44)*	*2.1 (0.4)*	*2.5 (0.3)*	*2.2 (0.4)*
Median Dose	*2.4*	*2.9*	*2.46*	*2.1*	*2.5*	*2.2*
Range	*1.7-3.1*	*1.7-3.4*	*1.7-3.4*	*1.4-2.7*	*2.1-2.9*	*1.4-2.9*

Table 73: Definite Cure by Miltefosine Dose (mg/kg/day) – Study Z020a

	Definite Cure		
Miltefosine mg/kg Dose	*≥ 12 years*	*< 12 years*	*Total*
< 2	*4/10 (40.0%)*	*1/1 (100%)*	*5/11 (45.5%)*
2-2.4	*12/15 (80.0%)*	*4/6 (66.7%)*	*16/21 (76.2%)*
2.5-2.9	*9/13 (69.2%)*	*4/8 (50.0%)*	*13/21 (61.9%)*
3-3.9	*2/2 (100%)*	*5/5 (100%)*	*7/7 (100.0%)*
Total	*27/40 (67.5%)*	*14/20 (70.0%)*	*41/60 (68.3%)*

Secondary Endpoints

Apparent cure at 2 months post therapy was similar between the treatment arms. A higher percentage of meglumine subjects experienced a relapse.

Table 74: Apparent Cure – ITT - Study Z020a

	Miltefosine			Meglumine		
	≥ 12 years N = 40	< 12 years N = 20	Total N = 60	≥12 years N = 20	< 12 years N = 10	Total N = 30
Apparent Cure	29 (72.5%)	11 (55.0%)	40 (66.7%)	14 (70.0%)	7 (70.0%)	21 (70.0%)
Relapse	2 (5.0%)	0	2 (3.3%)	3 (15.0%)	1 (10.0%)	4 (13.3%)

Safety Evaluation

Extent of Exposure

Three adult miltefosine subjects received less than the planned 28 days of treatment: one was lost to follow up on day 10, one was withdrawn on day 12 due to intercurrent malaria and exposure beyond day 14 was not recorded for the third subject. None of the meglumine subjects received less than 20 days.

The mean miltefosine dose was 2.42 mg/kg/day (SD 0.45). The median dose was 2.4 mg/kg/d and the range was 1.4-3.4 mg/kg/day. The mean and median dose in adults was 2.3 mg/kg/d (SD 0.39) and the range was 1.5-3.1 mg/kg/day.

Concomitant Medications

9 (30.0%) meglumine recipients received a concomitant medication, most commonly albendazole and secnidazole.

38 (63.3%) miltefosine recipients received a concomitant medication, most commonly albendazole, secnidazole, H2 blockers, antibiotics (amoxicillin, ciprofloxacin, TMP/SMZ), NSAIDs and metoclopramide.

Reviewer's Comments
The more frequent use of metoclopramide and H2 blockers may reflect the more frequent GI adverse events associated with miltefosine exposure.

Treatment Emergent Adverse Events

42/60 (70.0%) miltefosine subjects experienced at least one AE. AEs were reported by severity and no AE was classified as serious. No subject experienced a severe AE. No subject discontinued miltefosine due to an AE.

13/30 (43.3%) meglumine subjects experienced at least one AE. One subject experienced a severe AE (back pain). No subject discontinued meglumine due to an AE.

There were no deaths.

Table 75: Summary of Adverse Events – Study Z020a

	Miltefosine			Meglumine		
	≥ 12 years N = 40	< 12 years N = 20	Total N = 60	≥ 12 years N = 20	< 12 years N = 10	Total N = 30
Subjects with at least one AE	31 (77.5%)	11 (55.0%)	42 (70.0%)	10 (50.0%)	3 (30.0%)	13 (43.3%)

Table 76: Treatment Emergent Adverse Events – All subjects - Study Z020a

MedDRA v. 12.0 System Organ Class	Miltefosine N = 60	Meglumine N = 30
Gastrointestinal	38 (63.3%)	1 (3.3%)
Abdominal pain upper	4 (6.7%)	1 (3.3%)
Diarrhea	4 (6.7%)	0
Nausea	10 (16.7%)	0
Vomiting	30 (50.0%)	0
General Disorders	17 (28.3%)	3 (33.3%)
Edema	2 (3.3%)	0
Pain at Lesion site	3 (5.0%)	0
Pyrexia	11 (18.3%)	3 (10.0%)
Infections/Infestations	9 (15.0%)	2 (6.7%)
"Infection"	4 (6.7%)	0
Lymphangitis	7 (11.7%)	0
Musculoskeletal	2 (3.3%)	8 (26.7%)
Arthralgias	1 (1.7%)	8 (26.7%)
Back Pain	0	0
Nervous System	5 (8.3%)	0
Dizziness	3 (5.0%)	**0**
Headache	2 (3.3%)	
Renal and Urinary	2 (3.3%)	0

Dysuria Nephrolithiasis	1 (1.7%) 1 (1.7%)	**0**
Reproductive	4 (6.7%)	0
Testicular pain	4 (6.7%)	**0**
Respiratory	2 (3.3%)	0
Tonsillitis Flu syndrome	1 (1.7%) 0	**0**
Skin and Subcutaneous	6 (10.0%)	1 (3.3%)
Pruritus Urticaria	3 (5.0%) 3 (5.0%)	0 1 (3.3%)

Table 77: Treatment Emergent Adverse Events – Subjects ≥12 years of Age – Study Z020a

MedDRA v. 12.0 System Organ Class	Miltefosine N = 40	Meglumine N = 20
Gastrointestinal	26 (65.0%)	1 (5.0%)
Abdominal pain upper	4 (10.0%)	1 (5.0%)
Diarrhea	4 (10.0%)	0
Nausea	8 (20.0%)	0
Vomiting	16 (40.0%)	0
General Disorders	10 (25.0%)	3 (15.0%)
Edema	2 (5.0%)	0
Pain	2 (5.0%)	0
Pyrexia	6 (15.0%)	3 (15.0%)
Infections/Infestations	9 (22.5%)	1 (5.0%)
“Infection”	4 (10.0%)	1 (5.0%)
Lymphangitis	7 (17.5%)	0
Musculoskeletal	2 (5.0%)	7 (35.0%)
Arthralgias	1 (2.5%)	7 (35.0%)
Back Pain	1 (2.5%)	0
Nervous System	4 (10.0%)	0
Dizziness Headache	2 (5.0%) 2 (5.0%)	0
Renal and Urinary	2 (5.0%)	0
Dysuria Nephrolithiasis	1 (2.5%) 1 (2.5%)	0
Reproductive	4 (10.0%)	0
Testicular pain	4 (10.0%)	0
Respiratory	1 (2.5%)	0
Tonsillitis Flu syndrome	1 (2.5%) 0	0
Skin and Subcutaneous	3 (7.5%)	0
Pruritus Urticaria	0 3 (7.5%)	0

Reviewer's Comments
Within the miltefosine and meglumine groups, adverse events in adult and pediatric subjects were similar (data shown for all subjects and for adult subjects).

AEs occurring more frequently in miltefosine subjects included abdominal pain, nausea, vomiting, diarrhea, headache, dizziness, pyrexia, urticaria and pruritus. Infection at the lesion site with lymphangitis was also noted more frequently in miltefosine recipients and four cases (6.7% of all miltefosine subjects, 10% of adult subjects) of testicular pain were reported. Musculoskeletal AEs were more frequently noted in meglumine recipients.

The frequency of GI adverse events in miltefosine recipients was not dose dependent.

Table 78: GI Adverse Events in Subjects ≥ 12 years of Age by Miltefosine Dose – Study Z020a

	Miltefosine Dose mg/kg			
	1.4-2.2 N = 20	*2.3-<3 N = 18*	*≥ 3 N = 2*	*Total N = 40*
Diarrhea	*3 (15.0%)*	*1 (5.6%)*	*0*	*4 (10.0%)*
Nausea	*6 (30.0%)*	*2 (11.1%)*	*0*	*8 (20.0%)*
Vomiting	*5 (25.0%)*	*9 (50.0%)*	*2 (100.0%)*	*16 (40.0%)*

Renal Toxicity

At EOT, mean Cr increased from 0.7 to 1.0 in miltefosine subjects and from 0.7 to 0.8 in meglumine subjects.

A higher percentage of miltefosine subjects experienced Cr increase above baseline during therapy and post therapy. The increases occurred among adult and pediatric subjects. At or after Day 14, approximately 80% of miltefosine subjects ≥ 12 years of age experienced Grade 1 and 2 Cr increase above baseline. Approximately 20% of miltefosine subjects had Grade 2 elevations at EOT and at 1 month post therapy. However, of the 9 subjects with Cr increase CTCAE grade 2 and 3 at 1 month post therapy, 4 had persistent increases from EOT and 5 were new. This suggests that renal injury may occur after discontinuation of therapy, consistent with the long half-life of the drug. The highest absolute Cr value at EOT was 3.6, and the highest absolute Cr value at 1 month post therapy was 1.2. No subject discontinued the drug due to elevated Cr. Cr increase above baseline occurred at all miltefosine dose levels and was not dose dependent.

Table 79: Cr Change above baseline – Study Z020a

	Miltefosine			*Meglumine*		
Cr >baseline	*≥ 12y N = 40*	*< 12 y N = 20*	***Total N = 60***	*≥ 12 y N = 20*	*< 12 y N = 10*	***Total N = 30***
Day 7						
>1-<1.5x baseline	*19 (47.5%)*	*4 (20.0%)*	***23 (38.3%)***	*7 (35.0%)*	*1 (10.0%)*	***8 (26.7%)***
1.5-<3x baseline	*1 (2.5%)*	*3 (15.0%)*	***4 (6.7%)***	*0*	*1 (10.0%)*	***1 (3.3%)***
3-<6 baseline	*0*	*1 (5.0%)*	***1 (1.7%)***			

Day 14						
>1-<1.5x baseline	*27 (67.5%)*	*6 (30.0%)*	***33 (55.0%)***	*5 (25.0%)*	*0*	***5 (16.7%)***
1.5-<3x baseline	*4 (10.0%)*	*3 (15.0%)*	***7 (11.7%)***	*1 (5.0%)*	*1 (10.0%)*	***2 (6.7%)***
3-<6 baseline	*1 (2.5%)*	*0*	***1 (1.7%)***	*0*	*0*	***0***
Day 21 (Meglumine EOT)						
>1-<1.5x baseline	*24 (60.0%)*	*10 (50.0%)*	***34 (56.7%)***	*10 (50.0%)*	*2 (20.0%)*	***12 (40.0%)***
1.5-<3x baseline	*7 (17.5%)*	*4 (20.0%)*	***11 (18.3%)***	*0*	*1 (10.0%)*	***1 (3.3%)***
3-<6 baseline	*1 (2.5%)*	*0*	***1 (1.7%)***	*0*	*0*	***0***
Day 28 (Miltefosine EOT)						
>1-<1.5x baseline	*24 (60.0%)*	*2 (10.0%)*	***26 (43.3%)***	-	-	-
1.5-<3x baseline	*6 (15.0%)*	*4 (20.0%)*	***10 (16.7%)***	-	-	-
3-<6 baseline	*2 (5.0%)*	*1 (5.0%)*	***3 (5.0%)***	-	-	-
1 Month Post Therapy						
>1-<1.5x baseline	*22 (55.0)*	*5 (25.0%)*	***27 (45.0%)***	*13 (65.0%)*	*4 (40.0%)*	***17 (56.7%)***
1.5-<3x baseline	*4 (10.0%)*	*4 (20.0%)*	***8 (13.3%)***	*1 (5.0%)*	*0*	***1 (3.3%)***
3-<6 baseline	*1 (2.5%)*	*0*	***1 (1.7%)***	*0*	*0*	***0***

Table 80: Mean Cr Change – Study Z020a

	Miltefosine			*Meglumine*		
Mean Cr	*≥ 12 yrs N = 40*	*< 12 yrs N = 20*	***Total N = 60***	*≥ 12 yrs N = 20*	*< 12 yrs N = 10*	***Total N = 30***
Baseline	*0.8 (0.2) 0.3-1.4*	*0.5 (0.2) 0.3-1.0*	***0.7 (0.3) 0.3-1.4***	*0.8 (0.1) 0.6-1.1*	*0.4 (0.1) 0.3-0.5*	***0.7 (0.3) 0.3-1.1***
Day 7	*0.9 (0.2) 0.4-1.5*	*0.5 (0.2) 0.2-0.8*	***0.8 (0.3) 0.2-1.5***	*0.9 (0.2) 0.6-1.2*	*0.4 (0.1) 0.2-0.7*	***0.7 (0.3) 0.2-1.2***
Day 14	*1.0 (0.2) 0.4-1.6*	*0.5 (0.2) 0.2-1*	***0.9 (0.3) 0.2-1.6***	*0.9 (0.2) 0.5-1.2*	*0.4 (0.2) 0.2-0.7*	***0.7 (0.3) 0.2-1.2***
Day 21	*1.1 (0.4) 0.4-2.6*	*0.6 (0.2) 0.2-0.9*	***0.9 (0.4) 0.2-2.6***	*0.9 (0.2) 0.5-1.3*	*0.5 (0.1) 0.3-0.7*	***0.8 (0.3) 0.3-1.3***
Day 28	*1.2 (0.5) 0.5-3.6*	*0.5 (0.2) 0.2-0.9*	***1.0 (0.5) 0.2-3.6***	-	-	-
1 month post RX	*1.0 (0.2) 0.6-1.4*	*0.5 (0.1) 0.3-0.7*	***0.8 (0.3) 0.3-1.4***	*1.0 (0.2) 0.7-1.2*	*0.4 (0.2) 0.1-0.8*	***0.8 (0.3) 0.1-1.2***

Table 81: Effect of Dose on Cr – Adults – Z020a

	Miltefosine Dose mg/kg			
Cr EOT	*1.4-2.2 N =20*	*2.3-<3 N = 18*	*≥ 3 N = 2*	*Total N = 40*
>1-<1.5x baseline	*12 (60.0%)*	*12 (66.7%)*	*0*	*24 (60.0%)*
1.5-<3x baseline	*3 (15.0%)*	*3 (16.7%)*	*0*	*6 (17.5%)*
3-<6 baseline	*1 (5.0%)*	*1 (5.6%)*	*0*	*2 (5.0%)*

Hepatic Toxicity

ULN values were not provided in the lab dataset, but the dataset flags ALT, AST and AP values < 65, 37 and 170 respectively as within normal limits. Using these values as the ULN, a higher percentage of miltefosine subjects had ALT elevations, while a higher percentage of meglumine subjects had AST and AP elevations. The elevations were mostly CTCAE grade 1.

Table 82: Changes in Transaminases at EOT – Study Z020a

	Miltefosine			*Meglumine*		
EOT	*≥ 12 yrs N = 40*	*< 12 yrs N = 20*	***Total N = 60***	*≥ 12 yrs N = 20*	*< 12 yrs N = 10*	***Total N = 30***
ALT >1-3x ULN	*8 (20.0%)*	*2 (10.0%)*	***10 (11.1%)***	*1 (5.0%)*	*0*	***1 (3.3%)***
ALT >3-5x ULN			***0***	*1 (5.0%)*		***1 (3.3%)***
AST >1-3x ULN	*5 (12.5%)*	*5 (25.0%)*	***10 (16.7%)***	*5 (25.0%)*	*4 (40.0%)*	***9 (30.0%)***
AST >3-5 x ULN	*0*	*1 (5.0%)*	***1 (1.7%)***	*1 (5.0%)*	*0*	***1 (3.3%)***
AP > 1-2.5x ULN	*5 (12.5%)*	*15 (75.0%)*	***20 (33.3%)***	*3 (15.0%)*	*9 (90.0%)*	***12 (40.0%)***
AP >2.5-5x ULN	*0*	*0*	***0***	*0*	*0*	***0***
Bilirubin 1-1.5x ULN	*0*	*0*	***0***	*0*	*0*	***0***

Hematologic Toxicity

Lower levels of normal were not provided in the dataset. There were no significant changes in hemoglobin or WBC compared to baseline. One meglumine subject had a platelet count of 40,000 at EOT. One miltefosine subject had a platelet count of 138 at EOT which was unchanged compared to baseline.

Study Conclusions

This study did not have a pre-specified statistical hypothesis, and did not provide reasons for early withdrawals. Miltefosine and meglumine resulted in similar cure rates at 2 months and at 6 months in subjects with CL due to *L. guyanensis*. Cure rates were not affected by age or gender, but subjects who failed miltefosine received a lower mean dose compared to subjects who were cured (2.2 mg/kg/day vs. 2.46 mg/kg/day) and miltefosine doses < 2-2.3 mg/kg/d were associated with lower cure rate in subjects at least 12 years of age.

Adverse reactions noted occurring more frequently in miltefosine recipients included abdominal pain, nausea, vomiting, diarrhea, dizziness, headache, pruritus, pyrexia and infection and pain at lesion site. 10% of adult miltefosine subjects complained of testicular pain. Musculoskeletal symptoms occurred more frequently in meglumine recipients.

A higher percentage of miltefosine subjects had Cr elevations above baseline during and at the end of therapy and at one month follow up. In some subjects, Cr increased after the end of therapy. This late injury is consistent with the long half-life of the drug. Cr elevations occurred at all miltefosine doses and were not dose related. Liver enzyme elevations were mild and reversible. There were no significant changes in hematologic parameters.

Study Z020b

This study was conducted between July 7, 2007 and April 22, 2009 at a single center at Corte de Pedra, Federal University of Bahia, Brazil.

Study Design

This study protocol was the same as Z020a with the exception that diagnosis was initially made either by visualization of the amastigote in an aspirate or biopsy of the skin lesion or by intradermal skin testing (Montenegro test).

Disposition

Table 83: Subject Disposition – Study Z020b

	Miltefosine			Meglumine		
	Adult ≥ 12 years	Pediatric < 12 years	Total	Adult ≥ 12 years	Pediatric < 12 years	Total
Randomized	40	20	60	20	10	30
Early Withdrawal	4 (10.0%)	7 (35.0%)	11 (18.3%)	9 (45.0%)	1 (10.0%)	10 (33.3%)

Reviewer's Comments

The disposition dataset did not indicate the reason(s) for early withdrawal or whether these withdrawals occurred during the treatment period or during the follow up period. A higher percentage of meglumine subjects were withdrawn early.

There is also a discrepancy between the study report and the published article. The article states that 87 subjects were followed for the entire 6 months after therapy, whereas the study report states that 8 subjects (3 miltefosine and 5 meglumine) left the study early (i.e., 82 subjects were followed for the entire 6 months after therapy).

Demography and Other Subject Characteristics

Table 84: Subject Characteristics – Study Z020b

	Miltefosine			Meglumine		
	≥ 12 years N = 40	< 12 years N = 20*	Total N = 60	≥ 12 years N = 20	< 12 years N = 10	Total N = 30
Male	31 (77.5%)	13 (68.4%)	44 (66.7%)	11 (55.0%)	5 (50.0%)	16 (53.3%)
Female	9 (22.5%)	6 (31.6%)	15 (25.0%)	9 (45.0%)	5 (50.0%)	14 (46.7%)
Mean Age, yrs (SD)	29.4 (14.2)	7.7 (1.98)	22.1 (14.5)	29.5 (13.4)	9.0 (1.49)	22.7 (14.7)
12-17 years	6 (15.0%)	-	6 (10.0%)	4 (20.0%)		4 (13.3%)
≥ 18 years	34 (85.0%)		34 (56.7%)	16 (80.0%)		16 (53.3%)
Mean Weight, kg (SD)	56.3 (10.2)	23.4 (4.4)	45.3 (17.9)	60.6 (11.8)	27.8 (8.2)	49.6 (18.9)
Subjects with one lesion	29 (72.5%)	12 (60.0%)	41 (68.3%)	19 (95.0%)	8 (80.0%)	27 (90.0%)
Subjects with two lesions	7 (17.5%)	7 (35.0%)	14 (23.3%)	0	0	0
Subjects with 3 lesions	4 (10.0%)	0	4 (6.7%)	1 (5.0%)	1 (10.0%)	2 (6.7%)

Subjects with 4 lesions	0	1 (5.0%)	1 (1.7%)	0	1 (10.0%)	1 (3.3%)
Mean N of lesions per subject (SD)	1.4 (0.7)	1.5 (0.8)	1.4 (0.7)	1.1 (0.5)	1.5 (1.0)	1.2 (0.7)
Mean ulcer area per lesion (SD)	414 (349)	219 (191)	345 (316)	432 (309)	188 (171)	333 (286)
Mean ulcer area per subject (SD)	570 (337)	328 (229)	489 (324)	476 (291)	382 (160)	411 (268)
Mean induration area per lesion	254 (218)	159 (148)	220 (201)	220 (151)	102 (73.8)	172 (138)
Mean induration area per subject	349 (229)	239 (213)	312 (228)	243 (143)	153 (64.6)	213 (128)

*The gender of one miltefosine subject < 12 years of age was not recorded.

Reviewer's Comments
A higher percentage of miltefosine subjects had more than one lesion, and the lesions were on average slightly larger compared to meglumine subjects.

The results of the Montenegro skin test were not provided in the CRF but the PI certified that all subjects had a positive test. 89/90 subjects has an organism identified by PCR as *L. braziliensis*. The one adult subject who did not have an organism identified by culture had positive microscopy at baseline.

Table 85: Parasitology - Study Z020b

	Miltefosine N = 60	Meglumine N = 30
L. braziliensis	59 (98.3%)	30 (100%)

Reviewer's Comments
The published article states that L. braziliensis was identified by culture in 52/90 patients but states that neither PCR nor culture identified Leishmania in 26 subjects.

Efficacy Results

Primary Endpoint

The primary endpoint was Definite Cure at 6 months.

Table 86: Definite Cure – ITT - Study Z020b

	Miltefosine			Meglumine		
	≥ 12 yrs N = 40	< 12 yrs N = 20	Total N = 60	≥ 12 yrs N = 20	< 12 yrs N = 10	Total N = 30
Definite Cure	34 (85.0%)	13 (65.0%)	47 (78.3%)	9 (45.0%)	9 (90.0%)	18 (60.0%)
Failure	6 (15.0%)	7 (35.0%)	13 (21.7%)	11 (55.0%)	1 (10.0%)	12 (40.0%)

Reviewer's Comments
Miltefosine cure rate was higher in subjects at least 12 years of age, whereas meglumine cure rate was higher in the 2-11 years age group. In the adult subjects, meglumine –

miltefosine cure difference was -40% (-63.5%, -8.6%). In the overall enrolled population, the 95% CI for the difference is (-30.1, 12.5%) which does not indicate that miltefosine is superior to meglumine.

Cure was not affected by gender.

The mean miltefosine dose in subjects who failed and subjects who were cured was similar. Miltefosine dose ranged between 1.7-3.3 mg/kg/day. Cure was not related to the mg/kg dose, but the number of subjects who received < 2 mg/kg was small. Cure was affected by duration of therapy; 6/7 subjects who received 14 days of miltefosine failed (3 adults and 3 pediatric).

Table 87: Definite Cure by Age – Z020b

Age (Years)	*Miltefosine N = 60*	*Meglumine N = 30*	*Difference MLT-MEG*
2-11	*13/20 (65.0%)*	*9/10 (90.0%)*	*-25.0%*
12-17	*6/6 (100%)*	*2/4 (50.0%)*	*50.0%*
≥ 18	*28/34 (82.4%)*	*7/16 (43.8%)*	*38.6%*
Total	*47 (78.3%)*	*18 (60.0%)*	*18.3%*

Table 88: Definite Cure by Gender – Z020b

	Miltefosine N = 60	*Meglumine N = 30*	*Difference MLT-MEG*
Male	*35/44 (79.5%)*	*10/16 (62.5%)*	*27.0%*
Female	*11/15 (73.3%)*	*8/14 (57.1%)*	*16.2%*
Not reported	*1/1 (100%)*	-	-
Total	*47 (78.3%)*	*18 (60.0%)*	*18.3%*

Table 89: Mean Miltefosine Dose – Study Z020b

	Miltefosine Cured		*Miltefosine Failed*	
Dose mg/kg/d	*≥ 12 yrs*	*< 12 yrs*	*≥ 12 yrs*	*< 12 yrs*
Mean Dose (SD)	*2.6 (0.3)*	*2.2 (0.3)*	*2.6 (0.2)*	*2.5 (0.4)*
Median (Range)	*0.3 (1.9-3.3)*	*2.2 (1.7-2.7)*	*2.6 (2.3-2.9)*	*2.3 (2.1-3.1)*

Table 90: Effect of Miltefosine Dose on Cure – Z020b

	Definite Cure		
Miltefosine mg/kg	*≥ 12 years*	*< 12 years*	*Total*
< 2	*2/2 (100%)*	*2/2 (100%)*	*4/4 (100%)*
2-2.4	*7/9 (77.7%)*	*8/13 (61.5%)*	*15/22 (68.2)*
2.5-2.9	*20/24 (83.3%)*	*2/4 (50.0%)*	*22/28 (78.6%)*
3-3.9	*5/5 (100%)*	*1/1 (100.0%)*	*6/6 (100%)*
Total	*34/40 (85.0%)*	*13/20 (65.0%)*	*47/60 (78.3%)*

The prevalent species in this study was L. braziliensis, consistent with the epidemiology of CL in this region of Brazil. The cure rate at 6 months in this study is comparable to the cure rate in Study Soto in Bolivia and higher than the cure rate in Guatemala in Study 3168. Some of the difference may be explained by the later timing of initial cure in this

study and Study Soto compared to Study 3168, but geographic variation in the susceptibility of L. braziliensis to miltefosine cannot be ruled out.

The failure rate of meglumine is comparable to what is reported in the literature. A study from Brazil[25] reported meglumine failure rates at 6 months of 73.7% for L. guyanensis and 49.2% for L. braziliensis. In Studies Z020a and b, the failure rate of L. guyanensis treated with meglumine was lower (39.3%), while the failure rate of L. braziliensis was comparable (40%).

Secondary Endpoints

Table 91: Apparent Cure – Study Z020b

	Miltefosine			Meglumine		
	≥ 12 yrs N = 40	< 12 yrs N = 20	Total N = 60	≥ 12 yrs N = 20	< 12 yrs N = 10	Total N = 30
Apparent Cure	35	16	51 (85.0%)	13	10	23 (76.6%)
Initial Failure	4	4	8 (13.3%)	6	0	6 (20.0%)
Missing Data	1	0	1 (1.7%)	1	0	1 (3.3%)

Safety Evaluation

Extent of Exposure

Seven (7 subjects) in the miltefosine arm received 14 days (2 pediatric subjects and 5 adults). Overall, the mean miltefosine dose was 2.5 mg/kg/day (SD 0.3) and the median dose was 2.5 mg/kg/day (range 2.1-3.1). The mean dose was 2.6 mg/kg/d (SD 0.33) in adults and 2.27 mg/kg/d (SD 0.34) in pediatric subjects. The mean duration of drug exposure was 19.5 days and the median 20 days.

Four adults in the meglumine group received 2 weeks and one subject received one week.

Concomitant Medications

All 30 meglumine subjects and all 60 miltefosine subjects received at least one concomitant medication, most commonly albendazole, acetaminophen or NSAIDs, and cephalexin or amoxicillin.

Treatment Emergent Adverse Events

All subjects in both arms experienced at least one adverse event. There were no deaths. AEs were classified by severity, not seriousness. One miltefosine subject and 2 meglumine subjects had AEs categorized as severe (limb fracture, and urticaria and

[25] Romero G, De Farias Guerra M, et al. Comparison of cutaneous leishmaniasis due to *L. braziliensis* and *L. guyanensis* in Brazil. Therapeutic response to meglumine antimoniate. Am J Trop Med Hyg 2001;65:456-465

syncope respectively). The study report and dataset indicate that no AEs led to drug discontinuation.

Table 92: Treatment Emergent AE – All Subjects – Study Z020b

MedDRA v. 12.0 System Organ Class	Miltefosine N = 60	Meglumine N = 30
Blood/Lymphatics	6 (10.0%)	3 (10.0%)
Anemia	1 (1.7%)	0
Lymphadenopathy	5 (8.3%)	3 (10.0%)
Ear and Labyrinth	2 (3.3%)	0
Ear Pain	2 (3.3%)	0
Eye Disorders	4 (6.7%)	1 (3.3%)
Conjunctiva irritation	2 (3.3%)	0
Eye irritation	1 (1.7%)	0
Hordeolum	2 (3.3%)	1 (3.3%)
Gastrointestinal	50 (83.3%)	12 (40.0%)
Abdominal pain	15 (25.0%)	4 (13.3%)
Diarrhea	9 (15.0%)	2 (6.7%)
Dyspepsia	9 (15.0%)	3 (10.0%)
Flatulence	2 (3.3%)	0
Nausea	28 (46.7%)	3 (10.0%)
Toothache	3 (5.0%)	0
Vomiting	29 (48.3%)	2 (6.7%)
General/Admin Site	34 (56.7%)	20 (66.7%)
Application Site Pain	0	1 (3.3%)
Asthenia	7 (11.7%)	4 (13.3%)
Chills	0	1 (3.3%)
Pain at Lesion Site	14 (23.3%)	5 (16.7%)
Pyrexia	19 (31.7%)	15 (50.0%)
Vestibulitis	2 (3.3%)	1 (3.3%)
Infections/Infestations	14 (23.3%)	10 (33.3%)
Ecthyma	5 (8.3%)	6 (20.0%)
Parasitic	0	1 (3.3%)
Dermatophytosis	0	1 (3.3%)
Lesion infection	6 (10.0%)	1 (3.3%)
Varicella	3 (5.0%)	0
Injury	22 (36.6%)	10 (33.3%)
Excoriation in scar	3 (5.0%)	2 (6.7%)
Injury	16 (26.7%)	8 (26.7%)
Fracture	0	1 (3.3%)
Fall	1 (1.7%)	0
Thermal burn	1 (1.7%)	0
Metabolism	8 (13.3%)	4 (13.3%)
Decreased Appetite	8 (13.3%)	4 (13.3%)
Musculoskeletal	12 (20.0%)	11 (36.6%)
Arthralgia	1 (1.7%)	11 (36.6%)

Myalgia	1 (1.7%)	5 (16.7%)
Back Pain	4 (6.7%)	1 (3.3%)
Neck Pain	2 (3.3%)	0
Tendonitis	1 (1.7%)	0
Muscle weakness	1 (1.7%)	0
Nervous System	41 (68.3%)	21 (70.0%)
Dizziness	13 (21.7%)	5 (16.7%)
Headache	34 (56.7%)	20 (66.7%)
Paresthesia	2(3.3%)	1 (3.3%)
Syncope	2 (3.3%)	1 (3.3%)
Amnesia	1 (1.7%)	0
Psychiatric	1 (1.7%)	0
Somnolence	1 (1.7%)	0
Renal/Reproductive	1 (1.7%)	1 (3.3%)
Dysuria	1 (1.7%)	1 (3.3%)
Respiratory/Thoracic	23 (38.3%)	14 (46.7%)
Bronchitis	0	1 (3.3%)
Bronchospasm	1 (1.7%)	1 (3.3%)
Influenza	9 (15.0%)	9 (30.0%)
Cough	11 (18.3%)	3 (10.0%)
URI	2 (3.3%)	0
Pharyngitis	3 (5.0%)	1 (3.3%)
Tonsillitis	3 (5.0%)	0
Skin/Subcutaneous	15 (25.0%)	10 (33.3%)
Acne	2 (3.3%)	0
Angioedema	0	1 (3.3%)
Pruritus	7 (11.7%)	2 (6.7%)
Pyoderma	1 (1.7%)	3 (10.0%)
Rash	3 (5.0%)	3 (10.0%)
Urticaria	1 (1.7%)	1 (3.3%)
Vascular Disorders	3 (5.0%)	1 (3.3%)
Hypotension	0	1 (3.3%)
Epistaxis	3 (5.0%)	0

Table 93: Treatment Emergent AE – Subjects ≥12 years of Age – Study Z020b

MedDRA v. 12.0 System Organ Class	Miltefosine N = 40	Meglumine N = 20
Blood/Lymphatics	5 (12.5%)	2 (10.0%)
Anemia	1 (2.5%)	0
Lymphadenopathy	4 (10.0%)	2 (10.0%)
Ear and Labyrinth	1 (2.5%)	0
Vestibulitis	1 (2.5%)	0
Eye Disorders	2 (5.0%)	1 (5.0%)
Eye irritation	1 (2.5%)	0
Hordeolum	1 (2.5%)	1 (5.0%)
Gastrointestinal	34 (85.0%)	8 (40.0%)

Abdominal pain	8 (20.0%)	3 (15.0%)
Diarrhea	8 (20.0%)	2 (10.0%)
Dyspepsia	7 (17.5%)	2 (10.0%)
Flatulence	1 (2.5%)	0
Nausea	23 (57.5%)	3 (15.0%)
Toothache	2 (5.0%)	0
Vomiting	18 (45.0%)	0
General/Admin Site	27 (67.5%)	13 (65.0%)
Asthenia	7 (17.5%)	3 (15.0%)
Chills	0	1 (5.0%)
Pain	14 (35.0%)	5 (25.0%)
Pyrexia	14 (35.0%)	8 (40.0%)
Infections/Infestations	7 (17.5%)	4 (20.0%)
Ecthyma	4 (10.0%)	1 (5.0%)
Dermatophytosis	0	1 (5.0%)
Lesion infection	3 (7.5%)	2 (10.0%)
Injury	14 (35.0%)	4 (20.0%)
Excoriation in scar	2 (5.0%)	0
Injury	10 (25.0%)	2 (10.0%)
Fracture	0	1 (5.0%)
Fall	1 (2.5%)	0
Thermal burn	1 (2.5%)	1 (5.0%)
Metabolism	6 (15.0%)	3 (15.0%)
Decreased Appetite	6 (15.0%)	3 (15.0%)
Musculoskeletal	12 (30.0%)	10 (50.0%)
Arthralgia	4 (10.0%)	10 (50.0%)
Myalgia	1 (2.5%)	5 (25.0%)
Back Pain	4 (10.0%)	0
Neck Pain	2 (5.0%)	0
Tendonitis	1 (2.5%)	0
Muscle weakness	1 (2.5%)	0
Nervous System	31 (77.5%)	14 (70.0%)
Dizziness	12 (30.0%)	4 (20.0%)
Headache	25 (62.5%)	13 (65.0%)
Paresthesia	2 (5.0%)	1 (5.0%)
Syncope	1 (2.5%)	1 (5.0%)
Amnesia	1 (2.5%)	0
Psychiatric	1 (2.5%)	0
Somnolence	1 (2.5%)	0
Renal/Reproductive	1 (2.5%)	0
Dysuria	1 (2.5%)	0
Respiratory/Thoracic	11 (27.5%)	9 (45.0%)
Bronchitis	0	1 (5.0%)
Influenza	3 (7.5%)	5 (25.0%)
Cough	3 (7.5%)	3 (15.0%)

URI	1 (2.5%)	0
Pharyngitis	3 (7.5%)	0
Tonsillitis	2 (5.0%)	0
Skin/Subcutaneous	12 (30.0%)	5 (25.0%)
Acne	2 (5.0%)	0
Angioedema	0	1 (5.0%)
Pruritus	6 (15.0%)	0
Pyoderma	0	1 (5.0%)
Rash	3 (7.5%)	2 (10.0%)
Urticaria	1 (2.5%)	1 (5.0%)
Vascular Disorders	2 (5.0%)	1 (5.0%)
Hypotension	0	1 (5.0%)
Epistaxis	2 (5.0%)	0

Reviewer's Comments
No subjects were reported as having discontinued the drugs due to AE although 7 miltefosine subjects and 3 meglumine subjects were reported as not having received the full treatment course. The reasons for discontinuation of treatment in these subjects were not reported.

AEs noted more frequently in miltefosine recipients included abdominal pain, nausea, vomiting, diarrhea, dizziness, pruritus, decreased appetite, lesion pain and lesion infection with regional lymphadenopathy. AEs noted more frequently in meglumine recipients were musculoskeletal. Within each study arm, the AEs noted were similar in adult and pediatric subjects.

GI adverse events were noted at all miltefosine doses and were not dose dependent.

Table 94: GI AE in Adult Subjects – Study Z020b

	Miltefosine Dose mg/kg			
	1.4-2.2 N = 6	*2.3-<3 N = 29*	*≥ 3 N = 5*	*Total N = 40*
Diarrhea	*2 (33.3%)*	*6 (20.7%)*	*0*	*8 (20.0%)*
Nausea	*5 (83.3%)*	*15 (51.7%)*	*3 (60.0%)*	*23 (57.5%)*
Vomiting	*2 (33.3%)*	*15 (51.7%)*	*1 (20.0%)*	*18 (45.0%)*

Renal Toxicity

A similar percentage of miltefosine and meglumine subjects had Cr elevations 1-1.5x above baseline (CTCAE grade 1) during and post therapy, but a higher percentage of miltefosine subjects had elevations 1.5-3x above baseline (CTCAE grade 2). However, only one subject had an absolute Cr value of 2, and all the other values were ≤ 1.5. Cr increases were noted at all miltefosine dose levels and were not dose dependent. In

contrast to the other CL studies, mean Cr in miltefosine subjects did not change during or after therapy.

Table 95: Cr Changes Above Baseline – Study Z020b

	Miltefosine			*Meglumine*		
Cr >baseline	*≥ 12y N = 40*	*< 12 y N = 20*	***Total N = 60***	*≥ 12 y N = 20*	*< 12 y N = 10*	***Total N = 30***
Day 7						
>1-<1.5x baseline	*14 (35.0%)*	*4 (20.0%)*	***18 (30.0%)***	*4 (20.0%)*	*2 (20.0%)*	***6 (20.0%)***
1.5-<3x baseline	*1 (2.5%)*	*1 (5.0%)*	***2 (3.3%)***	*0*	*1 (10.0%)*	***1 (3.3%)***
3-<6 baseline	*0*	*0*	***0***			
Day 14						
>1-<1.5x baseline	*13 (%)*	*7 (35.0%)*	***20 (33.3%)***	*7 (35.0%)*	*3 (30.0%)*	***10 (33.3%)***
1.5-<3x baseline	*4 (10.0%)*	*0*	***4 (6.7%)***	*0*	*1 (10.0%)*	***1 (3.3%)***
3-<6 baseline	*0*	*0*	***0***	*0*	*0*	***0***
Day 21						
>1-<1.5x baseline	*11 (27.5%)*	*1 (5.0%)*	***12 (20.0%)***	*7 (35.0%)*	*0*	***7 (23.3%)***
1.5-<3x baseline	*3 (7.5%)*	*2 (10.0%)*	***5 (8.3%)***	*1 (5.0%)*	*1 (10.0%)*	***2 (6.7%)***
3-<6 baseline	*0*	*0*	***0***	*0*	*0*	***0***
Day 28						
>1-<1.5x baseline	*12 (30.0%)*	*6 (30.0%)*	***18 (30.0%)***	-	-	-
1.5-<3x baseline	*6 (15.0%)*	*0*	***6 (10.0%)***	-	-	-
3-<6 baseline	*0*	*0*	***0***	-	-	-
1 Month Post RX						
>1-<1.5x baseline	*12 (30.0)*	*2 (10.0%)*	***14 (23.3%)***	*6 (30.0%)*	*6 (60.0%)*	***12 (40.0%)***
1.5-<3x baseline	*3 (10.0%)*	*1 (20.0%)*	***4 (6.7%)***	*1 (5.0%)*	*0*	***1 (3.3%)***
3-<6 baseline	*0*	*0*	***0***	*0*	*0*	***0***

Table 96: Changes in Mean Cr – Study Z020b

Mean Cr (SD) Range	*Miltefosine N = 60*			*Meglumine N = 30*		
	≥ 12 y	*< 12 y*	***Total***	*≥ 12 y*	*< 12 y*	***Total***
Baseline	*0.7 (0.1) 0.4-0.9*	*0.6 (0.1) 0.4-0.9*	***0.7 (0.1) 0.4-0.9***	*0.7 (0.1) 0.5-1.0*	*0.6 (0.1) 0.4-0.8*	***0.6 (0.1) 0.4-1.0***
Day 7	*0.7 (0.1) 0.5-1.0*	*0.6 (0.1) 0.5-0.8*	***0.7 (0.1) 0.5-1.0***	*0.7 (0.1) 0.5-0.9*	*0.6 (0.1) 0.4-0.8*	***0.6 (0.1) 0.4-0.9***
Day 14	*0.7 (0.2) 0.5-1.1*	*0.6 (0.1) 0.4-0.8*	***0.7 (0.2) 0.4-1.1***	*0.7 (0.1) 0.5-0.9*	*0.6 (0.1) 0.4-0.7*	***0.6 (0.1) 0.4-0.9***
Day 21	*0.7 (0.2) 0.5-1.4*	*0.6 (0.1) 0.5-0.9*	***0.7 (0.2) 0.5-1.4***	*0.7 (0.1) 0.5-0.9*	*0.6 (0.1) 0.5-0.6*	***0.7 (0.1) 0.5-0.9***
Day 28	*0.8 (0.3) 0.5-2.0*	*0.6 (0.1) 0.4-0.8*	***0.7 (0.2) 0.4-2.0***	-	-	-
1 month post Rx	*0.7 (0.1) 0.5-1.2*	*0.6 (0.1) 0.5-0.8*	***0.7 (0.1) 0.5-1.2***	*0.7 (0.1) 0.5-0.9*	*0.6 (0.1) 0.5-0.8*	***0.7 (0.1) 0.5-0.9***

Table 97: Effect of Dose on Cr adults Z020b

	Miltefosine Dose mg/kg			
Cr EOT	*1.4-2.2 N = 6*	*2.3-<3 N = 29*	*≥ 3 N = 5*	*Total N = 40*
>1-<1.5x baseline	*1 (16.7%)*	*10 (34.5%)*	*1 (20.0%)*	*12 (30.0%)*
1.5-<3x baseline	*1 (16.7%)*	*5 (17.2%)*	*0*	*6 (15.0%)*

3-<6 baseline	*0*	*0*	*0*	*0*

Hepatic Toxicity

The lab dataset did not provide ULN values, but ALT, AST and alkaline phosphatase values < 16, 20 and 170 respectively were flagged as within normal limits. No subject in either arm had increases in AST or alkaline phosphatase or bilirubin.

Table 98: Changes in Transaminases – Study Z020b

	Miltefosine			Meglumine		
EOT	≥ 12 y N = 40	< 12 y N = 20	Total N = 60	≥ 12 y N = 20	< 12 y N = 10	Total N = 30
ALT >1-3x ULN	1 (2.5%)	0	1 (1.7%)	3 (15.0%)	0	3 (10.0%)
ALT 3-5x ULN	1 (2.5%)	0	1 (1.7%)	0	0	0

Hematologic Toxicity

There were no significant changes in hemoglobin, WBC or platelets during or after therapy.

Study Conclusions

The study did not have pre-specified statistical hypothesis, with imbalance in early withdrawals. Reasons for early withdrawals were not provided. Definite Cure at 6 months occurred in 78% of miltefosine recipients and 60% in meglumine recipients in subjects with CL due to *L. braziliensis*. Miltefosine cure rate was higher in adult subjects while meglumine cure rate was higher in pediatric subjects. The treatment difference in the adult subpopulation indicated that miltefosine was superior to meglumine. However, in the enrolled population as a whole, superiority was not substantiated.

Cure rates for *L. braziliensis* in the miltefosine arm were similar to those achieved in Study Soto, but higher than the cure rate achieved in Guatemala in Study 3168. Regional geographic variations in *L. braziliensis* susceptibility to miltefosine cannot be ruled out.

In Studies Z020a and b, the efficacy of meglumine was 60%. This may be an underestimate due to the number of subjects who withdrew from the study in the meglumine arm, but may also be indicative of increasing antimony resistance in South America. A study from Brazil reported failure to meglumine in approximately 70% of CL cases caused by *L. guyanensis* and approximately 40% of CL cases caused by *L. braziliensis*.

Cure in the miltefosine arm was duration dependent but not dose dependent: 6 of the 7 miltefosine failures received 2 weeks rather than the planned 4 weeks of treatment.

AEs noted more frequently in miltefosine recipients were related to the gastrointestinal and nervous systems (nausea, vomiting, diarrhea, abdominal pain, and dizziness). Similar to the other CL studies, pruritus and lesion infection with associated lymphadenopathy

also occurred. AEs noted more frequently in meglumine recipients were musculoskeletal. CTCAE grade 2 Cr elevations above baseline occurred more frequently in miltefosine recipients at EOT, and, in contrast to the other CL studies, were not dose dependent. ALT elevations were mild. There were no significant changes in AST, alkaline phosphatase, bilirubin or hematologic parameters.

Study Conclusions for Z020

Combining the data from Z020a and b, the meglumine-miltefosine difference is -13.3% (95% CI -28.4, 1.4).

Table 99: Miltefosine Efficacy – Study Z020 – Subjects ≥12 years of Age

	Miltefosine	Meglumine	Difference MEG –MLT 95% CI
Z020a			
Definite Cure - ITT	27/40 (67.5%)	12/20 (60.0%)	-7.5% (-34.6,17.9)%
Z020b			
Definite Cure - ITT	34/40 (85.0%)	9/20 (45.0%)	-40% (-63.5,-8.6)%
Z020			
Definite Cure - ITT	61/80 (76.3%)	21/40 (52.5%)	-23.8% (-41.9,-5.2)%

Table 100: Miltefosine Efficacy – Z020 – All Subjects

Definite Cure - ITT	Miltefosine	Meglumine	Difference MEG –MLT 95% CI
< 12 years of age	27/40 (67.5%)	15/20 (75.0%)	7.5% (-18.7, 30.4)%
≥ 12 years of age	61/80 (76.3%)	21/40 (52.5%)	-23.8% (-41.9, -5.2)%
All Subjects	88/120 (73.3%)	36/60 (60.0%)	-13.3% (-28.4, 1.4)%

Other Studies in Support of CL Indication

Study Z026

This study was a Phase IIb study conducted at one center in Kabul, Afghanistan. The study started enrollment in February 2004. Only an interim study report dated March 2005 was submitted.

The original study design was described as a randomized, open label, 3-arm trial comparing miltefosine target dose of 2.5 mg/kg daily administered orally for 28 days to one of two stibogluconate (SSG) regimens: 21 daily IM injections or 3-5 intralesional injections administered every 4-6 days.

Subjects > 10 years of age with parasitologically confirmed disease by visualization of the amastigotes on skin scraping smear were enrolled. The primary efficacy endpoint was complete re-epithelialization at 2 months. At the time of the report, 344 subjects were randomized, 147 to the miltefosine arm, 71 to IM SSG and 126 to intralesional SSG. The

IM SSG arm of the trial was closed prematurely because subjects could not travel daily to receive the injection. 19 subjects withdrew consent, all in the IM SSG arm.

Table 101: Subject Disposition and Cure Rates – Study Z026

	Miltefosine	IM SSG	Intra-lesion SSG
Randomized	147	71	126
Received Treatment	145	67	123
Withdrew Consent	0	19	0
Completed Treatment	104	48	102
Completed 2-4 month visit	46	23	32
2-4 months follow up cure rates	29/46 (63%)	15/23 (65%)	23/32 (72%)

No SAEs were reported.

Reviewer's Comments
There was a very high rate of loss to follow up in this trial. The premature closure of the IM SSG arm illustrates the difficulties administering daily IM injections under suboptimal social circumstances. Among patients who were not lost to follow up, the response rate to miltefosine was similar to the rates achieved by topical or systemic SSG. The response rate at 2-4 months in this trial is what is referred to as apparent cure in studies 3168, Soto and Zo20. Of note, CL in Afghanistan is caused by L. major or L. tropica.

The response to miltefosine treatment was reported in 34 Dutch military personnel with CL returning from Afghanistan[26]. 31 had failed prior therapy with intralesional SSG. Leishmania species was identified as L. major in 27. The dose administered was 150 mg/day (range 1.3 to 2.1 mg/kg/day) for 28 days. At EOT, none of the patients were cured and parasitology was still positive in 13. At 6 months, 28/34 (82.3%) had experienced cure which was sustained at 12 months. Nausea, vomiting, and abdominal discomfort were common (26, 19 and 16 subjects, or 76.5%, 55.6% and 47.1% respectively). 24 (70.1%) subjects were unable to fulfill their military duties. Five (14.7%) subjects spontaneously reported decreased ejaculate volume and 16 (47.1%) additional subjects reported the same after specific questioning. Two of these subjects reported complete temporary absence of ejaculation. Four (11.8%) subjects complained of scrotal tenderness and epididymitis was diagnosed in one (3.0%). All AEs resolved.

Study 3092

This was an open label, dose finding Phase I/II trial conducted at a single center in Colombia between April 1998 and December 1999[27]. The objective was to define a dosing regimen for a subsequent confirmatory trial.

[26] Von Thiel P, Leenstra T, et al. Miltefosine treatment of Leishmania major infection: An observational study involving Dutch military personnel returning from Northern Afghanistan. Clin Infect Dis 2010;50:80-83
[27] Soto J, et al. Treatment of American cutaneous leishmaniasis with miltefosine, an oral agent. Clin Infect Dis 2001;33:e57-e61

Male Colombian soldiers > 16 years of age with newly diagnosed or resistant/relapsing CL, confirmed by aspirate and parasitologic examination of each lesion, were enrolled into 4 sequential groups:

- Group 1: 50 mg/day on day 1-20 (16 patients)
- Group 2: 50 mg/day on day 1-7, followed by 50 mg bid on day 8-20 (19 patients)
- Group 3: 50 mg bid on day 1-7, followed by 50 mg tid on day 8-20 (17 patients)
- Group 4: 50 mg tid on day 1-28 (20 patients)

Definite cure was defined as complete re-epithelialization at 6 months after EOT. For a patient to be cured, all lesions had to be cured. Apparent cure was defined as complete re-epithelialization at 2 weeks after EOT. Initial partial cure was defined as 75-99% epithelialization and no increase in size of lesions 2 weeks after EOT. Clinical failure was defined as the appearance of any new lesions or enlargement of previously documented lesions or less than 75% epithelialization of lesions.

31 of the 72 patients (43.1%) had received prior treatment with Glucantime (meglumine). The mean weight was approximately 67 kg in all groups. The mean age was 21-24 years. 48.6% of evaluable subjects (72) had one lesion. *L. amazonensis* was identified in a total of 5 subjects, and *L. panamensis* in 10.

Cure rates in the ITT population were 60% in groups 1 and 2 combined, and 81.1% in groups 3 and 4 combined (P value 0.070). Cure rates in the PP population were 65.6% in groups 1 and 2 combined and 93.8% in groups 3 and 4.

No subject discontinued therapy because of an AE. There were no SAEs. One subject died in an accident 2 months after EOT. The most common AE was motion sickness occurring in 40% of patients overall. 15.8% of subjects in group 2, 76.5% in group 3 and 50% in group 4 reported motion sickness that lasted 1-7 days. However, motion sickness did not prevent the soldiers from performing their normal duties. Other AEs included vomiting (10-23%), diarrhea (0-12%), headache (15-30%), and abdominal pain (20-31%).

Reviewer's Comments
The study design and endpoints are the same as in Study 3168. The cure rate in Groups 3 and 4 was comparable to the cure rate among Colombian subjects treated with miltefosine in Study 3168. As already noted, Colombia is the only study site that coded the AEs of headache and nausea as motion sickness.

Study Z027

This was a pilot open-label study to evaluate the efficacy of miltefosine in the treatment of patients with diffuse cutaneous leishmaniasis DCL[28].

[28] Zerpa O. et al. Diffuse cutaneous leishmaniasis responds to miltefosine but then relapses. Br J Derm 2007; 156:1328-1335

16 subjects (13 males and 3 females) with DCL from rural Venezuela were enrolled. The submitted study report included interim analysis of 12 subjects, but the published article reported on all 16. Because the publication had more complete data, this will be presented.

All subjects had received prior therapy with multiple cycles of pentavalent antimony and immunotherapy, and 2 had also received amphotericin B. Subjects received 2-2.5 mg/kg/d of miltefosine for 75-218 days.

At day 30, 15 patients showed greater than 60% improvement. At day 45, 15 patients showed 80-90% improvement. However, all patients but one relapsed after therapy was suspended. All patients had a negative Leishmanin skin test at the beginning of therapy. The Leishmanin skin test remained negative in the 15 who relapsed, but turned positive in the one patient who did not.

12 relapsed patients received a second cycle of miltefosine therapy; 5 of the 12 (41.7%) did not respond.

Leishmania amastigotes were observed on smears in all patients, and specimen from all patients showed growth in hamsters before therapy. The isolate was identified as *L. amazonensis* in 11, *L. mexicana* in 2, and could not be identified in 3. Parasites were observed on smears until day 45 in 7/16 patients, and until day 60 in 2/16 patients. Growth in hamsters was positive at day 45 in 4/16.

No patient discontinued therapy for an adverse event. Two patients experienced nausea and vomiting and reduced their dose on day 15 without consultation. The adverse events improved, but these two patients had a slower response to therapy. One patient experienced dizziness on day 2, and one patient had urticaria on day 20 that improved with antihistamine therapy. One patient died of pneumonia.

Reviewer's Comments
Disseminated cutaneous leishmaniasis (DCL) manifests as chronic, disseminated, non-ulcerative skin lesions with abundant parasites. DCL patients have Leishmania-specific anergy. Its epidemiology is limited to a few geographic areas, occurring in Venezuela (L. amazonensis), some islands of the Caribbean, and Ethiopia (L. aethiopica). DCL patients usually relapse after therapy.

A second course of miltefosine resulted in lower response rates compared to those achieved by the first course. The failure of a repeat course of therapy in relapsed patients is worrisome for development of resistance.

Integrated Efficacy – CL Indication

Studies and datasets submitted in support of seeking the CL indication included Study 3168 (Colombia and Guatemala), Study Soto (Bolivia) and Study Z020 (Brazil). These studies were all randomized. Study 3168 was placebo-controlled study, while the other studies were active-controlled, with meglumine, a pentavalent antimony preparation, as the comparator. The active controlled trials did not have a pre-specified statistical hypothesis.

Miltefosine was administered at a target dose of 2.5 mg/kg/day for 28 days in all the studies. The primary endpoint was definite cure, defined as complete resolution of all lesions at 6 months follow up. In Study 3168, failure at 2 weeks post therapy was carried forward, while failures at 2 months or 3 months were carried forward in Studies Z020 and Soto respectively.

Study 3168 was placebo-controlled and will be considered the main pivotal study. In this study, miltefosine was superior to placebo in the overall population and at each of the two study centers. However, the response rate was lower in Guatemala compared to Colombia in both treatment arms, possibly explained by differences in the prevalent *Leishmania* species in each country. Parasitology was not reported for Study 3168. Epidemiologically, approximately 75% of CL in Guatemala is caused by *L. braziliensis* and approximately 25% by *L. mexicana*. In Colombia, approximately 55% of CL lesions are caused by *L. panamensis*, 30% by L. *braziliensis* and 15% are caused by 5 other species. *L. braziliensis* results in more protracted disease with lower placebo response rates compared to *L. mexicana* or *L. panamensis*. In addition, *L. braziliensis* may be less able to internalize miltefosine, resulting in higher IC50 compared to the other species.

Table 102: Primary Endpoint – Partial and Apparent Cure at 2 weeks and Definite Cure at 6 Months - Study 3168

Definite Cure	Placebo N = 44	Miltefosine N = 89	Difference MLT-PLA 95% CI	P value
ITT				
Colombia	9/24 (37.5%)	40/49 (81.6%)	44.1%	0.0002
Guatemala	4/20 (20.0%)	19/40 (47.5%)	27.5%	0.0406
Total	13/44 (29.6%)	59/89 (66.3%)	36.7% (20.1, 53.4)	< 0.0001
PP				
Colombia	9/24 (37.5%)	40/47 (85.1%)	47.6%	< 0.0001
Guatemala	4/18 (22.2%)	19/38 (50.0%)	27.8%	< 0.0505
Total	13/42 (31.0%)	59/85 (69.4%)	38.5% (21.4, 55.5)	< 0.0001

Studies Soto and Z020 were active controlled. Both studies will be considered supportive because there was no pre-specified statistical hypothesis of superiority or non-inferiority.

Study Z020 was split into two studies according to the prevalent epidemiologic species in Brazil. This study also enrolled children 2-11 years of age. Because the sponsor is seeking the indication for treatment of patients at least 12 years of age, integrated efficacy will focus on this population.

As already noted, early failure was imputed as failure in these studies but the timing of failure differed. Definite Cure for Study 3168 was re-calculated using the definition used in Study Soto. Integrated efficacy will be presented for Studies Soto, Z020a and Z020b, with and without including the re-calculated cure rate for Study 3168.

Table 103: Integrated Efficacy for Subjects ≥ 12 years of age – Studies Soto and Z020

Definite Cure - ITT	Miltefosine	Meglumine	Difference MLT-MEG	Mean MLT Dose
Soto	32/40 (80.0%)	13/18 (72.2%)	7.8%	2.6 (0.38)
Z020a	27/40 (67.5%)	12/20 (60%)	7.5%	2.3 (0.39)
Z020b	34/40 (85.0%)	9/20 (45.0%)	40.0%	2.6 (0.33)
Total	93/120 (77.5%)	34/58 (58.6%)	18.9%	2.5 (0.39)

Table 104: Integrated Efficacy for Subjects ≥ 12 years of age – Studies 3168, Soto and Z020

Definite Cure - ITT	Miltefosine	Meglumine	Placebo	Difference MLT-COMP	Mean MLT Dose
Soto	32/40 (80.0%)	13/18 (72.2%)	-	7.8%	2.6 (0.38)
Z020a	27/40 (67.5%)	12/20 (60%)	-	7.5%	2.3 (0.39)
Z020b	34/40 (85.0%)	9/20 (45.0%)	-	40.0%	2.6 (0.33)
3168	59/89 (66.3%)	-	13/44 (29.6%)	36.7%	2.5 (0.33)
3168 Recalculated	63/89 (70.8%)	-	14/44 (31.8%)	39%	2.5 (0.33)
Total	156/209 (74.6%)	34/58 (58.6%)		16%	2.5 (0.37)
	156/209 (74.6%)		14/44 (31.8%)	42.8%	

The mean miltefosine dose in each study approximated the target dose of 2.5 mg/kg/day with the exception of Study Z020a.

With the exception of Study Z020a, the mean miltefosine mg/kg dose was similar in subjects who were cured and subjects who failed. Combining the results of all the studies, a dose < 2 mg/kg results in lower cure rates compared to higher doses. In Study Z020b, 6/7 miltefosine subjects who failed received 2 weeks instead of 4 weeks of therapy. The relation of duration of therapy to cure could not be explored further because all evaluable subjects in the other studies received the full duration of treatment.

Table 105: Effect of Miltefosine Dose – Studies 3168, Z020 and Soto – Subjects ≥ 12 years of age

Miltefosine mg/kg Dose	Definite Cure
1.4 - < 2	9/18 (50.0%)
2-2.4	56/81 (69.1%)
2.5-2.9	71/90 (78.9%)
3-3.9	16/20 (80.0%)
Total	152/209 (72.7%)

The infecting *Leishmania* species was identified as *L. guyanensis* in Study Z020a and *L. braziliensis* in Study Z020b. Epidemiologically, the infecting species is presumed to be *L. braziliensis* in Study Soto (Bolivia). Parasitology was not reported for Study 3168.

Table 106: Efficacy of Miltefosine by Species – Subjects ≥ 12 years of age - Studies Z020 and Soto

	Miltefosine			Meglumine	Difference MLT-MEG
	Soto + Z020b	Z020a	Total		
L guyanensis	-	26/39 (66.7%)	26/39 (66.7%)	12/19 (63.2%)	3.5%
L. braziliensis	66/80 (82.5%)	1/1 (100%)	67/81 (82.7%)	22/38 (67.9%	14.8%

Even after recalculation to account for the earlier definition of failure, the point estimate of miltefosine cure rate in Guatemalan subjects enrolled in Study 3168 (where *L. braziliensis* is expected to cause approximately 75% of CL lesions) is lower compared to the other studies. Geographic differences in *L. braziliensis* susceptibility to miltefosine cannot be ruled out.

Table 107: Miltefosine Efficacy by Geographic Region - Subjects ≥ 12 years of age - Studies 3168, Z020 and Soto

	Miltefosine Definite Cure	Miltefosine Definite Cure (If Failure is at 3 months)
Guatemala* (3168)	19/40 (47.5%)	23/40 (57.5%)
Bolivia (Soto) *	32/40 (80.0%)	
Bahia, Brazil* (Z020b)	34/40 (85.0%)	
Colombia	40/49 (81.6%)	
Manaus, Brazil (Z020a)	27/40 (67.5%)	

**L. braziliensis* epidemiologically most prevalent

In addition to the above submitted studies, two more recent studies comparing miltefosine to meglumine in South America were identified in the literature. The first study was randomized, open-label study conducted in Colombia[29]. 145 soldiers received miltefosine 150 mg (50 mg TID) for 28 days and 143 received meglumine 10 mg/kg/day IM for 28 days. In the ITT population, miltefosine cure rate was 85/145 (58.6%) and meglumine cure rate was 103/143 (72%). In the PP population, cure rates were 85/122 (69.8%) vs. 103/121 (85.1%) for miltefosine and meglumine respectively. The higher efficacy of meglumine was noted for *L. braziliensis* and *L. panamensis*, but *L. panamensis* responded more favorably to either treatment compared to *L. braziliensis*. The sponsor speculates that the reason for the lower efficacy of miltefosine in this study compared to the efficacy in Colombia site of Study 3168 or in Study 3092 was that the soldiers did not take the oral medication as prescribed. PK was not performed but the sponsor cites a study evaluating Malarone for malaria prophylaxis in the Colombian military that demonstrated poor compliance by soldiers by measuring Malarone blood levels.

[29] Velez I, Lopez L. et al. Efficacy of miltefosine for the treatment of American cutaneous leishmaniasis. Am J Trop Med Hyg 2010;83:351-356

The second study[30] was at 3 locations conducted in Colombia where *L. panamensis* and *L. guyanensis* predominate. 116 children 2-12 years of age with parasitologically confirmed CL were randomized, 58 to receive meglumine 20 mg/kg/day IM for 20 days and 58 to receive miltefosine 2.5 mg/kg/d for 28 days. The primary efficacy endpoint was treatment failure at or before Week 26 after initiation of treatment. 111/116 children completed follow up evaluation. ITT failure rate was 17.2% for miltefosine and 31% for meglumine. The difference was 13.8% (95% CI 24.5%, 32%) (p=0.04). At the site where *L. panamensis* is endemic, the failure rate for miltefosine was 7.4% and for meglumine 33.3% (p = 0.02). At the site where *L. guyanensis* is endemic, the failure rate for both drugs was 32%. The results of this study are similar to the studies submitted in support of this NDA application.

Although the sponsor is not seeking the indication of treatment of Old World CL, Study Z026 evaluated the efficacy of miltefosine in Old World CL in Afghanistan. This study was terminated early and a high percentage of subjects were lost to follow up. However, of the subjects who were not lost to follow up, cure at 2-4 months was similar to apparent cure in the Studies in South America. Efficacy in Old World CL was reported in the literature for 34 Dutch soldiers returning from Afghanistan, of whom 31 had failed antimony. Miltefosine resulted in 82.3% cure at 6 months.

In conclusion, miltefosine was superior to placebo in the treatment of CL in Colombia and Guatemala in Study 3168, and resulted in overall similar cure rates compared to meglumine in the treatment of CL in Bolivia and Brazil where *L. braziliensis* and *L. guyanensis* were either documented or epidemiologically prevalent. Doses less than 2 mg/kg/day result in lower cure rates compared to higher doses. Published literature post-marketing in South America shows comparable efficacy to that demonstrated in this trial in a study in children, but lower efficacy in Colombian soldiers. Post-marketing literature also demonstrates clinical effectiveness in Dutch soldiers with Old World CL who failed antimony therapy.

Integrated Safety – CL

The sponsor integrated the adverse events reported in subjects ≥ 12 years of age enrolled in studies 3168, Soto, Z020 and 3092. The primary data for Study 3092 (dose ranging study) were not submitted, and our analysis will not include this study. However, excluding this study which was conducted in Colombia only alters the frequency of motion sickness, because only Colombian study sites used that term to code headache and nausea. These subjects were also coded for headache and nausea individually.

249 subjects age ≥ 2 years received miltefosine in these studies, 40 subjects 2-11 years of age, and 209 at least 12 years of age. 78 subjects received meglumine (20 subjects 2-11 years of age) and 44 subjects received placebo.

[30] Rubiano LC, Miranda MC et al. Non-inferiority of miltefosine versus meglumine antimoniate for cutaneous leishmaniasis in children. J Infect Dis 2012;205:684-92

Approximately 80% of miltefosine subjects experienced at least one AE, compared to 73% and 52% of meglumine and placebo subjects respectively. One miltefosine subject (0.4%) discontinued treatment on Day 27 due to motion sickness. There were no serious AEs and no deaths.

Table 108: Summary of Treatment Emergent AEs – Studies 3168, Soto, Z020 - All Subjects

	Miltefosine N = 249	Meglumine N = 78	Placebo N = 44
N with at least one AE	201 (80.7%)	57 (73.1%)	23 (52.3%)
N who discontinued due to AE	1 (0.4%)	0	0

Table 109: Summary of Treatment Emergent AEs – Studies 3168, Soto, Z020 – Subjects ≥12 years of Age

	Miltefosine N = 209	Meglumine N = 58	Placebo N = 44
N with at least one AE	170 (81.3%)	44 (75.9%)	23 (52.3%)
N who discontinued due to AE	1 (0.5%)	0	0

Adverse reactions that occurred more frequently in miltefosine subjects ≥12 years of age compared to placebo were diarrhea, nausea, vomiting, dizziness, headache, somnolence, pyrexia, pruritus, asthenia, decreased appetite, infection at lesion site and lymphadenopathy/lymphangitis. Diarrhea and nausea in miltefosine subjects were not dose dependent, but the frequency of vomiting increased as the miltefosine mg/kg increased.

Adverse reactions noted more frequently in miltefosine subjects ≥12 years of age compared to meglumine were abdominal pain, diarrhea, dyspepsia, nausea, vomiting, pyrexia, dizziness, somnolence, pruritus and lymphadenopathy/lymphangitis.

Table 110: AEs Occurring in ≥ 2% of All Subjects - Studies 3168, Soto and Z020a

MedDRA System Organ Class	Miltefosine N = 249	Meglumine N = 78	Placebo N = 44
Blood and Lymph	6 (2.4%)	3 (3.8%)	0
Lymphadenopathy	5 (2.0%)	3 (3.8%)	0
Ear and Labyrinth	28 (11.2%)	0	11 (25.0%)
Motion Sickness	26 (10.5%)	0	10 (22.7%)
Gastrointestinal	155 (62.2%)	14 (17.9%)	13 (29.6%)
Abdominal Pain	26 (10.5%)	4 (5.1%)	4 (9.1%)
Diarrhea	26 (10.5%)	3 (3.8%)	2 (4.5%)
Dyspepsia	14 (5.6%)	3 (3.8%)	3 (6.8%)
Nausea	89 (35.7%)	3 (3.8%)	5 (11.4%)
Vomiting	78 (31.3%)	2 (2.6%)	0
General/Admin Site	63 (25.3%)	30 (38.5%)	3 (6.8%)
Application site	0	6 (7.7%)	0
Asthenia	8 (3.2%)	5 (6.4%)	0
Malaise	4 (1.6%)	1 (1.3%)	1 (2.3%)
Pain at lesion	19 (7.6%)	5 (6.4%)	0

Pyrexia	37 (14.9%)	6 (7.7%)	2 (4.5%)
Infections	38 (15.3%)	12 (15.4%)	4 (9.1%)
Ecthyma	5 (2.0%)	6 (7.7%)	0
Infection	8 (3.2%)	0	0
Localized abscess	4 (1.6%)	0	1 (2.3%)
Lymphangitis	7 (2.8%)	0	0
Lesion Infection	6 (2.4%)	1 (1.3%)	0
Parasitic	5 (2.0%)	1 (1.3%)	1 (2.3%)
Injury	22 (8.8%)	10 (12.8%)	0
Injury	16 (6.4%)	8 (10.3%)	0
Metabolism	15 (6.0%)	5 (6.4%)	0
Decreased appetite	15 (6.0%)	5 (6.4%)	0
Musculoskeletal	18 (7.2%)	26 (33.3%)	3 (6.8%)
Arthralgia	4 (1.6%)	25 (32.1%)	1 (2.3%)
Back pain	5 (2.0%)	1 (1.3%)	0
Myalgia	2 (0.8%)	7 (9.0%)	2 (4.5%)
Nervous System	90 (36.1%)	29 (37.2%)	10 (22.7%)
Dizziness	21 (8.4%)	5 (6.4%)	0
Headache	72 (28.9%)	27 (34.6%)	10 (22.7%)
Somnolence	8 (3.2%)	0	0
Respiratory/Thoracic	32 (12.9%)	14 (18.0%)	1 (2.3%)
Cough	12 (4.8%)	0	0
Influenza	10 (4.0%)	9 (11.5%)	0
Pharyngitis	9 (3.6%)	1 (1.3%)	1 (2.3%)
Skin/SC	26 (10.5%)	11 (14.1%)	0
Pruritus	14 (5.6%)	2 (2.6%)	
Pyoderma	1 (0.4%)	3 (3.8%)	0
Rash	3 (1.2%)	3 (3.8%)	

Table 111: AEs Occurring in ≥ 2% of Subjects ≥ 12 years of age - Studies 3168, Soto and Z020

MedDRA v. 12.0 System Organ Class	Miltefosine N = 209	Meglumine N = 58	Placebo N = 44
Blood and Lymph	5 (2.4%)	2 (3.4%)	0
Lymphadenopathy	4 (1.9%)	2 (3.4%)	0
Ear and Labyrinth	27 (12.9%)	0	11 (25.0%)
Motion Sickness	26 (12.4%)	0	10 (22.7%)
Gastrointestinal	127 (60.8%)	10 (17.2%)	13 (29.6%)
Abdominal Pain	19 (9.1%)	3 (5.2%)	4 (9.1%)
Diarrhea	25 (12.0%)	3 (5.2%)	2 (4.5%)
Dyspepsia	12 (5.7%)	2 (3.4%)	3 (6.8%)
Nausea	82 (39.2%)	3 (5.2%)	5 (11.4%)
Vomiting	37 (17.7%)	0	0
General/Admin Site	49 (2.4%)	23 (39.7%)	3 (6.8%)
Application site	0	6 (10.3%)	0
Asthenia	8 (3.8%)	4 (6.9%)	0

Malaise	4 (1.9%)	1 (1.7%)	1 (2.3%)
Pain at lesion	18 (8.6%)	5 (8.6%)	0
Pyrexia	27 (12.9%)	6 (10.3%)	2 (4.5%)
Infections	31 (14.8%)	5 (8.6%)	4 (9.1%)
Infection	8 (3.8%)	1 (1.7%)	0
Lymphangitis	7 (3.3%)	0	0
Lesion Infection	3 (1.4%)	2 (3.4%)	0
Parasitic	4 (1.9%)	0	1 (2.3%)
Injury	14 (6.7%)	4 (6.9%)	0
Injury	10 (4.8%)	2 (3.4%)	0
Metabolism	13 (6.2%)	4 (6.9%)	0
Decreased appetite	13 (6.2%)	4 (5.8%)	0
Musculoskeletal	18 (8.6%)	24 (41.4%)	3 (6.8%)
Arthralgia	7 (3.3%)	23 (39.7%)	1 (2.3%)
Back pain	6 (2.9%)	1 (1.7%)	0
Myalgia	2 (1.0%)	7 (12.1%)	2 (4.5%)
Nervous System	79 (3.8%)	21 (36.2%)	10 (22.7%)
Dizziness	19 (9.1%)	4 (6.9%)	0
Headache	63 (30.1%)	20 (34.5%)	10 (22.7%)
Somnolence	5 (2.4%)	0	0
Respiratory/Thoracic	19 (9.1%)	9 (15.5%)	1 (2.3%)
Cough	4 (1.9%)	3 (5.2%)	0
Influenza	4 (1.9%)	5 (8.6%)	0
Pharyngitis	7 (3.3%)	0	1 (2.3%)
Skin/SC	20 (9.6%)	5 (8.6%)	0
Pruritus	11 (5.3%)	0	0
Rash	3 (1.4%)	2 (3.4%)	

Table 112: GI AE by Dose – Subjects ≥ 12 years of Age - Studies 3168, Soto and Z020

Miltefosine mg/kg dose	1.4-<2.3 N = 58	2.3-<3 N = 131	≥3 N = 20	Total N = 209
Diarrhea	6 (10.3%)	18 (13.7%)	1 (5.0%)	25 (12.0%)
Nausea	26 (44.8%)	50 (38.2%)	6 (30.0%)	82 (39.2%)
Vomiting	8 (13.8%)	37 (28.2%)	8 (40.0%)	53 (25.4%)

At EOT, approximately 66% of miltefosine subjects experienced some degree of Cr elevation above baseline, compared to approximately 35% meglumine subjects and 50% placebo subjects. Most of the elevations were CTCAE grade 1 (1-1.5x above baseline). A higher percentage of miltefosine subjects had CTCAE grade 2 Cr elevations (1.5-3x above baseline) compared to meglumine or placebo. In all the studies except Z020b, mean Cr increased at EOT in miltefosine recipients but remained stable in the comparator arm. The percentage of subjects with CTCAE grade 2 Cr increase above baseline was higher at doses > 2.2 mg/kg/day, but grade 1 increases were not dose dependent. No subject discontinued miltefosine due to renal impairment.

Elevations in ALT were mild and more frequent in miltefosine recipients compared to placebo, but similar to meglumine recipients. Elevations in AST were more frequent in meglumine recipients. No miltefosine subject discontinued therapy due to hepatic impairment. There were no significant changes in bilirubin. There were no significant changes in hematology parameters.

Table 113: Summary of Lab Abnormalities at EOT in Subjects ≥ 12 years of Age – Studies 3168, Soto and Z020

EOT	Miltefosine N = 209	Meglumine N = 58	Placebo N = 44
Cr			
Cr >1-<1.5x baseline	99 (47.4%)	17 (29.3%)	24 (45.5%)
Cr 1.5-<3x baseline	36 (17.2%)	3 (5.1%)	2 (4.5%)
Cr 3-<6x baseline	2 (1.0%)	0	0
ALT			
ALT >1-3x ULN	13 (7.7%)	4 (6.9%)	2 (4.5%)
ALT >3-5x ULN	0	1 (1.7%)	0
AST			
AST > 1-3x ULN	7 (4.1%)	5 (8.6%)	1 (2.3%)
AST >3-5x ULN	0	1 (1.7%)	0
AP			
AP >1-2.5x ULN	18 (10.7%)	3 (5.1%)	7 (15.9%)
AP >2.5-5x ULN	0	0	0
Total Bilirubin			
Bilirubin ≥1.5 mg/dL	1 (0.5%)	0	2 (4.5%)

Table 114: Effect of Miltefosine Dose on Cr at EOT in Subjects ≥ 12 years of Age – Studies 3168, Soto, Z020a and Z020b

	Miltefosine			
EOT	1.4-2.2 N = 58	2.3-<3 N = 131	≥ 3 N = 20	Total N =209
Cr >1-<1.5x baseline	32 (55.2%)	62 (47.3%)	5 (25.0%)	99 (47.4%)
Cr ≥ 1.5-< 3 x baseline	7 (12.1%)	25 (19.1%)	4 (20.0%)	36 (17.7%)
Cr ≥ 3-6x baseline	1 (1.7%)	1 (0.8%)	0	2 (1.0%)
Total	40 (69.0%)	88 (67.2%)	9 (45.0%)	137 (65.6%)

Mucosal Leishmaniasis Due to Members of the Subgenus Viannia

In support of the ML indication, study report and datasets for Study Z022 were submitted.

Study Z022

This was a Phase 2 study conducted between April 2, 2004 and May 14, 2006 at a single center at the Palos Blancos clinic in Bolivia[31]. Two ENT physicians from the department

[31] Soto J. et al. Treatment of Bolivian mucosal leishmaniasis with miltefosine. Clin Infect Dis 2007;44:350-6

of Hospital de Clinicas in La Paz travelled to the site to perform all mucosal examinations.

Study Design

The initial study design was an open-label randomized trial to compare oral miltefosine to parenteral pentavalent antimony in the treatment of ML. Because the study center's experience indicated that pentavalent antimony was ineffective, the trial was modified to compare oral miltefosine 2.5 mg/kg/day target dose to intravenous amphotericin B deoxycholate administered every other day for a total of 45 injections (the standard therapy at the investigation site). However, patients and their physicians refused randomization "when the efficacy of miltefosine became apparent in the initial patients". The study design was changed from a comparative trial to a single arm trial.

Subjects ≥ 18 years of age with a scar of previous CL and mucosal signs and symptoms compatible with ML (erythema, edema, infiltration, erosion of the nares and/or nasal septum and/or epiglottis, uvula or palate), and *Leishmania* seen in histopathologic examination of the lesion aspirates or isolated from cultures, OR positive Montenegro test and no previous treatment for ML (or if previously treated, treatment must have been at least 6 months prior to enrollment and symptoms must have progressed over the past 3 months) and no clinically significant lab abnormalities or abnormalities on physical exam other than the *Leishmania* related findings were enrolled. Women of childbearing potential had to agree to contraception for the duration of therapy and 2 months after therapy.

Subjects were followed at 2 weeks, 2 months, 6 months, 9 months and 12 months after EOT. Parasitology and Photography of the lesions were planned at each visit. Hematology and chemistry labs were obtained at screening, Day 14 and EOT (Day 28).

The primary efficacy endpoint in the original protocol was assessment of individual lesions at 5 anatomical sites: nasal skin, nasal mucosa, palate, pharynx and larynx. Because of the complexity of analyzing data pertaining to 5 anatomic sites at 6 time points, the composite mucosal severity score was created. This composite lesion severity score consisted of the sum of the grades for all lesion sites: 1-3 points for each of four pathologic signs (erythema, edema, infiltration, erosion) at each of the five sites (nasal skin, nasal mucosa, palate, pharynx, and larynx). The maximum severity score possible was 60.

The primary efficacy endpoint was cure at 12 months, defined as ≥ 90% improvement in mucosal severity score at 12 months compared to baseline. Clinical response was otherwise defined as Improved (50% to < 90% improvement in mucosal severity score), Not Changed (25% worsening to < 50% improvement), Worsened (> 25% worsening) and Presumptive failure (discontinued follow up because cure at 12 months was unlikely).

The ITT population included all subjects exposed to at least on dose of study drug. The Per Protocol population included all subjects who received the study drug for at least 90% of the planned treatment days and who were assessed for 12 months.

Descriptive statistics were used to present the data. Sample size had originally been planned for 75 subjects in the miltefosine arm and 25 subjects in the pentavalent antimony arm, assuming an efficacy rate of 55% for the pentavalent antimony and a non-inferiority margin of 20-30%.

Protocol Amendments

The protocol amendments included change in study design to a single arm study, increased follow up times to add 9 and 12 months evaluation, and a change in the primary efficacy parameter from individual assessment of lesions to the composite lesion severity score.

Disposition

79 subjects were enrolled and treated with miltefosine. The disposition dataset was not provided. One subject was lost to follow up, one subject died and one subject had nasal paracoccidioidomycosis.

Table 115: Subject Disposition, - Study Z022

	Miltefosine
Subjects enrolled	79
ITT	79
Lost to follow up at 12 months	1 (1.3%)
Died	1 (1.3%)
Wrong Diagnosis	1 (1.3%)
Evaluable	76

Demographics and Other Subject Characteristics

Table 116: Subject Characteristics – Study Z022 - ITT

	Miltefosine N = 79
Age (years)	
Mean (SD)	39.4 (16.5)
Males (%)	58 (73.4%)
Race	
Moseten	2 (2.5%)
White/Aymara	68 (86.1%)
White/Quechua	5 (6.3%)
Unknown	4 (5.1%)
Ethnicity	
Black	1 (1.3%)

Mestizo	73 (92.4%)
Native Indian	4 (5.1%)
Unknown	1 (1.3%)
Weight kg	
Mean (SD)	58.0 (9.0)
Median (range)	58.0 (35-85)
Previous treatment	
None	67 (84.8%)
Pentavalent antimony	11 (13.8%)
Amphotericin B	2 (2.5%)
Microscopy at screening	
Positive	34 (43.0%)
Negative	37 (46.8%)
Not done or missing	8 (10.1%)
Severity score	
Mean (SD)	10.0 (8.2)
Median (Range)	6 (1-38)

Reviewer's Comments
The published article states that parasites were observed or cultured in 50 subjects, but that only 7 cultures multiplied sufficiently to allow speciation by isoenzyme electrophoresis. All were identified as L. braziliensis. This is consistent with the epidemiology of CL in Bolivia, where 87% of CL lesions are caused by L. braziliensis, which has propensity to cause ML.

Efficacy Evaluation

Primary Endpoint

The primary endpoint was cure at 12 months, defined as ≥ 90% improvement in mucosal severity score at 12 months compared to baseline.

Table 117: Cure Rate – Study Z022 – ITT and PP

	ITT 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%)	0

Reviewer's Comments
All 49 cured subjects had mucosal severity scores of zero at 12 months, indicating complete resolution of edema, erythema, infiltration and erosion from the involved mucosal sites.

There were few subjects below the age of 17 or above the age of 65, and few subjects whose ethnicity was not Aymera to draw any conclusions regarding the effect of age or ethnicity on cure. Cure rates were higher in women compared to men. Cure rates for proximal disease (nasal skin and nasal mucosa) only or for distal disease (palate, pharynx and larynx) were similar.

Mean miltefosine mg/kg dose was similar in subjects who cured compared to subjects who failed or improved. Subjects who received less than 2 mg/kg or more than 3 mg/kg had lower cure rates compared to subjects who received a dose between 2-3 mg.

Table 118: Cure by Age – Study Z022

Age (years)	*Cured*
12-17	*1/4 (25.0%)*
18-64	*43/69 (62.3%)*
≥ 65	*5/6 (83.3%)*
Total	*49/79 (62.0%)*

Table 119: Cure by Gender – Study Z022

	Cured
Males	*33/58 (56.9%)*
Females	*16/21 (76.2%)*
Total	*49/79 (62.0%)*

Table 120: Cure by Race – Study Z022

	Cured
White/Aymara	*44/68 (64.7%)*
White/Quechua	*1/5 (20.0%)*
Moseten	*2/2 (100%)*
Not specified	*2/4 (50.0%)*
Total	*49/79 (62.0%)*

Table 121: Cure by Location of Infected Sites – Z022

	Cured
Nasal skin and mucosa only	*27/41 (65.8%)*
Palate, pharynx or larynx	*22/38 (57.9%)*

Table 122: Effect of Miltefosine Dose – Study Z022

Miltefosine mg/kg	*Cured*	*Improved*	*Cured plus Improved*
< 2	*2/4 (50.0%)*	*2/4 (50.0%)*	*4/4 (100%)*
2-2.4	*15/19 (79.0%)*	*2/19 (10.5%)*	*17/19 (89.5%)*
2.5-2.9	*26/38 (68.4%)*	*7/38 (18.4%)*	*33/38 (86.8%)*
3-3.9	*5/16 (31.2%)*	*5/16 (31.2%)*	*10/16 (62.5%)*
≥4	*1/1 (100%)*	-	*1/1 (100%)*

Table 123: Mean Miltefosine Dose – Study Z022

Dose mg/kg	*Cured*	*Improved*	*Unchanged*	*Failed*
Mean (SD)	*2.57 (0.39)*	*2.64 (0.44)*	*2.78 (0.26)*	*2.87 (0.36)*
Median (Range)	*2.54 (1.76-4.28)*	*2.68 (1.8-3.3)*	*2.72 (2.45-3.12)*	*3 (2.3-3.26)*

A published article reports on 2-year follow up for the subjects enrolled in Study Z022 and on the efficacy of extended duration of miltefosine treatment[32]. 41 of the cured subjects were located and re-examined by an ENT physician at 2 years after the end of therapy. 39 were still cured, and 2 had relapsed with infiltration of the palate and vocal cords respectively. 4 additional subjects were contacted by phone. 3 reported no symptoms and were presumed cured, and one reported bleeding and pain and was presumed relapsed. The cure at 2 years was 42/79 subjects (53.1%) of the originally enrolled population, or 42/76 (55.3%) of the evaluable population.

17 of the subjects who were not cured in Study Z022 were located and re-treated with miltefosine for 6 weeks. At 12 months after re-treatment, 11 were cured and 6 failed (cure rate 65%). Final severity score was zero in 9 of the 11.

In addition, 21 new subjects with ML received 6 weeks of miltefosine. One was lost to follow up, 15 were cured (71.4%) and 5 failed. The authors conclude that extending the follow up to 24 months or extending the treatment duration to 6 weeks do not alter the original conclusions of Study Z022.

Published studies that report the response to pentavalent antimony preparations or amphotericin B in patients with ML were identified and reviewed. The published article that reported the results of Study Z022 also reported clinical response of 19 historical control subjects treated with amphotericin B deoxycholate at the same study center. The mean mucosal severity score at baseline was 10 (SD 5, range 5-23), comparable to that in the miltefosine subjects. Of the 19 amphotericin subjects, 3 discontinued the drug due to an adverse event and 2 were lost to follow up. 7 of the 14 evaluable subjects were cured (50.0%). The cure rate in the ITT population is therefore 7/19 (36.8%), lower than the 62% miltefosine cure rate. This study center had refused to participate in a trial using antimony preparation as the comparator because in their experience, antimony preparations were not effective.

In a study in Peru[33], 10/20 enrolled subjects who received 28 days of antimony treatment had resolution of infiltrated ulcers 12 months later (50% - 10/16 evaluable subjects, 63%) compared to 12/20 enrolled subjects who received 42 days of antimony (60% - 12/19 evaluable subjects, 63%). In another study from Peru[34], a total of 81 subjects with ML were enrolled to receive SSG with or without allopurinol. L. braziliensis was isolated from 35 subjects. 11 subjects withdrew because of adverse events. 37 subjects sustained clinical cure at 12 months (45.7% in ITT, and 52.8% in the evaluable population).

[32] Soto J, Rea J, Valderrama M et al. Short report: efficacy of extended (six weeks) treatment with miltefosine for mucosal leishmaniasis in Bolivia. Am J Trop Med Hyg 2009;81:387-389
[33] Franke E, Llanos-Cuentas A, et al. Efficacy of 28-day and 40-day regimens of sodium stibogluconate in the treatment of mucosal leishmaniasis. Am J Trop Med Hyg 1994;51:77-82
[34] Llanos-Cuentas A et al. Efficacy of sodium stibogluconate alone and in combination with all allopurinol for the treatment of mucosal leishmaniasis. Clin Infect Dis 1997; 25: 677-684

Studies from Brazil report a higher response to antimony preparations. In a study from Brazil[35], 11 subjects with ML received SSG plus oral pentoxifylline and 12 subjects received SSG with placebo. 18 subjects in the two groups combined sustained a cure at 6 months (69.2%) and all sustained cure at 12 months (100%) with no relapses at 2 years. Another study from Brazil[36] reported on a cohort of 140 patients with ML treated with meglumine, pentamidine, amphotericin B or itraconazole. Meglumine treated patients had a cure rate (healing of all lesions at 1 year after therapy) of 91% and a recurrence rate of 22%. Amphotericin treated patients had a cure rate of 82% and a recurrence rate of 18%.

ML treatment responses to various therapies are summarized in the table below.

Table 124: Summary of ML Treatment Responses - Literature

Resolution at 12 months	*Country*	*Cure ITT*	*Cure Evaluable*
Z022	*Bolivia*	*49/79 (62.0%)*	*49/76 (64.5%)*
Miltefosine 6 weeks	*Bolivia*	*15/21 (71.4%)*	*15/20 (75%)*
Amphotericin B	*Bolivia*	*7/19 (36.8%)*	*7/14 (50%)*
Antimony 28 days	*Peru*	*10/20 (50%)*	
Antimony 42 days	*Peru*	*12/20 (60%)*	*12/19 (63%)*
Antimony +/- allopurinol	*Peru*	*37/81 (45.7%)*	*37/70 (52.8%)*
Antimony +/- pentoxifylline	*Brazil*	*18/18 (100%)*	
Amphotericin (any formulation)	*Brazil*	*17/30 (56.7%)*	
Antimony	*Brazil*	*58/73 (79.5%)*	
Pentamidine	*Brazil*	*20/22 (91.0%)*	
Itraconazole	*Brazil*	*11/15 (73.3%)*	

Safety Evaluation

Extent of exposure

78 subjects received 150 mg daily and one subject received 100 mg daily. The mean duration of exposure was 28.9 days (SD 2.1) and the median was 28 days (range 16-32) The mean miltefosine dose was 2.63 mg/kg/day (SD 0.4). The median dose was 2.6 mg/kg/day (range 1.8-4.3).

Concomitant Medications

39 (49.4%) subjects received at least one concomitant medication, most commonly acetaminophen, H2 blockers/proton pump inhibitors or metoclopramide.

[35] Machado PR, Lessa H et al. Oral pentoxifylline combined with pentavalent antimony: a randomized trial for mucosal leishmaniasis. Clin Infect Dis 2007; 44:788-793

[36] Amato VS, Tuon FF et al. Mucosal leishmaniasis: description of case management approaches and analysis of risk factors for treatment failure in a cohort of 140 patients in Brazil. Journal of European Academy of Dermatology and Venereology 2009;23:1026-1034

Treatment Emergent Adverse Events

74 of the 79 subjects (93.7%) experienced at least one AE. One subject experienced two serious AEs that led to discontinuation of the drug (RUQ abdominal pain and dehydration). This subject died. The death was not noted in the AE dataset which reported all adverse event outcomes as recovered/resolved.

Table 125: Summary of AEs – Study Z022

	Miltefosine N = 79
Subjects with at least one AE	74 (93.7%)
Subjects with at least one serious AE	1 (1.3%)
Subjects who discontinued the drug due to an AE	1 (1.3%)
Deaths	1 (1.3%)

Table 126: Treatment Emergent AE – Study Z022

MedDRA v. 12.0 System Organ Class/Preferred Term	Miltefosine N = 79
Ear and Labyrinth	1 (1.3%)
Sudden Hearing Loss	1 (1.3%)
Eye	1 (1.3%)
Excessive Blinking	1 (1.3%)
Gastrointestinal	46 (58.2%)
Abdominal Distention	1 (1.3%)
Abdominal Pain	21 (26.6%)
Diarrhea	1 (1.3%)
Dysphagia	3 (3.8%)
Flatulence	1 (1.3%)
Gastritis	10 (12.7%)
Nausea	25 (31.6%)
Toothache	1 (1.3%)
General/Admin Site	20 (25.3%)
Malaise	5 (6.3%)
Non-Cardiac Chest Pain	4 (5.1%)
Pyrexia	11 (13.9%)
Infections/Infestations	6 (7.6%)
Tonsillitis	3 (3.8%)
Influenza	3 (3.8%)
Pharyngitis	1 (1.3%)
Metabolism and Nutrition	9 (11.4%)
Anorexia	1 (1.3%)
Decreased appetite	8 (10.1%)
Dehydration	1 (1.3%)
Musculoskeletal	16 (20.3%)
Arthralgias	4 (5.1%)
Back pain	12 (6.6%)
Myalgia	2 (2.5%)
Pain in extremity	1 (1.3%)
Nervous system	47 (59.5%)

Dizziness	11 (13.9%)
Headache	40 (50.6%)
Hemiparesis	1 (1.3%)
Paresthesia	4 (5.1%)
Somnolence	1 (1.3%)
Torticollis	1 (1.3%)
Respiratory/Thoracic	6 (7.6%)
Cough	5 (6.3%)
Rhinalgia	1 (1.3%)
Skin	22 (27.8%)
Sweating	2 (2.5%)
Dermatitis	1 (1.3%)
Erythema	1 (1.3%)
Pruritus	18 (22.8%)
Rash	1 (1.3%)
SC abscess	2 (2.5%)

Renal Toxicity

Mean Cr remained relatively stable during therapy. Approximately a third of the subjects had some degree of Cr elevation above baseline, but the majority of elevations were CTCAE grade 1 or 2. At EOT, three subjects had grade 3 elevations above baseline, and two subjects grade 4 elevations. The highest absolute Cr value was 1.5.

Table 127: Cr Changes –Study Z022

	Miltefosine N = 79
Day 14	
Cr 1-<1.5x baseline	13 (16.5%)
Cr 1.5-<3 x baseline	7 (8.9%)
Cr 3-<6x baseline	1 (1.3%)
Cr ≥ 6 x baseline	1 (1.3%)
Day 28	
Cr 1-<1.5x baseline	15 (18.9%)
Cr 1.5-<3 x baseline	7 (8.9%)
Cr 3-<6x baseline	3 (3.8%)
Cr ≥ 6 x baseline	2 (2.5%)
Mean Cr (SD)	
At Baseline	0.84 (0.31)
Day 14	0.87 (0.36)
Day 28	0.83 (0.34)

Hepatic Toxicity

No subject had an increase in ALT, AST, AP or bilirubin above baseline or above ULN.

Hematologic Toxicity

There were no changes in hemoglobin, WBC or platelets.

Deaths

One subject died during the study. This was a 26 year old woman with newly diagnosed ML and self-reported history of gallbladder problems and *Giardia* infection by stool parasitology at enrollment. On Day 9, she experienced CTC grade 1 nausea and diarrhea. On day 13, she experienced occasional vomiting. On day 14, she suffered soft tissue trauma to the leg and received diclofenac IM and orally. On the same night, she complained of abdominal pain, malaise, vomiting and was observed to have a transient pruritic rash. She was hospitalized on day 16 for parenteral hydration. On day 17, she developed fever (38° C), tachypnea, hypotension (SBP 80) and severe abdominal pain in the RUQ. She received IV fluids, scopolamine, Dioxadol IM (combination of octatropine methylbromide and metamizole). Five hours later, she was transferred to the ICU where she remained in shock, developed multiple ecchymotic areas, and experienced cardiopulmonary arrest which did not respond to resuscitation measures.

The narrative stated that the patient was at a family dinner on the same night that she developed symptoms of abdominal pain, and that 2 other family members were later diagnosed with typhoid fever. The narrative also stated that the liver specimen revealed non-specific reactive hepatitis with diffuse steatosis which was not considered indicative of drug toxicity or viral hepatitis. The report assessed the death as likely due to typhoid fever.

Reviewer's Comments
AEs noted in miltefosine recipients included abdominal pain, nausea, gastritis, headache, dizziness, pyrexia, pruritus, and decreased appetite. Approximately a third of the subjects experienced some degree of Cr elevation above baseline, and 5 (6.3%) subjects had CTC grade 3 and 4 Cr elevations at EOT, but all absolute values were < 1.5 mg/dL. There were no hepatic or hematologic toxicities.

The clinical course of the one patient who died is not compatible with typhoid fever. Her systemic symptoms developed shortly after soft tissue injury and she progressed rapidly to shock and cardiovascular collapse. She complained of abdominal pain and the narrative provided did not comment as to whether there was evidence of soft tissue infection. The results of laboratory studies, blood cultures or abdominal imaging were not provided, and the patient did not receive antibiotics but was treated with a variety of analgesics/NSAIDs. The clinical history is more compatible with septic shock, possibly related to an abdominal catastrophic event, or possibly toxic shock syndrome. The narrative stated that liver specimen did not show evidence of hepatitis or drug toxicity but did not state how that specimen was obtained and whether an autopsy was performed. My assessment is that death was likely due to septic or toxic shock and unlikely to be related to miltefosine.

Study Conclusions

In this single arm study, 62% of subjects with mucosal leishmaniasis treated with miltefosine experienced cure. The mucosal severity score, a composite score grading edema, erythema, infiltration and erosion at 5 anatomical sites (nasal skin, nasal mucosa, palate, pharynx and larynx) was zero at 1 year after EOT, indicating complete healing. The published article that reported the results of this study also reported cure rate in 19 historical controls who received amphotericin B. The amphotericin cure rate was 37% in the ITT population and 50% in the evaluable/PP population. The same study center had refused to enroll patients in a study comparing miltefosine to antimony because of concerns regarding the efficacy of antimony preparations, which was poor in their experience.

The miltefosine cure rate in Study Z022 is comparable to antimony cure rates reported in published studies from Peru (50-60%), but lower than amphotericin or antimony cure rates in Brazil.

Similar to the AEs noted in CL studies, the main adverse events associated with miltefosine were nausea, abdominal pain, gastritis, headache, dizziness, pyrexia, pruritus, decreased appetite and renal impairment.

Visceral Leishmaniasis Due to L. donovani

In support of seeking the VL indication, the sponsor submitted the study report and datasets for Study 3154, and study report and safety datasets pertaining to the subjects who died for Study Z025. These studies have been published in medical journals.

Summary study reports for dose ranging studies 033, 3089, 3091, 3109, 3127, and Z019 were also submitted. Study reports for Study 3206, conducted in pediatric patients 2-11 years of age, and for the post marketing studies Z013 and Z013b were also submitted.

Study 3154

This study was conducted between July 25, 1999 and December 29, 2000 at 3 clinical centers in Bihar, India[37]. The study was planned and conducted in coordination with the WHO, and was approved by the Indian health authorities. The study protocol and informed consent were reviewed by Independent Ethics Committees (IEC). The study conduct was jointly monitored by the WHO and ASTA Medica. The study centers and the central laboratory were audited by ASTA Medica's quality control department for GCP.

[37] Sundar S., Jha TK., et al. Oral miltefosine for Indian visceral leishmaniasis. NEJM 2002;347: 1739-46

Study Design

The study was a randomized, open-label, non-inferiority design trial comparing oral miltefosine 2.5 mg/kg given daily for 28 days to amphotericin B deoxycholate 1 mg/kg every other day for 15 injections in the treatment of VL. Amphotericin was chosen as the comparator drug instead of pentavalent antimony because resistance to antimony is prevalent in Bihar.

A central randomization procedure was used, and treatment was started within one week of screening. Randomization ratio was 3 miltefosine: 1 amphotericin B. Subjects ≥ 25 kg received 50 mg capsule of miltefosine twice a day after meals. Subjects weighing less than 25 kg received 50 mg capsule of miltefosine once in the morning after a meal. Amphotericin was administered over 6 continuous hours every other day.

Subjects ≥ 12 years of age with clinical signs and symptoms compatible with VL (fever, splenomegaly and cytopenia) confirmed by the presence of *Leishmania* amastigotes in spleen or bone marrow aspirates were eligible. Pregnant or lactating women and women unable to maintain contraception for the treatment period plus 2 months were excluded. Subjects with platelets < 50 x 10^9/L, WBC < 1 x 10^9/L, hemoglobin (Hb) < 6 g/100ml, ALT or AST or alkaline phosphatase ≥ 3x ULN, bilirubin ≥ 2x ULN, Cr or BUN ≥ 1.5x ULN or PT ≥ 5 seconds above control were excluded. Subjects who had undergone major surgery within the previous 2 weeks or had any uncontrolled condition, such as HIV infection, active tuberculosis, malaria or malignancy were also excluded, as were subjects who were receiving other concomitant anti-*Leishmania* drugs or had failed prior amphotericin B therapy.

All subjects were hospitalized during treatment, and were monitored weekly until the end of therapy, and at six months after completion of therapy. Spleen or bone marrow aspirate was done at screening and at EOT (Day 28 for miltefosine group and Day 30 for amphotericin B group). A marrow or spleen aspirate was also performed for subjects who had signs or symptoms suggestive of VL relapse at the 6 months visit. All smears were read by the same pathologist, and one out of 10 slides marked with a code number only was forwarded to an external pathologist for review under blinded conditions. Parasite density was scored microscopically from 0 (no amastigote per 1000 fields) to 6+ (> 100 amastigotes per field).

Hematology and chemistry labs were obtained at screening, weekly during therapy and at 6 months follow up. ECG was obtained at screening and weekly during therapy. Ophthalmology exam was done at screening, at EOT and at 6 months follow up.

Treatment response was classified as Initial Cure, Final Cure, Relapse or Failure. The primary efficacy endpoint was Final Cure. Initial Cure was defined as absence of parasites at the end of therapy (parasite score 0 on spleen or bone marrow aspirates). Subjects with parasite density of 1 at EOT were re-assessed 1 month later, and designated as initial cure if the score was 0 or treatment failure if the score was > 0. Final Cure was defined as Initial Cure plus no relapse and absence of clinical signs and symptoms attributable to leishmaniasis during the 6 months follow up. Treatment failure was

defined as spleen or marrow aspirate score > 1 at EOT or score > 0 any time one month after EOT. Subjects designated as treatment failure were treated with rescue medication (AmBisome® – liposomal amphotericin B).

Subjects who had experienced initial cure but who had reappearance of signs and symptoms during the follow up period underwent a repeat aspirate. Those with a negative aspirate were evaluated for another explanation for their clinical symptoms. Those with a positive aspirate were classified as relapse.

Absence of clinical signs and symptoms attributable to VL was defined as

- Loss of fever that is attributed to VL and
- Spleen size at least 30% smaller than at pre-treatment (only applicable if spleen size was > 1 cm below the costal margin at pre-treatment). If palpable spleen was ≤ 1 cm at pre-treatment, it must not be > 1 cm when clinical response is assessed, and
- Hemoglobin ≥ 10.0 g/dl for female subjects or ≥ 11.5 g/dl for male subjects (or at EOT, residual decrement from the lower limit of normal < 10% of the decrement at baseline), and
- Platelets ≥ 100,000/µl (or at EOT, residual decrement from the lower limit of normal < 30% of the decrement at baseline), and
- Leukocytes ≥ 3500/µl (or at EOT, residual decrement from the lower limit of normal < 30% of the decrement at baseline)

Sample size was calculated based on one-sided alpha 0.025, power 0.80 and NI margin of 15%, assuming final cure rates of 88 to 92% for miltefosine of and 94 to 98% for amphotericin.

The Intent-to-Treat (ITT) population included all subjects who received at least one dose of study medication. The Per Protocol (PP) population included the ITT subjects who were treated as planned and followed up for at least 6 months after EOT or until treatment failure. The Safety population included all subjects who were exposed to at least one dose of study medication.

Protocol Amendments

There were 4 amendments. The first was issued before treatment of the first patient and pertained to including a test dose of 5 mg of amphotericin B to be administered over 1 hour one day prior to the first dose. The second amendment pertained to instructions regarding reconstitution of amphotericin vials and to excluding subjects who had received prior treatment with amphotericin. The third amendment pertained to clarification regarding withdrawal of subjects due to lack of tolerability and the fourth pertained to adding a coordinating investigator.

Disposition

Subject disposition is shown in the table below.

Table 128: Subject Disposition – Study 3154

	MLT	AMB
Screened	301	99
Randomized	301	99
Not Exposed to Study Drug	-1	-1
Received the Other Drug	-1	+1
ITT Population	299	99
Did Not Complete Treatment	9 (3.0%)	3 (3.0%)
Lack of tolerability/AE	4	2
"Intercurrent disease"	3	0
Withdrawal of consent	1	1
Death	1	0
Excluded from PP	12 (4.0%)	5 (5.0%)
Lack of tolerability/AE	4	2
"Intercurrent disease"	3	0
Withdrawal of consent	1	1
Death	2	0
Lost to Follow up	2	2
PP	287	94
Safety Population	299	99

Demography and Other Subject Characteristics

Table 129: Subject Characteristics – Study 3154

	MLT N = 299	AMB N = 99
Male*	211 (70.6%)	58 (58.6%)
Mean Age, years (SD)	26.5 (12.7)	26.3 (12.0)
Median Age, years (Range)	25.0 (12-64)	25.0 (12-60)
Age ≤ 17 years	102 (34.1%)	31 (31.3%)
Mean Weight. kg (SD)	38.6 (10.0)	38.3 (12.1)
Median Weight, kg (Range)	40.0 (15-67)	40.0 (14-64)
Mean BMI (SD)	16.1 (2.5)	16.3 (2.9)
Median BMI (Range)	15.9 (8.2-24)	16.4 (9.4-27.4)
Karnofsky score		
60	89 (29.8%)	31 (31.3%)
70	102 (34.1%)	32 (32.3%)
80	4 (1.3%)	1 (1.0%)
90	104 (34.8%)	35 (35.4%)
Newly diagnosed VL	214 (71.6%)	71 (71.7%)
Prior therapy**	85 (28.4%)	28 (28.3%)
Unresponsive	69	21
Relapse	16	7
Parasitology score		
1-10 per 1000 fields	130 (43.5%)	48 (48.5%)
1-10 per 100 fields	91 (30.4%)	25 (25.3%)
1-10 per 10 fields	53 (17.7%)	15 (15.2%)

1-10 per 1 field	22 (7.4%)	8 (8.1%)
10-100 per 1 field	3 (1.0%)	3 (3.0%)
Parasitology score		
Mean (SD)	1.9 (0.99)	1.9 (1.1)
Median (Range)	2 (1-5)	2 (1-5)
Median Duration of Fever	9.4 weeks	8.9 weeks
Splenomegaly, cm		
Mean (SD)	6.9 (4.3)	6.9 (4.3)
Range	0.5-27.0	1.0-21.0

*p = 0.035
**Pentavalent antimony

Reviewer's Comments
The treatment arms were matched for age, weight, BMI, performance status, prior VL therapy, parasite density/organism burden and signs, symptoms and duration of VL. They were not matched for gender. A statistically significantly higher percentage of males were randomized to miltefosine. This raises concerns regarding a flawed randomization process in this open label study especially because miltefosine is teratogenic and females were advised to use effective contraception during treatment and for 2 months after EOT. The gender imbalance was most obvious at study site 1 (M/F ratio 4.2 in miltefosine arm vs. 1.8 in amphotericin arm) and to a lesser extent at study site 3 (M/F ratio 2.3 in miltefosine arm vs. 1.1 in amphotericin arm), but not at study site 2 (M/F ratio 1.6 in the miltefosine arm vs. 1.4 in the amphotericin arm).

Approximately a third of the enrolled population had received prior antimony therapy and approximately a third were 12 to 17 years of age.

Efficacy Results

Primary Efficacy Endpoint

The primary efficacy endpoint was Final Cure, defined as Initial Cure plus no relapse and absence of clinical signs and symptoms attributable to leishmaniasis during the 6 months follow up period.

Initial Cure was defined as absence of parasites at the end of therapy (parasite score 0 on spleen or bone marrow aspirates). Subjects with parasite density of 1 at EOT were re-assessed 1 month later, and designated as initial cure if the score was 0 or treatment failure if the score was > 0.

Initial Cure rates were similar in the two treatment arms. No subject had a score >1. In the miltefosine group, 5 subjects had a score of 1 at EOT. 4 were retested one month later and all had a score of 0. In the amphotericin B group, 1 had a score of 1 at EOT. This subject was retested one month later and was negative.

Table 130: Initial Cure – ITT - Study 3154

	MLT N = 299	AMB N = 99

Initial Cure	293 (98.0%)	97 (98.0%)
Parasitology score 0 at EOT	289 (96.7%)	96 (97.0%)
Parasitology score 1 at EOT	5 (1.7%)	1 (1.0%)

Final Cure was defined as Initial Cure plus absence of signs and symptoms (S/S) attributable to VL at 6 months follow up. 6 months evaluation was not available for 6 subjects in the miltefosine arm and 3 subjects in the amphotericin arm. These un-evaluable subjects were classified as failure. The study report states that at the 6 months follow up visit, 97 subjects in the miltefosine arm and 16 subjects in the amphotericin arm had did not have absence of symptoms compatible with VL. An alternative diagnosis was made in 86 of these subjects. In the remaining 27 subjects, a spleen aspirate was performed. *Leishmania* was seen in 9 subjects and the aspirate was parasitologically negative in 18. All 9 subjects with a positive aspirate had received miltefosine. These 9 subjects were classified as relapse.

Two deaths occurred in the miltefosine arm, one during therapy due to bacterial meningitis and one 2 months after therapy in a subject who experienced Initial Cure and was treated for *P. vivax* malaria.

Table 131: Final Cure - Study 3154 – Sponsor's analysis

	MLT N = 299	AMB N = 99	Difference AMB-MLT	P Value
ITT				
Final Cure 95% CI	282 (94.3%) 91.1%, 96.7%	96 (97.0%) 91.4%, 99.4%	2.7% (-1.62%, 6.93%)	0.43
Relapse	9 (3.0%)	0		
Deaths	2 (0.7%)	0		
Not-assessable	6 (2.0%)	3 (3.0%)		
PP				
	MLT N = 287	AMB N = 94	Difference AMB-MLT	P Value
Final Cure	279 (97.2%)	94 (100%)	2.8% (0.88, 4.69%)	0.21

Reviewer's Comments
The study was designed to demonstrate that miltefosine is non-inferior to amphotericin B deoxycholate by a non-inferiority margin of 15%. On February 15, 2012, the sponsor submitted a non-inferiority margin justification. There were no literature reports that allowed estimation of placebo effect for the primary endpoint of final cure at 6 months. Because resistance to antimony is prevalent in Bihar, India, the cure rates achieved by antimony therapy were used to conservatively estimate placebo effect. Reports of final cure rates achieved by amphotericin B in Bihar were used to estimate amphotericin treatment effect, or M1. The Division of Anti-Infective Products indicated to the sponsor that although the large M1 could support a non-inferiority margin (M2) of 15%, a 10% margin is clinically more acceptable (Please refer to the NI margin justification reviews by me and the statistical reviewer Dr. Zeng, both filed in DARRTS). This 10% margin will be used for this review.

There are inconsistencies between the study report and the datasets. The study report and the published article state that a total of 113 subjects (97 in the miltefosine arm and 16 in the amphotericin arm) did not have absence of symptoms compatible with VL at the 6 months follow up period, that alternative diagnoses explained these symptoms in 86 subjects and that bone marrow or spleen aspirates performed in the remaining 27 subjects were positive in 9 subjects, all in the miltefosine arm. The abnormality was anemia in most of the remaining 86 subjects.

However, the clinical response dataset (ADCR) lists 29 subjects who underwent a marrow or spleen aspirate at 6 months follow up, not 27. The additional 2 subjects included one in the miltefosine arm and one in the amphotericin arm (subjects 1/003 and 1/104 respectively). Subject 1/104 had resolution of fever and decrease in spleen size from 20.5 cm at screening to 4 cm at 6 months follow up and Subject 1/003 had decrease in spleen size from 13.5 cm to 6.5 cm. Both had resolution of fever and anemia and normalization of WBC and platelets. The aspirate in both was negative. In response to an information request, the sponsor confirmed that 29 aspirates were performed, and that 2 aspirates were performed on subjects who did not meet the protocol criteria for failure.

The protocol defined absence of signs and symptoms of VL at 6 months as any of the following findings: resolution of fever, at least 30% decrease in spleen size, Hb ≥ 10.0 if female and ≥ 11.5 if male, platelet count ≥ 100k or WBC ≥ 3500. According to these criteria, 100 subjects were identified from the DC dataset, 88 in the miltefosine arm and 12 in the amphotericin arm. The VS dataset (for fever response), OM dataset (for spleen size), and LB dataset (for hematology parameters) also identify 88 miltefosine subjects and 12 amphotericin subjects with residual S/S suggestive of VL at 6 months.

However, 4 subjects flagged in the DC dataset as having residual S/S do not fit the S/S criteria outlined in the protocol (subjects 2/025, 2/046, 2069 and 2/129 – all with anemia but Hb greater than 10 if female and 11.5 if male), and 4 subjects identified from the other datasets were not flagged in the DC dataset (subjects 1/061, 2/111, 2/128 and 3/106). These 4 subjects not flagged in the DC dataset had spleen that increased from 6.5 cm to 9 cm at follow up, and Hb 5.3, 4.6 and 11.2 respectively).

The sponsor's 113 subjects with residual signs or symptoms of VL at 6 months were listed in Table 12.1 of the study report. Of the 16 amphotericin subjects listed, 3 subjects were not assessed at 6 months (subjects 1/137 and 2/021 and 3/052), one subject was not listed in the individual subject listing dataset, the response dataset, the AE dataset or the exposure dataset, but was listed in the DM dataset and in the DS dataset as having increased SGOT and "other disposition event" (3/024). The remaining 12 subjects listed in the sponsor's table were the same 12 subjects identified from the datasets. None underwent further evaluation with a marrow or spleen aspirate.

Of the 97 miltefosine subjects listed in table 12.1 of the sponsor's study report, 9 were not assessed at 6 months (1/086, 2/009, 2/043, 2/048, 2/092, 3/030, 3/038, 3/069, 3/092). The

remaining 88 subjects were the same 88 subjects identified from the VS, OM and LB datasets.

The subjects with residual S/S at 6 months are therefore 100, not 113. In response to an information request, the sponsor confirms that the 100 subjects who had 6 months follow up visit and listed in table 12.1 of the study report are the subjects who did not have absence of VL s/s.

These 100 subjects were distributed among the 3 study sites: 27 at site 1 (1 amphotericin, 26 miltefosine), 35 at site 2 (5 amphotericin, 30 miltefosine), and 38 at site 3 (6 amphotericin, 32 miltefosine). 23 of the 27 subjects at study site 1 underwent an aspirate (85.2%) compared to 2/35 (5.7%) and 2/38 (5.3%) at sites 2 and 3 respectively. This indicates significant variability in adherence to the protocol between the study sites.

To resolve the inconsistent approach to follow up evaluations, the clinical data for these 100 subjects were reviewed, blinded as to which subject underwent an aspirate.

Two amphotericin subjects had residual abnormalities that in my opinion may warrant further investigation: subject 3/019 who had persistent unexplained thrombocytopenia (78k at screening, 54k at follow up, though with stable Hb and WBC and complete resolution of splenomegaly and fever), and subject 2/101 (no improvement in baseline borderline platelets, though resolution of splenomegaly and some improvement in Hb which remained < 9). The residual abnormality in all others was isolated anemia (Hb 9.6-11.4 range) with normalization of WBC and platelets and complete resolution of fever and splenomegaly. A conservative analysis would be to consider these two subjects therapeutic failure. The conservative estimate of amphotericin cure rate is 94/99 (94.9%) in ITT and 92/94 (97.9%) in PP.

In the miltefosine arm, further investigation was thought to be warranted for 25 subjects: the nine subjects who had a positive follow up aspirate (seven at site 1 and two at site 3), four subjects who had a negative aspirate (two at site 1 and two at site 2), and twelve subjects who did not undergo a follow up aspirate (ten at study site 3 and two at site 2). Findings in these twelve subjects included persistence of severe anemia (4), thrombocytopenia (7), and leukopenia and anemia (1). The residual abnormality in all other subjects was isolated anemia (range 9.4-11.3), with normalization of WBC and platelets and complete resolution of fever and splenomegaly. A conservative analysis would be to consider these 12 subjects therapeutic failure. The conservative estimate of miltefosine cure rate is 270/299 (90.3%) in ITT and 267/287 (93.0%) in PP populations.

Table 132: Follow Up Aspirates by Study Site – Study 3154

Study Site	*1* *N = 145*	*2* *N = 144*	*3* *N = 109*	*Tota1*
Any S/S suggestive of VL	*27/145 (18.6%)*	*35/144 (24.3%)*	*38/109 (34.8%)*	*100/398 (25.0%)*
Aspirate done	*23/27 (85.2%)*	*2/35 (5.7%)*	*2/38 (5.3%)*	*27/100 (27.0%)*
Further work up warranted (Reviewer's Assessment)	*9/27 (33.3%)*	*5/35 (14.3%)*	*13/38 (34.2%)*	*27/100 (27.0%)*

Table 133: Final Cure – Study 3154 – Conservative Estimates of Cure - Reviewer's Analysis

	MLT	***AMB***	***Difference AMB-MLT***	***P Value***
ITT				
Final Cure	*270/299 (90.3%)*	*94/99 (94.9%)*	*4.6% (-2.0%, 9.8%)*	*0.21*
PP				
Final Cure	*267/287 (93.0%)*	*92/94 (97.9%)*	*4.9% 4.8% (-0.70%, 8.99%)*	*0.12*

The revised cure rates do not alter the conclusion that miltefosine is non-inferior to amphotericin B in the ITT and PP populations for the primary endpoint of final cure, where final cure was defined as initial cure at EOT and absence of clinical signs and symptoms attributable to VL at 6 months.

The 9 subjects with documented relapse did not differ in baseline characteristics from the overall population for age, spleen size, parasite density, or receipt of prior treatment. However, the group that relapsed had a higher mean weight and lower mean miltefosine dose per kg compared to the group that was cured.

Table 134: Mean Miltefosine Dose – Study 3154

	Miltefosine Cured N = 282	Miltefosine Relapse N = 9	Total N = 299
Mean weight (SD) Median (Range)	38.3 kg (10.1) 40 (15-67)	44.3 (5.9) 45 (35-53)	38.6 (10) 40 (15-67)
Mean (SD) mg/kg	2.58 (0.54)	2.29 (0.32)	2.57 (0.53)
Median (Range)	2.5 (1.5-4)	2.22 (1.9-2.9)	2.5 (1.5-4)

Reviewer's Comments
Because follow aspirates were not performed in the majority of subjects who did not have absent VL signs or symptoms, the data correlating per kg dose with relapse may be difficult to interpret. Assuming that only 9 relapses occurred, the relapse rate was higher among subjects who received less than 2.5 mg/kg/day compared to subjects who received ≥ 2.5 mg/day (9.6% vs. 1.7%); 7 of the 9 subjects with documented relapse received a dose less than 2.5 mg/kg.

If the additional 12 miltefosine subjects that may have warranted further workup are also considered relapses, the mean dose in those relapsed remains lower compared to the dose in those cured (2.39, SD 0.45, median 2.27 and range 1.85-3.7, versus mean 2.59, SD 0.54, median 2.5, range 1.5-4). The relapse rate remains higher among subjects who received less than 2.5 mg/kg compared to subjects who received ≥ 2.5 mg/kg/day (21.1% vs. 8.4%).

Table 135: Effect of Miltefosine Dose – Study 3154 – Sponsor's Cure Rate

Miltefosine Dose mg/kg	*Final Cure*	*Relapse*
1.7 -< 2	*24/26 (92.3%)*	*1/26 (3.8%)*

2- <2.5	*96/104 (92.3%)*	*6/104 (5.8%)*
2.5-< 3	*114/121 (94.2%)*	*2/121 (1.7%)*
3-3.9	*39/39 (100%)*	*0*
≥ 4	*9/9 (100%)*	*0*
Total	*282/299 (94.3%)*	*9/299 (3.0%)*

Table 136: Effect of Dose – Modified Analysis of Cure – Study 3154

Miltefosine Dose mg/kg	*Final Cure*	*Relapse*
1.7- < 2	*22/26 (84.6%)*	*3/26 (11.5%)*
2- <2.5	*92/104 (88.5%)*	*10/104 (9.6%)*
2.5-< 3	*109/121 (90.1%)*	*7/121 (5.8%)*
3-3.9	*38/39 (97.4%)*	*1/39 (2.6%)*
≥ 4	*9/9 (100%)*	*0*
Total	*270/299 (90.3%)*	*21/299 (7.0%)*

Reviewer's Comments

Issues pertaining to resistance were not addressed. VL in India is caused by L. donovani (epidemiologic data - cultures were not obtained in this study). VL in India is anthroponotic, so resistance developing in patients who relapse can potentially spread. Development of resistance is a concern because the long half-life of miltefosine may result in potentially sub-inhibitory concentrations for several weeks after therapy. Exposure to sub-inhibitory concentrations has been demonstrated to induce resistance in L. donovani promastigotes in vitro due to a mutation in the alleles coding for the LdMT transporter that internalizes miltefosine into the parasite[7].

Evidence is emerging that miltefosine final cure is decreasing. As already indicated in the reviewer's comment under the Microbiology section, a published article compared the susceptibility to miltefosine of 16 clinical isolates of L. donovani obtained from Bihar, India, where miltefosine is extensively used, to 12 clinical isolates obtained from a non-endemic area in India (eastern Uttar Pradesh) where miltefosine use is not extensive. The amastigote ED_{50} was not statistically significantly different between the two regions, but the amastigote ED_{90} was statistically significantly higher in Bihar (mean 17.5+/-2.4 versus mean 13.7+/-3.6, p = 0.005)[8]. Clinical outcomes were not reported in this study.

Another published report evaluated the effectiveness of miltefosine in the treatment of VL after a decade of use in Bihar, India[38]. The study was conducted at one of the Study centers that participated in Study 3154 (Site 2 - the Kala Azar Medical Research Center). 567 patients (333 males, 234 females) with VL were enrolled and given the drug daily under direct observation. The eligibility criteria, definitions of initial and final cure and miltefosine dosing were the same as for Study 3154. 432 patients were 12 years of age or older. Mean parasite density, spleen size, body weight, Hb and WBC at baseline were similar to those for Study 3154. Five patients died: two during treatment (one due to vomiting resulting in volume depletion and shock and also severe pancytopenia, and one

[38] Sundar S, Singh A., et al. Efficacy of miltefosine in the treatment of visceral leishmaniasis in India after a decade of use. CID 2012;55(4)543-50

sudden death), and three during the follow up period (one patient with parasitologic relapse at 5 months with severe pancytopenia and grade 3 renal impairment, one patient with severe pancytopenia but unspecified cause of death, and one patient committed suicide). Treatment was discontinued in 9 patients due to AEs (renal impairment, diarrhea, vomiting, hepatic dysfunction, pancytopenia, severe anemia). No patients were lost to follow up. 553 (97.5%) achieved initial cure in the ITT population and 39 patients relapsed (7.2%), for a final cure rate of 90.3%. The authors expressed their concern that the decrease in final cure rate compared to Study 3154 overall (94.3%, lower limit of 95% CI 91.1%) and compared to Site 2 specifically (97.2%) may be due to emergence of resistance. This concern could not be confirmed at the time of the publication because in vitro susceptibility data were still being processed. The results of this study are concerning not only because of the higher incidence of relapse but also because 3 of the 5 deaths may be related to VL that inadequately responded to treatment or relapsed.

In another study in Nepal[39], a cohort of 120 VL patients was prospectively monitored for clinical outcomes up to 12 months after completion of therapy with miltefosine. Doses were the same as in Study 3154. Definitions of initial and final cure were also the same as in Study 3154 except that final cure was assessed at 12 months after therapy rather than at 6 months. The study initially enrolled 217 patients, including children and women. Amphotericin was given to 35% of those enrolled because miltefosine was not thought to be clinically appropriate (severely ill patient, sepsis, abnormal liver or kidney function, pregnant or lactating, infants, severe anemia or non-availability of the 10 mg capsule). 12 patients with previous history of miltefosine treatment followed by relapse were also excluded.

3/120 did not tolerate miltefosine and were switched to amphotericin B, one patient died after one week of treatment and one patient discontinued the study after 14 days. The remaining 115 subjects experienced initial cure at the EOT (115/120, 95.8%).
13 patients relapsed within the first 6 months yielding 6 months cure rate of 99/120 (82.5%). 11 relapsed during the second 6 months, yielding 12 months cure rate of 88/120 (73.3%). The total number of relapses was 24, or 20%. There were also 2 additional deaths during the follow up period. Causes of deaths were not provided in the article.

In the Nepal study, miltefosine concentrations at EOT were available from 48 cured and 16 relapsed cases (representing 54.5% of cured and 66.6% of relapses). There was no significant difference in miltefosine exposure between cured and relapsed patients, with mean whole blood concentrations of 46.7 ug/mL (SD 15) and 44.5 ug/mL (SD 16.6) respectively. Only age < 12 years was significantly associated with relapse. Gender, Hb at baseline, spleen size at baseline, fever duration, BMI or past VL treatment were not associated with relapse.

Parasite fingerprinting was obtained for 8 paired bone marrow samples from patients who relapsed. Relapses were not associated with re-infection with a new strain. In

[39] Rijal S, Ostyn B, et al. Increasing failure of miltefosine in the treatment of Kala-azar in Nepal and the potential role of parasite drug resistance, reinfection, or noncompliance. CID 2013;56:1530-8

addition, IC50s were obtained for 17 strains in patients who were cured and compared to IC50s for isolates obtained from 26 patients who relapsed. The mean IC50s were not statistically different and also not statistically different compared to historical isolates. For relapsed strains, no increase in IC50 was demonstrated pre- and post-therapy.

In the above study from Nepal, the initial cure rate achieved by miltefosine treatment was high (95%) and comparable to that achieved in Study 3154, but the cure rate at 6 months was considerably lower. Relapses occurred during the 12 months of follow up, suggesting that 6 month follow up, which has been the standard in VL trials, may not be sufficient to capture all the relapses. The Nepal study failed to identify a definite reason for the higher therapeutic failure or relapse, as the IC50 did not increase pre and post-therapy and the exposures were not different at EOT between relapsed and cured patients. It is possible that some relapses are occurring later due to the long half-life of miltefosine.

Another issue that pertains to resistance is compliance. All subjects in Study 3154 were hospitalized. Because miltefosine is orally administered, the effectiveness of miltefosine may be lower under outpatient conditions due to poor compliance. To investigate that, 1132 VL patients were enrolled in a Phase 4 trial conducted at 13 centers in Bihar, India[40]. 95.5% completed the full 28 day treatment course, and 85.8% returned for 6 month follow up visit (compared to 98% in Study 3154). Final cure at 6 months was 82% in ITT and 95% in PP. The lower final cure rate in the ITT population could be due to considering patients who failed to return for follow up as treatment failures, but decreased performance of miltefosine under actual circumstances of use is also possible.

Primary End point in Study Subpopulations

Table 137: Final Cure by Age, Gender, Study Site, Prior VL Therapy and Weight

Final Cure	*MLT N = 299*	*AMB N = 99*	*Difference MLT-AMB*
Age ≤ 17 years	*100/102 (98.0%)*	*30/31 (96.8%)*	*2.2%*
Age > 17 years	*182/197 (92.4%)*	*66/68 (97.1%)*	*-4.7%*
Females	*83/88 (94.3%)*	*40/41 (97.6%)*	*-3.3%*
Males	*199/211 (94.3%)*	*56/58 (96.6%)*	*-2.3%*
Study Site 1	*101/109 (92.7%)*	*35/36 (97.2%)*	*-4.5%*
Study Site 2	*105/108 (97.2%)*	*35/36 (97.2%)*	*0*
Study Site 3	*76/82 (92.7%)*	*26/27 (96.3%)*	*-3.6%*
Newly diagnosed	*202/214 (94.4%)*	*70/71 (98.6%)*	*-4.2%*
Previously treated	*80/85 (94.1%)*	*26/28 (92.9%)*	*1.2%*
Persons weighing ≥ 25 kg	*254/271 (93.7%)*	*80/83 (96.4%)*	*-2.7%*
Persons weighing < 25 kg	*28/28 (100%)*	*16/16 (100%)*	*0*

Reviewer's Comments

[40]Battacharya SK, Sinha PK, et al. Phase 4 trial of miltefosine for the treatment of Indian visceral leishmaniasis. CID 2007; 196:591-598.

There were no significant differences in response between the two treatment arms by age, gender, prior treatment or weight at baseline.
There were also no differences in response by study site using the original sponsor's analysis. The reviewer's conservative estimate of cure yield indicates a lower miltefosine cure rate at site 3.

Table 138: Cure Rates by Study Site – Modified Cure Rate Analysis – Study 3154

	MLT N = 299	*AMB N = 99*	*Difference MLT-AMB*
Study Site 1	*101/109 (92.7%)*	*35/36 (97.2%)*	*-4.5%*
Study Site 2	*103/108 (95.4%)*	*34/36 (94.4%)*	*1.0%*
Study Site 3	*66/82 (80.5%)*	*25/27 (92.6%)*	*-12.1%*
Total	*270/299 (90.3%)*	*94/99 (94.9%)*	*-4.6%*

Individual Signs and Symptoms Related to VL

Spleen Size

At 6 months follow up, the spleen was no longer palpable in 262 subjects in the miltefosine arm (87.6%) compared to 88 in the amphotericin arm (89.9%). The degree of resolution of splenomegaly over time was similar in both groups.

Table 139: Spleen Size – Study 3154

Spleen Size cm	*MLT N = 299*	*AMB N = 99*
Screening		
Mean (SD)	*6.9 (4.3)*	*7.0 (4.4)*
Median	*6*	*6*
Range	*0.5-27*	*1-21*
Day 7		
Mean (SD)	*5.3 (3.8)*	*5.1 (3.7)*
Median	*5*	*4*
Range	*0-25*	*0.5-19*
Day 14		
Mean (SD)	*3.1 (2.9)*	*3.5 (3.5)*
Median	*2.25*	*2.5*
Range	*0-19*	*0-19*
Day 21		
Mean (SD)	*1.8 (2.9)*	*2.1 (3.1)*
Median	*1*	*1*
Range	*0-15*	*0-19*
EOT		
Mean (SD)	*0.9 (1.6)*	*1.1 (2.1)*
Median	*0*	*0.5*
Range	*0-10*	*0-11*
Follow up 6 months		
Mean (SD)	*0.3 (1.3)*	*0.1 (0.6)*
Median	*0*	*0*
Range	*0-10*	*0-4*

Fever
The mean body temperature at screening and follow up visits were similar in the two groups. During therapy, fever occurrence was temporally related to amphotericin infusion in amphotericin recipients. Fever was attributed to VL in miltefosine recipients (also see safety section).

Table 140: Temperature Response – Study 3154

Temperature ^{o}F	MLT N = 299	AMB N = 99
Screening		
Mean (SD)	101 (1.5)	101 (1.3)
Median	101	101
Range	96-105	96-104
Follow up 6 months		
Mean (SD)	97 (0.9)	96.8 (0.6)
Median	97	97
Range	96-101	96-98.2

Weight
Subjects in both treatment arms experienced an increase in body weight. The degree of weight increase was similar in both arms.

Table 141: Weight Response – Study 3154

Weight kg	MLT N = 299	AMB N = 99
Screening		
Mean (SD)	38.5 (10)	38.3 (12)
Median	40	40
Range	15-67	14-64
Day 7		
Mean (SD)	38.9 (10)	38.7 (12)
Median	40	40
Range	16-66	14-65
Day 14		
Mean (SD)	39.3 (10)	39.2 (12)
Median	40	40
Range	16-66	14-65
Day 21		
Mean (SD)	39.8 (10)	39.7 (12)
Median	41	41
Range	17-68	15-66
EOT		
Mean (SD)	40.4 (10)	40.2 (12)
Median	41	42
Range	18-68	16-67
Follow up 6 months		
Mean (SD)	44 (10.7)	43.5 (12.5)
Median	45	44.5
Range	17-80	20-71

Hematology Parameters and Albumin
Hematology parameters (hemoglobin, total WBC, % neutrophils and platelet counts) and albumin improved in both treatment arms. The degree of improvement was similar in both treatment arms except for Hb which improved more rapidly in miltefosine recipients, probably reflecting the hematologic adverse effects associated with amphotericin B exposure (see also safety section).

Table 142: Changes in Albumin and Hematology Parameters– Study 3154

	MLT N = 299	AMB N = 99
Hemoglobin (Mean, SD)		
Screening	8 (1.6)	8.2 (1.8)
EOT	9.4 (2)	8.7 (1.6)
6 month FU	12 (1.9)	12.2 (1.4)
WBC (Mean, SD)		
Screening	3300 (1684)	3694 (1860)
EOT	6339 (3511)	6041 (2532)
6 month FU	8500 (2780)	9260 (2980)
% Neutrophils (Mean, SD)		
Screening	43 (13)	43 (12.4)
EOT	49 (13)	49 (14)
6 month FU	50 (12)	53 (14)
Platelets (Mean, SD)		
Screening	119 (67)	115 (50)
EOT	228 (125)	223 (114)
6 month FU	202 (76)	203 (70)
Albumin (Mean, SD)		
Screening	3 (0.6)	3 (0.6)
EOT	3.4 (0.7)	3.3 (0.6)
6 month FU	4.2 (0.5)	4.2 (0.5)

Safety Evaluation

Extent of Exposure
28 (9.4%) miltefosine subjects received 50 mg/day and 271 (90.6%) received 100 mg/day. 290 (97.0%) subjects received the full 28 days. Treatment duration was between 3 and 22 days in the 9 subjects who prematurely discontinued treatment (3, 6, 8, 11, 11, 12, 14, 15 and 22 days). The mean dose was 2.58 mg/kg/day (SD 0.53). The median dose was 2.5 mg/kg (range 1.5-4).

96 amphotericin subjects received 1 mg/kg for 30 days. The three subjects who discontinued therapy received 6, 8 and 20 days. The absolute daily dose was between 14 and 64 mg. The mean dose was 38.3 mg/day.

Concomitant Medications

82/299 (27.4%) in the miltefosine group and 93/99 (93.9%) in the amphotericin group received at least one concomitant medication. Analgesics and antihistamines were significantly more frequently administered to amphotericin recipients.

Table 143: Concomitant Medications – Study 3145

WHO Drug Reference List Therapeutic Class	*MLT N = 299*	*AMB N = 99*
Analgesics	*9 (3.0%)*	*84 (84.8%)*
Vitamins	*51 (17.1%)*	*18 (18.2%)*
*Anti-protozoal**	*33 (11.0%)*	*6 (6.1%)*
Anti-histamines for systemic use	*1 (0.3%)*	*36 (36.4%)*
Anti-emetic	*11 (3.7%)*	*3 (3.0%)*
Anti-bacterial for systemic use	*12 (4.0%)*	*1 (1.0%)*
Plasma substitutes and perfusion solutions	*7 (2.3%)*	*2 (2.0%)*
Anti-asthmatic	*0*	*2 (2.0%)*

* Mainly metronidazole +/- diloxanide, but also albendazole, chloroquine, primaquine

Reviewer's Comments
The cited indication for the significantly higher analgesic and anti-histamine use in the amphotericin group was prophylaxis/prevention of amphotericin infusion reaction. There were no significant differences in use of other concomitant medications.

Treatment Emergent Adverse Events

125 miltefosine recipients (41.8%) and 44 amphotericin recipients (44.5%), experienced at least one AE. Treatment was discontinued due to an AE in 8 miltefosine recipients and 3 amphotericin recipients (2.7% and 3.0% respectively).

6 miltefosine subjects (2.0%) and one amphotericin subject (1.0%) experienced at least one serious AE. Two miltefosine subjects died, one during therapy and one during the follow up period, assessed by the sponsor as due to bacterial meningitis and to *P. vivax* malaria respectively.

Table 144: Summary of AE – Study 3154

	MLT N = 299	*AMB N = 99*
Subjects with at least one AE	*125 (41.8%)*	*44 (44.5%)*
Subjects with Serious AE	*6 (2.0%)*	*1 (1.0%)*
Subjects with AE leading to drug discontinuation	*8 (2.7%)*	*3 (3.0%)*
Death	*2 (0.7%)*	*0*

The treatment emergent AEs as derived from the AE dataset are shown in the table below.

Table 145: Treatment Emergent AEs – Study 3154

MedDRA v. 12.0 System Organ Class	MLT N = 299	AMB N = 99

Blood and Lymphatics	2 (0.7%)	2 (2.0%)
Anemia	2 (0.7%)	1 (1.0%)
Thrombocytopenia	2 (0.7%)	2 (2.0%)
Cardiac disorders	2 (0.7%)	0
AV block	1 (0.3%)	0
BBB	1 (0.3%)	0
Ear and Labyrinth	2 (0.7%)	0
Earache	2 (0.7%)	0
Gastrointestinal	17 (5.7%)	9 (9.1%)
Abdominal Pain	1 (0.3%)	0
Constipation	1 (0.3%)	0
Diarrhea	9 (3.0%)	2 (2.0%)
Dyspepsia	2 (0.7%)	0
Gingival bleeding	0	1 (1.0%)
Melena	1 (0.3%)	0
Nausea	1 (0.3%)	0
Vomiting	3 (1.0%)	7 (7.1%)
General and Administration Site	53 (17.7%)	16 (16.2%)
Asthenia	19 (6.3%)	4 (4.0%)
Edema generalized	0	1 (1.0%)
Edema peripheral	0	1 (1.0%)
Pyrexia	28 (9.3%)	11 (11.1%)
Rigors	10 (3.3%)	1 (1.0%)
Hepatobiliary Disorders	3 (1.0%)	0
Hepatic Function abnormal	2 (0.7%)	0
Jaundice	1 (0.3%)	0
Infections and Infestations	5 (1.7%)	3 (3.0%)
Herpes simplex	0	1 (1.0%)
Malaria	1 (0.3%)	1 (1.0%)
Meningitis	1 (0.3%)	0
Otitis media	1 (0.3%)	1 (1.0%)
Parasitic infection	2 (0.7%)	0
Investigations	2 (0.7%)	1 (1.0%)
ECG abnormal	1 (0.3%)	0
BUN increased	1 (0.3%)	1 (1.0%)
Metabolism and Nutrition	69 (23.1%)	23 (23.2%)
Anorexia	69 (23.1%)	22 (22.2%)
Dehydration	0	1 (1.0%)
Hypokalemia	0	1 (1.0%)
Musculoskeletal	1 (0.3%)	0
Arthritis	1 (0.3%)	0
Nervous System	5 (1.7%)	2 (2.0%)
Convulsions	1 (0.3%)	0
Headache	4 (1.4%)	2 (2.0%)
Hemiplegia	1 (0.3%)	0
Nystagmus	0 (0.3%)	1 (1.0%)
Paresthesia	1 (0.3%)	0
Psychiatric	1 (0.3%)	0
Somnolence	1 (0.3%)	0

Renal and Urinary	0	1 (1.0%)
Renal function abnormal	0	1 (1.0%)
Reproductive	1 (0.3%)	0
Testis disorder*	1 (0.3%)	0
Respiratory and Thoracic	12 (4.0%)	4 (4.0%)
Bronchitis	0	1 (1.0%)
Cough	8 (2.7%)	2 (2.0%)
Dyspnea	2 (0.7%)	2 (2.0%)
Hemoptysis	1 (0.3%)	1 (1.0%)
Influenza-like illness	1 (0.3%)	0
Pneumonia	1 (0.3%)	0
Skin and Subcutaneous	3 (1.0%)	0
Rash	2 (0.7%)	0
Stevens-Johnson	1 (0.3%)	0
Vascular	1 (0.3%)	1 (1.0%)
Epistaxis	1 (0.3%)	0
Hemorrhage NOS* *	0	1 (1.0%)

*Verbatim is pain due bilateral hydrocele
* * Miscoded as hemorrhage; verbatim is agglutination of RBC in collection tube

In addition to the spontaneously reported adverse events, the sponsor elicited adverse events related to amphotericin infusion reactions and to vomiting and diarrhea. The elicited AE data set included daily temperature, investigator's assessment of whether a fever was related to VL or to amphotericin infusion, and toxicity grades for vomiting, diarrhea and rigors. The table below was derived from the elicited AE dataset.

Table 146: Elicited AE – Study 3154

	MLT *N = 299*	*AMB* *N = 99*
Temperature ≥ 100^{o} F	*254 (84.9%)*	*84 (84.8%)*
Investigator-Assessed as related to study drug	*0*	*72 (72.7%)*
Associated with rigors	*1 (0.3%)*	*68 (68.7%)*
Rigors	*1 (0.3%)*	*90 (90.1%)*
Vomiting	*113 (37.8%)*	*20 (20.2%)*
Diarrhea	*61 (20.4%)*	*6 (6.1%)*

Reviewer's comments
According the elicited AE data, a similar percentage of subjects had fever, but the fever was assessed as related to VL in miltefosine subjects and as related to amphotericin infusion in the majority of amphotericin B subjects. The assessment of whether the fever was related to amphotericin was based on temporal association with amphotericin administration, but knowing that amphotericin infusion may be associated with such reactions may have biased the assessment of relatedness. Approximately two thirds of subjects who experienced fever associated with amphotericin also experienced rigors, which were described as pronounced or prolonged. Overall, 90% of subjects receiving amphotericin experienced rigors. In contrast, only one subject in the miltefosine arm experienced rigors, which were described as brief or mild. A higher percentage of

miltefosine recipients experienced vomiting at least once in 24 hours and diarrhea (increase of 2-3 or 4-6 stools per day over pretreatment).

Un-elicited, spontaneously reported AEs occurred in similar percentage of subjects in the two treatment arms. The un-elicited AE dataset reported significantly fewer subjects who experienced fever, rigors, diarrhea or vomiting compared to the elicited AE dataset. Two miltefosine subjects had cardiac electrophysiology disturbance, one first degree AV block and one right bundle branch block. These did not lead to the discontinuation of miltefosine administration.

The relationship of dose to AE frequency was derived from the AE and elicited AE datasets and is presented below. Subjects who received doses < 2 mg/day had a lower frequency of elicited vomiting, but spontaneously reported AEs were not dose-dependent.

Table 147: Effect of Miltefosine mg/kg on Frequency of Treatment Emergent AEs – Study 3154

MedDRA v. 12.0 System Organ Class/Preferred Term	Miltefosine Dose mg/kg			
	< 2 N = 26	2-<3 N = 225	≥3 N = 48	Total N = 299
Blood and Lymphatics	0	1 (0.4%)	1 (2.1%)	2 (0.7%)
Anemia	0	1 (0.4%)	1 (2.1%)	2 (0.7%)
Thrombocytopenia		1 (0.4%)	1 (2.1%)	2 (0.7%)
Cardiac disorders	0	2 (0.9%)	0	2 (0.7%)
AV block	0	1 (0.4%)	0	1 (0.3%)
BBB		1 (0.4%)		1 (0.3%)
Ear and Labyrinth	0	2 (0.9%)	0	2 (0.7%)
Earache	0	2 (0.9%)	0	2 (0.7%)
Gastrointestinal	1 (3.8%)	13 (5.8%)	3 (6.3%)	17 (5.7%)
Abdominal pain	0	1 (0.4%)	0	1 (0.3%)
Constipation	0	1 (0.4%)	0	1 (0.3%)
Diarrhea	1 (3.8%)	8 (3.6%)	0	9 (3.0%)
Dyspepsia	1 (3.8%)	1 (0.4%)	0	2 (0.7%)
Gingival bleeding	0	0	0	0
Melena	0	0	0	1 (0.3%)
Nausea	0	1 (0.4%)	0	1 (0.3%)
Vomiting	0	1 (0.4%)	2 (4.2%)	3 (1.0%)
General and Administration Site	5 (19.2%)	40 (17.8%)	8 (16.7%)	53 (17.7%)
Asthenia	1 (3.8%)	16 (71.1%)	2 (4.2%)	19 (6.3%)
Edema generalized	0	0	0	0
Edema peripheral	0	0	0	0
Pyrexia	0	25 (11.1%)	3 (6.3%)	28 (9.3%)
Rigors	4 (15.4%)	4 (1.8%)	2 (4.2%)	10 (3.3%)
Hepatobiliary Disorders	0	3 (1.3%)	0	3 (1.0%)
Hepatic function abnormal	0	2 (0.9%)	0	2 (0.7%)
Jaundice		1 (0.4%)		1 (0.3%)
Infections and Infestations	0	3 (1.3%)	2 (4.2%)	5 (1.7%)
Herpes simplex	0	0	0	0
Malaria		1 (0.4%)	0	1 (0.3%)
Meningitis		1 (0.4%)	0	1 (0.3%)
Otitis media		0	1 (2.1%)	1 (0.3%)
Parasitic infection		0	2 (4.2%)	2 (0.7%)
Investigations	0	1 (0.4%)	1 (2.1%)	2 (0.7%)

ECG abnormal	0	0	1 (2.1%)	1 (0.3%)
BUN increased		1 (0.4%)	0	1 (0.3%)
Metabolism and Nutrition	8 (30.8%)	52 (23.1%)	9 (18.8%)	69 (23.1%)
Anorexia	8 (30.8%)	52 (23.1%)	9 (18.8%)	69 (23.1%)
Dehydration	0	0	0	0
Hypokalemia	0	0	0	0
Musculoskeletal	1 (3.8%)	0	0	1 (0.3%)
Arthritis	1 (3.8%)	0	0	1 (0.3%)
Nervous System	1 (3.8%)	2 (0.9%)	2 (4.2%)	5 (1.7%)
Convulsions	0	0	1 (2.1%)	1 (0.3%)
Headache	0	2 (0.9%)	2 (4.2%)	4 (1.4%)
Hemiplegia	1 (3.8%)	0	0	1 (0.3%)
Nystagmus	0	0	0	0 (0.3%)
Paresthesia	1 (3.8%)	0	0	1 (0.3%)
Psychiatric	0	1 (0.4%)	0	1 (0.3%)
Somnolence	0	1 (0.4%)	0	1 (0.3%)
Reproductive	1 (3.8%)	0	0	1 (0.3%)
Testis disorder*	1 (3.8%)	0	0	1 (0.3%)
Respiratory and Thoracic	0	10 (4.4%)	2 (4.2%)	12 (4.0%)
Bronchitis	0	0	0	0
Cough		7 (3.1%)	1 (2.1%)	8 (2.7%)
Dyspnea		1 (0.4%)	1 (2.1%)	2 (0.7%)
Hemoptysis		1 (0.4%)	0	1 (0.3%)
Influenza-like illness		1 (0.4%)	0	1 (0.3%)
Pneumonia		1 (0.4%)	0	1 (0.3%)
Skin and Subcutaneous	0	3 (1.3%)	0	3 (1.0%)
Rash	0	2 (0.9%)	0	2 (0.7%)
Stevens-Johnson		1 (0.4%)		1 (0.3%)
Vascular	0	1 (0.4%)	0	1 (0.3%)
Epistaxis	0	1 (0.4%)	0	1 (0.3%)

Table 148: Effect of Miltefosine mg/kg Dose on Frequency of Elicited AEs of Diarrhea and Vomiting – Study 3154

	Miltefosine mg/kg				*AMB*
	1.4-< 2 N = 26	*2-<3 N = 225*	*≥3 N = 48*	*Total N = 299*	*N = 99*
Diarrhea	*3 (11.5%)*	*52 (23.1%)*	*6 (12.5%)*	*61 (20.4%)*	*6 (6.1%)*
Vomiting	*6 (23.1%)*	*85 (37.8%)*	*22 (45.8%)*	*113 (37.8%)*	*20 (20.2%)*

Deaths

There were two deaths in the miltefosine arm, one occurring during therapy and one occurring in the follow up period. The first death occurred in a 13 year old male subject who became drowsy on Day 11 of miltefosine treatment after complaining of earache for 4 days. Examination revealed a stiff neck and positive Kernig sign. CSF evaluation revealed 4000 WBC and increased intracranial pressure. He was started on penicillin, chloramphenicol and Magnamycin (cefoperazone). CSF culture grew a “coliform” organism sensitive only to ciprofloxacin. He died 2 days later. The meningitis was considered unrelated to miltefosine.

The second death was a 15 year old female who had finished miltefosine course with fever resolution but persistent splenomegaly and severe anemia. At EOT, her Hb dropped from 7.1 to 3.9. Spleen aspirate was negative for *Leishmania* but positive for *P. vivax*. She was treated with chloroquine, followed by primaquine. She was assessed as "well" two weeks prior to death. She died three weeks after finishing the primaquine course (2 months after discontinuation of miltefosine). Her death was assessed as unrelated to miltefosine.

Reviewer's comments
One subject died of bacterial meningitis. Subjects with VL are prone to bacterial infections. I agree that this death is unlikely to be related to miltefosine. The second patient died 2 months after discontinuation of miltefosine, and the cause of death is unclear.

Serious AEs

The study report states that 6 miltefosine subjects and one amphotericin subject experienced serious AEs. These included the meningitis and malaria with fatal outcomes. The other AEs included hemiparesis, hemiplegia, convulsions, Stevens-Johnson syndrome, melena and thrombocytopenia and parasitic infection in the miltefosine arm, and renal impairment and nystagmus in the amphotericin arm. The AE dataset indicates 4 miltefosine subjects and one amphotericin subject with serious AEs (meningitis, hemiparesis and hemiplegia, Stevens-Johnson syndrome, melena and thrombocytopenia in the miltefosine arm). With the exception of the fatal cases, the AEs resolved.

The narratives for 6 miltefosine subjects and one amphotericin subjects were provided in the study report. In the miltefosine arm, one subject had a cerebral mass and biopsy revealed perivascular inflammation and malaria gametocytes, one subject developed Stevens-Johnson syndrome on Day 6 of miltefosine treatment, one had melena and thrombocytopenia (platelets 19k) on Day 17 and evidence of esophagitis on upper endoscopy and hemorrhoids on proctosigmoidoscopy, and one subject had convulsions with CT of the brain revealing granulomas suggestive of neurocysticercosis. Stevens-Johnson syndrome was assessed as related to miltefosine, melena and thrombocytopenia as possibly related, and the other AEs were assessed as unrelated.

Adverse Events Leading to Drug Discontinuation

Eight subjects in the miltefosine arm and 3 subjects in the amphotericin arm discontinued treatment due to an adverse reaction. These included the 4 subjects with SAEs in the miltefosine arm, and the one amphotericin subject with renal impairment and nystagmus. The other miltefosine subjects included arthritis and skin rash on Days 9 and 10 of treatment, and CTC grade 4 diarrhea on Day 14, CTC grade 3 jaundice on Day 14, epistaxis and thrombocytopenia on Day 8, anemia with weakness and dyspnea on Day 22. The additional two amphotericin subjects had worsened dyspnea, and thrombocytopenia. Arthritis, rash, diarrhea and jaundice were assessed as drug related.

Renal Toxicity

Mean Cr increased among amphotericin recipients at EOT, but remained stable in the miltefosine arm. Mean Cr was similar in both arms at 6 months follow up. Absolute Cr values were between 2 and 5.5 in 6 subjects in each arm at EOT (2% vs. 6% in the miltefosine and amphotericin arms respectively), and did not exceed 2.1 at follow up in any subject.

Table 149: Changes in Mean Cr – Study 3154

Mean Cr (SD)	MLT N = 299	AMB N = 99
Screening	0.9 (0.3)	0.9 (0.3)
EOT	0.9 (0.4)	1.1 (0.4)
6 Months Follow Up	0.9 (0.2)	0.9 (0.2)

Reviewer's Comments

All (100%) amphotericin subjects experienced some degree of Cr elevation above baseline during therapy compared to approximately 50% of miltefosine subjects. Nephrotoxicity is a recognized adverse event associated with amphotericin B exposure. At EOT, a higher percentage of amphotericin recipients had grade 2 Cr elevations compared to miltefosine recipients (40% vs. 10%), but at 6 months, the frequency was similar at 10% each. Of the 40 amphotericin subjects with CTCAE grade 2 Cr increase at EOT, 31 (77.5%) resolved at 6 months and 9 persisted. Of the 29 miltefosine subjects with CTCAE grade 2 Cr increase at EOT, 20 resolved and 9 had persistent increase. This indicates that at 6 months one new amphotericin subject and 21 new miltefosine subjects developed Cr elevations, suggesting that the risk of kidney impairment associated with miltefosine exposure may persist beyond the treatment period, consistent with the long half-life of the drug.

In the miltefosine arm, grade 2 Cr elevation above baseline occurred less frequently in subjects who received a dose < 2 mg/kg/day compared to subjects who received higher doses, but grade 1 elevations were not dose dependent.

Table 150: Cr Increase above Baseline – Study 3154

	MLT N = 299	*AMB N = 99*
EOT		
Cr 1-<1.5x baseline	*120 (40.1%)*	*59 (59.6%)*
Cr 1.5-<3x baseline	*25 (8.4%)*	*40 (40.4%)*
Cr ≥ 3x baseline	*4 (1.3%)*	*0*
6 Months Follow Up		
Cr 1-<1.5x baseline	*93 (31.1%)*	*33 (33.3%)*
Cr 1.5-<3x baseline	*31 (10.3%)*	*10 (10.1%)*
Cr ≥ 3x baseline	*0*	*0*

Table 151: Effect of Miltefosine Dose on Cr – EOT – Study 3154

	Miltefosine Dose mg/kg	

	1.4-< 2 N = 26	*2-<3 N = 225*	*≥3 N = 48*	*Total N = 299*
Cr 1-<1.5x baseline	*12 (46.2%)*	*90 (40.0%)*	*18 (37.5%)*	*120 (40.1%)*
Cr 1.5-<3x baseline	*1 (3.8%)*	*20 (8.9%)*	*4 (8.3%)*	*25 (8.4%)*
Cr ≥ 3x baseline	*0*	*4 (1.8%)*	*0*	*4 (1.3%)*

Hepatic Toxicity

Mean transaminases, mean alkaline phosphatase and mean total bilirubin did not change during therapy in either treatment arm.

Table 152: Changes in Mean Transaminases, bilirubin and Alkaline Phosphatase – Study 3154

Value (SD)	*MLT N = 299*	*AMB N = 99*
ALT		
Screening	*48 (32)*	*46 (32)*
EOT	*50 (32)*	*44 (39)*
6 Months Follow UP	*42 (29)*	*41 (21)*
AST		
Screening	*63 (35)*	*63 (44)*
EOT	*61 (36)*	*48 (33)*
6 Months Follow UP	*42 (25)*	*43 (48)*
Total Bilirubin		
Screening	*0.7 (0.2)*	*0.7 (0.3)*
EOT	*0.7 (0.3)*	*0.7 (0.3)*
6 Months Follow UP	*0.7 (0.2)*	*0.7 (0.2)*
Alkaline Phosphatase		
Screening	*212 (177)*	*186 (130)*
EOT	*218 (173)*	*194 (133)*
6 Months Follow UP	*210 (128)*	*204 (112)*

A higher percentage of miltefosine subjects experienced increases above ULN in ALT, AST and AP at EOT and 6 months follow up. The elevations were mild in most subjects. The ULN for bilirubin in the lab dataset was reported in different units than the absolute value, and the units were not specified. This did not allow for evaluation of increases above baseline. One subject in the miltefosine arm developed jaundice (total bilirubin 7.3) on an "unscheduled visit" and the drug was discontinued on Day 14. ALT, AST and AP for that visit were normal. Bilirubin decreased in this subject to 3.9 on Day 28 and resolved by 6 months.

Table 153: Changes in Transaminases, Bilirubin, Alkaline Phosphatase at EOT – Study 3154

EOT	*MLT N = 299*	*AMB N = 99*
ALT		
ALT >1-3x ULN	*138 (46.2%)*	*31 (31.3%)*
ALT >3-5x ULN	*9 (3.0%)*	*1 (1.0%)*
ALT > 5-20x ULN	*0*	*1 (1.0)*
ALT >20x ULN	*0*	*0*

*AST**		
AST >1-3x ULN	*256 (85.6%)*	*73 (73.7%)*
AST > 3-5x ULN	*51 (17.1%)*	*9 (9.1%)*
AST > 5-20x ULN	*10 (3.3%)*	*2 (2.0%)*
AST > 20x ULN	*0*	*0*
Alkaline Phosphatase		
AP >1-2.5x ULN	*31 (10.4%)*	*6 (6.1%)*
AP > 2.5-5x ULN	*3 (1.0%)*	*1 (1.0%)*
AP >5x ULN	*0*	*0*
Total Bilirubin		
Bilirubin ≥ 1.5 mg/dL	*2 (0.7%)*	*1 (1.0%)*

*38 subjects had multiple AST determinations at EOT with discordant results.

Table 154: Changes in Transaminases, Bilirubin, Alkaline Phosphatase at 6 Month Follow Up – Study 3154

6 Months FU	MLT N = 299	AMB N = 99
ALT		
ALT >1-3x ULN	*36 (12.0%)*	*19 (19.2%)*
ALT >3-5 x ULN	*6 (2.0%)*	*0*
ALT >5-20 x ULN	*0*	*0*
AST		
AST >1-3x ULN	*157 (52.5%)*	*44 (44.4%)*
AST > 3-5x ULN	*4 (1.3%)*	*0*
AST > 5-20x ULN	*2 (0.7%)*	*1 (1.0%)*
Alkaline Phosphatase		
AP >1-2.5x ULN	*15 (5.0%)*	*4 (4.0%)*
AP >2.5-5 x ULN	*1 (0.3%)*	*0*
Total Bilirubin		
Bilirubin ≥ 1.5	*1 (0.3%)*	*0*

Hematologic Toxicity

Miltefosine is hemolytic when administered intravenously. The German product labeling was updated in 2008 to add thrombocytopenia as an AE.

The trends of mean Hb, WBC and platelets were described in the efficacy section. Mean Hb increased during therapy in both treatment arms, but was higher at EOT in the miltefosine arm, probably reflecting amphotericin toxicity. Mean Hb at FU was similar in both arms. Mean WBC, mean % neutrophils and mean platelets increased during therapy and were similar in both treatment arms at EOT and at 6 months FU.

Reviewer's Comments
No hematologic AEs were noted in CL studies, and hematology parameters are affected by VL, potentially confounding the interpretation of possible drug-related lab changes during and after therapy.

A higher percentage of amphotericin subjects had Hb decrease of at least 2 gm from baseline at EOT, but a higher percentage of miltefosine subjects had a decrease at 6 months. The findings at EOT are compatible with amphotericin hematologic toxicity while the findings at 6 months are probably explained by the higher relapse rate in the miltefosine arm.

Table 155: Subjects with Hb decrease ≥2 gm/dL compared to baseline – Study 3154

Hb decrease ≥2 gm From Baseline	*MLT N = 299*	*AMB N = 99*
EOT	*10 (3.3%)*	*8 (8.1%)*
6 months FU	*5 (1.7%)*	*0*

A higher percentage of miltefosine subjects had leukopenia at screening, EOT and follow up. The higher frequency of leukopenia at EOT is probably explained by the imbalance at screening, but a drug effect cannot be ruled out. The higher frequency at follow up is probably explained by the higher relapse rate in the miltefosine arm.

Table 156: WBC < Lower Limit Normal – Study 3154

	MLT N = 299	*AMB N = 99*
Screening		
WBC <4000 -3000	*83 (27.8%)*	*25 (25.6%)*
WBC <3000-2000	*98 (32.8%)*	*26 (26.3%)*
WBC <2000-1000	*44 (14.7%)*	*9 (9.1%)*
WBC <1000	*1 (0.3%)*	*0*
EOT		
WBC <4000 -3000	*75 (25.1%)*	*33 (33.3%)*
WBC <3000-2000	*67 (22.4%)*	*10 (10.1%)*
WBC <2000-1000	*19 (6.4%)*	*2 (2.0%)*
WBC <1000	*0*	*0*
6 months FU		
WBC <4000 -3000	*3 (1.0%)*	*1 (1.0%)*
WBC <3000-2000	*2 (0.7%)*	*0*
WBC <2000-1000	*1 (0.3%)*	*0*
WBC <1000	*0*	*0*

At screening, the percentage of subjects with platelets below the LLN (150k) was similar in both treatment arms, although a slightly higher percentage of miltefosine subjects had platelets < 75k. The percentage of subjects with thrombocytopenia was higher in the miltefosine arm at EOT and at 6 months. Because initial cure was similar in both arms at EOT, the possibility that thrombocytopenia at EOT was due to miltefosine cannot be ruled out. The higher frequency of thrombocytopenia at FU in miltefosine recipients is possibly explained by the higher frequency of relapse in that treatment arm.

Table 157: Platelet Count < 150, 000 – Study 3154

	MLT N = 299	*AMB N = 99*

Screening		
<150 – 75k	*146 (48.8%)*	*60 (60.6%)*
<75k-50k	*71 (23.7%)*	*20 (20.2%)*
<50-25	*7 (2.3%)*	*1 (1.0%)*
< 25	*2 (0.7%)*	*0*
EOT		
<150 – 75k	*145 (48.5%)*	*44 (44.4%)*
<75k-50k	*32 (10.7%)*	*8 (8.1%)*
<50-25	*5 (1.7%)*	*1 (1.0%)*
< 25	*2 (0.7%)*	*1 (1.0%)*
6 months FU		
<150 – 75k	*74 (24.8%)*	*20 (20.2%)*
<75k-50k	*4 (1.3%)*	*1 (1.0%)*
<50-25	*2 (0.7%)*	*0*
< 25	*0*	*0*

Ophthalmic Toxicity

Ophthalmologic examinations were performed at screening, at EOT and at 6 months follow up visit. One miltefosine recipient had "bilateral central retinosis" at EOT which resolved at 6 months follow-up. One amphotericin recipient had nystagmus, dilated pupils and pale disc at EOT, associated with renal impairment and volume depletion. The ophthalmologic findings were thought to be secondary to renal impairment.

Reviewer's Comments
It is unclear what the term bilateral central retinosis means. Visual symptoms were not reported in any miltefosine subject in the AE dataset.

Reproductive Toxicity

Women were asked to use contraception for the duration of treatment and for 2 months after treatment. None of the women enrolled in the study became pregnant.

Because of concerns regarding the effects of the drug on male fertility, the number of live and healthy infants born to sexual partners of male patients of reproductive age who did not use contraception was tracked for one year after therapy. 48 live infants were born to the sexual partners of 80 male patients who received miltefosine compared to 12 live infants born to 20 sexual partners of patients who received amphotericin (0.6 births per patient in each group). No infant had a congenital abnormality.

Study Conclusions

This non-inferiority design study was conducted at 3 study sites in India, and aimed to show that miltefosine given orally at a target dose of 2.5 mg/kg/day for 28 days was non-inferior by a NI margin of 10% to amphotericin deoxycholate given IV at 1mg/kg/day on alternate days for 15 doses in the treatment of VL. Initial cure was defined as a negative spleen aspirate at EOT (or if parasite score 1 at EOT, a score of 0 one month later). Final

cure was defined as initial cure plus absence of signs and symptoms related to VL at 6 months. Absence of signs and symptoms related to VL was defined as absence of fever, decrease in spleen size ≥ 30% compared to baseline, Hb ≥ 10.0 if female and ≥ 11.5 if male, platelet count ≥ 100K, and WBC ≥ 3500. Final cure was the protocol-defined primary endpoint.

98% of subjects achieved initial cure in each treatment arm. 88 miltefosine and 12 amphotericin subjects did not have absence of VL s/s as defined by the protocol. 27 of these subjects underwent a spleen or marrow aspirate at 6 months follow up, and two additional subjects who had absence of s/s as defined by protocol had a follow up aspirate. 9/27 subjects had a positive aspirate, all in the miltefosine arm. Final cure was 94.3% in miltefosine subjects and 97% in amphotericin subjects in the ITT population, a difference of 2.7% (95% CI -1.62%, 6.93%). Miltefosine was non-inferior to amphotericin B.

23 of 27 subjects who did not have absence of s/s of VL at 6 months underwent a follow up aspirate at study site 1 while the other two sites performed an aspirate on two subjects each (2/35 and 2/38 respectively). This indicates substantial imbalance among the sites in following the study protocol and in documentation of parasitologic relapse.

Because of the substantial variability in performing an aspirate at follow up among the study sites, the clinical data for all 100 subjects who did not have absence of signs or symptoms as defined by the protocol (fever, anemia, thrombocytopenia, leukopenia or residual splenomegaly that had not regressed by at least 30%) were reviewed with blinding as to aspirate status. Excluding subjects who had isolated anemia with Hb > 9.0, the reviewer identified 27 subjects who may have warranted further evaluation based on clinical findings. These included all nine subjects who had a positive aspirate, four of the subjects with negative aspirates), and an additional 14 subjects (2 amphotericin and 12 miltefosine). These additional subjects had persistent severe anemia, thrombocytopenia and/or leukopenia. Considering the subjects who the reviewer considered warranted further investigation failures, an amended conservative estimate of the final cure rate in the ITT population was 90.3% in the miltefosine arm and 94.9% in the amphotericin arm (difference 4.6%, 95% CI -0.2.0%, 9.8%). The conclusion that miltefosine was non-inferior to amphotericin B by an NI margin of 10% holds.

The higher incidence of relapse in the miltefosine arm raises concerns regarding emergence of resistance, especially because the drug has a long half-life and residual organisms may be exposed to sub-therapeutic concentrations. VL in India is anthroponotic, raising the concern for spread of resistance.

Several literature reports explore miltefosine resistance in the Indian Subcontinent. A study compared the ED50 and ED90 of *Leishmania* organisms from Bihar, India, where miltefosine use is extensive, to Uttar Pradesh, India, where miltefosine use is not extensive and concluded that ED50 was not statistically significantly different between the two regions, but the ED90 was statistically significantly higher in Bihar. The study did not report clinical outcomes.

A single arm study conducted at one of the sites that participated in Study 3154 investigated clinical response to miltefosine a decade later, and reported a similar initial cure rate, a lower final cure rate and a higher relapse rate compared to the response to miltefosine in Study 3154. Susceptibilities were not reported. Another single arm study from Nepal also reported decreasing final cure rates and increasing relapses in subjects treated with miltefosine. The Nepal study used DNA fingerprinting to demonstrate that *Leishmania* recurrence represented relapse rather than re-infection, and found no increase in IC50 of the relapsed *Leishmania* organisms. Of note, almost half of the relapses in the Nepal study occurred in the 6-12 months follow up period, suggesting that the usual 6 month follow up period in VL studies may no longer be sufficient. In contrast, a 12 month follow up study in a subset of 3154 subjects indicated that extending the follow up to 12 months would not have altered the study conclusions.

Two deaths occurred in Study 3154, both in the miltefosine arm. One death occurred during therapy and was due to bacterial meningitis. This death was assessed as unrelated to the drug. The other death occurred two months after EOT in a subject who experienced initial cure but had *P. vivax* malaria treated with chloroquine followed by primaquine. She died after finishing the malaria treatment. The circumstances of death were not known. It is unlikely that the death is related to the study drug but that cannot be ruled out with certainty.

Six miltefosine subjects experienced at least one SAE. These included hemiparesis, hemiplegia and convulsions in two subjects, one with a cerebral mass containing malaria gametocytes and one with brain CT indicative of neurocysticercosis, both assessed as unrelated to the study drug. Other SAEs that were assessed as probably related to the drug included thrombocytopenia and melena and Stevens-Johnson syndrome. SAEs in the amphotericin arm included renal impairment and nystagmus.

Miltefosine was discontinued in eight subjects due to an AE. AEs that led to drug discontinuation included the subjects with hemiparesis, hemiplegia, meningitis (all unrelated to drug), Stevens-Johnson syndrome, rash, diarrhea and hyperbilirubinemia (all probably drug related), thrombocytopenia with melena and arthritis, (possibly drug related).

AEs that occurred in a higher percentage of miltefosine subjects included vomiting and diarrhea. The frequency of vomiting increased as the mg/kg miltefosine dose increased. There were two cases of cardiac disorders, one right bundle branch block and one first degree AV block; neither led to change in miltefosine administration. Fever was reported in a similar percentage of subjects, but was attributed to VL in miltefosine subjects and to amphotericin infusion reaction in amphotericin subjects based on temporal association with amphotericin administration. A significantly higher percentage of amphotericin subjects experienced rigors, a known infusion-associated reaction of the drug. A significantly higher percentage of amphotericin subjects also received analgesics and anti-histamines to mitigate amphotericin reactions.

A higher percentage of miltefosine subjects developed elevations of transaminases and alkaline phosphatase that were mild and reversible. There were no cases that satisfied Hy's Law. One subject discontinued treatment due to isolated hyperbilirubinemia and jaundice.

All amphotericin subjects experienced some degree of Cr elevation above baseline at EOT, with CTCAE grade 2 increase (>1.5-3x baseline) occurring in approximately 40%. In comparison, approximately 50% of miltefosine subjects experienced some degree of Cr elevation at EOT, with grade 2 increase in approximately 10%. Some miltefosine subjects developed Cr elevations post-therapy, compatible with the long half-life of the drug.

Mean Hb at EOT was lower in the amphotericin arm, and a higher percentage of amphotericin subjects had decrease in Hb of at least 2 grams during therapy, probably reflecting amphotericin toxicity. A higher percentage of miltefosine subjects had thrombocytopenia at EOT and at follow up. The higher frequency of thrombocytopenia at follow up is probably explained by the higher relapse rate in the miltefosine arm, but the higher frequency of at EOT could possibly be due to miltefosine.

Study 3154a

This objective of this study was to provide relapse data at 12 month follow up for the subjects who participated at Study center 2 of Study 3154.

144 subjects had been enrolled at Study center 2, 36 in the amphotericin B arm and 108 in the miltefosine arm. One amphotericin recipient was lost to follow up. The remaining 143 subjects included 6 subjects who had discontinued the study treatment prematurely.

According to the study report, 111/143 (77.6%) were without signs or symptoms suggestive of VL at 12 months after treatment. Of the remaining 32 subjects, 23 were in the miltefosine arm and 9 in the amphotericin arm. One miltefosine subject underwent a spleen aspirate and was positive.

Overall, 107/108 of miltefosine treated subjects (99.0%) and 35/35 amphotericin treated subjects were clinically cured at 12 months. The study report concludes that extending the follow up time from 6 months to 12 months was unlikely to increase reliability of efficacy or safety findings.

Reviewer's comments
Clinical Response dataset was not submitted for this study. 105/108 subjects had final cure at 6 months at site 2 in Study 3154, while Study 3154 reports 107/108 cure at 12 months. It is unclear whether the two additional cured subjects were not assessed at 6 months.

The 12 month laboratory data for subjects enrolled at Site 2 were included in Study 3154 datasets. 32 miltefosine and 12 amphotericin subjects were identified as not having absent VL signs and symptoms as defined in Study 3154.

The miltefosine subject who underwent an aspirate had experienced final cure with resolution of splenomegaly and fever, normalization of WBC and improvement in Hb and platelet count to 11 gm/dL and 102k respectively at 6 months, but fever, splenomegaly, anemia, leukopenia and thrombocytopenia all recurred. Spleen aspirate demonstrated amastigotes, compatible with relapse. Review of the clinical data and change in lab parameters indicate that two additional miltefosine subjects, one with thrombocytopenia (subject 2/129) and one with borderline platelets and anemia (subject 2/092) warranted further evaluation with an aspirate. All remaining subjects had isolated residual anemia.

One amphotericin subject (2/032) also warranted an aspirate because of severe anemia and decrease in platelet count. The adjusted cure rate is 34/35 for amphotericin (97.1%) and 105/108 (97.2%) for miltefosine.

In the previously cited study from Nepal, approximately half of the relapses occurred during the second 6 months of follow up. Using DNA fingerprinting, these late relapses were demonstrated not to be due to reinfection. The Nepal study was conducted 10 years after Study 3154, and although it did not find a significant difference in the parasite's IC50 pre- and post-therapy, the higher incidence of relapse noted after a decade of miltefosine use remains concerning for emergence of resistance.

Study Z025

The study was conducted at Humera Hospital and Mycadra Health Center, Tigray region, Ethiopia, between the fall of 2003 and the winter of 2005 under the auspices of Medicins Sans Frontieres (MSF)[41]. It was reviewed by the ethics committee of the Federal Democratic Republic of Ethiopia Science and Technology Commission in Addis Ababa, and by the Tigray regional authorities and Medecins Sans Frontieres-Holland international ethics review board. Informed consent was obtained according to the current versions of the Declaration of Helsinki, Good Clinical Practice Guidelines and the respective national laws of Ethiopia. A Data Safety Monitoring Board reviewed the trial.

This NDA sponsor (Paladin) requested patient level data for all enrolled patients from the primary investigator, Koert Ritmeijer of the Public Health Department, Medicins Sans Frontieres-Holland. MSF could not accommodate the request because data sharing with industry was not included in the patient consent, the original Ethics Review Board approval did not include analysis of the data beyond what was in the study proposal, the

[41] 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. Clin Infect Dis 2006;43:357-364

Ethics Review Board was specifically critical of sharing data with industry, and there was no clear and direct benefit to the study community by sharing the data with industry. However, MSF agreed to share the case report forms of patients with serious adverse events as that may contribute to the pharmacovigilance database.

Study Design

The study was a randomized, open label trial comparing oral miltefosine 100 mg daily for 28 days to intramuscular sodium stibogluconate (SSG) 20 mg/kg daily for 30 days in the treatment of VL in male Ethiopian subjects aged ≥ 15 years. Female subjects were excluded because of the potential teratogenicity of miltefosine and compliance with birth control could not be assured in the study population which was described as semi-nomadic.

Males ≥ 15 years of age who met the WHO case definition for VL (history of > 2 weeks of fever, negative malaria smear, and evidence of splenomegaly or lymphadenopathy and wasting) were tested for *Leishmania* by direct agglutination test (DAT). Subjects with high DAT titer (≥1:6400) were randomized, whereas subjects with indeterminate titer (1:800 -1:3200) underwent spleen or lymph node biopsy for microscopic confirmation of *Leishmania* infection and were randomized if the aspirate revealed *Leishmania* amastigotes. Severely ill subjects underwent an aspirate. Subjects who had received prior VL treatment were enrolled only if they had a positive aspirate. The microscopist was blinded as to the assigned treatment. Women and subjects with less than one month life expectancy were excluded.

Subjects were asked to volunteer for HIV serology testing, typically 2 to 3 weeks after providing consent to be in the study. HIV serology was performed by parallel testing with two rapid tests, HIV-Determine and HIVCapillus. In the instance of discordant results, a third test (Unigold) was performed.

Subjects were monitored for six months after completion of therapy. Spleen or lymph node aspirates were performed at end of therapy (TOC, day 27-30). Subjects who had a positive TOC aspirate were re-treated with SSG until 2 consecutive TOC aspirates were negative. In subjects without a palpable spleen or enlarged lymph nodes, cure was determined clinically (resolution of fever, decrease in spleen size, and increase in Hb or weight gain). An aspirate was also performed in patients in whom relapse was suspected at the 6 months follow up.

Subjects who did not respond clinically or parasitologically to miltefosine or who were intolerant of miltefosine received treatment with SSG. Subjects who did not respond to SSG or were intolerant of SSG received ex-protocol amphotericin B deoxycholate.

The protocol-specified primary efficacy endpoint was final cure, defined as initial cure plus no relapse during the 6 months follow up. Initial cure was defined as absence of parasites in the TOC aspirate with clinical improvement, or clinical cure alone (clearance of fever, in combination with spleen regression, increased hemoglobin, or weight gain)

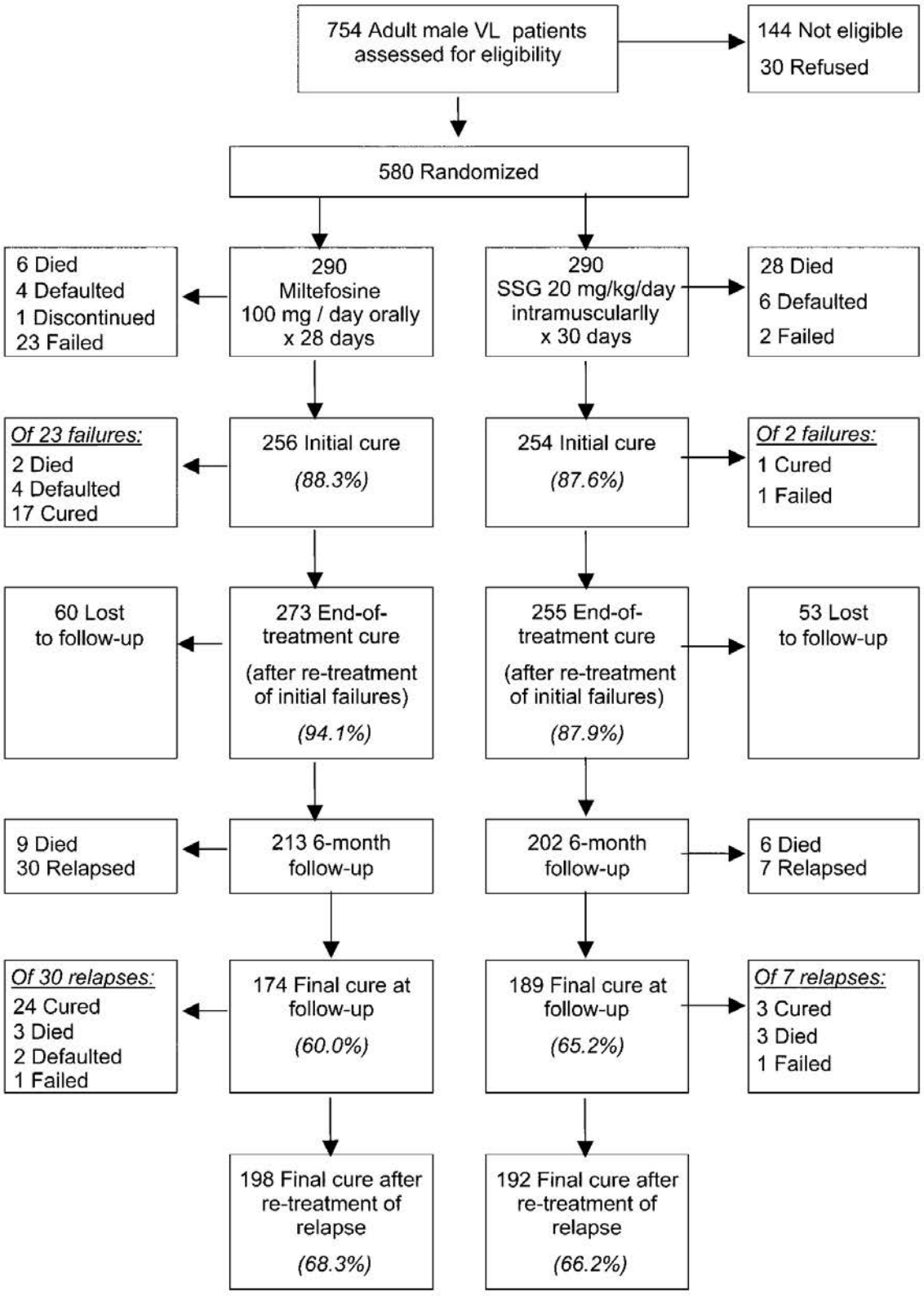
for a subject in whom the TOC aspirate could not be performed. Relapse was defined by clinical signs and symptoms re-appearing after initial cure and a positive *Leishmania* aspirate. Secondary efficacy endpoints included initial cure rate and death rate by the end of the study.

The published article did not specify the assumptions used to determine the sample size. The sponsor's study report stated that sample size was determined based on the protocol-specified primary endpoint in HIV-negative subjects. Assuming a non-inferiority margin of 10%, efficacy of SSG in HIV negative individuals of 95%, efficacy of miltefosine of 85%, power of .80 and alpha of 0.05, a sample size of 141 HIV negative subjects per treatment arm was calculated. Assuming HIV infection prevalence of 30%, 200 subjects with known HIV status per treatment arm would be needed. Assuming that 20% of subjects would decline HIV testing, 250 subjects per arm would be needed. Assuming a loss to follow up of 15%, 290 subjects would be needed.

The Intent-to-Treat population included all randomized subjects. The Per Protocol population included the ITT subjects who were not lost to follow up. The Safety population included all subjects who received at least one dose of study medication Because the primary trial data were not available to the sponsor, the sponsor used the data from the published article to generate the study report. The sponsor specified the primary analysis population to be the PP, and generated a post hoc primary outcome variable, death rate by the end of therapy. This was done because death occurring between the end of therapy and the 6 month follow up period could not be ascertained due to the high rate of loss to follow up in this trial.

Primary subject level data were not available for this study. Tables and Figures are adapted from the published article.

Figure 3: Disposition and Results Study Z025 Error! Bookmark not defined.



Disposition

580 males were randomized, 290 to receive oral miltefosine 100 mg daily for 28 days and 290 to receive IM SSG 20mg/kg daily for 30 days.

In the miltefosine arm, 6 miltefosine subjects died by the end of therapy, 4 defaulted and 1 discontinued treatment. During the follow up period, 11 subjects died, 4 defaulted and 60 were lost to follow up.

In the SSG arm, 28 died by the end of therapy and 6 defaulted. During the follow up period 6 subjects died and 53 were lost to follow up.

The following table was generated based on the published article.

Table 158: Subject Disposition – Study Z025

	MLT	SSG
Randomized	290	290
Deaths	17 (5.9%)	34 (11.7%)
During therapy	6 (2.1%)	28 (9.6%)
During Follow up period	11 (3.8%)	6 (2.1%)
Defaulted	10 (3.5%)	6 (2.1%)
During therapy	4 (1.4%)	6 (2.1%)
During Follow up	6 (2.1%)	0
Discontinued Therapy	1 (0.3%)	0
Lost to Follow up	60 (20.7%)	53 (18.3%)

Demography and Other Subject Characteristics

375/580 subjects (64.7%) underwent voluntary counseling and testing for HIV infection, 194 in the miltefosine arm and 181 subjects in the SSG arm. Overall, 107/375 (28.5%) were HIV infected. Among miltefosine subjects tested, 63/194 (32.5%) were HIV infected. Among SSG subjects tested, 44/181 (24.3%) were HIV infected.

Table 159: HIV Infection Status – Study Z025

	MLT N = 290	SSG N = 290	Total N = 580
HIV Tested	194 (66.9%)	181 (62.4%)	375 (64.7%)
HIV infected	63 (21.7%)	44 (15.2%)	107 (18.5%)
HIV negative	131 (45.2%)	137 (47.2%)	268 (46.2%)
HIV unknown	96 (33.1%)	109 (37.6%)	205 (35.3%)

Reviewer's Comments
The prevalence of HIV infection in the study population was high, approximating 20% in the entire population and 30% in those tested. The percentage of HIV infected individuals was higher in the miltefosine group (32.5% of those tested, 21.7% of the entire miltefosine population) compared to the SSG group (24% in those tested, 15% of the entire SSG population), whereas the percentage of subjects with unknown HIV status was

higher in the SSG group (37.6% vs. 33.1% in the overall SSG and miltefosine population respectively, and 60.2% vs. 49.5% in the tested SSG and miltefosine population respectively). The higher prevalence of HIV infection in the miltefosine population and the higher prevalence of unknown HIV status in the SSG population can probably be accounted for by the fact that HIV testing was done 2-3 weeks after enrollment and a higher number of SSG subjects had died by then (see efficacy and safety sections).

There were no differences in age, mean body mass index, Hb levels, spleen size or duration of illness between the two treatment groups. According to the published report, VL was confirmed by DAT in 449 (77%) and by positive microscopy in 131 (23%). DAT titers, spleen size, age and BMI were not significantly different between HIV-infected, HIV-negative and HIV unknown subjects. HIV-infected subjects had significantly higher parasite density compared to HIV negative and HIV unknown (mean 3.7 in HIV positive compared to 2.3 in HIV negative and 1.8 in HIV unknown, p = 0.0003).

Table 160: Subject Characteristics – Study Z025 - Published Article

	MLT N = 290	SSG N = 290
Mean Age, years (SD)	29 (9.9)	29 (9.6)
Mean BMI (SD)	17.3 (2.1)	17.4 (1.8)
Mean Hemoglobin g/dL (SD)	9.2 (2.3)	9.1 (2.3)
Mean Spleen size cm (SD)	9.3 (5.6)	9.5 (5.7)
Mean Duration of illness, months (SD)	2.8 (2.1)	2.6 (2.1)
Unable to walk unaided	32 (11.5%)	28 (9.7%)
HIV positive	63/194 (32%)	44/181 (24%)
HIV negative	131/194 (68%)	137/181 (76%)
HIV unknown	96/290 (33%)	109/290 (38%)

Reviewer's Comments
In contrast to Study 3154 where all screening diagnoses were parasitologic, most of the subjects in this study were enrolled on the basis of clinical symptoms and serology (high DAT), in accordance with WHO recommendations for VL diagnosis under field conditions. DAT titer decreases after successful therapy but may remain elevated for several years. In this study, subjects previously treated for VL but with clinical symptoms and subjects with indeterminate titer underwent an aspirate for a parasitologic diagnosis.

In contrast to Study 3154 which did not enroll HIV positive subjects, Z025 study population had a high prevalence of HIV infection, approximately 30% of those tested. HIV co-infection is known to result in significantly lower VL cure rates, and significantly higher mortality rates and higher relapse rates compared to HIV negative individuals.

The mean age, mean BMI and mean duration of illness in this study were comparable to those in Study 3154. Mean parasite score in HIV negative subjects was similar to the mean parasite score in Study 3154 subjects (1.8 vs. 1.9 respectively).

Efficacy Results

In the ITT population, 256/290 miltefosine subjects (88.3%) experienced initial cure, 23 subjects failed (7.9%) and 6 died (2.1%).

254/290 SSG subjects (87.6%) experienced initial cure, 2 subjects failed (0.7%) and 28 died (9.7%). The difference in initial cure rate was -0.7% (95% CI -6.1, -4.7), p value 0.799.

The initial failures in each arm were re-treated during the follow up period. Subjects who initially failed miltefosine received SSG while subjects who failed SSG received amphotericin B. 2 of the 11 deaths during the follow up period occurred during this re-treatment phase. Of the 23 failures in the miltefosine arm, 17 were cured, 2 died and 4 defaulted. Of the 2 failures in the SSG arm, one was cured and one failed.

Miltefosine final cure in the ITT population was 60%, compared to 65% SSG cure rate. The difference was -5.2%, 95% CI -13.0, 2.7.

The following table was generated from the data in the published article.

Table 161: Efficacy Results – ITT – Study Z025 – Published Article

	MLT N = 290	SSG N = 290	P value
Initial Cure at EOT	256 (88.3%)	254 (87.6%)	0.9
Died During Therapy	6 (2.1%)	28 (9.7%)	0.0001
Initial Failure	23 (7.9%)	2 (0.7%)	< 0.0001
Initial cure at end of re-treatment of failures	273 (94.1%)	255 (87.9%)	
Followed at 6 months	213 (73.5%)	202 (69.7%)	
Final Cure 95% CI	174 (60.0%) (54.1%, 65.7%)	189 (65.2%) (59.4%, 70.6%)	0.23
Died During Follow up	11 (3.8%)	6 (2.1%)	
Total Deaths	17 (5.9%)	34 (11.7%)	0.0001
Relapse	30 (10.3%)	7 (2.4%)	0.019

Excluding the subjects who defaulted, discontinued or were lost to follow up (71 miltefosine and 60 SSG), the final cure rate is 174/219 (79.5%) in the miltefosine arm and 189/230 (82.2%) in the SSG arm. The difference in cure rates is 2.7% (95% CI -4.6%, -10.0%).

Table 162: Efficacy Results – PP – Study Z025

	MLT *N = 219*	*SSG* *N = 230*	*Difference* *95% CI*
Final Cure	*174 (79.5%)*	*189 (82.2%)*	*2.7%* *(4.6%, -10.0%)*

The sponsor generated a post hoc primary endpoint of mortality by the end of therapy. In the ITT population, mortality by the end of therapy was 2.1% in the miltefosine arm and 9.7% in the SSG arm (p = 0.0001). For this endpoint, miltefosine was superior to SSG. Miltefosine was also superior for the post hoc secondary endpoint of death by end of study (5.9% vs. 11.7% miltefosine and SSG respectively, p = 0.0001).

Analysis of clinical outcome by HIV status is presented as in the published report.

Table 163: Efficacy Results by HIV Status – Study Z025 - Published Report

	HIV infected		HIV negative		HIV unknown		All	
	Milt N = 63	SSG N = 44	Milt N = 131	SSG N = 137	Milt N = 96	SSG N = 109	Milt N = 290	SSG N = 290
Initial Treatment Outcome								
Death	1 (1.6%)	3 (6.8%)	1 (0.8%)	4 (2.9%)	4 (4.2%)	21 (19.3%)	6 (2.1%)	28 (9.7%)
Initial Cure	49 (77.8%)	40 (90.1%)	123 (93.8%)	130 (94.9%)	84 (87.5%)	84 (77.1%)	256 (88.3%)	254 (87.6%)
Failure	11 (17.5%)	1 (2.3%)	6 (4.5%)	1 (0.7%)	6 (6.3%)	0	23 (7.9%)	2 (0.7%)
Discontinued	0	0	1 (0.8%)	0	0	0	1 (0.3%)	0
Default	2 (3.2%)	0	0	2 (1.5%)	2 (2.1%)	4 (3.7%)	4 (1.4%)	6 (2.1%)
Final Outcome at 6 months								
Final Cure	29 (46.0%)	25 (56.8%)	99 (75.6%)	106 (77.4%)	46 (47.9%)	58 (53.2%)	174 (60.0%)	189 (65.2%)
Relapse	16 (25.4%)	5 (11.4%)	6 (4.6%)	0	8 (8.3%)	2 (1.8%)	30 (10.3%)	7 (2.4%)
Death	7 (11.1%)	5 (11.4%)	1 (0.8%)	6 (4.4%)	8 (9.4%)	23 (21.1%)	17 (5.9%)	34 (11.7%)
Lost to Follow up	11 (17.5%)	9 (20.5%)	25 (19.1%)	25 (18.2%)	33 (34.4%)	26 (23.9%)	69 (23.8%)	60 (20.7%)

Final Cure in the PP population was generated using the disposition data in the publication.

Table 164: Final Cure by HIV Status – PP – Study Z025

	HIV Positive		*HIV Negative*		*HIV Unknown*		*Total*	
	MLT N = 50	*SSG N = 35*	*MLT N = 106*	*SSG N = 112*	*MLT N = 63*	*SSG N = 83*	*MLT N = 219*	*SSG N = 230*
Final Cure	*29 (58.0%)*	*25 (71.4%)*	*99 (93.4%)*	*106 (94.6%)*	*46 (73.0%)*	*58 (69.9%)*	*174 (79.5%)*	*189 (82.2%)*

Reviewer's Comments
The primary data for this study were not available for review.

In a previous submission for a non-inferiority margin justification, the sponsor proposed an NI margin of 15% for this study, for the endpoint of final cure. DAIP indicated that although the large treatment effect of SSG in East Africa could support a 15% margin, a 10% margin was more clinically acceptable. (Please refer to the NI margin justification review filed in DARRTS). Because of the high rate of loss to follow up in this study

population that is described as semi-nomadic, DAIP also indicated that either the ITT or the PP populations can be used as the primary analysis population.

SSG subjects had significantly higher mortality during therapy, whereas miltefosine subjects had significantly higher initial failure, resulting in similar initial cure rates. Possible explanations include population differences at baseline, Leishmania resistance to SSG in Ethiopia resulting in suboptimal treatment, or SSG toxicity (especially cardiac toxicity associated with antimonials). These reasons will be explored.

The data presented in the article indicate that there were no differences at baseline in mean BMI, spleen size, duration of illness, or ability to walk unaided. However, because of lack of access to primary data, we are unable to explore other differences at baseline, such as vital signs or co-morbid illnesses/co-infections that may introduce biases in an open-label study.

Similar to India, the epidemiologically prevalent Leishmania species in East Africa is L. donovani. Resistance to SSG is common in India, limiting its use. Although resistance to antimony is emerging in Africa, a recent study comparing SSG to SSG plus paromomycin in HIV negative subjects in East Africa reported SSG final cure rate (defined as parasitologic clearance at 6 months) in the ITT population to be 94.1%[42]. Mortality was < 1%. This suggests that the high mortality noted in the SSG arm in Study Z025 is unlikely to be due to suboptimal therapy due to resistance, but also suggests that the high mortality is unlikely to be due to SSG adverse events/cardiac toxicity.

A study from Ethiopia[43] summarized MSF experience treating 2364 patients with VL between 2005 and 2007, of whom 2296 were treated with SSG. Mortality rate was 4% among the 2177 patients for whom an outcome was known. Risk factors for death included older age, HIV infection, edema, severe malnutrition, pneumonia, tuberculosis and vomiting. In this study, the higher mortality during therapy in the SSG arm was noted among HIV positive, HIV negative and HIV status unknown subjects, but mainly among the HIV status unknown subjects. As noted in the demography section, a higher proportion of miltefosine subjects were documented to be HIV infected and lower proportion were HIV status unknown. Assuming that randomization resulted in an equal proportion of HIV infected subjects in each arm, the noted imbalance can possibly be explained by the higher early mortality in the SSG arm, prior to HIV testing.

Miltefosine subjects had a significantly higher early failure rate. The higher failure rate occurred in all HIV categories, but mainly in the HIV infected subjects. It can be concluded that among HIV infected subjects, treatment with SSG was associated with higher mortality while treatment with miltefosine was associated with higher initial failure rate.

[42] Musa A, Khalil E, et al. Sodium stibogluconate and paromomycin combination compared to SSG for visceral leishmaniasis in East Africa: A randomized controlled trial. PLoS Negl Trop Dis 2012;6:e1674. doi:10.1371/journal.pntd.0001674

[43] Herrero M, Orfanos G, et al. Natural history of a visceral leishmaniasis outbreak in Highland Ethiopia. Am J Trop Med Hyg 2009; 81: 373-377

At 6 months follow up, final cure in the ITT and PP populations was approximately 3-5% lower in the miltefosine arm, but within the 10% NI margin. Similar to initial cure, mortality was significantly higher at 6 months in the SSG arm; however, this was mostly driven by the incidence of early mortality. Relapses were significantly higher in the miltefosine arm in all HIV infection categories but mainly in the HIV infected group.

The publication states that subjects who failed initial therapy with miltefosine received SSG while subjects who failed SSG received amphotericin B. This confounds the interpretation of post therapy deaths and the interpretation of the final cure in the miltefosine arm. 23 initial miltefosine failures were re-treated with SSG. 17 of the 23 were cured and 2 died (2 of the 11 miltefosine deaths that occurred in the post-initial therapy period occurred during this retreatment period). It is unclear how many of the 17 who were cured later relapsed and how many contributed to the overall miltefosine final cure rate. In the SSG arm, only 2 initial failures occurred, with one cure after amphotericin treatment. The overall cure rate in the SSG is unlikely to be significantly impacted.

Because the primary data were not available, the effect of miltefosine dose (mg/kg) on cure could not be explored.

The sponsor proposed a post hoc primary endpoint of death by the end of the study and concluded that miltefosine is superior to SSG. While the difference in mortality is significant, we are unable to conclude that miltefosine is superior to SSG. We have no access to the primary data. The study was open-label, and it is conceivable that biases were introduced where sicker subjects were enrolled in the IM treatment arm rather than the oral treatment arm. The possibility that the population was unbalanced for HIV infection at the time of randomization cannot be ruled out as not all subjects were tested and testing occurred 2-3 weeks after enrollment. In addition, in the MSF analysis of its experience in Ethiopia, vomiting and TB were risk factors for death. According to the publication, vomiting was more severe in the SSG arm resulting in discontinuation of treatment in 29% of SSG recipients (compared to 9% of miltefosine recipients – see safety section). We do not have data regarding TB co-infection; however, many of the SSG deaths had TB diagnosis. The lack of primary data and lack of ability to examine these variables introduce considerable uncertainty in the interpretation of the mortality difference.

Safety Evaluation

The published article only included information regarding vomiting, diarrhea, bleeding and pneumonia. Vomiting was more frequent among miltefosine recipients (54.8% vs. 32.1%, $p < 0.0001$), but more severe among SSG recipients; 9% of patients who received miltefosine and 29% of patients who received SSG had the medication withheld due to vomiting. Approximately 50% of patient in each arm experienced diarrhea. The frequency of pneumonia was higher in the SSG arm (33% vs. 27%) while the frequency

of bleeding was similar (22% in each arm). One miltefosine patient discontinued treatment after 21 days due to skin rash.

Deaths

17 miltefosine recipients died, 6 during therapy and 11 post-therapy. MSF provided the sponsor with CRFs for 15 of the 17 miltefosine deaths. The mean and median duration of therapy for the 6 subjects who died during therapy was 7 days (range 2-19 days). The 9 subjects who died post therapy and for whom a CRF was available received the full 28 day course.

34 SSG recipients died, 28 during therapy and 6 post-therapy. The mean duration of therapy for the 28 subjects who died during therapy was 15.5 days and the median was 13 days (range 4-29 days). The mean and median duration in the six subjects who died post therapy were 32 and 30 days respectively (range 30-40 days).

Because deaths were more frequent in the SSG group, the sponsor provided a tabulated summary describing the clinical features at study entry for the 15/17 miltefosine subjects and the 34 SSG subjects who died.

Table 165: Clinical features at Study Entry for Subjects who Died by the End Study Z025

	Miltefosine N = 15	SSG N = 34	P value
Mean Age, yrs, (SD)	36 (12.2)	35.6 (9.9)	0.896
Mean Weight kg (SD)	44.9 (5.7)	47.1 (5.4)	0.209
Mean BMI, (SD)	16 (2.2)	16.6 (1.7)	0.301
Unable to walk unaided	7 (46.7%)	6 (18.8%)	0.120
Mean Spleen size cm (SD)	9.0 (5.1)	10.1 (4.8)	0.476
Jaundice	1 (6.7%)	2 (6.9%)	1.000
Respiratory distress	1 (6.7%)	5 (15.2%)	0.650
Bleeding	4 (26.7%)	7 (21.2%)	0.720
Edema	5 (41.7%)	7 (23.3%)	0.274
Duration of illness, months Mean (SD)	2.4 (1.5)	2.4 (1.4)	0.266
Prior treatment for VL	6 (40.0%)	6 (20%)	0.174
Mean Hematocrit (SD)	26.2 (5.6)	24.5 (4.2)	0.276
Mean DAT titer (SD)	8.8 (2.0)	8.3 (1.3)	0.804
Mean Aspirate score (SD)	3.9 (1.2)	3.2 (1.2)	0.376

Table 166: Clinical features at Study Entry for Subjects who Died by the End of Therapy – Study Z025

	Miltefosine N = 6	SSG N = 28	P value
Mean Age years (SD)	28.5 (8.9)	35.6 (10.4)	0.174
Mean Weight kg (SD)	43.2 (7.2)	46.8 (5.6)	0.185
Mean BMI (SD)	15.8 (3.0)	16.5 (1.6)	0.427
Unable to walk unaided	4 (66.7%)	5 (19.2%)	0.065
Mean Spleen size cm (SD)	11.6 (4.9)	10.3 (4.7)	0.567

Jaundice	0	1 (4.3%)	1.000
Respiratory distress	1 (16.7%)	5 (18.5%)	1.000
Bleeding	2 (33.3%)	6 (22.2%)	0.616
Edema	3 (60.0%)	5 (20.8%)	0.112
Duration of illness, months Mean (SD)	2.6 (1.3)	3.6 (2.4)	0.548
Prior treatment for VL	1 (16.7%)	5 (20.8%)	1.000
Mean Hematocrit (SD)	22.6 (7.3)	24.6 (4.3)	0.403
Mean DAT Titer (SD)	9.5 (2.1)	8.4 (1.3)	0.355
Mean Aspirate score (SD)	4.0 (2.45)	3.0 (1.9)	0.387

There were no significant differences among miltefosine and SSG subjects who died, although the number of miltefosine subjects who died and were unable to walk unaided was higher and approached statistical significance.

Narratives for the deaths were reviewed. Co-morbid illnesses that caused or contributed to death in the 28 SSG recipients who died during therapy included pulmonary and extra-pulmonary tuberculosis, pneumonia, diarrhea, giardiasis, sepsis syndrome, renal failure, cardiogenic shock, malaria, pancreatitis and CNS toxoplasmosis. Two subjects died suddenly and their death was attributed to SSG cardiac toxicity. Six subjects died of unknown reasons.

Co-morbid illnesses that caused/contributed to death in six miltefosine subjects who died during therapy were sepsis, tuberculosis and “suspected retroviral infection” with cough at study entry. Three subjects died of unknown reasons.

Details regarding the deaths post therapy were not available as these deaths were not observed.

No autopsies were performed.

Study Conclusions

This was a randomized, open-label non-inferiority study conducted under field conditions in Ethiopia in a semi-nomadic population with a high prevalence of HIV infection (approximately 30% of those tested). HIV testing was voluntary and performed 2-3 weeks after enrollment. A higher percentage of SSG subjects were HIV status unknown, while a higher percentage of miltefosine subjects were HIV infected. This is probably explained by the higher mortality in the SSG arm that occurred prior to HIV testing.

SSG treated subjects were significantly more likely to die during or after therapy, whereas miltefosine treated subjects were more likely to experience failure at EOT, and to relapse post-therapy. *Leishmania* resistance to SSG in East Africa was not a likely explanation for the excess early mortality in the SSG arm. Excess mortality in the SSG arm was noted across all HIV categories but mainly in the HIV unknown subgroup. Excess treatment failure and relapses in miltefosine recipients were noted across all HIV categories but mainly in the HIV infected subgroup. It may be concluded that HIV

infected subjects who received SSG were more likely to die while HIV infected subjects who received miltefosine were more likely to fail therapy and to relapse after therapy.

The excess early mortality in the SSG arm and the excess early treatment failure in the miltefosine arm eventually resulted in similar initial cure rate between the treatment arms. Final cure was lower in the miltefosine arm but within the 10% NI margin. Final cure was mainly lower in the HIV infected miltefosine subgroup, due to significantly higher relapse rate. Final cure in the miltefosine arm may also have been confounded by the treatment of miltefosine subjects who had initial failure with SSG.

While mortality by the end of therapy was significantly lower in the miltefosine arm, we do not agree with the conclusion that miltefosine was superior to SSG. The primary patient level data are not available for review and the open label nature of the study may introduce biases in baseline population characteristics (such as comorbid illnesses/co-infections and vital signs) that need to be examined.

Other Sponsored VL Studies

The sponsor submitted study reports for several dose-ranging studies in Indian patients, a brief report of a Brazilian study and brief report of the results of compassionate use in HIV co-infected subjects in Germany.
In addition, reports for two Phase 4 studies (Z013 and Z013b) conducted in India and Nepal were submitted.

Study 033

This was an open label, single arm, sequential group, dose-ranging study conducted at a single institution in India. 30 male patients at least 14 years of age with parasitologically confirmed VL were enrolled, 5 subjects per dose group. Doses administered were 50 mg every other day, 100 mg every other day, 100, 150, 200 or 250 mg/day for 28 days.

Similar to Study 3154, the primary endpoint was definite cure at 6 months. All doses resulted in apparent or initial cure at EOT. Doses of 100 mg or greater were required to achieve definite cure (18/20, 90%). Lower doses achieved definite cure in 40% (2/5 subjects in each of the lower dose group). Doses of 200 and 250 mg/day were poorly tolerated due to nausea and vomiting, and one subject in the 250 mg group died of renal and cardiac failure.

Study 3089

This was an open label, randomized, dose-ranging study comparing 100mg/day to 150 and 200 mg/day for 28 days in subjects at least 14 years of age with VL in India. The endpoint was definite cure at 6 months. 46 subjects were randomized, and one did not receive study medication. Seven subjects discontinued miltefosine prematurely, 6 due to intolerance and one withdrew consent. Definite cure rates in the ITT population were

94% in the 100 mg arm and 100% in the 150 and 200 mg arm. In the 200 mg arm, CTC grade 3 renal and hepatic toxicities occurred in one subject each.

Study 3091

This was an open label single arm, sequential group, dose-ranging study in subjects 2-11 years of age with VL in India. 21 subjects received 1.5 mg/kg/d and 18 received 2.5 mg/kg/day for 28 days. Final cure rates were 19/21 (90.5%) and 15/18 (83.3%) respectively.

Study 3109

This was an open label, single arm, sequential group, dose-ranging study conducted in India in patients with VL at least 12 years of age. Miltefosine was administered to four groups at 50 mg/day for 6 weeks, 50 mg per day for one week followed by 100 mg/d for 3 weeks, 100 mg/d for 4 weeks and 100 mg/d for one week followed by 150 mg/day for 3 weeks. The primary endpoint was final cure at 6 months. 120 subjects were enrolled, 30 in each group. Final cure in the ITT population was 28/30 (93.3%) in each of the first 2 groups and 29/30 (96.7%) in the each of the second 2 groups. Main AEs were nausea, vomiting and diarrhea. Two subjects discontinued the medication prematurely, one due to increase in AST and ALT and one due to vomiting, anorexia, elevated BUN and Cr and oliguria.

Study 3127

This was an open label, single arm, parallel group, dose-ranging study in Indian patients with VL at least 12 years of age. Miltefosine was administered at 100 mg daily for 2, 3 or 4 weeks of treatment to 3 groups (18 subjects each) of Indian patients with VL. The endpoint was final cure at 6 months. Cure rates were 16/18 (88.9%) in the group that received the 2 week treatment and 100% in the other 2 groups. Main adverse events included vomiting (approximately 60%) and diarrhea (approximately 13%).

Study 3206

The study was an open label trial of oral miltefosine 2.5 mg/kg daily for 28 days for the treatment of VL in 80 Indian patients 2-11 years of age. Eligibility criteria and primary efficacy endpoint were similar to those used in study 3154.

One subject died during therapy. 79 subjects were assessed for parasitologic initial cure and all 79 were cured. In the post-treatment follow up phase, 3 subjects relapsed and one was lost to follow up. Final Cure in the ITT population was 75/80 (94%). One patient died on day 4 due to a pulmonary infection. No patient discontinued drug due to AE. Vomiting and diarrhea were noted in 25% of patients, and elevations of ALT in 55%.

Study Z019

This was dose finding study in Brazilian patients with VL. 23 subjects 2-12 years of age received miltefosine 2.5 mg/kg/d for 28 days and 19 subjects 13 to 60 years of age received 50 mg/ d if weight < 25 kg or 100 mg/ day if weight was ≥ 25 kg.

The study was conducted at 2 study sites. At the first site (Montes Claros), definite cure rates were 27% and 100% in the pediatric and adult populations respectively. At the second site (Teresina), the rates were 67% and 69% respectively.

Reviewer's Comments
The usual causative agent of VL in Brazil is L. chagasi, while in India, Nepal and East Africa it is L. donovani. The sponsor is not seeking the indication of treatment of VL caused by L. chagasi.

The mean weight in adults in this study was 63 kg, representing a miltefosine dose of 1.6 mg/kg/day, lower than the target 2.5 mg/kg and lower than the doses used in the Indian trials. This lower mg/kg dose may explain the lower efficacy of miltefosine in adults in this study but does not explain the low efficacy rates among pediatric patients.

Compassionate Use Program in HIV Co-infected Patients

This program was in effect prior to marketing the drug in Germany. 39 HIV infected subjects with VL not responding to other therapies received miltefosine 100 mg/day (mean dose of 1.77 mg/day) for durations at the discretion of the treating physician. Initial response was seen in 25/39 (64%) and clinical cure in 16 (41%).

Reviewer's Comments
These patients were mainly from Southern Europe where the infecting Leishmania species is L. chagasi/infantum. The initial and final cure rates are lower than the cure rates achieved in HIV co-infected subjects in Study Z025.

Study Z013

This was an open label, single arm, Phase 4 postmarketing study in Indian patients with VL treated as outpatients[40]. The study was conducted by the Indian Council of Medical Research with support from the WHO and Zentaris.

Children 2-11 years of age received 2.5 mg/kg/day. Subjects ≥ 12 years of age and weighing < 25 kg received 50 mg daily for 28 days. Subjects ≥ 12 years of age and weighing ≥ 25 kg received 100 mg daily for 28 days. Subjects were followed weekly during therapy and at 2 and 6 months.

The published article reported cure rates in the PP population. Cure rates for this review will be reported for the PP and ITT populations.

1132 subjects received miltefosine, 704 adults and 428 children (< 12 years of age). The following table was generated based on the numbers reported in the publication.

Table 167: Summary Results of Study Z013

	Study Z013
Enrolled	1132
Completed 2 weeks of Rx	96.8%
Completed 4 weeks of Rx	95.5%
Initial Cure	1055 (93.2%)
Initial Failure	6 (0.6%)
Returned for 6 month follow up	971
Relapse	44 (4.0%)
Final Cure ITT	927/1132 (81.9%)
Final Cure PP	922/971 (95.5%)
Deaths	3 (0.3%)

In adult subjects, the ITT initial and final cure rates were 654/704 (92.9%) and 592/704 (84.1%) respectively. Initial and final cure rates for the adult PP population were 98.6% and 96.5%.

Nausea and vomiting were the most common AEs, reported in approximately 8% of patients during the treatment period. Three subjects died during the treatment period, a 2 year old boy who presented with abdominal pain and swelling (no further details), and a 13 year old girl with history of bloody diarrhea for 4 months prior to VL diagnosis, and leukopenia/neutropenia and severe thrombocytopenia at initiation of miltefosine. She received broad spectrum antibiotics and continued to experience bloody stools, then developed abdominal distention on day 4, and expired on day 8 after cardiopulmonary arrest. One subject died in a car accident. Serious AEs occurred in 5 subjects: volume depletion and increased Cr, and diarrhea with or without vomiting. Miltefosine was discontinued in two subjects due to an AE: generalized pruritic macular rash, and vomiting with volume depletion. The latter subject was also receiving oral antibiotics for UTI and iron for anemia.

Two pregnancies were reported, one with estimated date of conception 2 weeks after EOT and one with estimated date of conception 3 months after EOT. Both babies were healthy.

CTCAE grade 1 elevations in ALT and AST occurred in 23% and 31% of subjects respectively, grade 2 elevations in 9% and 5% and grade 3 elevations in approximately 1%. CTCAE grade 1, 2 and 3 Cr elevations occurred in 14%, 1.6% and 0.6% of subjects respectively.

Reviewer's Comments
The rate of loss to follow up in the post-therapy period was higher compared to Study 3154, leading to a lower ITT cure rate. Relapse and PP cure rates were similar to Study 3154. The AE profile is also similar to the findings in Study 3154.

Study Z013b

This study was conducted in Nepal and was similar to Z013 in design.

125 subjects enrolled, 33 below the age of 12. Initial cure occurred in 121 subjects (96.8%), and final cure occurred in 105 subjects (84%). 12 subjects relapsed (9.6%) and 2 subjects died, a 13 year old girl secondary to sepsis due to foot abscess and a 26 year old woman with BMI 13 who was also receiving metronidazole for concomitant *E. histolytica* infection (report does not specify if intestinal and/or hepatic). On day 4 of study treatment, she developed pedal edema. ECG and respiratory evaluations were normal. On day 9, she developed SOB and lost consciousness. She was taken to a faith healer and died the same day. Her last study evaluation indicated that her VL fever had resolved and spleen had regressed. Liver and renal functions were normal on day 7. The sponsor assessed causality for both deaths as unlikely to be related to miltefosine.

Table 168: Summary Results of Study Z013b

	Study Z013b
Enrolled	125
Initial Cure	121 (96.8%)
Relapse	12 (9.6%)
Final Cure ITT	105 (84.0%)
Deaths	2 (1.6%)

The main AEs included vomiting, diarrhea and abdominal pain, occurring in 43%, 25% and 17% respectively. One subject was hospitalized with dehydration and increased creatinine. One pregnancy was reported with an estimated date of conception at week 2 of therapy. A healthy baby was delivered.

Reviewer's Comments
The initial cure rate and mortality were comparable to those in Study 3154, but a higher percentage of subjects relapsed (9% vs. 3%). AEs profile was similar to what was noted in pre-marketing studies.

Published VL Studies

Three published studies were retrieved: one in Bangladesh, one in Nepal and one in India. The studies in India[38] and Nepal[39] have already been discussed in the reviewer's comments section for Study 3154. The Bangladesh study[44] was similar to Z013. Children 2-11 years of age received 2.5 mg/kg/day. Subjects ≥ 12 years of age and weighing < 25 kg received 50 mg daily for 28 days. Subjects ≥ 12 years of age and weighing at least 25 kg received 100 mg daily for 28 days. Subjects were followed weekly during therapy and at 2 and 6 months.

[44] Rahman M et al. Phase IV trial of miltefosine in adults and children for treatment of visceral leishmaniasis (Kala-Azar) in Bangladesh. Am J Trop Med Hyg 2011;85:66-69

Initial cure at EOT was defined as loss of fever, spleen at least 30% smaller compared to baseline, Hb ≥ 10 or an increase with respect to pretreatment value of at least 10%. Final cure at 6 months was defined as loss of fever, spleen at least 70% smaller than at pretreatment, weight gain of at least 0.5 kg, and Hb ≥ 10 or an increase with respect to pretreatment value of at least 10%.

400 children and 577 adults (≥ 12 years of age) received at least one dose (the ITT population). The PP population included those who received at least 90% of treatment (at least 25 days – 941 subjects).

Initial cure at EOT and/or at 2 months was 865/977 (88.5%), and initial failure was 24/977 (2.6%) (52 were not assessable).

At 6 months follow up, 701 were cured, 95 failed and 69 were not assessable. 73/95 assessed as failures had isolated anemia. The authors state that if one assumes that all patients with anemia at follow up represent treatment failure, the PP cure rate is 701/941 (74%) and 701/820 in evaluated patients (85%). If one assumes that 1/3 of subjects with isolated anemia are failures, the cure rate increases in the PP population to 80% and to 92% in the evaluated patients.

13 subjects experienced a serious AE, and six died. Two deaths were attributed to vomiting occurring 19 and 33 days after EOT, one death due to diarrhea occurring on Day 21 of treatment, hemoptysis with cough, severe anemia, and one death in a patient who died 2 months after taking miltefosine for one week. Only the death attributed to diarrhea was assessed as drug related. The other SAE were tuberculosis and enteric fever. 25% of subjects experienced vomiting and 8% experienced diarrhea. These were mostly CTCAE grades 1 and 2, with 5% of subjects experiencing grade 3.

Reviewer's Comments
This study did not attribute isolated anemia to nutritional factors, in contrast to the studies in India (including Study 3154) where anemia was attributed to nutritional factors in the majority of subjects. The authors assumed that 1/3 of these subjects represent failure. The basis of this assumption is Study 3154 where 9 of the 27 subjects who underwent a follow up spleen or marrow aspirate were positive.

Integrated Efficacy – VL

The sponsor integrated results from all the prospective Phase 1, 2 and 3 trials conducted in VL subjects in India. These trials enrolled 667 subjects, including 119 children 2-11 years of age and including the 299 subjects enrolled in Study 3154. The results are summarized.

Table 169: Summary Miltefosine Efficacy – Phase 1, 2 and 3 Trials in India - Sponsor

All subjects	MLT N = 667	AMB N = 99
Final Cure	623 (93.4%)	96 (97.0%)

Not Cured	32 (4.8%)	0
No assessable	15 (2.0%)	3 (3.0%)

The sponsor also presented final cure rates by age category, by dose level and by prior treatment. Final cure was lower in subjects who received less than 2 mg/kg/day and was not affected by prior treatment. The response by age analysis added the amphotericin subjects to the miltefosine subjects (total 766 subjects) in the denominator. Final cure in the 119 children who received any miltefosine dose was 109/119 (91.6%).

Table 170: Miltefosine Final Cure by Dose Level – Phase 1, 2 and 3 Trials in India

Miltefosine mg/kg Dose	Final Cure
< 2	81/94 (86.2%)
2.0-2.4	174/191 (92.1%)
2.5-2.9	213/223 (95.5%)
3-3.9	89/92 (96.7%)
≥ 4	66/69 (95.7%)

Table 171: Miltefosine Final Cure by Prior Treatment – Phase 1, 2 and 3 Trials in India

	MLT		AMB	
	Newly Diagnosed	Prior Treatment	Newly Diagnosed	Prior Treatment
Final Cure	407/439 (92.7%)	218/228 (95.6%)	70/71 (98.6%)	26/28 (92.9%)

The sponsor stated that in Phase 4 trials in the Indian subcontinent (India, Bangladesh and Nepal), the PP cure rates for all 3 studies combined was 93%. The Phase 1 and 2 studies conducted in India were conducted by the investigators who conducted Study 3154. The enrolled adolescent and adult populations and the definitions and assessments of outcomes were similar. Outcomes in children were similar to outcomes in adults.

For this analysis, comparison between the results of Study 3154 and the HIV negative population enrolled in Study Z025, and a summary of the Phase 4 and published studies will be presented.

With the exception of gender, HIV negative subjects enrolled in Study Z025 in Ethiopia had similar baseline characteristics to the subjects enrolled in Study 3154 in India (mean age, BMI, weight, parasite density and spleen size), and VL in both countries is caused by *L. donovani*. Initial cure was slightly lower in Ethiopia compared to India, but in both studies initial cure in the miltefosine arm was high and comparable to the comparator drug. Mortality rate in the miltefosine arm in both studies was <1%, while relapses were only noted in the miltefosine treated subjects in both studies (3.5% in the studies combined, vs. no relapses in AMB or SSG recipients). Final cure was higher in Study 3154, mainly due to the high loss to follow up in the Ethiopian study.

Table 172: Final Cure – HIV Negative Subjects ≥12 years of age - Studies 3154 and Z025– ITT

	MLT			AMB	SSG
	3154	Z025	Total		
N	299	131	430	99	137
Initial Cure	293 (98.0%)	123 (93.8%)	416 (96.7%)	97 (98.0%)	130 (94.9%)

Initial Failure	0	6 (4.5%)	6 (1.4%)		1 (0.7%)
Final Cure	282 (94.3%)	99 (75.6%)	381 (88.6%)	96 (97.0%)	106 (77.4%)
Relapse	9 (3.0%)	6 (4.5%)	15 (3.5%)	0	0
Death	2 (0.7%)	1 (0.8%)	3 (0.7%)	0	6 (4.4%)
Lost to Follow Up	2 (0.7%)	25 (19.1%)	27 (6.3%)	2 (2.0%)	25 (18.2%)
Not assessable	4 (1.3%)	0	4 (0.9%)	1 (1.0%)	0

Table 173: Final Cure – HIV Negative Subjects ≥12 years of age - Studies 3154 and Z025 – PP

	MLT			AMB	SSG
	3154	Z025	Total		
N	287	106	393	94	112
Final Cure	279 (97.2%)	99 (93.4%)	378 (96.2%)	94 (100%)	106 (94.6%)

In phase 4 and published VL studies, the initial cure remained high. Final cure in the ITT population was lower compared to Study 3154, in part due to higher rate of loss to follow up, and in part due to higher rate of relapses. In the Bangladesh post-marketing study, final cure rate increases if one assumes that 1/3 of subjects, rather than all subjects, with residual anemia are relapses.

Table 174: Summary of Miltefosine Effectiveness in Phase 4 and Published VL Studies

Effectiveness in Post-Marketing Studies	Z013 N = 1132	Z013b N = 125	Rahman et al.[44] N = 977	Sundar et al.[38] N = 567	Rijal et al.[39] N = 120	Study 3154 N = 299
Country	India	Nepal	Bangladesh	India	Nepal	India
Initial Cure - ITT	1055 (93.2%)	121 (96.8%)	865 (88.5%)	553 (97.5%)	115 (95.8%)	293 (98.0%)
Final Cure - ITT	927 (81.9%)	105 (84%)	701 (71.8%)	512 (90.3%)	99 (82.5%)	282 (94.3%)
Final Cure - PP	927/971 (95.5%)	105/117 (89.7%)	701/820 (85%)	512/553 (92.6%)	99/115 (86.1%)	282/287 (98.3%)
Not assessable	158 (14.0%)	8 (6.4%)	121 (12.4%)	11 (1.9%)	7 (5.8%)	6 (2.0%)
6 month Relapse	44 (3.9%)	12 (9.6%)	95* (9.7%)	39 (7.2%)	13 (10.8%)	9 (3.0%)
6 month Mortality	3 (0.3%)	2 (1.6%)	6 (0.6%)	5 (0.9%)	1 (0.8%)	2 (0.7%)

*Assumes that all 73 subjects with residual isolated anemia are not cured.

Integrated Safety – VL

The sponsor presents treatment emergent AEs noted in the 548 adult subjects enrolled in Phase 1, 2 and 3 Indian studies, but only includes the AEs assessed as likely due to the drug or as not assessable. These are summarized.

Table 175: AEs Occurring in ≥ 2% of Indian VL Subjects ≥ 12 years of age in Phase 1, 2 and 3 Trials - Sponsor

	Miltefosine N = 548				AMB N = 99
	< 2 mg/kg	2-3 mg/kg	3-4 mg/kg	> 4 mg/kg	N = 99

	N = 74	N = 321	N = 84	N = 69	
Vomiting	27 (36.5%)	131 (40.8%)	47 (56.0%)	52 (75.4%)	21 (21.2%)
Diarrhea	15 (20.3%)	69 (21.5%)	22 (26.2%)	22 (31.9%)	6 (6.1%)
Anorexia	4 (5.4%)	24 (7.5%)	8 (9.5%)	2 (2.9%)	13 (13.1%)
Nausea	4 (5.4%)	3 (0.9%)	1 (1.2%)	1 (1.4%)	-
Abdominal pain	-	2 (0.6%)	1 (1.2%)	2 (2.9%)	-
Fever	2 (2.7%)	2 (0.6%)	1 (1.2%)	1 (1.4%)	0
Rigors	-	1 (0.3%)	-	-	90 (90.9%)
SGOT increased	-	1 (0.3%)	-	2 (2.9%)	-
Arthralgia	-	-	2 (2.4%)	1 (1.4%)	-
BUN increased	-	-	-	2 (2.9%)	-
Flatulence	-	-	1 (1.2%)	4 (5.8%)	-
Pain	-	-	-	2 (2.9%)	-
Thrombocytopenia	-	-	-		2 (2.0%)

The primary data from Phase 1 and 2 studies are not available, but it was possible from the study reports to determine the number of subjects who developed SAEs, discontinued the drug due to an AE or died. The number of subjects with any AE was difficult to determine, as AEs were presented only if assessed as likely due to drug or as not assessable and only if CTC grade 2 or higher.

Table 176: Summary of AE – Phase 1 and 2 Indian Studies and Study 3154

	MLT			AMB N = 99
	Phase 1 &2 N = 249	3154 N = 299	Total N = 548	
Subjects with at least one AE	-	125 (41.8%)	-	44 (44.5%)
Subjects with SAE	2 (0.8%)	6 (2.0%)	8 (1.5%)	1 (1.0%)
AE that led to drug discontinuation	13 (5.2%)	8 (2.7%)	21 (3.8%)	3 (3.0%)
Death	2 (0.8%)	2 (0.7%)	4 (0.7%)	0

The AEs and relation of AEs to miltefosine per kg dose was detailed in the safety section of study 3154. Elicited vomiting and diarrhea events occurred at all doses and vomiting was dose dependent, but spontaneously reported AEs were not dose dependent.

The post-marketing studies have already been described. Mortality was <1%-1.6%. Most deaths were either due to complications of VL, volume depletion with renal impairment or sepsis. Less than 1% of subjects discontinued therapy, usually due to vomiting, diarrhea, or impaired liver or renal function.

Renal Toxicity
In Study 3154, some degree of Cr elevation during therapy occurred in approximately 50% of miltefosine recipients, compared to 100% of amphotericin recipients. Approximately 10% of miltefosine recipients had CTCAE grade 2 elevations during therapy, compared to 40% of amphotericin subjects. At EOT, mean Cr increased among amphotericin recipients but remained stable among miltefosine recipients. No subject discontinued therapy due to renal impairment.

Renal impairment was also reported in the Phase 1 and 2 studies in India. In these studies, renal impairment was reported as a serious AE and led to drug discontinuation. One subject died with findings of grade 4 diarrhea and renal and cardiac failure.

In Study 3154, there was evidence that Cr elevation may occur after discontinuation of therapy. This is consistent with the long half-life of the drug. Monitoring of renal function is recommended during therapy.

Liver Toxicity
In Study 3154, approximately 50% of subjects experienced some degree of ALT elevation, and 91.6% of subjects had some degree of AST elevation during therapy. The majority were CTCAE grade 1. No subject discontinued therapy due to transaminase elevation, and one subject discontinued therapy due to isolated hyperbilirubinemia and jaundice.

Elevations of liver enzymes were also commonly reported in the Phase 1 and 2 Indian trials. In these trials, grade 3 elevations led to drug discontinuation in several subjects. Elevations of liver enzymes were also reported in Post-Marketing trials. Acute liver failure was not reported. Overall, elevations of liver enzymes were more frequently encountered in VL trials compared to CL trials.

Hematologic Toxicity
Although miltefosine is hemolytic in vitro and when administered IV, decreases in Hb were more frequently encountered in amphotericin recipients, and Hb improved more quickly in miltefosine recipients during therapy. A higher percentage of miltefosine subjects had leukopenia at screening, EOT and at 6 month follow up. The higher percentage at EOT is likely explained by an imbalance in the number of subjects with leukopenia at baseline and the higher frequency at follow up may be related to the higher relapse rate in the miltefosine arm.

A higher percentage of miltefosine subjects had thrombocytopenia at EOT and at 6 months follow up. The higher percentage at follow up may be related to the higher relapse rate; however, the higher percentage at EOT could possibly be drug related.

Integrated Safety

VL, CL and ML Clinical Studies

Table 177: Summary of AEs in VL, CL and ML studies

	Miltefosine N = 587*	Miltefosine N = 321	Amphotericin N = 99	Meglumine N = 58	Placebo N = 44
Study	3154, 3168, Soto, Z020, Z022	Dose Ranging VL and CL**	3154	Soto, Z020	3168
Death	3 (0.5%)	2 (0.6%)	0	0	0

SAE	7 (1.2%)	2 (0.6%)	1 (1.0%)	0	0
AE leading to drug discontinuation	9 (1.5%)	13 (4.0%)	3 (3.0%)	0	0
Vomiting	328 (55.6%)	128 (39.9%)	20 (20.2%)	0	0
Diarrhea	87 (14.8%)	85 (26.5%)	6 (6.1%)	3 (5.2%)	2 (4.5%)
Transaminases > 3x ULN	60 (10.2%)	46 (14.3%)	11 (11.1%)	2 (3.4%)	0
Cr elevation > 1.5x baseline	79 (13.5%)	20 (6.2%)***	40 (40.4%)	3 (5.1%)	2 (4.5%)

*Mean and median dose 2.5 mg/kg/day, range 1.5-4
**Includes doses of 200 and 250 mg/day
***Elevation above ULN rather than above baseline

The deaths in Studies 3154 and Z022 were assessed as unrelated to miltefosine. One of the two deaths in the dose ranging VL studies was assessed as probably drug related: Grade 4 diarrhea with renal and cardiac failure in a subject receiving 250 mg/day (6 mg/kg).

Serious AEs probably or possibly related to miltefosine included one case of Stevens-Johnson syndrome, diarrhea, renal impairment (in dose ranging VL studies), elevation of transaminases (in dose ranging VL studies) and melena with thrombocytopenia. AEs that led to drug discontinuation included vomiting, diarrhea, rash, jaundice, arthritis and thrombocytopenia.

Renal Toxicity
No miltefosine subject discontinued therapy due to renal impairment in Phase 3 trials. Elevations of Cr above baseline were common, and approximately 10% of subjects developed elevations > 1.5x baseline at EOT. Elevations > 1.5x baseline were dose dependent, but lower elevations were not. Some subjects developed Cr elevations post-therapy, likely reflecting the long half-life of the drug.

Hepatic Toxicity
Transaminase elevations were mainly noted in VL studies, but not CL studies. The elevations were mild and reversible. No subject in Phase 3 studies discontinued miltefosine due to elevations in transaminases, and one subject discontinued due to isolated hyperbilirubinemia.

Hematologic Toxicity
No CL subject developed thrombocytopenia during therapy. At EOT, a higher percentage of miltefosine subjects had thrombocytopenia compared to amphotericin in Study 3154, suggesting a possible drug effect.

Published Studies

The Phase 4 and published studies conducted in India, Nepal and Bangladesh enrolled a total of 2921 patients. There were 17 deaths at 6 months follow up (0.6%), mainly due to

VL complications, volume depletion with renal impairment or sepsis. Vomiting and diarrhea were common (30-45%). Less than 1% discontinued therapy due to an adverse reaction: vomiting, diarrhea or impaired liver or renal function.

Periodic Safety Update Reports

Oral miltefosine was launched in India in June 2003, Germany in December 2004, and Colombia in 2005. It is also marketed in Argentina, Bolivia, Guatemala, Ecuador, Honduras, Peru, Paraguay, Mexico, Nepal, Pakistan and Bangladesh for the treatment of VL and CL. Miltefosine is also registered in Germany as a topical drug to treat cutaneous cancers.

The sponsor submitted Periodic Safety Update Reports (PSUR) that were compiled for the German Regulatory Authorities (BfArM) and that covered the periods of September 19, 2004 and November 18, 2011. Based on the number of subjects enrolled in clinical trials and sales data, approximately 110,000 patients have been exposed to the drug as of November 2011.

PSUR 1
This PSUR covered the period of September 19, 2004 through May 18, 2005. During this reporting period, 6121 patients were exposed to marketed miltefosine and 80 were exposed in the course of clinical trials.

3 serious AEs were reported; two resulted in death: One death occurred in the course of clinical trial Z022 (see the death narrative in the safety section of Study Z022). The other death occurred in the course of trial Z013b in Nepal (see narrative in Z013b Study section of this review).

Other serious un-labeled AEs included one case of agranulocytosis reported from Germany in a 57 year old man hospitalized with 22 CL lesions, some secondarily infected with bacterial pathogens. He received miltefosine and clindamycin. On day 12, miltefosine was suspended due to increased Cr. The patient also had a UTI and ciprofloxacin was started. He developed leukopenia on Day 10 of ciprofloxacin, 10 days after discontinuation of miltefosine. He received GCSF and the WBC recovered. Cr also normalized. The treating physician assessed the agranulocytosis and renal impairment as possibly related to miltefosine, the sponsor assessed agranulocytosis as related to ciprofloxacin but could not exclude miltefosine. The sponsor assessed increased Cr as a serious AE possibly related to miltefosine.

One non-serious unlabeled AE was lymphadenopathy in a patient treated for CL. The enlarged lymph node was in the area of drainage of the lesion. This was assessed unrelated to miltefosine.

The PSUR also contained case reports of pregnancy. 3 female patients became pregnant, the estimated dates of conception 2 weeks after EOT, 3 months after EOT and during therapy for VL (in study Z013). All delivered healthy babies.

PSUR 2
This covered the period of May 19, 2005 to September 11, 2005.

Since the submission of PSUR 1, the product received market authorization in Argentina, Ecuador, Guatemala and Paraguay for the treatment of VL and CL. 55 new subjects were exposed in clinical trials, and an estimated 3000 new patients were exposed postmarketing.

One SAE was reported: renal impairment and proteinuria in a subject treated for VL in a clinical trial in Brazil. Three non-serious AEs were reported, one gout arthritis, and 2 reports of decreases sperm production. No case reports of pregnancy were received by the sponsor.

PSUR 3
This covered the period of September 11, 2005 and May 18, 2006. During this period, miltefosine received market authorization in Nepal and Honduras for the treatment of VL and CL.

137 new subjects were exposed in company-sponsored clinical trials, and 88 new subjects were enrolled in a clinical trial of miltefosine in the treatment of CL in Iran. An estimated (b) (4) patients were exposed based on sales data.

One serious AE of persistent vomiting was reported in a 5 year old female treated for VL. Non serious AEs reported included one report of decreased libido and ejaculation and one report of nausea and diarrhea. There were no reports of pregnancy.

PSUR 4
This covered the period of May 19, 2006 and September 18, 2006. During this period, miltefosine received market authorization in Bangladesh, Bolivia, Mexico, Pakistan, and Peru for the treatment of VL and CL.

190 new subjects were enrolled in company-sponsored clinical trials and 93 new subjects in investigator-initiated trials. Two more trials sponsored by the WHO and the Indian Council of Medical Research were also initiated, but the number of subjects enrolled was not known. According to sales data, an estimated (b) (4) patients were exposed.

Two serious unlisted AEs were reported: anemia in an HIV positive individual treated for VL sequentially with AmBisome then miltefosine, and renal impairment and jaundice on day 12 of miltefosine treatment for VL in an alcoholic patient. The patients recovered.

Sixteen cases of non-serious un-labeled AEs were reported, including 4 cases of epididymitis, 8 cases of reduced ejaculate volume, 2 cases of painful scrotum and epididymal swelling, and one case of fatigue. No cases of pregnancy were reported.

PSUR 5

This covered the period of September 19, 2006 to September 18, 2007. During this time, 1044 new subjects received miltefosine in the course of clinical trials sponsored by the company, by investigators or by the WHO. Most of these patients were enrolled in a post-marketing trial of miltefosine in the treatment of VL in Bangladesh (PDE 06-01, 1007 subjects – reviewed below). Based on sales data, an estimated (b) (4) patients were exposed to the drug.

Six deaths were reported, all in the course of the Bangladesh trial: Severe diarrhea in a 6 year old female 3 weeks after completing miltefosine course (with cure of VL), a 6 year old female treated for VL (with cure) who developed diffuse erythematous skin lesions and vomiting 5 weeks after completing miltefosine therapy, 18 year old man with pneumonia and hemoptysis on day 12 of miltefosine treatment for VL, a 60 year old woman with BMI 12.9 who was found dead 2 months after taking miltefosine for one week, 26 year old woman with severe anemia, fever and respiratory distress requiring intubation 3 weeks after starting miltefosine, and a 20 year old woman whose clinical findings due to VL were improving on day 21 of miltefosine but who developed cough and diarrhea after receiving an 'indigenous' medication and died 2 days later.

Ten serious unlisted AEs were reported, seven to the relevant regulatory authorities and 3 in the literature. The cases reported to the regulatory authorities included tonic-clonic seizure on day 15 of miltefosine, generalized edema and UTI on day 5 of therapy, cough and peripheral edema 3 months after end of therapy for VL, loss of consciousness on day 27, migraine headache on day 6, and renal impairment in an HIV positive individual who had been receiving miltefosine for seven months.

The 3 cases in the literature were all thrombocytopenia: 15 year old with VL not responding to miltefosine after 10 days of treatment who had thrombocytopenia, melena and abdominal pain, 38 year old with thrombocytopenia, epistaxis and gingival bleeding occurring on day 12 of miltefosine treatment for VL (platelet count responded to dexamethasone and a spleen aspirate on day 8 showed no parasites), and a 29 year old with thrombocytopenia, epistaxis and gingival bleeding occurring on day 6 of miltefosine and day 4 of SSG treatment for VL (spleen aspirate showed persistent infection and he received rescue treatment with amphotericin).

One non-serious AE of scrotal pain and reduced ejaculate volume was reported.

PSUR 6
This covered the reporting period of September 19, 2007 and September 18, 2008. In the interim since the last report, thrombocytopenia was added to the product labeling as an adverse event.

86 new subjects were exposed during the course of the WHO trial, and an estimated 1270 patients were exposed based on sales data. Two deaths were reported, 35 year old Indian man who developed CTCAE grade 3 elevations of bilirubin and Cr on day 15 of miltefosine treatment for VL and a 50 year old woman with VL who developed a hypersensitivity reaction to a test dose of amphotericin prompting a change to

miltefosine, then developed fever and dyspnea on day 5 of miltefosine treatment. She also became neutropenic and was started on broad spectrum antibiotics. On day 7, she developed increased transaminases and increased Cr, followed by mental status changes and died during peritoneal dialysis.

PSUR 7
This covered the period of September 19, 2008 and March 31, 2009. During this reporting period, an estimated (b) (4) patients were exposed based on sales data. There were no AEs reported either to the sponsor or in the literature. There were no reports of pregnancy and no changes to the drug labeling.

PSUR 8
This covered the period of November 19, 2008 to November 18, 2011. There were no regulatory actions taken. An estimated (b) (4) patients were exposed during this reporting period based on sales data.

Two deaths were reported: 26 year old female treated for VL who presented with severe anemia (Hb 4.2), respiratory distress and pneumonia on Day 21 of miltefosine treatment, and died the same day and an 18 year old man with VL and BMI of 6.7 who developed severe pneumonia 3 days after starting a combination of miltefosine and liposomal amphotericin.

SAEs reported included hyperbilirubinemia in a 40 year old 3 days after discontinuing miltefosine and starting paromomycin for the treatment of VL, 3 cases of PKDL (post-kala azar dermal leishmaniasis), and one case of renal impairment and hypertension diagnosed a week after starting miltefosine in a patient with history of diabetes.

Reviewer's Comments
The post marketing experience reported in the PSURs is similar to what was noted in clinical trials and to what was reported in published literature: vomiting, diarrhea, renal impairment and elevations of hepatic enzymes. The sponsor does not provide details regarding the specific data that prompted updating the German product labeling to include thrombocytopenia. Some of the deaths were not observed and are unexplained.

The PSURs included the safety data from the postmarketing studies conducted by the sponsor (Z013 in India and Z013b in Nepal), and the WHO/Bangladesh study. These studies have already been reviewed in the integrated efficacy and safety sections of this review. 3 additional published studies have also already been cited in this review: The first is the study reporting on 31 Dutch soldiers treated for CL was cited in the CL section. In that study, the majority of subjects were unable to fulfill their military duties due to fatigue and malaise, 21/31 reported decreased ejaculate volume, and one subject was diagnosed with epididymitis[26]. The other two studies were the Nepal [39] study that explored efficacy of miltefosine and the Indian study that explored efficacy of miltefosine after a decade of use[38].

Organ Toxicities of Interest

Eye Toxicity

Retinal degeneration that was dose and duration dependent was noted in the 8 week and 52 week rat toxicity studies, but was not noted in the dog toxicity studies. This was thought to be related to effects of the drug on retinal pigment epithelial cells and was reversible after cessation of administration.

25 cancer patients received oral miltefosine in Germany in 1992 and underwent ophthalmologic evaluations. The conclusion of the assessments was that miltefosine may induce electrophysiologically detectable changes in the retinal pigment epithelium of the human eye which are at least partially reversible, although these changes did not lead to subjective impairment of visual acuity, or to changes in the electroretinogram.

All Phase 1 and 2 studies and Study 3154 in India included weekly visual assessment (total 548 subjects). One subject in Study 3154 was noted as having “central retinosis”. Study 3168 in CL subjects also included weekly assessment. One subject had abnormal fundoscopy in one eye that was not specified and that returned to normal at 6 months. Visual findings were otherwise unremarkable, and no visual AEs were reported in any of the clinical studies, published literature or reported to the German regulatory authorities.

Reproductive Toxicity

Males

Massive seminiferous tubule atrophy, prostate atrophy, morphologically altered sperm and reduced fertility were noted in male rats at doses similar to or lower than the human therapeutic dose. Multifocal degeneration of seminiferous tubules was noted in dogs. The testicular changes were reversible within 10 weeks after discontinuation of the drug.

Spermiograms were obtained at screening, 2 weeks and 6 months in 15 men who participated in the CL study, Study 3168 (11 miltefosine recipients and 4 placebo recipients). There were large variations in sperm counts and motility. The results were judged by the sponsor as not significant and by the FDA consultants from the Division of Bone, Reproductive and Urology Products (DBRUP) as inconclusive.

220 male subjects who previously participated in Phase 2 VL studies and in Study 3154 in India and who had a female sexual partner were retrospectively tracked and queried regarding reproductive performance. These included 197 miltefosine recipients and 23 amphotericin recipients. Assessments were done 11-57 months after miltefosine therapy. 69% of miltefosine male recipients (136/197) had proven fertility documented by at least one delivery or ongoing pregnancy. 58% (56/96) of the subset of male subjects who were enrolled in Study 3154 had proven fertility compared to 52% (12/23) of amphotericin recipients.

Post treatment spermiograms were also obtained in 12 miltefosine subjects enrolled in 3154. In ten, the findings were normal. One man had oligospermia but had generated two pregnancies since end of treatment with miltefosine. The other man was 35 years old and had not generated progeny at any age. The oligospermia in this patient was documented 3 years after end of treatment.

Four cases of testicular pain were noted in miltefosine recipients in one of the CL studies (Z020a), which the sponsor attributes to epididymitis in the discussion section of the study report. In the study of Dutch soldiers with CL, 5/34 (15%) reported decreased or absent ejaculation during therapy and an additional 16 (47%) reported the same after specific questioning. Decreased ejaculate volume during therapy was also reported in PSURs.

These data all point to an adverse effect of miltefosine on human spermatogenesis, at least during therapy.

DBRUP considered the retrospective reproduction survey of the male subjects who participated in VL studies limited. DBRUP recommended one of the following: a primate study pre-marketing, a randomized, placebo-controlled study in healthy male volunteers to assess the effects on sex hormones and spermatogenesis (possibly enrolling men who are planning to undergo elective sterilization), or major warnings in the product labeling, with a requirement to conduct a postmarketing study of the effect of miltefosine on human spermatogenesis and male sex hormone in the target population.

A primate study is limited by the number of primates required and also limited by the fact that it is another animal study that does not fully resolve the concern regarding the effects on humans. The second option, a study in healthy volunteers, is not an option because the drug has to be given for at least 28 days to achieve steady state and is associated with significant organ toxicities. The limited ability to administer the drug to healthy volunteers was a factor in waiving a thorough QT study.

A post-marketing study to evaluate the effects of miltefosine on sperm count is recommended. The study design will be further discussed with the sponsor and with DBRUP. In the meantime, it is recommended that description of the possible effects on male fertility be described in the Warnings section of labeling and in the Medication Guide.

Females

At doses lower than the human therapeutic dose, there was a dose related increase of atretic follicles in the ovaries of female dogs that was reversible within six weeks after discontinuation of the drug. Estrus cycle arrest was noted in female dogs and rats.

The clinical studies do not comment as to whether changes in menstrual cycle were noted by female subjects who used non-hormonal forms of birth control. No AEs pertaining to menstrual changes have been reported in the literature or in PSURs. Long term

impairment of reproductive potential as a result of possible follicular atresia has not been explored. Describing the animal findings in the product labeling is recommended.

At doses lower than the therapeutic human dose, miltefosine was embryotoxic and teratogenic in mice, rats and rabbits. Malformed fetuses showed misshapen cerebral structures, misshapen eyes, and hemo-or hydrocephalus. A total of 143 women at least 12 years of age were enrolled in the CL, VL and ML Studies 3168, Soto, Z020, Z022 and 3154. All were required to use some form of birth control for the duration of treatment and for 2-3 months post therapy. No pregnancies were reported.

Three pregnancies were reported in the sponsored post-marketing trials. The estimated dates of conception were at 2 weeks during therapy, 2 weeks after EOT and 2 months after EOT. All babies were normal without birth defects. Based on sales data, approximately (b) (4) courses of miltefosine have been dispensed as of November 2011. Assuming a male to female ratio of 3:1 (based on the percentage of women enrolled in the leishmaniasis studies that evaluated miltefosine), at least (b) (4) women have been exposed to miltefosine post-marketing. It is expected that pregnancies would have occurred even if optimal birth control is used. Remarkably, no reports of pregnancies have been received by the sponsor, reported to the German regulatory authorities or reported in the literature. It is likely that pregnancies are under-reported, but an adverse effect on female fertility cannot be ruled out.

DBRUP recommended that the product labeling include a warning regarding risks during pregnancy, the need for birth control during therapy and (b) months post therapy. In addition, DBRUP recommended a voluntary post-marketing pregnancy and birth registry and a study to evaluate drug interactions between miltefosine and oral contraceptives. However, because miltefosine is not an inducer or inhibitor of CYP450 enzymes, the clinical pharmacology reviewer did not believe that a drug interaction study with oral contraceptives is needed.

Pediatric and Maternal Health Staff were consulted regarding designation of pregnancy category to miltefosine. There are no human data, but the animal data are clear regarding embryo and fetal lethality and teratogenicity. Because VL is fatal if untreated and can result in vertical transmission to the fetus, the benefits of miltefosine treatment to the mother may outweigh the risk to the fetus in some instances, especially given the limited therapeutic options and toxicity of pentavalent antimony preparations. CL in pregnancy may result in atypical lesions, and has been associated with preterm labor in one study[45]. PMHS recommended a pregnancy category (b) (4) for VL and ML and (b) (4) for CL and agreed with the division's recommendation for a Boxed Warning.

However, miltefosine was originally developed as an anti-neoplastic drug and is cytotoxic. Fetal toxicity in animal studies was noted at exposures much lower than the expected clinical exposure. The number of women expected to require miltefosine for the

[45] Morgan D et al. Cutaneous leishmaniasis during pregnancy: exuberant lesions and potential fetal complications. CID 2007;45:478-482

treatment of any form of leishmaniasis in the US is very small (less than 10 per year), and the number of pregnant women even smaller. The international product labeling contraindicates miltefosine during pregnancy for all forms of leishmaniasis, including in areas where the disease is endemic. Therefore, based on epidemiologic reasons, the easy availability of amphotericin in the United States, and the cytotoxic nature of the drug, contraindicating miltefosine in pregnancy and a pregnancy category D are recommended. In addition, a Boxed Warning is also recommended to convey the fetal risk.

Effective birth control in women of reproductive potential is recommended for the duration of therapy and for 5 months post-therapy (five half-lives).

DRISK were also consulted regarding a risk mitigation strategy. DRISK indicated that a Risk Evaluation and Mitigation Strategy (REMS) is not required beyond labeling and a Medication Guide to mitigate the reproductive risks associated with miltefosine exposure in men and women. Miltefosine has a terminal half-life of approximately 30 days, and a woman may become pregnant during or soon after the end of therapy, thus potentially extending the risk to the fetus beyond the duration of therapy. Mandating a negative pregnancy test prior to dispensing the drug will only partially mitigate the risk to the fetus. The number of women expected to use the drug in the United States is expected to be very low (less than 10/year), and the number of pregnant women requiring the drug is expected to be even lower. Most physicians will seek expert help in managing leishmaniasis, making an education plan for physicians or patients not feasible.

Pediatric Development Plan

Miltefosine was granted orphan designation and is therefore exempt from PREA.

Labeling Recommendations

Major labeling recommendations are:

- Limit the indications to geographic areas where *L. donovani* and members of *L. Viannia* subgenus are endemic
- Boxed Warning to contraindicate use in pregnancy and to advise effective contraception in women of reproductive potential
- Advise effective contraception in women of reproductive potential in the Warning section
- Describe possible adverse effects on male fertility during and after therapy in the Warning section
- Possible decreased effectiveness of oral contraceptives and the need to use another form of contraception in the event of vomiting and diarrhea
- Description of the adverse reproductive effects in animals in the Toxicology section and in the Use in Special Populations section (men and women of reproductive potential)
- Pregnancy category D

Product labeling and Medication Guide will be filed in DARRTS when finalized.

Advisory Committee Proceedings

The Advisory Committee met on October 18, 2013. The recommendations were to:

1. Approve miltefosine in the treatment of VL in geographic areas where *L. donovani* is prevalent (15-1 vote)
2. Approve miltefosine in the treatment of CL in geographic areas where members of the subgenus *Viannia* are prevalent (14-2 vote)
3. Approve miltefosine in the treatment of ML in geographic areas where members of the subgenus *Viannia* are prevalent (13-3 vote)

Discussions centered on the applicability of the data to the US population. The proposed dose is 150 mg for patients weighing more than 45 kg. In the VL and CL studies, the target miltefosine dose was 2.5 mg/kg/day and the mean weights of the enrolled patients were 40 kg and 63 kg, respectively. The average US patient (traveler or deployed personnel) is likely to have a higher weight, and thus receive a dose that is less than the target dose of 2.5 mg/kg. Discussions also centered on female reproductive toxicity with the recommendation that labeling include recommendations for birth control. Some committee members expressed concern regarding patient compliance with the drug and suggested that labeling include a recommendation for directly observed therapy.

DAIP assessment is that the potential for patient-to-patient *Leishmania* transmission in the United States is not a public health concern and directly observed therapy is therefore not needed to prevent spread of resistance (unlike the case for tuberculosis, for example). In addition, DOT is not likely to be feasible because miltefosine is given 3 times daily.

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/s/

HALA H SHAMSUDDIN
12/04/2013

THOMAS D SMITH
12/04/2013

Priority Review Determination and Tropical Diseases Voucher Eligibility Review

NDA	204-684 SN 006
Product	Miltefosine capsule 50 mg
Trade Name	Impavido®
Sponsor	Paladin Therapeutics
Indication	Treatment of visceral, mucosal and cutaneous leishmaniasis
Date of Submission	April 19, 2013
Reviewer	Hala Shamsuddin MD
Team Leader	Thomas Smith MD

Recommendations for Priority Review Determination
The recommendation is to grant NDA 204684 priority review.

- For visceral leishmaniasis (VL), miltefosine may provide significant improvement over available drug therapies.
- For cutaneous leishmaniasis (CL), miltefosine may provide significant improvement over available nondrug therapies and a potentially safe and effective drug therapy where none exists.
- For mucosal leishmaniasis (ML), miltefosine may provide safe and effective therapy where none exists.

The reasons for the recommendation are summarized:

1- For VL:
AmBisome is the only FDA-approved therapy, while sodium stibogluconate is available under an IND.

Preliminary estimates indicate that miltefosine may provide significant improvement over amphotericin preparations because of the convenience of the oral route of administration compared to multiple doses of intravenous administration over several weeks, the elimination of infusion-related reactions and the lower potential for nephrotoxicity.

Miltefosine may provide significant improvement over stibogluconate because of the convenience of the oral route of administration compared to intramuscular injections daily for 30 days and the elimination of musculoskeletal, cardiac and hepatic toxicities associated with stibogluconate use. Stibogluconate is also associated with significantly higher mortality in HIV co-infected individuals compared to miltefosine.

2- For ML and CL:
There are no FDA-approved therapies for CL or ML. Preliminary estimates indicate that miltefosine may provide a safe and effective therapy where no satisfactory alternative drug therapy exists. For CL, miltefosine may also provide significant improvement compared to the marketed ThermoMed device because it provides systemic therapy for patients with large or multiple lesions, and for lesions caused by organisms that may result in mucosal disease.

Recommendation for Tropical Diseases Voucher Eligibility
If priority review is granted, NDA 204684 would be eligible and recommended to receive the Tropical Diseases Priority Review Voucher. Miltefosine is intended for the treatment of a listed tropical disease, is submitted under section 505(b)1 of the FD&C act and is a new molecular entity.

Background
The sponsor requested priority review for NDA 204684 for miltefosine for the treatment of visceral, mucosal and cutaneous leishmaniasis (VL, ML and CL respectively) in the original NDA submission (SN000) which was refused filing. In this re-submission, the sponsor is re-iterating the priority review request and also requesting eligibility for the Tropical Diseases Voucher.

Priority review request for VL is based on the premise that miltefosine offers a "significant improvement compared to marketed products, including nondrug products or therapies". Priority review request for CL and ML is based on the premise that miltefosine offers a "safe and effective therapy where no satisfactory alternative therapy exists".

Tropical Diseases Voucher eligibility is requested because miltefosine is for the treatment of a listed tropical disease, is submitted under section 505(b)1 of the FD&C act, is a new molecular entity and is eligible for priority review.

Reviewer's Comments
Available Therapies for VL
AmBisome (liposomal amphotericin B) is the only FDA-approved agent for the treatment of VL. AmBisome was approved in 1997 for the treatment of VL based on published reports of uncontrolled trials in patients infected with L. chagasi/infantum. Amphotericin B deoxycholate is also highly effective and is used preferentially in many areas of the world instead of AmBisome because of the high cost and limited availability of AmBisome. The main adverse events associated with amphotericin preparations include nephrotoxicity and infusion-related reactions (fever, chills and hypotension).

Parenterally administered pentavalent antimonials (stibogluconate and meglumine) have been the mainstay of leishmaniasis therapy since the 1940s. In the US, sodium stibogluconate is available under an IND held by the CDC (IND 84, 831). Pentavalent antimonials have significant toxicities, including musculoskeletal, cardiac and hepatic effects, and are administered by intravenous or intramuscular injection daily for 30 days. In addition, they are increasingly ineffective in some parts of the world (mainly India) due to resistance.

The trials submitted in support of the VL indication include a randomized open label trial in India and a randomized open label trial in Ethiopia in subjects with VL. The Indian trial compared intravenous amphotericin B deoxycholate (15 doses administered on alternate days) to oral miltefosine daily for 28 days in HIV-negative subjects. Efficacy

was defined as resolution of clinical signs and symptoms related to VL and eradication of parasites at end of therapy plus no relapse at 6 months. Miltefosine was non-inferior to amphotericin B (cure rate 94.3% vs. 97.0% respectively, NI margin 15%). The Ethiopian trial compared intramuscular sodium stibogluconate daily for 30 days to oral miltefosine daily for 28 days. Approximately 30% of subjects who consented to HIV testing were positive. Statistically significantly more deaths occurred in subjects who received stibogluconate (10% vs. 2%). Because resistance to stibogluconate is infrequent in that geographic area, the study investigators attributed the increased mortality noted in the stibogluconate arm to toxicity.

The main adverse events associated with miltefosine are gastrointestinal (mainly nausea, vomiting and diarrhea) and nephrotoxicity, which occurred to a lesser extent than amphotericin B in the Indian VL study.

Available Therapies for ML
There are no FDA approved therapies for ML. The submitted trial in this NDA in support of the ML indication is a single arm trial. A planned randomized controlled trial comparing IV amphotericin B to miltefosine could not be performed because patients refused to be randomized to IV amphotericin B therapy upon realization that an oral agent was available. In this single arm trial, more than half of patients enrolled had previously failed antimony therapy. Cure was defined as at least 90% decrease in mucosal severity score, a composite score that reflected the extent of involvement of five anatomic sites (nasal skin, nasal mucosa, palate, pharynx and larynx). Miltefosine cure rate was 62%. The results of this study were published[1]. In the publication, a historical cohort of patients who had recently completed treatment with amphotericin B was compared to the patients who received miltefosine. The amphotericin B cure rate was 37%.

Available Therapies for CL
There are no FDA approved drug therapies for CL. The submitted trials in this NDA in support of the CL indication were conducted in South America (Colombia, Guatemala, Bolivia, and two regions in Brazil with epidemiologically different prevalent Leishmania species). The trials compared miltefosine to placebo (Colombia and Guatemala), or miltefosine to the pentavalent antimony meglumine (Bolivia, Brazil). Cure was defined as complete epithelialization of all the lesions and no appearance of new lesions at 6 months. Miltefosine was superior to placebo and showed numerically similar response rate to meglumine.

A device, ThermoMed, is cleared in the US for the treatment of CL. The rationale is that Leishmania organisms do not survive temperatures greater than 39-41^{o}C after cumulative exposure of at least 20 hours. The main adverse events associated with the device include skin blistering at the site of the device application with secondary bacterial infection and hypopigmentation. The device is not practical to use for larger lesions, in patients with multiple lesions or in patients with lesions on the face. In those

[1] Soto J. et al. Treatment of Bolivian Mucosal Leishmaniasis with Miltefosine. Clin Infect Dis 2007;44:350-6

patients with lesions caused by Leishmania species associated with mucosal disease, the device may not prevent mucosal involvement. In addition, the device cannot be autoclaved, raising concerns about proper infection control measures.

CDER Guidance

Regarding Priority Review eligibility, CDER MaPP 6020.3[2] states that "A drug is considered eligible for priority review if preliminary estimates indicate that the drug product, if approved, has the potential to provide, in the treatment, prevention, or diagnosis of a disease, one of the following: (1) safe and effective therapy where no satisfactory alternative therapy exists; or (2) a significant improvement compared to marketed products, including nondrug products or therapies.

Regarding Tropical Diseases Voucher Eligibility, the October 2008 Draft Guidance for Industry "Tropical Disease Priority Review Voucher" states that an application is eligible to receive a tropical disease voucher if the application is for a listed tropical disease, the application must be submitted under section 505(b)1 of the FD&C act or section 351 of the PHS act, the drug must not contain any active ingredient that had been previously approved under section 505(b)1 of the FD&C act or section 351 of the PHS act, and the application must qualify for a priority review. If priority review is granted, this miltefosine application would qualify for the voucher because miltefosine is new molecular entity, is submitted under section 505(b)1 of the FD&C act, and leishmaniasis is a listed tropical disease.

[2] CDER Manual of Policies and Procedures 6020.3 accessed at http://www fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm082000.pdf

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/s/

HALA H SHAMSUDDIN
05/20/2013

THOMAS D SMITH
05/28/2013

Clinical Filing Checklist for NDA/BLA or Supplement

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

Drug Name: Miltefosine/Impavido® **NDA/BLA Type: NME(1)**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD format
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			The modules in this submission contained addenda to the September 27, 2012 submission that received RTF due to deficiencies in the datasets.
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			The original submission did, this submission contains addenda to the previous submission. The addenda are indexed.
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt	X			**For CL**: Study 3092,

	Content Parameter	Yes	No	NA	Comment
	to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)?				54 subjects, 4 cohorts **For VL**: 1) study 033, 30 VL patients, 6 groups 2) study 3089, 54 VL patients, 3 groups 3) study 3091, VL children, 36 patients, 2 groups 4) study 3109, VL, 120 patients, 4 groups 5) study 3127, VL, 54 patients, 3 groups Doses 50 -250 mg range. All study reports located in Module M5
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	X			For visceral leishmaniasis (VL) indication, Two studies labeled pivotal: study 3154 and study Z025 plus one dose escalating study (study 033) For CL: 5 studies labeled pivotal: 3168, Soto, Z020a, Z020b, Z026 For ML: one study labeled pivotal: Z022 Datasets were provided for studies 3154, 3168, SOTO, Z020 and Z022. Study reports were submitted for the remaining studies.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding	X			The studies were all conducted prior to the initial IND meeting

	Content Parameter	Yes	No	NA	Comment
	primary/secondary endpoints.				with the sponsor. However, endpoints were considered clinically appropriate in the preNDA meeting.
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		Leishmaniasis is on the list of tropical disease, it is rare in the US
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X See Comment			On January 28, 2011, QT-IRT concluded that safety and tolerability issues precluded conducting a thorough QT study in healthy subjects, and ethical considerations precluded conducting a placebo-controlled QT evaluation in patients with leishmaniasis. QT-IRT recommended that the sponsor perform a study where ECGs are obtained at baseline and post-treatment steady state. Because the available non-clinical and clinical information did not suggest an overt cardiac signal, the review division (Division of Special Pathogens and Transplant Products) indicated that a study to evaluate the effect of miltefosine on cardiac repolarization can be conducted as a post-marketing requirement (PMR). (Review filed in DARRTS March 23,

	Content Parameter	Yes	No	NA	Comment
					2011 under IND 105,430)
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure) been exposed at the dose (or dose range) believed to be efficacious?			X	Duration of therapy is anticipated to be 28 days
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
23.	Has the applicant submitted the coding dictionary used for mapping investigator verbatim terms to preferred terms?	X			MedDRA version 12.0 for studies 3154, SOTO, Z020a/b, Z022, and 3168 Only prespecified AEs were submitted for the subjects who died in study Z025.
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	Drug is first in class
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			Narrative summaries for all deaths were provided, and CRF were provided for patients who developed SAE or discontinued due to AE
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Product has orphan designation and is exempt from pediatric studies required under PREA
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		
DATASETS					

	Content Parameter	Yes	No	NA	Comment
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			Previous submission was RTF because deficiencies in the datasets did not allow a meaningful review. Sponsor has re-formatted the legacy datasets using CDISC format
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			Reformatted datasets using CDISC domains
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?		X		Datasets for study are Z025 limited to prespecified AEs in patients who died during the study. This study was conducted by Medicins Sans Frontiers (MSF). The sponsor stated in the pre-NDA meeting that MSF did not agree to provide any other data to the sponsor.
34.	Are all datasets to support the critical safety analyses available and complete?		X		See above, datasets from Z025 limited to patients who died
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?		X		See above, datasets from Z025 limited to patients who died
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			Statement of GCP and ethical conduct was included in each individual study report.

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE?
Yes

Hala Shamsuddin MD May 6, 2013

Reviewing Medical Officer Date

Thomas Smith MD

Clinical Team Leader Date

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/s/

HALA H SHAMSUDDIN
05/20/2013

THOMAS D SMITH
05/28/2013

Clinical Filing Checklist for NDA/BLA or Supplement

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

Drug Name: Miltefosine/Impavido® **NDA/BLA Type: NME(1)**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD format
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? **For CL**: Study 3092, 54 subjects, 4 cohorts **For VL**: 1) study 033, 30 VL patients, 6 groups 2) study 3089, 54 VL patients, 3 groups 3) study 3091, VL children, 36 patients, 2 groups 4) study 3109, VL, 120 patients, 4 groups 5) study 3127, VL, 54 patients, 3 groups	X			Study 3092: CL, 54 subjects in 4 groups, dose 50mg, 50 mg followed by 100 mg, 100 mg, or 150 mg daily for 28 days. Study 033: VL, 30 patients, 6 groups, 50 mg QOD, 100 mg QOD, 100 mg QD,

	Content Parameter	Yes	No	NA	Comment
	All study reports located in Module M5				150 mg QD, 200 mg QD and 250 mg QD for 28 days Study 3089: VL, 54 patients, 3 groups: 100 mg, 150 mg or 200 mg daily for 28 days Study 3091: children VL, 36 patients, 2 groups: 1.5 mg/kg or 2.5 mg/kg for 28 days Study 3109: VL, 120 patients, 4 groups, 50 or 100 mg for 4 or 6 weeks, 100 mg followed by 150 mg for total of 4 weeks Study 3127: VL, 54 patients, 3 groups: 100 mg daily for 2, 3 or 4 weeks
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	X			For visceral leishmaniasis (VL) indication, 2 pivotal studies, 3154 and study Z025 plus one dose escalating study (study 033) labeled pivotal For CL: 5 studies labeled pivotal: 3168, Soto, Z020a, Z020b, Z026 For ML: one study labeled pivotal: Z022 Datasets were provided for studies 3154, 3168, SOTO, Z020 and Z022. Study reports were submitted for the remaining studies.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on	X			

	Content Parameter	Yes	No	NA	Comment
	proposed draft labeling?				
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			The studies were all conducted prior to the initial IND meeting with the sponsor
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			On January 28, 2011, QT-IRT concluded that safety and tolerability issues precluded conducting a thorough QT study in healthy subjects, and ethical considerations precluded conducting a placebo-controlled QT evaluation in patients with leishmaniasis. ECG tracings obtained for subjects enrolled in study 3154 were of poor quality and changes in QTc interval could not be assessed due to lack of PK information. In November 2010, QT-IRT recommended that the sponsor perform a study where ECGs are obtained at baseline and post-treatment steady state. The sponsor instead proposed that ECGs obtained during study 3154 be commissioned for assessment. QT-IRT indicated that proposal was not acceptable and deferred to the review division as to the timing of dedicated QT study. The review

	Content Parameter	Yes	No	NA	Comment
					division (Division of Special Pathogens and Transplant Products) agreed that a study is needed to evaluate the effect of miltefosine on QTc is needed, but that because the available non-clinical and clinical information did not suggest an overt cardiac signal, such a study can be conducted post-marketing as a post-marketing requirement (PMR). (Review filed in DARRTS March 23, 2011 under IND 105,430)
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			WHO classification for study 3154, 3168 MedDRA version 12.0 for study SOTO, Z020a/b, Z022 No adverse event dataset for study Z025
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	Drug is first in class
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			Narrative summaries for all deaths were provided, and CRF

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	Content Parameter	Yes	No	NA	Comment
					were provided for patients who developed SAE or discontinued due to AE
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Product has orphan designation and is exempt from pediatric studies required under PREA
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?		X		Datasets for study are Z025 limited to patients who died during the study. Sponsor had indicated in a pre-NDA meeting that the other data from that study is not available. Datasets for studies 3154 and 3168 do not have an individual column for unique subject ID.
34.	Are all datasets to support the critical safety analyses available and complete?		X		See above, datasets from Z025 limited to patients who died
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?		X		See above, datasets from Z025 limited to patients who died
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and	X			

	Content Parameter	Yes	No	NA	Comment
	adverse dropouts)?				
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			Statement of GCP and ethical conduct was included in each individual study report.

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? No

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

The application is not fileable from the clinical perspective because the submitted datasets do not allow a meaningful review of the efficacy and safety data. Specifically:

- The "define.pdf" file does not provide clear documentation. For example:
    - The "define.pdf" in Study 3168 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 or 6 months time point in dataset "response.xpt".
    - The "define.pdf" in Study 3154 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").
    - In Study 3154, DISCON in dataset "pop.xpt" has values of 0,1,2,3 but no meanings are provided. ALIVE in dataset "final-t.xpt" has values of 1, 2, 3 but no meanings are provided.
    - In Study 3168 dataset "response.xpt", RESP_P1 has values of 1,2,3,4 but they do not correlate with the codelist in "define.pdf" (1=yes and 2=no).
    - In Study Z025, CURETEST has entries of ln neg, na, neg, spleen neg but no meanings are provided. Likewise, no meanings are provided for PRE_RX (values: 1, 2), DAT (values: 7, 8, 9, 10, and 11), and ASPIR (values: 1, 2, 3, 4, 5, and 6).

- There is not enough information in the datasets to conduct the primary efficacy analysis for Study 3154 and Study 3168. For example, in Study 3154, the primary efficacy endpoint was the rate of patients with final cure 6 months after the end of treatment. Your dataset "response.xpt" contains a parameter RESP_FIN (response of study treatment: 1=final cure, 2=treatment failure, 3=not assessable). There are

apparently multiple records per subject (a total of 1321 observations on 397 subjects) but no identifier to show which record represents final efficacy outcome for each subject. The dataset contains a parameter VISIT with values of 50, 60, 70, and 100, none of which correlates with the timing of 6 months post treatment. Similar problems exist in Study 3168.

- Some key parameters are missing in the datasets. For example, start and stop date of study treatment and duration of study drug treatment is not provided for most studies. There is no variable in your datasets indicating if the actual treatment a subject received is the same as planned.

- Visit days in your datasets need to be clarified. For example, in Study 3154, visits are designated 50, 60, 70, 100 in "response.xpt". They do not correlate to the timing of assessments as per the protocol or with the days as designated in the "tv.xpt" dataset. Similar problem exists in Study 3168.

- The adverse events for Studies 3168 and 3154 were classified using WHO classification, while Studies Z020 and Soto were classified using MedDRA. Adverse events in all the submitted studies should be classified using the same version of a single dictionary, preferably MedDRA.

- Parasitology data were included for only 2 clinical studies (Z020b and Z022) and the results were presented as positive by either microscopy or PCR. For Study Z020b, *Leishmania* species identified was specified for some of the patients only. Parasitology data including *Leishmania* species, by test, identified for all patients in all the datasets should be submitted.

- Summary Tables of the results by baseline *Leishmania* species in the treatment arms. Patients with a single baseline pathogen and those patients with mixed infection should be shown separately. A separate summary Table should be included for each study.

- Submit details of all the parasitological methods used for identification of *Leishmania* species as well as measuring parasitologic response at follow up visits (e.g., 2 weeks, 2 months and 6 months after end of treatment for Study 3168).

The following issues, while not refuse to file issues, may cause difficulties in navigating the datasets and should be addressed in future submission:

- Datasets for Study Z020a and Study Z020b are combined. Please submit data for different studies under separate directory.
- There is no unique subject ID across Centers in Study 3154 and Study 3168. Variables CEN and PNO need to be merged to get unique subject IDs.
- Coded variables are used in SAS datasets but no formats are provided. Please submit 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 variable in one dataset and numeric variable 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"

Hala Shamsuddin MD	October 31, 2012
Reviewing Medical Officer	Date
Thomas Smith MD	
Clinical 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/

HALA H SHAMSUDDIN
11/08/2012

THOMAS D SMITH
11/08/2012