

**ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE
MEETING MATERIALS: AVAILABLE FOR PUBLIC RELEASE**

**Impavido® (miltefosine) Capsules for the Treatment
of Visceral, Cutaneous, and Mucosal Leishmaniasis**

NDA 204,684

Advisory Committee Briefing Book

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**Sponsor
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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
µg	Microgram
AE	Adverse event
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CDC	Centers for Disease Control and Prevention
CL	Cutaneous leishmaniasis
C _{max}	Maximum concentration
CTCAE	Common Terminology Criteria for Adverse Events (from the National Cancer Institute)
CV	Coefficient of variation
DCL	Diffuse cutaneous leishmaniasis
dL	Deciliter
DoD	Department of Defense
ECG	Electrocardiogram
FDA	Food and Drug Administration
h	Hour(s)
HIV	Human immunodeficiency virus
HPRT	Hypoxanthine-guanine phosphoribosyltransferase
ICMR	Indian Council of Medical Research
IND	Investigational New Drug
ITT	Intention-To-Treat
kg	Kilogram
<i>L</i>	<i>Leishmania</i>
MSF	Médecins Sans Frontières
ML	Mucosal leishmaniasis
mL	Milliliter
NDA	New drug application
PCR	Polymerase chain reaction
PK	Pharmacokinetics
PKDL	Post kala-azar cutaneous leishmaniasis
PI	Principal Investigator
PP	Per protocol
SD	Standard deviation
SSG	Sodium stibogluconate
t _{1/2α}	Elimination half life

Abbreviation	Definition
TESS	Treatment emergent signs and symptoms
TDR	Special Programme for Research and Training in Tropical Diseases of UNDP/World Bank/WHO
UDS	Unconditioned stimulus
ULN	Upper limit of the normal laboratory range
US	United States
<i>v</i>	<i>viannia</i>
VL	Visceral leishmaniasis
WHO	World Health Organization

2. EXECUTIVE SUMMARY

Impavido® (miltefosine) capsules are marketed in 14 countries for the treatment of visceral leishmaniasis and cutaneous leishmaniasis. Miltefosine is recommended by the World Health Organization (WHO) as an “essential medicine” for leishmaniasis.

2.1. Proposed Indication

Impavido (miltefosine) oral capsules is indicated in adolescents and adults ≥ 12 years of age weighing ≥ 30 kg (66 lbs) for treatment of:

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

2.2. Background

Infection of macrophages, visceral reticuloendothelial system, skin, and mucosal membranes with *Leishmania* gives rise to the major forms of leishmaniasis: visceral, cutaneous, and mucosal. *Leishmania* infection is endemic in 98 countries or territories with a yearly incidence of 0.5 million cases of visceral leishmaniasis (VL) and 1.5 million cases of cutaneous leishmaniasis (CL).

VL infection of the liver, spleen, and bone marrow presents with fever, hepatosplenomegaly, and pancytopenia. The majority of VL occurs in the Indian subcontinent with approximately 30% of the world's cases in East Africa. In both regions, the causative species is *L. donovani*. Once symptomatic, visceral disease is fatal if untreated. The classic treatment for VL is with pentavalent antimonials (Sb) administered intramuscularly or intravenously. Antimony-resistant cases are treated with intravenous amphotericin B formulations, classically amphotericin B deoxycholate, although more recently with liposomal amphotericin B. Failure of all agents is characteristic for patients with concomitant immunosuppression such as due to Human Immunodeficiency Virus (HIV) coinfection.

CL generally presents as a papule that enlarges to a nodule and if it ulcerates, does so over 1 to 3 months. Lesions can develop in anybody who enters into an endemic region and gets bitten by an infected sand fly. In recent years, industrialized nations have become more aware of the problem due to increasing numbers of imported cases either by military personnel or travelers.

Mucosal leishmaniasis (ML) in the New World may result from dissemination of cutaneous organisms (particularly *Leishmania* species of the subgenus *viannia*: *L. v. braziliensis*, *L.v. guyanensis* and *L.v. panamensis*) to the oro-nasal mucosa. Mucosal disease causes a progressive destruction of the mucosa and the cartilage and bones of nose and pharynx, and does not self-cure. Recently, it was shown that asymptomatic infection of the mucosal membranes is common for CL patients infected with members of the *L. viannia* subgenus. Cutaneous infection with any of these 3 species has to be regarded as leading to mucosal infection and potentially to mucosal disease with its possibly fatal outcome.

The classic treatment for New World CL and ML is intramuscular or intravenous pentavalent antimony.

In the United States, there are an estimated 75 new cases of leishmaniasis annually, of which the overwhelming majority is CL, mostly due to infection with *L. v. panamensis* and *L. v. braziliensis*.

2.3. Developmental History--Dose Selection

Pilot studies of oral miltefosine in Indian VL patients revealed that 50 mg/day was ineffective, 200 mg/day was poorly tolerated, and 100-150 mg/day was both effective and tolerated. Oral administration of 100 mg/day for 2 or 3 weeks was less effective than 100 mg/day for 4 weeks. As a result, 100 mg per day (approximately 2.5 mg/kg/day for these 40 kg patients) for 4 weeks was proposed as the treatment regimen for VL. When a dose ranging trial in CL was conducted, maximum efficacy was obtained with 150 mg/kg/day (approximately 2.5 mg/kg/day for these approximately 60 kg patients) for 4 weeks. Thus, a standard regimen for all indications of 2.5 mg/kg/day for 4 weeks was selected.

2.4. Visceral Leishmaniasis

2.4.1. Efficacy

A sponsor-supported pivotal trial in India compared oral miltefosine (target 2.5 mg/kg/day for 4 weeks) to standard of care intravenous amphotericin B deoxycholate (1 mg/kg every other day for 15 total injections) in this region of antimony-resistant *L. donovani*. The primary endpoint was final cure at 6 months after the end of therapy. The respective final cure rate using an intention-to-treat (ITT) analysis is shown in [Table 1](#).

Table 1: Efficacy in Pivotal Indian VL Trial (Study 3154)

ITT Analysis	Miltefosine (N=299)	Amphotericin B (N=99)
Final cure	282 (94.3%)	96 (97.0%)
Treatment failure	9 (3.0%)	0 (0.0%)
Not assessible	8 (2.7%)	3 (3.0%)
Difference amphotericin B -miltefosine of final cure rates (upper 97.5%-confidence bound)		
Center adjusted	2.6% (6.2%)	
Not center adjusted	2.7% (6.6%)	

For the 2.7% difference in final cure rate, the upper 97.5% confidence bound for the difference (6.2%) was well within the protocol pre-defined limit of 15%. Further, because the upper 99.9% confidence bound for the difference (9.6%) was below the FDA's non-inferiority margin of 10%, this result can be considered to be "statistically persuasive"; therefore, miltefosine is not inferior to amphotericin B in the treatment of patients with VL infected by *L. donovani*.

The FDA advised Paladin to present data from a Médecins Sans Frontières-sponsored trial, comparing oral miltefosine (290 patients) to intramuscular pentavalent antimony (290 patients) in frequently HIV-co-infected patients in Ethiopia, as a second pivotal trial. Of the several primary endpoints, the most clinically relevant for this fatal disease is the difference in death rates reflecting lack of efficacy. At the end of therapy, 2% of miltefosine patients vs. 10% of antimony patients had died ($p=0.0001$). By the end of 6 month follow up, 5% of miltefosine patients vs. 12% of antimony patients had died ($p=0.005$).

2.4.2. Safety

2.4.2.1. Adverse Effects

Miltefosine was associated with gastrointestinal symptoms that were usually mild to moderate and limited to periods of 1-2 days.

2.4.2.2. Laboratory Parameters

Miltefosine was occasionally associated with effects on renal and liver function that were reversible after end of treatment and often even during treatment. Increases in creatinine and blood urea nitrogen (BUN) for miltefosine were less severe than those seen with the amphotericin B deoxycholate comparator in the Indian study.

2.4.2.3. Female Reproductive Risk

Studies in animals have shown reproductive toxicity; the potential risk for humans is unknown. Female patients should take adequate reproductive contraception during treatment and for 3 months post therapy.

2.5. Cutaneous Leishmaniasis and Mucosal Leishmaniasis

2.5.1. Efficacy in Cutaneous Leishmaniasis

A sponsor-supported randomized, placebo-controlled, double-blinded trial in Colombia and Guatemala ([Study 3168](#)) evaluated miltefosine in *L. v. panamensis* (Colombia) and *L. v. braziliensis/L. mexicana* (Guatemala). The final cure rates after 6 months of follow up at both centers and overall are shown in [Table 2](#).

Table 2: Efficacy in Pivotal New World placebo-controlled CL trial (Study 3168)

Final cure (ITT)	Placebo	Miltefosine
Columbia	9/24 (37.5%)	40/49 (81.6%)
Guatemala	4/20 (20.0%)	19/40 (47.5%)
Overall	13/44 (29.5%)	59/89 (66.3%)

The difference in miltefosine efficacy versus placebo was statistically significant for each of: overall cure rate ($p < 0.001$); Colombia cure rate ($p < 0.001$); and Guatemala cure rate ($p = 0.04$).

The FDA advised Paladin to present data from any of three published investigator-sponsored comparisons of miltefosine to pentavalent antimony as a second pivotal trial. Not wishing to choose among the 3 trials, Paladin contacted the investigators to obtain primary data, constructed study reports for each trial, and constructed an integrated analysis of the 3 trials. Final cure rates after 6 months of follow-up for the 3 trials are shown in [Table 3](#).

Table 3: Efficacy in Pivotal New World Comparator-controlled CL Trial

Groups	ITT Final Cure Rate		
	Bolivia <i>L. v. braziliensis</i> (Study Soto)	Brazil <i>L. v. guyanensis</i> (Study Z020A)	Brazil <i>L. v. braziliensis</i> (Study Z020B)
Miltefosine	32/ 40 = 80%	27/40 = 67%	34/40 = 85%
Glucantime	13/18 = 72 %	12/20 = 60%	9/20 = 45%

For all 3 studies combined, the miltefosine final cure rate was $93/120 = 77.5\%$ according to each study's efficacy endpoint definition. The Glucantime final cure rate was $34/58 = 58.6\%$. The miltefosine cure rate was statistically superior to the Glucantime cure rate with a lower limit of the 95% confidence interval = 4.2 %.

If the initial cure criteria that was used in the Brazil studies had been adopted for the Bolivian study, 30 of 40 miltefosine patients (75%) would have final cure in Bolivia, and the overall final cure rate would be $91/120 = 75.8\%$ for miltefosine, statistically superior to $34/58 = 58.6\%$ for Glucantime (lower limit of the 95% confidence interval = 2.4%). With either method of analysis, oral miltefosine was statistically superior in efficacy compared to parenteral Glucantime.

2.5.2. Efficacy in ML

In a study on Bolivian mucosal leishmaniasis due to *L. v. braziliensis*, which was uncontrolled because patients refused to be randomized to non-oral standard of care, 62% of miltefosine-treated patients had final cure at 12 months after the end of treatment. This cure rate is comparable to historic cure rates with standards of care pentavalent antimony and amphotericin B, and suggests that oral miltefosine provides adequate therapy for ML.

2.5.3. Safety

2.5.3.1. Adverse Effects

As for VL, miltefosine in CL or ML patients was associated with gastrointestinal symptoms that were usually mild to moderate and limited to periods of 1-2 days.

2.5.3.2. Laboratory Parameters

In CL and ML patients, miltefosine does not lead to an increase in the values of liver function tests, although clinically non-relevant increases in creatinine (almost all Common Toxicity Criteria grade 1) occur.

2.5.3.3. Female Reproductive Risk

As per VL, patients with CL and ML must take adequate reproductive contraception during treatment and for 3 months post therapy.

2.6. Overall Benefit /Risk Considerations: Rationale for Approval

2.6.1. Visceral Leishmaniasis

2.6.1.1. Statement of Need

The only drug approved for VL in the United States is liposomal amphotericin B (AmBisome)[™]. Although amphotericin B is effective for the treatment of VL, the utility of all amphotericin B formulations is limited by the need for intravenous administration and intolerance. The unmet medical need for VL is for an alternative to AmBisome, either for the likely failure in VL that is complicated by concomitant immunosuppression or for intolerance to the drug.

2.6.1.2. Pivotal Trials

Oral miltefosine was compared to national standards of care intravenous amphotericin B deoxycholate in India and intramuscular pentavalent antimony in Ethiopia. Amphotericin B deoxycholate in India was impressively effective: the per protocol cure rate was 100% and the ITT cure rate was 97%. The cure rate for oral miltefosine was inferior to this impressive standard by only a small, 2.6% margin which was “statistically persuasive” such that a second pivotal trial might not be required to support an NDA. For the Médecins San Frontières comparison of miltefosine to antimony in a heavily HIV-coinfected population, the primary outcome parameter supported by the study data was survival which showed statistical superiority for the miltefosine group compared to the antimony group. Miltefosine does not generate immediate hypersensitivity reactions, and the incidence and severity of renal adverse effects was far diminished in patients treated with miltefosine compared to those treated with amphotericin B deoxycholate.

2.6.1.3. Summary

Oral Miltefosine satisfactorily addresses the unmet medical need of an alternative to intravenous AmBisome when AmBisome cannot be tolerated or for treatment failures.

2.6.2. Cutaneous Leishmaniasis and Mucosal Leishmaniasis

2.6.2.1. Statement of Need

Since there is no approved drug for CL or ML in the United States, the unmet medical need is for any agent that is superior to no-treatment/placebo.

2.6.2.2. Pivotal Trials

Against *L. v. panamensis* CL in Colombia and *L. v. braziliensis* / *L. mexicana* CL in Guatemala, miltefosine was superior to placebo overall and at each clinical site. The margin of superiority was statistically persuasive overall and in Colombia.

Against *L. v. braziliensis* CL in Brazil / Bolivia plus *L. v. guyanensis* CL in Brazil, oral miltefosine was superior to the worldwide standard of care intramuscular pentavalent antimony. The adverse effects of miltefosine (gastrointestinal reactions) were dissimilar from those of antimony (requirement for parenteral administration, musculoskeletal adverse reactions).

Against *L.v. braziliensis* ML in Bolivia, miltefosine cured 62% of patients.

2.6.2.3. Summary

Oral miltefosine satisfies the unmet medical need for an agent for CL and ML in the United States.

3. BACKGROUND

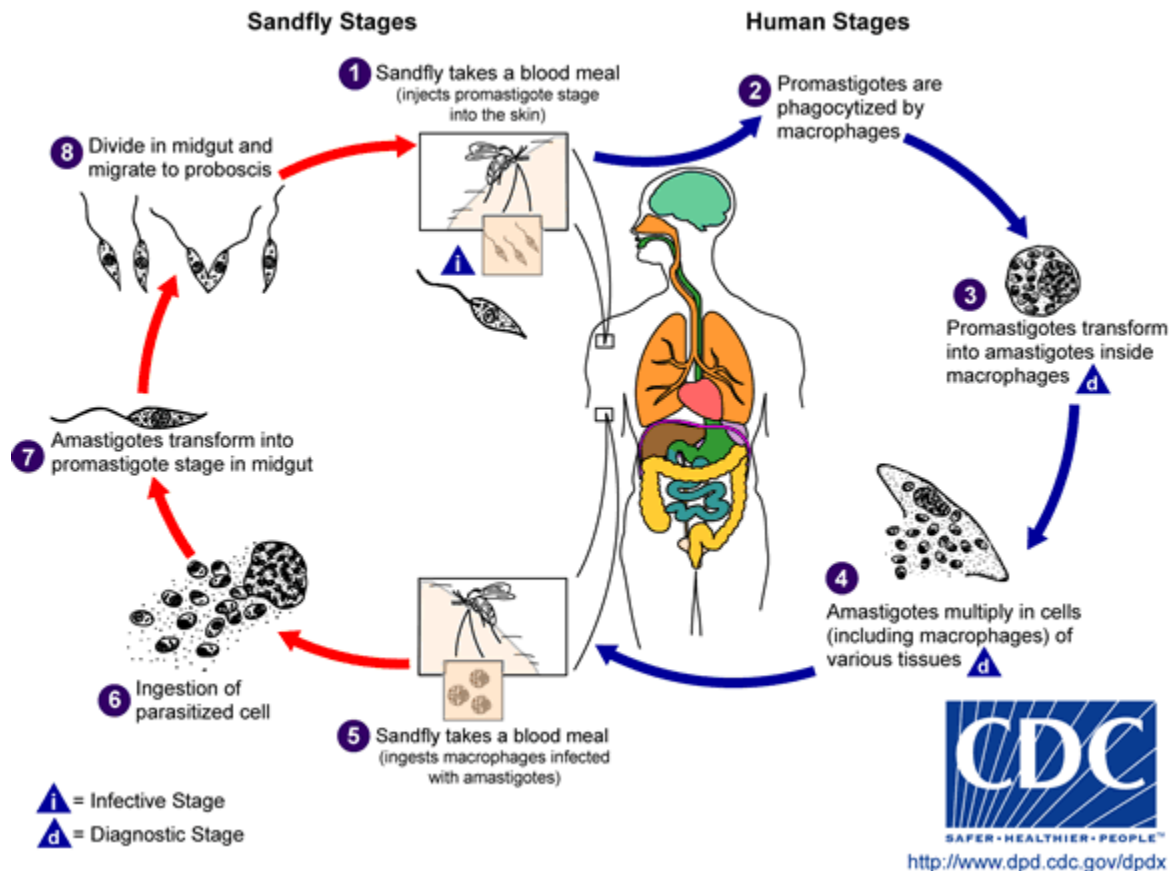
3.1. Introduction to Leishmaniasis

Infection of the macrophages of the skin, mucosal membranes, and visceral reticuloendothelial system with *Leishmania* gives rise to the major forms of leishmaniasis: cutaneous, mucosal, and visceral disease. The first recognition that *Leishmania* were the cause of these clinical presentations occurred in the 1880's when intracellular "corpuscles" were seen in cutaneous lesions. Firm attribution of disease to parasites was separately accomplished in 1903 by William Leishman and Charles Donovan who recognized parasites in the spleens of Indian VL patients and published their findings in separate issues of the British Medical Journal ([Leishman 1903](#); [Donovan 1903](#)). The genus *Leishmania* is in the Order *Kinetoplastidae* and Family *Trypanosomidae* due to the presence of a kinetoplast-mitochondrion rather than a mitochondrion.

3.2. Leishmania Lifecycle

In mammals, *Leishmania* exist as amastigotes within macrophages. The *Leishmania* lifecycle is initiated by the ingestion of amastigotes by a female sandfly during a blood meal ([Figure 1](#)). Within the gut of the sandfly, amastigotes transform into flagellated promastigotes which multiply and then transform into non-dividing metacyclic forms. When the sandfly takes a second blood meal, metacyclics are inoculated into the new host and invade phagocytic cells; phagocytized parasites transform into amastigotes within macrophages and the lifecycle is completed. The parasite lifecycles for *L. donovani* and *L. tropica* in the Old World are thought to be predominantly anthroponotic ---human-to-human transmission. The life cycles for *L. major* in the Old World and New World species have been thought to be zoonotic with peridomestic rodent and wild vertebrate reservoirs, respectively.

Figure 1: Leishmania Life Cycle



Reference: CDC website, accessed 2013

3.3. Epidemiology and Clinical Presentation

Leishmania infection is endemic in 98 countries or territories with a yearly incidence of 0.5 million cases of visceral leishmaniasis (VL) and 1.5 million cases of CL (WHO 2010). The risk of mucosal leishmaniasis secondary to CL in South America may be 2-3%.

3.3.1. Visceral Leishmaniasis

VL (Kala-azar) infection of the liver, spleen, and bone marrow presents with fever, hepatosplenomegaly, and pancytopenia. The majority of VL occurs in the Indian subcontinent (Figure 2) (WHO 2010). Approximately 30% of the world's cases occur in Africa especially Sudan, Ethiopia, and Kenya; there is also a focus of disease in Brazil. The main species causing VL are *L. donovani* in India and Africa, *L. infantum* in Europe and the Mediterranean, and *L. infantum chagasi* in the New World (WHO 2010) (Figure 3).

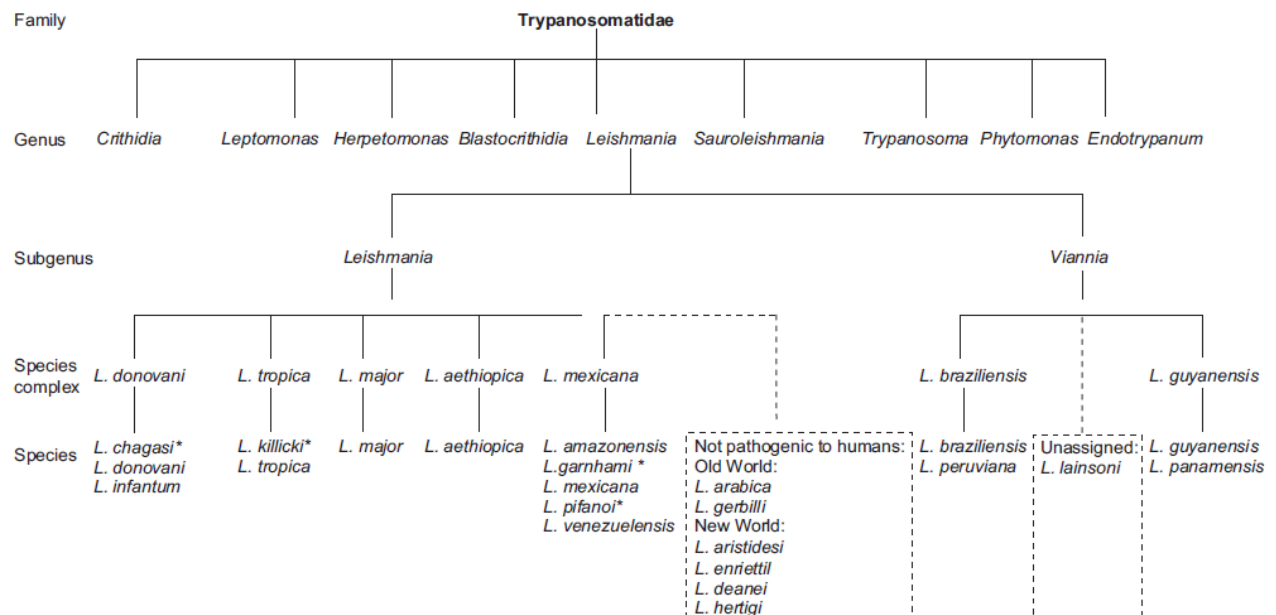
Figure 2: Distribution of Visceral Leishmaniasis
Geographical distribution of visceral leishmaniasis in the Old and New world



Reference: [WHO 2010](#)

Figure 3: Leishmania Taxonomy

Taxonomy of *Leishmania*



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

Reference: [WHO 2010](#)

In VL, sudden onset of fever with rigor and chills herald the onset of illness, which may subside only to reoccur. Splenomegaly soon follows and may become remarkable. Hepatomegaly and lymphadenopathy are other clinical features, though the latter is rare. Anemia is universal and may be severe leading to weakness, fatigue and heart failure. Thrombocytopenia and subsequent bleeding episodes such as epistaxis, intestinal bleeding, and retinal hemorrhages are not uncommon. Concurrent illnesses including pneumonia, herpes zoster, tuberculosis, amebic or bacillary dysentery, boils, and scabies are common. Co-infection with HIV or other immunocompromising diseases is increasingly a serious health threat ([Sindermann 2004](#)), for which ultimate failure after treatment with current agents is characteristic ([Alvar 2008](#)).

3.3.2. Cutaneous and Mucosal Leishmaniasis

CL generally presents as a papule that enlarges to a nodule and if it ulcerates, does so over 1 to 3 months ([Murray 2005](#)). CL lesions are often located at exposed areas of the skin (face, arms, legs), either as single or as multiple lesions. Lesions can develop in anyone who intrudes into an endemic region and gets bitten by an infected sand fly. In recent years, industrialized nations have become more aware to the problem due to increasing numbers of imported cases either by military personnel or travelers.

In the New World from the Texas-Mexico border down through South America to the level of the Tropic of Capricorn ([Figure 4](#)), ulcerative lesions are most common. In the Old World (the Mediterranean, North and Saharan Africa, the Middle East, the Indian subcontinent, and Central Asia), most lesions are papules, nodules, or nodule-ulcers. The primary species causing CL are diverse: *L. mexicana*, *L. amazonensis*, *L. viannia* (v.) *panamensis*, *L. v. braziliensis*, *L. v. peruviana*, and *L. v. guyanensis* in the New World and *L. major*, *L. tropica*, *L. aethiopica*, and *L. infantum* in the Old World.

Figure 4: Distribution of CL and ML in the New World

Geographical distribution of cutaneous and mucocutaneous leishmaniasis in the New World



Reference: [WHO 2010](#)

Mucosal disease (ML) in the New World may result from dissemination of cutaneous organisms (particularly *Leishmania* species of the subgenus *Viannia* (v): *L. v. braziliensis*, *L. v. guyanensis* ([Guerra 2011](#)) and *L. v. panamensis* ([Osorio 1998](#)) to the nares, nasal septum, palate, pharynx, and larynx. Mucosal disease causes a progressive destruction of the mucosa, cartilage and bones of nose and pharynx, leading to severe mutilation of the face. ML can be lethal by aspiration pneumonia or other complications. Classic ML occurs months to years after healing of CL, but ML can also occur virtually simultaneously with CL ([Osorio 1998](#)). Recently it was shown that asymptomatic infection of the mucosal membranes is common for CL patients infected with members of the *L. viannia* subgenus ([Figueroa 2009](#)). Two patients with ML and 26 patients with CL due to *L. v. panamensis*, *L. v. guyanensis*, and *L. v. braziliensis* had *Leishmania* kinetoplast minicircle DNA (kDNA) observed in mucosal tissues. kDNA was amplified from swab samples of nasal mucosa from 14 (58%) of 24 patients, tonsils from 13 (46%) of 28 patients, and conjunctiva from 6 (25%) of 24 patients. Although the reason that initially asymptomatic infection converts to clinical disease is unknown, cutaneous infection with any of these 3 species has to be regarded as leading to mucosal infection and potentially to mucosal disease with its possibly fatal outcome.

3.3.3. Rare Forms of Cutaneous Disease

Diffuse cutaneous leishmaniasis (DCL) and post kala-azar cutaneous leishmaniasis (PKDL) are chronic forms of CL. In DCL, a rare form associated with high parasite load and absence of a TH1 immune response, non-ulcerating nodules appear widely spread throughout the body. In India, post-kala azar dermal leishmaniasis is a sequelae to VL. Indian patients with VL may subsequently develop dermal infection (literally “post kala-azar dermal leishmaniasis”) within a year or up to 32 years after VL has been cured. The disease begins with hypopigmented macules, papules, or nodules on the face and then spreads to the other regions of the body.

3.4. Diagnosis

Diagnosis of infection by the genus *Leishmania* still generally relies upon techniques from the time of Leishman and Donovan in which parasites are visualized in Giemsa-stained slides of lesion scrapings, aspirates or biopsies. Diagnosis can also be made by culturing lesion samples on media which simulates the conditions of the sandfly gut and by then examining the cultures for motile promastigotes.

Speciation can be performed on cultured parasites via the electrophoretic mobility of isoenzymes of the glucose metabolic pathway ([Kreutzer 1993](#)), or directly on lesion material by a variety of nucleic-acid based (polymerase chain reaction - PCR) methods. There is no obvious link between isoenzymes or nucleic acid sequences and the pharmacodynamic parameters of natural history or response to drugs; thus, chemotherapeutic efficacy against one species cannot theoretically be extended to another species.

4. CHEMOTHERAPY

4.1. Visceral Leishmaniasis

The natural history of *Leishmania* infection depends on the ability of the host to mount an effective TH1 response to the intramacrophage parasites. TH1 responses are ineffective in routine visceral disease which is thought to be always fatal if untreated. Death is usually due to intercurrent infection such as pneumonia or gastroenteritis in these pancytopenic hosts. The death rate even with treatment is substantial, especially in Africa. In the 1990s in Sudan, 336 (11%) of 3076 patients died ([Seaman 1996](#)). More recently, 87 (4%) of 2177 Ethiopian patients died in spite of treatment with sodium stibogluconate ([Herrero 2009](#)).

The classic treatment of all forms of leishmaniasis including VL is with pentavalent antimonials (Sb), first used during World War II ([Berman 1997](#)) and now marketed as Pentostam (antimony gluconate) in English-speaking countries and Glucantime (meglumine antimoniate) elsewhere. Antimony must be administered parenterally and its disadvantages are its mode of administration and the 20 day (CL) to 28 day (VL, ML) duration of parenteral therapy; side effects reported as arthralgias, liver function abnormalities, a high rate of pancreatic enzyme abnormalities especially in HIV co-infected individuals, and rarely neutropenia and thrombocytopenia; and electrocardiogram (ECG) abnormalities such as t wave flattening, QTc prolongation, ventricular extrasystoles, and occasionally ventricular tachycardia and death ([Herwaldt & Berman 1992](#)). Since disease is anthroponotic (spread from human to human) in India, a further problem with antimonial treatment for VL is that when Indian patients fail, the resistant parasites return to the parasite reservoir to be a source of infection for other patients. Antimony resistance is now prevalent in key regions of India ([Sundar 1997](#)).

The drug of second choice has been intravenous amphotericin B deoxycholate. Like fungi, kinetoplastidae including *Leishmania* contain ergosterol, the biochemical target of amphotericin B, rather than cholesterol as in mammalian cells ([Berman 1988](#)). The well-known adverse effects include the immediate reactions of fever and/or chills, hyper/hypotension, and anorexia; and phlebitis, anemia, hypokalemia and renal function abnormalities ([Fungizone product brochure](#)).

Liposomal amphotericin B (AmBisome; Gilead) is the formulation of amphotericin B approved in the United States for VL in 1997. The lesser incidence but not elimination of side effects for patients with systemic fungal diseases is summarized in the [AmBisome product brochure \(2012\)](#): “AmBisome had a lower incidence of chills, hypertension [2.3%], hypotension [3.5%], tachycardia [2.3%], hypoxia [0.3%], hypokalemia, and various events related to decreased kidney function as compared to amphotericin B deoxycholate.” Even CL patients, who are systemically well, may poorly tolerate AmBisome. [Ramanathan \(2011\)](#) treated 7 CL patients with AmBisome. One patient had no side effects and completed the treatment course. Three patients had side effects of nephrotoxicity, nausea plus fleeting rash, and nausea plus dizziness, respectively, and completed the treatment course. Three patients had nephrotoxicity; flushing, shortness of breath, and chest pain; and hypokalemia and nephrotoxicity, respectively, and did not complete the treatment course.

Other drugs used to treat VL are allopurinol, paromomycin, dapsone, rifampicin, and interferon-gamma. The oral therapies (allopurinol, dapsone, rifampicin) have no proven value.

Thus, all effective therapies -- pentavalent antimony, amphotericin B, liposomal amphotericin B, and paromomycin-- have to be administered parenterally. Parenteral administration is inherently toxic due to the injections, which in turn leads to substantial compliance issues.

Based on the above considerations, the unmet clinical need is for an anti-leishmanial drug that is orally administrable, tolerated, and effective. Such a drug would facilitate VL treatment by increasing compliance and avoiding hospitalization to receive parenteral therapy, improving efficacy where resistance (antimony) is present, or providing an alternative to amphotericin B formulations when toxicity precludes their administration or in the likely failure of co-immunosuppressed (frequently HIV-infected) patients.

4.2. Cutaneous and Mucosal Leishmaniasis

TH1 responses are generally present in routine CL, which self-heals in 3 to 15 months ([Murray 2005](#)). The specific infecting species causing CL determines where in this wide range of time periods self-cure is likely to occur. ML does not self-heal, but slowly inflames the mucosa or erodes the cartilage of the affected tissues ([Marsden 1986](#); [Marsden 1991](#)).

Whereas for VL, a potentially fatal non-self-curing disease, the need for therapy is clear and efficacy data can be compared to a natural cure rate which is “0%”, treatment of CL involves more complex considerations. Many therapeutic options are available for CL, in general ranging from observation only, local treatments, and oral therapies, up to intramuscular/intravenous treatment with antimonials or intravenous amphotericin B formulations. A wide variety of specific local therapies (intralesional application of drugs (antimony, interferon), topical application of botanicals (garlic cream, herbal extract Z-HE), topical application of drugs (paromomycin), local application of physical measures (cold, heat, photodynamic therapy), trichloroacetic acid, zinc sulfate, and oral therapies (the imidazoles fluconazole, itraconazole, ketoconazole; allopurinol, azithromycin, dapsone, pentoxifylline, rifampicin) have been reported ([Gonzalez 2010](#)) in addition to parenteral antimony, paromomycin, and amphotericin B formulations. Evaluation of the therapeutic index for each of these interventions requires knowledge of their side effects in comparison to the morbidity of the disease being treated, and treatment cure rates in comparison to the natural cure rate. However, disease morbidity and natural cure rate vary with the infecting species, of which there are at least 12; the choice of “standard comparator” therapy differs between countries and medical centers; and “important weaknesses in the adequacy and transparency of randomization, loss of participants, causative *Leishmania* species, outcome measures, and follow-up times distort the evidence base”([Gonzalez 2010](#)).

The present choice of no treatment, parenteral treatment with antimony or amphotericin B formulations, or treatment with a vast array of non-parenteral therapies of unclear value in studies with important weaknesses creates a bewildering treatment situation for CL. No treatment may be insufficient; parenteral therapy creates toxicities simply due to the route of administration comparable to the morbidity of the disease itself; the other therapies cannot be recommended. There is no therapy that can be confidently recommended for CL.

An effective, well tolerated drug with the specific feature of being orally administrable is the key unmet clinical need for CL worldwide. In the United States, where there is no approved drug at all for CL or ML, any treatment of CL and ML is an unmet medical need.

5. LEISHMANIASIS IN THE UNITED STATES

5.1. Yearly Incidence

The US Military reports that for the 5 years between 2003 and 2008, approximately 1446 patients with leishmaniasis were identified ([MSMR 2008](#)). One thousand and five of these were identified in 2003-2004, during the period of Operation Iraqi Freedom ([Weina 2004](#)). The 96, 52, and 33 cases in 2006, 2007, and 2008, respectively, represent cases seen under more routine geopolitical conditions.

US civilian cases when referred to the United States Centers for Disease Control and Prevention (CDC) are generally treated with pentavalent antimony (“Pentostam”--sodium antimony gluconate) via a CDC IND. Leishmaniasis is not a reportable disease, and we are unable to find incidence or other data on patients treated under the CDC IND. However, a reasonable assumption would be that the number of civilian patients treated under the CDC IND is roughly the same as the number of patients treated by the US military. If so, there are approximately 75 cases of leishmaniasis routinely treated in the US per year.

5.2. Clinical Presentation (Cutaneous Leishmaniasis vs Visceral Leishmaniasis)

For the Department of Defense (DoD) military cases treated with Pentostam at the Walter Reed Army Medical Center between 1989 and 1996, 82 (93%) were CL, 1 (1%) was ML, and 5 (6%) were VL ([Aronson et al 1998](#)).

This data indicates that in the United States, the best estimate is that $\geq 90\%$ of routine leishmaniasis cases are CL.

5.3. Infecting Species (CL)

Of the 82 military CL cases between 1989 and 1996, 48 were tested for the specific species causing the infection. Eighteen were *L. panamensis*, 10 were *L. braziliensis*, 6 were *L. major*, 5 were *L. mexicana*, 5 were *L. guyanensis*, 3 were *L. tropica*, and 1 was *L. donovani* ([Aronson et al 1998](#)). Therefore, 79% (38/48) of the CL cases were contacted in the New World, with a predominance of *L. panamensis* / *L. braziliensis* responsible for infection.

For 38 military patients seen in 1990-1991 and from 1996-2001, *L. panamensis* predominated. Eighteen were *L. panamensis*, 2 were *L. braziliensis*, 1 was *L. guyanensis*, 6 were *L. major*, and 1 was *L. tropica* ([Wortmann et al 2002](#)).

For military patients seen between 2002 and 2008, 31 New World cases were speciated. *L. braziliensis* and *L. panamensis* and predominated: 15 cases were *L. braziliensis*, 9 cases were *L. panamensis*, 3 cases were *L. guyanensis*, 3 cases were *L. mexicana*, and one case was *L. amazonensis* (Dr. Peter Weina, Walter Reed Army Institute of Research, personal communication).

Overall, of the 107 military New World cases, 72 (67%) were due to *L. panamensis* / *L. braziliensis*. These two species combined make up the majority of all cases of cutaneous disease seen in the US.

5.4. Patient Ages

Military cases are adult except in unusual circumstances. Between 1989 and 1996, all patients were between 18 and 53 years of age ([Aronson et al 1998](#)).

5.5. Treatment

Since historically there has not been a registered drug treatment available for the leishmaniasis in the United States, leishmaniasis has been treated with Pentostam (Sodium stibogluconate, GlaxoSmithKline) under IND protocols held either by the CDC or the DoD.

In 1997, AmBisome was registered for the treatment of VL.

There remains no drug registered for CL or for ML.

In 2003, a device that heats the skin with radio waves (“ThermoMed”) was registered by the FDA for CL. The clinical trial used to support registration (510 K063748) is described: “A single center study of 60 patients was conducted to summary evaluate the safety and efficacy of the ThermoMed Model 1.8 device in the treatment of *basal cell carcinoma* [emphasis added].” This device has been used for CL, but not widely.

6. NONCLINICAL STUDIES

6.1. Parasitology

6.1.1. Efficacy In Vitro

The activities of miltefosine against the intracellular amastigote stage, the relevant target cell for drugs in mammals, have been mainly performed in an established mouse peritoneal macrophage model. In a series of studies, miltefosine proved to be more active than the standard antileishmanial pentavalent antimonial drugs (sodium stibogluconate and meglumine antimoniate), having activity in the range of 1 to 11 μM in studies that involved exposure to drugs over either 96 or 120 h ([Croft 1987](#); [Croft 1996](#); [Escobar 2002](#)). In these studies, >95% killing of intracellular parasites was observed at 30 μM , the maximum concentration tolerated by the host cells in these assays ([Table 4](#)).

Table 4: Efficacy of Miltefosine against *Leishmania* spp. Amastigotes in Mouse Peritoneal Macrophages

<i>Leishmania</i> spp. ^a	ED ₅₀ (μM)
<i>L. donovani</i> (HOM/ET/67/L82)	3.3, 4.6
<i>L. donovani</i> (L82)	11.4
<i>L. donovani</i> (L82)	3.9
<i>L. donovani</i> (NANDI II)	0.2
<i>L. aethiopica</i> (MHOM/ET/84/KH)	2.6, 4.9
<i>L. tropica</i> (MHOM/AF/82/K001)	5.8, 10.2
<i>L. mexicana</i> (MHOM/BZ/82/BEL21)	6.8, 10.1
<i>L. panamensis</i> (MHOM/PA/67/Boynton)	10.6, 10.6
<i>L. major</i> (MHOM/SA/85/JISH118)	31.6, 37

^a [Croft 1987](#), [Croft 1996](#), [Escobar 2002](#)

The rank order of sensitivity was: *L. donovani* > *L. aethiopica* > *L. tropica* > *L. mexicana* > *L. panamensis* > *L. major*. However, as [Van Thiel \(2010\)](#) reported a miltefosine cure rate of 30 of 34 (88%) patients infected with *L. major* in Afghanistan, the relevance of *in vitro* rank order of miltefosine susceptibilities to clinical outcome is unknown.

6.1.2. Mechanism of Action and of Resistance

Miltefosine (hexydecylphosphocholine) is a close analog of lecithin and it has long been assumed that the mechanism of action of miltefosine involves lipid biochemistry. In a review by [Barratt \(2009\)](#), the proposed mechanism of miltefosine uptake was summarized as follows: miltefosine inserts into the outer leaflet of the plasma membrane as monomers when its concentration is below the critical micellar concentration and as both monomers and oligomers when it is above the critical micellar concentration. Thereafter, a two subunit aminophospholipid translocase, LdMT-LdRos3, internalizes the drug. [Lira \(2001\)](#) has reported that miltefosine selectively inhibited phosphocholine synthesis in *Trypanosoma cruzi*, a parasite closely related to *Leishmania*, and that these parasites have a different metabolic pathway compared to host cells. Ultrastructural studies on *T. cruzi* also suggested that the parasite membrane was a primary target ([Santa-Rita 2000](#)).

The main mechanism of miltefosine resistance in *Leishmania* is proposed to relate to the involvement of LdMT, since inactivation of LdMT causes miltefosine resistance both in promastigote and amastigote forms that persists *in vivo* ([Barratt 2009](#)).

6.2. Toxicology

The purpose of preclinical toxicology is to suggest, based on abnormal findings at clinically relevant exposures, organs that might demonstrate toxicity in the clinic.

Oral administration, repeat-dose toxicity studies have been conducted in the rat and dog for up to 52 weeks in duration. The effect of miltefosine on the fertility and reproductive performance in the rat and rabbit has been evaluated. Miltefosine has also been evaluated in the standard battery of genotoxicity studies.

6.2.1. Repeat Dose Toxicology Studies

In the 52 week rat study, miltefosine was administered at daily doses of 4.64, 10.0, and 21.5 mg/kg, and plasma levels after 52 weeks were 24.9, 52.4, and 83.1 µg/mL, respectively. Calculated mean C_{max} after the clinical target of 2.5 mg/kg/day is 38.5 µg/mL (see Section 7, Clinical Pharmacology).

The oral administration of miltefosine in rats was associated with lesions affecting the eyes (retinal degeneration), kidneys (nephropathy), and organs with rapidly dividing cell tissues (atrophy/hyperplasia), as well as reproductive organs (atrophy). These alterations were observed after 8 weeks treatment at doses of 10 mg/kg/day.

In the 52 week dog study, miltefosine was administered at daily doses of 1.00, 3.16, and 10.0 mg/kg which was reduced to 6.19 mg/kg/day at week 7 due to inappetance. After 52 weeks, plasma levels in the 3.16 and 6.19 mg/kg/day groups were 40.6 and 69.7 µg/mL, respectively. No effects were noted on the eyes. Examination of the clinical chemistry data including BUN and creatinine revealed only slight changes in some parameters, but they failed to have a clear dose dependency. Microscopic examination revealed the genital tract and skin as target organs. Individual-high-dose males, including recovery animals, exhibited testicular multifocal atrophy and-degeneration of seminiferous tubules, invariably associated with focal mononuclear infiltration. A dose-related increase in the incidence and severity of atretic follicles in the ovary was observed, with follicular development arrested at the secondary stage. The arrest of development was also reflected in the cycle stage of the uterus, vagina, and mammary gland. The findings returned to normal during the recovery period.

6.2.2. Reproductive Toxicity Studies

Reproductive toxicity studies in rats during early embryonic development (up to Day 7 of pregnancy) indicate an embryotoxic, fetotoxic, and teratogenic risk following miltefosine doses of 1.2 mg/kg/day and higher. Embryotoxic and fetotoxic findings were also observed in rabbits after oral administration of miltefosine during the phase of organogenesis (2.4 mg/kg/day and higher). Testicular atrophy and impaired fertility were observed in rats following daily oral doses of 8.25 mg/kg. These findings were reversible within a recovery period of 10 weeks.

6.2.3. Mutagenicity/Carcinogenicity Studies

Miltefosine tested negative in the AMES Salmonella test, DNA-amplification test, chromosomal aberration test *in vitro*, unconditioned stimulus (UDS)-test *in vivo/in vitro*, and oral mouse micronucleus

test *in vivo*. The V 79 mammalian cell hypoxanthine-guanine phosphoribosyltransferase (HPRT) gene mutation test showed an increase in mutant frequency without dose dependency. In view of all mutagenicity test results, the single positive finding in the V 79 HPRT test is considered to be not of toxicological relevance with respect to a mutagenic risk to humans.

6.2.4. Metabolism and Excretion

No oxidative metabolism by 15 different cytochrome P450 isozymes (1A1, 1A2, 1B1, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, 3A4, 3A5, 3A7, and 4A1) was observed *in vitro*.

A slow metabolic breakdown could be shown in human hepatocytes, resulting in the release of choline by phospholipase D-like cleavage of the miltefosine molecule. The fatty alcohol-containing fragment of miltefosine can enter the metabolism of fatty acids after being oxidized to palmitic acid. This oxidation is blocked in patients with Sjogren-Larsson syndrome, which is caused by a genetic defect in fatty aldehyde dehydrogenase activity. In visceral leishmaniasis, <0.2% of the administered dose was excreted into the urine.

There was little or no evidence of time- or metabolism-dependent inhibition of the cytochrome P450 isozymes examined at up to approximately 40 µg miltefosine/mL.

Oral administration of miltefosine did not markedly induce the content of hepatic CYP3A assayed by demethylation activity of erythromycin in rats. Therefore, miltefosine is unlikely to induce oxidative metabolism of other drugs metabolized by CYP3A (e.g., contraceptive hormones).

7. CLINICAL PHARMACOLOGY

7.1. Pharmacokinetics

Main pharmacokinetic (PK) parameters were calculated for a sponsor-initiated study in VL, an academic study in *L. major* CL, and (via an earlier product development program) cancer. The elimination half life ($t_{1/2\alpha}$) was approximately 7 days.

A comparison of the C_{\max} and AUC plasma levels in all clinical studies on the adolescent/adult population, normalized to a dose of 1 mg/kg/day, is given in [Table 5](#).

Table 5: Pharmacokinetic Parameters across Studies for Adolescents/Adults

Human dose (mg/kg/day: indication)	PK parameter and value	C_{\max} /1 mg/kg/day	AUC ₀₋₂₄ /1 mg/kg/day
1.6: VL	C_{\max} 23.5 µg/mL; AUC ₀₋₂₄ 428 µg·h/mL	14	267
1.6: Cancer	C_{\max} 12.0 µg/mL	7.5	Not done
1.85 (wk 1), 3.71 (wk 2–4): VL	C_{\max} 40.7 µg/mL; AUC ₀₋₂₄ 716 µg·h/mL	11	193
2.2: cancer	C_{\max} 27.4 µg/mL	12	
2.64 (wk 1), 3.96 (wk 2–4): VL	C_{\max} 82.2 µg/mL; AUC ₀₋₂₄ 1320 µg·h/mL	20	330
3.13: VL	C_{\max} 71.9 µg/mL; AUC ₀₋₂₄ 1344 µg·h/mL	23	433
1.8: CL	C_{\max} 37 µg/mL; AUC ₀₋₂₄ 884 µg·h/mL	20	491
	mean	15.4	342.8
	SD	5.7	120.9
	%CV	37	35

When C_{\max} and AUC₀₋₂₄ values were normalized to 1 mg/kg/day, the coefficient of variation (CV) was 35% - 37% for both C_{\max} and AUC. Thus, miltefosine plasma levels are comparable in human populations irrespective of age, indication, or dose level. This conclusion indicates that a common dosing regimen can be proposed for all indications and ages.

The mean C_{\max} was 15.4 µg/mL (standard deviation (SD) = 5.7 µg/mL) per 1 mg/kg/day of miltefosine dosing. For the target clinical dose of 2.5 mg/kg/day, calculated mean C_{\max} is 38.5 µg/mL.

In the academic study of *L. major* infection acquired in Afghanistan treated with miltefosine (150 mg/day for 28 days), sparse sampling for a population PK analysis was performed ([Study PK3](#)). Miltefosine PK during multiple dosing were best described by a 2-compartment with first-order absorption population model. The $t_{1/2\alpha}$ was 6.75 days, in agreement with prior studies in VL. The apparent terminal $t_{1/2}$ was approximately 30 days. Simulated miltefosine plasma concentrations from Days 60 to 200 post-dosing were low: 1.48 µg/mL on Day 60 and 0.04 µg/mL on Day 120. In the most sensitive animal, the rat, a dose of 0.6 mg/kg/day had no teratogenic potential and a dose of 0.4 mg/kg/day for 13 weeks results in

serum concentrations of 1.8 µg/mL. Since simulated miltefosine concentrations on day 60 post therapy were 1.5 µg/mL, concentrations beyond 60 days are less than the peak concentration which did not have teratogenic potential in the most sensitive animal. The recommendation in the original Zentaris label, that female contraception be continued for 3 months post therapy, seems conservative and adequate.

7.2. Metabolism

To summarize non-clinical data: *In vitro* studies indicate that miltefosine is metabolized by being cleaved between the phosphate group and choline by phospholipase D. There is no evidence of oxidation of miltefosine by cytochromes, inhibition of cytochromes by miltefosine, or induction of cytochromes by miltefosine. In preclinical studies, small amounts of labeled choline have been identified in urine and feces, whereas the major part of the drug substance appears to enter intermediary metabolism and to be incorporated into physiological substances. The metabolic fate of the hexadecanol part of the miltefosine molecule has not been characterized in experimental studies, although cleavage of the phosphor-ester bond by phosphatase(s) is a reasonable assumption. This hydrolytic step should be followed by either incorporation of hexadecanol into physiological ether lipids or – to the major extent – by oxidation leading to hexadecanoic acid (palmitic acid) which can be further oxidized or utilized for the synthesis of physiological lipids.

8. VISCERAL LEISHMANIASIS

8.1. Overview of the Visceral Leishmaniasis Program Worldwide

Originally, miltefosine was investigated as an anticancer agent. A topical formulation of miltefosine (Miltefosine®) was studied for the treatment of skin metastases from breast cancer and was eventually approved for this indication in several countries. Oral use of miltefosine in cancer patients was found to be associated with gastrointestinal side effects, preventing the long-term administration of therapeutically active dosages in this patient population. Daily doses of 150 mg and higher were often associated with dose-limiting side effects, including nausea and vomiting and loss of appetite. In the absence of convincing therapeutic activity, the drug eventually was not studied any more for the systemic treatment of cancer where long-term use would be required.

During a night shift at University Hospital, Goettingen ([Croft 2006](#)), experts involved in the miltefosine anticancer development program became aware of the need for an oral antileishmanial drug and planned a dose-ranging study in leishmaniasis.

The first dose ranging trial (pilot study 0033) was sponsored by ASTA Medica/Zentaris and investigated doses between 50 mg every other day and 250 mg/day for 4 weeks in 5 patients per treatment group. The lower doses (50 mg every other day and 100 mg every other day) were not effective; the higher doses (200 mg per day and 250 mg per day) were poorly tolerated. The middle doses (100 mg per day and 150 mg per day) appeared both effective and tolerated.

At that point, WHO/TDR (TDR: Special Program for Research and Training in Tropical Diseases of UNDP/World Bank/WHO) set up a study program to jointly develop miltefosine as an oral treatment for VL. During the progress of this work, the study program and its progress were also discussed with the Indian Council of Medical Research (ICMR).

The first jointly sponsored trial was a dose-finding study in ≥ 12 year old patients with Indian VL ([Study 3109](#)) that was followed by a co-sponsored randomized controlled pivotal study ([Study 3154](#)). The dose ranging trial 3109 investigated 4 regimens corresponding to the “middle” doses of [Study 033](#): A total of 120 patients were randomly allocated to: 50 mg/day x 6 weeks, 50 mg/day x 1 week then 100 mg/day x 3 weeks, 100 mg/day x 4 weeks, and 100 mg/day x 1 week, then 150 mg/day x 3 weeks. When the latter 2 groups had identical ITT cure rates (97%), the simpler regimen of 100 mg/day x 4 weeks was adopted for the pivotal trial 3154. In the pivotal trial, patients were randomized 3:1 between oral miltefosine 100 mg/day (which for these 40 kg patients dose = 2.5 mg/kg/day) for 4 weeks vs. intravenous amphotericin B.

Further to the above development program, ASTA Medica/Zentaris sponsored 2 additional exploratory studies in Indian patients. One trial ([Study 3089](#)) further varied the dose between 100 mg/day, 150 mg/day, and 200 mg/day; one study ([Study 3127](#)) varied the duration of treatment with 100 mg/day between 2 weeks, 3 weeks, and 4 weeks.

The clinical program was extended to cover children from ages 2-11 years as a special subgroup (studies [3091](#) and [3206](#)).

In all, the above studies evaluated the safety and efficacy of miltefosine in a total of 766 Indian patients in the target indication VL (out of 768 randomized patients), of whom 99 patients were treated with

amphotericin B as the reference drug in the Phase 3 study, leaving a total of 667 patients treated at therapeutic doses of miltefosine.

More recently, Phase 4 studies have been completed in India ([Study Z013](#)), Nepal ([Study Z013b](#)), and [Bangladesh \(phase 4\)](#) which included a total of 2,234 patients for all countries together. In contrast to prior studies, which were conducted in hospitalized patients only, these studies were performed in an out-patient setting where patients were handed out the amount of medication needed for one week which the patients had to take at home. These studies represent a relevant extension of the clinical experience, particularly on the safe use of miltefosine under field conditions.

The range of doses and number of patients in each of these trials is shown in [Table 6](#), [Table 7](#), and [Table 8](#).

Table 6: Dose Groups in Indian VL Trials - Phase 1-3 Adolescent and Adult Patients

Study	Principal Investigator(s)	Group: Dosage ranges tested	No. of Patients ^a
0033	S. Sundar	Group 1: 50 mg q2d x14 days Group 6: 250 mg/day x 28 days	30 (6 pts/ group x 5 groups)
3089	S. Sundar	Group 1: 100 mg/day x 28 days Group 3: 200 mg/day x 28 days	46 (18 pts/group x 2 groups + 10 in group #3)
3109	T.K. Jha, S. Sundar, C.P. Thakur	Group 1: 50 mg/day x 42 days Group 4: 100 mg /day x7+150 mg /day x 21	120 (30 pts /group x 4 groups)
3127	S. Sundar	Group 1 :100 mg/day x 14 days Group 3: 100 mg/day x 28 days	54 (18 pts/group x 3 groups)
3154	T.K. Jha, S. Sundar, C.P. Thakur (WHO)	Miltefosine: for 28 days >25 kg b.w.: 100mg/day <25 kg b.w.: 50 mg /day AMP: every other day x 15 days 1 mg/kg/application	400 (300 miltefosine pts+100 amphotericin B pts)

^a 12 years and older

Table 7: Dose groups in Indian VL trials - Phase 1-3 Pediatric Patients

Study	Principal Investigator(s)	Groups: Dosages tested	No. of Patients ^a
3091	S. Sundar	Group 1: 1.5mg/kg/day x 28 days Group 2: 2.5 mg/kg/day x 28 days (10 mg dose increments)	39 (total pts)
3206	T.K. Jha, S. Sundar, C.P. Thakur, Bhattacharya	2.5 mg/day x 28 days (10 mg dose increments)	80

^a 2-11 years old

Table 8: Dose Groups in Indian VL trials - Phase 4 Studies on the Indian Subcontinent

Study	Principal Investigator(s)	Group: Dosages tested	No. of Patients
Z013	S.K. Bhattacharya (ICMR/India)	Miltefosine for 28 days ≥ 25 kg b.w.: 100 mg/day <25 kg b.w.: 50 mg /day for patients <12 years: 2.5 mg/kg/day x 28 days (10 mg dose increments)	1,132
Z013b	S. Koirala (Dahran/Nepal)	Miltefosine for 28 days ≥ 25 kg b.w.: 100 mg/day <25 kg b.w.: 50 mg /day for patients <12 years: 2.5 mg/kg/day x 28 days (10 mg dose increments)	125
Bangladesh Phase 4	M. Rahman (Bangladesh)	Miltefosine for 28 days ≥ 25 kg b.w.: 100 mg/day <25 kg b.w.: 50 mg /day for patients <12 years: 2.5 mg/kg/day x 28 days (10 mg dose increments)	977

In addition to the Indian studies, Médecins Sans Frontières performed a study comparing miltefosine (290 patients) to standard of care pentavalent antimony in a heavily HIV-co-infected population in rural Ethiopia ([study Z025](#)). Finally, a small exploratory trial in 43 Brazilian patients with VL was performed.

8.2. Registration and Marketing Worldwide

As a result of this development program, miltefosine is now marketed for VL (and CL) in 14 countries worldwide ([Table 9](#)).

Table 9: Worldwide Marketing Status

Country	Registration Date	Launch Date	Approved Indication
Argentina	Sep 2005		Visceral and cutaneous leishmaniasis
Bangladesh	Jun 2006		Visceral and cutaneous leishmaniasis
Bolivia	Mar 2006		Visceral and cutaneous leishmaniasis
Columbia	Mar 2005	2 nd half 2005	Visceral and cutaneous leishmaniasis
Ecuador	Nov 2005		Visceral and cutaneous leishmaniasis
Germany	Nov 2004	Dec 2004	Visceral and cutaneous leishmaniasis
Guatemala	Nov 2005		Visceral and cutaneous leishmaniasis
Honduras	Feb 2005		Visceral and cutaneous leishmaniasis
India	Mar 2002	Jun 2003	Visceral and cutaneous leishmaniasis
Mexico	Jul 2006		Visceral and cutaneous leishmaniasis
Nepal	Jan 2006	Jun 2006	Visceral and cutaneous leishmaniasis
Pakistan	Sep 2006		Visceral and cutaneous leishmaniasis
Paraguay	Sep 2005		Visceral and cutaneous leishmaniasis
Peru	May 2005		Visceral and cutaneous leishmaniasis

8.3. Visceral Leishmaniasis Data Included in NDA 204684

Paladin Laboratories Inc. purchased miltefosine from ASTA Medica/Zentaris in 2008.

A pre-NDA meeting was held in 2009. Paladin proposed to support the VL indication in the United States with the comparative study of miltefosine to pentavalent antimony in India ([Study 3154](#)).

In the FDA's Advice letter of Apr 13, 2010, the Agency noted that "Study 3154 is an adequate and well-controlled study that can be submitted to support the indication for the treatment of VL caused by *L. donovani*. A second controlled study is needed for VL indication. [Study Z025](#) (miltefosine compared to stibogluconate for the treatment of VL in Ethiopia) a potential other study."

Following FDA advice, data from these two pivotal trials was submitted to the Agency and, supported by the other trials mentioned above, form the core of the VL dossier.

Although the core studies of the dossier were not prospectively coordinated, the core studies nevertheless well-represent VL and its standard therapy worldwide. VL is predominantly caused by *L. donovani* and the predominant endemic regions are the Indian subcontinent and East Africa: the two pivotal trials were performed against *L. donovani* in India and in Ethiopia. VL is treated with pentavalent antimony or, in antimony resistant regions, amphotericin B. The Indian trial was performed in an antimony resistant region and compared miltefosine to amphotericin B; the Ethiopian trial compared miltefosine to pentavalent antimony.

Because 50 mg capsules provide appropriate dosing for patients ≥ 12 yrs of age (adolescents and adults), adolescents and adults are the proposed population for the United States.

8.4. Efficacy

8.4.1. Indian VL: General Considerations for Phase 1-3 Trials

Efficacy and safety of miltefosine in the treatment of VL have been investigated in prospective Phase 1-3 clinical trials involving 766 patients, of whom 667 patients (out of 669 randomized patients), including 119 children younger than 12 years, were treated with miltefosine. Additionally 99 patients received amphotericin B as the active control drug in a randomized controlled Phase 3 trial (Study 3154) that is considered as an adequate and well-controlled study to prove the efficacy of miltefosine in the target indication.

All trials were performed by experienced investigators in VL research centers in India. Protocols for therapeutic dose-finding as well as for pivotal confirmatory trials were set up and studies were performed in co-operation with WHO/TDR.

8.4.1.1. Patient Numbers and Overview of Efficacy

Table 10 shows, for the pooled study population, the final cure rates and the numbers of patients with missing data as well as with documented treatment failure, including data from patients treated at dosages that were subsequently identified as insufficient.

Table 10: Pooled Efficacy Rate in Phase 1 to 3 Trials in India

	Final Cure, ITT Population						All
	Missing/not assessable		No		Yes		
	n	%	n	%	n	%	n
All patients treated with miltefosine (any age)	12	1.8	32	4.8	623	93.4	667
Study 3154 (patients allocated to treatment with amphotericin B)	3	3.0	0	0	96	97.0	99
All patients (any treatment)	15	2.0	32	4.2	719	93.9	766

No trial was terminated prematurely due of lack of tolerability. There was only one trial ([Study 3089](#)) in which one study arm, with the highest dosage (200 mg/day), was closed prematurely because of tolerability concerns.

The percentage of patients with missing data or patients whom the investigators classified as not assessable was very low: only 12 of 667 cases (1.8%). According to ITT principles, these patients were added to the documented treatment failures in the calculated overall cure rate across all studies (623 of 667 = 93.4%).

8.4.1.2. Patient Characteristics

The below list of inclusion and exclusion criteria are taken from the pivotal [Study 3154](#), and are applicable to the Indian VL trials generally.

Inclusion criteria - signs and symptoms comprising the indication for treatment:

1. Adolescents (12 - 17 years of age) and adults (except for pediatric trials which were 2-11 years of age).
2. Newly diagnosed or resistant/relapsing VL, confirmed by splenic or bone marrow aspiration.
3. Clinical signs and symptoms compatible with VL (e.g. fever, splenomegaly and anemia).

Exclusion criteria:

1. Safety concerns:
 - a. Platelet count $<50 \times 10^9/L$.
 - b. Leukocyte count $<1 \times 10^9/L$.
 - c. Hemoglobin $<6 \text{ g}/100 \text{ mL}$.
 - d. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP) >3 times upper limit of normal range.
 - e. Bilirubin >2 times upper limit of normal range.
 - f. Prothrombin time >5 seconds above control.
 - g. Serum creatinine or BUN >1.5 times upper limit of normal range.
 - h. Major surgery within last 2 weeks.
 - i. Any non-compensated or uncontrolled condition, such as active tuberculosis, malignant disease, severe malaria, human immunodeficiency virus (HIV), or other major infectious diseases.
 - j. Lactation, pregnancy (to be determined by adequate test) or inadequate contraception in females of childbearing potential for treatment period plus 2 months.
2. Lack of suitability for the trial:
 - a. Concomitant treatment with other anti-leishmaniasis drugs (it should be noted that pretreatment for leishmaniasis was not an exclusion criterion in any of the studies of oral miltefosine).
 - b. Lactation, pregnancy (to be determined by adequate test) or inadequate contraception in females of childbearing potential for treatment period plus 2 months.
3. Administrative reasons:
 - a. Lack of ability or willingness to give informed consent (patient and / or parent / legal representative).
 - b. Anticipated non-availability for study visits/procedures.

8.4.1.3. Primary Endpoint

In accordance with general standards in the evaluation of drugs in VL, patients were accepted as being cured ("final" cure) only after a 6-month period had elapsed. The algorithm to determine final cure vs. failure was:

1. Determine if the patient had signs or symptoms indicative of possible treatment failure: fever, spleen that had not regressed by at least 30% of baseline, hemoglobin < 10 g/dL if female and < 11.5 g/dL if male, platelets < 100,000/mm³ and WBC < 3500/mm³. If no signs or symptoms, the patient is a final cure.
2. If there is a sign of symptom possibly reflecting VL, the Principal Investigator determines if there is a clinical etiology for the sign or symptom other than VL. If there is a non-VL clinical etiology, the patient is a final cure.
3. If there is no non-VL explanation for the sign or symptom, a repeat aspirate (spleen or bone marrow) was performed. If no parasites were found, the patient was a final cure. If parasites were found, the patient was a failure.

German Drug Regulatory Authorities raised the question whether a 6-month follow-up period may be too short to assess “definite” cure. To address this question, all patients from Center 2 (Prof. Sundar) in the Phase 3 trial (3154) were re-assessed 12 months after end of treatment. One hundred eight miltefosine-treated patients were re-evaluated, and all but one were still relapse-free at the 12-month follow-up. For comparison, all 35 patients with definite cure 6 months after end of treatment with amphotericin B had their cure confirmed after 12 months. These data confirm that cure rates based on 6-month follow-up data are reliable to assess the efficacy of the drug.

In order to be followed for 6 months and evaluated at that time for final cure, each patient would have to first demonstrate “initial cure” defined as being without parasites soon after the end of therapy.

In all the phase 1-3 studies on adolescents/adults (Studies [033](#), [3089](#), [3109](#), [3127](#), [3154](#)), each patient who underwent parasitologic investigation at the end of therapy demonstrated initial parasitological cure, except for 1 patient in the 2-week treatment group in [Study 3127](#).

8.4.2. Efficacy of Miltefosine in the Pivotal Phase III Trial in India (Study 3154)

8.4.2.1. Study Design

[Study 3154](#) was a randomized, active-comparator controlled trial. Amphotericin B was chosen as reference treatment because the predominantly used pentavalent antimonial drugs showed an increasing rate of drug resistance in Bihar ([Sundar 1997](#)), the territory where this trial was conducted. This choice of the comparator drug allowed for the inclusion of patients pre-treated with pentavalent antimony and for the assessment of cross-resistance between antimonials and miltefosine. Centralized randomization was used to avoid a selection bias in this open label trial.

To obtain the miltefosine target dose of 2.5 mg/kg/day, 271 of 299 patients of weight ≥ 25 kg received the drug at a dosage of 100 mg/day, while a lower dosage of 50 mg/day was used in a subgroup of 28 patients with a body weight below 25 kg.

A very high cure rate, close to 100%, was expected for intravenously-administered amphotericin B, and previous studies had shown similarly high response rates for oral treatment with miltefosine. In terms of feasibility and convenience, the possibility for oral administration was considered a potentially major advantage of miltefosine over the comparator. Therefore, a non-inferiority hypothesis was chosen to primarily rule out a significantly poorer efficacy of the test drug miltefosine. In addition, a 3-times higher number of patients were allocated to receive the test drug than the reference drug to ensure a sufficiently broad safety database for the test drug.

The final cure assessment included the verification of clinical and parasitological cure. An independent central laboratory in Muzaffarpur (Dr. CPN Thakur) was employed to read all aspirate slides of Centers 1 and 2 for the determination of the parasite score.

There were no relevant deviations from the clinical protocol, and only few patients were not assessable or lost to follow-up. In conclusion, this trial met the criteria for an adequate and well-controlled trial and was considered pivotal for supporting the present NDA.

8.4.2.2. Entrance Characteristics

Entrance characteristics are shown in [Table 11](#).

Table 11: Patient Characteristics Study 3154

		Miltefosine (n=299)	Amphotericin B (n=99)
Sex (Male/ Female)	No. of patients, %	211 (70.6%) / 88 (29.4%)	58 (58.6%) / 41 (41.4%)
Age (years)	Mean \pm SD	26.5 \pm 12.7	26.3 \pm 12.0
	Median (range)	25.0 (12-64)	25.0 (12-60)
Weight (kg)	Mean \pm SD	38.6 \pm 10.0	38.3 \pm 12.1
	Range	15-67	14-64

8.4.2.3. Primary Efficacy Outcome - Final Cure

The final cure rate for the miltefosine and amphotericin B groups is shown in [Table 12](#).

Table 12: Summary of Efficacy – Study 3154 (ITT Population)

ITT Analysis	Miltefosine (N=299)	Amphotericin B (N=99)
Final cure	282 (94.3%)	96 (97.0%)
Treatment failure	9 (3.0%)	0 (0%)
Not assessable	8 (2.7%)	3 (3.0%)
Difference Amphotericin B -miltefosine of final cure rates – Delta % (upper 97.5%-confidence bound)		
Center adjusted	2.6% (6.2%)	
Not center adjusted	2.7% (6.6%)	

Of 299 patients who started oral treatment with miltefosine, 282 were verified to be cured after a 6-month post-treatment follow-up. This is a 94.3% cure rate for miltefosine-treated patients while a 97% cure rate (96 of 99 patients) was documented after treatment with amphotericin B. The 2.7% difference in cure rate is small, and the 97.5%-confidence bound for the difference was well within the protocol pre-defined limit of 15% and the FDA pre-defined limit of 10% for accepting non-inferiority: 6.2% and 6.6%, with and without center-adjustment, respectively. Further, since the upper 99.9% confidence bounds (9.6%) for the 2.7% difference are also below the non-inferiority margin of 10%, this result can be considered to be “statistically persuasive”.

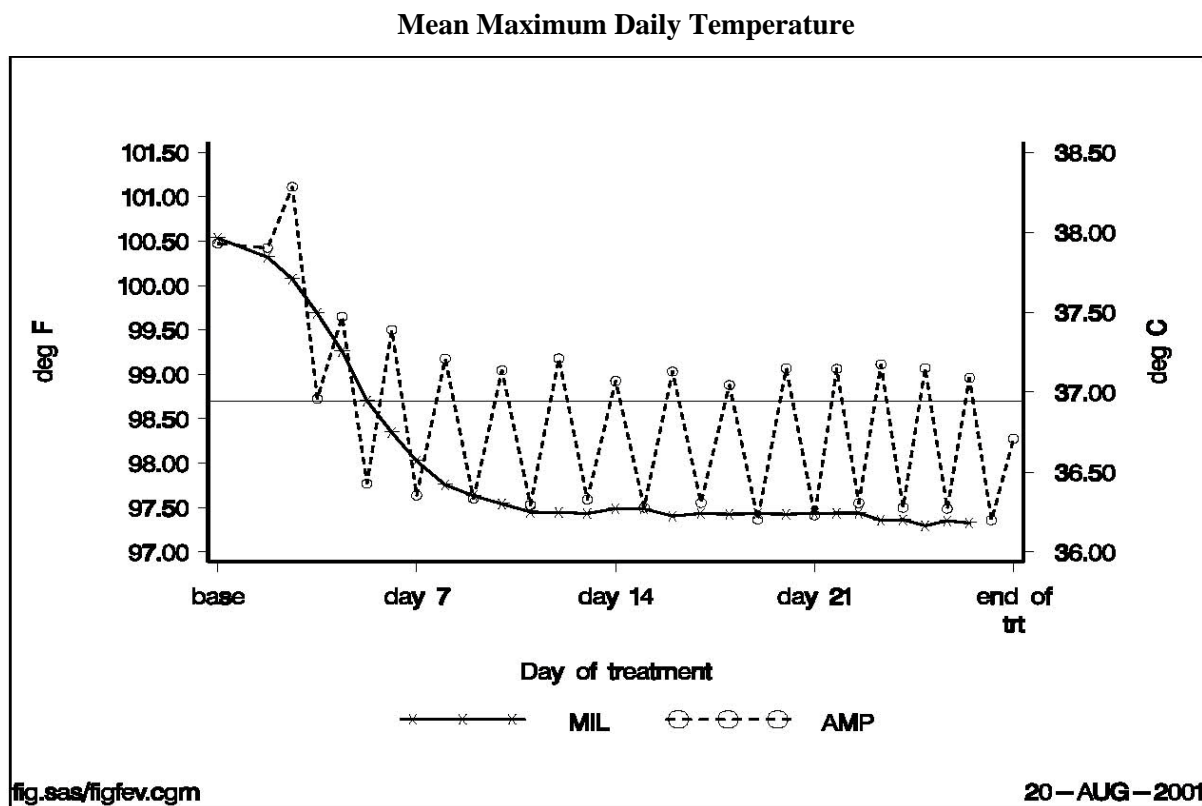
The miltefosine treated group included 85 patients who had received prior therapy for their leishmaniasis infection and the majority of these patients (69 patients) was considered primary unresponsive while the others were treated for a relapse of their disease. Eighty of the pre-treated patients (94.1%) had a final cure diagnosed 6 months after end of treatment with miltefosine, while 3 patients failed to be cured with miltefosine, and 2 patients were not assessable for final cure. In the reference group, 26 of 28 pre-treated

patients (92.9%) were finally cured after treatment with amphotericin B, while 2 patients were not assessable for this endpoint. Thus, both miltefosine and amphotericin B were highly effective in pre-treated patients.

8.4.2.4. Secondary Efficacy Outcome - Resolution of Signs and Symptoms

In patients with fever at baseline, normalization of body temperature was the leading sign of response to treatment (Figure 5). After about 1 week, fever had completely resolved in miltefosine-treated patients and body temperature remained low until the end of treatment.

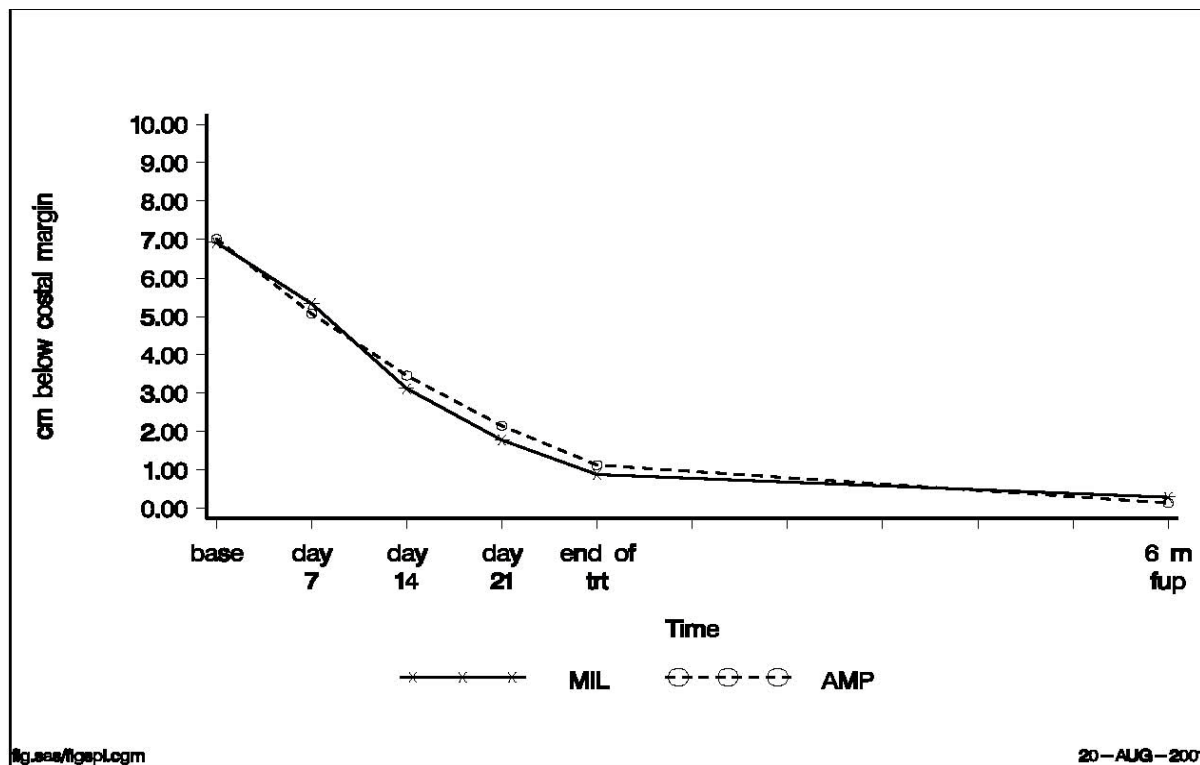
Figure 5: Body Temperature Response in Study 3154



In contrast, each infusion of amphotericin B was followed by an increase in body temperature of about 2°C. As most patients had fever at baseline, the start of treatment with amphotericin B resulted in an exacerbation of fever that often (27.3%) reached common terminology criteria (CTC) for adverse events (AEs) grade 3 (corresponding to a body temperature above 40°C). Throughout the dosing period, the mean body temperature in the amphotericin B treated patients periodically exceeded 37°C. Thus, the recurrent fever associated with the use of amphotericin B is an adverse drug reaction.

Leishmania parasites infiltrate spleen, liver, and bone marrow leading to organ enlargement and/or impairment of organ function. Spleen size was monitored weekly, and splenomegaly rapidly regressed in both treatment groups (Figure 6).

Figure 6: Spleen Size - Study 3154



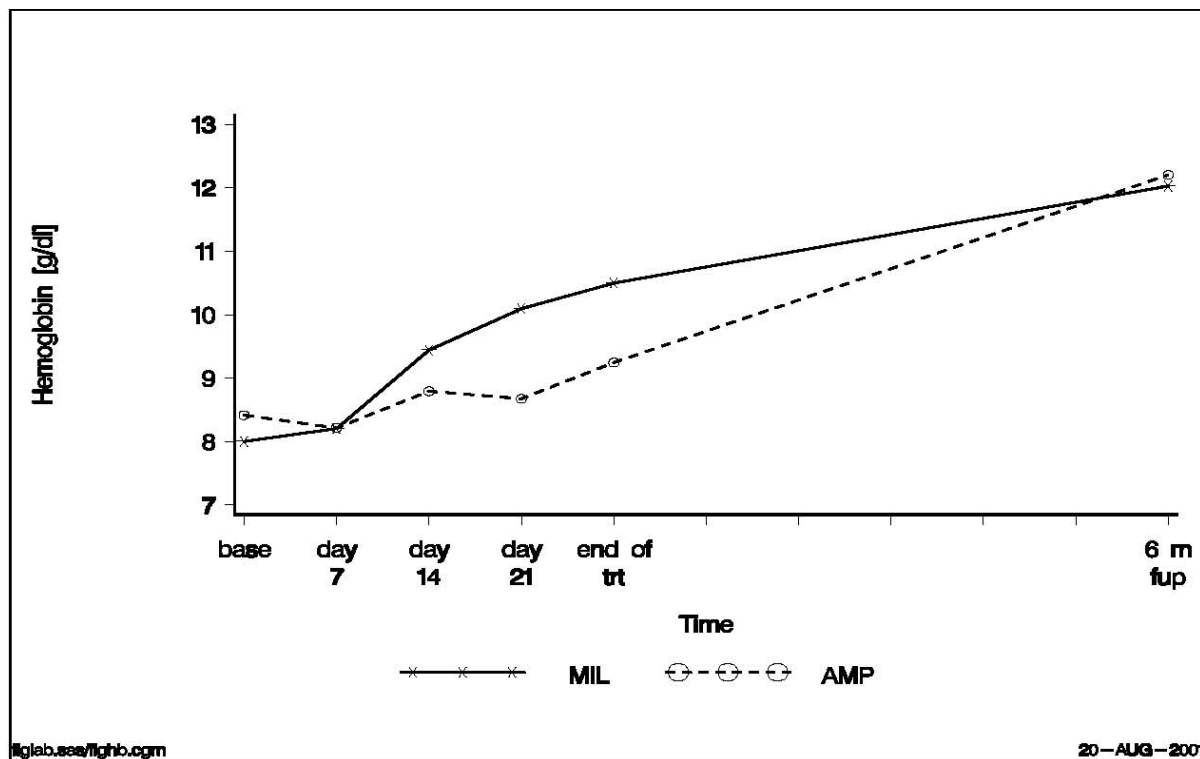
There was no clinically relevant difference between groups with a minor trend towards a more rapid normalization in the miltefosine treated group.

Recovery from leishmaniasis was also reflected by global changes of several laboratory variables. In particular, this includes changes in leukocytes, hemoglobin, thrombocytes, and differential white blood cell counts, albumin, ALT and AST. For all variables with such changes, there was no relevant difference in the values between treatment groups at baseline and at 6-months follow-up.

It is interesting to note, however, that for some variables the time course for these changes was different between the treatment groups. For example, leukocytes, hemoglobin, platelets, and albumin normalized distinctly faster in patients treated with miltefosine than in patients treated with amphotericin B.

For illustration, the time course of hemoglobin normalization is shown in [Figure 7](#).

Figure 7: Hemoglobin Response - Study 3154



In studies in cancer patients, it has previously been shown that oral use of miltefosine may lead to an increase in leukocyte and thrombocyte counts, thus supporting hematological recovery from abnormalities in blood counts.

8.4.2.5. Conclusions

Similar final cure rates from VL were achieved after oral use of miltefosine (target of 2.5 mg/kg/day generally achieved by 100 mg/kg/day for 28 days) and after intravenous use of amphotericin B (1 mg/kg every other day for 30 days): 94.3% vs. 97.0%, respectively. The difference was not clinically relevant and within the predefined statistical limits for non-inferiority of miltefosine. The upper limit of the 95% confidence limit for the difference in efficacy is 6.6 %, less than the FDA prescribed margin of 10% for the upper limit of the 95% confidence limit. The upper limit of the 99.9% confidence limit for the difference in efficacy is 9.6%, which indicates that this pivotal trial provides a statistically persuasive result. Miltefosine was equally effective in patients pre-treated and non-pretreated with pentavalent antimonial drugs.

This randomized controlled trial confirmed earlier studies showing that miltefosine, at a convenient oral dose regimen, was safe and highly effective in the treatment of VL in patients aged 12 years and older, including patients without response to standard treatment.

8.4.3. Efficacy Conclusions across Phase 1 to 3 Studies

As stated above, the combined data for all miltefosine-treated patients from all studies added up to an impressive 93.4% rate of definite cures (623 of 667 patients) (Table 10). The fact that even the efficacy

outcome in the low-dose group of the first dose ranging (Study 0033) is included in this global result indicates that only limited variability in analysis of subgroups may be expected.

8.4.3.1. Efficacy in Relation to Patients' Age

Miltefosine capsules with a unit content of 10 mg were produced to allow for a dose adaptation in patients ranging down to an age as young as 2 years where variability in body weight is considerable and dosages lower than 50 mg/day are expected to be sufficient. Table 13 shows the final cure rate by age group.

Table 13: Efficacy in Indian Phase 1 to 3 Studies with Respect to Age Groups

Age(years)	Final Parasitological Cure, ITT Population						All
	Missing/not assessable		No		Yes		
	n	%	n	%	n	%	n
12-14	2	1.4	1	0.7	139	97.9	142
≥15	10	2.0	24	4.8	471	93.3	505
all	12	1.9	25	3.9	610	94.3	647

The lower final parasitological cure rate in the group of patients aged 15 years and above results from the inclusion of early dose-finding studies. These studies with higher failure rates due to under-dosing, had a lower age limit of 14 years. Thus, the higher cure rate in the age group 12 - 14 years is due to the fact that this intermediate age group comprised patients from studies excluding sub-optimal dosage schedules.

Because of the similarity in PK parameters between age groups, efficacy of miltefosine is not expected to differ systematically if a similar dose-intensity is used.

8.4.3.2. Efficacy in Relation to Dose per Body Weight

In the majority of studies, patients with a body weight of 25 kg and above were allocated to a particular dosage arm and were treated at that dosage irrespective of actual body weight. Table 14 shows the cure rates for dosages normalized for actual body weight.

Table 14: Efficacy in Indian Phase 1 to 3 Studies with Respect to Dose per Body Weight

(Daily) Dose per kg body weight	Final Parasitological Cure, ITT Population						All
	Missing/not assessable		Yes		No		
	n	%	n	%	n	%	n
< 2mg	12	12.8	81	86.2	1	1.1	94
2.0-2.4 mg	12	6.3	174	92.1	3	1.6	191
2.5-2.9 mg	3	1.3	213	95.5	7	3.1	223
3.0-3.9 mg	2	2.2	89	96.7	1	1.1	92
≥4 mg	3	4.3	66	95.7	0	0	69
all	32	4.8	623	93.4	12	1.8	667

Only the group of patients treated at a dosage below 2 mg/kg/day showed a slightly reduced cure rate of 86.2%, while patients treated at all other dosages showed cure rates of 92.1% and higher.

It should be mentioned that no patients with a body weight above 67 were included in the clinical trials of miltefosine. Still, increasing the dosage for a patient weighing more than 67 kg to 150 mg/day would result in the same normalized dosage as the dosage that was shown to be safe and effective in Indian patients with VL.

8.4.3.3. Efficacy in Relation to Pre-treatment

Studies in Indian patients included a significant percentage of patients who had received prior treatment for their infection. Most of the patients had been pre-treated with pentavalent antimonial drugs, while pretreatment with other drugs, for example amphotericin B or particularly liposomal preparations of this active substance, was less common in this population, primarily due to treatment costs.

Table 15 shows the cure rates in relation to presence or absence of pre-treatment. It is evident that pre-treated and non-pretreated patients showed a similar cure rates after oral use of miltefosine.

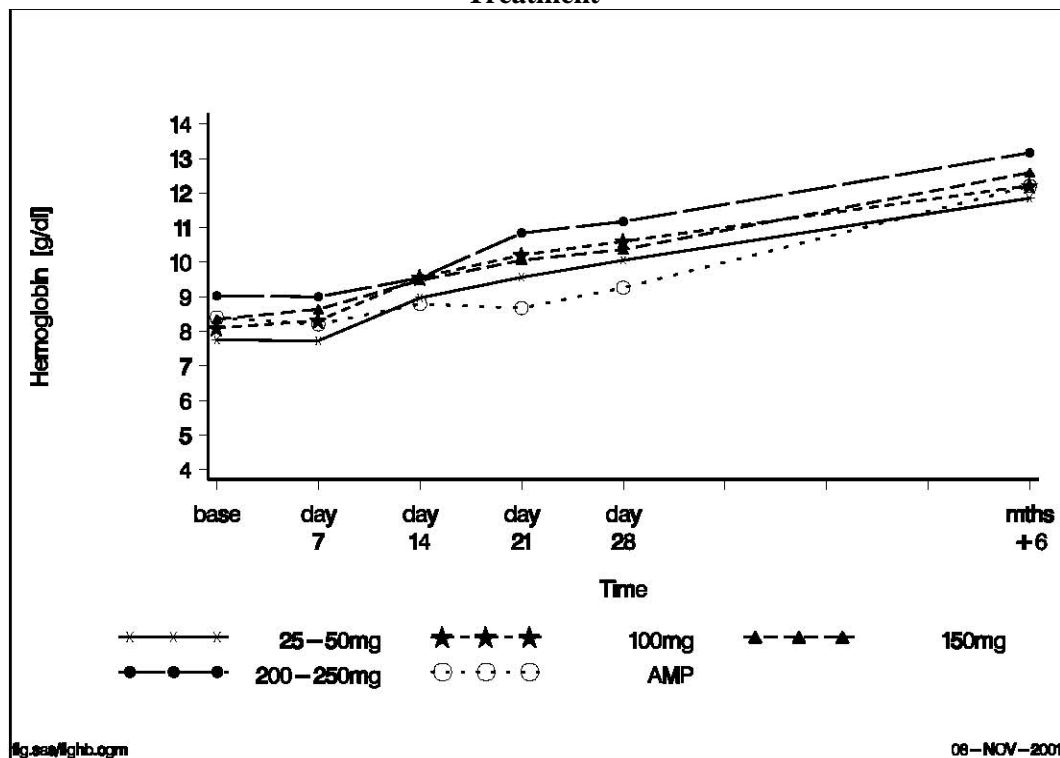
Table 15: Efficacy in Indian Phase 1 to 3 Studies with Respect to Previous Failure with Other Therapy

Treatment/Status of Leishmaniasis		Final Parasitological Cure, ITT Population						All
		Missing/ not assessable		No		Yes		
		n	%	n	%	n	%	
Miltefosine	Newly diagnosed	9	2.1	24	5.5	407	92.7	439
	Previously treated	3	1.3	8	3.5	218	95.6	228
Miltefosine	All patients	12	1.8	32	4.8	623	93.4	667
Amphotericin B	Newly diagnosed	1	1.4	0	0	70	98.6	71
Amphotericin B	Previously treated	2	7.1	0	0	26	92.9	28

8.4.3.4. Laboratory and Clinical Parameters Reflecting Recovery from Visceral Leishmaniasis

VL is a serious systemic disease that is associated with clinically relevant impairment of clinical parameters. Hemoglobin, leukocytes, thrombocytes, and body weight improved with ongoing treatment and in the follow-up period. The time course in recovery from anemia is shown in Figure 8.

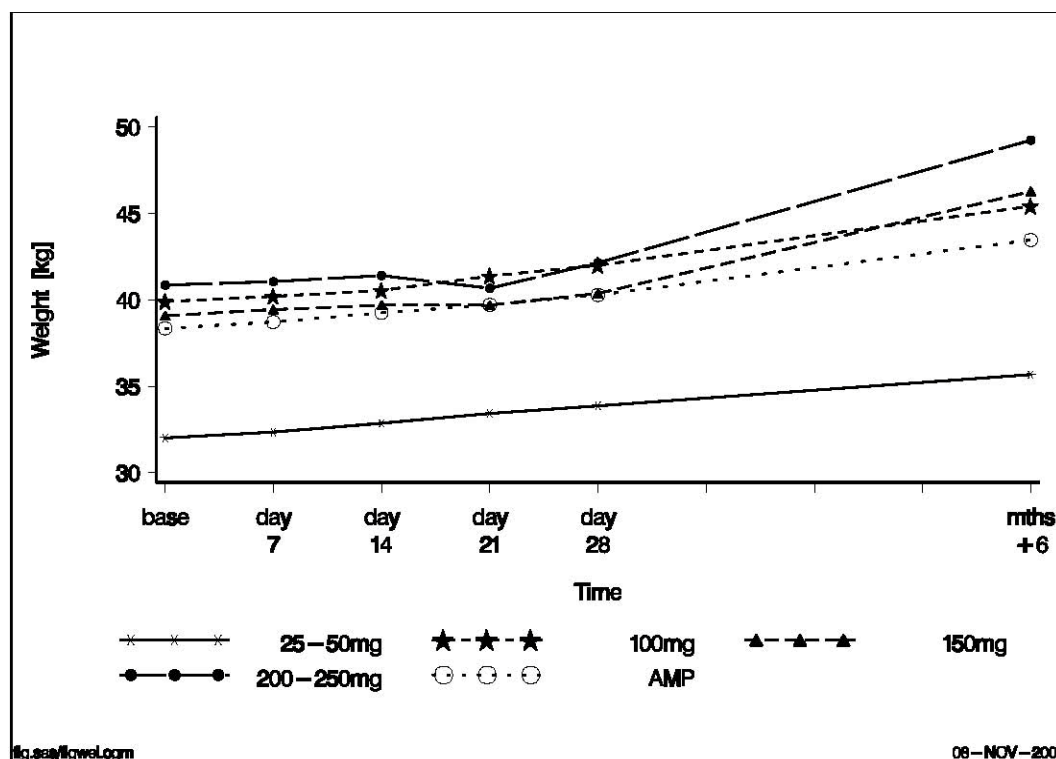
Figure 8: Hemoglobin Response in Phase 1 to 3 Indian Studies
Time Course of Hemoglobin Concentration During and After Treatment



The hemoglobin response rate curves indicate a more rapid recovery for patients treated with miltefosine compared with those treated with amphotericin B. The time course for the resolution of fever has been presented in figure 7 for Study 3154 where the course for treatment with miltefosine shows a striking difference to the recurrent drug-induced fever during treatment with amphotericin B.

Demonstration of weight gain during ongoing treatment with miltefosine (Figure 9) is of particular importance. First, it is a global indicator of recovery from infection. Second, it shows the limited clinical relevance of gastrointestinal signs and symptoms associated with the use of miltefosine. Short-lasting episodes of vomiting and/or diarrhea had no relevant impact on food intake and thus did not prevent weight gain.

Figure 9: Body Weight Response in Phase 1 to 3 Indian Studies
Patients' Body Weight During and After Treatment



In conclusion, improvement in laboratory and clinical parameters consistently paralleled the curative process.

8.4.4. Phase 4 Trials in Patients with VL in the Indian Subcontinent

For Phase 4 trials, patients who were lost to follow-up were likely to have been cured rather than to have failed, and the per-protocol cure rate may be more meaningful than the ITT cure rate.

The cure rates in the per-protocol population for India was $927 / 971 = 95\%$, for Nepal was $105/118 = 89\%$, and for Bangladesh was $726/796$ (on the assumption that 1/3 of the patients with isolated anemia at 6 months were therapeutic failures) = 91% . Together, 1758 of 1885 (93%) of the per-protocol population was cured. This 93% cure rate is only 4% less than the 97% per protocol cure rate in the Phase 3 study of hospitalized patients treated with miltefosine in India (Study 3154).

8.4.5. Efficacy in HIV Co-infected Patients in Ethiopia

This was a Phase 3 study conducted under sponsorship of the Dutch branch of Médecins Sans Frontières. The study compared efficacy and tolerability of miltefosine and sodium stibogluconate (SSG) in the treatment of VL in Humera, Ethiopia. A formal study report was retrospectively constructed from the case report form data made available by Médecins San Frontières to Paladin.

8.4.5.1. Study Design

This was an open-label, randomized, active-comparator controlled Phase 3 trial. The 580 patients were randomly allocated either to miltefosine (290 patients) or to pentavalent antimony (SSG) (290 patients) treatment. SSG was given at 20 mg antimony/kg/day by intramuscular injection for 30 days. The study was conducted in male patients only, aged 15 years and older, as these represented by far the majority of the infected population so that it was considered justifiable to exclude from study participation the small number of female patients who would have required contraception. The only exclusion criterion was being thought unlikely to survive 1 month's treatment because of severe comorbidity. Patients were encouraged to undergo testing for HIV infection, to allow for retrospective evaluation of outcome in relation to HIV status. The patients were hospitalized during the treatment, thus drug administration and other clinical phenomena during treatment were observed.

At end of treatment (Days 28-30), patients had a repeat parasitological assessment. At 6 months follow-up, patients were re-assessed: patients with clinical signs or symptoms attributable to VL, suggesting a relapse, were to be re-examined by bone marrow aspiration.

8.4.5.2. Patient Characteristics.

Patient characteristics are shown in [Table 16](#). Body mass index was low, approximately 10% were unable to walk unaided, and HIV seropositivity was substantial.

Table 16: Entrance Characteristics for Patients in Study Z025

Characteristic	Miltefosine (N =290)	SSG (N=290)	p-value
Age (years) ^a	29 (9.9)	29 (9.6)	0.62
Body Mass Index ^a	17.3 (2.1)	17.4 (1.8)	0.72
Hemoglobin (g/dL) ^a	9.2 (2.3)	9.1 (2.3)	0.72
Spleen size (cm) ^a	9.3 (5.6)	9.5 (5.7)	0.65
Duration of illness (months) ^a	2.6 (2.1)	2.6 (2.1)	0.8
Unable to walk unaided ^b	32/290 (11)	28/290 (9.7)	0.68
HIV serostatus ^b			
Positive	63/194 (32)	44/181 (24)	0.10
Negative	131/194 (68)	137/181 (76)	0.10
Unknown	96/290 (33)	109/290 (38)	0.30

^a Mean (SD)

^b Number (%)

8.4.5.3. Efficacy

Four endpoints were evaluated:

1. Initial cure at the end of therapy in the ITT population.
2. Final cure at 6 months in the per-protocol population. The per-protocol population was used because of the high numbers of lost-to-follow-up at 6 months.
3. Initial death at the end of therapy in the ITT population.
4. Final death at 6 months in the ITT population.

Efficacy endpoints are given in [Table 17](#).

1. Initial cure in the ITT population: The cure rates in the miltefosine and SSG group were identical: 88%. The lower limit of the 95% confidence interval was 6% less than the SSG cure rate, a value that is less than the pre-specified non-inferiority margin of 10%.
2. Final cure in the per-protocol population: The final cure rate in the miltefosine group was $174/219 = 79\%$. The final cure rate in the SSG group was $189 / 223 = 82\%$. The lower limit of the 95% confidence interval was 10.0% less than the SSG cure rate, which met the pre-specified non-inferiority margin of 10%.
3. Initial death rate (1 month) in the ITT population: There were significantly fewer deaths in the miltefosine group ($p = 0.0001$).
4. Final death rate in the ITT population: There were significantly fewer deaths in the miltefosine group ($p = 0.005$).

Table 17: Efficacy Outcomes in Study Z025

ITT population	Miltefosine (N = 290)	SSG (N = 290)	p-value
Initial outcomes at end of treatment			
Initial cure	256 (88%)	254 (88%) ^a	0.9
Failure	23 (8%)	2 (1%)	<0.0001
Not evaluable: dead	6 (2%)	28 (10%)	0.0001
Not evaluable: discontinued treatment or lost to follow-up	5 (2%)	6 (2%)	
Final outcomes after 6 months follow-up			
Final cure	174 (60%)	189 (65%)	0.23
Failure	30 (10%)	7 (2%)	0.0001
Not evaluable: dead	15 (5%)	34 (12%)	0.005
Not evaluable: lost to follow-up	70 (24%)	60 (21%)	

8.4.5.4. Conclusions

Miltefosine was non-inferior with respect to cure rate to the SSG comparator by a margin smaller than the Agency's acceptable margin for cure rates, and statistically superior to SSG for the more clinically important endpoint of survival.

8.4.6. Literature Review of Other Controlled Studies on *L. donovani* VL

A PubMed search for “miltefosine---all clinical trials” on 12 July 2013 did not reveal any other controlled trial in the adolescent/adult population.

8.4.7. Summary of the VL Efficacy Studies and Implications for Labeling

For VL the two standards of care are parenteral pentavalent antimony and, in antimony-resistant regions such as parts of India, intravenous amphotericin B. *L. donovani* is the cause of VL in India and in most of Africa.

Oral miltefosine was non-inferior to amphotericin B in a Phase 3 trial against *L. donovani* VL in India. The efficacy of miltefosine has since been confirmed in approximately 2,000 additional patients in Phase 4 trials in the Indian subcontinent.

Oral miltefosine was non-inferior to pentavalent antimony in a second Phase 3 trial against Ethiopian *L. donovani* VL in patients often co-infected with HIV in terms of cure rate, and superior to pentavalent antimony in terms of the more clinically meaningful endpoint of death rate.

On the basis of these pivotal trials and supporting Phase 4 trials, oral miltefosine can be recommended for VL due to *L. donovani*.

Controlled trials against the less frequent causes of VL, *L. infantum* in Europe and *L. chagasi* in Brazil were not performed, thus the efficacy of miltefosine for VL due to those species cannot presently be specified.

8.5. Safety in the VL Population

8.5.1. Overview

The core safety information on miltefosine in the treatment of VL has been derived from the same studies as the core efficacy information: Phase 1 to 3 clinical trials in the Indian subcontinent. These studies involved 766 patients, of whom 667 patients, including 119 children younger than 12 years, were treated with miltefosine and 99 patients received amphotericin B as the active control drug in a randomized controlled Phase 3 trial ([Study 3154](#)) ([Table 18](#)).

Table 18: Number of Subjects in Phase 1 to 3 Trials of VL in India

Population	Study	Phase	Number of Centers	Number of Patients Exposed	
				Miltefosine	Amphotericin B
Adolescent or adults	033	1/2	1	30	
	3089	2	2	45	
	3109	2	3	120	
	3127	2	1	54	
	3154	3	3	299	99
Total				548	99
Children	3091	1/2	2	39	
	3206	2/3	4	80	
Total				119	

Beyond this core data set, there is also information from the academic Phase 4 trials in approximately 2,000 VL patients in India, Nepal, and Bangladesh.

The Ethiopian trial does not provide additional safety data, since the recorded AEs (vomiting, diarrhea, pneumonia, bleeding) are more likely to reflect lack of efficacy than drug intolerance.

8.5.2. Adverse Events in Phase 1-3 Studies

The incidences of treatment emergent signs and symptoms (TESS) from Phase 1 to 3 studies in VL patients (irrespective of severity) are shown in [Table 19](#), grouped according to dosages per body weight, and in comparison to the data on amphotericin B from the Phase 3 study ([Study 3154](#)).

At all dosages of miltefosine, vomiting and diarrhea were the most frequently reported TESS. Of the patients who received miltefosine at 2-3 mg/kg/day (which brackets the target daily dose of 2.5 mg/kg/day), 41% and 22% of patients reported at least one episode of vomiting and diarrhea, respectively. Despite the lack of prophylactic and symptomatic treatment, vomiting and diarrhea were commonly limited to a few days and treatment could be completed as planned.

Table 19: Incidence of TESS with Respect to Daily Dose per Body Weight

	Incidence of TESS classified as “likely” or “not assessable” ^a									
	Miltefosine (daily dose per body weight)								Amphotericin B	
	<2 mg/kg (N=74)		2-3 mg/kg (N=321)		3-4 mg/kg (N=84)		≥4 mg/kg (N=69)		(N=99)	
	N	%	N	%	N	%	N	%	N	%
Overall incidence	43	58.1	173	53.9	56	66.7	53	76.8	94	94.9
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	73	73.7
Rigors	-	-	1	0.3	-	-	-	-	90	90.9
Arthralgia	-	-	-	-	2	2.4	1	1.4	-	-
Flatulence	-	-	-	-	1	1.2	4	5.8	-	-
Pain	-	-	-	-	-	-	2	2.9	-	-

^a This table shows all terms classified as “likely” or “not assessable” which occurred with an incidence of ≥2% in any of the dose or treatment groups sorted by the incidences in the 2-3 mg/kg group.

The information on the duration and severity of gastrointestinal reactions is best derived from the Phase 3 trial ([Study 3154](#)). This trial evaluated the duration and maximum intensity in detail, by specific daily recording of corresponding episodes ([Table 20](#)). In the majority of patients treated with miltefosine, gastrointestinal signs and symptoms were commonly limited to 1 to 2 days. For comparison, the duration of rigors, the most common and expected adverse reaction to treatment with amphotericin B, was distinctly more frequent and prolonged (5 to 16 days) in patients allocated to this reference treatment.

Table 20: Incidence and Severity of Vomiting, Diarrhea, and Rigors in Study 3154

		Miltefosine (N=299)		Amphotericin B (N=99)		p-value
		N	%	N	%	
Vomiting						
number of days	1 or more	113	37.8	20	20.2	P<0.01 ^a
	1-2	82	27.4	15	15.2	
	3-4	23	7.7	3	3.0	
	>4	8	2.7	2	2.0	
maximum intensity	CTCAE grade 1	79	26.4	16	16.2	
	CTCAE grade 2	34	11.4	4	4.0	
Diarrhea						
number of days	1 or more	61	20.4	6	6.1	P<0.01
	1-2	46	15.4	4	4.0	
	3-4	14	4.7	1	1.0	
	>4	1	0.3	1	1.0	
maximum intensity	CTCAE grade 1	48	16.1	3	3.0	
	CTCAE grade 2	12	4.0	3	3.0	
	CTCAE grade 4	1	0.3	-	-	
Rigors						
number of days	1 or more	1	0.3	90	90.9	p<0.001
	1-2	1	0.3	13	13.1	
	3-4			14	14.1	
	5-16			63	63.6	
maximum intensity	mild or brief	1	0.3	54	54.5	
	pronounced or prolonged	-	-	36	36.4	

^a Chi-square test**8.5.3. Severe and Life-threatening Adverse Events in Phase 1-3 Studies**

The incidence of higher-severity AEs (grades 3-4) is shown in [Table 21](#), according to administered dose. A dose of 100 mg of miltefosine corresponds to approximately 2.5 mg/kg in these approximately 40 kg patients.

The analysis shows that the incidence of clinically important gastrointestinal symptoms was higher when miltefosine was used at doses higher than the recommended target of 2.5 mg/kg/day. In particular, dosages of 200 mg/day and 250 mg/day on an absolute basis, thus doses of >4 mg/kg/day and perhaps >3 mg/kg/day on a weight basis for these approximately 40 kg patients, were associated with a wider spectrum and more severe AEs.

Table 21: Incidence of TESS of CTCAE Grade 3-4 with Respect to Daily Dose

	Incidence of TESS Classified as “Likely” or “Not Assessable” with CTC AE Grade 3-4									
	Miltefosine (daily dose per body weight)								Amphotericin B	
	<2 mg/kg (N=74)		2-3 mg/kg (N=321)		3-4 mg/kg (N=84)		≥4 mg/kg (N=69)		(N=99)	
	N	%	N	%	N	%	N	%	N	%
Overall incidence	0	0	5	1.6	2	2.4	10	14.5	5	5.1
Diarrhea	-	-	1	0.3	2	2.4	3	4.3	-	-
Jaundice	-	-	1	0.3	-	-	-	-	-	-
Stevens Johnson Syndrome	-	-	1	0.3	-	-	-	-	-	-
Vomiting	-	-	1	0.3	-	-	4	5.8	1	1.0
Anorexia	-	-	-	-	-	-	1	1.4	-	-
Circulatory Failure	-	-	-	-	-	-	1	1.4	-	-
Dehydration	-	-	-	-	-	-	1	1.4	-	-
Dyspnea	-	-	-	-	-	-	1	1.4	-	-
Nystagmus	-	-	-	-	-	-	-	-	1	1.0

Irrespective of the above statements on incidences and trends for subgroups of patients, TESS associated with the use of miltefosine in Indian patients at the recommended dosage (target of 2.5 mg/kg/day, which in these patients was 100 mg/day) were usually well tolerated. This is reflected by the low number of TESS with a severity of CTCAE grade 3 or 4, comprising single mentions each for diarrhea, jaundice, Stephen Johnson syndrome, and vomiting. Correspondingly, only 4 of 407 (1%) patients discontinued treatment prematurely due to an AE (clinical protocols did not allow for dose reduction or delay of treatment in case of dose-limiting events or reactions).

It should be noted that intravenous use of amphotericin B, the reference treatment in the Phase 3 study, was associated with a two-fold higher rate of anorexia than was oral treatment with miltefosine. Moreover, use of amphotericin B caused drug-induced fever and rigors in 74% and 91% of patients, respectively. The latter types of AEs were virtually absent in patients treated with miltefosine.

8.5.4. Clinical Laboratory Findings in Phase 3 study

8.5.4.1. Liver Function Tests

In the miltefosine group, mean AST values were 10 U/L higher than mean baseline values (58 U/L) at Week 1 then decreased to less than baseline; mean ALT values were 1 U/L higher than mean baseline values (46 U/L) at Week 1, 5-6 U/L higher than baseline at Weeks 2-4, then decreased to less than baseline at the 6 month follow-up.

In the amphotericin B group, AST values were 1 U/L higher than baseline at Week 1 then remitted; ALT values were 8 U/L higher than baseline at Week 1 then decreased. Elevated AST at baseline is common for VL (for all Phase 1-3 patients, 57% had CTCAE grade 1 and 15% had CTCAE grade 2 elevations at baseline) and AST elevations are commonly considered a marker for cell necrosis. The increase in AST early during treatment may reflect cell necrosis due to both parasitological and drug influences prior to parasitological eradication. For individual patients, AST elevations and ALT elevations were seen at

approximately comparable percentages for miltefosine and amphotericin B groups (Table 22). One miltefosine patient discontinued treatment prematurely due to an increase in total bilirubin, which reached CTC AE grade 4 two weeks after start of treatment. Total bilirubin improved to CTC AE grade 3 at Day 28 and was found to be completely recovered at 6 month follow-up.

8.5.4.2. Renal Function Tests

In the miltefosine group, mean creatinine values were less than at baseline at all time periods. In the amphotericin B group, mean creatinine values were 27 $\mu\text{mol/L}$ higher than mean baseline values (78 $\mu\text{mol/L}$) at Week 1; 17-21 $\mu\text{mol/L}$ higher at Weeks 2-4, then 4 $\mu\text{mol/L}$ higher at 6 months.

For individual patients, all grades of creatinine elevations were less frequent for miltefosine patients than for amphotericin B patients, except for the 2 patients with grade 3 elevations (Table 22).

Table 22: Incidence and Severity of Laboratory Changes in the Phase 3 Indian VL Trial (Study 3154)

Parameter	AE CTCAE grade of increases compared to baseline	Miltefosine (N=299) No. Patients with increases (% total patients)	Amphotericin B (N = 99) No. Patients with increases (% total patients)
AST	All grades	177 (59%)	46 (46%)
	1	91 (30%)	28 (28%)
	2	70 (23%)	16 (16%)
	3	16 (5%)	2 (2%)
ALT	All grades	155 (52%)	29 (29%)
	1	133 (44%)	26 (26%)
	2	21 (7%)	2 (2%)
	3	1 (0.3%)	1 (1%)
Creatinine	All grades	28 (9%)	42 (42%)
	1	20 (7%)	33 (33%)
	2	6 (2%)	9 (9%)
	3	2 (0.7%)	0
BUN	All grades	30 (10%)	43 (43%)
	1	20 (7%)	30 (30%)
	2	6 (2%)	10 (10%)
	3	4 (1%)	3 (3%)

For miltefosine, an increase in creatinine and BUN concentrations is consistent with toxicity studies in rats that revealed a nephrotoxic potential of miltefosine. Also, in studies in cancer patients, increases in creatinine and BUN were noticed. The median creatinine increase after a treatment duration of 12 weeks was 0.1 mg/dL and the 75th percentile indicated an increase by 0.25 - 0.3 mg/dL. Treatment interruption, e.g., after a non-tolerated escalation to a dose of 200 mg/day, was usually followed by rapid normalization

of renal function. Accordingly, changes in renal function, if occurring during treatment courses for leishmaniasis, should generally be expected to be reversible.

8.5.5. Serious Adverse Events

Please see Section 10 for an integrated evaluation of Serious Adverse Events (SAEs).

9. CUTANEOUS LEISHMANIASIS AND MUCOSAL LEISHMANIASIS

9.1. Overview of the Cutaneous and Mucosal Leishmaniasis Program Worldwide

Further to the studies in VL, oral use of miltefosine was evaluated in patients with different forms of CL. The primary studies were conducted in South American patients, a dose-finding trial in Colombia ([Study 3092](#)) where *L. v. panamensis* predominates, and a placebo-controlled confirmatory trial involving centers both in Colombia (*L. v. panamensis*) and Guatemala (*L. v. braziliensis* and *L. mexicana*) ([Study 3168](#)). Also, for the first time in the clinical development of oral miltefosine, [Study 3168](#) included a control group treated with placebo, thus allowing for an assessment of AEs and abnormalities in laboratory parameters in relation to either drug exposure or underlying disease.

As miltefosine became generally available in South America, academic investigators performed trials comparing the recommended regimen of miltefosine to the accepted regimen of standard of care pentavalent antimony for *L. v. braziliensis* in Bolivia ([Study Soto](#)), *L. v. braziliensis* in Brazil ([Study Z020B](#)), and *L. v. guyanensis* in Brazil ([Study Z020A](#)). An originally comparative study that reduced to a single arm miltefosine study due to refusal of the patient population to be randomized to comparator was performed against ML due to *L. v. braziliensis* in Bolivia ([Study Z022](#)).

9.2. Patient Numbers

There were 161 miltefosine patients in the 2 Industry sponsored trials ([Table 23](#)) and 120 patients in the investigator-sponsored pivotal trials ([Table 24](#)). Of these 281 patients, 246 received the 150 mg (2.5 mg/kg/day) dose ultimately proposed for the US new drug application (NDA).

Table 23: Patient Numbers in Industry-Sponsored CL Trials

Study	Principal Investigator (country)	Groups: Dosage Schemes Tested	Group: No. of Patients
3092	J. Soto (Colombia)	Miltefosine: 1: 50 mg/day on Day 1-20 2: 50 mg/day on Day 1-7, followed by 100 mg/day on day 8-20 3: 100 mg/day on Day 1-7 followed by 150 mg/day on day 8-20 4: 150 mg/day on Day 1-28	1: 16 2: 19 3: 17 4: 20
3168	J. Soto (Colombia) B. Arana (Guatemala)	A: Miltefosine for 28 days > 45 kg b.w. ^a : 150 mg/day ≤ 45 kg b.w.: 100 mg/day B: Matching Placebo	A: 89 B: 44

^a bw=body weight

Table 24: Patient Numbers in Investigator-Sponsored CL trials

Study No.	Principal Investigator	Country/Species	Dosage Regimen	No. Subjects ^a
Soto	Soto	Bolivia/ <i>L. braziliensis</i>	Miltefosine: target 2.5 mg/kg/day x 28 days meglumine antimoniate: 20 mg/kg/day x 20 days	40 adol/adult 18 adol/adult
Z020A	Dietze	Brazil/ <i>L. guyanensis</i>	Miltefosine: target 2.5 mg/kg/day x 28 days meglumine antimoniate: 20 mg/kg/day x 20 days	40 adol/adult + 20 ped 20 adol/adult + 10 ped
Z020B	Machado	Brazil/ <i>L. braziliensis</i>	Miltefosine: target 2.5 mg/kg/day x 28 days meglumine antimoniate: 20 mg/kg/day x 20 days	40 adol/adult + 20 ped 20 adol/adult + 10 ped

^a Adol = adolescent (12-17 yr). Adult = >17 yr. Ped=pediatric 2-11 yr

There are 4 supporting studies in CL for which Zentaris was tangentially involved or which was sponsored by the collaborating partner TDR/WHO (Table 25):

1. a single group investigator-sponsored study on CL due to *L. major* in Afghanistan in the course of which pharmacokinetics (PK) was evaluated in the CL population and Paladin sponsored the PK study report (“PK 3” study);
2. a comparative study on CL due to *L. tropica* in Afganistan (Study Z026);
3. a dose-ranging study for PKDL in India in coordination with TDR/WHO (“PKDL” study);
4. and a single group investigator-sponsored study for diffuse CL caused by *L. (m) amazonensis* in Venezuela (Study Z027).

Table 25: Supporting Studies in CL

Study	Principal Investigator	Country/Species or Indication	Dosage Regimen	No Subjects
PK 3	Dorlo	Afganistan / <i>L. major</i>	Miltefosine: target 2.5 mg/kg/day x 28 days	31 adults
Z026	Reithinger	Afganistan	Miltefosine: target 2.5 mg/kg/day x 28 days	145 adults
			Intralesional pentavalent antimony (2-7 ml, q4-6 days, x 3-5)	123 adults
			Intramuscular pentavalent antimony: 20 mg/kg/day x 21 days	67 adults
Z027	Convit	DCL / <i>L. amazonensis</i>	Miltefosine: target 2.5 mg/kg/day x 75-218 days	16 ped/adol/adults ^a
PKDL	Sundar	India - PKDL	Miltefosine: target 2.5 mg/kg/day x 8 weeks	25 adol/adults
			Miltefosine: target 2.5 mg/kg/day x 12 weeks	24 adol/adults

^a Ped=pediatric patients ages 5 to 11. Adol = adolescent patients ages 12 to 17.

In addition, because there is controversy in the literature as to the effectiveness of miltefosine for *L. v. panamensis* in Colombia, we review literature data for miltefosine vs. antimony for Colombian military members (Velez 2010, Investigator-sponsored) and miltefosine vs. antimony for Colombian children (Rubiano/Saravia 2012, also Investigator-sponsored (Table 26).

Table 26: Literature Studies of New World CL

Principal Investigator	Country/species	Dosage Regimen	No. Subjects
Velez (2010)	Colombian army/ <i>L. panamensis</i> / <i>L. braziliensis</i>	Miltefosine: target 2.5 mg/kg/day x 28 days	145 adults
		Intramuscular pentavalent antimony: 20 mg/kg/day x 20 day	143 adults
Rubiano/Saravia (2012)	<i>L. guyanensis</i> / <i>L. panemensis</i>	Miltefosine: target 2.5 mg/kg/day x 28 days	58 pediatric
		Intramuscular pentavalent antimony: 20 mg/kg/day x 20 day	58 pediatric

In the single-group mucosal study submitted to extend the indication from CL to ML ([Study Z022](#)), 79 patients were entered.

9.3. CL/ML Clinical Data Included in NDA 204684

For the pre-NDA meeting in 2009, Paladin proposed to support the CL indication in the United States with the placebo-controlled [Study 3168](#) and the ML indication with [Study Z022](#).

In the FDA's Advice letter of April 13, 2010, the Agency noted that "Study 3168 is an adequate and well controlled study that can be submitted to support the indication for the treatment of CL caused by *L. panamensis*, *L. mexicana*, and *L. braziliensis*. A second controlled study is needed for CL indication. Studies [Z020A](#) or [Z020B](#) (miltefosine compared to meglumine for the treatment of CL in Brazil), or the study by [Soto et al \(2008\)](#) [were identified as] potential other studies."

So as not to exclude studies, Paladin obtained access to the raw data for each of the 3 proposed studies, and prepared study reports for each of the three Investigator-initiated pivotal studies in addition to [Study 3168](#).

These 4 pivotal trials form the core of the CL clinical data, supported by the other trials mentioned above.

With respect to ML, the agency noted that in spite of effort, [Study Z022](#) was uncontrolled, and stated "We acknowledge the feasibility difficulties that prevented [Study Z022](#) from using concurrent controls. As previously indicated, if upon review miltefosine is found to provide substantial effectiveness for CL and VL, this study may be potentially used to support a treatment indication for ML. Additional supportive information may be required." To support an extension of the CL indication to ML, the data on [Study Z022](#) is also contained below.

Although the core studies of the NDA were not prospectively coordinated, the core clinical data nevertheless well-represents potentially disseminating CL and its standard therapy. CL which disseminates to the naso-oral mucosa is caused by the *L. viannia* subgenus: *L. v. braziliensis*, *L. v. panamensis*, and *L. v. guyanensis*. The other member of the *L. viannia* subgenus, *L. v. peruviana*, is not known to cause mucosal disease ([Reyes-Urbe 2012](#)). The clinical data included in the NDA are for studies of miltefosine for *L. v. braziliensis*, *L. v. panamensis*, and *L. v. guyanensis*. Standard therapy for New World CL is pentavalent antimony, but disease due to non-disseminating, rapidly self-curing species such as *L. mexicana* may initially be only observed. In the United States, the treatment situation is reversed in a regulatory sense. There is no approved chemotherapy for CL and "observation" is by definition standard, but pentavalent antimony has been used under IND for decades. In comparison, the NDA includes studies that compared miltefosine to placebo in pivotal [Study 3168](#) and compared miltefosine to pentavalent antimony in pivotal Studies [Soto](#), [Z020A](#), and [Z020B](#).

As for VL, the population for the US NDA for the CL and ML indications is adolescents and adults ≥ 12 years of age.

9.4. Efficacy in Cutaneous Leishmaniasis and Mucosal Leishmaniasis

9.4.1. General Considerations on Clinical Efficacy Studies for Cutaneous Leishmaniasis

9.4.1.1. Patient Characteristics

Patient characteristics for the dose-ranging and pivotal trials were:

Inclusion criteria:

1. Age: ≥ 12 years (except for Studies Z020A and Z020B which included pediatric patients aged 2-11 years).
2. Gender: male and female.
3. Disease characteristics: newly diagnosed CL or relapsing CL without mucosal involvement, presenting with at least one skin ulcer with positive parasitology.

Exclusion Criteria:

1. Liver function tests: AST, ALT, alkaline phosphatase ≥ 2 or ≥ 3 times upper limit of normal range, depending on the trial. Total bilirubin ≥ 1.5 or ≥ 2 times upper limit of normal range, depending on the trial.
2. Renal function tests: Serum creatinine or blood urea nitrogen (BUN) >1.5 times upper limit of normal range.

9.4.1.2. Primary Endpoint

The endpoint for all CL trials was complete re-epithelialization of the ulcer at 6 months after therapy. This endpoint is synonymous with clinical cure, i.e., is the clinically relevant endpoint not a surrogate endpoint, and is accepted in the CL field. To be eligible to be evaluated at 6 months, the patient must not have previously been shown to fail at an earlier time period. Reflecting the lack of consensus in the CL field with respect to exactly how much improvement at exactly what initial time after therapy is to be expected, differing studies employed different initial time points and different criteria for failure at that time point. The definitions for initial failure are given below for the Phase 1 dose ranging study and the pivotal trials.

9.4.1.3. Dose Ranging Study to Specify Dose to be Used in Pivotal Trials

The dose-ranging study ([Study 3092](#)) was conducted to assess the efficacy and safety of different dosages of oral miltefosine in patients with South American CL, in order to define a dosage regimen for the subsequent confirmatory trial. The study was conducted at a military hospital in Colombia (Universidad Militar Nueva Granada, SantaFe de Bogota). Mean weight of the all male patient population was 67 kg.

Miltefosine (50 mg capsules) was given orally with meals and at the following dosage regimens:

Group 1: 50 mg/day on Days 1-20.

Group 2: 50 mg/day on Days 1-7, followed by 100 mg/day on Days 8-20.

Group 3: 100 mg/day on Days 1-7, followed by 150 mg/day on Days 8-20.

Group 4: 150 mg/day on Days 1-28.

Definition of Final Cure: No initial failure (initial failure was defined as: < 25% diminution in lesion size at 2 weeks after the end of therapy, incomplete re-epithelialization at 2-3 months after the end of therapy) followed by complete re-epithelialization at 6 months after the end of therapy.

ITT and per-protocol cure rates are shown in Table 27 for the separate treatment groups. In addition, the 2 lower dose groups (Groups 1 and 2) were combined for statistical analysis, as were the 2 higher dose groups (Groups 3 and 4).

Table 27: Cure Rates in Study 3092

ITT Population	Group 1	Group 2	Group 3	Group 4
Rate of final cure	9/16 (56.3%)	12/19 (63.2%)	14/17 (82.4%)	16/20 (80.0%)
95% (90%) lower confidence bound	33.3% (37.5%)	41.8% (45.9%)	60.4% (64.8%)	59.9% (63.9%)
Per Protocol Population	Group 1	Group 2	Group 3	Group 4
Rate of final cure	9/14 (64.3%)	12/18 (66.7%)	14/14 (100.0%)	16/18 (88.9%)
95% (90%) lower confidence bound	39.0% (43.7%)	44.6% (48.8%)	80.7% (84.8%)	69.0% (73.1%)

9.4.1.4. Conclusions

The final cure rate at 6 months after end of therapy was 94% (per-protocol analysis) for the combined higher dose treatment groups 3 and 4. In the combined analysis of lower dose treatment groups 1 and 2, a final cure rate of 66% (per-protocol analysis) was achieved. An ITT analysis also showed a high final cure rate (81%) for the combined two higher dose groups when compared with the two lower dose groups (60%).

Oral miltefosine at dosages of 133 (mean) or 150 mg/day over 3 and 4 weeks, respectively, were effective regimens to treat patients with CL. In the absence of clinically relevant intolerability, the dosage regimen with the highest dose intensity (150 mg/day for 4 weeks) was chosen for a confirmatory trial.

Since the mean patient weight was 67 kg, the effective regimen provided 2.2 mg/kg/day, which is approximately the same dosage that was effective for VL. Hence, a common dosage target of 2.5 mg/kg/day for 4 weeks for CL as well as VL was generated.

9.4.2. Efficacy in Placebo Controlled Phase 3 Study in CL Study 3168

The study involved centers in two countries, Colombia (Consorcio de Investigaciones Bioclinicas, SantaFe de Bogota) and Guatemala (Universidad del Valle de Guatemala), with Dr. J. Soto and Dr. M. Gilardi (successor to Dr. B. Arana) as the Principal Investigators, respectively. The study was performed between 2000 and 2002.

9.4.2.1. Design

The primary objective of this study was to demonstrate that miltefosine is superior to placebo in CL when assessed 2 weeks and 6 months after end of treatment (apparent cure at 2 weeks after completing treatment and final cure at 6 months after completing treatment).

Study treatment comprised miltefosine (50 mg) or matching placebo capsules, given orally for 28 days according to the following dosages:

- Patients ≥ 45 kg body weight: 3 capsules per day (1 capsule in the morning, 1 capsule at lunch, and 1 capsule in the evening, following meals).
- Patients < 45 kg body weight: 2 capsules per day (1 capsule in the morning and 1 capsule in the evening, following meals).

9.4.2.2. Patient Characteristics

A total of 133 patients entered the study, with main characteristics as shown in [Table 28](#). Ten of the 44 patients (22.7%) on placebo and 13 of the 89 patients (14.6%) on miltefosine were pre-treated for leishmaniasis, most frequently with Glucantime.

Table 28: Patient Demographics and Disease Characteristics in Study 3168

Characteristic	Colombian Site		Guatemalan Site	
	Miltefosine group (n=49)	Placebo group (n=24)	Miltefosine group (n=40)	Placebo group (n=20)
Age, mean years \pm SD	24 \pm 10	25 \pm 13	26 \pm 10	28 \pm 12
Male sex, %	86	75	98	100
Weight, mean kg \pm SD	60 \pm 13	57 \pm 14	59 \pm 8	60 \pm 8
Median no. of lesions (range)	1 (1-8)	1 (1-5)	1 (1-10)	1 (1-3)
Ulcer size, median mm ² (range)	171 (72-1775)	238 (6-2110)	165 (6-1650)	154 (6-3300)
No. (%) of patients with previous therapy failure	3 (6)	2 (8)	10 (25)	8 (40)

9.4.2.3. Results

Final cure was defined as: no initial failure (initial failure was defined as: $\geq 50\%$ enlargement in lesion size at 2 weeks after the end of therapy; if parasitologically evaluated, parasites at 2 weeks after the end of therapy; incomplete re-epithelialization at 2 months after the end of therapy) followed by complete re-epithelialization at 6 months after the end of therapy.

Overall, 72 of 133 patients had final cure, i.e., they had cure verified after a 6-month follow-up ([Table 29](#)) based on an ITT analysis.

Table 29: Efficacy in Placebo Controlled CL Trial (3168)

Final cure (ITT)	Miltefosine	Placebo
Center 1 (Colombia)	40/49 (81.6%)	9/24 (37.5%)
Center 2 (Guatemala)	19/40 (47.5%)	4/20 (20.0%)
Total	59/89 (66.3%)	13/44 (29.5%)

The difference in miltefosine efficacy versus placebo efficacy was statistically significant for each of: overall cure rate ($p < 0.001$; chi square test); Colombia cure rate ($p < 0.001$; chi square test); and Guatemala cure rate ($p = 0.04$; chi square test). Thus, although the miltefosine cure rate in Guatemala was

less than in Colombia, the placebo cure rates showed a parallel decrease between countries and the difference in cure rates (miltefosine versus placebo) was statistically significant in both countries.

Because of the apparent differences in the cure rates in both countries, the information of *Leishmania* speciation may be of relevance. In Colombia, cultures of 7 baseline lesion aspirates from this trial were speciated by monoclonal antibody binding; all 7 lesions were infected by *L. v. panamensis*. In Guatemala, 46 of the 60 infecting parasites were speciated by polymerase chain reaction (PCR); 63% of speciated parasites were *L. v. braziliensis* and 37% of speciated parasites were *L. mexicana*. The apparent distribution of *L. v. braziliensis* and *L. mexicana* with cure and failure in response to miltefosine and placebo in the Guatemalan patients is shown in [Table 30](#).

Table 30: Infecting *Leishmania* Species in Study 3168

	Miltefosine-Treated Patients			Placebo-Treated Patients		
	<i>L. braziliensis</i>	<i>L. mexicana</i>	Unknown	<i>L. braziliensis</i>	<i>L. mexicana</i>	Unknown
Cured	5	9	6	1	1	2
Failed	10	5	3	11	2	2
Non-evaluable	1	0	1	1	0	0
Total	16	14	10	12	3	4

9.4.2.4. Conclusions

Miltefosine was safe and effective in the treatment of patients with CL with a cure rate of 66.3% (ITT) compared with a placebo cure rate of 29.5% ($p < 0.001$, two-sided Cochran-Mantel-Haenszel test). Definite cure rates were higher in Colombia (81.6%) than in Guatemala (47.5%), but in both countries 2.2-fold higher and statistically significant compared to patients on placebo ($p < 0.001$ in Colombia; $p = 0.04$ in Guatemala). Because there was only one species at the Colombian site, efficacy data at that site is straightforward to interpret. Miltefosine was highly superior to placebo for *L.v. panamensis*.

9.4.3. Efficacy in Pivotal Comparator Trials in CL

In addition to comparing miltefosine to placebo in the Industry-sponsored trial, the Agency suggested and Paladin obtained access to the primary data from 3 investigator-sponsored trials.

9.4.3.1. Study Design

The 3 Investigator-initiated pivotal trials involved a total of 3 sites, each with its own endemic species of *Leishmania*; 2 of the trials (Z020a, Z020b) were conducted simultaneously according to a common protocol while the third study ([Soto](#)) was conducted separately. The parasite causing disease was *L. v. guyanensis* for [Study Z020A](#) in Brazil; *L. v. braziliensis* for [Study Z020B](#) in Brazil, and *L. v. braziliensis* for [Study Soto](#) in Bolivia. Although species and study periods differed between the Investigator-initiated pivotal trials, there were also 3 species and 2 sites for Industry-sponsored [Study 3168](#) which was analyzed in an integrated fashion. Therefore, it is reasonable to analyze the investigator-initiated pivotal trials in an integrated analysis.

9.4.3.2. Patient Characteristics

An integrated analysis of the investigator-initiated pivotal trials is further justified by their similar entrance characteristics: miltefosine regimen, choice of comparator, comparator regimen, randomization schemes, and almost identical sample sizes. There was a common age range (≥ 12 years in each case), although Studies [Z020A](#) and [Z020B](#) also included patients 2-11 years. The data on this pediatric population is not relevant to the proposed product indication and is therefore omitted from the present briefing document. Disease entrance characteristics were comparable among the 3 studies, although lesion characteristics for Study [Z020B](#) were more similar to the values for Soto study than for Study [Z020A](#) (Table 31).

Table 31: Integrated Analysis of Investigator-sponsored Pivotal Studies

Parameter	Study Soto	Study Z020A	Study Z020B
Infecting species	<i>L. v. braziliensis</i>	<i>L. v. guyanensis</i>	<i>L. v. braziliensis</i>
Age range for adolescents / adults	≥ 12 years	≥ 12 years	≥ 12 years
Miltefosine target dose	Miltefosine: target 2.5 mg/kg/day x 28 days	Miltefosine: target 2.5 mg/kg/day x 28 days	Miltefosine: target 2.5 mg/kg/day x 28 days
Comparator target dose	meglumine antimoniate (Glucantime): 20 mg/kg/day x 20 days	meglumine antimoniate (Glucantime): 20 mg/kg/day x 20 days	meglumine antimoniate (Glucantime): 20 mg/kg/day x 20 days
Randomization	2:1	2:1	2:1
Entrance data			
Gender	78 % male	82% male	70% male
Weight (mean)	58 kg	66 kg	58 kg
Lesion area (mean)	285 mm ²	209 mm ²	419 mm ²
% patients with 1 lesion	59%	45%	80%
Primary endpoint	100% re-epithelialization of all ulcers at 6 months after therapy	100% re-epithelialization (and loss of induration) of all ulcers at 6 months after therapy	100% re-epithelialization (and loss of induration) of all ulcers at 6 months after therapy
ITT cure rate miltefosine group	32/ 40 = 80% ^a	27/40 = 67%	34/40 = 85%
ITT cure rate antimony group	13/18 = 72 %	12/20 = 60%	9/20 = 45%

^a 30/40=75% if criteria for initial cure used in Brazil had been used in Bolivia.

9.4.3.3. Primary Efficacy Parameter

The primary efficacy endpoint in the 3 studies was initial cure (complete re-epithelialization of the ulcer 2 months after the end of therapy (studies [Z020A](#) and [Z020B](#)), or at least 50% diminution in ulcer size at 3 months after therapy ([Study Soto](#)), followed by final cure (100% re-epithelialization at 6 months after the end of therapy) in all studies. The 2 Brazilian studies additionally required 100% loss of the induration at 6 months, but this criterion was not utilized since no patient ended up failing for that reason. As mentioned above, the common final endpoint but differing initial endpoint reflects a well-established consensus among experts about the final endpoint, but lack of consensus with respect to exactly how

much improvement at exactly what time after therapy is to be initially expected. To provide efficacy data for the Soto study that utilized the same initial efficacy definition as for the 2 Brazilian studies, the Soto data was analyzed both according to the Soto criteria for initial cure and according to the Brazilian definition of initial cure.

9.4.3.4. Results

For the 3 investigator-pivotal trials combined, the miltefosine cure rate was $93/120 = 77.5\%$ according to each study's efficacy criteria. The Glucantime cure rate was $34/58 = 58.6\%$. The miltefosine cure rate was statistically superior to the Glucantime cure rate with a lower limit of the 95% confidence interval = 4.2 %.

If the criterion of complete re-epithelialization of the ulcer at 3 months that was used in the Brazil studies had been adopted for the Bolivian study, 30 of 40 miltefosine patients (75%) would have cured in Bolivia, and the overall cure rate would be $91/120 = 75.8\%$ for miltefosine, statistically superior to $34/58 = 58.6\%$ for Glucantime (lower limit of the 95% confidence interval = 2.4%).

9.4.3.5. Conclusions

Industry-sponsored placebo controlled pivotal data show that miltefosine is superior to placebo for *L. v. panamensis* in Colombia and for *L. v. braziliensis* in Guatemala. Investigator-sponsored positive comparator-controlled pivotal data show that miltefosine is superior to *L. v. braziliensis*/*L. v. guyanensis* in Brazil and Bolivia. The pivotal data indicate that miltefosine is effective against members of the *L. vianna* subspecies (*L. v. panamensis*, *L. v. braziliensis*, *L. v. guyanensis*) in the New World that disseminate to the oro-nasal mucosa.

Because dosing can only involve 50, 100, or 150 mg/day (1, 2, or 3 of the 50 mg capsules), patients with relatively high or low weight receiving the same number of capsules would receive relatively lower or higher dosing on a mg/kg basis. Although the target daily dose is 2.5 mg/kg, most patients will not have exactly that dosage. It is of interest to evaluate whether relatively low or high dosage effected efficacy.

Table 32 displays final cure rates in relation to daily dose of treatment for the miltefosine group in the 4 controlled pivotal trials.

Table 32: Final Cure Rates with Respect to Miltefosine Dose: Integrated Analysis of Studies 3168, Soto, Z020A, Z020B

Dose Group (mg/kg/day)	N	Failed N (%)	Cured N (%)
1.7-2.2	38	12 (27.9)	26 (60.5)
2.3-2.8	128	24 (17.8)	104 (77.0)
2.9-3.3	27	6 (22.2)	21 (77.8)

The p-value for the linear trend was 0.13, indicating that cure rate is not statistically affected by dose within the range 1.7 mg/kg/day to 3.3 mg/kg/day.

9.4.4. Mucosal Leishmaniasis (Study Z022)

9.4.4.1. Design

This study was originally designed as a Phase 2, randomized, equivalency study of oral miltefosine versus standard therapy with pentavalent antimony in the treatment of ML. The trial was amended when the study team became aware that pentavalent antimony had been rejected as ineffective for ML at this site. The study was conceptually modified to compare oral miltefosine with intravenous amphotericin B as used at the site (1 mg/kg amphotericin B every other day for a total of 45 injections over 3 months). When the efficacy of oral miltefosine became apparent in initial patients, however, additional patients refused to be entered into an amphotericin B arm. Therefore, the final study design became an evaluation of 1 cohort of 79 patients who received miltefosine.

The patients who met the inclusion criteria were administered miltefosine (50 mg capsules) at a target dose of 2.5 mg/kg/day for 28 days with meals. Tolerance to miltefosine was determined twice a week during therapy by recording elicited AEs. At the end of therapy, screening laboratory tests were repeated. The efficacy of miltefosine was evaluated by examining the nasal and oral mucosa of each patient at the beginning of therapy; the end of therapy; and at 2, 6, 9, and 12 months after the end of therapy.

9.4.4.2. Entrance Characteristics

The main criteria for inclusion were male and female patients >18 years of age; the presence of leishmaniasis by history with evidence of a cutaneous scar plus either parasites observed microscopically or cultured from lesion material or a positive skin test; no clinically significant concomitant disease as ascertained by history, clinical examination, and laboratory tests.

Patients in this study were 73% male with a mean age of 39 years and weight of 58 kg.

9.4.4.3. Results

The primary efficacy variable was defined as a composite variable: the ML severity score. At any assessment time point, the composite score was computed by adding a severity score (0 =none, 1 = mild, 2 = moderate, 3 = severe) for each of 4 pathological signs (erythema, edema, infiltration, and erosion) for each disease site. For example, at any time point, the maximum mucosal severity score for a subject who presented with lesions involving the nasal skin, nasal mucosa, palate, pharynx, and larynx patient is 60 because 3 severity points would be assigned for each of 4 pathological signs (erythema, edema, infiltration, and erosion) at each of the 5 sites (nasal skin, nasal mucosa, palate, pharynx, and larynx). Thus, larger scores appropriately reflected any of the following: increased severity of involvement for any sign, increased number of signs of involvement at any site, and increased number of disease sites.

For all 79 patients, the values of the ML severity parameter at each time point are shown in [Table 33](#).

Table 33: Change of Mean Efficacy Scores over Time in ML Study Z022

Visit	N	Mean
Screening	79	10.03
End of treatment + 2 weeks	76	5.61
End of treatment + 2 months	76	4.04
End of treatment + 6 months	72	2.60
End of treatment + 9 months	68	2.00
End of treatment + 12 months	73	1.96

Final cure was prospectively defined as a >90% diminution in the mucosal severity score at 12 months after the end of treatment.

Final cure rates for the 79 modified ITT (mITT) patients and the 76 per protocol patients are shown in [Table 34](#). Of the 76 per protocol patients, 49 (64% of the 76 evaluable patients, 62% of the 79 mITT patients) achieved cure, with all 49 cured patients showing 100% improvement in their mucosal severity scores.

Table 34: Efficacy in ML Study Z022

Clinical Response	Per Protocol N=76		mITT N=79	
	N	%	N	%
Final cure	49	64.5	49	62.0
Improved	16	21.1	16	20.3
No change	6	7.9	6	7.6
Worsened	1	1.3	1	1.3
Presumptive failure	4	5.3	4	5.1
Not Evaluable			3	3.8

9.4.5. Conclusion

The standard of care for ML is parenteral antimony or amphotericin B, and the original study was designed to compare miltefosine to antimony. Refusal of the patients and medical staff at the site to use these parenteral agents, with their well-known toxicities, led to a single-group study of miltefosine. The cure rates of 62% in the ITT analysis and 64.5% in the per-protocol analysis were comparable to cure rates for historic controls: 28-89% for antimony and 29-90% for amphotericin B.

9.4.6. Literature Review of other Controlled Studies on *L. v. braziliensis*, *L. v. panamensis*, and *L. v. Guyanensis*

9.4.6.1. *L. panamensis* / *L. braziliensis* in Colombian Soldiers

Study by [Velez et al 2010](#): According to the abstract, “An open-label, randomized, Phase 3 clinical trial that was carried out in the Colombian army population. Miltefosine, 50 mg capsule was taken orally three times per day for 28 days (n = 145) or Glucantime (meglumine antimoniate), 20 mg/kg body weight per day for 20 days by intramuscular injection (n = 143). The efficacy of miltefosine by protocol was 69.8% (85/122 patients) and 58.6% (85/145 patients) by ITT. For Glucantime, the efficacy by protocol was

85.1% (103/121 patients) and 72% (103/143 patients) by ITT. No association was found between drug efficacy and *L. (v) braziliensis* or *L. (v) panamensis* species of *Leishmania* responsible for infection.”

Comment: The data reported in this study may be reviewed with the following points in mind: Colombian military patients in a Malarone study for malaria were shown by blood level data not to take their clinical trial materials irrespective of assurances to study investigators ([Soto 2006](#)). The data of the Machado study ([Z020B](#)), in which there was a significant association of a short duration of therapy with clinical failure, suggests that the reason for the low cure rate for the miltefosine group in the [Velez \(2010\)](#) study could have been incomplete duration of drug administration. The statement in the [Van Thiel et al \(2010\)](#) study, that gastrointestinal side effects caused Dutch military personnel to have difficulty with normal vigorous military activities, supplies the reason for the possible low adherence to miltefosine administration.

9.4.6.2. *L. panamensis* / *L. guyanensis* in Colombian Children

Study by [Rubiano 2012](#): According to the abstract, “A randomized, non-inferiority clinical trial with masked evaluation was conducted at 3 locations in Colombia where *L. panamensis* and *L. guyanensis* predominated. One hundred sixteen children aged 2 to 12 years with parasitologically confirmed CL were randomized to directly observed treatment with Glucantime (20 mg Sb/kg/day for 20 days; intramuscular) (n = 58) or miltefosine (1.8 to 2.5 mg/kg/day for 28 days; by mouth) (n = 58). The primary efficacy endpoint was treatment failure at or before Week 26 after initiation of treatment. Ninety-five percent of children (111/116) completed follow-up evaluation. By ITT analysis, failure rate was 17.2% for miltefosine and 31% for Glucantime. The difference between treatment groups was 13.8%, (p = 0.04). For the Tumaco site, where *L. panamensis* is endemic, the failure rate for miltefosine was 7.4% and the failure rate for Glucantime was 33.3% (p = 0.02). At Chapparal, where *L. guyanensis* is endemic, the failure rate was 32% for both drugs.”

Comment: In this study in Colombia (pediatric population), the cure rate for miltefosine was statistically superior to the cure rate for Glucantime for *L. panamensis* and similar for *L. guyanensis*.

9.4.7. Literature Review of Other Controlled Studies on CL

A PubMed search for “Miltefosine---all clinical trials” revealed one controlled trial for *L. major*: ([Mohebbi 2007](#)). The Abstract for this publication is:

“This study was a randomized, open label comparison that was designed to determine efficacy and safety of miltefosine as the first oral drug for the treatment of zoonotic cutaneous leishmaniasis caused by *Leishmania major* in comparison with meglumine antimoniate. Complete clinical response was defined as 100% re-epithelialization of the lesion. Definitions of lesion cure and failure were based on both clinical and parasitological criteria two weeks after the end of treatment and clinical recovery three months after this period. Of 32 patients enrolled for miltefosine treatment 28 patients completed treatment, of which 26 were cured at three months, corresponding to a cure rate of 92.9% on a per protocol analysis, and 81.3% according to intention to treat analysis. There was one failure (3.1%), one relapse (3.1%) and four dropouts due to lack of tolerability (12.5%) during the first week of treatment. Of 31 patients who received intramuscular meglumine antimoniate (20 mg Sb5 [*pentavalent antimony*] /kg body weight daily for 14 days) 25 were cured (83.3% on a per protocol basis, 80.6% on intention to treat basis), five failed (16.1%) and one was lost (3.2%) at 3-month follow-up. At 6-month follow-up after the end of treatment, no relapse was observed. Both regimens were tolerated but averages of nausea (32.2%) and vomiting (21.5%) were observed in patients during two weeks after initiation of miltefosine treatment. Other

gastrointestinal, musculoskeletal, and total AEs were not statistically different in the two groups during one to four weeks after therapy initiation. No relevant changes were observed in levels of liver enzymes, creatinine and hematological tests before and after end of treatment in both groups. In conclusion, miltefosine is apparently at least as good as meglumine antimoniate for the treatment of cutaneous leishmaniasis caused by *L. major* in Iran, based on parasitological as well as clinical criteria two weeks, three months, and six months after end of treatment.”

9.4.8. Summary of Efficacy for CL and ML and Implications for Labeling

Miltefosine was statistically superior compared with placebo against *L.v. panamensis* (Colombia) and *L. v. braziliensis* / *L. mexicana* (Guatemala). Miltefosine was statistically superior to standard of care Glucantime against *L. v. braziliensis* (Bolivia and Brazil) plus *L. v. guyanensis* (Brazil) in an integrated analysis.

Miltefosine can be recommended for the treatment of CL caused by *Leishmania viannia* complex species including *L. v. panamensis*, *L. v. braziliensis*, and *L. v. guyanensis* acquired in the New World.

This recommendation is particularly important given the efficacy of miltefosine against ML in Bolivia and the now-recognized routine parasitization of the mucous membranes when parasites of the *L. viannia* complex cause CL ([Figueroa 2009](#)). Patients with cutaneous infection with these species would benefit from likely eradication of parasites from the mucosal membranes in addition to cure of the clinically apparent site of cutaneous involvement.

The efficacy of miltefosine against other species causing CL was not evaluated in controlled trials and cannot presently be specified.

9.5. Safety in CL and ML Studies

9.5.1. Safety Database

Data is compiled from dose-ranging and pivotal trials for which the target dose of 2.5 mg/kg/day was used. These adolescent and adult patients consist of the 37 patients in the higher dose groups of dose ranging trial [3092](#), the 89 patients in pivotal trial [3168](#), and the 40 patients in each of the pivotal trials [Soto, 2020A](#), and [2020B](#).

9.5.2. Adverse Events in Randomized Controlled Trials of CL

[Table 35](#) summarizes the incidence of AEs for the 5 CL trials in which the recommended target dose of 2.5 mg/kg/day was used. The table contains data for all miltefosine patients combined, for Glucantime patients and placebo patients separately, and for all comparator patients combined. The incidence of TESS present in ≥ 2 % in either the miltefosine group or antimony comparator group is portrayed.

Table 35: Adverse Events \geq 2% incidence - CL studies Soto/Z020A/Z020B/3168/3092 Miltefosine-Treated Adolescents/Adults (>11 years)

System, organ, class	Preferred Term^a	Miltefosine All Doses N = 246 n (%)	Antimony N = 58 n (%)	Placebo N = 44	Controls N = 102 n (%)
Blood and lymphatic system disorders					
	Lymphadenopathy	3 (1.2)	2 (3.4)		2 (2.0)
Ear and labyrinth disorders					
	Motion sickness	50 (20.3)		10 (22.7)	10 (9.8)
Gastrointestinal disorders					
	Abdominal pain	25 (10.2)	2 (3.4)	3 (6.8)	5 (4.9)
	Abdominal pain upper	4 (1.6)	2 (3.4)		2 (2.0)
	Diarrhoea	29 (11.8)	3 (5.2)	2 (4.5)	5 (4.9)
	Dyspepsia	8 (3.3)	2 (3.4)	1 (2.3)	3 (2.9)
	Nausea	83 (33.7)	2 (3.4)	4 (9.1)	6 (5.9)
	Vomiting	87 (35.4)		2 (4.5)	2 (2.0)
General disorders and administration site conditions					
	Asthenia	9 (3.7)	4 (6.9)		4 (3.9)
	Injection Site Pain		5 (8.6)		5 (4.9)
	Pain	18 (7.3)	4 (6.9)		4 (3.9)
	Pyrexia	27 (11.0)	12 (20.7)	2 (4.5)	14 (13.7)
Infections and infestations					
	Ecthyma	3 (1.2)	2 (3.4)		2 (2.0)
	Infection	8 (3.3)	2 (3.4)		2 (2.0)
	Lymphangitis	8 (3.3)			
Injury, poisoning and procedural complications					
	Injury	9 (3.7)	2 (3.4)		2 (2.0)
Metabolism and nutrition disorders					
	Anorexia	6 (2.4)	1 (1.7)		1 (1.0)
	Anorexia and bulimia syndrome	2 (0.8)	2 (3.4)		2 (2.0)
	Decreased appetite	6 (2.4)	1 (1.7)		1 (1.0)
Musculoskeletal and connective tissue disorders					
	Arthralgia	5 (2.0)	23 (39.7)	1 (2.3)	24 (23.5)
	Back pain	5 (2.0)	1 (1.7)		1 (1.0)
	Myalgia	2 (0.8)	7 (12.1)	1 (2.3)	8 (7.8)
Nervous system disorders					
	Dizziness	19 (7.7)	4 (6.9)		4 (3.9)
	Headache	73 (29.7)	20 (34.5)	9 (20.5)	29 (28.4)

Table 35: Adverse Events \geq 2% incidence– CL studies Soto/Z020A/Z020B/3168/3092 Miltefosine-Treated Adolescents/Adults (>11 years) (Continued)

System, organ, class	Preferred Term ^a	Miltefosine All Doses N = 246 n (%)	Antimony N = 58 n (%)	Placebo N = 44	Controls N = 102 n (%)
Respiratory, thoracic and mediastinal disorders					
	Cough	2 (0.8)	2 (3.4)		2 (2.0)
	Influenza	5 (2.0)	5 (8.6)		5 (4.9)
	Pharyngitis	6 (2.4)	1 (1.7)	1 (2.3)	2 (2.0)
Skin and subcutaneous tissue disorders					
	Pruritus	9 (3.7)	1 (1.7)		1 (1.0)
	Rash		2 (3.4)		2 (2.0)

^a The AEs include all levels and all relationships. Only count one subject per SOC/Preferred Term.

An AE that should not be related to either drug, pyrexia, was of approximately equal percentage in miltefosine vs. the combined comparator patients.

AEs related to the gastrointestinal system (abdominal pain, diarrhea, nausea, and vomiting) were more frequent in the miltefosine arm.

Injection site pain and arthralgias/myalgias were more frequent in the Glucantime arm.

The severity grade for vomiting and diarrhea in miltefosine patients was specifically elicited in studies [3168](#), [Z020A](#), and [Z020B](#). Vomiting was CTCAE grade 1 in 80%, 62%, and 61% of cases in these respective trials. Diarrhea was CTCAE grade 1 in 100%, 75%, and 87% of cases, respectively.

[Table 36](#) shows the relationship between gastrointestinal AEs and dose on a mg/kg/day basis. The percentage of patients with gastrointestinal AEs did not significantly increase between dose groups ($p = 0.37$ (chi-square test)).

Table 36: Toxicity vs. Dose – CL studies Soto/Z020A/Z020B/3168 Miltefosine-Treated Adolescents/Adults (>11Years)

Dose Group (mg/kg/day)	N	No GI AE Present n (%)	GI AE Present n (%)
1.7-2.2	43	15 (34.9)	28 (65.1)
2.3-2.8	135	49 (36.3)	86 (63.7)
2.9-3.3	27	6 (22.2)	21 (77.8)

8.4.1 Clinical Laboratory Findings

[Table 37](#) integrates the changes in creatinine and liver function values in all miltefosine CL patients receiving the target dose and in comparators.

Table 37: Integrated Summary of Creatinine and Liver Function Changes for Adolescent/Adult Patients in CL Trials

Study	Soto	Z020A	Z020B	3092 (groups 3+4)	3168	Integrated
Study Drug	Miltefosine	Miltefosine	Miltefosine	Miltefosine	Miltefosine	Miltefosine
Creatinine						
% patients elevated end therapy	10	10	5	24	33	19.6
% CTCAE grade 1	100	75	100	67	94	88.8
Comparator	Glucantime	Glucantime	Glucantime	(none)	Placebo	Comparator
Creatinine						
% patients elevated end therapy	5	5	0		9	5.7
% CTCAE grade 1	100				100	100.0
Study Drug	Miltefosine	Miltefosine	Miltefosine	Miltefosine	Miltefosine	Miltefosine
AST and/or ALT						
% patients elevated end therapy	0	25	5	20	18	14.4
Comparator	Glucantime	Glucantime	Glucantime	(none)	Placebo	Comparator
AST and/or ALT						
% patients elevated end therapy	0	20	15		29	19.4

Creatinine was elevated more frequently in the miltefosine groups than in the comparator groups, whether antimony or placebo. Twenty percent of miltefosine patients demonstrated elevated creatinine at the end of therapy, but 89% of the elevations were CTCAE grade 1.

AST/ALT was not more frequently elevated in the miltefosine groups compared to the comparator groups, whether antimony or placebo.

10. SERIOUS ADVERSE EVENTS: DEATHS, OTHER SAES, PREMATURE DISCONTINUATIONS

10.1. Deaths and other SAEs

As of November 18, 2011, eight Periodic Safety Update Reports (PSUR) for Impavido® 10 mg and 50 mg capsules has been compiled for and submitted to the German Regulatory Authorities (Bundesinstitut für Arzneimittel und Medizinprodukte) post registration of miltefosine in Germany.

Based on the total patient exposure reported in previous PSURs, approximately 90,693 patients have received miltefosine world-wide from its launch in 2002 to the data-lock date of PSUR No. 8.

SAEs including deaths reported in the study reports for Phase 1 to 3 studies, preliminary reports on the Phase 4 studies in India and Nepal, and the 8 PSURs post launch are tabulated in [Table 38](#).

SAEs thought at least possibly attributable to miltefosine treatment are in italics.

Table 38: SAEs in Developmental Trials and Post Marketing

Source	No. SAE	Details
Study No. 0033 (VL)	2	<i>Creatinine elevation in patient receiving 250 mg daily</i> <i>diarrhea, renal impairment, cardiac arrest and death in patient receiving 250 mg daily</i>
Study No. 3089 (VL)	(none)	
Study No. 3091 (VL)	(none)	
Study No. 3109 (VL)	(none)	
Study No. 3127 (VL)	(none)	
Study No. 3206 (VL)	1	Anorexia, anemia, pneumonia
Study No. 3154 (VL)	6	Paresthesia, hemiplegia <i>Stevens-Johnson Syndrome</i> Melana and thrombocytopenia Malaria Meningitis Seizure
Z013 (Indian Phase 4) preliminary report (VL)	4	Abdominal pain and swelling with death on day 9 Bloody diarrhea, present prior to VL, continued with death on day 8 <i>Macular skin rash</i> <i>Nausea, vomiting, diarrhea</i>

Table 38: SAEs in Developmental Trials and Post Marketing (Continued)

Source	No. SAE	Details
Z013b (Nepal phase 4) preliminary report (VL)	3	<i>Creatinine increase</i> Septicemia after a foot abscess Death due to Loss of consciousness on day 9 of miltefosine, for a patient lost after 7 days of treatment
Study 3092 (CL)	(none)	
Study No. 3168 (CL)	(none)	
PSUR No. 1	3	Z022 (ML): death presumably due to intercurrent infection Z013b (Nepal VL): death for unknown reasons (already included under Z013b above) Agranulocytosis and <i>increase in creatinine</i> from Germany
PSUR No. 2	1	Z019 (Brazil VL): <i>renal impairment</i>
PSUR No. 3	1	Z019 (Brazil VL): <i>persistent vomiting</i>
PSUR No. 4	2	Anemia in an HIV coinfecting patient from Germany Z019 (Brazil VL): <i>hepatic and renal failure after miltefosine and AmBisome</i>
PSUR No. 5	15 ^a	Phase 4 Bangladesh: death (and diarrhea) 3 weeks after end of therapy Phase 4 Bangladesh: death (and erythema) 33 days after end of therapy Phase 4 Bangladesh: death (and hemoptysis) Phase 4 Bangladesh: death (and "senility") Phase 4 Bangladesh: death (and anemia) Phase 4 Bangladesh: death (and diarrhea) Seizure in Colombia Edema Edema and pneumonia in VL Loss of consciousness in VL <i>Migraine headache in VL</i> Renal failure in HIV coinfecting patients from Germany <i>Thrombocytopenia in Indian VL (3 cases in one literature report)</i>
PSUR No. 6	2	<i>Death after AmBisome and miltefosine in an Indian VL patient</i> <i>Death after AmBisome (test dose), miltefosine, cefpirome for presumed pneumonia in an Indian VL patient</i>
PSUR No. 7	(none)	

Table 38: SAEs in Developmental Trials and Post Marketing (Continued)

Source	No. SAE	Details
PSUR No. 8	9	<p>Death following anemia in VL (probably due to treatment failure)</p> <p>Hyperbilirubinemia in VL (thought unrelated by the PI)</p> <p>PKDL following miltefosine treatment for VL</p> <p>Erythema in PKDL patient</p> <p>Upper respiratory tract infection in VL patient</p> <p>Severe pneumonia in VL patient</p> <p><i>Creatinine massive increase in ML patient after Glucantime and miltefosine</i></p> <p><i>Erythema and necrosis in PKDL patient</i></p> <p>Hypertension</p>

^a PSUR gives total as "16", but only 15 cases are narrated.

Of the 49 SAEs, 17 SAEs were assessed as at least possibly related to treatment with miltefosine:

Study No. 0033: In this initial dose-ranging study, 2 patients with the highest administered dose of miltefosine had renal dysfunction thought related to drug.

Study No. 3154: The case of Stevens Johnson Syndrome was thought likely related to drug therapy.

Study No. Z013: The macular skin rash was thought possibly related to drug. The nausea, vomiting, diarrhea were thought possibly related to drug.

Study No. Z013b: The creatinine increase was thought possibly related to drug.

PSUR No. 1:

German patient: the creatinine increase was possibly attributable to drug.

PSUR No. 2:

Brazil VL: Patient participation in the study was interrupted because of renal toxicity and initial treatment failure. According to the investigator, the renal impairment was likely caused by miltefosine.

PSUR No. 3:

Brazil VL: A girl (5 years old) vomited prior to drug administration, then received drug, then had persistent vomiting and miltefosine was discontinued. Vomiting was likely attributable to drug.

PSUR No. 4:

Brazil VL: A 26 year old, who later was recognized to be a severe alcoholic since age 14, did not show improvement of fever after 1 week of miltefosine therapy. On Day 12 of therapy, the patient developed jaundice (total bilirubin 8.0 mg/dL and direct bilirubin 7.0 mg/dL). A moderate increase of aminotransferases, and a mild increase in creatinine (1.5 to 1.7 mg/dL) were observed. Miltefosine was stopped and rescue treatment started.

PSUR No. 5:

The case of “Migraine” was considered possibly related to drug, because vomiting and diarrhea in combination with possibly insufficient fluid intake may have caused some dehydration which may have contributed to the intensification of the pre-existing migraine headache.

Two of the 3 cases of thrombocytopenia were in patients in whom only miltefosine was administered; in the 3rd case, pentavalent antimony was also administered. In the 2 cases, the investigator thought that diminished platelets were related to miltefosine therapy.

PSUR No. 6:

The two SAEs of death were seen in patients with combination therapy. Contribution of miltefosine in the combined regimen to the SAEs is possible.

PSUR No. 8:

The creatinine increase was attributed both to miltefosine and to dehydration.

The case of erythema and necrosis was possibly attributed to a hypersensitivity reaction to drug.

Conclusions:

Attributable SAEs reported in Industry-sponsored clinical trials and post-marketing in PSURs almost entirely consist of events related to gastrointestinal dysfunction or renal dysfunction, and to skin reactions.

All attributable SAEs but two occurred in VL patients. For CL/ML, there was one instance of creatinine increase in a patient co-treated with Glucantime, and one instance of skin reaction.

Although reported SAEs may underestimate actual SAEs, it is of interest that there have been reports of 48 SAEs per 90,693 courses of treatment (0.05%) and 17 possibly attributable SAEs (including those of overdosage) per approximately 90,000 courses of treatment (0.02%).

10.2. Premature Discontinuations

The few premature discontinuations that occurred in pivotal trials are tabulated in [Table 39](#).

Table 39: Patient Premature Discontinuations by Study: Controlled Trials of Adolescents/Adults

Study	Drug	Premature Discontinuations (N)	Reason for Discontinuation		
			AE N (%)	Lack of efficacy N (%)	Other N (%)
3154 (VL)	Miltefosine	9	8 (89)		1 (11)
	Amphotericin B	3	3 (100)		
Z025 (VL)	Miltefosine	1	1 (100)		
	Pentavalent antimony	0			
3168 (CL)	Miltefosine	4	1 (25)		3 (75)
	Placebo	2			2 (100)
Soto (CL)	Miltefosine	0			
	Pentavalent antimony	0			
Z020A (CL)	Miltefosine	3			3 (100)
	Pentavalent antimony	0			
Z020B (CL)	Miltefosine	5			5 (100)
	Pentavalent antimony	4			4 (100)
Z022 (ML)	Miltefosine	0			

11. SAFETY TOPICS OF SPECIAL INTEREST

11.1. Visual Function

Studies in rats indicated a risk of retinal damage after prolonged oral use of miltefosine (no similar findings in dogs). Therefore, it is important to note that sophisticated electrophysiological studies in cancer patients revealed only asymptomatic changes in electrooculograms that were reversible even after prolonged oral use of miltefosine. These functional changes were not paralleled by an abnormality in any other parameter of the broad ophthalmologic screen. Sophisticated electrophysiological ophthalmologic examinations were not feasible in Indian patients; however, these patients were consistently monitored by ophthalmoscopy and assessment of visual acuity.

11.2. Male Fertility

Toxicological studies in rats have shown that miltefosine dose-dependently targeted male reproductive organs and suppressed fertility and reproductive performance. As mentioned, the effect of miltefosine on testis function and sperm viability in rats were reversible at a dose of 8.25 mg/kg/day. Because C_{\max} for rats receiving 10 mg/kg/day is approximately 40 µg/mL, which is the target C_{\max} for clinical dosing, the rat data suggest that reversible effects on the male reproductive system is a theoretical possibility.

The decision was made to investigate the potential impact of orally administered miltefosine on the fertility of male patients. As treatment phases of studies in VL in India were completed at that time, a dual track approach was chosen after discussions involving principal investigators and WHO/TDR:

1. Male subjects who had participated in clinical trials of miltefosine in India and who were aged 18 years and older should be re-assessed for reproductive performance in the post-study period, as a measure for possible long-term suppression of fertility.
2. Male patients with CL entering the ongoing [Study 3168](#) in Colombia should have sperm analyses before and after treatment with miltefosine to assess the risk of an immediate effect of miltefosine on sperm production and viability.

11.2.1. Reproductive Performance after Treatment for VL in India

Data addressing reproductive performance after miltefosine treatment comes from a retrospective study in former participants of therapeutic trials.

There were some methodological issues in this study. This was a retrospective study, based on the male participants in all VL studies conducted in Indian patients. Because of cultural reservations, re-invitation of former patients for sperm analysis was considered non-feasible; moreover, in the absence of reference data before drug exposure, interpretation of such results would have been difficult. Instead, the number of pregnancies that were generated by the former study participants was considered a feasible and meaningful endpoint for the purpose of such investigation. A minimal age of 18 years at the time of re-evaluation was selected as a meaningful cut-off limit. The data base was selected for such patients and for each study each center was provided with lists identifying the patients to be re-assessed. After information about the purpose of the re-evaluation, sexual activity and reproductive performance since the end of study were to be documented.

A total of 345 patients were identified in the data base that would match the eligibility criteria for this retrospective analysis.

In total, information for 341 of 345 (98.8%) former study participants was retrieved for the evaluation of reproductive performance in the post-treatment period. Assessments were done between 11 and 57 months after start of miltefosine treatment (median 34 months) and between 19 and 28 months after start of amphotericin B treatment (median 24 months). In total, 220 study participants were identified as "relevant population" for this fertility assessment. Of these, 197 had been treated with miltefosine and 23 with amphotericin B.

Table 40 summarizes the data for all studies:

Table 40: Male Reproductive Function in Phase 1 to 3 Indian VL Trials

Study/ Treatment	Number of Male Patients			Number of		
	Total ^a	Relevant population ^b	Proven fertility: any delivery or pregnancy ^c	Deliveries	Babies	Ongoing pregnancies ^d
0033/ miltefosine	30	16	16 (100%)	16	21	0
3089/ miltefosine	33	22	18 (82%)	18	23	0
3109/ miltefosine	64	39	24 (62%)	25	26	3
3127/ miltefosine	32	24	21 (88%)	20	21	1
3154/ miltefosine	141	96	56 (58%)	52	53	7
ALL/ miltefosine	300	197	136 (69%)	131	144	11
3154/ amphotericin B	41	23	12 (52%)	11	10	1

^a Total - total number of males meeting the eligibility criteria for the reproductive performance assessment

^b Relevant population - number of patients who were not without sexual partner and/or did not use contraceptives all of the time.

^c Proven fertility - number of patients for whose female partner at least one delivery or ongoing pregnancy has been reported; the percentage of proven-fertile, related to the "relevant population" shown in brackets.

^d Ongoing pregnancies - number of pregnancies that were reported as ongoing at the time of the assessment.

Overall 69% (136 of 197 males) of the "relevant population" of miltefosine-treated patients had proven maintenance of fertility, as documented by at least one delivery or ongoing pregnancy in their female partner.

In study 3154, miltefosine was compared with amphotericin B, and the proportion of males with delivery/pregnancy-proven fertility was similar for both treatment arms, being 58% and 52%, respectively.

Beyond protocol, center 3 provided spermogram results from 13 of the predominantly younger patients (12 patients treated with miltefosine, 1 patient treated with amphotericin B). In 10 of the 12 patients treated with miltefosine, the spermogram was completely normal with regard to sperm count, viability,

and morphology. One patient was reported with oligospermia but also with 2 generated pregnancies in the post-study period and thus can be considered as proven fertile. Finally, one patient, aged 35 years at treatment and 38 years at assessment of the spermiogram was found to have oligospermia, decreased sperm motility, and an increased percentage of abnormal (60%) or degenerated (25%) sperm. In the absence of pre-study childbirth or pre-study spermiogram data, the relevance of this observation remains unclear.

Participants were asked for congenital abnormalities or birth defects. One patient in study 3154 reported an abortion of a first pregnancy, which was followed by a currently ongoing second pregnancy. No malformations or other birth defects were noted.

In conclusion, male study participants were found to show a high reproduction rate in the post study period, both for patients treated with miltefosine and patients treated with amphotericin B.

In all, the results of this retrospective re-evaluation provide rather strong evidence that orally administered miltefosine is unlikely to induce infertility in male patients treated for leishmaniasis.

11.2.2. Sperm Viability in Patients Treated for CL

[Study 3168](#) was a multicenter, double-blind, placebo-controlled trial of orally administered miltefosine (100 mg/day for 28 days) in patients with CL. Patient recruitment for this trial was completed in Guatemala but was ongoing in Colombia at the time when sponsor and WHO/TDR concluded that the potential impact of oral treatment with miltefosine on male fertility should be investigated prospectively. The study procedures were amended to include spermiograms according to the study flow chart shown in [Table 41](#).

Table 41: Flow Chart for Spermiograms – Study 3168

	Visit	1	2	3	4	5	6
Assessment	Day	Before	Weekly during treatment (day 7, 14, 21)	Day 28 or end of treatment	2 weeks after end of treatment	2 month after end of treatment	6 month after end of treatment
Spermiogram (male patients)		X			X		X

Spermiograms were to assess the following sperm characteristics: density, progressive motility, morphology. Recruitment of patients for the amended study procedure turned out to be more difficult than anticipated. Patients were reluctant to consent in sperm collection primarily because of religious reasons. In addition, female study personnel members were replaced with males in order to reduce psychological barriers; as a consequence, completion of the trial was significantly delayed.

Spermiograms were performed in 15 patients (4 placebo, 11 miltefosine) at center 1. The examinations were performed at screening, 2 weeks after end of treatment and in 11 patients additionally after 6 months of follow up. [Table 42](#) summarizes the results:

Table 42: Spermiogram Data – Study 3168

Variable	Treatment	N	Values			Changes to Baseline	
			Screening	+2 weeks	+6 months ^a	+2 weeks	+6 months ^a
Volume	Placebo	4	2.6	1.9		-0.8	
[mL]	Miltefosine	11	3.2	2.3	3.3	-1.0	-0.1
Liquefaction	Placebo	4	23.8	30.0		6.3	
Time [min]	Miltefosine	11	23.4	23.2	16.5	-0.2	-7.2
Concentration	Placebo	4	76.3	106.3		30.0	
[1,000,000/mL]	Miltefosine	11	64.9	79.9	82.1	15.0	14.8
Progress. Motility	Placebo	4	60.0	57.5		-2.5	
of grade IV [%]	Miltefosine	11	49.1	54.5	57.5	5.5	7.5
Sperms alive	Placebo	4	93.3	91.0		-2.3	
[%]	Miltefosine	11	92.8	94.6	94.6	-1.5	1.9
Normal	Placebo	4	59.8	64.3		4.5	
Morphology [%]	Miltefosine	11	70.9	62.3	66.8	-8.6	2.7

^{sa} N=9-10 for miltefosine, N=1 for placebo (not shown).

A comparison of observed changes between treatments is problematic due to the small number of placebo patients investigated and a generally high variation. The direction of the changes for placebo and miltefosine differed for the rates of sperms with a progressive motility of grade IV (highest grade = highest motility) and the rates of sperms with normal morphology. In both cases, however, larger differences between groups were observed at screening so that subsequent changes may represent a "regression to the mean", rather than a specific effect of the treatment. In all, these data support the assumption that a 28-day course of oral miltefosine in human patients has no clinically relevant effect on sperm viability or on spermatogenesis.

11.2.3. Epididymo-orchitis

In one of the 7 pivotal trials ([Study Z020A](#)), there were 4 cases of mild testicular pain in the adolescent/adult miltefosine group which in each case the Investigators did not attribute to drug. The symptoms lasted for 1, 1, 1, and 6 days, and in each case was associated with infection of a host organ.

Epididymo-orchitis in persons with normal renal anatomy has been thought to be due to bacterial infection such as with *Chlamydia trachomatis* or *N. gonorrhea* ([Trojan 2009](#)). Another view is that epididymitis is mostly a post-infectious inflammatory phenomenon, since serology revealed significantly elevated titers to *M. pneumoniae* (53% vs 20%), enteroviruses (62.5% vs. 10%) and adenoviruses (20% vs. 0%) in epididymitis subjects vs controls ([Somekh 2004](#)). For postinfectious epididymitis, symptoms resolved in 1 to 7 days ([Somekh 2004](#)).

In the present study, symptoms of epididymitis occurred for 6 days concurrent with a urinary tract infection, for 1 day during the 3rd or 4th week of continued therapy, or for 1 day on the last day of therapy of this drug with a half-life of 7 days. The time to resolution in the presence of continued miltefosine therapy suggest that the present events are unlikely due to miltefosine. The case with 6 days of symptoms was likely caused by the concurrent urinary tract infection. The 3 other cases with 1 day of

symptoms are likely due to a post-infectious inflammatory reaction. The clinical staff's interpretation that each event was unrelated to miltefosine treatment seems valid.

Because there were a total of 4 events per 246 CL patients investigated at 2.5 mg/kg/day, epididymo-orchitis is listed as one of the more than 50 AEs that occur with an incidence of <2% and for which the relationship to drug administration is unknown.

11.3. Females of Child-bearing Potential

Because of the teratogenicity of miltefosine in toxicological studies, pregnant and lactating women were excluded from all clinical studies with miltefosine. Use of miltefosine in female patients with child-bearing potential was allowed provided a pre-therapeutic pregnancy test was negative and patients consented in using appropriate contraceptive measures during treatment and for 2 months beyond the end of the treatment period.

None of the follow-up evaluations in Phase 1 to 3 studies revealed an inter-current pregnancy warranting further follow-up. A total of 3 pregnancies, however, were reported from the Phase 4 studies in India and Nepal with an estimated conception date during the period for which prevention of pregnancy was indicated (Table 43). Specifically the Indian Phase 4 trial under sponsorship of the Indian Council of Medical Research included the monitoring for unexpected pregnancies and their outcome as a safety objective. Because of the low number of observations, the uneventful completion of these pregnancies does not allow for a change in the contraindication for miltefosine in pregnant females or in the proposed period for contraception beyond the end of treatment.

Table 43: Pregnancy Outcomes

Investigator/ Study	Patient ID/ Patient No.	Treatment Period	Estimated Time of Conception	Pregnancy Outcome
Dr. Nath (ZO13, India)	(b) (6) /52	8 Feb - 8 Mar 2003	2 weeks after end of treatment period	(b) (6) :healthy child birth (gest. wk: 39)
Dr. Mukherjee (ZO13, India)	(b) (6) /312	27 Apr – 19 May 2003	3 months after end of treatment period	(b) (6) : healthy child birth (gest. wk: 40)
Dr. Rijal, (ZO13b, Nepal)	(b) (6) /103	21 Mar – 17 Apr 2004	3 Apr 2004 (calculated from ultrasound)	(b) (6) healthy child birth (gest. wk: 42)

11.4. Patients with Impaired Renal Function

Patients with pre-existing impairment of renal function, defined as “serum creatinine or blood urea nitrogen (BUN) ≥ 1.5 times upper limit of normal range” were excluded from clinical trials as both pre-clinical studies and studies in cancer patients had previously shown a nephrotoxic potential of miltefosine. Therefore, data on the tolerability of miltefosine in patients with pre-existing impairment of renal function are not available.

On the other hand, data from the controlled Phase 3 trial in India (Study 3154) and the pivotal CL trials indicate that the risk of developing a clinically relevant nephrotoxicity at the recommended dose of miltefosine is low for patients meeting entrance criteria.

11.5. Patients with Impaired Liver Function

VL is a disease that is frequently associated with elevated serum levels of liver enzymes. Treatment of VL patients with miltefosine was frequently associated with a transient elevation in liver enzyme levels. The increase in AST one week after treatment start is probably related to residual parasite load. The lack of a clear dose-response relationship in the frequency of remarkable liver function abnormalities does not point to a need of a dose adjustment or of closer monitoring of laboratory parameters in relation to the degree of pre-existing abnormalities within the range seen at entrance in the reported clinical trials.

In the placebo-controlled CL [Study 3168](#), the miltefosine group and the placebo group demonstrated similar increases in liver function enzyme levels.

11.6. QTc Inteval/Cardiogenic Potential

In [Study 3154](#), ECGs were recorded at baseline, and at the end of each of the 4 weeks of treatment for miltefosine and amphotericin B as comparator. Absolute values of heart rate and QT are shown in [Table 44](#). It is apparent that mean increases in QTc for miltefosine were less than 30 msec and less than the mean increases for patients on the comparator agent.

Table 44: Changes in ECG Parameters in Study 3154

Parameter	Treatment	Mean Baseline Value	Mean differences to baseline			
			Day 7	Day 14	Day 21	End of treatment
Heart rate [1/min]	Miltefosine	99.35	-9.39 ^a	-11.28 ^a	-11.75 ^a	-11.77 ^a
	Amphotericin B	100.21	-17.40 ^a	-14.53 ^a	-19.77 ^a	-18.20 ^a
PQ time [msec]	Miltefosine	144.53	1.76	3.16 ^a	1.66	1.13
QT time [msec]	Miltefosine	348.35	14.40 ^a	18.44 ^a	15.12 ^a	18.37 ^a
	Amphotericin B	340.91	39.35 ^a	27.35 ^a	33.18 ^a	30.60 ^a

^a p-value sign rank test (two sided) compared with baseline: <0.01.

11.7. Patients with Severe Concomitant Diseases and Conditions

Most clinical protocols excluded “Any non-compensated or uncontrolled condition, such as active tuberculosis, malignant disease, severe malaria, HIV, or other major infectious diseases”. Miltefosine was however used in comparison to pentavalent antimony in the frequently HIV-coinfected population in Ethiopia.

11.8. Longer Term Use

Although the duration of treatment with miltefosine is proposed to be 28 days, in the clinic, mis-use with a longer period of dosing might occur, and literature reports of > 28 days use are relevant in this regard.

11.8.1. Diffuse Cutaneous Leishmaniasis due to *L. amazonensis* in Venezuela

Sixteen patients with DCL were treated with miltefosine, 2.0–2.5 mg/kg/day, for variable periods of time (75–218 days; [Study Z027](#)). Patients were hospitalized for the first month and evaluated every 2 weeks until the termination of treatment with routine laboratory chemistry and AEs. Further cycles of treatment were given in some of these patients, particularly after suspension of treatment was followed by relapse.

Side-effects were observed in four patients: two complained of nausea and vomiting and reduced the dose without consultation, with improvement in symptoms. One patient presented dizziness on the second day of treatment. On Day 20 one patient presented urticaria, that improved with systemic antihistamines. None presented alterations of laboratory parameters during the study. One patient, a 15-year-old boy, died during the course of this study with a clinical diagnosis of pneumonia. He had no hematological, hepatic or renal alterations.

11.8.2. PKDL in India

Miltefosine was administered at a target dose of 2.5 mg/kg/day for 8 weeks (8 week group) or 12 weeks (12 week group) (TDR [Study PKDL](#)). A total of 35 patients were randomized between the two treatment groups in equal allocation. The clinical type, day of onset, duration, and severity grade of AEs was determined during treatment. Entrance laboratory parameters were evaluated every two weeks during treatment. Severity was assigned using the CTCAE.

The mean weight of the patients was 51 kg thus when the patients received 2 of the 50 mg miltefosine capsules per day, a dose of 2.0 mg/kg/day was administered.

Evaluation of safety parameters is shown in [Table 45](#). For these patients, clinical abnormalities consisted of vomiting reported by 4 patients in each group and one case of diarrhea. The duration of vomiting was one day for all but 2 patients. The severity of vomiting was CTC grade 1 for 6 patients and CTCAE grade 2 for 2 patients. Laboratory abnormalities were limited to one case of elevated bilirubin in the 8 week group.

In summary, gastrointestinal AEs occurred in 9 of the 35 patients (26%) in whom they were recorded. All events were CTCAE grade 1 or 2, and lasted for 1 day in 6 of 9 cases.

Table 45: Adverse Events in PKDL Trial

Group	Adverse event	Number of patients	Duration (days)	Day of onset	CTCAE grade
12 week	Vomiting	4	1, 1, 1, 5	48, 52, 69, 76	1, 1, 1, 2
	Diarrhea	1	4	76	1
8 week	Vomiting	4	1, 1, 1, 5	38, 32, 39, 33	2, 1, 1, 2
	Elevated total bilirubin	1	12	16	2

11.8.3. Conclusion on Longer Term Use of Miltefosine

Extension of the dosing period beyond 28 days did not meaningfully increase adverse reactions.

12. BENEFITS AND RISKS CONCLUSIONS

12.1. Conclusions on Benefits

12.1.1. Visceral Leishmaniasis

A series of dose-finding studies established a dosage regimen (target of 2.5 mg/kg/day for 28 days) for the oral use of miltefosine which proved to be safe and effective in the treatment of VL due to *L. donovani* in adequate and well controlled trials in patients ≥ 12 years (Study 3154 for Indian VL, [Study Z025](#) for Ethiopian VL). Miltefosine can be recommended for VL due to *L. donovani* or for VL acquired in regions for which epidemiologic data indicate that *L. donovani* is the cause of disease. There is insufficient data on other species causing VL to make a recommendation in such cases.

Compared with amphotericin B, the active comparator drug in the controlled trial for Indian VL, miltefosine was non-inferior to the intravenous comparator treatment by a justified margin. Considering the advantage in feasibility for oral treatment with miltefosine, oral miltefosine is proposed as superior overall to amphotericin B for *L. donovani*. Miltefosine was not associated with drug-induced fever or rigors; these adverse drug reactions of the comparator drug commonly required symptomatic treatment.

Compared with pentavalent antimony, the active comparator drug in the controlled trial for Ethiopian VL, miltefosine was non-inferior to the comparator treatment by a justified margin and superior to the comparator treatment in the death rate for this population presumed to be highly co-infected with HIV. Considering both endpoints and the advantage in feasibility for the oral treatment with miltefosine, oral miltefosine is proposed as superior overall to pentavalent antimony for *L. donovani*, including in immunocompromised populations.

The Phase 4 studies in the Indian subcontinent demonstrate that oral miltefosine can be given on an out-patient basis and can be taken by the patient at home. The ability to minimize/avoid clinic visits is a decided advantage compared to the need for supervised administration of the comparators, the standard agent pentavalent antimony which is administered intramuscularly or intravenously, and amphotericin B formulations which are administered intravenously.

All Phase 1 to 3 studies enrolled patients with parasitological verification of VL diagnosis, as well as evaluations at 6-month post-treatment follow-up for definite cure. This allowed for dose-response and sub-group analyses of efficacy data across these studies. Patients with newly diagnosed disease and patients who failed to be cured from the disease by prior therapy, commonly with pentavalent antimonial drugs, received the same dosages of oral miltefosine and there was no difference in cure rate with regard to treatment history.

The reduction in parasite load in repeated biopsies was paralleled by the resolution of the typical signs and symptoms of this disease: regression of splenomegaly and hepatomegaly, resolution of fever, and recovery from anemia, thrombocytopenia, and leukocytopenia.

To achieve the target dose of 2.5 mg/kg/day in the indicated population of adolescents/adults weighing ≥ 30 kg, the two dosing choices are 2 or 3 of the 50 mg capsules daily.

Because daily doses much higher than 3 mg/kg might result in less tolerance, the transition from 2 to 3 capsules is recommended to occur at 45 kg so that the maximum daily dose is 3.3 mg/kg/day.

The recommended daily dose therefore is:

30 - 44 kg: two 50 mg capsules daily (3.3 – 2.3 mg/kg/day)

≥45 kg: three 50 mg capsules daily (≤3.3 mg/kg/day)

12.1.2. Cutaneous and Mucosal Leishmaniasis

A dose-finding study ([Study 3092](#)) established a dosage regimen (target of 2.5 mg/kg/day for 28 days) for the oral use of miltefosine which proved to be safe and effective in the treatment of CL in adequate and well controlled trials in patients ≥ 12 yrs ([Study 3168](#)) and the three investigator initiated studies ([Study Soto](#), [Study Z020A](#), [Study Z020B](#)).

CL is caused by a wide range of *Leishmania* species, and proof of drug efficacy by prospective studies in each species would be practically impossible. Activity of oral miltefosine has been shown in studies including members of the *L. viannia* complex of species---*L. v. panamensis*, *L. v. braziliensis*, *L. v. guyanensis*---in the New World, and can be recommended for disease due to those species or acquired in regions for which epidemiological data suggest that those species are the cause of the disease. There is insufficient data for other species to make recommendations in such cases.

CL patients, with a mean weight of approximately 60 kg, generally received 3 of the 50 mg capsules to achieve the target dose and there is no clinical trial experience with 4 of the 50 mg capsules per day. To achieve the target dose of 2.5 mg/kg/day in the indicated population of adolescents/adults weighing ≥30 kg, the two dosing choices are 2 or 3 of the 50 mg capsules daily. Because daily doses much higher than 3 mg/kg might result in less tolerance, and in conformity with the VL recommendations, the recommended daily dose for CL is:

30 - 44 kg: two 50 mg capsules daily (3.3 – 2.3 mg/kg/day)

≥45 kg: three 50 mg capsules daily (≤3.3 mg/kg/day)

The same dosage regimen as proposed for CL has also been shown to be highly active in ML, a serious, non-self-curing disseminated sequelae to CL.

12.2. Conclusions on Risks

Irrespective of the type of leishmaniasis treated, oral miltefosine was associated with episodes of gastrointestinal signs and symptoms that were usually mild to moderate and limited to periods of 1-2 days, without prophylactic or symptomatic treatment. A patient should be advised to take adequate fluid intake in case of prolonged gastrointestinal intolerance, in order to avoid dehydration and to reduce the risk of renal function impairment.

Increasing the dosage of miltefosine above the recommended dose, which was tested only in VL patients, led to a higher incidence and severity of reactions. In a few VL patients, dosages up to 250 mg/day were used in clinical trials. Acute accidental or intentional over dosage is expected to cause vomiting and/or diarrhea as leading symptoms. While vomiting and/or diarrhea should limit the systemic uptake of the active substance in case of an over dosage, these reactions could lead to dehydration requiring appropriate fluid replacement.

Oral use of miltefosine was occasionally associated with effects on renal function (VL and CL patients) and liver function (VL patients) which were reversible after the end of treatment and often even during treatment. Compared with amphotericin B, increases in creatinine and BUN in VL patients were less severe after the use of miltefosine. As a precaution, monitoring of VL patients for renal and liver function during treatment with miltefosine is recommended. In CL patients, laboratory tests did not reveal

clinically relevant abnormalities that would have an impact on the continuation of treatment with miltefosine, although clinically non-relevant increases in creatinine did occur. Therefore, in CL patients the routine monitoring of renal and liver functions parameters does not appear to be necessary in the absence of clinical signs or specific risk factors, although monitoring of creatinine levels would not be inappropriate.

Oral use of miltefosine at the recommended dosage was not associated with clinically relevant morbidity as is known to occur with currently available standard treatments. For example, miltefosine did not induce myalgias/arthralgias or cardiotoxicity (compared with pentavalent antimonials), nor infusion-related fever and rigors or other immediate reactions (compared with amphotericin B formulations).

Toxicological studies have shown an impairment of reproductive function in male rats. Therefore, reproductive performance of 300 male Indian subjects who had received miltefosine in clinical trials was evaluated. Results suggest the absence of a clinically relevant risk for an impairment of fertility in male patients treated with miltefosine. Data on sperm viability after use of miltefosine support this conclusion.

No adequate data are available to support the use of miltefosine in pregnant women. Studies in animals have shown reproductive toxicity; the potential risk for humans is unknown, although 3 cases of healthy childbirths with conception in the immediate post-dosing period have been reported. Because of the low number of events, the contraindication for the use of miltefosine during pregnancy or in the immediate post-dosing period must be maintained. Female patients should be advised to use contraceptive measures during treatment and for a period of 3 months after the end of treatment. The recommended period of 3 months takes into account that after that waiting period, the plasma concentration of miltefosine in patients has fallen to the plasma concentration below the no-effect-dose level for teratogenicity in rats.

The efficacy of oral contraception may be compromised after episodes of vomiting. If necessary, suitable alternative methods of contraception must be used. In case of a suspected pregnancy, the patient should be advised to immediately contact her physician for a pregnancy test and a discussion of risks. The patient must be informed accordingly by her physician.

Sjögren-Larsson Syndrome (SLS; congenital ichthyosis), a rare congenital disease, is associated with a block in the oxidation of long chain fatty aldehydes that leads to an accumulation of hexadecanol, a putative intermediate in the metabolic degradation of miltefosine. As there is a risk of disease exacerbation, SLS should be considered as a contraindication for the use of miltefosine.

Since miltefosine did not markedly induce hepatic CYP3A assayed in rats, miltefosine is unlikely to induce oxidative metabolism of other drugs metabolized by CYP3A (e.g., contraceptive hormones). In compassionate-use HIV patients, miltefosine was well tolerated when given concomitantly with antiretroviral drugs and, although in few patients only, in combination with other antileishmanial drugs, suggesting the absence of a major risk for adverse drug interactions.

12.3. Other Conclusions and Recommendations

A limited number of VL patients were successfully treated with a miltefosine regimen using a dosage of 100 mg/day (target of 2.5 mg/kg/day) for 3 weeks ([Study 3127](#)). The confirmatory trial ([Study 3154](#)), however, used a 4-week (28-day) treatment course and only for this duration of treatment has proof of efficacy been shown in a sufficiently large number of patients. Therefore, treatment for a period of 28 days is recommended. Considering the risk of patient non-compliance and incomplete systemic uptake of drug due to transient episodes of vomiting or diarrhea, the treatment duration of 28 days may provide a beneficial safety margin for therapeutic efficacy.

Rapid resolution of typical signs and symptoms of VL, such as fever, splenomegaly, and hepatomegaly may tempt a patient to discontinue treatment prematurely. Patients should be seriously advised to complete the treatment course, in order not to increase the risk of treatment failure.

Adequate and well-controlled trials in CL, and the trial in ML, used a treatment duration of 28 days. Therefore, treatment for a period of 28 days in CL and ML is also recommended.

Delay of drug intake or failure to take a single or a few consecutive doses should not be compensated by an increase in subsequent doses. The long terminal elimination half-life will most likely prevent an immediate drop in drug concentration. Patients who missed doses should be advised to extend the dosing period accordingly.

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