Treatment of Leishmaniasis with Impavido® (Miltefosine): Higher-Weight Patient Registry

Protocol No. IMP 2127-4

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1 LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
AE	adverse event
AST	Aspartate aminotransferase
CL	cutaneous leishmaniasis
FDA	Food and Drug Administration
HX	History
IND	Investigational New Drug Application
IRB	Institutional Review Board
kDNA	kinetoplast minicircle deoxyribonucleic acid
ML	mucosal leishmaniasis
L.	*Leishmania*
MRHD	maximum recommended human dose
NDA	New drug application
PI	Principal Investigator
PL	Product Label
PMR	Post Marketing Requirement
US	United States
VL	visceral leishmaniasis
WHO	World Health Organization

2 STUDY SCHEDULE OF ASSESSMENTS

Parameter	Study Time Period				
	Screening	End of Treatment Period	1 Month Post Treatment	3 Months Post Treatment	6 Months Post Treatment
Consent	X				
Demographics (gender/age/weight/race)	X				
Leishmaniasis Hx	X				
Concomitant Diseases	X	X			
Miltefosine treatment	(a)	X			
Clinical Laboratory Tests	X (b,c)	X(b,c)	X (c)	X (c)	X (c)
Concomitant Medications	X	X			
Adverse Events	X	X			
Efficacy		X	X	X	X

(a): Patients may contact the Registry after having been administered at least one dose of miltefosine
(b): AST and creatinine at screening and end of treatment; white blood cells (WBC), hemoglobin, and platelet count for patients with VL at all time

3 SYNOPSIS

Impavido® (miltefosine) was approved in the United States (US) in March 2014 for the treatment of visceral, cutaneous, and mucosal leishmaniasis due to specified *Leishmania* species. Impavido is the first drug approved in the US for cutaneous or mucosal leishmaniasis, and is the only oral drug worldwide that is generally effective for the leishmaniases.

Since oral miltefosine is administered at 2 capsules for day to patients of 30-44 kg and 3 capsules per day to patients > 44 kg, in each weight bracket, higher weight patients will receive less drug on a mg/kg basis than lighter patients. For example, patients who weigh 45 kg and receive 3 capsules per day will receive 3.3 mg/kg/day whereas patients who weigh 90 kg and receive 3 capsules will receive 2.0 mg/kg/day.

Whether higher-weight US patients will have efficacy rates that are lower on an absolute basis is unknown.

Objective: The purpose of this observational study is to fulfill PMR 2127-4: implement a higher-weight-patient registry for the time period Mar 2015-Mar 2020.

Study Design: This study is a prospective observational study in which patients undergoing treatment for leishmaniasis with Impavido in the US and who weigh > 75 kg can volunteer to provide information about their clinical response to treatment up to 6 months after the start of treatment.

Population: Leishmaniasis patients treated with Impavido who weigh more than 75 kg.

Drug Product:
Drug name: Impavido (50 mg capsules).
Dosing regimen: as per the Impavido Product Label

Study Procedures: Patients who weigh more than 75 kg will become aware of the Impavido Higher-Weight Patient Registry via the Impavido website. By calling 1-866-588-5405, the patient will be connected to the Impavido Higher-Weight Patient Registry Coordinating Center. A trained staff member will acquaint the patient with the goals and procedures of the study. If the patient tentatively agrees to participate in the study over the telephone, the patient will be mailed information forms, the Consent/Assent Forms, and the Consent for the patient's physician to release medical information. Receipt of the two signed Consent and/or Assent Forms by the Coordinating Center will signify patient consent. The Coordinating Center will contact the patient's physician at the end of treatment, and at 1, 3, and 6 months after completing treatment, to collect data on efficacy and adverse effects (only during treatment).

Sample Size and Study Duration: Estimated 3-10 patients per year for 5 years.

Outcome Parameters:
Efficacy
Adverse effects

Analysis: Baseline data, compliance to prescribed treatment, and outcomes will be reported for individual patients and for all patients.

4 INTRODUCTION AND RATIONALE

4.1 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.

According to the World Health Organization (WHO), *Leishmania* infection is endemic in 98 countries or territories with a yearly incidence of 0.5 million cases of visceral leishmaniasis (VL) and l.5 million cases of cutaneous leishmaniasis (CL) (WHO 2010).

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. 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 *Leishmania (L). donovani* in India and Africa, *L. infantum* in Europe and the Mediterranean, and *L. infantum chagasi* in the New World.

In VL, Sudden onset of fever with rigor and chills herald the onset of illness, which may subside to recur again. 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 quite 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. VL and coinfection with HIV or other immunocompromising diseases is increasingly a serious health threat.

CL generally presents as a papule that enlarges to a nodule and if it ulcerates, does so over 1 to 3 months. 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 anybody 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, ulcerative lesions are most common. In the Old World (the Mediterranean, North and Sahelian 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.

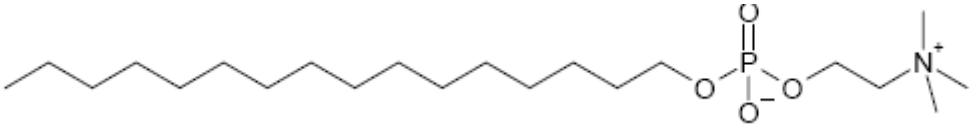
Mucosal disease (ML) in the New World may result from dissemination of cutaneous organisms (particularly *Leishmania* species of the subgenus *Vianna*: *L. (v).braziliensis*, *L.(v). guyanensis* and *L.(v) panamensis*) to the nares, nasal septum, palate, pharynx, and larynx. Mucosal disease causes a progressive destruction of the mucosa, the cartilage and bones of nose and pharynx, leading to a 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. Recently, it was shown that asymptomatic infection of the mucosal membranes is common for CL patients infected with members of the *L. viannia* subgenus. 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 deoxyribonucleic acid (kDNA) examined 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.

4.2 Miltefosine

4.2.1 Structural Formula

Miltefosine (hexadecylphosphocholine) is a phosphatidylcholine analogue. The structural formula of miltefosine is:



4.2.2 Worldwide Registration

The drug was registered in India in 2002 and in Germany in 2004 to treat visceral leishmaniasis. Impavido was registered in Columbia in 2005 to treat visceral and cutaneous leishmaniasis, and post-2005 to treat CL (and by extension ML) in many other countries in the Americas.

4.2.3 US Registration and Indications [Impavido PL, 2014]

On 19 Mar 2014, miltefosine (trade name Impavido®) was approved in the US for treatment of visceral, cutaneous, and mucosal leishmaniasis due to specific species of *Leishmania* (Impavido PL, 2014).

- Visceral leishmaniasis (VL) due to *Leishmania donovani*
- Cutaneous leishmaniasis (CL) due to *Leishmania braziliensis, Leishmania guyanensis,* and *Leishmania panamensis*
- Mucosal leishmaniasis (ML) due to *Leishmania braziliensis*

4.2.4 Recommended Dosage [Impavido NDA, 2014]

Each IMPAVIDO capsule for oral use contains 50 mg miltefosine.

Administer with food to ameliorate gastrointestinal adverse reactions.

30 to 44 kg: one 50 mg capsule twice daily for 28 consecutive days.

45 kg or greater: one 50 mg capsule three times daily for 28 consecutive days.

4.2.5 Higher-Weight-Patient Considerations

Since oral miltefosine is administered at 2 capsules for day to patients of 30-44 kg and 3 capsules per day to patients > 44 kg, in each weight bracket, higher patients will receive less drug on a mg/kg basis than lighter patients. For example, patients who weigh 45 kg and receive 3 capsules per day will receive 3.3 mg/kg/day whereas patients who weigh 90 kg and receive 3 capsules will receive 2.0 mg/kg/day.

In developmental studies for both VL and CL, there appeared to be a trend towards less efficacy with a lower mg/kg/day dose.

For VL, the cure rate in patients receiving < 2 mg/kg/day (86%) was less than the cure rate in higher mg/kg/day patients (Table 1).

Table 1: Cure Rate by Dose Level in VL Studies in India (mg/kg/day)

(Daily)Dose per kg body weight	Final parasitological cure, ITT population[a]						All
	No		Yes		Missing/ not assessable		
	n	%	n	%	n	%	n
<2 mg	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

For CL, there was a trend towards a lower cure rate in patients receiving a lower mg/kg/day dose (Table 2).

Table 2: Final Cure Rates with respect to Miltefosine Dose: Integrated Analysis of CL 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)

Whether higher-weight US patients will have cure rates that are low on an absolute basis is unknown.

4.3 Post Marketing Requirement [Impavido NDA, 2014]

4.2.1 FDA Post-Marketing Requirement # 2127-4:

"Conduct a descriptive study regarding efficacy outcome and adverse reactions in patients with leishmaniasis who weigh more than 75kg."

Final Protocol Submission: March 2015
Interim Report Submission: March 2016
Interim Report Submission: March 2017
Interim Report Submission: March 2018
Interim Report Submission: March 2019
Study Completion: March 2020
Final Report Submission: March 2021"

4.3.2 Previous Advice from the FDA Concerning this Requirement

"Conduct a descriptive study regarding efficacy outcome and adverse reactions in patients with leishmaniasis who weigh more than 75kg. This study should cover the period of five years following drug approval. Patient demographics (including age, weight, sex, race, prior medications, geographic area where *Leishmania* infection was acquired and immune status), total daily dosage of Impavido and mg/kg dosage received, treatment duration and site of infection should be described. Efficacy outcome and adverse reactions should be described. Yearly reports summarizing this data should be submitted." (information request of 24 Jan 2014)

4.4 Rationale for Protocol

In an operational sense, the purpose of this protocol is to fulfill post-marketing requirement 2127-4 in accord with the specifics of the information request of 24 Jan 2014.

In a scientific sense, the purpose of this protocol is to provide as much data as possible on the possible relationship of lower mg/kg daily doses of miltefosine and efficacy.

For these purposes, a Higher-weight Patient Registry will be instituted and maintained from March, 2015 to March, 2020.

5 STUDY OBJECTIVES

Implement a higher-weight-patient registry for Impavido in the US for the time period March, 2015 to March 2020.

6 STUDY DESIGN

This study is a prospective observational study in which patients undergoing treatment for leishmaniasis with Impavido in the US and who weigh > 75 kg can volunteer to provide information about their clinical response to treatment up to 6 months after the start of treatment.

7 STUDY SUBJECTS

7.1 Estimated Number of Subjects

Estimated 3-10 per year.

7.2 Inclusion Criteria

To be eligible for the study, the following must be answered "YES":

1. Did the subject give consent to collect data from her or her physician?
2. Was the subject treated for leishmaniasis with miltefosine?
3. Does the subject weigh more than 75 kg?

8 DRUG PRODUCT

Impavido (capsules of 50 mg strength) obtained through purchase in the US.

8.1 Storage and Administration

Appropriate storage and administration of Impavido in accord with the Product Label is the responsibility of the patient.

Storage and administration data will be recorded on appropriate pages of the data form.

8.2 Concomitant Therapy

All concomitant medications will be recorded on the data form.

9 PROCEDURES

Parameter	Study Time Period				
	Screening	**End of Treatment Period**	**1 Month Post Treatment**	**3 Months Post Treatment**	**6 Months Post Treatment**
Consent	X				
Demographics (gender/age/weight/race)	X				
Leishmaniasis Hx	X				
Concomitant Diseases	X	X			
Miltefosine treatment	(a)	X			
Clinical Laboratory Tests	X (b,c)	X(b,c)	X (c)	X (c)	X (c)
Concomitant Medications	X	X			
Adverse Events	X	X			
Efficacy		X	X	X	X
(a): Patients may contact the Registry after having been administered at least one dose of miltefosine (b): AST and creatinine at screening and end of treatment; (c): White blood cells (WBC), hemoglobin, and platelet count for patients with VL at all time					

9.1 Subject Recruitment

Patients will be alerted to the Impavido Higher-weight-patient Registry availability via the Impavido website which will supply a toll free number (1-866-588-5405) to call.

9.2 Subject Consent/Assent

When the subject or parent/legal guardian calls the toll free number (1-866-588-5405) of the Impavido Higher-Weight Patient Registry Coordinating Center, a trained staff member will summarize information on the goals, eligibility requirements, and procedures of the registry. This information will also be on the website.

If on the telephone the patient or parent/legal guardian expresses a tentative desire to participate in the registry, the patient or parent/legal guardian will be mailed paper copies of the goals, eligibility requirements, and procedures of the registry, the Patient Information Sheet/Consent Form/Assent Form ("Consent Form/Assent Form"), and the Release of Medical Information by the Patient's Physician ("Medical Information Form").

Consent and assent will be in effect when the patient (or, for adolescents aged 12-17 years, the patient plus the parent/guardian) signs the Consent/Assent Form and the Medical Information Form and mails them back to the Impavido Higher-Weight Patient Registry Coordinating Center.

9.3 Screening Procedures

Physician will complete data form sections relevant to demographics, history of leishmaniasis, history of Impavido treatment (if any), pre-treatment clinical laboratory tests [aspartate aminotransferase (AST), creatinine, and if the patient has VL WBC, hemoglobin, and platelet count], concomitant diseases, concomitant medications.

From this information, eligibility to participate in the Higher-Weight Patient Registry will be determined.

9.4 Outcomes

The Impavido Higher-Weight Patient Registry Coordinating Center will contact the patient's physician at the end of the treatment period, and at 1, 3, and 6 months after the end of therapy, and request that the relevant data forms be completed and submitted.

10 DATA TO BE OBTAINED

10.1 Screening

Demographic Data

Age
Weight
Sex
Race
Prior medications
Geographic area where *Leishmania* infection was acquired
Immune status [normal vs abnormal. If latter, specify disease]

Leishmaniasis History

Site of infection [mark body chart]
Disease parameters

VL : Spleen size
Hemoglobin, platelets, white cell count
ML: Symptoms, Physical status at site of infection
CL : Lesion characteristics at entrance: ulcer, nodule, plaque, scab
Lesion size at entrance: Approximate size [length x width in inches, cm, or finger widths]

Clinical Laboratory Tests

AST, creatinine, and if the patient has VL WBC, hemoglobin, and platelet count

Concomitant Diseases

Concomitant Medications

10.2 Treatment Data

Miltefosine Treatment Regimen

Daily dose in mg, dose in mg/kg, duration of therapy

Adverse events

Symptoms: gastrointestinal, other
Laboratory parameters (if available)

10.3 Efficacy Data at 1, 3, and 6 months

VL : Spleen size
Hemoglobin, platelets, white cell count
ML: Symptoms, physical status at original site of infection
CL : Lesion characteristics: ulcer, nodule, plaque, scab
Lesion size: Approximate size [length x width in inches, cm, or fingerwidths]

11 ANALYTICAL PLAN

11.1 Sample Size

Since there is no hypothesis for this study, there is no formal sample size calculation.

11.2 Analytical Populations

Data for all eligible subjects will be analyzed. An eligible subject is anyone who received at least one administration of Impavido for leishmaniasis.

11.3 General Analytical Procedures

Descriptive statistics will be used to present study data. Continuous variables will be presented as number of observations (n), mean, standard deviation (SD), median, minimum and maximum values. Categorical variables will be presented as counts and percentages.

11.4 Analysis of Baseline Data

By-subject and summaries of the baseline data will be provided.

11.5 Analysis of Treatment Compliance Data

By subject and summaries of compliance with prescribed treatments will be provided, including total exposure (number of days, total dose in mg, daily dose in mg/kg) to Impavido.

11.6 Analysis of Outcomes

By-subject and summaries of the outcome data will be provided.

12 ADMINISTRATIVE AND REGULATORY STANDARDS

This protocol will be submitted to IND# 105,430. The Principal Investigator (PI) will sign a Form FDA 1572.

12.1 Ethical Review of Protocol

The PI will obtain protocol approval from a central IRB before starting the study.

12.2 Informed Consent

Subject consent will be obtained in accord with protocol section 9.2

12.3 Responsibility for Subject Care

The patient’s physician is responsible for the care of his/her subject.

12.4 Treatment Cost

The patient is responsible for the cost of treatment including miltefosine.

13 STUDY DOCUMENTATION/DATA MANAGEMENT

13.1 Subject Identification (ID) Code

Each subject will be assigned a subject ID code. The Subject ID code will be used on all data forms and reports of the data to the IRB and FDA.

13.2 Data Collection and Monitoring

Data forms will be collected by mail from the patient and/or from the patient's physician. Upon receipt at the Impavido Higher-Weight Registry Coordinating Center, data forms will be stored in a secure controlled access location.

The patient and/or the patient's physician will be responsible for the accuracy of the data.

13.3 Data Editing and Control

Data received at the Impavido Higher-Weight Patient Registry Coordinating Center will be reviewed prior to being entered into the main study database. If incomplete or inaccurate data are found, a data clarification request will be forwarded to the patient and/or patient's physician for a response.

13.4 Data Analysis

An analysis of all data will be performed at the intervals specified by 2127-4.

A final clinical study report will be prepared in accordance with International Committee on Harmonization E3 Structure and Content of Final Clinical Study Reports.

13.5 Publication

The results of the full study may be published at the discretion of the sponsor. No personal identifying data will be available in any external communication or publication.

13.6 Subject Confidentiality

To maintain subject confidentiality, all electronic records and data reports using the subject ID code. Data forms and other records containing the patient's name, address, and telephone number will be stored in a secure location and only the protocol staff will have access to the records.

14 ROLES AND RESPONSIBILITIES OF STUDY PERSONNEL

14.1 Principal Investigator

Signs the protocol agreement, below, and the Form FDA 1572. The PI is responsible for passage of the protocol and any amendments through a "central" IRB before starting the study. The PI is responsible for interaction with the Impavido Higher-Weight Patient Registry Coordinating Center to ensure protocol adherence, data integrity, and overall coordination of the study.

14.2 Subinvestigators

Subinvestigators are responsible for performing the PI's duties in his/her absence. In all sections of this protocol, "PI" is taken to mean "PI or subinvestigator in the absence of the PI".

14.3 Higher-Weight Patient Registry Coordinating Center

The Impavido Higher-Weight Registry Coordinating Center maintains and staff's personnel who respond to calls from patients and enrolled subjects. It also prepares and provides data forms; designs, develops, and validates the clinical trial database; performs data entry into the clinical trial database and performs database quality control and data analysis.

15 STATEMENT OF AGREEMENT

The PI has carefully read this protocol and agrees to oversee the clinical study as described in a professional and competent manner in accordance with the generally accepted standards of Good Clinical Practice.

SIGNATURES

_____	_____
Principal Investigator	Date
_____	_____
Sponsor	Date

16 REFERENCES

Impavido NDA 2014. Product label.
http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/204684s000lbl.pdf

WHO 2010. Control of the Leishmaniases. WHO Technical Report Series # 949.