



Drugs for Neglected Diseases *initiative*

## CLINICAL TRIAL PROTOCOL SYNOPSIS

**A randomized, open-label, phase II, single-centre study to evaluate the efficacy, safety and pharmacokinetics of LXE408 in patients with primary visceral leishmaniasis in Ethiopia**

<b>Clinical Trial Protocol title</b>	A randomized, open-label, phase II, single-centre study to evaluate the efficacy, safety and pharmacokinetics of LXE408 in patients with primary visceral leishmaniasis in Ethiopia <u>Short title:</u> LXE408 Phase II Ethiopia
<b>Protocol number</b>	DNDi-LXE408-02-VL / CLXE408A12202R
<b>Phase</b>	Phase II
<b>Indication</b>	Primary visceral leishmaniasis
<b>Background Information and Trial Rationale</b>	<p>Visceral Leishmaniasis (VL), also known as kala-azar, is one of the most neglected tropical diseases, with a distribution in South Asia, Eastern Africa, Latin America and the Mediterranean region. It is caused by the anthroponotic <i>Leishmania donovani</i> in Asia and Africa, and by the zoonotic <i>Leishmania infantum</i> in Latin America and the Mediterranean region, and is transmitted through the bite of an infected female sandfly. The disease is characterized by splenomegaly, irregular fevers, pancytopenia, weight loss and weakness occurring progressively over a period of weeks or even months, leading to death if untreated.</p> <p>Following significant VL elimination efforts in South Asia, Eastern Africa is currently the region with the highest VL disease burden (World Health Organization, 2021) In this region, the disease affects mainly children (approximately 60-70% of patients are &lt;15 years old) living in poor communities in remote rural areas (Alves et al., 2018; Harhay et al., 2011).</p> <p>The current WHO-recommended treatment for primary VL in Eastern Africa is a combination of sodium stibogluconate (SSG) and paromomycin (PM) administered for 17 days, with an efficacy, or definitive cure at six months, of 91% (Musa et al., 2012). This treatment</p>

(SSG/PM), administered as 2 separate daily injections, requires 17 days of hospitalization and is challenging to deliver, particularly in resource-poor settings. In addition, the antimonial SSG exhibits life-threatening toxicities such as cardiotoxicity, hepatotoxicity and pancreatitis. The second line treatment for specific target populations such as pregnant women, severe disease or HIV co-infection, as well as patients who are <2 years and >45 years, is multiple dose liposomal amphotericin B (AmBisome®) which has an efficacy rate of approximately 85% (Khalil et al., 2014). It is given as a 5 mg/kg/day infusion over a 6-day period up to a total dose of 30 mg/kg. The need for cold chain, high cost and the difficult intravenous administration requiring two-dilution steps in sterile conditions and a test dose to assess risk of anaphylactic reaction, limit its widespread use in Eastern Africa.

New innovative treatments are, therefore, needed that can respond to the needs of the communities affected by VL. The target product profile (TPP) seeks a new VL treatment that can reach an efficacy of at least 90%, preferably 95%. An efficacious, safe, oral therapy would be a user-friendly solution that could be integrated in primary health care units in the remote areas where VL occurs. This would allow for shortening the time between onset of symptoms and treatment, as recommended by WHO.

LXE408 is a first-in-class parasite-selective inhibitor of the kinetoplastid proteasome with potent and uniform anti-parasitic activity against all kinetoplastid parasites, including *Leishmania* species causing VL (*L. donovani* and *L. infantum*), as well as parasites causing Chagas disease (*T. cruzi*) and human African trypanosomiasis (*T. brucei*).

The antileishmanial activity of LXE408 was determined in a macrophage infection assay against three strains of viscerotropic *Leishmania* species, which originated from three key regions where VL is endemic: *L. donovani* (Ethiopia), *L. donovani* (India) and *L. infantum* (Morocco).

#### **Purpose of the phase II clinical trial:**

This is a phase II, randomized, open-label, single-centre study to assess the efficacy, safety and PK profile of LXE408 in patients with primary VL in Ethiopia. An SSG/PM arm (standard of care) will be included as a calibrator arm, to collect efficacy and safety data in a comparable patient population and timeframe of study conduct.

The study will be conducted in male and female adult and adolescent patients ≥15 years and <45 years. As per Ethiopia VL guidelines, treatment with SSG/PM is contraindicated in patients ≥45 years due to the higher risk of mortality and lower efficacy observed with SSG/PM treatment in this age group (Kimutai et al., 2017). Therefore, patients ≥45 years will be excluded from this trial.

In North Ethiopia where the trial will be conducted, the disease affects mainly young male adults in work-related settings and, therefore, the majority of patients recruited in the trial are expected to be male.

	<p>Adolescent patients <math>\geq 15</math> years represent approximately 10% of the patient population. They are part of the population at risk of VL in Ethiopia and are expected to have similar characteristics and responses to LXE408 treatment as adult patients. They are included in the trial in order to collect data on a representative patient population with VL, and toxicology data supports their inclusion.</p> <p>If LXE408 is shown to be efficacious and to have a favourable safety profile in future confirmatory studies, this therapy may be an alternative to the use of SSG/PM in Eastern Africa. It could be a safer and more convenient oral option for use at any health care level (including primary health care settings closer to the communities affected) in all foci of the disease. This would improve and simplify current case management and reduce time between onset of symptoms and access to treatment, thereby reducing morbidity and mortality, whilst reducing transmission and contributing to disease control and elimination.</p> <p>In addition, exploratory biomarkers will be assessed in this phase II study, aiming to identify potential surrogate markers of cure/failure at the end of treatment and prognostic markers of relapse. In order to obtain data from the patients' perspective, patient reported outcomes (PROs) will also be collected as an exploratory objective.</p>
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<b>Trial Objectives, Endpoints and Estimands</b>	<b>Primary Objective &amp; Clinical Research Question</b>	<b>Primary Endpoint / Estimand</b>
	<p><b>Primary objective:</b>                      To assess the efficacy at Day 28 of a 14-day treatment course of LXE408 in patients with primary VL</p> <p><b>Clinical research question:</b>                      What is the effect of LXE408 treatment on achieving cure at Day 28 in patients with primary VL in Ethiopia?</p>	<ul style="list-style-type: none"> <li>• <b>Population:</b> Patients with confirmed primary VL</li> <li>• <b>Treatment condition:</b> LXE408 300 mg oral once daily for 14 days</li> <li>• <b>Endpoint:</b> Initial cure at Day 28 (clinical improvement of VL, absence of parasites in the spleen or bone marrow (microscopy) and no rescue therapy up to and including Day 28)</li> </ul> <p>Definition for clinical improvement of VL at Day 28 includes all the following parameters*:</p> <ul style="list-style-type: none"> <li>- absence of fever attributed to VL</li> <li>- spleen size reduction of any magnitude in relation to baseline</li> <li>- any increase (if abnormal at baseline) or no worsening (if normal at baseline) in haemoglobin, WBC and platelet values in relation to baseline</li> </ul> <p>*In the absence of any other intercurrent illness which, in the opinion of the investigator, is causing the observed lack of improvement or the worsening</p> <ul style="list-style-type: none"> <li>• <b>Summary measure:</b> Proportion of patients with initial cure at Day 28 in the LXE408 arm (the number of evaluable subjects exhibiting initial cure out of total number of evaluable subjects)</li> <li>• <b>Intercurrent events:</b> <ul style="list-style-type: none"> <li>a) Use of rescue therapy (following treatment discontinuation due to AE(s) or lack of efficacy) and death due to VL or study treatment will be handled with a composite strategy (i.e., considered as failure)</li> <li>b) Discontinuation of study treatment due to AE(s) or any other reasons without rescue therapy and use of prohibited medication will be handled with a treatment policy strategy (i.e., as per assessment at Day 28)</li> </ul> </li> </ul>
	<b>Secondary Objectives</b>	<b>Secondary Endpoints</b>
	<p>To assess the safety and tolerability of LXE408</p> <p>To assess the safety and tolerability of the standard of care SSG/PM</p>	<ul style="list-style-type: none"> <li>• <b>Endpoints:</b> <ul style="list-style-type: none"> <li>a) Occurrence and severity of treatment-emergent adverse events (TEAEs) and SAEs from first dose of treatment through the last visit (EOS visit), and AEs requiring treatment discontinuation</li> <li>b) Abnormalities from physical exam, vital signs, ECG abnormalities, and clinically significant safety laboratory assessments including clinical chemistry, haematology</li> </ul> </li> </ul>

		<p>and urinalysis results up to and including end-of-study (EOS) visit.</p> <p>c) All-cause mortality through days 28 and 180 and mortality not associated with VL through days 28 and 180</p> <ul style="list-style-type: none"> <li>• <b>Summary measure:</b> Proportion of patients with an endpoint, receiving at least one dose of study treatment</li> </ul>
	To assess the pharmacokinetics (PK) of LXE408	<ul style="list-style-type: none"> <li>• <b>Endpoints:</b> <math>C_{max}</math>, <math>T_{max}</math>, <math>AUC_{tau}</math>, CL/F on D1 and D13</li> <li>• <b>Summary measure:</b> Geometric mean <math>C_{max}</math>, <math>AUC_{tau}</math> and CL/F, median <math>T_{max}</math></li> </ul>
	To assess the efficacy of LXE408 at Day 180	<ul style="list-style-type: none"> <li>• <b>Endpoint:</b> Definitive cure at Day 180 (initial cure at Day 28, no requirement for rescue treatment throughout the study, no death associated with VL and absence of any clinical parameters of VL up to and including D180)</li> <li>• <b>Summary measure:</b> Proportion of patients with definitive cure at Day 180 in LXE408 arm (the number of evaluable subjects exhibiting definitive cure out of total number of evaluable subjects)</li> </ul>
	To assess the effect of LXE408 on blood and tissue parasite clearance	<ul style="list-style-type: none"> <li>• <b>Endpoints:</b> <ol style="list-style-type: none"> <li>a) Blood parasite clearance over time, as measured by quantitative polymerase chain reaction (qPCR) from blood samples, at screening, D1, D2 (PK/PD intensive cohort only), D3, D5, D7, D10, D14, D28, D56 and at any suspicion of relapse during the trial</li> <li>b) Tissue parasite loads, as measured by qPCR from tissue samples (spleen or bone marrow) collected at baseline, Day 28 and at any suspicion of relapse during the trial</li> </ol> </li> <li>• <b>Summary measure:</b> Proportion of patients with positive/negative qPCR, time to parasite clearance and parasite quantification over time</li> </ul>
	To describe the efficacy of the standard of care SSG/PM at Day 28 and Day 180	<ul style="list-style-type: none"> <li>• <b>Endpoints:</b> initial cure at Day 28 and definitive cure at Day 180, as defined in the LXE408 efficacy endpoints.</li> <li>• <b>Summary measure:</b> Proportion of patients with initial cure at Day 28 and definitive cure at Day 180 in SSG/PM arm (the number of evaluable subjects exhibiting initial cure and definitive cure out of total number of evaluable subjects.)</li> </ul>
	<b>Exploratory Objectives</b>	<b>Exploratory Endpoints</b>
	To assess PK and PD relationships of LXE408	<ul style="list-style-type: none"> <li>• To be performed, if applicable</li> </ul>

	<p>To explore the role of the blood transcriptome as a predictive biomarker for efficacy</p>	<ul style="list-style-type: none"> <li>• <b>Endpoints:</b> differentially expressed genes and pathways in peripheral blood at D3, D7, D14, D28, D56 and at relapse, compared to baseline, by study drug, treatment outcomes and drug related (S)AEs</li> <li>• <b>Summary Measure:</b> area under the ROC curve (AUC) with the test's sensitivity, specificity, negative predictive value and positive predictive value</li> </ul>
	<p>To assess the impact of each of the treatments, LXE408 and SSG/PM, on health-related quality of life (QoL)</p>	<ul style="list-style-type: none"> <li>• <b>Endpoints:</b> <ul style="list-style-type: none"> <li>- Change in WHOQoL-BREF scores from baseline to D14, D28 and D180/EOS</li> <li>- Change in EQ-5D-5L scores from baseline to D14, D28 and D180/EOS.</li> <li>- PGIC scale at D14, D28 and D180/EOS</li> </ul> </li> <li>• <b>Summary measure:</b> Mean, standard deviation, median, Q1, Q3, minimum and maximum scores for WHOQoL-BREF and EQ-5D-5L. Number and percentage of patients in each category for PGIC scale</li> </ul>
<p><b>Study Design</b></p>	<p>This is a randomized, open-label, phase II, single-centre study, with one LXE408 regimen and one calibrator arm with the standard of care SSG combined with PM, to be conducted in male and female adult and adolescent (<math>\geq 15</math> years and <math>&lt; 45</math> years) patients with confirmed primary visceral leishmaniasis in Ethiopia.</p> <p>The study will be conducted at the Leishmaniasis Research and Treatment Centre (LRTC), University of Gondar site in Ethiopia. A referral network from other hospitals will be used to boost recruitment numbers.</p> <p>The study will enrol and randomize approximately 52 patients aged <math>\geq 15</math> years and <math>&lt; 45</math> years in a ratio of 3:1 (arm 1 to arm 2):</p> <ul style="list-style-type: none"> <li>• Arm 1: LXE408 300 mg p.o. once daily for 14 days (39 patients)</li> <li>• Arm 2: Standard of care sodium stibogluconate 20 mg/kg/day intravenous/intramuscular (IV/IM) q.d. and paromomycin 15 mg/kg/day IM q.d. for 17 days (13 patients)</li> </ul> <p>Patients <math>\geq 45</math> years will be excluded from the trial. As per Ethiopia VL guidelines, treatment with SSG/PM is contraindicated in patients <math>\geq 45</math> years due to the higher risk of mortality and lower efficacy observed with SSG/PM treatment in this age group (Kimutai et al., 2017).</p> <p>In both arms, the study will consist of a screening period of up to 7 days, a treatment duration of 14 or 17 days, and a follow-up period from end of treatment to Day 180. All patients will be hospitalized for approximately 21-24 days, from the first day of the screening period to the Day 14 or Day 17 visit (LXE408 or SSG/PM arms, respectively), after which they are expected to be discharged. They will return to the study sites at the scheduled Day 28 visit (<math>\pm 1</math> day) for the initial test of cure (primary endpoint), at Day 56 visit (<math>\pm 7</math> days) and for the EOS visit at Day 180 (<math>\pm 14</math> days) for the final assessment of cure (secondary endpoint). In</p>	

	<p>addition, during follow-up between Day 56 and Day 180, the study team will contact the study patients by phone on a monthly basis to check on their well-being and any reappearance of VL symptoms.</p> <p>Safety of the study treatments will be assessed through regular monitoring of accrued clinical data.</p> <p>No interim analysis (IA) is planned in this study and efficacy in the single investigational arm will be estimated precisely, without an early stopping rule. In case of treatment failure, patients will receive rescue treatment.</p> <p>The study will have an independent data and safety monitoring board (DSMB) which will evaluate ongoing safety data, especially SAEs related to IMPs, assess the risk/benefit, give recommendations for the study and review protocol amendments related to safety parameters.</p> <p>Any substantial change in the study protocol will require an amendment to be approved by the relevant authorities.</p> <p><u>Proposed dose regimen for the phase II study:</u></p> <p>Adult patients with VL are expected to have lower weight compared to adult HVs, which may result in higher exposures for the same dose. While the extent to which weight may influence LXE408 exposure is currently unknown, the exposures achieved in toxicology studies, along with the human single and multiple ascending dose data, support a dose of 300 mg to maximise efficacy in this phase II study in patients. Given the seriousness of the disease, the vulnerable target population and the anticipated PK variability based on data in healthy volunteers, LXE408 will be tested at a dose that has been well tolerated in HVs and provides a 2-3-fold margin of exposure above the target efficacious exposures to account for the potential PK variability and to maximize efficacy, while ensuring that the safety of patients is closely monitored.</p> <p><b>Assessments</b></p> <p><u>Efficacy assessments</u> will include clinical parameters (fever clearance, spleen and liver sizes, haematological parameters) and parasitological evaluation at screening, at Day 28 (initial test of cure) and at any suspicion of relapse during the trial.</p> <p>Parasitological assessment will be done through spleen or bone marrow aspiration and microscopic examination. Spleen aspirate is preferable, due to its higher sensitivity. However, it should not be performed if the platelet count is <math>&lt;40,000/\text{mm}^3</math>, Hb <math>\leq 5\text{ g/dL}</math>, prothrombin time of more than 5 seconds difference compared to normal control, if the patient has signs of bleeding, jaundice or if the spleen is not palpable. In these cases, bone marrow aspiration is recommended.</p> <p><u>Safety assessments</u> will include physical examinations, vital signs, clinical laboratory evaluations (haematology, clinical chemistry, urinalysis), ECG, adverse event (AE) and serious adverse event (SAE) monitoring.</p> <p>The AE reporting period will begin upon patient enrolment in the trial (after</p>
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	<p>giving informed consent) and will end at the end of the patient participation in the trial (D180 EOS visit).</p> <p>The reporting period is different for AEs and for SAEs:</p> <ul style="list-style-type: none"><li>• All AEs will be reported upon administration of the first dose of study treatment until the end of patient participation in the trial (including follow-up period up to D180). Furthermore, AEs that occur in the screening period AND are judged as study-related will also be reported.</li><li>• All SAEs must be reported upon patient enrolment in the trial (after signature of informed consent during screening period) until the end of the patient participation in the trial (including follow-up period up to D180).</li><li>• Screening failure: beyond the date of screening failure, only serious study-related events will be followed-up.</li></ul> <p>AEs will be assessed by temporality (start and end dates), causality, severity, seriousness and outcome.</p> <p>Severity of AEs will be graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE version 5.0). The AE data will be coded using the latest version of the MedDRA dictionary.</p> <p>Monitoring of clinical data will be performed regularly to look for trends in safety and clinical parameters. Details of the ongoing safety evaluations will be provided in the medical monitoring plan. The role of the DSMB in the review of safety data will be outlined in the charter.</p> <p><u>Pharmacokinetics of LXE408</u></p> <p>Intensive PK will be performed for the first 15 patients included in the LXE408 arm. The sampling times will be as follows:</p> <ul style="list-style-type: none"><li>• D1 at 0 (pre-dose), 1, 2, 3, 4 and 8 hours and D13 at: 0 (pre-dose), 1, 2, 3, 4 and 8 hours.</li><li>• Troughs (pre-dose samples) will be on days 2, 3, 5, 7, 10 and Day 14.</li></ul> <p>For all remaining patients, sparse sampling will be performed, that is prior to dosing, on D3, D5, D7, D10 and D14 (pre-dose samples).</p> <p><u>Parasite dynamics and biomarkers</u></p> <p>qPCR will be performed on blood samples to assess parasite clearance over time, before, during and after treatment.</p> <p>The first 15 patients with LXE408 intensive PK sampling will have matching daily pre-dose PD blood samples to be collected for qPCR, i.e., at screening, D1, D2, D3, D5, D7, D10 and D14, plus additional samples at D28, D56 and before administering rescue treatment, in case of initial treatment failure or at any suspicion of relapse.</p> <p>For the remaining patients in all arms, qPCR will be performed at</p>
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	<p>screening, and pre-dose at D1, D3, D5, D7, D10 and D14. In addition, all patients will have qPCR done at D28, D56 and before administering rescue treatment, in case of initial treatment failure or at any suspicion of relapse during the trial.</p> <p>qPCR will also be performed using tissue samples at screening, D28 and at any suspicion of relapse.</p> <p>In addition, patients in both arms will have extra blood samples collected at D1 (pre-dose), D3, D7, D14, D28, D56 and, if relevant, at relapse to assess host biomarkers.</p> <p><u>Patient reported outcomes</u></p> <p>Patient reported outcomes will be collected at baseline (Day 1), D14, D28 and D180 using WHO-QoL-BREF (among adult patients) and EQ-5D-5L questionnaires, and at D14, D28 and D180 using Patient Global Impression of Change (PGI-C).</p> <p><u>Dose interruptions and rescue treatment</u></p> <p>Rescue treatment will be indicated in case of initial failure (during treatment up to day 28 initial test of cure), in case of relapse between day 29 and day 180, or in circumstances when study medication needs to be discontinued early and patient has persistence of clinical signs and symptoms of VL (see further details below). All cases of relapse must be documented with a positive parasitological diagnosis.</p> <p>Rescue treatment for lack of treatment response:</p> <ul style="list-style-type: none"><li>- Before Day 28 visit: if the patient presents signs of no response, persistence of fever attributed to VL, or the condition deteriorates, microscopy on tissue samples (spleen or bone marrow aspirate) will be performed at the discretion of the investigator; if microscopy is positive, the study treatment will be discontinued, and rescue treatment will be initiated. The investigator may also opt to initiate rescue treatment based only on persistence of clinical signs and symptoms of VL, if microscopy on tissue samples cannot be performed. The reason for not performing tissue aspiration will be collected in the patient's source documents and in the eCRF.</li><li>- At Day 28 assessment: if the patient has a positive microscopy of spleen or bone marrow aspirate, rescue treatment will be initiated.</li><li>- From day 29 up to day 180: if a patient presents signs and symptoms of VL at any time and relapse is suspected, a parasitological examination should be performed (microscopy of spleen or bone marrow aspirate). If the result is positive, rescue treatment will be initiated.</li></ul> <p>Rescue treatment for patients who have discontinued the investigational drug:</p> <p>For patients allocated to the LXE408 study arm, if AEs (including clinically significant laboratory abnormalities) are noted and investigational treatment is discontinued, the investigator will assess the clinical</p>
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	<p>condition of the patient.</p> <ul style="list-style-type: none"><li>- If a patient has received less than 7 days of study therapy, rescue treatment will be initiated.</li><li>- For patients who received a minimum of 7 days of therapy:</li></ul> <p>If the patient's VL condition is evolving well and there are signs of clinical improvement (absence of fever, reduction of spleen size, improvement of general patient status and of haematological parameters), the patient can continue to be observed until the Day 28 visit, when the initial test of cure will be performed.</p> <p>However, if the patient has signs of no response, persistence of fever attributed to VL, or their condition deteriorates, microscopy on tissue samples (spleen or bone marrow aspirate) will be performed at the discretion of the investigator; if microscopy is positive, rescue treatment will be initiated. The investigator may also opt to initiate rescue treatment based on persistence of clinical signs and symptoms of VL if microscopy on tissue samples cannot be performed. The reason for not performing tissue aspiration will be collected in the patient's source documents and in the eCRF.</p> <p>Rescue treatment per study arms:</p> <ul style="list-style-type: none"><li>- Patients allocated to the LXE408 arm will be rescued with SSG/PM (SSG 20 mg/kg/day IV/IM q.d. and PM 15 mg/kg/day IM q.d. for 17 days) or AmBisome® 5 mg/kg/day administered every day over a period of 6 days (i.e., 30 mg/kg in total). The investigator will judge which rescue treatment is appropriate based on the patient's clinical condition.</li><li>- Patients allocated to the SSG/PM arm will be rescued with AmBisome® (same regimen as described above).</li></ul> <p>All patients who receive rescue treatment will be considered treatment failures and will continue in the study and complete the study procedures.</p>
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<p><b>Entry Criteria</b> Inclusion Exclusion</p>	<p>Patients who fulfil all inclusion criteria and do not present any of the exclusion criteria are eligible for enrolment in this study.</p> <p><b>Inclusion criteria:</b></p> <ul style="list-style-type: none"><li>• Male and female patients <math>\geq 15</math> and <math>&lt; 45</math> years (at the time of the screening visit) who are able to comply with the study protocol.</li><li>• Written informed consent must be obtained before any study protocol specific assessment is performed, other than procedures performed as part of standard of care.<ul style="list-style-type: none"><li>○ Written informed consent must be signed by adult patients and by a parent or legal guardian for patients under 18 years of age</li><li>○ In the case of minors, assent from the adolescent also needs to be obtained</li></ul></li><li>• Primary symptomatic VL (defined as typical parameters including, but not limited to, fever for <math>&gt; 2</math> weeks, weight loss and splenomegaly)</li><li>• Visualization of <i>Leishmania</i> amastigotes by microscopy in tissue samples (spleen or bone marrow)</li></ul> <p><b>Exclusion criteria:</b></p> <ul style="list-style-type: none"><li>• Clinical signs of severe VL (including for example jaundice, spontaneous bleeding, oedema, ascites, coma, organ failure)</li><li>• Laboratory abnormalities including ALT/SGPT <math>&gt; 3</math> times ULN, total bilirubin <math>&gt; 1.5</math> times ULN, creatinine <math>&gt; 1.5</math> times ULN, serum amylase or lipase <math>&gt; 1.5</math> times ULN, haemoglobin <math>&lt; 6</math> g/dL or other clinically significant abnormal laboratory parameters which, in the opinion of the investigator, may indicate severe VL</li><li>• Patients with history of visceral leishmaniasis and confirmed relapse</li><li>• Patients with para-kala-azar dermal leishmaniasis</li><li>• Patients with severe malnutrition (for patients <math>\geq 15</math>-<math>&lt; 18</math> years: Mid-Upper Arm Circumference (MUAC) cut-off based on MUAC-for-height reference table; for patients <math>\geq 18</math> years: MUAC <math>&lt; 170</math> mm)</li><li>• History of congenital or acquired immunodeficiency, including positive HIV (test at screening), as these patients present lower efficacy rates, higher toxicity and higher lethality compared to non-HIV patients, requiring different case management and care</li><li>• ECG abnormalities, either historic (no longer present) or current which, in the view of the investigator, indicate a significant risk to</li></ul>
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	<p>study participation. These include, but are not limited to, the following:</p> <ul style="list-style-type: none"><li>- Clinically significant cardiac arrhythmias (e.g., sustained ventricular tachycardia and clinically significant second- or third-degree AV block without a pacemaker)</li><li>- QTcF <math>\geq</math> 450 ms</li><li>- History of familial long QT syndrome or known family history of Torsades de Pointes</li><li>- Resting heart rate (physical exam or 12 lead ECG) <math>&lt;</math>60 bpm</li></ul> <ul style="list-style-type: none"><li>• Concomitant known infections, including tuberculosis, severe malaria and any other serious underlying disease that may interfere with disease assessment (e.g., cardiac, renal, hepatic, haematologic and pancreatic)</li><li>• Infection with hepatitis B (HBV) or hepatitis C virus (HCV). Patients with a positive HBV surface antigen (HBsAg) test, or if standard local practice, a positive HBV core antigen test, and patients with a positive HCV antibody test must be excluded and will be followed up as per local practice.</li><li>• Known history of hearing impairment and/or clinical signs and symptoms of hearing impairment identified during routine physical examination</li><li>• Patients with previous history of hypersensitivity reaction or known drug class allergy to any of the study treatments or excipients</li><li>• Pregnant or nursing (lactating) women</li><li>• Women of childbearing potential who do not agree to have a pregnancy test done at screening and who do not agree to use highly effective contraception while taking the investigational drug and for 5 days after stopping the investigational drug</li><li>• Sexually active males unwilling to use a condom during intercourse while taking the investigational drug and for 5 days after stopping the investigational drug</li><li>• Patients who cannot comply with the planned scheduled visits and procedures of the study protocol</li></ul>
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<p><b>Study Duration</b></p>	<p>Patient participation in the trial will consist of a 7-day screening period, a treatment duration of 14 days with LXE408 or 17 days with SSG/PM, and a follow-up period until Day 180 (with a test of cure at Day 28 for the primary endpoint assessment). Total study duration is approximately 6 months.</p> <p>Recruitment for the entire trial is expected to take approximately 12 months assuming that 15% of all screened patients will meet the eligibility criteria. Therefore, study duration from first patient first visit (FPFV) to last patient last visit (LPLV) is expected to take approximately 18 months. Total study duration from FPFV to key results shall be approximately 24 months.</p>
<p><b>Study treatments</b></p>	<p>Patients will be randomized to one of two treatment arms in a ratio of 3:1 (Arm1: Arm2):</p> <ul style="list-style-type: none"> <li>• Arm 1: oral LXE408 300 mg q.d. for 14 days</li> <li>• Arm 2: Standard of care, sodium stibogluconate 20 mg/kg/day intravenous/intramuscular (IV/IM) q.d. and paromomycin 15 mg/kg/day IM q.d. for 17 days</li> </ul> <p>LXE408 should be administered in the morning and preferably before the first meal.</p>
<p><b>Statistics</b></p>	<p>For new VL treatments, the target product profile (TPP) states that the minimal efficacy should be <math>\geq 90\%</math>, while the ideal efficacy is 95% (mean population point estimate).</p> <p>In this study, the desirable cure rate will be at least 80%.</p> <p>Approximately 52 patients aged between <math>\geq 15</math> and <math>&lt; 45</math> years will be randomised to one of two treatment arms in a ratio of 3:1 with approximately 39 patients in the LXE408 arm and 13 patients in the SSG/PM arm.</p> <p>The SoC arm is included as a calibrator arm, to have efficacy and safety data in a comparable patient population and timeframe of the study conduct, and to aid in the attribution of AEs. Descriptive statistics on efficacy and safety will, therefore, be summarized for SSG/PM arm, but no statistical comparisons will be performed between the LXE408 arm and the SoC arm.</p> <p>The primary endpoint and summary measure is the proportion of patients with initial cure at Day 28 for the LXE408 arm. The sample size calculations are based on the precision of this estimate as no formal statistical comparison is planned with the SSG/PM arm. Calculations of</p>

	<p>precision are based on exact binomial methods.</p> <p>For the primary estimand, intercurrent events of use of rescue therapy (following treatment discontinuation due to AE(s) or lack of efficacy), and death due to VL or study treatment, will be handled with a composite strategy (i.e., considered as failures). Intercurrent events of discontinuation of study treatment for other reasons not requiring rescue therapy will be handled with a treatment policy strategy (i.e., as per Day 28 assessment).</p> <p>Patients may have missing data due to study withdrawal for reasons other than treatment failure or death associated with VL or study treatment. These patients will be excluded from the primary analysis; further sensitivity analysis will be performed for these missing data. Details of missing data handling will be provided in the separate Statistical Analysis Plan (SAP).</p> <p>No increase in sample size is required for events handled with a composite strategy. However, it is expected that up to 10% of patients will discontinue the study for other reasons and therefore will have missing data for their Day 28 assessment.</p> <p>It is expected that approximately 39 patients will receive LXE408 and, conservatively, that approximately 3 patients may have missing data at Day 28.</p> <p>If the true cure rate is at least 80%, this study with 39 patients assigned to LXE408 has a probability of &lt;10% of observing a cure rate below 70% and a probability of &lt;2% of observing a cure rate below 64%.</p> <p>It is estimated that 39 patients receiving LXE408 will provide the study with sufficient precision for an informative trial.</p> <p>Trends in safety and clinical parameters will be monitored regularly.</p> <p>No interim analysis (IA) is planned in this study and the single investigational arm efficacy will be estimated precisely without an early stopping rule.</p>
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