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CLINICAL TRIAL PROTOCOL

APL-B-021-13

A Phase II Study of Plitidepsin in Patients with Relapsed or Refractory Angioimmunoblastic T-cell Lymphoma

INVESTIGATIONAL MEDICINAL PRODUCT: **Plitidepsin (Aplidin®)**

Protocol Code: APL-B-021-13

EudraCT No: 2015-001909-14

NCT Code: 03070964

Protocol version 4.0 (including amendments #1 dated 6 July 2016, #2 dated 9 June 2017 and #3 dated 07 May 2018)

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This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirements.

Confidentiality statement

STUDY CONTACTS	NAME AND ADDRESS	PHONE, FAX NUMBER, AND E-MAIL ADDRESS
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[1] Abbreviated as PharmaMar or Sponsor in the rest of the protocol.

PRINCIPAL INVESTIGATORS

A full list of Investigators will be available as a separate document.

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SYNOPSIS

TITLE	A Phase II Study of Plitidepsin in Patients with Relapsed or Refractory Angioimmunoblastic T-cell Lymphoma
PROTOCOL CODE	APL-B-021-13
INVESTIGATORS	A full list of Investigators will be available as a separate document.
NUMBER OF SITES/TRIAL LOCATION	This is an international, multicenter study (with approximately 25 investigative sites).
STUDY OBJECTIVES	**Primary:** To evaluate the efficacy of plitidepsin on the basis of overall response rate (ORR) in patients with relapsing/refractory angioimmunoblastic T-cell lymphoma (AITL). **Secondary:** • To evaluate other efficacy endpoints (time-to-event parameters: duration of response [DoR], progression-free survival [PFS], PFS at 6/12 months [PFS6/PFS12], intrapatient PFS/TTP, overall survival [OS] and OS at 6/12 months [OS6/OS12]). • To evaluate the safety profile of plitidepsin in this patient population. • To characterize the pharmacokinetics (PK) of plitidepsin. • To identify biomarkers that may be clinical endpoint surrogates for future plitidepsin studies or that may be predictive of plitidepsin activity.
STUDY DESIGN	Prospective, multicenter, phase II clinical trial to determine the efficacy of plitidepsin in patients with relapsed/refractory (R/R) AITL. The primary endpoint will be ORR according to the Lugano classification response criteria per independent review. An Independent Review Committee (IRC) consisting of medical specialists (radiologists and hematologists) who are directly involved in the care of patients with AITL (but are not participating in this trial as investigators) will review all efficacy data (including radiological assessments, bone marrow biopsies) and will assign the best response and the date of objective response or progression/censoring according to their independent evaluation. Central pathological review of each patient's original diagnosis report(s) will be required before inclusion. Two futility analyses of the primary endpoint (ORR according to the Lugano classification criteria and per IRC) are planned around six months after approximately 25% and 50% of eligible patients (i.e., 15 and 30 patients respectively with AITL confirmed by central pathological review) have been treated. Two or less responders out of 15 patients or seven or less responders out of 30 patients, according to

	boundaries and sample size assumptions, will mean that the alternative hypothesis could be rejected, and thus recruitment might be stopped at the time of the first or second futility analysis, respectively. Otherwise, accrual will continue to 60 patients with AITL confirmed by central pathological review. This decision will be taken at the time by an Independent Data Monitoring Committee (IDMC). The IDMC, which will include specialists in peripheral T-cell lymphomas (PTCL) supported by a medical statistician, will review data provided by the Investigators, the IRC efficacy assessments and safety information and will advise whether the study should continue. Recruitment can continue during the review period. If there are 19 or more responders of 60 patients, the efficacy of plitidepsin will be considered as clinically relevant in AITL patients. Operational details for the IRC and IDMC will be detailed in corresponding charters.
CENTRAL PATHOLOGICAL REVIEW	Central pathological review will be conducted by experienced pathologists appointed by the Sponsor and available to the investigative sites for consultation about AITL diagnosis confirmation. Central pathological review is required for (a) local histopathology reports prior to patient treatment, and (b) tumor samples before each futility analysis and at the end of the study. The central laboratory pathologists will be responsible for (a) approving patient inclusion on the basis of investigative site pathology reports provided during screening, (b) analyzing tumor biopsies (initial diagnosis and/or relapses) to confirm the AITL diagnosis, and (c) analyzing blood samples to identify plasma biomarkers and extract DNA. Tumor samples (initial diagnosis and relapses) are required for central review to confirm AITL diagnosis but not to approve inclusion. Archived tissue samples of representative tumors must be sent for central review and biomarker analysis. If the diagnosis biopsy is not available (because the patient was diagnosed at another site, for example), the most recent representative biopsy (relapse and/or progression) will be used. Submitting both, however, is strongly recommended. Tumor blocks will be returned to the centers.
STUDY POPULATION	Adult patients with a diagnosis of AITL and with R/R disease. Patients must have measurable disease according to the Lugano classification criteria.
PATIENT ELIGIBILITY **INCLUSION CRITERIA**	1) Voluntary written informed consent of the patient (both to participate in the study and to provide biopsy samples) obtained before any study-specific procedure. 2) Age ≥ 18 years. 3) Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2. 4) Life expectancy ≥ 3 months. 5) Histologically confirmed diagnosis of R/R AITL (eligibility

	needs to be confirmed by central pathological review.*) 6) At least a two-week washout period since the end of the last therapy (six weeks for a prior nitrosourea-containing regimen), recovery to grade ≤ 1 from any non-hematological adverse event (AE) derived from previous treatment (excluding alopecia). 7) Adequate bone marrow (BM), renal, hepatic, and metabolic function (assessed ≤ 14 days before inclusion in the study): a) Absolute neutrophil count (ANC) ≥ 1.0×10^9/L. ▪ Screening of ANC should be independent of granulocyte-colony stimulating factor (G-CSF) support for at least one week and of pegylated G-CSF for at least two weeks. b) Platelet count ≥ 75×10^9/L. c) Hemoglobin ≥ 9 g/dL. ▪ Patients may receive red blood cells (RBC) and/or erythropoietin (EPO) and/or platelet transfusions in accordance with institutional guidelines. d) Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3.0 × the upper limit of normal (ULN). e) Total bilirubin ≤ 1.5 × ULN. f) Alkaline phosphatase (ALP) ≤ 3.0 × ULN (< 5 × ULN if isolated ALP increase, i.e., without ALT/AST or bilirubin increase). g) Calculated creatinine clearance (CrCL) ≥ 30 mL/minute (Cockcroft-Gault formula). h) Creatine phosphokinase (CPK) ≤ 2.5 × ULN. i) Albumin ≥ 2.5 g/dL. j) Normal value of electrolytes, including potassium, magnesium and calcium. 8) Left ventricular ejection fraction (LVEF) by echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan within normal range (according to institutional standards). * Patient inclusion can be approved based on local histopathological report(s). Eligibility will be confirmed using diagnosis and/or relapse biopsy specimens submitted for central pathological review prior to each futility analysis/end of the study.
PATIENT ELIGIBILITY EXCLUSION CRITERIA	1) Prior treatment with plitidepsin. 2) Concomitant diseases/conditions: a) History or presence of angina, myocardial infarction, clinically relevant valvular heart disease, uncontrolled hypertension, or congestive heart failure within the previous 12 months. b) Symptomatic arrhythmia (excluding grade ≤ 2 anemia-related sinusal tachycardia) or any arrhythmia requiring ongoing treatment, and/or prolonged grade ≥ 2 QT-QTc, or presence of unstable atrial fibrillation. Patients with stable atrial fibrillation on treatment are allowed provided they do not meet any other cardiac or prohibited drug exclusion criterion.

	c) History (or family history) of long QT syndrome. d) Corrected QT interval (QTcF, Fridericia correction) ≥ grade 2 on screening electrocardiogram (ECG). e) Clinically significant resting bradychardia, or history of syncope. f) History or presence of ventricular arrhythmias, including ventricular tachycardia or Torsades de Pointes. g) Patients receiving treatment with any medication with known risk of producing Torsade de Pointes (see Appendix 8). h) Active uncontrolled infection. Active hepatitis B or C virus (HBV or HCV), or human immunodeficiency virus (HIV) infection. i) Morphological or cytological features of myelodysplasia and/or post-chemotherapy aplasia on BM assessment. j) Myopathy > grade 2 or any clinical situation that causes significant and persistent elevation of CPK (> 2.5 × ULN in two different determinations performed one week apart). k) Limitation of the patient's ability to comply with the treatment or follow-up requirements. l) Diagnosis of another invasive malignancy unless free of disease for at least three years following therapy with curative intent. Patients with early-stage basal cell or squamous cell skin cancer, cervical intraepithelial neoplasia, cervical carcinoma *in situ*, or superficial bladder cancer, may be eligible to participate at the Investigator's discretion. m) Any other major illness that, in the Investigator's judgment, will substantially increase the risk associated with the patient's participation in this study. 3) Central nervous system (CNS) involvement. 4) Women who are pregnant or breast feeding. Fertile patients (men and women) who are not using an effective method of contraception. All patients (men and women) must agree to use an effective contraceptive measure (if applicable) up to six months after treatment discontinuation. 5) Concomitant medications that include corticosteroids, chemotherapy, or other therapy that is or may be active against AITL, within the two weeks prior to treatment start. Concurrent corticosteroids are allowed, provided they are administered at an equivalent prednisone dose of ≤ 10 mg daily, as premedication for blood products and/or for the relief of the symptoms derived from the disease. 6) Major upper gastrointestinal bleeding episode occurring during the previous year before screening. 7) Known hypersensitivity to any of plitidepsin's formulation components (see Study Drug Formulation).
EXPECTED NUMBER OF PATIENTS	A total of 60 patients with AITL confirmed by central pathological review are to be included in this study (unless one of the two planned futility analyses stops recruitment after the inclusion of approximately

	15 and 30 patients).
STUDY DRUG Formulation	Plitidepsin will be supplied as a powder and solvent for concentrate for solution for infusion. The 2-mg vial should be reconstituted with a 4-mL ampoule of reconstitution solution. The list of excipients is: D-mannitol, nitrogen, polyoxyl 35 castor oil (Macrogolglycerol Ricinoleate Ph.Eur.), absolute ethanol, and water for injections. The composition of the reconstitution solution is: polyoxyl 35 castor oil/ethanol/water for injection (15/15/70% v/v/v).
Administration route	One-hour intravenous infusion (fixed rate) via central or peripheral venous catheter.
Starting dose and schedule	A cycle is defined as a four-week period. Patients will receive 3.2 mg/m^2 plitidepsin on Day 1, 8 and 15 every four weeks (q4wk). A 1-day window is allowed for plitidepsin administration.
PROPHYLACTIC MEDICATION	All patients must receive the following prophylactic medication 30–60 min before infusion of plitidepsin: 1) Dexamethasone (8 mg i.v. or equivalent) 2) 5-HT3 receptor antagonist: palonosetron 0.25 mg i.v. or tropisetron 5 mg i.v. or granisetron 3 mg i.v. (avoid ondansetron as this drug is categorized within a known risk of producing Torsade de Pointes) (see Appendix 8). Alternatively, metoclopramide or other antiemetic drugs may be used instead as per Investigator's criteria/institutional guidelines, and 3) Diphenhydramine hydrochloride (25 mg i.v.) or equivalent, and 4) Ranitidine (50 mg i.v.) or equivalent. Oral metoclopramide and/or extended oral 5-HT3 receptor antagonist may be used as per Investigator's criteria/institutional guidelines. Additional dexamethasone can only be used as an antiemetic in the event alternative antiemetics cannot be used; and only if the Investigator considers the options above as insufficient.
CRITERIA FOR TREATMENT CONTINUATION	Patients can continue to receive plitidepsin infusions (Day 1, 8, 15 of each cycle) for a maximum of six cycles (unless with PR or SD after Cycle 6) if they fulfill the following requirements: ▪ ANC $\geq$ 1.0 $\times$ 10^9/L (or baseline values in the case of extensive bone marrow infiltration). ▪ Platelet count $\geq$ 75 $\times$ 10^9/L. ▪ Hemoglobin $\geq$ 9.0 g/dL. ▪ Calculated CrCL $\geq$ 30 mL/min (Cockcroft-Gault formula). ▪ Total bilirubin $\leq$ 1.5 $\times$ ULN ($\leq$ grade 1). ▪ AST, ALT $\leq$ 3.0 $\times$ ULN ($\leq$ grade 1). ▪ Normal value of electrolytes, including potassium, magnesium and calcium. ▪ Muscular toxicity (myalgia, muscular weakness, CPK

	increase) < grade 2. ▪ Other non-hematological drug-related AEs [except for increased gamma glutamyltransferase (GGT), not optimally-treated nausea and vomiting, hypertension or alopecia] ≤ grade 1. ▪ No clinically relevant ECG changes compared with grade at baseline. ▪ QTc must be ≤ grade 1 before receiving the study treatment. In case of grade 1 QTc prolongation during treatment, and after discussion with the Sponsor, treatment must be continued with a normal value of electrolytes, including potassium, magnesium and calcium, being mandatory before the re-administration of plitidepsin. ▪ In case of QTc ≥ grade 2, the study treatment must be discontinued, and the patient must be followed until recovery. If these criteria are not met on Day 1 of any cycle after Cycle 1, the new cycle is to be delayed for up to two weeks until recovery. If these toxicities do not recover after a 2-week delay, the patient is to discontinue treatment and start the follow-up period unless there is obvious clinical benefit, in which case the patient might restart treatment at the Investigator's discretion and after obtaining approval from the Sponsor. If these criteria are not met on Day 8 and 15 of any cycle (including Cycle 1), the scheduled infusion is to be omitted. Omitted doses for a given cycle are not to be recovered. "Cycle delay", therefore, is only applicable to the first infusion of a new cycle (i.e., Day 1) and not when an infusion takes place within the protocol-permitted window (one day) and not when treatment resumes after radiological assessment.
DOSE REDUCTION	Dose adjustments are to be based on the worst toxicity occurring during the previous cycle. The following table shows the plitidepsin dose levels used in this study. **Dose level** | **Plitidepsin dose (mg/m^2)** 0 | 3.2 –1 | 2.7 –2 | 2.3 Once the dose given to a patient is reduced, it cannot be re-escalated. Patients requiring dose reduction below dose level –2 should discontinue treatment and enter follow-up (except in cases of obvious clinical benefit when further dosing changes must be agreed with the Sponsor). The plitidepsin dose should be reduced if the patient meets any of the following criteria: • Less than 50% compliance with the treatment schedule. • Febrile neutropenia. • Grade 4 neutropenia and infection, or grade 4 neutropenia lasting > 7 days. • Grade 4 thrombocytopenia.

	• Grade ≥ 2 muscular toxicity (weakness, myalgia and/or CPK elevations). • Grade ≥ 3 AST/ALT increase. • Any grade ≥ 3 clinically relevant, non-hematological toxicity (except non-optimally treated nausea and vomiting, diarrhea lasting < 48 h and/or grade ≥ 3 fatigue lasting < 5 days).
ALLOWED MEDICATIONS/ THERAPIES	1) Erythropoietin. 2) Therapies for the treatment of pre-existing and/or emergent medical conditions not specifically forbidden as per protocol elsewhere. 3) Antiemetics according to institutional or American Society of Clinical Oncology (ASCO) guidelines. 4) G-CSFs according to institutional or ASCO guidelines (except for primary prophylaxis and when screening for eligibility). 5) Systemic and/or local therapies for symptomatic relief, particularly in the case of diarrhea or skin toxicity. 6) Adequate analgesic medication, including opioids for symptomatic pain relief if indicated. 7) Platelet and red cell transfusions are allowed within one week prior to the infusion and during the study.
PROHIBITED MEDICATIONS/ THERAPIES	1) Concomitant administration of any other antineoplastic therapy. 2) Other investigational agents. 3) Immunosuppressive therapies, except hydrocortisone used on isolated occasions as treatment for hypersensitivity reactions, or for the relief of the symptoms derived from the disease, if required. 4) Primary prophylaxis with colony-stimulating factors such as G-CSF. 5) Any medication with known risk of producing Torsade de Pointes, including ondansetron (see Appendix 8).
EFFICACY EVALUATIONS	Main efficacy analyses will be assessed in all eligible and treated patients with AITL diagnosis confirmed after central pathological review. Supportive efficacy analyses will be assessed in all treated patients and in all evaluable patients—defined as eligible patients who receive at least two plitidepsin cycles in which at least two complete infusions have been administered and had at least one disease assessment—as well as in patients who discontinue treatment without Cycle 3 tumor assessment after at least two plitidepsin infusions due to disease progression (PD) (or death due to PD) or toxicity (or death due to toxicity), defined as "early PD" and "treatment failures" respectively.
SAFETY EVALUATIONS	Patients will be evaluable for safety if they have received any partial or complete treatment cycle. All AEs will be graded according to the National Cancer Institute Common Terminology Criteria for

	Adverse Events (NCI-CTCAE) v.4. Cycle delays, skipped doses, dose reduction requirements, and reasons for treatment discontinuation will be monitored throughout the study. The safety profile of patients will be monitored throughout the treatment and up to 30 days after the last treatment dose (end of treatment, EOT), or until the patient starts a new antitumor therapy or until the date of death, whichever occurs first. Any treatment-related AEs will be followed until recovery to at least grade 1 or stabilization of symptoms, whenever possible.
PHARMACO-KINETICS	All patients included in the study will be sampled for pharmacokinetics (PK). Twelve PK samples will be obtained on Days 1, 8 and 15 of Cycle 1 and will be evaluated by standard non-compartmental analysis (population pharmacokinetic modeling may be performed if appropriate).
BIOMARKER ANALYSIS	The assessment of potential predictive factors to plitidepsin treatment will be analyzed on available paraffin-embedded tumor tissue samples (obtained at diagnosis and relapse) and on blood samples. These factors will include molecular markers related to the mechanism of action of plitidepsin or to the pathogenesis of the disease. The following analysis will be carried out, whenever relevant: a) alterations in DNA and RNA, including DNA mutational status, RNA expression levels and miRNA expression, for common genetic lesions affecting the AITL clone; b) alteration in tumor tissue biomarkers including (but not limited to) assessment of pathways and mechanisms of action of plitidepsin, mainly status at the protein expression level; and c) peripheral blood analyses, to identify plasma biomarkers including (but not limited to) cancer-related mutations and to extract DNA.
STATISTICAL METHODS	**Primary Endpoint** ▪ Overall response rate (ORR), defined as the percentage of patients with remission, either complete (CR) or partial remission (PR), according to the Lugano classification response criteria per independent review. An external IRC will assign the objective response and a progression or censoring date for each patient according to a predefined algorithm provided in a separate charter. **Secondary Endpoints** ▪ ORR per Investigator assessment (IA). ▪ CR rate, defined as the percentage of patients with complete remission according to the Lugano classification per IRC and per IA. ▪ Duration of response (DoR), defined as the time from the date when the remission criteria (PR or CR, whichever is first achieved) are fulfilled to the first date when PD, recurrence or death (due to any cause) is documented. Response will be assessed according to Lugano classification

	and per IRC and IA. ▪ Progression-free survival (PFS), defined as the time from the date of first drug administration to the date of PD, death (of any cause), or last tumor evaluation per IRC and IA. ▪ Progression-free survival at 6/12 months (PFS6/PFS12), defined as the Kaplan-Meier estimate of the percentage of patients who are progression-free at six/twelve months after the first drug administration per IRC and IA. ▪ Intrapatient PFS/TTP, defined as the ratio of PFS achieved with the experimental treatment versus prior last TTP in the R/R setting. ▪ Overall survival (OS), defined as the time from the date of the first dose to the date of death (of any cause) or last patient contact. ▪ Overall survival at 6/12 months (OS6/OS12), defined as the Kaplan-Meier estimate of the percentage of patients who are alive at six/twelve months after first drug administration. ▪ Treatment safety [AEs, serious adverse events (SAEs) and laboratory abnormalities] graded according to the NCI-CTCAE, v.4. Dose reductions, omitted doses or cycle delays due to treatment-related AEs, and reasons for treatment discontinuations will be analyzed. ▪ Pharmacokinetics (PK), samples for PK analysis will be obtained during Cycle 1 exclusively. ▪ Exploratory Biomarker Analysis, biopsy samples (initial and relapse) and blood samples will be analyzed in order to examine any correlation of efficacy with molecular markers related to the mechanism of action of plitidepsin or to the pathogenesis of the disease. A total of 60 patients with AITL confirmed by central pathological review will be treated, 19 or more responders will be needed to get an overall estimate for response rate higher than 30% and its lower limit for the 95% confidence interval (CI) greater than 20% (31.7% CI95% 20.3–45.0% following the binomial distribution). Two futility analyses of the primary endpoint (ORR according to the Lugano classification response criteria per independent review) are planned to reject the alternative hypothesis around six months after approximately 25% and 50% of eligible patients have been treated (15 and 30 patients, respectively).
ADDITION OF PATIENTS	All eligible and treated patients with AITL diagnosis confirmed after central pathological review will be included in the main efficacy analyses (primary and secondary endpoints). If a patient is treated but AITL diagnosis is not finally confirmed after central pathological review of the biopsy (even if inclusion was approved on the basis of the local histopathological report) then an additional patient will be included. Specifically, cases with features of follicular-PTCL and PTCL-NOS with T_{FH} phenotype or with features of progression/ transformation from AITL to Diffuse Large B-cell Lymphoma need to be excluded from the main efficacy analysis so additions are permitted

	in the event such patients are included before (or in spite of) central pathological exclusion. All patients without central confirmation will be excluded from the main efficacy analyses but included in safety analyses and, as supportive analyses, efficacy assessments will be done including all treated patients.
PLANNED TRIAL PERIODS (individually per patient)	Patients will be evaluated at scheduled visits in three study periods: ▪ **Pretreatment:** from signature of informed consent to first dose of study treatment. ▪ **Treatment:** from first dose of study treatment to **End of treatment (EOT).** EOT is standardly defined as 30 days (± one week) after the day of last administration of study treatment or as soon as possible after the End of Cycle 6 radiological and clinical assessments (if the patient discontinues), unless the patient starts a new antitumor therapy or dies within 30 days from the last dose, in which case the date of administration of this new antitumor therapy or the date of death will be considered the EOT date. ▪ **Follow-up:** after EOT, patients will be followed every four weeks until resolution or stabilization of toxicities (if any). Patients who discontinue treatment without disease progression will be followed every four months (+ two weeks) for the first two years of follow-up, and every six months (+ two weeks) thereafter, unless clinically indicated, until PD, start of other antitumor therapy, death or the date of study termination (clinical cutoff), whichever occurs first. After documented progression or start of a new antitumor therapy, patients will be followed for survival approximately every four months during the first two years, and then approximately every six months until death or the date of study termination, whichever occurs first. For the purpose of collecting information on the patient's survival exclusively, a documented telephone call is acceptable; follow-up for survival will be completed for all patients only if results of the primary endpoint confirm the trial as positive. Patients will be considered to be **on-study** from the signature of the informed consent form (ICF) to the end of the follow-up period (or screening failure). Investigators can appraise potential study candidates in a pre-screening period but only perform study-specific screening assessments after the patient formally consents. Patients will be considered to be **on-treatment** from the date of first dose until EOT. Patients will receive study treatment until: ▪ Disease progression (PD). ▪ Maximum of six cycles unless the patient is in: • PR 4–8 weeks after last dose of Cycle 6: in accordance with Investigator decision, the patient may then continue in treatment until CR or progression. • SD 4–8 weeks after last dose of Cycle 6: in accordance with Investigator decision, the patient may continue in treatment until CR or progression. ▪ If patient is in CR after six treatment cycles, treatment

	should be stopped. ▪ The patient achieves PR or CR at any time during the planned six cycles and is eligible for consolidation with autologous or allogeneic stem cell transplant (SCT) as per Investigator criteria. ▪ There is unacceptable toxicity. ▪ There is intercurrent illness of sufficient magnitude to preclude safety continuation of the study. ▪ There is patient refusal and/or non-compliance with study requirements. ▪ Investigator's decision. ▪ There is a protocol deviation with an effect on the risk/benefit ratio management of the patient. ▪ There is a treatment delay > 15 days from the treatment due date (except in case of clear clinical benefit, with the Sponsor's approval). ▪ There is a requirement of > 2 dose reductions (except in case of clear clinical benefit and with the Sponsor's approval).
PLANNED TRIAL PERIODS (for the whole study)	The total duration of the study will be approximately 42 months. **Planned start date** (first patient on study): 2Q2016. **Planned enrollment period**: 36 months. **Planned end-of-study date** (clinical cutoff): 12 months after the last patient's inclusion. If there are patients still being treated at the planned cutoff date, the actual cutoff date will be the date when those patients have completed the ongoing treatment cycle and the corresponding EOT visit. The study will be closed earlier if fewer than 15 patients are recruited in the first year after most of the sites are in active enrollment. Recruitment reviews will continue annually to assess the feasibility of meeting the study objectives and study continuation.

SCHEDULE OF ASSESSMENTS AND PROCEDURES

Study day	Screening/ Baseline	Cycle 1				Further cycles				End of Cycle 6	EOT [1]	Follow-up [5,6]
		1	8	15	22	29=1	8	15	22			
Written IC (before any study procedures)	●	-	-	-	-	-	-	-	-	-	-	-
Plitidepsin administration	-	●	●	●	-	●	●	●	-	-	-	-
Demographic data	–28 to 0	-	-	-	-	-	-	-	-	-	-	-
Medical history/baseline conditions	–28 to 0	-	-	-	-	-	-	-	-	-	-	-
Cancer history [2]	–28 to 0	-	-	-	-	-	-	-	-	-	-	-
Complete physical examination (weight, BSA)	–14 to 0	●	-	-	-	●	-	-	-	●	●	-
Basic neurological examination	–14 to 0	●	-	-	-	●	-	-	-	●	●	-
Performance status (ECOG)	–14 to 0	●	-	-	-	●	-	-	-	●	●	-
Vital signs (HR, ABP, temp)	–14 to 0	●	-	-	-	●	-	-	-	●	●	-
Hematology [3]	–14 to 0	●	●	●	●	●	●	●	-	●	●	-
Biochemistry-A [3, 4]	–14 to 0	●	●	●	●	●	●	●	-	●	●	-
Biochemistry-B [4]	–14 to 0	●	-	-	-	●	-	-	-	-	●	-
Coagulation tests	–14 to 0	●	-	-	-	●	-	-	-	-	●	-
Serum beta-2 microglobulin	–14 to 0	-	-	-	-	-	-	-	-	-	-	-
ECG [7]	–14 to 0	●	●	●	-	●	●	●	-	-	-	-
Pregnancy test [8]	–14 to 0	-	-	-	-	●	-	-	-	-	●	-
Urine elemental dipstick and sediment	–14 to 0	Repeat if clinically indicated									-	-
Complete serology (viral load tests if indicated)	–14 to 0	Repeat if clinically indicated									-	-
Coombs test	–14 to 0	Repeat if clinically indicated									-	-
Serum immunoglobulin quantification (immunoelectrophoresis)	–14 to 0	Repeat if clinically indicated									●	-
Serum protein electrophoresis	–14 to 0	Repeat if clinically indicated									●	-
LVEF (ECHO or MUGA)	–28 to 0	Repeat if clinically indicated									-	-
Chest X-ray (if needed)	–28 to 0	Repeat if clinically indicated									●	-
Tumor assessment (PET/CT + CT) [9]	–28 to 0	1–2 wks after last dose of Cycle 3 and 4–8 wks after last dose of Cycle 6 (or at suspected clinical progression) [9]									-	-
Tumor assessment (CT) [10]	-	-									-	● [10]
Bone marrow biopsy/aspirate	–14 to 0	Repeat if clinically indicated									If involved at diagnosis	-
Biopsy/blood sample	● [11]	● [11]	-								-	-
Concomitant therapies	–14 to 0	← Throughout the on-treatment period →										-
Pharmacokinetics	-	●	●	●	-	-	-	-	-	-	-	-
Adverse events [12]	–14 to 0	← Throughout the on-treatment period →										● [5,6]

Day 0 = registration, confirmation of eligibility; Day 1 = day of first cycle administration (with infusion start); Day 29 = Day 1 of the next cycle. Note that registration may or may not be the calendar day prior to Day 1 but Day 0 implies that there should be no gap in the collection of relevant patient data; in either case, the total screening duration must be no longer than the 28-day period prior to Day 1.
If an infusion is delayed beyond the permitted protocol window, assessments planned for the original infusion day must be repeated on the day infusion finally takes place. Assessments for a particular visit do not need to all take place on the same day but should all be within the planned time window. Physical examination and laboratory assessments, for example, can be performed more frequently during the study if clinically required.

Permitted windows for assessments
±1 day for study treatment administration and clinical assessments (ECOG PS, vital signs, weight, BSA, neurological assessment—always prior to infusion).
–2 days for hematology, biochemistry-A, serum β-2 microglobulin, biochemistry-B and coagulation tests. Note: windows for laboratory assessments only apply prior to the scheduled infusion, that is within 48 hours before the next scheduled infusion (except C1D1).

(1) EOT assessments should take place approximately 30 days (± one week) after discontinuation of study treatment or as soon as possible after the End of Cycle 6 radiological and clinical assessments (if the patient discontinues). Failure to attend the EOT visit exclusively due to a deteriorated clinical condition will not be considered a protocol deviation. The listed assessments are required if no recent data are available (i.e. within the previous 10 days) or if the last data available show a grade ≥ 2 treatment-related alteration whenever the medical condition of the patient allows.

(2) The patient's anonymized local histopathology report must be provided as early as possible in the screening process for central pathological review. Cancer history includes: primary diagnosis; prognostic factors at first diagnosis (PIT, IPI, PIAI); prior treatment(s) with best response and TTP; documented relapse or refractory disease. Prognostic Index for Peripheral T-cell lymphoma (PIT) uses four variables as predictive for survival: age, PS, LDH level, and BM involvement (see Appendix 3). The standard International Prognostic Index (IPI) comprises the following variables: age ≥ 60 years, disease stages III to IV, LDH > normal, extranodal sites (ENSs) > one and PS ≥ 2. The alternative Prognostic Index for AITL (PIAI) comprises the following factors: age ≥ 60 years, PS ≥ 2, ENSs > one, B symptoms and platelet count < 150×10^9/L (see Appendix 4). Ann-Arbor staging is also required (see Appendix 5).

(3) Not necessary on C1D1 if performed within the seven previous days and there is no change in the patient's clinical status and medications. To be performed at least every other day in the presence of grade 4 non-febrile neutropenia or febrile neutropenia, and every day in the presence of grade 4 thrombocytopenia until recovery.

(4) Not necessary on C1D1 if performed within the seven previous days and there is no change in the patient's clinical status and medications. Biochemistry-A to be performed at least every other day in the presence of grade 3/4 vomiting or any other drug-related SAE.

(5) Patients discontinuing treatment due to a drug-related AE should be followed until recovery/stabilization. Beyond 30 days after the last administration of the study drug, only those procedures that are relevant to response assessment or any remaining toxicity need to be performed.

(6) Patients who discontinue treatment without progression will be followed until PD, start of other antitumor therapy, death or the date of study termination (clinical cutoff), whichever occurs first: see schedule in point (10). After documented progression or start of a new antitumor therapy, patients will be followed for survival approximately every four months during the first two years, and then approximately every six months until death or the date of study termination, whichever occurs first. For the purpose of collecting information on patient's survival, a documented telephone call is acceptable; follow-up for survival will be completed for all patients only if results of the primary endpoint confirm the trial as positive.

(7) First cycle, Day 1**:** Prior to the first infusion (unless performed as part of screening within the previous 14 days), at the end of the first infusion, at 30 min post-infusion and at 1-hour post-infusion. First cycle, Day 8 and Day 15: Prior to the infusion, and at 1-hour post-infusion (see Table 6). Further cycles: Prior to each infusion.
Rhythm, frequency and QT interval should be specifically described, as well as any ECG anomaly or variation with respect to baseline.

(8) Assessment of β-hCG only if the patient is a WOCBP. During the on-treatment period, testing should be every cycle (or, at least, every month).

(9) Clinical and radiological assessment. When PET-CT is performed it must be in combination with diagnostic quality CT with intravenous contrast (except medically contraindicated). Two alternatives are allowed: Hybrid PET CT scanners may be used to acquire diagnostic quality CT which includes intravenous contrast *OR* PET CT without intravenous contrast and diagnostic quality CT images with intravenous contrast using a standalone CT scanner must be performed.
A PET-CT scan for radiological tumor assessment is required at baseline, one to two weeks after last dose of Cycle 3 and at least four weeks (but no more than 8 weeks) after last dose of Cycle 6 (or earlier in the event of treatment discontinuation for whatever reason; no radiological assessment is necessary in the event of withdrawal due to any reason other than PD during or after Cycle 4 if the Cycle 3 radiological assessment has been performed correctly) or at suspected clinical progression while on treatment. Cycle 4 can be started without waiting for the results of the Cycle 3 tumor assessment. The End of Cycle 6 visit should take place 4–8 weeks after last dose of Cycle 6 (when the PET-CT results are available). If a patient is shown to have SD or PR at this assessment, treatment can resume (Cycle 7), and tumor assessment may be evaluated by CT scans every four months (+ 2 weeks) for the first two years and every six months (+ 2 weeks) thereafter, but any subsequent improvement in response should be confirmed by PET-CT. If a patient is shown to have CR or PD, the patient should be discontinued and the EOT visit performed as soon as possible. Disease progression at any time during the study should be confirmed by imaging (if the physical condition of the patient permits).

(10) Clinical and radiological assessment. A CT scan may be used for radiological tumor assessment of patients who showed clinical benefit (SD, PR, CR) every four months (+2 weeks) for the first two years of follow-up, and every six months (+2 weeks) thereafter, unless clinically indicated. In the case a patient continues in treatment beyond Cycle 6 (see section 5.2.1.2), CT may be used but any subsequent improvement in response should be confirmed by PET-CT.

(11) Diagnosis and/or re-biopsy specimens are required for central pathological review and prior to each futility analysis. An incisional or excisional biopsy is preferred but a core-needle biopsy can be considered when excisional biopsy is not possible. Archived tissue samples of representative tumors: a formalin-fixed paraffin-embedded (FFPE) tissue block (preferred) or freshly-cut unstained tumor slides. Collect 10 mL blood at the same time as the first PK sample on Day 1: one whole blood sample for germline DNA extraction (6 mL) and another blood sample (4 mL) to obtain plasma. A separate instruction manual for sites will be provided.

(12) Clinical assessment of the patient's signs and symptoms (if any and including nurses' assessment and patient-reported issues) should continue on an ongoing basis throughout the study and be reported at least every cycle as AEs graded according to NCI-CTCAE v.4: between IC and Day 0, AEs are considered baseline and non-treatment emergent.

Hematology: Differential white blood cells (WBC), hemoglobin, hematocrit and platelets.

Biochemistry-A: AST, ALT, total bilirubin (direct bilirubin if total bilirubin > 1.5 × ULN), ALP, creatinine, calculated creatinine clearance (Cockcroft-Gault formula), glucose, serum electrolytes (Na^+, K^+, Mg^{++}, Ca^{++}) and CPK (CPK-MB fraction should be measured if CPK is abnormally high).

Biochemistry-B: Uric acid, LDH, total proteins, albumin and C-reactive protein.

Coagulation tests: PT, PTT and INR.

ABP, arterial blood pressure; AE, adverse event; ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; BM, bone marrow; CPK, creatine phosphokinase; CPK-MB, creatine phosphokinase-isoenzyme MB; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; EOT, end of treatment; HR, heart rate; IC, Informed Consent; INR, international normalized ratio; LDH, lactic dehydrogenase; LVEF, left ventricular ejection fraction; MUGA, multiple-gated acquisition scan; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PD, progressive disease; PS, performance status; PT, prothrombin time; PTT, partial thromboplastin time; SAE, serious adverse event; TTP, time to progression; ULN, upper limit of normality; WBC, white blood cells; wk, week; WOCBP, woman of childbearing potential.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACVBP	Doxorubicin, Cyclophosphamide, Vindesine, Bleomycin and Prednisone
AE(s)	Adverse Event(s)
AITL	Angioimmunoblastic T-cell Lymphoma
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
ASCT	Autologous Stem Cell Transplantation
AST	Aspartate Aminotransferase
BM	Bone Marrow
BSA	Body Surface Area
CHOP	Cyclophosphamide, Doxorubicin, Vincristine and Prednisone
CI	Confidence Interval
CLL	Chronic Lymphocytic Leukemia
CNS	Central Nervous System
CPK	Creatine Phosphokinase
CPK-MB	Creatine Phosphokinase-isoenzyme MB
CR	Complete Remission/Complete Response
CrCL	Creatinine Clearance
CRF	Case Report Form
d/D	Day(s)
DoR	Duration of Response
EBV	Epstein-Barr Virus
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	Ethylenediaminetetraacetic Acid
EOI	End of Infusion
EOT	End of Treatment
EPO	Erythropoietin
FDA	Food and Drug Administration (United States)
FDC	Follicular Dendritic Cells
FFPE	Formalin-fixed Paraffin-Embedded
FFS	Failure-free Survival
FUP	Follow-up
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-stimulating Factor

GELA	Groupe d'Etude des Lymphomes de l'Adulte
GGT	Gamma-glutamyltransferase
GMT	Greenwich Meridian Time
H	Hour
HBV	Hepatitis B Virus
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
i.v.	Intravenous (Intravenously)
IA	Investigator's Assessment
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICOS	Inducible T-cell Co-stimulator
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committees
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IPI	International Prognostic Index
IRB	Institutional Review Board
IRC	Independent Review Committee
ISH	In Situ Hybridization
IWG	International Working Group
LDH	Lactate Dehydrogenase
LLN	Lower Limit of Normal
LVEF	Left Ventricular Ejection Fraction
MR	Minimal Response
MUGA	Multiple-gated Acquisition Scan
MVD	Microvessel Density
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NE	Not Evaluable
NGS	Next-generation Sequencing
NHL	Non-Hodgkin Lymphoma
ORR	Overall Response Rate
OS	Overall Survival
OS12	Overall Survival at 12 Months
OS6	Overall Survival at 6 Months
p.o.	Per os (orally)

PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PFS12	Progression-Free Survival at 12 Months
PFS6	Progression-Free Survival at 6 Months
PhV	Pharmacovigilance
PIAI	Prognostic Index for AITL
PIT	Prognostic Index for Peripheral T-cell Lymphoma
PK	Pharmacokinetic
PR	Partial Remission/Partial Response
PRE TT	Pretreatment
PS	Performance Status
PT	Prothrombin Time
PTCL	Peripheral T-Cell Lymphoma
PTCL-NOS	Peripheral T-Cell Lymphoma - Not Otherwise Specified
PTT	Partial Thromboplastin Time
q4wk	Every Four Weeks
R/R	Relapsed/Refractory
RBC(s)	Red Blood Cell(s)
SAE(s)	Serious Adverse Event(s)
SCT	Stem Cell Transplantation
SD	Stable Disease
SPEP	Serum Protein Electrophoresis
SUSAR/SUA	Suspected Unexpected Serious Adverse Reaction
T_{FH}	T Follicular Helper
TT	Treatment
TTP	Time to Progression
ULN	Upper Limit of Normal
VEGF	Vascular Endothelial Growth Factor
VEGF-R	Vascular Endothelial Growth Factor Receptor
WBC	White Blood Cells
WMA	World Medical Association
WOCBP	Woman/Women of Childbearing Potential
β-hCGs	Beta Subunit of Human Chorionic Gonadotropins

1. INTRODUCTION

1.1 DISEASE BACKGROUND: ANGIOIMMUNOBLASTIC T-CELL LYMPHOMA

Angioimmunoblastic T-cell lymphoma (AITL) is the second most common form of peripheral T-cell lymphoma (PTCL), accounting for approximately 20% of PTCLs and 2% of non-Hodgkin lymphomas (NHL) (1). In the United States, the incidence is approximately 0.05 cases per 100,000 person years (2). The disease is more common in Europe (29% of PTCL cases) than in the United States or Asia (3).

1.1.1 Clinical Features of Angioimmunoblastic T-cell Lymphoma

AITL characteristically affects elderly people, particularly those aged 60 to 80 years, with male predominance. Interestingly, some cases present as a subacute or acute systemic illness, which may manifest after the administration of drugs, especially antibiotics, or after a viral infection.

Immune dysregulation is an important characteristic of this disease. Generalized lymphadenopathy is almost constant, as well as the presence of constitutional symptoms such as fever and weight loss (4). Extranodal disease is common, with hepatosplenomegaly and bone marrow (BM) involvement in up to 70% of cases. The presence of circulating tumor cells is frequent and approximately 50% of cases show a maculopapular rash (5).

Other variable manifestations of AITL include arthralgias, pleural effusions, ascites, lung involvement with irregular infiltrates, neurological manifestations and gastrointestinal involvement. Stage III or IV is observed in more than 80% of AITL cases (6, 7).

Some laboratory abnormalities are frequently observed: anemia (often hemolytic and Coombs positive), hypereosinophilia, polyclonal hypergammaglobulinemia as well as lactate dehydrogenase (LDH) elevation are characteristic aspects of the disease. Other less common laboratory abnormalities include lymphopenia, thrombocytopenia and the presence of various autoantibodies (rheumatoid factor, antinuclear factor, anti-smooth muscle, cryoglobulins or cold agglutinins) (8).

Distinguishing pathological features include the presence of diffuse polymorphous infiltrate consisting of typical tumor cells admixed to small lymphocytes, histiocytes, immunoblasts, eosinophils and plasma cells. Prominent branching high endothelial cells and irregular proliferation of follicular dendritic cells are frequently observed and represent unique histological features among the PTCL subtypes. B immunoblasts may be numerous in areas between follicular dendritic cells (FDC) and they often harbor Epstein-Barr virus (EBV). Occasionally in the course of the disease, this immunoblast EBV-expressed population gives rise to secondary large B-cell lymphomas (9, 10).

The malignant T-cell has been characterized as an unusual subset of CD4 positive follicular T helper (T_{FH}) cells, and typical markers may help in the diagnosis of the disease, such as CD10, CXCL13, PD-1 and bcl-6 as well as the expression of ICOS (11-14). CD10 positivity is observed in up to 30% of cases of AITL in contrast to other PTCL subtypes. These markers are distinctive enough to help in the diagnosis of the disease in contrast with other PTCL subtypes (15).

AITL has been associated with some viruses, specifically EBV and herpes virus 6 (HPV6) genomes (16). Although there is not a single characteristic genetic alteration in the disease, trisomy 3, trisomy 5 and an additional X chromosome may be observed (17).

Recently, critical insights into AITL have been gained from molecular analysis. A global molecular signature of AITL has been described which defines characteristically the disease and contrasts with the molecular signature of other PTCL subtypes (18, 19). The contribution of tumor and microenvironment has been highlighted by these studies. Indeed, characteristic overexpression of B-cell related genes, chemokines and chemokine receptors as well as genes related to the extracellular matrix and angiogenesis have been clearly delineated (19, 20). This signature is unique among the PTCL setting and offers the opportunity to target these events as therapeutic strategies.

1.1.2 Pathogenesis of Angioimmunoblastic T-cell Lymphoma

AITL is a tumor of T_{FH} cells (14, 21). In this context, the expression of the CXCL13 chemokine is a key pathogenic factor. Throughout this chemokine, recruitment of B-cell lymphocytes into the germinal centers takes place. Furthermore, the expression of this chemokine by tumor cells activates this B-cell component and expands and facilitates plasmacytic differentiation, which in turn results in hyperglobulinemia and secretion of Il 21 (22).

The tumor microenvironment displays characteristic functional alterations. For instance, quantitative and qualitative abnormalities of T-cell subsets lead to paraneoplastic immunological dysfunction. Aside from the expanded B-cell component and T-cell alterations, other stroma alterations are important in the pathogenesis of AITL. Indeed, vascular endothelial growth factor (VEGF) and its receptors, as well as angiopoietin 1 are typically expressed and secreted by both tumor cells and FDC, then stimulating tumor angiogenesis (19, 20). Thus, angiogenesis might be a therapeutic target of AITL.

1.1.3 Natural History of Angioimmunoblastic T-cell Lymphoma and Prognostic Factors

The clinical course of AITL varies, with occasional spontaneous remissions. Nevertheless, the prognosis of the disease is dismal, with median survival < 3 years, and with 20–30% of long-term survivors (3, 23). Different clinical risk factors as well as biological parameters have been described as prognostic factors. In a retrospective study of 157 cases of AITL, a multivariate analysis showed the following covariates as adversely associated with prognosis: male gender, anemia and the presence of mediastinal lymphadenopathy (7).

Other systems such as the International Prognostic Index (IPI) (24) or the prognostic index for peripheral T-cell lymphoma (PIT) (Appendix 3) were of limited value in this disease (25). Recently, a risk model for AITL (prognostic index for AITL, PIAI) was designed based on the following adverse covariates: age > 60 years, performance status ≥ 2, extranodal sites > 1, B-symptoms, and platelet count < 150,000/mL (23). The simplified PIAI had a low-risk group (zero to one factors) with a 5-year survival of 44%, and a high-risk group (two to five factors) with a 5-year survival of 24% (Appendix 4).

1.1.4 Definition and Pathological Diagnosis of Angioimmunoblastic T-cell Lymphoma

Definition and diagnosis of AITL will be based on current standard criteria (Appendix 1).

Systemic clinical manifestations are a hallmark of AITL and include: generalized lymphadenopathy, hepatosplenomegaly, skin rash (often with pruritus), bone marrow

involvement, advanced clinical stage, and polyclonal hypergammaglobulinemia. In the absence of systemic clinical syndrome, an AITL diagnosis is doubtful.

Pathologically, AITL is a morphologically heterogeneous T-cell lymphoma characterized by a polymorphous infiltrate of the lymph nodes by small to medium-size lymphocytes, with clear to pale cytoplasm, and with expression of T_{FH} markers (PD1, BCL6, CXCL13, CD10, ICOS), associated with a prominent proliferation of high endothelial venules and follicular dendritic cells (26). Several morphologic variants have been described, including classic (diffuse +/- epithelioid cells), rich in large cells, and hyperplastic germinal centers.

1.1.5 Treatment for Angioimmunoblastic T-cell Lymphoma

Conventional chemotherapy regimens with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) or CHOP-like fail to increase the long-term survival rate to more than 30% (7). Different single agents (cyclosporine, thalidomide, lenalidomide or gemcitabine) have been associated with responses, including complete durable responses. Activity has also been observed with nucleoside analogs, such as fludarabine, 2-chlorodeoxyadenosine, interferon-alfa corticosteroids and others (27). In the International Peripheral T-cell lymphoma project, the 5-year overall survival (OS) and failure-free survival (FFS) were 33% and 18%, respectively (3).

Due to the poor prognosis of the disease, more intensive conventional chemotherapeutic regimens have been tested in AITL, such as adding etoposide to CHOP or the *Groupe d'Etude des Lymphomes de l'Adulte* (GELA) regimen of ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone) (7). However, no substantial improvement has been observed. In retrospective analyses, consolidation of response with autologous stem cell transplantation (ASCT) yielded superior results than conventional chemotherapeutic regimens (28, 29). However, the role of ASCT as consolidation in the first-line therapy of AITL has not been proven to date.

Data on allogeneic transplantation are encouraging but population size is limited. Other available agents, such as alemtuzumab or Ontak®, or therapies targeting VEGF (e.g., bevacizumab) have shown anecdotal activity in PTCL (7, 30-33). More robust data evaluating the efficacy and safety of bendamustine as single agent in refractory or relapsed PTCL were reported from the BENTLY trial (34). In this study, 60 patients were included with 27 of them (45%) being refractory to their last prior chemotherapy. The median number of previous lines of chemotherapy was one and 33% of patients received fewer than three cycles of bendamustine, mostly because of progression. In an intention-to-treat analysis, the overall response rate (ORR) was 50%, with 28% of patients showing complete remissions (CRs). The duration of response (DoR), progression-free survival (PFS) and OS were 3.5, 3.6 and 6.2 months, respectively. The response rate of AITL patients in this population was not significantly different from the overall PTCL group. To date, three single agents, pralatrexate, romidepsin and bendamustine, are considered active drugs in PTCL, with higher activity for the AITL subtype with romidepsin and bendamustine.

Since the tumor microenvironment has a key role in the pathogenesis of AITL, several therapeutic maneuvers have been tested in this regard. For instance, the GELA group tested the regimen of CHOP-rituximab targeting the B-cell component of the disease, which may have importance in the maintenance of the tumor cell. However, the results of this study do not demonstrate any improvement over the results obtained with CHOP alone. Few case reports in the literature have shown complete remissions with

immunomodulators such as thalidomide or lenalidomide (35). Other drugs target the epigenetic alterations typically observed in AITL, with some responses with histone deacetylase inhibitors such as SAHA (suberoylanilide hydroxamic acid), depsispeptide or bellinostat. Furthermore, mutations in genes involved in the control of chromatin structures, such as IDH 1, 2 and TET2 have been recently described (36, 37); this opens the door to testing hypomethylating agents in this disease. Other compounds like aurora kinase inhibitors are currently the subject of intensive investigation.

In any case, due to the poor prognosis of the disease, new specific active agents are needed. Since PTCL represents a heterogeneous group of lymphomas, with several subtypes biologically different, the search of specific agents for the different subtypes must continue. Research challenges include the fact that these are very rare diseases with low frequency and, therefore, many logistic difficulties are encountered in these trials. Nevertheless, if we want to make progress in therapeutics, we need specific agents to treat these neoplastic diseases.

Two drugs (pralatrexate and romidepsin) have been approved by the FDA for the wide group of PTCL, in the particular case of refractory or relapsing patients after conventional or high-dose chemotherapy supported with stem cell transplantation, on the basis of modest activity in this group of Non-Hodgkin, poor prognosis lymphomas. However, the activity of these two drugs in the small number of treated patients with AITL, which were included in the more general group of PTCL, was variable. Indeed, only one of 13 patients with AITL (8%) who received pralatrexate responded to treatment, whereas eight of 27 patients (30%) treated with romidepsin responded, being included 5 CRs (19%) (38, 39).

In the search for new active drugs, promising activity has been observed with plitidepsin in AITL. A phase II study evaluating plitidepsin in non-cutaneous PTCL (study APL-B-013-02), showed a response rate of 20.7% in the whole group of treated patients. The response rate increased to 33.3% in the nine patients with AITL treated in this clinical trial (including CR in 22.2% of patients). Interestingly, one complete remission was obtained in a patient who had previously received ASCT; this remission was durable after more than 29 months since he was treated.

On the basis of the promising activity observed in this small cohort of AITL patients, this phase II clinical trial will evaluate plitidepsin as a treatment for patients with R/R AITL.

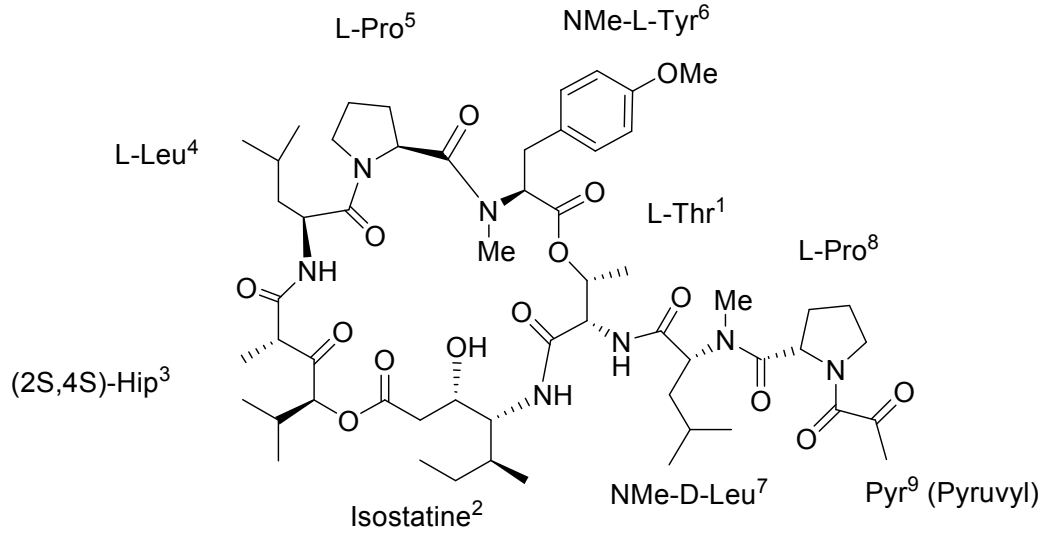
1.2 INFORMATION ON THE STUDY DRUG: PLITIDEPSIN

Please refer to the Investigator's Brochure (IB) for more detailed information on plitidepsin.

1.2.1 Name and Chemical Information

Plitidepsin (Aplidin®) is a cyclic depsipeptide originally isolated from a Mediterranean marine tunicate, *Aplidium albicans*. The molecular formula is C57H87N7O15 with a molecular weight of 1,110.341. Plitidepsin is manufactured by total synthesis.

Figure 1. Molecular formula of plitidepsin.



1.2.2 Non-clinical Data

1.2.2.1 *Mechanism of Action*

Plitidepsin interacts and forms different complexes with eEF1A in two subcellular regions, first bound to the inner side of the plasma membrane and then free in the cytoplasm of tumor cells. This interaction leads to a decrease in production of intracellular glutathione, an increase in reactive oxygen species and ultimately to activation of the Rac1/JNK pathway and caspase-dependent apoptosis (40-42). In addition to the pro-apoptotic properties of plitidepsin, the molecule has demonstrated anti-angiogenic properties in several preclinical models via direct activity on VEGF-stimulated angiogenesis. In fact, plitidepsin has been shown *in vitro* to reduce the secretion of VEGF and its receptor type 1 (VEGFR-1) from MOLT-4 human leukemia cells (43). It seems that the majority of the pharmacologic activity of plitidepsin can be attributed to a combination of these cellular effects *in vivo*.

1.2.2.2 *In Vitro and In Vivo Activity*

Plitidepsin showed antitumor activity with *in vitro* and *in vivo* models. *In vitro* studies showed cytotoxic effects of plitidepsin against a broad panel of cell lines with values of $IC_{50} \leq 1$ nM. Plitidepsin was particularly active against multiple myeloma cell lines, human leukemia and lymphoma (48), as well as against pancreas, non-small cell lung, breast, melanoma, sarcoma, bladder, gastric, ovarian, and colon tumor cell lines. *In vivo* studies showed an antitumor effect of plitidepsin in xenograft models of multiple myeloma (as a single agent or in combination with dexamethasone) and T-cell lymphoma (48).

1.2.3 Clinical Data

As of 31 March 2015 (cutoff date for the Investigator's Brochure version 15.0), 1103 cancer patients had been included in the clinical development program of plitidepsin: 381 in phase I studies, 474 in phase II studies (24 in one investigator-initiated phase II trial), and 248 in a phase III study.

Two clinical trials in patients with relapsed/refractory multiple myeloma are ongoing at the time of the last analysis: a pivotal randomized phase III trial (APL-C-001-09–ADMYRE) comparing plitidepsin in combination with dexamethasone against

dexamethasone alone that started in 2010; and a phase I trial (APL-A-012-13) of plitidepsin in combination with bortezomib and dexamethasone that started in 2014.

1.2.3.1 *Phase I Trial in Multiple Myeloma*

A phase I clinical trial (APL-A-012-13) of plitidepsin in combination with bortezomib and dexamethasone in patients with relapsed/refractory multiple myeloma started in April 2014. The primary objective is to determine the recommended dose of the combination. Fourteen patients had been included up to July 2015.

1.2.3.2 *Phase II Trials in Hematological Malignancies*

Table 1 summarizes the completed phase II clinical trials conducted with plitidepsin in patients with hematological malignancies.

Table 1. Completed phase II trials evaluating plitidepsin in hematological malignancies.

Study	Study design and objectives	Dose (infusion)	Treated patients	Efficacy (objective response or TTP > 3 months)
Fortnightly schedule (d1,15 q4wk)				
APL-B-014-03 (49, 50)	Phase II multicenter, open-label, clinical and PK study of plitidepsin as a 3-hour infusion every 2 weeks alone or in combination with dexamethasone, in pre- treated patients with **relapsing or refractory multiple myeloma**	Plitidepsin 5 mg/m^2 (3-h i.v.)	51	(n=47): 2 PR and 4 MR as per the Myeloma Response Criteria (ORR: 12.8%).
		Plitidepsin 5 mg/m^2 (3-h iv) + dexamethasone 20 mg p.o. d1-4 q4wk	19*	(n=18): 2 PR and 2 MR as per the Myeloma Response Criteria (ORR: 22.2%). Median TTP = 4.2 months; median PFS = 3.8 months.
APL-B-020-10 (51)	Open-label, phase II clinical trial of plitidepsin in patients with **primary myelofibrosis** and **post polycythemia vera/essential thrombocythemia myelofibrosis**	Plitidepsin 5 mg/m^2 (3-h i.v.)	12	(n=11): 1 clinical improvement as per the IWG-MRT consensus criteria (ORR: 9.1%). Median PFS = 4.6 months.
Weekly schedule (d1,8,15 q4wk)				
APL-B-012-02 (52)	A Phase II multicenter, open-label, clinical and PK study of plitidepsin as a 1-hour weekly iv infusion, in patients with **relapsed or refractory indolent non-Hodgkin lymphoid neoplasms**	Plitidepsin 3.2 mg/m^2 (1-h i.v.)	8	(n=6): No objective responses as per the NCI-sponsored Working Group guidelines for NHL and CLL. SD in 5 patients. Median TTP = 4.0 mo; median PFS = 4.7 months; median OS = 12.4 months.
APL-B-013-02 (53, 54)	A Phase II multicenter, open-label, clinical and PK study of plitidepsin as a 1-hour weekly iv infusion, in patients with **relapsed or refractory aggressive non-Hodgkin lymphoma**	Plitidepsin 3.2 mg/m^2 (1-h i.v.)	64	Non-cutaneous PTCL (n=29): 2 CR and 4 PR as per the IWG criteria for NHL (ORR: 20.7%). Median TTP/PFS = 1.6 months; median OS = 10.2 months. AITL (subgroup included in PTCL cohort; n=9): 2 CR and 1 PR as per the IWG criteria for NHL (ORR: 33.3%). Duration of response of 121, 12 and 4 weeks. Other lymphomas (n=30): No objective responses as per the IWG criteria for NHL. Median TTP/PFS = 1.3 months; median OS = 4.5 months.

Study	Study design and objectives	Dose (infusion)	Treated patients	Efficacy (objective response or TTP > 3 months)
APL-B-015-04 (55)	A Phase II multicenter, open-label, clinical and PK study of plitidepsin as a 1-hour weekly iv infusion, in patients with **relapsed or refractory acute lymphoblastic leukemia**	Plitidepsin 3.2 mg/m^2 (1-h i.v.)	17	(n=13): No complete or partial remissions. Median PFS = 0.6 months, median OS = 2.1 months.

*All 19 patients were first given plitidepsin alone in this study, and after showing suboptimal response their treatment was supplemented with dexamethasone.

The underlined n value shown in the efficacy column refers to patients evaluable for efficacy.

CLL, chronic lymphocytic leukemia; CR, complete remission/complete response; i.v., intravenous; IWG, International Working Group; IWG-MRT, International Working Group for Myelofibrosis Research and Treatment; MR, minimal response; NCI, National Cancer Institute; NHL, non-Hodgkin lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic; p.o., orally; PR, partial remission/partial response; PTCL, peripheral T-cell lymphoma; q4wk, every four weeks; SD, stable disease; TTP, time to progression.

1.2.3.2.1 Phase II Trials in Non-Hodgkin Lymphoma

Two phase II clinical trials evaluated the efficacy of the weekly (D1, 8 and 15 q4wk) schedule in patients with NHL. In one of these two studies (APL-B-012-02), no remissions were found. Evidence of antitumor activity was found in trial APL-B-013-02, in which the D1, 8 and 15 q4wk schedule was administered to 64 patients with relapsed/refractory aggressive NHL: 32 with non-cutaneous PTCL and 32 with other lymphomas. In the PTCL cohort, two CRs and four PRs as per the International Working Group (IWG) criteria for NHL occurred in 29 evaluable patients (ORR=20.7%), and two patients had SD for >3 months. Within the PTCL cohort, two CRs and one PR were reported in nine patients with AITL (ORR=33.3%). No treatment responses were found in the cohort of patients with other lymphomas. Research efforts, including pharmacogenomic studies, are currently ongoing to elucidate the potential mechanism responsible for the observed clinical activity in patients with non-cutaneous mature PTCL.

1.2.3.2.2 Phase II Trials in Multiple Myeloma

A phase II trial (APL-B-014-03) evaluated the fortnightly schedule [plitidepsin on day 1 and 15 every four weeks (q4wk)] in 51 patients with R/R multiple myeloma. Antitumor response was evaluated according to the Myeloma Response Criteria. Two partial responses (PRs) and four minimal responses (MRs) were found in 47 evaluable patients treated with plitidepsin (ORR=12.8%). Twenty-four other patients had stable disease (SD), which lasted for >3 months in four patients. Nineteen patients who showed disease progression (PD) or SD after receiving four cycles of plitidepsin had dexamethasone added to treatment. Two PRs and two MRs were found in 18 evaluable patients in this cohort (ORR=22.2%), while SD for >3 months occurred in eight patients. When response was assessed as per Investigator's criteria, the ORR was 12.8% for plitidepsin and 27.8% for plitidepsin combined with dexamethasone. Overall, these results suggest that plitidepsin administered alone or in combination with dexamethasone have clinical activity in patients with R/R multiple myeloma.

1.2.3.2.3 Phase II Trials in Myelofibrosis

The D1, 15 q4wk plitidepsin schedule was evaluated in 12 patients with myelofibrosis in other phase II trial (APL-B-020-10). Response was evaluated according to the International Working Group for Myelofibrosis Research and Treatment criteria. Clinical improvement was found in one of 11 evaluable patients (ORR=9.1%). In

addition, one patient had SD for >3 months. This antitumor activity was considered too modest to warrant further evaluation of plitidepsin in patients with myelofibrosis.

1.2.3.2.4 Phase II Trials in Acute Lymphoblastic Leukemia

A phase II clinical trial (APL-B-015-04) evaluated the efficacy of the weekly (D1, 8 and 15 q4wk) schedule in patients with R/R acute lymphoblastic leukemia. No responses or remissions were found.

1.2.3.3 *Phase III Trials in Multiple Myeloma (ADMYRE trial)*

An ongoing multicenter, open-label, randomized, phase III clinical trial (APL-C-001-09, ADMYRE) started in June 2010 and is currently comparing the efficacy and safety of plitidepsin combined with dexamethasone *vs.* dexamethasone alone in patients with relapsed/refractory multiple myeloma previously treated with at least three but no more than six therapeutic regimens. This is the first plitidepsin pivotal trial and is expected to randomize up to 250 patients worldwide to receive either plitidepsin 5 mg/m^2 i.v. as a 3-hour infusion on D1 and 15 q4wk plus dexamethasone 40 mg orally on D1, 8, 15 and 22 q4wk (Arm A), or dexamethasone alone at the same dose and schedule (Arm B). On 9 December 2012, the evaluation by an Independent Data Monitoring Committee (IDMC) of efficacy and safety data from 60 patients included in the first stage resulted in a recommendation to continue the trial unmodified, as the study met the established efficacy threshold of 30% pre-specified in the protocol. No safety issues were reported. At the last cutoff date (31 March 2015), recruitment was almost complete with a total of 248 patients included into this trial. Of 243 patients treated so far, 162 were in Arm A and 81 in Arm B; of those 81, 29 subsequently crossed over to Arm A.

1.3 STUDY RATIONALE

In phase I studies conducted with plitidepsin, the schedule consisting of 1-hour i.v. infusion given weekly on D1, 8 and 15 q4wk was found to be the most convenient for patients with NHL. An exploratory phase II clinical trial (APL-B-013-02) was conducted to evaluate the efficacy, tolerability and pharmacokinetics of this weekly plitidepsin schedule at a starting dose of 3.2 mg/m^2 in patients with R/R aggressive NHL. This phase II trial included two cohorts: patients with non-cutaneous PTCL and patients with other aggressive lymphomas (53, 54). No remissions were found in the cohort of 33 patients with other aggressive lymphomas. However, interesting antitumor activity was observed in 29 evaluable patients from the non-cutaneous PTCL cohort: ORR was 20.7% (95% CI, 8.0–39.7%) and SD rate was 20.7% (Table 2).

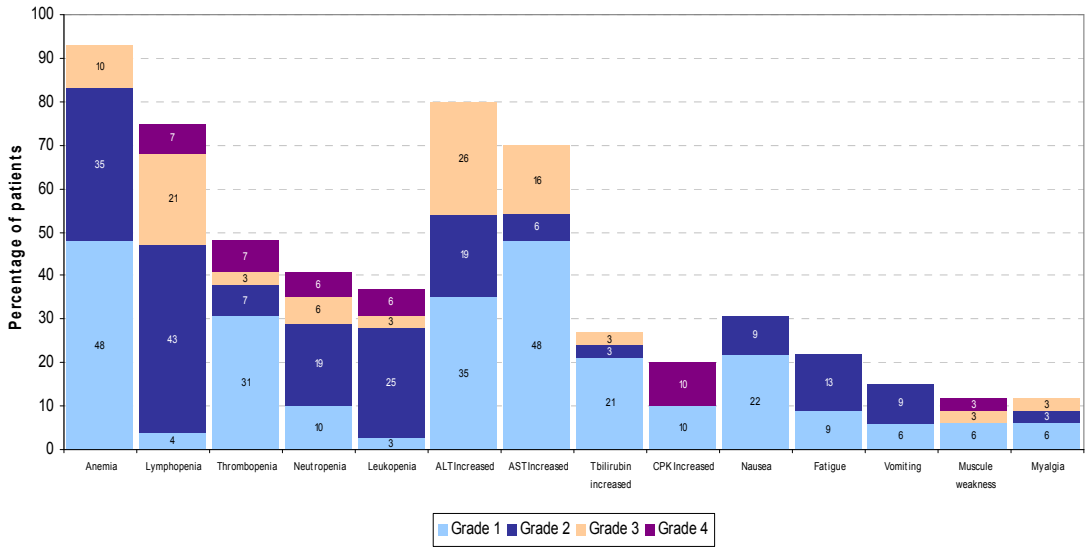
Table 2. Objective tumor response according to IWG criteria in evaluable patients with relapsed/refractory non-Hodgkin lymphoma treated with plitidepsin (study APL-B-013-02).

Patient response	Non-cutaneous PTCL (n=29)*		Other lymphomas (n=30)*	
	n	%	n	%
CR	2	6.9	-	-
PR	4	13.8	-	-
SD	6	20.7	6	20.0
PD	17	58.6	24	80.0
ORR (95% CI)	20.7% (8.0–39.7%)		.	

* There were 5 non-evaluable patients in the Non-cutaneous PTCL group and 3 in the Other lymphomas group.
PTCL, peripheral T-cell lymphoma; CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease; NE, not evaluable; ORR; overall response rate; CI, confidence interval.

Plitidepsin was well tolerated in this trial. The most common adverse events (AEs) in the non-cutaneous PTCL cohort were nausea, fatigue, vomiting, myalgia, muscle weakness and pyrexia. The most common grade 3/4 hematological abnormalities were lymphopenia, neutropenia, anemia and thrombocytopenia found in 28%, 12%, 10% and 10% of the cases, respectively (Figure 2).

Figure 2. Most common AEs (related to plitidepsin or with unknown relationship) in the cohort of patients with PTCL treated in study APL-B-013-02.



Nine patients with AITL were included in the cohort of 34 non-cutaneous PTCL patients. Of note, ORR in these nine patients was 33.3%, with CR in two patients (22.2%) and PR in one patient (11.1%). Furthermore, SD was reported in other two patients. Table 3 shows the clinical and treatment characteristics of these nine patients. The median number of previous lines was 2 and the DoR of the three responders was 121, 12 and 4 weeks, respectively. It should be highlighted that the two patients with CR had bone marrow involvement at diagnosis and had previously failed high dose chemotherapy with stem cell transplantation (SCT) support.

Table 3. Characteristics of the nine patients with angioimmunoblastic T-cell lymphoma included in the APL-B-013-02 clinical trial.

	Lymphoma history			Prior therapy		Baseline				Plitidepsin treatment		Efficacy			
Gender/Age (years)	**Bulky disease**	**IPI risk**	**Ann-Arbor**	**CT lines**	**SCT**	**PS**	**LDH**	**B2-m**	**BM**	**No. of cycles**	**End of treatment**	**Best response**	**Response duration (weeks)**	**PFS (months)**	**OS (months)**
Male/56	**Yes**	**H**	**IV**	**3**	**Yes**	**1**	**H**	**NA**	**Involved**	**8**	**Treatment complete**	**CR**	**121.0**	**29.6**	**41.7+**
Male/35	**No**	**I/H**	**IV**	**2**	**Yes**	**0**	**N**	**≤3**	**Involved**	**4**	**Toxicity (rash maculo-papular)**	**CR**	**12.0**	**4.4**	**31.6**
Male/69	**No**	**I/H**	**IV**	**2**	**No**	**0**	**N**	**>3**	**Normal**	**3**	PD	**PR**	**4.4**	**2.7**	**3.3+**
Female/71	No	H	IV	2	No	2	N	>3	Involved	5	PD	SD	.	4.5	5.7
Male/36	No	L/I	IV	2	Yes	1	H	>3	Normal	2	Toxicity (CPK increase)	SD	.	2.4+	7.9+
Male/69	No	I/H	IV	1	No	1	H	NA	Involved	2	PD	PD	.	1.7	1.7+
Male/80	No	I/H	IV	2	No	1	H	>3	Involved	1	PD	PD	.	0.9	6.5
Male/61	No	NA	III	2	No	0	H	>3	Normal	1	PD	PD	.	0.8	0.9
Male/75	No	I/H	IV	2	No	2	N	>3	Normal	1	Death	PD	.	0.4	0.4

Patients with remission (CR or PR) to plitidepsin treatment are indicated in shaded columns.
B2-m, beta-2 microglobulin; BM, bone marrow; CPK, creatine phosphokinase; CR, complete remission; CT, chemotherapy; H, high risk/high; I, intermediate risk; IPI, International Prognostic Index; L, low risk; LDH, lactate dehydrogenase; N, normal; NA, not available; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial remission; PS, performance status; SCT, stem cell transplantation; SD, stable disease.

In summary, the interesting antitumor activity observed with plitidepsin in non-cutaneous PTCL was mainly found in patients with AITL. Bearing in mind the small number of agents with meaningful activity in non-cutaneous PTCL and, in particular, the lack of specific agents with reliable and specific activity in AITL, and considering the important signs of activity of plitidepsin in this disease, this phase II clinical trial was designed to evaluate plitidepsin as single-agent treatment for patients with R/R AITL.

The rationale of the exploratory biomarker objectives is related to recent studies exploring the genetic basis of the disease: a study by Odejide and colleagues showed high incidences of gene mutations of TET2, for example, in 85 AITL tissue samples, as well as in DNMT3A, and IDH2: common and frequent mutations that make AITL more comparable to myeloid disorders than other PTCLs and suggest the need to re-evaluate therapeutic strategies (56, 57).

Several studies have shown that plitidepsin induces apoptosis in a cell type- and dose-dependent manner, and these effects are related to the induction of early oxidative stress, the activation of Rac1 GTPase and the inhibition of protein phosphatases, which in conjunction cause the sustained activation of JNK and p38 MAPK. The final consequence is the triggering of the mitochondrial apoptotic pathway with caspase 9 and caspase 3 activation (44). Additional effects may be mediated by indirect effects on the cell microenvironment, mainly mediated by antiangiogenic properties (43, 52, 58) and indirect effects on monocyte-derived cells, including follicular dendritic cells (59).

2. STUDY OBJECTIVES

2.1 PRIMARY

To evaluate the efficacy of plitidepsin on the basis of overall response rate (ORR) in patients with relapsing/refractory (R/R) angioimmunoblastic T-cell lymphoma (AITL).

2.2 SECONDARY

- To evaluate other efficacy endpoints (time-to-event parameters: duration of response [DoR], progression-free survival [PFS], PFS at 6/12 months [PFS6/PFS12], intrapatient PFS/TTP, overall survival [OS] and OS at 6/12 months [OS6/OS12]).
- To evaluate the safety profile of plitidepsin in this patient population.
- To characterize the pharmacokinetics (PK) of plitidepsin.
- To identify biomarkers that may be clinical endpoint surrogates for future plitidepsin studies or that may be predictive of plitidepsin activity.

3. OVERALL STUDY DESIGN

This is a prospective, multicenter, phase II clinical trial to determine the efficacy of plitidepsin in patients with R/R AITL. The primary endpoint will be the ORR according to the Lugano classification response criteria (see Appendix 2) per independent review (60, 61).

Tumor radiological assessments will be by PET-CT in combination with diagnostic quality CT[2] one to two weeks after last dose of Cycle 3 and at least four weeks after last dose of Cycle 6 (but no more than eight weeks), and by CT-scan every four months (+ two weeks) for the first two years, and every six months (+ two weeks) thereafter, at suspected clinical progression, unless otherwise clinically indicated. Patients who discontinue treatment without disease progression will be followed every four months (+ two weeks) for the first two years, and then every six months (+ two weeks) until progressive disease (PD), start of other antitumor therapy, death or the date of study termination (clinical cutoff), whichever occurs first. After documented progression or the start of a new antitumor therapy, patients will be followed for survival approximately every four months during the first two years, and then approximately every six months until death or the date of study termination, whichever occurs first.

An Independent Review Committee (IRC) consisting of medical specialists (radiologists and hematologists) who are directly involved in the care of patients with AITL (but are not participating in this trial as investigators) will review all efficacy data (including radiological assessments, bone marrow biopsy) and will assign the best response and the date of objective response or progression/censoring according to their independent evaluation.

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[2] When PET-CT is performed it must be in combination with diagnostic quality CT with intravenous contrast (except medically contraindicated). Two alternatives are allowed: Hybrid PET CT scanners may be used to acquire diagnostic quality CT which includes intravenous contrast *OR* PET CT without intravenous contrast and diagnostic quality CT images with intravenous contrast using a standalone CT scanner must be performed.

The diagnostic pathological criteria of AITL are still quite arbitrary and the availability of extensive immunophenotype panels and molecular testing for proper classification are limited in most institutions. Also, several reports have described low rates of agreement in the diagnosis of AITL, with around 30% of discordant diagnosis when comparing the initial (referring) and the final pathology reports in academic centers (62). Central pathological review of each patient's original diagnosis report(s) will be required before inclusion. Molecular diagnosis by miRNA will be used to confirm the investigative centers' AITL diagnosis and will include:

- Differential diagnosis with other entities can be difficult (Hodgkin lymphoma, rare B-cell neoplasms, reactive processes, etc.). Extensive phenotype studies and molecular testing are needed in many instances.
- The **differential diagnosis between PTCL NOS and AITL** needs the integration of clinical data including histomorphological features of tumors, phenotype markers of T_{FH} cells (PD1, CD10, BCL6, CXCL13, ICOS), EBV detection.
- The boundaries between **follicular-PTCL** and **PTCL-NOS with T_{FH} phenotype** are still unknown. For consistency of the analyses, diagnosis of AITL will be based on standard criteria (Appendix 1), and these controversial cases will be excluded from the trial.

For all patients, immunophenotyping studies must consist of a minimum panel of T-cell markers, including markers of T_{FH} cells and follicular dendritic cells. The presence of EBV must be identified by *in situ* hybridization (ISH), since LMP-1 immunohistochemistry is not sufficient in AITL.

Major immunophenotyping criteria for diagnosis:

- Markers of T_{FH} cells in the neoplastic population: CD4+/CD8-, BCL6, CD10, PD1, CXCL13, ICOS (at least three markers must be positive) (63, 64).
- Hyperplasia of follicular dendritic cells: CD23+, CD21+
- Variable presence of CD30 + EBV + B-cell blasts (in most cases).

The differential diagnosis between AITL and PTCL/NOS with T_{FH} phenotype will be integrated with miRNA analysis as recently described by Laginestra and colleagues (65). Cases with features of follicular-PTCL and PTCL-NOS with T_{FH} phenotype or with features of progression/transformation from AITL to Diffuse Large B-cell Lymphoma will not be included in the trial.

Two futility analyses of the primary endpoint (ORR according to Lugano classification response criteria and per IRC) are planned around six months after approximately 25% and 50% of eligible patients (i.e., 15 and 30 patients respectively with AITL confirmed by central pathological review) have been treated. Two or less responders out of 15 patients or seven or less responders out of 30 patients, according to boundaries and sample size assumptions, will mean that the alternative hypothesis could be rejected, and thus recruitment might be stopped at the time of the first or second futility analysis, respectively. Otherwise, accrual will continue to a total of 60 patients with AITL confirmed by central pathological review. This decision will be taken at the time by an Independent Data Monitoring Committee (IDMC). The IDMC, which will include specialists in PTCL supported by a medical statistician, will review data provided by the Investigators, the IRC efficacy assessments and safety information and will advise whether the study should continue. Recruitment can continue during the review period.

If there are 19 or more responders over the total of 60 patients, the efficacy of plitidepsin will be considered as clinically relevant in AITL patients.

Operational details for the IRC and IDMC will be detailed in the corresponding charters.

3.1 PRIMARY ENDPOINT

The primary endpoint is ORR—defined as the percentage of patients with either complete (CR) or partial (PR) remission—according to the Lugano classification response criteria per Independent Review Committee (IRC). An IRC will assign the objective response and progression or censoring dates for each patient according to a predefined algorithm provided in a separate charter.

3.2 SECONDARY ENDPOINTS

- ORR per Investigator assessment (IA).
- CR rate, defined as the percentage of patients with complete remission according to Lugano classification response criteria per IRC and IA.
- Duration of response (DoR), defined as the time from the date when the remission criteria (PR or CR, whichever is achieved first) are fulfilled to the first date when PD, recurrence or death (due to any cause) is documented. Response will be assessed according to Lugano classification per IRC and IA.
- Progression-free survival (PFS), defined as the time from the date of first drug administration to the date of PD, death (of any cause), or last tumor evaluation; both IRC and IA will be used.
- Progression-free survival at 6/12 months (PFS6/PFS12), defined as the Kaplan-Meier estimate of the percentage of patients who are progression-free at six/twelve months after the first drug administration; both IRC and IA will be used.
- Intrapatient PFS/TTP, defined as the ratio of PFS achieved with the experimental treatment versus prior last TTP in the R/R setting.
- Overall survival (OS), defined as the time from the date of the first dose to the date of death (of any cause) or last patient's contact.
- Overall survival at 6/12 months (OS6/OS12), defined as the Kaplan-Meier estimate of the percentage of patients who are alive at six/twelve months after first drug administration.
- Treatment safety [AEs, serious adverse events (SAEs) and laboratory abnormalities] graded according to the NCI-CTCAE, v.4. Dose reductions, omitted doses or cycle delays due to treatment-related AEs, and reasons for treatment discontinuations will be analyzed.
- Pharmacokinetics (PK), samples for PK analysis will be obtained during Cycle 1 exclusively (see Section 6).
- Exploratory biomarker analysis, correlation of efficacy with molecular markers (targets/pathways) related to the mechanism of action of plitidepsin or to the disease (see Section 8.4).

4. SELECTION OF PATIENTS

4.1 INCLUSION CRITERIA

1) Voluntary written informed consent of the patient (both to participate in the study and to provide biopsy samples) obtained before any study-specific procedure.
2) Age ≥ 18 years.
3) ECOG PS ≤ 2.
4) Life expectancy ≥ 3 months.
5) Histologically confirmed diagnosis of R/R AITL (eligibility needs to be confirmed by central pathological review.*)
6) At least a two-week washout period since the end of the last therapy (six weeks for a prior nitrosourea-containing regimen), recovery to grade ≤ 1 from any non-hematological AE derived from previous treatment (excluding alopecia).
7) Adequate BM, renal, hepatic, and metabolic function (assessed ≤ 14 days before inclusion in the study):
   a) Absolute neutrophil count (ANC) ≥ 1.0×10^9/L.
      - Screening of ANC should be independent of granulocyte-colony stimulating factor (G-CSF) support for at least one week and of pegylated G-CSF for at least two weeks.
   b) Platelet count ≥ 75×10^9/L.
   c) Hemoglobin ≥ 9 g/dL.
      - Patients may receive red blood cells (RBC) and/or erythropoietin (EPO), and/or platelet transfusions in accordance with institutional guidelines.
   d) Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3.0 × the upper limit of normal (ULN).
   e) Total bilirubin ≤ 1.5 × ULN.
   f) Alkaline phosphatase (ALP) ≤ 3.0 × ULN (< 5 × ULN, if isolated ALP increase, i.e., without ALT/AST or bilirubin increase).
   g) Calculated creatinine clearance (CrCL) ≥ 30 mL/minute (Cockcroft-Gault formula).
   h) Creatine phosphokinase (CPK) ≤ 2.5 × ULN.
   i) Albumin ≥ 2.5 g/dL.
   j) Normal value of electrolytes, including potassium, magnesium and calcium.
8) Left ventricular ejection fraction (LVEF) by echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan within normal range (according to institutional standards).

* Patient inclusion can be approved based on local histopathological report(s). Eligibility will be confirmed using diagnosis and/or relapse biopsy specimens submitted for central pathological review prior to each futility analysis/end of study.

4.2 EXCLUSION CRITERIA

1) Prior treatment with plitidepsin.
2) Concomitant diseases/conditions:
   a) History or presence of angina, myocardial infarction, clinically relevant valvular heart disease, uncontrolled hypertension, or congestive heart failure within the previous 12 months.
   b) Symptomatic arrhythmia (excluding grade ≤ 2 anemia-related sinusal tachycardia) or any arrhythmia requiring ongoing treatment, and/or prolonged grade ≥ 2 QT-QTc, or presence of unstable atrial fibrillation. Patients with stable atrial fibrillation on treatment are allowed provided they do not meet any other cardiac or prohibited drug exclusion criterion.
   c) History (or family history) of long QT syndrome.
   d) Corrected QT interval (QTcF, Fridericia correction) ≥ grade 2 on screening electrocardiogram (ECG).
   e) Clinically significant resting bradychardia, or history of syncope.
   f) History or presence of ventricular arrhythmias, including ventricular tachycardia or Torsades de Pointes.
   g) Patients receiving treatment with any medication with known risk of producing Torsade de Pointes (see Appendix 8).
   h) Active uncontrolled infection. Active hepatitis B or C virus (HBV or HCV), or human immunodeficiency virus (HIV) infection.
   i) Morphological or cytological features of myelodysplasia and/or post-chemotherapy aplasia on BM assessment.
   j) Myopathy > grade 2 or any clinical situation that causes significant and persistent elevation of CPK (> 2.5 × ULN in two different determinations performed one week apart).
   k) Limitation of the patient's ability to comply with the treatment or follow-up requirements.
   l) Diagnosis of another invasive malignancy unless free of disease for at least three years following therapy with curative intent. Patients with early-stage basal cell or squamous cell skin cancer, cervical intraepithelial neoplasia, cervical carcinoma *in situ*, or superficial bladder cancer, may be eligible to participate at the Investigator's discretion.
   m) Any other major illness that, in the Investigator's judgment, will substantially increase the risk associated with the patient's participation in this study.
3) Central nervous system (CNS) involvement.
4) Women who are pregnant or breast feeding. Fertile patients (men and women) who are not using an effective method of contraception. All patients (men and women) must agree to use an effective contraceptive measure (if applicable) up to six months after treatment discontinuation. Valid methods to determine the childbearing potential, adequate contraception and requirements for women of childbearing potential (WOCBP) and their partners are described in Appendix 6.
5) Concomitant medications that include corticosteroids, chemotherapy, or other therapy that is or may be active against AITL, within the two weeks prior to treatment start. Concurrent corticosteroids are allowed, provided they are

administered at an equivalent prednisone dose of ≤ 10 mg daily, as premedication for blood products and/or for the relief of the symptoms derived from the disease.

6) Major upper gastrointestinal bleeding episode occurring during the previous year before screening.
7) Known hypersensitivity to any of plitidepsin's formulation components (See Section 7.1.1, Study Drug Formulation).

5. PLAN OF THE STUDY

5.1 PLANNED TRIAL PERIODS (FOR THE WHOLE STUDY)

The total duration of the study will be approximately 42 months.

Planned start date (first patient on study): 2Q2016.

Planned enrollment period: 36 months.

Planned end-of-study date (clinical cutoff): 12 months after the last patient's inclusion. If there are patients still being treated at the planned cutoff date, the actual cutoff date will be the date when those patients have completed the ongoing treatment cycle and the corresponding EOT visit.

The study will be closed earlier than planned if less than 15 patients are recruited in the first year after most of the sites are in active enrollment. Recruitment reviews will continue annually to assess the feasibility of meeting the study objectives and study continuation.

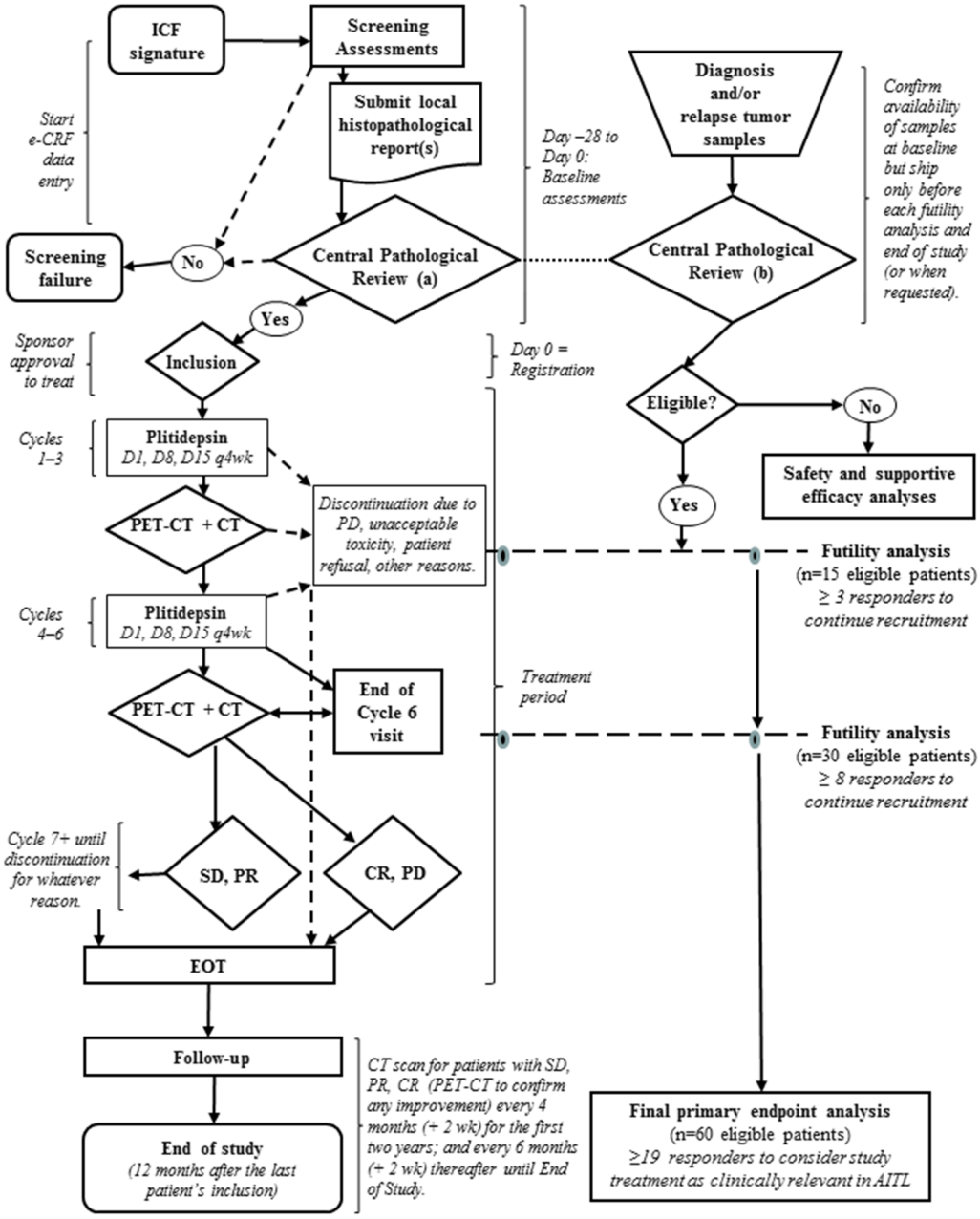
5.2 PLANNED TRIAL PERIODS (INDIVIDUALLY PER PATIENT)

Patients will be evaluated at scheduled visits in three study periods:

- **Pretreatment:** from signature of the informed consent to the first dose of study treatment.
- **Treatment:** from first dose of study treatment to EOT (see Section 5.2.1.1). EOT is defined as 30 days (± one week) after the day of last administration of study treatment or as soon as possible after End of Cycle 6 radiological and clinical assessments (if the patient discontinues: see Figure 3 below), unless the patient starts a new antitumor therapy or dies within 30 days from the last dose, in which case the date of administration of this new antitumor therapy or the date of death will be considered the EOT date.
- **Follow-up:** after EOT, patients will be followed every four weeks until resolution of all toxicities (if any). Patients who discontinue treatment without progression will be followed every four months (+ two weeks) for the first two years of follow-up, and every six months (+ two weeks) thereafter, unless clinically indicated, until PD, start of other antitumor therapy, death or the date of study termination (clinical cutoff), whichever occurs first. After documented progression or start of a new antitumor therapy, patients will be followed for survival approximately every four months during the first two years, and then approximately every six months until death or the date of study termination, whichever occurs first. For the purpose of collecting information on patient's survival exclusively, a documented telephone call is acceptable; follow-up for survival will be completed for all patients only if results of the primary endpoint confirm the trial as positive.

Patients will be considered to be **on-study** from the signature of the informed consent form (ICF) to the end of the follow-up period (or screening failure). Investigators can appraise potential study candidates in a pre-screening period but only perform study-specific screening assessments after the patient formally consents. Patients will be considered to be **on-treatment** from the date of first dose until EOT.

Figure 3. Study design.



Central pathological review involves different analyses in two separate processes: ***(a)*** *of local histopathology reports before approving patient inclusion, and* ***(b)*** *of tumor samples before each futility analysis and at the end of study.*

CR, complete response; D, day; EOT, end of treatment; ICF, informed consent form; PD, progressive disease; PR, partial response; SD, stable disease; wk, week.

Patients may withdraw their consent at any time; if consent to study participation is withdrawn, no further study activities will be conducted on them (5.2.1.3 Study Discontinuation). If consent only to the study treatment is withdrawn, treatment will be stopped and other study procedures performed as normal (see 5.2.1.1 below).

5.2.1 Discontinuations

5.2.1.1 *Treatment Discontinuation*

Treatment discontinuation occurs when an enrolled patient ceases to receive plitidepsin regardless of the circumstances. By convention, the date of the end of treatment is defined as 30 days after the day of the last dose of plitidepsin (treatment discontinuation), the start of a new antitumor therapy or death, whichever occurs first, in which case the date of administration of this new therapy or the date of death will be considered the date of EOT. In this study, however, EOT will also be conditioned by an End of Cycle 6 visit in which a radiological assessment 4–8 weeks after the last dose of Cycle 6 will determine whether treatment can continue to Cycle 7.

The primary reason for any treatment discontinuation will be recorded on the patient's Case Report Form (CRF).

If a patient discontinues treatment, every effort should be made to complete the scheduled assessments as appropriate, whenever possible.

5.2.1.2 *Reasons for Treatment Discontinuation*

Patients will receive study treatment until:

- Disease progression (PD).
- Maximum of six cycles unless the patient is in:
  - PR 4–8 weeks after last dose of Cycle 6: in accordance with Investigator decision, the patient may then continue in treatment until CR or progression.
  - SD 4–8 weeks after last dose Cycle 6: in accordance with Investigator decision, the patient may then continue until CR or progression.
- If patient is in CR after six treatment cycles, treatment should be stopped.
- The patient achieves PR or CR at any time during the planned six cycles and is eligible for consolidation with autologous or allogeneic stem cell transplant (SCT) as per Investigator criteria.
- There is unacceptable toxicity.
- There is intercurrent illness of sufficient magnitude to preclude safety continuation of the study.
- There is patient refusal and/or non-compliance with study requirements.
- Investigator's decision.
- There is a protocol deviation with an effect on the risk/benefit ratio management of the patient.
- There is a treatment delay > 15 days from the treatment due date (except in case of clear clinical benefit and with the Sponsor's approval).
- There is a requirement of > 2 dose reductions (except in case of clear clinical benefit and with the Sponsor's approval).

Patients who are withdrawn for any reasons must not be re-treated in the context of this study at any time. For follow-up activities, please refer to Section 5.11.

5.2.1.3 *Study Discontinuation*

Study discontinuation occurs when an enrolled patient ceases to participate in the study, regardless of the reason (as detailed under "Follow-up" in Section 5.2). Patients have the right to withdraw consent at any time; if this is the case, no further study procedures should be performed.

The date and reason for study discontinuation will be clearly documented on the patient's CRF.

5.2.2 Protocol Deviations

A protocol deviation is defined as any departure from what is described in the protocol of a clinical trial approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB) and the Competent Authorities. Therefore, it applies to deviations related to patient inclusion and clinical procedures (e.g., assessments to be conducted or parameters to be determined), and also to other procedures described in the protocol that concern Good Clinical Practice (GCP) guidelines or ethical issues (e.g., issues related to obtaining the patients' Informed Consent, data reporting, Investigator's responsibilities, etc.).

Deviations with no effects on the risk/benefit ratio of the clinical trial (such as minimal delays in assessments or visits) will be distinguished from those that might have an effect on this risk/benefit ratio, such as:

- Deviations that might affect the clinical trial objectives, such as those involving inclusion/exclusion criteria (which could mean that the patient is not eligible for the trial) and those having an effect on patient's evaluability.
- Deviations that might affect the patient's well-being and/or safety, such as incorrect dosing of the investigational medicinal product (plitidepsin) due to not following dose adjustment specifications or an incorrect preparation of the medication.
- Deviations related to the following of GCP guidelines as described in the protocol and regulations in force, such as deviations when obtaining the Informed Consent or not following the terms established for reporting Serious Adverse Events, etc.

As a general rule, NO deviations that may have an effect on the risk/benefit ratio of the clinical trial will be authorized. All protocol deviations detected during the study will be appropriately documented, and those considered particularly relevant (i.e., those related to ethical issues, fulfillment of GCP guidelines and with an effect on the risk/benefit ratio) will be notified to the pertinent IEC/IRB and, if applicable, to the Competent Authorities as established by local regulations.

Failure to attend the EOT visit exclusively due to a deteriorated clinical condition will not be considered a protocol deviation.

Furthermore, non-availability or non-evaluability of a diagnosis or re-biopsy specimen for central pathological review will not be considered a deviation (given that, in some instances, re-biopsy may not be feasible because of disease location) but eligibility must first be confirmed with the sponsor prior to inclusion.

5.3 ADDITION OF PATIENTS

All eligible and treated patients with AITL diagnosis confirmed after central pathological review will be included in the main efficacy analyses (primary and secondary endpoints).

If a patient is treated but AITL diagnosis is not finally confirmed after central pathological review of the biopsy (even if inclusion was approved on the basis of the local histopathological report) then an additional patient will be included. Specifically, cases with features of follicular-PTCL and PTCL-NOS with T_{FH} phenotype or with features of progression/transformation from AITL to Diffuse Large B-cell Lymphoma need to be excluded from the main efficacy analysis so additions are permitted in the event such patients are included before (or in spite of) central pathological exclusion. All patients without central confirmation will be excluded from the main efficacy analyses but included in safety analyses and, as supportive analyses, efficacy assessments will be done including all treated patients.

5.4 PRETREATMENT ASSESSMENTS

During the pretreatment (or screening) period, following signature of the Informed Consent Form, the Investigator will assess the patient's eligibility for inclusion in the study by conducting the assessments summarized below. The Sponsor must confirm eligibility before the patient starts treatment: see also Figure 3. Study design.

Table 4. Screening period: pretreatment assessments.

	ASSESSMENT	TIME
1. Written informed consent	The informed consent process involves an explanation and discussion with the patient including time for questions and answers and culminates in signing and dating the consent form if the patient agrees. Document participation in the patient's medical chart as well.	Before any study-specific procedures.
2. Medical and cancer history/ clinical examination	◆ Demographic data (race/ethnicity [if permitted], age, sex, height). ◆ Medical and cancer history/baseline condition: ○ Primary diagnosis. ○ Prognostic factors at first diagnosis.* ○ Prior treatments (with best response and TTP, when available). ○ Documented date of relapse or refractory disease. ○ Ann-Arbor staging (see Appendix 5)	Within 28 days prior to Day 0.
	◆ Complete physical examination, including weight and BSA. ◆ Basic neurological examination. ◆ Performance status (ECOG PS). ◆ Vital signs: heart rate, blood pressure and body temperature. ◆ Concomitant therapies.	Within 14 days prior to Day 0.
3. Laboratory tests	◆ **Hematology:** differential WBC, hemoglobin, hematocrit and platelets. ◆ **Biochemistry-A:** AST, ALT, total bilirubin (direct bilirubin if total bilirubin > 1.5 × ULN), ALP, creatinine, calculated creatinine clearance (Cockcroft-Gault formula), glucose, serum electrolytes (Na^+, K^+, Mg^{++}, Ca^{++}) and CPK (CPK-MB fraction should be measured if CPK is abnormally high). ◆ **Biochemistry-B:** Uric acid, LDH, total proteins, albumin and C-reactive protein. ◆ **Coagulation tests:** PT, PTT and INR. ◆ **Serum beta-2 microglobulin.** ◆ **Complete serology:** including viral load (if indicated). ◆ **Coombs test.** ◆ **Serum immunoglobulin quantification.** ◆ **Serum protein electrophoresis.**	Within 14 days prior to Day 0. **

	ASSESSMENT	TIME
	◆ **Urine** elemental dipstick and sediment.	
4. Central pathological review	To confirm patient eligibility, the original diagnosis histopathology report must be provided for central pathological review.	Within 28 days and with sufficient time to allow confirmation of eligibility prior to Day 0.
	Archived tissue samples of representative tumors [a **formalin-fixed paraffin-embedded (FFPE) tissue block** (preferred) or freshly-cut unstained tumor slides] must be available. An incisional or excisional biopsy is preferred but a core-needle biopsy can be considered when excisional biopsy is not possible. Other sample specifications (number and thickness) must be confirmed in advance with the central laboratory: see separate instruction manual.	Although availability of the diagnosis and/or relapse sample is required for central pathological review, the specimens need not be sent or evaluated until later in the study (before each futility analysis or when instructed).
5. Biomarker analysis	Available archived paraffin-embedded tumor tissue samples obtained at diagnosis or/and relapse.	See point 4 above.
6. Pregnancy test	Only if the patient is a WOCBP. Assessment of β-hCG.	Within 14 days prior to Day 0, if applicable.
7. Cardiac assessment	◆ ECG: Rhythm, frequency and QT interval should be specifically described.	Within 14 days prior to Day 0.
	◆ LVEF by ECHO or MUGA	Within 28 days prior to registration.
8. Bone marrow biopsy/aspirate		Within 14 days prior to Day 0.
9. Chest X-ray	If needed.	Within 28 days prior to Day 0.
10. Tumor assessment	Radiological (PET-CT + CT***) and clinical tumor assessment.	Within 28 days prior to Day 0.
11. Adverse events	Clinical assessment of the patient's signs and symptoms (if any and including nurses' assessment and patient-reported issues) should continue on an ongoing basis throughout the study and be reported at least every cycle as AEs: between IC and Day 0, AEs are considered baseline and non-treatment emergent. Grading should be as per the NCI-CTCAE v.4.	Within 14 days prior to Day 0.

* Prognostic Index for Peripheral T-cell lymphoma (PIT) uses four variables as predictive for survival: age, PS, LDH level and BM involvement (Appendix 3). The standard International Prognostic Index (IPI) comprises the following variables: age ≥ 60 years, disease stages III to IV, LDH > normal, ENSs > one and PS ≥ 2. The alternative Prognostic Index for AITL (PIAI) comprises the following factors: age ≥ 60 years, PS ≥ 2, ENSs > one, B symptoms and platelet count $<150 \times 10^9$/L (Appendix 4).

** Hematology and Biochemistry-A, -B not to be repeated prior to C1D1 if performed within the seven previous days and there are no changes in the patient's clinical status and medications.

*** When PET-CT is performed it must be in combination with diagnostic quality CT with intravenous contrast (except medically contraindicated). Two alternatives are allowed: Hybrid PET CT scanners may be used to acquire diagnostic quality CT which includes intravenous contrast *OR* PET CT without intravenous contrast and diagnostic quality CT images with intravenous contrast using a standalone CT scanner must be performed.

ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; BSA, body surface area; CPK, creatine phosphokinase; CPK-MB, creatine phosphokinase-isoenzyme MB; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; β-hCG, beta subunit of human chorionic gonadotropin; INR, international normalized ratio; LDH, lactate dehydrogenase; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PS, performance status; PT, prothrombin time; PTT, partial thromboplastin time; SAE, serious adverse event; TTP, time to progression; WBC, white blood cells; WOCBP, woman of childbearing potential.

5.5 PATIENT REGISTRATION

The patient will be allocated a patient number in the e-CRF after signing the ICF and screening begins. This patient number should be used on all future documentation and correspondence referring this patient. Eligibility will be checked before inclusion and registration (approval from the central pathological review of the local histopathology report) confirmed by the Sponsor. The patient will be a screening failure if not all inclusion criteria are met, if any exclusion criterion is met, if central pathological review of the local histopathology report does not confirm the AITL diagnosis, or if the Sponsor does not approve inclusion. Regardless of circumstances, Investigators will not

be allowed to treat any patient before appropriate receipt of the Sponsor's agreement to proceed with inclusion: see also Figure 3. Study design.

A patient who has been treated without the Sponsor's agreement will not be considered evaluable for the study and will need to be replaced (although can continue in treatment until discontinuation for any other reason).

For patients included in the study (all registered patients) but never treated, only baseline and off-study visit modules of the e-CRF should be completed.

For screen failures (patients who started screening but were not finally included), only the screening form of the e-CRF should be completed but SAEs occurring during screening need to be reported.

5.6 CENTRAL PATHOLOGICAL REVIEW

Central pathological review will be conducted by experienced pathologists appointed by the Sponsor and available to the investigative sites for consultation about AITL diagnosis confirmation. Central pathological review is required for (a) local histopathology reports prior to patient treatment, and (b) tumor samples before each futility analysis and at the end of the study: see also Figure 3. Study design.

The central laboratory pathologists will be responsible for (a) approving patient inclusion on the basis of investigative site pathology reports provided during screening, (b) analyzing tumor biopsies (initial diagnosis and/or relapses) to confirm the AITL diagnosis, and (c) analyzing blood samples to identify plasma biomarkers and extract DNA.

Tumor samples (initial diagnosis and relapses) are required for central review to confirm AITL diagnosis but not to approve inclusion. Archived tissue samples of representative tumors must be sent for central review and biomarker analysis. If the diagnosis biopsy is not available (because the patient was diagnosed at another site, for example), the most recent representative biopsy (relapse and/or progression) will be used. Submitting both, however, is strongly recommended. Tumor blocks will be returned to the centers.

Samples requirements are as follows:

- Archived tissue samples of representative tumors:
    - A formalin-fixed paraffin-embedded (FFPE) tissue block (preferred), usually from lymph node excisional biopsy.

or

    - Freshly-cut unstained tumor slides.
- One whole blood sample for germline DNA extraction (6 mL) and another blood sample (4 mL) to obtain plasma are required for biomarker analyses: 10 mL will be collected in EDTA tubes will be collected at the same time as the first PK sample (prior to infusion) on Day 1 of Cycle 1.

Central pathological confirmation of AITL diagnosis for the 15 and 30 patients in the futility analyses is mandatory and for all patients at the end of the study; the central review pathologists will also be available when required for consultation in controversial cases and at the investigators' discretion.

Tissue sample specifications (number and thickness) must be confirmed in advance with the central laboratory. Procedures for collection, handling, and shipping of the samples will be provided in a separate instruction manual for sites.

5.7 PATIENT RANDOMIZATION

Not applicable.

5.8 EVALUATIONS DURING TREATMENT

The assessments listed in Table 5 below will be made while the patient is on treatment: see also Figure 3. Study design.

Table 5. Evaluations during treatment.

	ASSESSMENT	TIME
1. Clinical examination	◆ Complete physical examination, including weight and BSA. ◆ Basic neurological examination. ◆ Performance status (ECOG PS). ◆ Vital signs: heart rate, blood pressure and body temperature.	By Day 1 of each cycle (always prior to plitidepsin administration).
	◆ Concomitant therapies.	Throughout the on-treatment period.
2. Laboratory tests	◆ **Hematology:** differential WBC, hemoglobin, hematocrit and platelets.	Cycle 1: Day 1, 8, 15 and 22 (always prior to plitidepsin administration). Not necessary on C1D1 if performed within the seven previous days and there is no change in the patient's clinical status and medications. To be performed at least every other day in the presence of grade 4 non-febrile neutropenia or febrile neutropenia, and every day in the presence of grade 4 thrombocytopenia until recovery. Cycle 2 and beyond: Day 1, 8 and 15 of each cycle (always prior to plitidepsin administration).
	◆ **Biochemistry-A:** AST, ALT, total bilirubin (direct bilirubin if total bilirubin > 1.5 × ULN), ALP, creatinine, calculated creatinine clearance (Cockcroft-Gault formula), glucose, serum electrolytes (Na^+, K^+, Mg^{++}, Ca^{++}) and CPK (CPK-MB fraction should be measured if CPK is abnormally high).	Cycle 1: Day 1, 8, 15 and 22 (always prior to plitidepsin administration). Not necessary on C1D1 if performed within the seven previous days and there is no change in the patient's clinical status and medications. To be performed at least every other day in the presence of grade 3/4 vomiting or any other drug-related SAE. Cycle 2 and beyond: Day 1, 8 and 15 of each cycle (always prior to plitidepsin administration).
	◆ **Biochemistry-B:** Uric acid, LDH, total proteins, albumin and C-reactive protein.	Day 1 of each cycle (always prior to plitidepsin administration). Not necessary on C1D1 if performed within the seven previous days and there is no change in the patient's clinical status and medications.
	◆ **Coagulation tests:** PT, PTT and INR.	Day 1 of each cycle (always prior to plitidepsin administration).
	◆ **Urine** elemental dipstick and sediment.	Repeat if clinically indicated.
	◆ Complete serology ◆ Coombs test ◆ Serum immunoglobulin quantification. ◆ Serum protein electrophoresis.	Repeat if clinically indicated.
3. Central pathological review	Tumor tissue sample.	Ship prior to futility analysis (or as instructed).

	ASSESSMENT	TIME
4. Pharmacokinetics	See Table 6 Sampling schedule for the determination of plitidepsin.	Day 1, 8 and 15 of Cycle 1.
5. Biomarker analysis	Tumor tissue sample. Collect 10 mL blood: one whole blood sample for germline DNA extraction (6 mL) and another blood sample (4 mL) to obtain plasma. A separate instruction manual for sites will be provided.	Tumor biopsy obtained at diagnosis or relapse. (See point 3 above.) Blood draw C1D1: with the first PK sample (before plitidepsin infusion).
6. Pregnancy test	Only if the patient is a WOCBP. Assessment of β-hCG.	Repeat every cycle (or, at least, every month).
7. Cardiac assessment	◆ ECG: Rhythm, frequency and QT interval should be specifically described, besides any ECG anomaly or variation respect to baseline.	First cycle, Day 1: Prior to the first infusion (unless performed as part of screening within the previous 14 days), at the end of the first infusion, at 30 min post-infusion and at 1-hour post-infusion (see Table 6). First cycle, Day 8 and Day 15: Prior to the infusion, and at 1-hour post-infusion (see Table 6). Further cycles: prior to each infusion.
	◆ LVEF by ECHO or MUGA.	Repeat if clinically indicated.
8. Bone marrow biopsy/aspirate		Repeat if clinically indicated.
9. Chest X-ray		Repeat if clinically indicated.
10. Tumor assessment	Radiological (PET-CT + CT*) and clinical tumor assessment. In the case a patient continues in treatment beyond Cycle 6, CT scans may be used every four months (+ 2 weeks) for the first two years and every six months (+ 2 weeks) thereafter, but any subsequent improvement in response should be confirmed by PET-CT*. Disease progression at any time during the study should be confirmed by imaging (if the physical condition of the patient permits).	One to two weeks after last dose of Cycle 3 and at least 4 weeks (but no more than 8 weeks) after last dose of Cycle 6 (or earlier in the event of treatment discontinuation for whatever reason). Cycle 4 can be started without waiting for the results of the Cycle 3 tumor assessment. No radiological assessment is necessary in the event of discontinuation due to any reason other than PD during or after Cycle 4 if the Cycle 3 radiological assessment has been performed correctly.
11. Concomitant medications	All concomitant therapies taken by the patient (including any not prescribed by the Investigator) should be documented with indication from two weeks prior to starting study treatment.	Throughout the on-treatment period.
12. Adverse events **	As per NCI-CTCAE v.4.	Throughout the on-treatment period.

* When PET-CT is performed it must be in combination with diagnostic quality CT with intravenous contrast (except medically contraindicated). Two alternatives are allowed: Hybrid PET CT scanners may be used to acquire diagnostic quality CT which includes intravenous contrast *OR* PET CT without intravenous contrast and diagnostic quality CT images with intravenous contrast using a standalone CT scanner must be performed.

** Clinical assessment of the patient's signs and symptoms (if any and including nurses' assessment and patient-reported issues) should continue on an ongoing basis throughout the study and be reported at least every cycle (unless relevant enough to program an unscheduled visit or the criteria for seriousness are reached and an SAE report is required). Assessments for a particular visit do not need to all take place on the same day but should all be within the planned time window. Physical examination and laboratory assessments, for example, can be performed more frequently during the study if clinically required.

Permitted windows for assessments

±1 day for study treatment administration and clinical assessments (ECOG PS, vital signs, weight, BSA, neurological assessment—always prior to infusion).

–2 days for hematology, biochemistry-A, serum β-2 microglobulin, biochemistry-B and coagulation tests. Note: windows for laboratory assessments only apply prior to the scheduled infusion, that is within 48 hours before the next scheduled infusion (except C1D1).

ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; BSA, body surface area; CPK, creatine phosphokinase; CPK-MB, creatine phosphokinase-isoenzyme MB; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; β-hCG, beta subunit of human chorionic gonadotropin; INR, international normalized ratio; LDH, lactate dehydrogenase; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PS, performance

	ASSESSMENT	TIME

status; PT, prothrombin time; PTT, partial thromboplastin time; SAE, serious adverse event; WBC, white blood cells; WOCBP, woman of childbearing potential.

5.9 EVALUATIONS AT END OF CYCLE 6

A PET-CT + CT[3] scan for radiological tumor assessment is required at least four weeks (but no more than 8 weeks) after last dose of Cycle 6 (or earlier in the event of treatment discontinuation for whatever reason; no radiological assessment is necessary in the event of withdrawal due to any reason other than PD during or after Cycle 4 if the Cycle 3 radiological assessment has been performed correctly) or at suspected clinical progression while on treatment.

The End of Cycle 6 visit should take place 4–8 weeks after last dose of Cycle 6 (when the PET-CT results are available). If a patient is shown to have SD or PR at this assessment, treatment can resume (Cycle 7) and evaluations will continue as described in Section 5.8. If a patient is shown to have CR or PD, the patient should be discontinued and the EOT visit performed as soon as possible: see also Figure 3. Study design.

The following assessment should be performed/evaluated:

- Assessment of disease-related symptoms.
- Complete physical examination (including weight and BSA).
- Basic neurological examination.
- ECOG PS.
- Vital signs (heart rate, blood pressure, body temperature).
- Concomitant therapies.
- Hematology.
- Biochemistry-A.
- Tumor assessment (clinical and radiological using PET-CT + CT).
- Adverse events.
- Bone marrow biopsy/aspirate assessment (if involved at diagnosis).

If the patient does not resume treatment in Cycle 7, adverse events must be reported during 30 days after the last study drug administration. All serious adverse events (SAEs) occurring within 30 days of the last study drug administration will be reported. Beyond this period of time, only those suspected to be treatment-related SAEs will be reported (Section 8.6.2).

5.10 EVALUATIONS AT END OF TREATMENT

The *end-of-treatment visit* (EOT) should take place approximately 30 days (± one week) of the last plitidepsin administration or as soon as possible after the End of Cycle 6 radiological and clinical assessments (if the patient discontinues), unless the patient

[3] When PET-CT is performed it must be in combination with diagnostic quality CT with intravenous contrast (except medically contraindicated). Two alternatives are allowed: Hybrid PET CT scanners may be used to acquire diagnostic quality CT which includes intravenous contrast *OR* PET CT without intravenous contrast and diagnostic quality CT images with intravenous contrast using a standalone CT scanner must be performed.

starts any subsequent antitumor therapy, in which case the EOT visit should be performed immediately before the start of the new therapy (ideally the day before or the same day): see also Figure 3. Study design.

Treated patients, regardless of the reason for ending the treatment, will undergo the following EOT assessments:

- Assessment of disease-related symptoms.
- Complete physical examination (including weight and BSA).
- Basic neurological examination.
- ECOG PS.
- Vital signs (heart rate, blood pressure, body temperature).
- Concomitant therapies.
- Hematology.
- Biochemistry-A.
- Biochemistry-B.
- Pregnancy test.
- Coagulation tests.
- Serum immunoglobulin quantification.
- Serum protein electrophoresis.
- Adverse events.

For individual patients (and if clinically indicated according to Investigator's criteria), it might also include the following:

- Chest X-ray (if needed).
- Bone marrow biopsy/aspirate (if involved at diagnosis).
- Other tests as appropriate.

All these evaluations will only have to be repeated for those parameters for which no measurement is available within ten days before the EOT visit, or for those parameters with values that were out of range in the last assessment (grade ≥ 2 according to NCI-CTCAE v.4).

Adverse events must be reported during 30 days after the last study drug administration. All serious adverse events (SAEs) occurring within 30 days of the last study drug administration will be reported. Beyond this period of time, only those suspected to be treatment-related SAEs will be reported (Section 8.6.2).

The Sponsor will evaluate all safety information that is spontaneously reported by an Investigator beyond the time frame specified in the protocol.

Failure to attend the EOT visit exclusively due to a deteriorated clinical condition will not be considered a protocol deviation.

5.11 FOLLOW-UP AFTER END-OF-TREATMENT VISIT

The date and reason of the study discontinuation will be recorded on the patient's e-CRF (see Section 5.2.1.1).

Patients who discontinue treatment without disease progression will be followed every four months (+ two weeks) for the first two years of follow-up, and every six months (+

two weeks) thereafter, unless clinically indicated, until PD, start of other antitumor therapy, death or the date of study termination (clinical cutoff), whichever occurs first. Tumor assessment (clinical and radiological using CT-scan) is required only for patients who showed clinical benefit, every four months (+ two weeks) for the first two years, and approximately every six months (+ two weeks) thereafter (unless clinically indicated).

After documented progression or start of a new antitumor therapy, patients will be followed for survival approximately every four months during the first two years, and then approximately every six months until death or the date of study termination, whichever occurs first. For the purpose of collecting information on the patient's survival exclusively, a documented telephone call would be acceptable; follow-up for survival will be completed for all patients only if results of the primary endpoint confirm the trial as positive.

The end-of-study date (clinical cutoff) is defined as 12 months after the last patient's inclusion. If there are patients still being treated at the planned cutoff date, the actual cutoff date will be the date when those patients have completed the ongoing treatment cycle and the corresponding EOT visit. The study will be closed earlier than planned if fewer than 15 patients are recruited in the first year after most sites are in active enrollment.

All AEs suspected to be related to the study treatment must be followed every four weeks after the end of treatment until the event or its sequelae resolve or stabilize at a level acceptable to the Investigator and the clinical monitor or his/her designated representative.

Patients who withdraw consent will not be followed with any study procedures (unless only consent to treatment was withdrawn).

Additional parameters and/or increased frequency of observations should be performed at the Investigator's discretion and according to the nature of the observed AEs. When available, autopsy data should be provided in case of death possibly related to treatment.

5.12 INDEPENDENT REVIEW COMMITTEE

Radiological tumor assessment and all efficacy data will be reviewed and evaluated by an Independent Review Committee (IRC) made up of radiologists and hematologists. Operational details and instructions to centers on the data entry and transfer will be given in a separate charter.

5.13 INDEPENDENT DATA MONITORING COMMITTEE

An independent expert advisory group commissioned by the Sponsor will evaluate efficacy and safety data in enrolled patients. The primary objectives of this Independent Data Monitoring Committee (IDMC) are as follows:

- To maintain the integrity of the trial conduct, to evaluate risk/benefit where possible of the APL-B-021-13 patients by monitoring the efficacy and safety data and making recommendations regarding treatment continuation and options for those on active treatment.

- To inform the Sponsor's Executive Committee regarding the outcome of the planned futility analyses as specified in the trial's Statistical Analysis Plan (SAP) and to make recommendations.

The IDMC's procedures will be detailed in a separate charter: investigators may be expected to provide complete and timely patient data for committee meetings in addition to normal CRF data entry.

6. PHARMACOKINETICS

All patients included in the study will be sampled for PK.

All sample collection dates and times will be recorded on the CRF. Samples will be obtained on infusion days, i.e., Days 1, 8 and 15 of the Cycle 1 for the PK analysis of plitidepsin.

Twelve blood samples will be collected at the time points detailed in Table 6 for the determination of whole blood concentrations of plitidepsin.

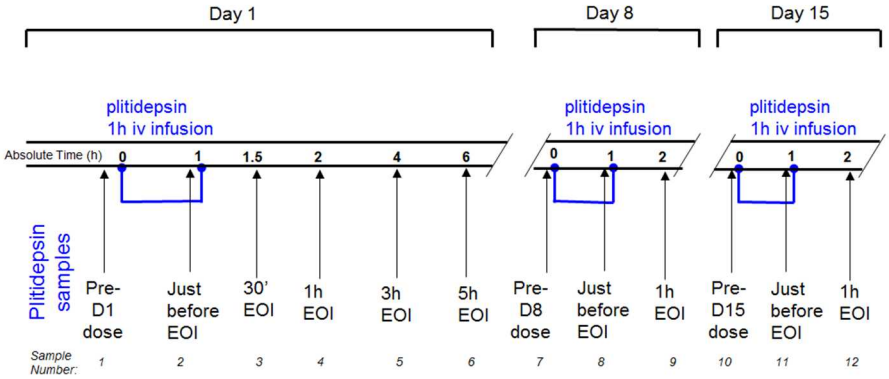
Table 6. Sampling schedule for the determination of plitidepsin, including concomitant ECG measurements.

Sample Number	Day	Absolute time (h) from the start of plitidepsin infusion	Time-points for plitidepsin samples	ECG measurement
1[#]	1	0	Just before first infusion	Just before first infusion
2	1	1	Just before EOI	At EOI
3	1	1.5	30 min after EOI	30 min after EOI
4	1	2	1h after EOI	1h after EOI
5	1	4	3h after EOI	-
6	1	6	5h after EOI	-
7	8	168	Just before Day 8 infusion start	Just before Day 8 infusion start
8	8	1	Just before EOI	-
9	8	2	1h after EOI	1h after EOI
10	15	168	Just before Day 15 infusion start	Just before Day 15 infusion start
11	15	1	Just before EOI	-
12	15	2	1h after EOI	1h after EOI

EOI, End of infusion; h, hour.

[#] Apart from the first PK sample (2 mL), a second sample (10 mL in total: 6 mL whole blood sample and 4 mL to obtain plasma) for biomarker analysis review should be drawn at this time-point.

Figure 4. PK sampling schedule during Cycle 1



The sampling times may be changed while maintaining or decreasing the total number and volume of samples if information obtained during the evaluation allows improvement of the schedule. Samples for the measurement of plitidepsin will have a volume of 2 mL.

The accurate recording of actual dosing and sampling times is much more important than the strict adherence to the scheduled times. The exact recording of the time of drug administration and sampling times is crucial on treatment days with PK sampling (and should be noted accurately even if not according to the planned time schedule). The infusion rate of plitidepsin will be established in order to ensure that the total dose is infused in 1 h. The drug will be infused at a constant rate throughout the 1-hour period. In order to obtain reliable PK information, the infusion rate should not be modified once the infusion begins. If a variation in the infusion time does occur, it is very important to reflect this in the e-CRF, writing clearly the time of the beginning and the end of the infusion. The infusion rate should not be changed to maintain the scheduled duration of infusion. It would be enough just to record the actual duration in the CRF and on the PK sampling sheet.

Blood samples for PK will be obtained through a peripheral vein located in the contralateral side to that of administration of plitidepsin. In any case, the sampling vein has to be different to that in which drugs are administered. Even the last sample must never be collected from the catheter used for the drug administration.

If the blood sample is obtained from a catheter, the first milliliter (mL) of blood will be discarded to avoid the dilution of the sample with the solution used to keep it clean. Heparin (10 U/mL in normal saline solution) or a slow drip of normal saline solution (10 mL/h) can be used to keep the catheter permeable between extractions.

Samples should be collected in a sodium heparin tube and gently inverted several times to ensure proper mixing. After sampling, the test tubes containing the blood samples will be immediately frozen until analysis.

All material for PK procedures will be provided by the Sponsor. A separate instruction manual for sites describing sample extraction, labeling, storage, and shipment will be provided as a separate document.

7. TREATMENT

7.1 DESCRIPTION OF TREATMENT

7.1.1 Drug Formulation and Supply

Plitidepsin will be supplied as a powder and solvent for concentrate for solution for infusion. The 2-mg vial should be reconstituted with a 4-mL ampoule of reconstitution solution. The list of excipients is: D-mannitol, nitrogen, polyoxyl 35 castor oil (Macrogolglycerol Ricinoleate Ph.Eur.), absolute ethanol, and water for injections. The composition of the reconstitution solution is: polyoxyl 35 castor oil/ethanol/water for injection (15/15/70% v/v/v).

For instructions regarding drug inventory, handling, reconstitution, dilution, storage, accountability and disposal, please refer to the Preparation Guide for plitidepsin and the Aplidin® IB, both provided as separate documents.

7.2 ADMINISTRATION OF STUDY MEDICATION

Plitidepsin will be administered intravenously as a 1-hour infusion (fixed rate) via central or peripheral venous catheter.

Patients will receive plitidepsin at a starting dose of 3.2 mg/m^2 on Day 1, 8 and 15 every four weeks (q4wk). A 1-day window is allowed for plitidepsin administration.

A cycle is defined as a four-week period.

7.3 PROPHYLACTIC MEDICATION

All patients must receive the following prophylactic medication 30–60 min before infusion of plitidepsin:

1) Dexamethasone (8 mg i.v. or equivalent)
2) 5-HT3 receptor antagonist: palonosetron 0.25 mg i.v. or tropisetron 5 mg i.v. or granisetron 3 mg i.v. (avoid ondansetron as this drug is categorized within a known risk of producing Torsade de Pointes) (see Appendix 8). Alternatively, metoclopramide or other antiemetic drugs may be used instead as per Investigator's criteria/institutional guidelines, and
3) Diphenhydramine hydrochloride 25 mg i.v. or equivalent, and
4) Ranitidine 50 mg i.v. or equivalent.

Oral metoclopramide and/or extended oral 5-HT3 receptor antagonist may be used as per Investigator's criteria/institutional guidelines. Additional dexamethasone can only be used as an antiemetic in the event alternative antiemetics cannot be used; and only if the Investigator considers the options above as insufficient.

7.4 CRITERIA FOR TREATMENT CONTINUATION

Patients can receive plitidepsin infusions (Day 1, 8, 15 of each cycle) for a maximum of six cycles (unless with PR or SD after Cycle 6: see Section 5.2.1.2) if they fulfill the following requirements:

- ANC $\geq 1.0 \times 10^9$/L.
- Platelet count $\geq 75 \times 10^9$/L.
- Hemoglobin ≥ 9.0 g/dL.
- Calculated CrCL ≥ 30 mL/min (Cockcroft-Gault formula).
- Total bilirubin $\leq 1.5 \times$ ULN ($\leq$ grade 1).
- AST, ALT $\leq 3.0 \times$ ULN ($\leq$ grade 1).
- Normal value of electrolytes, including potassium, magnesium and calcium.
- Muscular toxicity (myalgia, muscular weakness, CPK increase) < grade 2.
- Other non-hematological drug-related AEs [except for increased gamma glutamyltransferase (GGT), not optimally treated nausea and vomiting, hypertension or alopecia] $\leq$ grade 1.
- No clinically relevant ECG changes compared with grade at baseline.
- QTc must be $\leq$ grade 1 before receiving the study treatment. In case of grade 1 QTc prolongation during treatment, and after discussion with the Sponsor, treatment must be continued with a normal value of electrolytes, including potassium, magnesium and calcium, being mandatory before the re-administration of plitidepsin.

- In case of QTc ≥ grade 2, the study treatment must be discontinued, and the patient must be followed until recovery.

If these criteria are not met on Day 1 of any cycle after Cycle 1, the new cycle is to be delayed for up to two weeks until recovery. If these toxicities do not recover after a 2-week delay, the patient is to discontinue treatment and start the follow-up period unless there is obvious clinical benefit, in which case the patient might restart treatment at the Investigator's discretion and after obtaining the approval of the Sponsor.

If these criteria are not met on Day 8 and 15 of any cycle (including Cycle 1), the scheduled infusion is to be omitted. Omitted doses for a given cycle are not to be recovered.

"Cycle delay", therefore, is only applicable to the first infusion of a new cycle (i.e., Day 1) and not when an infusion takes place within the protocol-permitted window (one day) and not when treatment resumes after radiological assessment (see Section 5.10).

7.5 DOSE REDUCTION

Dose adjustments are to be based on the worst toxicity occurring during the previous cycle. Table 7 shows the plitidepsin dose levels used in this study.

Table 7. Dose levels.

Dose level	Plitidepsin dose (mg/m^2)
0	3.2
–1	2.7
–2	2.3

Once the dose given to a patient is reduced, it cannot be re-escalated. Patients requiring dose reduction below dose level –2 are to discontinue treatment and start the follow-up period (except in cases of obvious clinical benefit when further dosing changes must be agreed with the Sponsor).

The plitidepsin dose should be reduced if the patient meets any of the following criteria:

- Less than 50% compliance with the treatment schedule.
- Febrile neutropenia.
- Grade 4 neutropenia and infection, or grade 4 neutropenia lasting > 7 days.
- Grade 4 thrombocytopenia.
- Grade ≥ 2 muscular toxicity (weakness, myalgia and/or CPK elevations).
- Grade ≥ 3 AST/ALT increase.
- Any grade ≥ 3 clinically relevant, non-hematological toxicity (except non-optimally treated nausea and vomiting, diarrhea lasting < 48 h and/or grade ≥ 3 fatigue lasting < 5 days).

7.6 CONCOMITANT MEDICATION

All treatments received by the patient during the on-treatment period of the trial must be documented in the e-CRF. The details to be entered for each type of treatment will depend on factors such as relationship to, for example, AEs, underlying disease and symptoms, and will be defined in the study's Monitoring Plan.

7.6.1 Allowed Medications/Therapies

1) Erythropoietin.

2) Therapies for the treatment of pre-existing and/or emergent medical conditions not specifically forbidden as per protocol elsewhere.
3) Anti-emetics according to institutional or ASCO guidelines.
4) G-CSFs according to institutional or ASCO guidelines (except for primary prophylaxis and when screening for eligibility).
5) Systemic and/or local therapies for symptomatic relief, particularly in the case of diarrhea or skin toxicity.
6) Adequate analgesic medication, including opioids for symptomatic pain relief if indicated.

7.6.1.1 *Transfusions*

Platelet and red cells transfusions are allowed within one week prior to the infusion and during the study.

7.6.2 Prohibited Medications/Therapies

1) Concomitant administration of any other antineoplastic therapy.
2) Other investigational agents.
3) Immunosuppressive therapies, except hydrocortisone used on isolated occasions as treatment for hypersensitivity reactions, or for the relief of the symptoms derived from the disease**,** if required.
4) Primary prophylaxis with colony-stimulating factors such as G-CSF.
5) Any medication with known risk of producing Torsade de Pointes, including ondansetron (see Appendix 8).

7.7 DRUG ACCOUNTABILITY

Proper drug accountability will be done by the pharmacist and/or appropriately trained study personnel. Each study site will keep records to allow a comparison of quantities of drug received and used at each site for monitoring purposes. The Investigator at each study site will be the person ultimately responsible for drug accountability at the site.

All unused drug supplied by the Sponsor will be properly destroyed at the study site. Documentation of this procedure must be provided to the clinical trial monitor. If the Sponsor agrees, unused drug supplies may be returned to the drug repository.

7.8 TREATMENT COMPLIANCE

The Investigator is ultimately responsible for supervising compliance with the instructions described in this study protocol.

8. STUDY EVALUATIONS

8.1 EFFICACY

The aim of this clinical trial is to determine the antitumor activity of plitidepsin in patients with AITL. The primary endpoint will be the ORR according to the Lugano classification response criteria per independent central review (see Section 3.1 and Appendix 2 for more details). Secondary endpoints of efficacy include ORR per investigator assessment (IA), CR, DoR, PFS, PFS6/12, OS and OS6/12 (see Section 3.2 for more details).

All eligible and treated patients with AITL diagnosis confirmed after central pathological review will be included in the main efficacy analyses (primary and secondary endpoints). If a patient is treated but AITL diagnosis is not finally confirmed after central pathological review of the biopsy (even if inclusion was approved on the basis of the local histopathological report) then an additional patient will be included. Specifically, cases with features of follicular-PTCL and PTCL-NOS with T_{FH} phenotype or with features of progression/transformation from AITL to Diffuse Large B-cell Lymphoma need to be excluded from the main efficacy analysis so additions are permitted in the event such patients are included before (or in spite of) central pathological exclusion.

Supportive efficacy analyses will be assessed in all treated patients and in all evaluable patients—defined as eligible patients who receive at least two plitidepsin cycles in which at least two complete infusions have been administered and had at least one disease assessment—as well as in patients who discontinue treatment without Cycle 3 tumor assessment after at least two plitidepsin infusions due to disease progression (PD) (or death due to PD) or toxicity (or death due to toxicity) defined as "early PD" and "treatment failures" respectively.

Patients without confirmation of AITL by central pathological review be excluded from the main efficacy analyses but, as supportive analyses, efficacy assessment will be done including all treated patients.

Radiological tumor assessment will be performed by PET-CT in combination with diagnostic quality CT[4] one to two weeks after last dose of Cycle 3 and at least four weeks after last dose of Cycle 6 (but no more than eight weeks), and by CT-scan every four months (+ two weeks) for the first two years, and every six months (+ two weeks) thereafter or at suspected clinical progression, unless otherwise clinically indicated. An IRC consisting of medical specialists (radiologists and hematologists) who are directly involved in the care of patients with AITL—but not investigators in this trial—will review all efficacy data (including radiological assessments, bone marrow biopsies) and will assign the best response and the date of objective response or progression/censoring according to their independent evaluation.

Two futility analyses of the primary endpoint (ORR according to the Lugano classification criteria and per IRC) are planned for the time six months after ~25% and ~50% of eligible patients have been treated (i.e., 15 and 30 patients, respectively). For example, if there are two or less responders out of 15 patients or seven or less responders out of 30 patients, according to boundaries and sample size assumptions, the alternative hypothesis could be rejected, and thus recruitment might be stopped at the time of the first or second futility analysis, respectively. Otherwise, accrual will continue to a total of 60 patients with AITL confirmed by central pathological review. This decision will be taken at the time by an IDMC. The IDMC, which will include specialists in PTCL supported by a medical statistician, will review data provided by the

[4] When PET-CT is performed it must be in combination with diagnostic quality CT with intravenous contrast (except medically contraindicated). Two alternatives are allowed: Hybrid PET CT scanners may be used to acquire diagnostic quality CT which includes intravenous contrast *OR* PET CT without intravenous contrast and diagnostic quality CT images with intravenous contrast using a standalone CT scanner must be performed.

Investigators, the IRC efficacy assessments and safety information and will provide advice on whether the study should continue.

Operational details (including procedures for review data submission) for the IRC and IDMC will be detailed in the corresponding charters.

8.2 SAFETY

Patients will be evaluable for safety if they have received any partial or complete treatment cycle. All AEs will be graded according to the NCI-CTCAE, v.4 and will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Cycle delays, skipped doses, dose reduction requirements, and reasons for treatment discontinuation will be monitored throughout the study.

The safety profile of patients will be monitored throughout the treatment and up to 30 days after the last treatment dose (EOT), or until the patient starts a new antitumor therapy or until the date of death, whichever occurs first.

Any treatment-related AEs will be followed until recovery to at least grade 1 or stabilization of symptoms, whenever possible.

8.3 PHARMACOKINETICS

All patients included in the study will be sampled for pharmacokinetics (PK). Twelve PK samples will be obtained on Day 1, 8 and 15 of Cycle 1 and will be evaluated by standard non-compartmental analysis (population pharmacokinetic modeling may be performed if appropriate).

The following parameters will be calculated: AUC, C_{max}, CL, and half-life ($t_{1/2}$).

The area under the blood concentration-time curve (AUC) will be determined using the log-linear trapezoidal method with extrapolation to infinity using the terminal rate constant k (C_{last}/k, where C_{last} is the last measured analyte concentration). The C_{max} will be derived directly from the experimental data. The terminal rate constant (k) will be estimated by log linear regression analysis of the terminal phase of the blood concentration vs. time curve. The $t_{1/2}$ will be calculated from the equation 0.693/k; total blood CL will be determined by dividing the total administered dose by the AUC.

If considered appropriate by the Sponsor, compartmental analysis on the study results will also be performed, and population PK analysis will be made in pooled results of the different studies. If applicable, PK/PD parameters will be correlated.

8.4 BIOMARKERS AND EXPLORATORY EVALUATIONS

Biomarker analyses will look for a correlation of efficacy with molecular markers related to the mechanism of action of plitidepsin or to the pathogenesis of the disease, such as a) alterations in DNA and RNA, including DNA mutational status, RNA expression levels and miRNA expression for common genetic lesions affecting the AITL clone, b) alteration in tumor factors including (but not limited to) assessment of pathways and mechanisms of action of plitidepsin, at the RNA and/or protein expression level, and c) peripheral blood analyses, to identify plasma biomarkers including (but not limited to) cancer-related mutations and to extract DNA. Examples of exploratory evaluations and analyses, whenever relevant and depending on sample availability, include:

- Common genetic lesions affecting the AITL clone: for example, TET2, IDH2, DNMT3A, RHOA, ITK or SYK.
- Transcriptional profile of AITL.

- Microenvironment factors: for example, markers of B cells (CD40, ICOS), endothelial cells (VEGF, Angiopoietin), follicular dendritic cells (CXCL13), and other T-cell subpopulations (IL10, IL21, TGF-β).
- Factors associated with the mechanism of action of plitidepsin: for example, eEF1A2, Rac1 GTPase, JNK/phospo-JNK.
- Predictive and prognostic tissue or plasma biomarkers associated with response to treatment: to identify possible mechanisms of resistance to plitidepsin through the comparative analysis of potential biomarkers in the pretreatment samples, and comparison with the post-progression biopsy tissue samples (when available), and in peripheral blood. For this objective, new representative biopsies in relapsed patients would be optimal.

8.5 ADVERSE EVENTS DEFINITIONS

8.5.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign, (e.g., an abnormal laboratory finding), or a disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Illnesses with onset during the study or exacerbations of pre-existing illnesses, including but not limited to clinically significant changes in physical examination findings and abnormal objective test findings (e.g., X-ray, ECG) should be recorded. The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- The test result is associated with clinically significant symptoms, and/or
- The test result leads to a change in the study dosing or discontinuation from the clinical trial, significant additional concomitant drug treatment or other therapy, and/or
- The test result leads to any of the outcomes included in the definition of a SAE (see definition below), and/or
- The test result is considered to be clinically relevant by the Investigator.

For the purposes of this protocol, disease progression, worsening of the underlying disease or appearance of new tumor lesions, or any sign or symptom clearly related with this circumstance is NOT an AE.

8.5.2 Serious Adverse Event (SAE)

A SAE is any adverse experience occurring at any dose that:

- Results in death (is fatal),
- Is life-threatening,
- Requires or prolongs inpatient hospitalization,
- Results in persistent or significant disability or incapacity,
- Is a congenital anomaly or birth defect,
- Is medically significant, or
- Is any suspected transmission of an infectious agent via a medicinal product.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the above definition.

8.5.3 Death

Death as such is the outcome of a SAE and should not be used as the SAE term itself, whenever possible. The cause of death should be recorded as the SAE term instead. When available, the autopsy report will be provided by the Sponsor.

Grade 5 should be used only for events for which there is a causal relationship with the patient's death (e.g. the event was the direct cause of the death). Grade 4 should be used for the events with the outcome of death but there is no causal relationship between them (e.g. the death was not directly caused by the reported event but related to other comorbidities or complications).

8.5.4 Life-threatening Event

Any event in which the patient was at risk of death at the time of the event is considered life-threatening; it does not refer to an event which hypothetically might have caused death if it were more severe.

8.5.5 Hospitalization or Prolongation of Hospitalization

Any AE requiring hospitalization (or prolongation of hospitalization) that occurs or worsens during the course of a patient's participation in a clinical trial must be reported as a SAE unless exempted from SAE reporting. Prolongation of hospitalization is defined as any extension of an inpatient hospitalization beyond the stay anticipated/required for the initial admission, as determined by the Investigator or treating physician.

Hospitalizations that do not meet the criteria for SAE reporting are:

a. Reasons described in the protocol [e.g., investigational medicinal product (IMP) administration, protocol-required intervention/investigations, etc.]. However, events requiring hospitalizations or prolongation of hospitalization as a result of a complication of therapy administration or clinical trial procedures will be reported as SAEs.
b. Hospitalization or prolonged hospitalization for technical, practical or social reasons, in the absence of an AE.
c. Pre-planned hospitalizations: any pre-planned surgery or procedure must be documented in the source documentation. Only if the pre-planned surgery needs to be performed earlier due to a worsening of the condition, should this event (worsened condition) be reported as a SAE.

Other situations that MUST NOT be considered as hospitalizations are the following:

d. An emergency visit due to an accident where the patient is treated and discharged.
e. When the patient is held 24 hours for observation and finally is not admitted.
f. Planned treatments at sites not associated to a hospital and generally considered as minor surgical procedures (i.e., laser eye surgery, arthroscopy, etc.).

8.5.6 Unlisted/Unexpected Adverse Event

An AE, the nature or severity of which is not consistent with the applicable reference safety information.

The Sponsor will use as the reference safety information for the evaluation of listedness/expectedness the most updated IB for plitidepsin.

8.5.7 Adverse Reactions

All untoward and unintended responses to an investigational medicinal product related to any dose administered. This definition covers also medication errors and uses outside what is foreseen in the protocol, including overdose, lack of efficacy, misuse and abuse of the product.

8.5.8 Adverse Events Related to the Study Drug

An AE is considered related to a study drug/IMP if the Investigator's assessment of causal relationship to the IMP(s) is "Y (yes)" (see Section 8.5.10).

The Investigator will assess the causal relationship of the IMP(s) to the SAE.

The Sponsor may also consider related to the study drug(s)/IMP(s) those events for which the Investigator assesses the causal relationship with the IMP(s) as "Uk (unknown)" when it cannot rule out a role of the IMP(s) in the event.

8.5.9 Expedited Reporting

The Sponsor is responsible for the appropriate expedited reporting of serious unlisted/unexpected and related adverse events (SUSAR/SUA), including misuse, overuse and abuse, to the Competent Authorities. The Sponsor will also report all SAEs, including misuse, overuse and abuse, which are unlisted/unexpected and related to the study drug(s) [IMP(s)] to the Investigators and to the IECs/IRBs according to the current legislation, unless otherwise required and documented by the IECs/IRBs.

8.5.10 Assessment of Causal Relationship to the Study Drug

The Investigator must provide an assessment of the causal relationship of the clinical trial IMP(s) to each SAE according to the following scale:

Y There is a reasonable possibility that the IMP(s) caused the SAE.

N There is no reasonable possibility that the IMP(s) caused the SAE and other causes are more probable.

Uk. (Unknown). Only to be used in special situations where the Investigator has insufficient information (i.e., the patient was not seen at his/her center) if none of the above can be used.

8.6 ADVERSE EVENTS REPORTING PROCEDURES

8.6.1 Reporting Adverse Events

The Sponsor will collect AEs until 30 days after administration of the last dose of study drug(s)/IMP(s) or until the start of a new antitumor therapy, whichever occurs first. All AEs suspected to be related to the study drug/IMP must be followed-up after the time of therapy discontinuation until the event or its sequelae resolve or stabilize at an acceptable level to the Investigator and the Sponsor.

All AEs, including misuse, overdose, abuse and medication error, must be recorded in English using medical terminology in the source document and the e-CRF. Whenever

possible, the Investigator will record the main diagnosis instead of the signs and symptoms normally included in the diagnoses.

Investigators must assess severity (grade) of the event following the NCI-CTCAE v.4 and assign a relationship to each study drug(s)/IMP(s); and pursue and obtain information adequate both to determine the outcome and to assess whether it meets the criteria for classification as a SAE requiring immediate notification to the Sponsor or its designated representative. The Investigator must provide any relevant information as requested by the Sponsor in addition to that on the e-CRF.

Abnormal laboratory tests occurring during the study should only be recorded in the AE section of the e-CRF if the disorder:

- is associated with clinically significant symptoms, and/or
- leads to a change in study dosing or discontinuation from study treatment, significant additional concomitant drug treatment or other therapy, and/or
- leads to any of the outcomes included in the definition of a SAE.

Otherwise, laboratory results should be reported in the corresponding section of the e-CRF (e.g. biochemistry, hematology).

Disease progression or appearance of new tumor lesions, or any sign or symptom clearly related with this circumstance is NOT an AE.

8.6.2 Reporting Serious Adverse Events

The Sponsor will collect SAEs from the time of signing of the ICF until 30 days after administration of the last dose of study drug(s)/IMP(s) or until the start of a new antitumor therapy, whichever occurs first (or until screening failure, if applicable). Beyond this period of time, only those SAEs suspected to be related to the IMP will be collected. Nonetheless, the Sponsor will evaluate any safety information that is spontaneously reported by an Investigator beyond the time frame specified in the protocol.

All SAEs (as defined above) that occur after patient registration, regardless of relationship to the study drug(s)/IMP(s) must be reported immediately and always within 24 hours to the PharmaMar Pharmacovigilance Department electronically by completing the applicable e-CRF sections. Only in the event of electronic system failure can SAEs be reported using a paper "SAE form" by fax (+34 91 846 6004), e-mail (phv@pharmamar.com), or by telephone (+ 34 91 823 4633). Out of office hours [Greenwich Meridian Time (GMT)], assistance on SAE reporting can be obtained by calling the Pharmacovigilance Department at +34 91 823 4742. SAEs initially reported by alternative (i.e., not electronic) methods must be followed by a completed electronic SAE reporting on e-CRF from the investigational staff within one working day.

Those SAEs occurring during the screening phase (from ICF signature to registration) and after off-study will be reported using a paper "SAE Form" that must be forwarded as mentioned above always within 24 hours to the Pharmacovigilance Department by fax or e-mail.

All SAEs suspected to be related to the IMP(s) must be followed until the event or its sequelae resolves or stabilizes at an acceptable level by the Investigator and the clinical monitor or his/her designated representative.

Disease progression or appearance of new tumor lesions, or any sign or symptom clearly related with this circumstance should NOT be reported as an SAE.

8.6.3 Reporting Pregnancy Cases Occurred within the Clinical Trial

National regulations require that clinical trial Sponsors collect information on pregnancies occurring during clinical trials, in which exposure to the IMP(s) at any time during pregnancy, via either maternal or paternal exposure, is suspected.

Therefore, pregnancy and suspected pregnancy (including a positive pregnancy test regardless of age or disease state) of a female patient or the female partner of a male patient occurring while the patient is on study drug, or within 30 days of the patient's discontinuation visit, are considered immediately reportable events.

The Investigator will report the following events immediately and always within 24 hours from first knowledge:

- Any occurrence of a pregnancy where any kind of exposure to the IMP(s) is suspected.
- Possible exposure of a pregnant woman [this could involve a partner of a male patient or a pregnant female who came in contact with the clinical trial IMP(s)].
- All reports of elevated/questionable or indeterminate beta human chorionic gonadotropins (β-hCGs).

Immediately after detecting a case of suspected pregnancy in a female clinical trial patient, the decision on her continued participation in the clinical trial will be jointly taken by the trial patient, the Investigator and the Sponsor, with the patient's best interest in mind. A decision to continue the pregnancy will require immediate withdrawal from the trial.

Any pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Sponsor Pharmacovigilance immediately by facsimile using the Pregnancy Report form. In the case of pregnancy of the female partner of a trial patient, the Investigator will obtain her informed consent to provide the information by using the applicable form provided by the Sponsor who will also advise the Investigator in these situations.

The Investigator will follow the pregnancy until its outcome, and must notify PharmaMar Pharmacovigilance of the outcome of the pregnancy within 24 hours of first knowledge as a follow-up to the initial report.

For any event during the pregnancy which meets a seriousness criterion (including fetal or neonatal death or congenital anomaly) the Investigator will also follow the procedures for reporting SAEs (complete and send the SAE form to PharmaMar Pharmacovigilance by facsimile within 24 hours of the Investigator's knowledge of the event).

All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death at any time thereafter that the Investigator suspects is related to the exposure to the study drug(s)/IMP(s) should also be reported to PharmaMar Pharmacovigilance by facsimile within 24 hours of the Investigators' knowledge of the event.

8.7 ADVERSE EVENTS MONITORING

Safety review will be performed by the Sponsor once SAE forms have been received electronically or by fax and the CRFs have been electronically completed by the Investigator.

Periodic safety review of clinical data will be performed; however, no formal Data Safety Monitoring Board has been appointed for this trial. AEs will be monitored by the

Investigators and by the Sponsor study team. The personnel in charge of this process are defined in the Study Contacts section of this protocol. In general, a clinical oncologist medical monitor, together with a member of the PharmaMar Pharmacovigilance Department will review the safety data of this trial on an ongoing basis.

SAEs will be collected, assessed and reported as per the applicable Regulations by the Pharmacovigilance Department. Periodic safety reviews of SAE reports are to be conducted by the clinical oncologist every 3–6 months, depending on recruitment.

As per the applicable regulations, the Sponsor will report to the IECs/IRBs, Investigators and Competent Authorities:

- expeditedly: all serious, related, unlisted/unexpected AEs or critical safety findings from this and any other clinical trial with plitidepsin and,
- periodically: all relevant safety information generated in all clinical trials with the IMP(s) within the Development Safety Update Report.

Non-serious AEs will be verified during monitoring visits by the monitor, who will discuss them with the Investigators.

Any protocol deviation will also be discussed with the Investigator during monitoring visits.

9. STATISTICAL METHODS

9.1 SAMPLE SIZE

The primary endpoint for this study is ORR according to the Lugano classification criteria per independent review.

A total of 60 patients with AITL confirmed by central pathological review will be treated, 19 or more responders will be needed to get an overall estimate for response rate higher than 30% and its lower limit for the 95% confidence interval greater than 20% (31.7% CI95% 20.3%–45.0% following the binomial distribution).

The type I error (alpha) associated with this one-sided test is 0.025 and the type II error (beta) is 0.1; hence, statistical power is 90%. The null hypothesis (H0) is set at ORR $\leq$ 20% (P_0=0.208) versus the alternative hypothesis (H1) at $\geq$ 40% patients (P_a=0.41) having an objective response, the variance of the standardized test is under the null hypothesis.

Two futility analyses of the primary endpoint (ORR according to Lugano classification and per IRC) are planned to reject the alternative hypothesis six months after 25% and 50% of eligible patients have been treated (15 and 30 patients, respectively). Pocock boundary and the actual number of patients confirmed by central pathological review will be used to control type II error for both analyses. For example, if there are two or less responders out of 15 patients or seven or less responders out of 30 patients, according to boundaries and sample size assumptions, the alternative hypothesis could be rejected, and thus recruitment might be stopped at the time of the first or second futility analysis, respectively. Otherwise, accrual will continue to a total of 60 patients AITL confirmed by central pathological review. Active recruitment will not be halted while the analysis is being carried out.

Therefore, if there are 19 or more responders of 60 patients, the null hypothesis can be rejected, allowing consideration of the observed activity plitidepsin as clinically relevant in the setting of patients with AITL.

9.2 STATISTICAL ANALYSIS

9.2.1 Efficacy

For ORR and CR rate, the exact binomial estimator and its 95% confidence interval (CI) will be used. The test statistic for stopping boundaries and final analysis will be calculated using observed results and normal distribution.

Time-to-event variables (DoR, PFS and OS) will be analyzed according to the Kaplan-Meier method. Time to event endpoints will be used as exploratory endpoints.

Intra-patient PFS/TTP ratio will be categorized and analyzed as a dichotomous variable. Clinical benefit will be defined in the event of > 33% longer PFS with the experimental treatment vs. TTP with the immediate prior chemotherapy in R/R setting (ratio >1.33) (66, 67).

Frequency tables will be prepared for categorical variables, whereas continuous variables will be described by means of summary tables that will include the median, mean, standard deviation, minimum, and maximum of each variable.

9.2.2 Safety

Safety analyses will consider AEs and SAEs, according to their relationship with the study treatment, as well as analytical results, deaths and the reasons for cycle delays, omitted doses and/or dose reductions. All AEs and SAEs will be graded according to NCI-CTCAE, v.4.

9.2.3 Pharmacokinetics

PK parameters will be tabulated and selected parameters will be graphically displayed. The dose-exposure relationship will be evaluated.

The potential influence on selected PK parameters of selected demographic and clinical dichotomous variables (gender, laboratory test results above/below selected cutoff values, etc.) will be evaluated by a Student's t test or a Mann-Whitney's U test as appropriate.

For multinomial variables, analysis of variance will be used. For selected continuous demographic and clinical variables (age, laboratory test results, etc.), relationship with selected PK parameters will be graphically explored and assessed using correlation and regression methods.

Other tests may be applied if the results of the above evaluations suggest that they may yield additional relevant information.

9.2.4 Biomarkers Analysis

Biomarkers will be analyzed from pharmacodynamic parameters tabulated and selected parameters will be graphically displayed describing specimen analysis, gene mutations, gene/protein expression profiles, microenvironment analysis and any potential AITL biomarkers identified.

Other tests may be applied if the results of the above evaluations suggest that they may yield additional relevant information regarding plitidepsin's mechanism of action.

9.3 INTERIM ANALYSIS

Two futility analyses of the primary endpoint (ORR according to the Lugano classification criteria and per IRC) are planned to reject the alternative hypothesis six months after approximately 25% and 50% of eligible patients have been treated (15 and

30 patients, respectively). Pocock boundary and the actual number of patients confirmed by central pathological review will be used to control type II error for both analyses. An IDMC, which will include specialists in PTCL supported by a medical statistician, will review data provided by the Investigators, the IRC efficacy assessments and safety information and will provide advice on whether the study should continue. For example, if there are two or less responders out of 15 patients or seven or less responders out of 30 patients, according to boundaries and sample size assumptions, the alternative hypothesis could be rejected, and thus recruitment might be stopped at the time of the first or second futility analysis, respectively. Otherwise, accrual will continue to a total of 60 patients with AITL confirmed by central pathological review. Active recruitment will not be halted while the analysis is being carried out.

10. ADMINISTRATIVE SECTION

10.1 ETHICS

This clinical trial will be conducted in accordance with the ethical principles that have their origin in the World Medical Association (WMA) Declaration of Helsinki (see Appendix 7) and will be consistent with GCP guidelines and pertinent regulatory requirements.

The study personnel involved in conducting this trial will be qualified by education, training and experience to perform their respective task(s).

The study will be conducted in compliance with the protocol. The protocol, any amendments and the patient informed consent will receive Competent Authorities authorization and IEC/IRB approval/favorable opinion prior to initiation, according to pertinent regulations.

The Competent Authorities authorization and the decision of the IEC/IRB concerning the conduct of the study will be made in writing to the Investigator, and a copy of this these authorizations will be provided to the Sponsor before the beginning of the study.

The Investigator and/or the Sponsor is/are responsible for keeping the Competent Authorities and the IEC/IRB informed of any significant new information about the study drug.

All protocol amendments will be agreed upon by the Sponsor and the Investigator.

Administrative changes of the protocol are minor corrections and/or clarifications that have no impact on the way the study is to be conducted.

10.2 MONITORING, AUDITING AND INSPECTING

The study will be monitored by regular site visits and telephone calls to the Investigator by the clinical trial monitor designated by the Sponsor.

During site visits, the trial monitor should revise original patient records, drug accountability records and document retention (study file). Additionally, the trial monitor should observe study procedures and will discuss any problems with the Investigator.

Adequate time for these visits should be allocated by the Investigator. The Investigator should also ensure that the monitor is given direct access [as per International Conference on Harmonization (ICH) Topic E6 Guideline for Good Clinical Practice, Sections 4.9.7 and 6.10] to source documents (i.e., hospital or private charts, original laboratory records, appointment books, etc.) of the patient which support data entered in

the case report forms, as defined in the ICH Topic E6 Guideline for Good Clinical Practice, Sections 1.51 and 1.52.

Systems and procedures will be implemented to ensure the quality of every aspect of the trial.

During the course of the trial, the Sponsor's Clinical Quality Assurance department or external auditors contracted by the Sponsor may conduct an onsite audit visit (ICH Topic E6 Guideline for GCP, Section 1.6).

Participation in this trial implies acceptance of potential inspection by national or foreign Competent Authorities.

10.3 PATIENT INFORMED CONSENT

The rights, safety and well-being of the trial patients are the most important considerations and should prevail over interests of science and society.

The informed consent process will include all elements required by ICH, GCP and applicable regulatory requirements (such as the biobanks 1716/2011 decree and biomedical research 14/2007 legislation).

Prior to inclusion into the trial, the Investigator or a person designated by the Investigator, must provide the patient with one copy of the Informed Consent Form (ICF). This copy must provide written full information about the clinical trial, in a language that is non-technical and easily understood. The Investigator should allow the necessary time for the patient or his/her legally acceptable representative to inquire about the details of the clinical trial; then, the ICF must be freely signed and personally dated by the patient and by the person who conducted the informed consent discussion before the beginning of the study. The patient should receive a copy of the signed ICF and any other written information provided to study patients prior to participation in the trial.

During a patient's participation in the trial, any updates to the consent forms and any updates to the written information will be provided to him/her.

If there is a need to obtain new consent from the patients, the Investigator or a person designated by the Investigator should inform the patients of any new information relevant to the patients' willingness to continue participation in the study, before obtaining the written consent.

10.4 CONFIDENTIALITY/ PATIENTS IDENTIFICATION

The collection and processing of personal data from the patients enrolled in this clinical trial will be limited to those data that are necessary to investigate the efficacy, safety, quality and usefulness of the study drug used in this trial.

It is the Investigator's responsibility that sufficient information on the identity of the patients will be retained.

The trial monitor, the Sponsor's auditor, the IECs/IRBs and the Competent Authorities should have direct access to all requested trial-related records, and agree to keep the identity of study patients confidential.

The data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations.

Explicit consent for the processing of personal data will be obtained from the participating patient before data collection, if applicable, and this consent should also address the transfer of the data to other entities and countries.

The Sponsor shall comply with the Directive 95/46/EEC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

10.5 CASE REPORT FORMS

CRFs will be used to record all data for each patient. It is the responsibility of the Investigator to ensure that CRFs are properly and completely filled in, in English. CRFs must be completed for all patients who have given their informed consent and have been enrolled into the study.

A patient's source documentation is the physician's patient records and original documents, and as such they should be maintained at the study site.

The data collected in the CRF will be entered into the Sponsor's databases, which comply with the Spanish Act implementing the Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data.

10.6 INSURANCE

The Sponsor will provide insurance or indemnity in accordance with the applicable regulatory requirements.

10.7 RETENTION OF RECORDS

The Investigator/Institution should maintain trial documents according to Section 8 of the ICH Topic E6 Guideline for Good Clinical Practice and as required by applicable regulatory requirements.

Essential documents should be retained as per the aforementioned ICH guideline or for a longer period of time, if required by the applicable regulations.

10.8 USE OF INFORMATION AND PUBLICATION

Before the investigators of this study submit a paper or abstract for publication or otherwise publicly disclose information concerning the study drug or products, the Sponsor must be provided with at least 60 days to revise and approve the proposed publication or disclosure to ensure that confidential and proprietary data are protected.

If the Sponsor determines that patentable patient matter is disclosed in the proposed publication or disclosure, the publication or disclosure will be withheld for a period of time considered convenient. If the study is part of a multicenter study, the first publication of the study shall be made in conjunction with the presentation of a joint, multicenter publication of the study results with the investigators and the institutions from all appropriate sites that are contributing data, analysis and comments. However, if such a multicenter publication is not submitted within 12 months after conclusion, abandonment or termination of the study at all sites, the present study may be published individually in accordance with the procedure established above.

The order of the co-authors will reflect the relative contribution of each one to study development and analysis. In general, the first author will be the investigator who recruits the highest number of patients with information finally available for data

analysis. Relevant Sponsor personnel who have fully participated in the study must be considered for co-authorship of the publication.

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12. APPENDICES

APPENDIX 1: WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues

Extract from *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*, Fourth Edition, WHO Classification of Tumours, Volume 2, Swerdlow, S.H., Campo, E., Harris, N.L., Jaffe, E.S., Pileri, S.A., Stein, H., Thiele, J., Vardiman, J.W. (IARC, Lyon, 2008), pp309–11.

Definition

Angioimmunoblastic T-cell lymphoma (AITL) is a peripheral T-cell lymphoma characterized by systemic disease, a polymorphous infiltrate involving lymph nodes, with a prominent proliferation of high endothelial venules and follicular dendritic cells.

ICD-O code

9705/3

Synonyms and historical annotation

AITL was previously felt to be an atypical reactive process, angioimmunoblastic lymphadenopathy, with an increased risk of progression of lymphoma. Currently, overwhelming evidence suggests that AITL rises *de novo* as a peripheral T-cell lymphoma.

Epidemiology

AITL occurs in the middle-aged and elderly, with an equal incidence in males and females. It is one of the more common specific subtypes of peripheral T-cell lymphoma, accounting for approximately 15–20% of cases, or 1–2% of all non-Hodgkin lymphomas.

Etiology

The nearly constant association with Epstein Barr virus (EBV) has suggested a possible role for the virus in the etiology, possibly through antigen-drive. However, the neoplastic T cells are EBV negative.

Sites of involvement

The primary site of disease is the lymph node and virtually all patients present with generalized lymphadenopathy. In addition, spleen, liver, skin and bone marrow (BM) are frequently involved.

Clinical features

AITL typically presents with advanced stage disease, generalized lymphadenopathy, hepatosplenomegaly, systemic symptoms, and polyclonal hypergammaglobulinemia. Skin rash, often with pruritus, is frequently present. Other common findings are pleural effusion, arthritis and ascites. Laboratory findings include circulating immune complexes, cold agglutinins with hemolytic anemia, positive rheumatoid factor and anti-smooth muscle antibodies.

Patients exhibit immunodeficiency secondary to the neoplastic process. In the majority of cases (75%), expansion of B-cells positive for EBV is seen, thought to be a consequence of underlying immune dysfunction.

Morphology

AITL is characterized by partial effacement of the lymph node architecture, often with perinodal infiltration but sparing of the peripheral cortical sinuses. There is marked proliferation of arborizing high endothelial venules (HEV). There is predominantly paracortical polymorphic infiltrate composed of small to medium-sized lymphocytes, with clear to pale cytoplasm and distinct cell membranes and minimal cytological atypia. The neoplastic cells often form small clusters around the follicles and HEV and are admixed with variable numbers of small reactive lymphocytes, eosinophils, plasma cells and histiocytes. The polymorphic infiltrate is frequently associated with increased follicular dendritic cell meshworks. Early cases may contain hyperplastic follicles with ill-defined borders and the characteristic histology may be limited to the perifollicular areas with predominance of clear cells. The relationship between AITL showing limited paracortical involvement and the follicular variant of peripheral T-cell lymphoma, NOS remains to be clarified. An expansion of B immunoblasts is usually present in the paracortex. The expansion of normal B-cells and follicular dendritic cells in the lesions has been linked to the functional properties of the neoplastic cells as follicular helper T-cells (TFH) of the normal follicle. The expression of CXCL13 mediates expansion of follicular dendritic cells, and, adhesion of B-cells to HEV with subsequent entry to the lymph nodes. EBV-positive B-cells are nearly always present. They range in cell size and expansion of B immunoblasts may be prominent. The EBV-positive B immunoblastic proliferation may progress, either composite with AITL, or at relapse to EBV-positive diffuse large B-cell lymphoma. EBV-positive Reed-Sternberg-like cells of B-cell lineage may be present and may simulate classical Hodgkin lymphoma. In advanced cases, the inflammatory component is diminished, and the proportion of clear cells and large cells is increased.

Immunophenotype

The neoplastic T-cells express most pan T-cell antigens such as CD3, CD2 and CD5 and, in vast majority of the cases, CD4 although numerous reactive CD8+ T-cells are often present. Characteristically, the tumor cells show the phenotype of normal TFH expressing CD10, CXCL13 and PD-1 in 60–100% of the cases. This phenotype is helpful in distinguishing AITL from atypical paracortical hyperplasia and other peripheral T-cell lymphomas as well as diagnosing extranodal dissemination. B immunoblasts and plasma cells are polytypic; however, secondary EBV-positive B-cell proliferations including diffuse large B-cell lymphoma, classical Hodgkin lymphoma or plasmacytoma may be seen. Follicular dendritic cell meshworks expressing CD21, CD23, CD35 and CNA42 are expanded, usually surrounding the high HEV.

Postulated normal counterpart

CD4+ follicular helper T-cell.

Genetics

T-cell receptor genes show clonal rearrangements in 75–90% of cases. Clonal immunoglobulin gene rearrangements may be found in around 25–30% of cases, and correlate with expanded EBV+ B-cells. The most frequent cytogenetic abnormalities are trisomy 3, trisomy 5 and an additional X chromosome and comparative genetic

hybridization has shown gains of 22q, 19 and 11q13 and losses of 13q in subset of cases. Gene expression profiling studies have shown that the neoplastic cells show features of CD4+ TFH.

Prognosis and predictive factors

The clinical course is aggressive with a median survival of less than three years. Patients often succumb to infectious complications, which makes delivery of aggressive chemotherapy difficult. Supervening large B-cell lymphoma (often but not invariably EBV-positive) can occur.

APPENDIX 2: THE LUGANO CLASSIFICATION: REVISED CRITERIA FOR RESPONSE ASSESSMENT

Response and Site	PET-CT-Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
	Score 1, 2, or 3[*] with or without a residual mass on 5PS[†]	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
Lymph nodes and extra-lymphatic sites	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
	Score 4 or 5[†] with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
Lymph nodes and extra-lymphatic sites	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease

Response and Site	PET-CT-Based Response	CT-Based Response
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Footnotes on following page

Footnotes refer to table on previous pages

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

* A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

† PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

Source: *Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification*
Bruce D. Cheson, Richard I. Fisher, Sally F. Barrington, Franco Cavalli, Lawrence H. Schwartz, Emanuele Zucca and T. Andrew Lister.
JCO September 20, 2014 vol. 32 no. 27 3059-3067
Available at http://jco.ascopubs.org/content/32/27/3059.long (accessed 30 July 2015).

APPENDIX 3: PROGNOSTIC INDEX FOR PERIPHERAL T-CELL LYMPHOMA (PIT)

Source: Gallamini A, Stelitano C, Calvi R, Bellei M, Mattei D, Vitolo U, et al. Peripheral T-cell lymphoma unspecified (PTCL-U): a new prognostic model from a retrospective multicentric clinical study. Blood. 2004;103(7):2474-9.

Available at http://www.bloodjournal.org/content/bloodjournal/103/7/2474.full.pdf (accessed 30 July 2015).

To assess the prognosis of peripheral T-cell lymphoma unspecified, 385 cases were retrospectively analyzed fulfilling the criteria defined by the World Health Organization classification. Multivariate analysis showed that age (relative risk, 1.732; 95% CI, 1.300–2.309; P < .0001), PS (relative risk, 1.719; 95% CI, 1.269–2.327, P < .0001), lactate dehydrogenase (LDH) level (relative risk, 1.905; 95% CI, 1.415–2.564; P < .0001), and bone marrow involvement (relative risk, 1.454; 95% CI, 1.045–2.023; P = .026) were factors independently predictive for survival (**Table 1**).

Table 1. Clinical parameters influencing survival in PTCL (multivariate analysis)

Parameter	Significance, P	Relative risk	95% CI, low	95% CI, high
Age	< .0001	1.732	1.300	2.309
PS	< .0001	1.719	1.269	2.327
LDH level	< .0001	1.905	1.415	2.564
BM involvement	.026	1.454	1.405	2.023

BM, bone marrow; CI, confidence interval; PS, performance status; LDH, lactate dehydrogenase.

Using these four variables a new prognostic model (PIT, Prognostic Index for PTCL) that singled out four groups of patients at different risk was constructed (P ≤ .0001; log-rank, 66.79):

- Group 1: no adverse factors, with 5-year and 10-year OS of 62.3% and 54.9%, respectively.
- Group 2: one factor, with a 5-year and 10-year OS of 52.9% and 38.8%, respectively.
- Group 3: two factors, with 5-year and 10-year OS of 32.9% and 18.0%, respectively.
- Group 4: Three or four factors, with a 5-year and 10-year OS of 18.3 and 12.6%, respectively.

APPENDIX 4: PROGNOSTIC INDEX FOR ANGIOIMMUNOBLASTIC T-CELL LYMPHOMA (PIAI)

Source: Federico M, Rudiger T, Bellei M, Nathwani BN, Luminari S, Coiffier B, et al. Clinicopathologic characteristics of angioimmunoblastic T-cell lymphoma: analysis of the international peripheral T-cell lymphoma project. J Clin Oncol. 2013;31(2):240-6.

Available at http://jco.ascopubs.org/content/31/2/240.long (accessed 30 July 2015).

The International Peripheral T-Cell Lymphoma Project was undertaken to better understand the subtypes of T-cell and natural killer-cell lymphomas. Angioimmunoblastic T-cell lymphoma (AITL) was diagnosed according to the 2001 WHO criteria by a central review process consisting of panels of expert hematopathologists. Clinical, pathologic, immunophenotyping, treatment, and survival data were correlated. Of 1,314 patients, 243 (18.5%) were diagnosed with AITL. At presentation, generalized lymphadenopathy was noted in 76% of patients, and 89% had stages III to IV disease. Skin rash was observed in 21% of patients. Hemolytic anemia and hypergammaglobulinemia occurred in 13% and 30% of patients, respectively. Five-year overall and failure-free survivals were 33% and 18%, respectively.

At presentation, prognostic models were evaluated, including the standard International Prognostic Index, which comprised the following factors: age ≥ 60 years, stages III to IV disease, lactic dehydrogenase (LDH) > normal, extranodal sites (ENSs) > one, and performance status (PS) ≥ 2 (see Appendix 3).

The Prognostic Index for Peripheral T-Cell Lymphoma comprised: age ≥ 60 years, PS ≥ 2, LDH > normal, and bone marrow involvement; and the alternative Prognostic Index for AITL (PIAI) proposed by the authors, comprised: age > 60 years, PS ≥ 2, ENSs > one, B symptoms, and platelet count < 150 × 10^9/l. The simplified PIAI had a low-risk group (zero to one factors), with 5-year survival of 44%, and a high-risk group (two to five factors), with 5-year survival of 24% (P = .0065) (**Table 1**).

Table 1. Survival of patients with AITL by prognostic model

No. of Risk Factors	Patients (%)	5-year OS (%)	5-year FFS (%)
IPI			
0/1	14	56	34
2	28	38	21
3	30	20	12
4/5	28	25	16
PIT			
0/1	36	46	22
2	37	19	12
3/4	27	30	22
PIAI			
0/1 (low-risk group)	30	44	28
2-5 (high-risk group)	70	24	15

AITL, angioimmunoblastic T-cell lymphoma; FFS, failure-free survival; IPI, International Prognostic Index; OS, overall survival; PIAI, Prognostic Index for AITL; PIT, Prognostic Index for Peripheral T-Cell Lymphoma, Unspecified.

APPENDIX 5: ANN ARBOR STAGING SYSTEM

Source: Lister TA, Crowther D, Sutcliffe SB, et al. (November 1989). "Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting". *J. Clin. Oncol.* **7** (11): 1630–6.

Cotswold Modification

Stage	**Area of Involvement**
I	Single lymph node group
II	Multiple lymph node groups on same side of diaphragm
II	Multiple lymph node groups on both sides of diaphragm
IV	Multiple extranodal sites or lymph nodes and extranodal disease
X	Bulk > 10 cm
E	Extranodal extension or single, isolated site of extranodal disease

APPENDIX 6: CONTRACEPTION AND PREGNANCY TESTING

This document is based on the Heads of Medicines Agencies' Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials, published by the Clinical Trial Facilitation Group (CTFG) on 15 September 2014 and available at http://www.hma.eu/ctfg.html (accessed 30 July 2015)

A woman is considered of childbearing potential (WOCBP) following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. Immediately after detecting a case of suspected pregnancy in a patient, the decision on her continued participation in the clinical trial will be jointly taken by the patient, the Investigator and the Sponsor, with the patient's best interest in mind. A decision to continue the pregnancy will require immediate discontinuation any investigational medicinal product (IMP).

A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy. Fertile male patients included in this study should refrain from fathering a child or donating sperm during the study and for four months following the last IMP dose. If they have WOCBP partners the male subject should use condom during treatment and for four months following the last IMP dose.

Highly effective birth control methods are:

1. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation [1]:
    a. oral
    b. intravaginal
    c. transdermal
2. Progestogen-only hormonal contraception associated with inhibition of ovulation [1]:
    a. oral
    b. injectable
    c. implantable [2]
3. Intrauterine device (IUD) [2]
4. Intrauterine hormone-releasing system (IUS) [2]
5. Bilateral tubal occlusion [2]
6. Vasectomized partner [2,3]
7. Sexual abstinence [4]
8. A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods.

[1] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method (see below).

[2] Contraception methods that are considered to have low user dependency.

[3] Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.

[4] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

Contraception methods with low user dependency should preferably be used, in particular when contraception is introduced as a result of participation in this trial. It cannot be excluded that the IMP may reduce exposure to substrates of CYP3A through enzyme induction; the efficacy of hormonal contraceptives may be reduced if co-administered with the IMP.

APPENDIX 7: DECLARATION OF HELSINKI

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.
   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.
2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
5. Medical progress is based on research that ultimately must include studies involving human subjects.
6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.
8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.
9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or

other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.
11. Medical research should be conducted in a manner that minimises possible harm to the environment.
12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.
17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.
18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.
The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.
In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.
The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.
26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

    All medical research subjects should be given the option of being informed about the general outcome and results of the study.
27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.
28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.
29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.
30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must

be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

    Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

    and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

    Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports

of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

APPENDIX 8: LISTS DRUGS THAT PROLONG THE QT INTERVAL AND/OR INDUCE TORSADES DE POINTES VENTRICULAR ARRHYTHMIA

Source: www.azcert.org

Because the evidence for risk of Torsade de Pointes (TdP) is often imperfect, AZCERT, inc. has divided the drugs into four groups based on their analysis of the evidence:

1. Known Risk of TdP: Substantial evidence supports the conclusion that these drugs prolong the QT interval AND are clearly associated with a risk of TdP, even when taken as directed in official labeling. In **bold** at the listing below.

Generic Name (Brand Name)	Drug Class / Clinical Usage	Risk List
Amiodarone (Cordarone®)	Anti-arrhythmic/abnormal heart rhythm	**1**
Anagrelide (Agrylin®, Xagrid®)	Phosphodiesterase inhibitor/thrombocythemia	**1**
Arsenic trioxide (Trisenox®)	Anti-cancer/leukemia	**1**
Astemizole (Hismanal®)	Antihistamine/allergic rhinitis	**1**
Azithromycin (Zithromax®)	Antibiotic/bacterial infection	**1**
Bepridil (Vascor®)	Anti-anginal/heart pain	**1**
Chloroquine (Aralen®)	Anti-malarial/malaria infection	**1**
Chlorpromazine (Thorazine®)	Anti-psychotic/anti-emetic/schizophrenia/nausea	**1**
Cilostazol (Pletal®)	Phosphodiesterase inhibitor/intermittent claudication	**1**
Cisapride (Propulsid®)	GI stimulant/heartburn	**1**
Citalopram (Celexa®)	Anti-depressant/depression	**1**
Clarithromycin (Biaxin®)	Antibiotic/bacterial infection	**1**
Cocaine	Local anesthetic	**1**
Disopyramide (Norpace®)	Anti-arrhythmic/abnormal heart rhythm	**1**
Dofetilide (Tikosyn®)	Anti-arrhythmic/abnormal heart rhythm	**1**
Domperidone (Motilium®)	Anti-nausea/nausea	**1**
Donepezil (Aricept®)	Cholinesterase inhibitor/Dementia	**1**
Dronedarone (Multaq®)	Anti-arrhythmic/atrial fibrillation	**1**
Droperidol (Inapsine®)	Sedative;anti-nausea/anesthesia adjunct, nausea	**1**
Erythromycin (E.E.S.®)	Antibiotic;GI stimulant/bacterial infection; increase GI motility	**1**
Escitalopram (Cipralex®)	Anti-depressant/depression/ anxiety disorders	**1**
Flecainide (Tambocor®)	Anti-arrhythmic/abnormal heart rhythm	**1**
Halofantrine (Halfan®)	Anti-malarial/malaria infection	**1**
Haloperidol (Haldol®)	Anti-psychotic/schizophrenia, agitation	**1**
Ibutilide (Corvert®)	Anti-arrhythmic/abnormal heart rhythm	**1**
Levomethadyl (Orlaam®)	Opiate agonist/pain control, narcotic dependence	**1**
Mesoridazine (Serentil®)	Anti-psychotic/schizophrenia	**1**
Methadone (Methadose®)	Opiate agonist/pain control, narcotic dependence	**1**
Moxifloxacin (Avelox®)	Antibiotic/bacterial infection	**1**
Ondansetron (Zofran®)	Anti-emetic/nausea and vomiting	**1**
Pentamidine (Pentam®)	Anti-infective/pneumocystis pneumonia	**1**
Pimozide (Orap®)	Anti-psychotic/Tourette's tics	**1**
Probucol (Lorelco®)	Antilipemic/hypercholesterolemia	**1**
Procainamide (Procan®)	Anti-arrhythmic/abnormal heart rhythm	**1**
Quinidine (Quinaglute®)	Anti-arrhythmic/abnormal heart rhythm	**1**
Sevoflurane (Ulane®)	Anesthetic, general/anesthesia	**1**
Sotalol (Betapace®)	Anti-arrhythmic/abnormal heart rhythm	**1**
Sparfloxacin (Zagam®)	Antibiotic/bacterial infection	**1**
Sulpiride (Dogmatil®, Dolmatil®)	Anti-psychotic, atypical/schizophrenia	**1**

Generic Name (Brand Name)	Drug Class / Clinical Usage	Risk List
Terfenadine (Seldane®)	Antihistamine/allergic rhinitis	**1**
Thioridazine (Mellaril®)	Anti-psychotic/schizophrenia	**1**
Vandetanib (Caprelsa®)	Anti-cancer/thyroid cancer	**1**

2. Possible risk of TdP: Substantial evidence supports the conclusion that these drugs can cause QT prolongation BUT there is insufficient evidence at this time that these drugs, when used as directed in official labeling, are associated with a risk of causing TdP.

3. Conditional risk of TdP: Substantial evidence supports the conclusion that these drugs are associated with a risk of TdP BUT only under certain conditions (e.g. excessive dose, hypokalemia, congenital long QT or by causing a drug-drug interaction that results in excessive QT interval prolongation).

1 to 4. Drugs to Avoid in Congenital Long QT: Substantial evidence supports the conclusion that these drugs pose a risk of TdP for patients with congenital long QT. Drugs on this list include those in the above three risk cathegories 1, 2 and 3, and other drugs, 4, that do not prolong the QT interval per se but they have a theoretical risk of causing arrhythmia that is based on their known stimulant actions on the heart.

Generic Name (Brand Name)	Drug Class / Clinical Usage	Risk List
Albuterol/salbutamol (Proventil®, Ventolin)	Bronchodilator/Asthma	4
Alfuzosin (Uroxatral®)	Alpha1-blocker/benign prostatic hyperplasia	2
Amantadine (Symmetrel®)	anti-viral/anti-infective/Parkinson's disease	3
Amphetamine (Adderal-XR®, Dexedrine®)	CNS stimulant/ADHD	4
Amiodarone (Cordarone®)	Anti-arrhythmic/abnormal heart rhythm	**1**
Amisulpride (Solian® and others)	Antipsychotic, atypical/psychosis	3
Amitriptyline (Elavil®)	Tricyclic antidepressant/depression	3
Amoxapine (Asendin®, Amokisan®)	Tetracyclic anti-depressant/depression	3
Anagrelide (Agrylin®, Xagrid®)	Phosphodiesterase inhibitor/thrombocythemia	**1**
Apomorphine (Apokyn®, Ixense®)	Dopamine agonist/Parkinson's disease	2
Aripiprazole (Abilify®, Aripiprex®)	Antipsychotic/psychosis, adjunct for depression	2
Arsenic trioxide (Trisenox®)	Anti-cancer/leukemia	**1**
Arformoterol (Brovana®)	Bronchodilator/Chronic obs. lung disease	4
Astemizole (Hismanal®)	Antihistamine/allergic rhinitis	**1**
Atazanavir (Reyataz®)	Protease inhibitor/HIV	2
Atomoxetine (Strattera®)	Norepinephrine reuptake inhibitor/ADHD	4
Azithromycin (Zithromax®)	Antibiotic/bacterial infection	**1**
Bedaquiline (Sirturo®)	Anti-infective/drug-resistant tuberculosis	2
Bepridil (Vascor®)	Anti-anginal/heart pain	**1**
Bortezomib (Velcade®, Bortecad®)	Proteasome inhibitor/multiple myeloma,lymphoma	2
Bosutinib (Bosulif®)	Tyrosine kinase inhibitor/leukemia	2
Chloral hydrate (Noctec®)	Sedative/sedation/insomnia	3
Chloroquine (Aralen®)	Anti-malarial/malaria infection	**1**
Chlorpromazine (Thorazine®)	Anti-psychotic/anti-emetic/schizophrenia/nausea	**1**
Cilostazol (Pletal®)	Phosphodiesterase inhibitor/intermittent claudication	**1**
Ciprofloxacin (Cipro®)	Antibiotic/bacterial infection	3
Cisapride (Propulsid®)	GI stimulant/heartburn	**1**
Citalopram (Celexa®)	Anti-depressant/depression	**1**
Clarithromycin (Biaxin®)	Antibiotic/bacterial infection	**1**

Generic Name (Brand Name)	Drug Class / Clinical Usage	Risk List
Clomipramine (Anafranil®)	Tricyclic Antidepressant/depression	3
Clozapine (Clozaril®)	Anti-psychotic/schizophrenia	2
Cocaine	Local anesthetic	**1**
Crizotinib (Xalkori®)	Kinase inhibitor/anti-cancer	2
Dabrafenib (Tafinlar®)	Anti-cancer/melanoma	2
Dasatinib (Sprycel®)	Tyrosine kinase inhibitor/leukemia	2
Desipramine (Pertofrane®)	Tricyclic antidepressant/depression	3
Dexmedetomidine (Precedex®, Dexdor®)	Sedative/sedation	2
Dexmethylphenidate (Focalin®)	CNS stimulant/ADHD	4
Dextroamphetamine (Dexedrine®)	CNS stimulant/ADHD	4
Dihydroartemis.+piperaquine (Eurartesim®)	Anti-malarial/malaria	2
Diphenhydramine (Benadryl®)	Antihistamine/allergic rhinitis, insomnia	3
Disopyramide (Norpace®)	Anti-arrhythmic/abnormal heart rhythm	**1**
Dobutamine (Dobutrex®)	Inotrope/Heart failure, shock	4
Dopamine (Intropine®)	Inotrope/Heart failure, shock	4
Dofetilide (Tikosyn®)	Anti-arrhythmic/abnormal heart rhythm	**1**
Dolasetron (Anzemet®)	Anti-nausea/nausea, vomiting	2
Domperidone (Motilium®)	Anti-nausea/nausea	**1**
Donepezil (Aricept®)	Cholinesterase inhibitor/Dementia	**1**
Doxepin (Sinequan®)	Tricyclic antidepressant/depression	3
Dronedarone (Multaq®)	Anti-arrhythmic/atrial fibrillation	**1**
Droperidol (Inapsine®)	Sedative;anti-nausea/anesthesia adjunct, nausea	**1**
Ephedrine (Rynatuss®, Broncholate®)	Bronchodilator, decongestant/Allergies, asthma	4
Epinphrine (Primatene®, Bronkaid®)	Vasoconstrictor/Anaphilaxis, allergic reactions	4
Eribulin (Halaven®)	Anti-cancer/metastatic breast neoplasias	2
Erythromycin (E.E.S.®)	Antibiotic;GI stimulant/bacterial infection; increase GI motility	**1**
Escitalopram (Cipralex®)	Anti-depressant/depression/ anxiety disorders	**1**
Famotidine (Pepcid®)	H2-receptor antagonist/peptic ulcer/GERD	2
Felbamate (Felbatrol®)	Anti-convulsant/seizure	2
Fenfluramine (Pondimin®, Ponderax®)	Appetite suppressant/Dieting, weight loss	4
Fingolimod (Gilenya®)	Immunosuppressant/multiple sclerosis	2
Flecainide (Tambocor®)	Anti-arrhythmic/abnormal heart rhythm	**1**
Fluconazole (Diflucan®)	Anti-fungal/fungal infection	3
Fluoxetine (Sarafem®)	Anti-depressant/depression	3
Formoterol (Foradil, Foralide)	Bronchodilator /Asthma	4
Foscarnet (Foscavir®)	Anti-viral/HIV infection	2
Fosphenytoin (Cerebyx®)	Anti-convulsant/seizure	2
Furosemide/Frusemide (Lasix®, Fusid®)	Diuretic/Increase urine & salt loss	3
Galantamine (Reminyl®)	Cholinesterase inhibitor/ dementia, Alzheimer's	3
Gatifloxacin (Tequin®)	Antibiotic/bacterial infection	2
Gemifloxacin (Factive®)	Antibiotic/bacterial infection	2
Granisetron (Kytril®)	Anti-nausea/nausea and vomiting	2
Halofantrine (Halfan®)	Anti-malarial/malaria infection	**1**
Haloperidol (Haldol®)	Anti-psychotic/schizophrenia, agitation	**1**
Hydrochlorothiazide (Apo-Hydro®)	Diuretic/increase urine & salt loss	3
Ibutilide (Corvert®)	Anti-arrhythmic/abnormal heart rhythm	**1**
Iloperidone (Fanapt®)	Antipsychotic, atypical/schizophrenia	2
Imipramine (Norfranil®)	Tricyclic antidepressant/depression	3
Indapamide (Lozol®)	Diuretic/stimulate urine & salt loss	3
Isoproterenol (Medihaler-Iso®, Isuprel®)	Bronchodilator/Allergic reaction	4
Isradipine (Dynacirc®)	Anti-hypertensive/high blood pressure	2
Itraconazole (Sporanox®)	Anti-fungal/fungal infection	3

Generic Name (Brand Name)	Drug Class / Clinical Usage	Risk List
Ivabradine (Procoralan®, Coralan®)	Anti-anginal/angina pectoris (heart pain)	3
Ketoconazole (Nizoral®)	Anti-fungal/fungal infection	3
Lapatinib (Tykerb®)	Anti-cancer/breast cancer, metastatic	2
Levalbuterol (Xopenex®, Levolin®)	Bronchodilator/Asthma	4
Levofloxacin (Levaquin®)	Antibiotic/bacterial infection	2
Levomethadyl (Orlaam®)	Opiate agonist/pain control, narcotic dependence	**1**
Lisdexamfetamine (Vyvanse®)	CNS stimulant/ADHD	4
Lithium (Lithobid®)	Anti-mania/bipolar disorder	2
Mesoridazine (Serentil®)	Anti-psychotic/schizophrenia	**1**
Metaproterenol (Metaprel®), Alupent®)	Bronchodilator/Asthma	4
Methadone (Methadose®)	Opiate agonist/pain control, narcotic dependence	**1**
Methamphetamine (Desoxyn®, Pervitin®)	CNS stimulant/Obesity, ADHD	4
Methylphenidate (Ritalin®, Concerta®)	CNS stimulant/ADHD	4
Metronidazole (Flagyl®)	Antibiotic/trichomoniasis, amebiasis, bacterial infection	3
Midodrine (ProAmatine®, Amatine®)	Vasoconstrictor/Low blood pressure, fainting	4
Mifepristone (Korlym®, Mifeprex®)	Progesterone antagonist/pregnancy termination	2
Mirabegron (Myrbetriq®)	Beta3 adrenergic antagonist/overactive bladder	2
Mirtazapine (Remeron®)	Anti-depressant/depression	2
Moexipril/HCTZ (Uniretic®)	Anti-hypertensive/high blood pressure	2
Moxifloxacin (Avelox®)	Antibiotic/bacterial infection	**1**
Nelfinavir (Viracept®)	Anti-viral/HIV/AIDS	3
Nicardipine (Cardene®)	Anti-hypertensive/high blood pressure	2
Nilotinib (Tasigna®)	Anti-cancer/leukemia	2
Norepinephrine (Levophed ®)	Vasoconstrictor/Shock, low blood pressure	4
Norfloxacin (Noroxin®, Ambigram®)	Antibiotic/bacterial infection	2
Nortriptyline (Pamelor®)	Tricyclic Antidepressant/depression	3
Ofloxacin (Floxin®)	Antibiotic/bacterial infection	2
Olanzapine (Zyprexa®)	Antipsychotic, atypical/schizophrenia, bipolar	2
Ondansetron (Zofran®)	Anti-emetic/nausea and vomiting	**1**
Oxytocin (Pitocin®)	Oxytocic/labor stimulation	2
Paliperidone (Invega®)	Antipsychotic, atypical/schizophrenia	2
Paroxetine (Paxil®)	Anti-depressant/depression	3
Pasireotide (Signifor®)	Somatostatin analog/Cushings Disease	2
Pazopanib (Votrient®)	Tyrosine kinase inhibitor/anti-cancer	2
Pentamidine (Pentam®)	Anti-infective/pneumocystis pneumonia	**1**
Perflutren lipid microspheres (Definity®)	Imaging contrast agent/echocardiography	2
Phentermine (Adipex P®, Adiphene®)	Appetite suppressant/Dieting, weight loss	4
Phenylephrine (Neosynephrine®)	Vasoconstrictor/Low blood pressure, allergies	4
Phenylpropanolamine (Acutrim,Dexatrim®)	Appetite suppressant/Obesity	4
Pimozide (Orap®)	Anti-psychotic/Tourette's tics	**1**
Pipamperone (Dipiperon®, Propitan®)	Antipsychotic/schizophrenia	2
Posaconazole (Noxafil®, Posamol®)	Anti-fungal/fungal infection	3
Probucol (Lorelco®)	Antilipemic/hypercholesterolemia	**1**
Procainamide (Procan®)	Anti-arrhythmic/abnormal heart rhythm	**1**
Promethazine (Phenergan®)	Anti-psychotic-anti-emetic/nausea	2
Protriptyline (Vivactil®)	Tricyclic antidepressant/depression	3
Pseudoephedrine (PediaCare®, Sudafed®)	Descongestant/Allergies, sinusitis, asthma	4
Quetiapine (Seroquel®)	Anti-psychotic/schizophrenia	2
Quinidine (Quinaglute®)	Anti-arrhythmic/abnormal heart rhythm	**1**
Quinine sulfate (Qualaquin®)	Anti-malarial/malaria or leg cramps	3
Ranolazine (Ranexa®)	Anti-anginal/chronic angina	2

Generic Name (Brand Name)	Drug Class / Clinical Usage	Risk List
Rilpivirine (Edurant®, Complera®)	Anti-viral/HIV/AIDS	2
Risperidone (Risperdal®)	Anti-psychotic/schizophrenia	2
Ritodrine (Yutopar®)	Muscle relaxant/Prevent premature labor	4
Ritonavir (Norvir®)	Protease inhibitor/HIV	3
Roxithromycin* (Rulide®)	Antibiotic/bacterial infection	2
Saquinavir (Invirase®)	Anti-viral/HIV/AIDS	2
Salmeterol (Serevent®, Advair®)	Bronchodilator/Asthma, COPD	4
Sertindole (Serdolect®)	Antipsychotic, atypical/anxiety, schizophrenia	2
Sertraline (Zoloft®)	Anti-depressant/depression	3
Sevoflurane (Ulane®)	Anesthetic, general/anesthesia	**1**
Sibutramine (Meridia®)	Appetite suppressant/Dieting, weight loss	4
Solifenacin (VESIcare®)	muscarinic recptr. anatagonist/overactive bladder	3
Sorafenib (Nexavar®)	Tyrosine kinase inhibitor/anti-cancer	2
Sotalol (Betapace®)	Anti-arrhythmic/abnormal heart rhythm	**1**
Sparfloxacin (Zagam®)	Antibiotic/bacterial infection	**1**
Sulpiride (Dogmatil®, Dolmatil®)	Anti-psychotic, atypical/schizophrenia	**1**
Sunitinib (Sutent®)	Anti-cancer/RCC, GIST	2
Tacrolimus (Prograf®)	Immunosuppressant/immune suppression	2
Tamoxifen (Nolvadex®)	Anti-cancer/breast cancer	2
Telaprevir (Incivek®, Incivo®)	Anti-viral/hepatitis C	3
Telavancin (Vibativ®)	Antibiotic/bacterial infection	2
Telithromycin (Ketek®)	Antibiotic/bacterial infection	2
Terbutaline (Brethine®, Bricanyl®)	Bronchodilator/Asthma, premature labor	4
Terfenadine (Seldane®)	Antihistamine/allergic rhinitis	**1**
Tetrabenazine (Nitoman®, Xenazine®)	Monoamine transptr inhibitor/chorea	2
Thioridazine (Mellaril®)	Anti-psychotic/schizophrenia	**1**
Tizanidine (Zanaflex®)	Muscle relaxant/spasticity	2
Tolterodine (Detrol®, Detrusitol®)	Muscle relaxant/bladder spasm	2
Toremifene (Fareston®)	Estrogen agonist/antagonist/anti-cancer	2
Trazodone (Desyrel®)	Anti-depressant/depression, insomnia	3
Trimethoprim-Sulfa (Septra® or Bactrim®)	Antibiotic/bacterial infection	3
Trimipramine (Surmontil®)	Tricyclic antidepressant/depression	3
Vandetanib (Caprelsa®)	Anti-cancer/thyroid cancer	**1**
Vardenafil (Levitra®)	Phosphodiesterase inhibitor/vasodilator	2
Vemurafenib (Zelboraf®)	Kinase inhibitor/anti-cancer	2
Venlafaxine (Effexor®)	Anti-depressant/depression	2
Voriconazole (Vfend®)	Anti-fungal/fungal infection	3
Vorinostat (Zolinza®)	Anti-cancer/lymphoma	2
Ziprasidone (Geodon®)	Anti-psychotic/schizophrenia	2

A note about <u>brand names</u>: drugs are listed with up to two common brand names. There are many more brand names for some of the common drugs, such as pseudoephedrine and erythromycin.