1. CLINICAL STUDY PROTOCOL

- Protocol Title: A PHASE 1 DOSE ESCALATION STUDY OF THE SAFETY AND PHARMACOKINETICS OF LAM-002A (APILIMOD DIMESYLATE CAPSULES) ADMINISTERED ORALLY IN SUBJECTS WITH RELAPSED OR REFRACTORY B-CELL NON-HODGKIN'S LYMPHOMA
- Protocol Number: LAM-002A-NHL-CLN01 v9 Amend 8
- Protocol Date: 18 FEB 2020
- NCT: NCT02594384

A PHASE 1 DOSE ESCALATION STUDY OF THE SAFETY AND PHARMACOKINETICS OF LAM-002A (APILIMOD DIMESYLATE CAPSULES) ADMINISTERED ORALLY IN SUBJECTS WITH RELAPSED OR REFRACTORY B-CELL NON-HODGKIN'S LYMPHOMA

Protocol Number:	**LAM-002A-NHL-CLN01**
Sponsor:	**AI Therapeutics, Inc.** **(formerly known as LAM Therapeutics, Inc.)** [redacted]
Protocol Version and Date:	**Version 9, 18 Feb 2020**

Conduct: In accordance with the ethical principles that originate from the Declaration of Helsinki and that are consistent with International Conference on Harmonisation (ICH) Guidelines on Good Clinical Practice (GCP) and regulatory requirements as applicable.

AI THERAPEUTICS SIGNATURE PAGE

Name:	[redacted]	
Title:	Head, Clinical Operations/Project Management AI Therapeutics, Inc.	Date:
Signature:	[redacted]	18 Feb 2020
Name:	[redacted]	
Title:	Clinical Consultant AI Therapeutics, Inc.	Date:
Signature:	[redacted]	18 Feb 2020

INVESTIGATOR'S AGREEMENT

I have read the attached Protocol entitled "A Phase 1 Dose Escalation Study of the Safety and Pharmacokinetics of LAM-002A (apilimod dimesylate capsules) Administered Orally in Subjects with Relapsed or Refractory B-cell Non-Hodgkin's Lymphoma" dated 18 Feb 2020. I agree to abide by all provisions set forth herein. I agree to comply with the International Conference on Harmonisation Guidelines on Good Clinical Practice, effective in the United States from 09 May 1997, and applicable United States Food and Drug Administration regulations set forth in 21 Code of Federal Regulations (CFR) §50, 54, 56, and 312 and any applicable local regulatory requirements. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical investigation without the prior written consent of AI Therapeutics, Inc. 530 Old Whitfield Street, Guilford CT 06437, United States.

Printed Name of Investigator

Signature of Investigator

Date

PROCEDURES IN CASE OF EMERGENCY

Prior to initiation of the study, the sponsor (or its designee) will provide a study roster with contact information for applicable study personnel.

The medical monitor, [redacted] can be reached by telephone at [redacted] and by email at [redacted]

1. SYNOPSIS

Name of Sponsor/Company:

AI Therapeutics, Inc. (AI Therapeutics)

530 Old Whitfield Street

Guilford, CT 06437

Name of Investigational Product:

LAM-002A (apilimod dimesylate capsules)

Name of Active Ingredient:

(E)-4-(6-(2-(3-methylbenzylidene)hydrazinyl)-2-(2-(pyridin-2-yl)ethoxy)pyrimidin-4-yl)morpholine dimesylate

Title of Study:

A Phase 1 Dose-Escalation Study of the Safety and Pharmacokinetics of LAM-002A (apilimod dimesylate capsules) Administered Orally in Subjects with Relapsed or Refractory B-cell Non-Hodgkin's Lymphoma

Study Center(s):

Dose Escalation Stage: Up to ~10 US sites are planned

Expansion Stage: ~15 US sites are planned

Extension Stage: Up to 2 US sites are planned

Objectives:

The overall purpose of this Phase 1 study is to explore the safety and tolerability of LAM-002A when given alone and in combination for the treatment of subjects with relapsed or refractory B-cell non-Hodgkin lymphoma (NHL).

Primary:

- To determine the maximum tolerated dose (MTD) of daily oral administration of LAM-002A in subjects with relapsed or refractory B-cell non-Hodgkin lymphoma (NHL).

Secondary:

- To evaluate the plasma pharmacokinetics (PK) of apilimod, and its active metabolites, administered orally in subjects with relapsed or refractory NHL.
- To evaluate the safety and tolerability of daily oral administration of LAM-002A in subjects with relapsed or refractory B-cell NHL.
- To evaluate the preliminary anti-tumor activity of LAM-002A.

Exploratory:

- To evaluate the pharmacodynamic effects of LAM-002A, administered orally, in plasma assays and surrogate tissue (gene expression in peripheral blood mononuclear cells [PBMCs]/B cells and plasma cytokines [including (IL)-12 and IL-23]).
- To evaluate tumor and/or plasma for gene expression and genetic alterations (with saliva or B-cell-depleted PBMC collection for germ-line control) and surrogate tissue (PBMC/B cells) for gene expression that may predict anti-lymphoma activity.
- To evaluate plasma for changes in analytes or tumor for protein expression that may predict anti-lymphoma activity.

Methodology:

This is a Phase 1, single–arm, open-label, dose-escalation and cohort-expansion study evaluating the safety, pharmacokinetics, pharmacodynamics, and antitumor activity of LAM-002A administered orally in subjects with relapsed or refractory B-cell NHL. The study consists of 3 stages, a dose-escalation stage, an expansion stage, and an extension stage.

In the dose-escalation stage (Stage 1), a 3 + 3 design will be utilized to define an MTD of LAM-002A, first when administered continuously and then when administered intermittently. Cohorts of 3 to 6 subjects will be sequentially enrolled at progressively higher starting dose levels of LAM-002A, as indicated in Table S-1. The initial cohort of subjects will be prescribed LAM-002A at Dose Level 0 (50 mg twice per day [BID]). Dose level -1 (25 mg BID) is provided to permit a dose decrement in subjects experiencing DLT at Dose Level 0.

Table S-1. LAM-002A Provisional Starting Dose Levels

Continuous Administration		
Dose Level	**LAM-002A Dose and Schedule**	**LAM-002A Total Daily Dose**
-1	25 mg BID	50 mg
0 (Initial Dose Level)	50 mg BID	100 mg
1	100 mg BID	200 mg
1a	125 mg BID	250 mg
1b	75 mg TID	225 mg
1c	100 mg TID	300 mg
1d	125 mg TID	375 mg
2	150 mg BID	300 mg
3	200 mg BID	400 mg
4	275 mg BID	550 mg
Intermittent Administration		
Dose Level	**LAM-002A Dose and Schedule**	**LAM-002A Total Daily Dose**
5	150 mg BID	300 mg
6	200 mg BID	400 mg
7	250 mg BID	500 mg
8	300 mg BID	600 mg

Abbreviations: BID: Twice daily (or 2 times per day); TID: Thrice daily (or 3 times per day)

For each cohort of 3 subjects in the continuous and intermittent administration approaches, dose escalation to the next higher dose may proceed if no dose-limiting toxicity (DLT) is observed within the first cycle of the 3 subjects accrued to a cohort. If 1 of 3 subjects in the cohort experiences a DLT, up to a total of 6 subjects will be enrolled. If 2 or more of the 3-6 subjects in a cohort experience a DLT, dose escalation will cease, and additional subjects will be treated at a lower dose level or with another schedule. If de-escalation to the previous dose cohort is undertaken, this cohort will be expanded to ≥6 subjects. Additional subjects (up to 12 total per cohort) may be evaluated to refine the estimation of the MTD and RP2D at the planned dose levels or at an intermediate dose level between the highest previously tolerated total dose and the next planned total daily dose. The MTD is defined as the highest dose at which < 33% of subjects experiences a DLT in the total dose and schedule cohort. The investigators and sponsor will review available data including toxicity, PK and anti-tumor activity data to reach consensus on dose levels and determination of the MTDs with continuous and intermittent dosing.

Once the MTD and/or recommended phase 2 dose (RP2D and schedule is determined, the study will enter the expansion stage (Stage 2), in which cohorts of subjects will be accrued in order to obtain additional information on safety, tolerability, preliminary anti-tumor activity, PK, and pharmacodynamic data at the RP2D and schedule when LAM-002A is administered alone or in combination with rituximab/rituximab hyaluronidase human or atezolizumab. Expansion-stage cohorts will comprise groups of subjects with specific types of previously treated, relapsed, progressive, and measurable NHL who will receive LAM-002A monotherapy or LAM-002A-containing combination therapy as shown in Table S-2. For both monotherapy and combination cohorts, the starting dose of LAM-002A will be 125 mg BID administered continuously.

Table S-2. Expansion Stage Disease Types and Therapies

Cohort Number	NHL Type	Investigational Regimen	Combination Drug	Evaluable Subjects, n
1	FL	LAM-002A	--	Up to ~20
2	MZL	LAM-002A	--	6
3	DLBCL-GCB	LAM-002A	--	6
4	DLBCL-ABC	LAM-002A	--	6
5	FL or MZL	LAM-002A	Rituximab or rituximab hyaluronidase human	Up to ~20 with FL
6	DLBCL-GCB or DLBCL-ABC	LAM-002A	Rituximab or rituximab hyaluronidase human	6
7	FL or MZL	LAM-002A	Atezolizumab	6
8	DLBCL-GCB or DLBCL-ABC	LAM-002A	Atezolizumab	6

Abbreviations: ABC: activated B-cell (subtype); DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; GCB: germinal center B-cell (subtype); MZL: marginal zone lymphoma; NHL: non-Hodgkin lymphoma

The extension stage (Stage 3) can begin once the last study subject has completed at least 8 cycles of study treatment. At this time, the study sponsor will conclude the dose-escalation and expansion stages of the study, will collate and verify all study data through an appropriate data cutoff date, and will lock the study database for preparation of a study

report. Subjects who are still safely benefiting from Stage 1 or Stage 2 study therapy as of the data cutoff date may electively continue their current regimen of study therapy in Stage 3, receiving clinical care and diagnostic testing consistent with conventional practice standards as deemed appropriate by the treating investigator. Therapy in Stage 3 may continue in the absence of protocol-defined reasons to discontinue therapy. During Stage 3, collection of clinical data by the sponsor will be limited to serious adverse event (SAE) reports. Study drug accountability will be managed per site procedures; relevant pharmacy records may be collected by the sponsor to document study drug disposition.

Each subject's course on study will consist of the following periods:

- Pre-Treatment Period: The subject is consented and undergoes screening assessments to be qualified for the study.
- Treatment Period: The subject is treated, monitored for safety (including assessments of adverse events [AEs], vital signs, electrocardiograms [ECGs], laboratory tests and concomitant medications), and PK and biomarker samples are collected.
- Post-Treatment Period: Subjects should be followed until the later of either 30 days after the last dose of study treatment or until resolution/stabilization of any ongoing drug-related AEs and/or SAEs. For subjects with events that require follow-up, information regarding concomitant medications should be collected. Any necessary follow-up may be obtained in person or by telephone contact.

Subjects who have discontinued study treatment for reasons other than progressive disease (PD) will be assessed per standard response criteria for NHL or chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) at a minimum of every 12 weeks until documentation of PD, start of new anti-cancer therapy or for up to 1 year from the last enrolled subject's first treatment (Cycle 1 Day 1), whichever comes first.

Long-term follow-up survival information will be obtained in all surviving subjects who permanently discontinue study therapy. Such information may be collected at ~3- to 6-month intervals at the sponsor's discretion through 3 years. This long-term follow-up information will be gathered during routine clinic visits, other study site contact with the subjects, or via telephone or e-mail with the subjects/caregivers or referring physician offices.

Number of Subjects (planned):

As many as 145 future subjects may be enrolled, assuming that:

- In the dose-escalation stage of the study, the total number of subjects will depend upon the numbers of subjects accrued to each dose level and the number of dose levels evaluated. If 6 subjects are enrolled at all open starting dose levels (Dose Levels 5, 6, 7, and 8) and 6 additional subjects are enrolled at the MTD or RP2D, as many as 30 subjects could be enrolled. To allow for the possibility that some subjects may not be fully evaluable for DLT or that an intermediate dose level might be evaluated, up to ~45 subjects may be enrolled.
- In the expansion stage of the study, if all 8 potential expansion cohorts are accrued, as many as ~76 subjects could be enrolled. To allow for the possibility that some subjects may not be fully evaluable for efficacy or to establish bounds on efficacy estimates with

greater confidence, up to ~100 subjects may be enrolled.

- In the extension stage of the study, the total number of subjects will include ≤4 subjects who have participated in the expansion stage of the study and are still receiving study therapy on the data cutoff date that concludes the dose-escalation and expansion stages of the clinical trial.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Inclusion Criteria:

1. The subject is capable of understanding and complying with the protocol requirements and has signed the informed consent document. The subject is able to provide signed and dated informed consent prior to initiation of any study-specific procedures.
2. Subjects must have a histologically confirmed diagnosis of B-cell NHL limited to FL, DLBCL, mantle cell lymphoma (MCL), MZL, primary mediastinal B-cell lymphoma (PMBL), or CLL/SLL according to the World Health Organization (WHO) classification, that has progressed and for which standard curative measures do not exist or are no longer effective.
3. Subjects with DLBCL must have progressed after transplant, or be unwilling, unable or not an appropriate candidate for an autologous stem cell or bone marrow transplant.
4. Subjects must have radiographically measurable lymphadenopathy or extranodal lymphoid malignancy (defined as the presence of ≥ 1 lesion that measures ≥ 2.0 cm in the longest dimension [LD] and ≥ 1.0 cm in the longest perpendicular dimension [LPD] as assessed radiographically).
5. The subject is ≥ 18 years old.
6. The subject has an Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 2.
7. The subject has organ and marrow function as follows:
    a. Absolute neutrophil count (ANC) ≥ 1.0×10^9/L ($1{,}000/mm^3$) without hematopoietic-stimulating factor support
    b. Platelets ≥ 50×10^9/L ($50{,}000/mm^3$)
    c. Total bilirubin ≤ 1.5 x the upper limit of normal (ULN) except for subjects with known Gilbert disease (total bilirubin ≤ 3 x ULN permitted)
    d. Serum creatinine ≤ 1.5 x ULN or calculated creatinine clearance ≥ 60 mL/min (based on the Cockcroft-Gault formula)
    e. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x ULN if no liver involvement, or ≤ 5 x ULN with liver involvement
    f. Albumin ≥ 2 g/dL
    g. ***Note: Grade ≥ 3 neutropenia or thrombocytopenia is permitted if the abnormality is related to bone marrow involvement with hematological malignancy (as documented by bone marrow biopsy/aspirate obtained since the last prior therapy).***

8. The subject has the ability to swallow oral capsules without difficulty.
9. Sexually active subjects (men and women), even if on oral contraceptives, must agree to remain abstinent (refrain from heterosexual intercourse) or use appropriate contraceptive methods (see Section 6.10.2) during the treatment period and for 5 months after the last dose of study therapy.
10. Women of childbearing potential (WCBP) must have a negative serum or urine pregnancy test at screening. WCBP include any woman who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal. Postmenopausal is defined as:
    a. Amenorrhea ≥ 12 consecutive months without another cause or
    b. For women with irregular menstrual periods and on hormone replacement therapy, a documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL
11. For subjects with lymphoma: The subject is willing to undergo a pretreatment core needle, excisional, or incisional biopsy of a lymphoma nodal lesion (preferred); or is willing to undergo a pretreatment bone marrow aspirate if there is known bone marrow involvement (≥ 50% NHL cells). If a biopsy or bone marrow aspirate is not possible, archived tumor tissue that was obtained within 4 months prior to the start of screening can be used, provided adequate quantities are available.
12. For subjects with CLL/SLL: The subject has sufficient circulating cells in the peripheral blood (e.g., ALC ≥ 10 x 10^9/L) or is willing to undergo a pretreatment bone marrow aspirate to obtain CLL cells.

Exclusion Criteria:

1. Subjects with central nervous system (CNS) lymphoma are not eligible for the trial unless the disease had been treated and the subject remained asymptomatic (for at least 6 months) with no active CNS lymphoma, as determined by lumbar puncture, computed tomography scan (CT), or magnetic resonance imaging (MRI).
2. The subject has received cytotoxic chemotherapy (including investigational cytotoxic chemotherapy) within 3 weeks, or nitrosoureas/ mitomycin C within 6 weeks before the first dose of study treatment.
3. The subject has received treatment with a therapeutic antibody less than 4 weeks before the first dose of study treatment. For subjects with rapidly progressive or aggressive subtypes of lymphoma, a minimum period of 2 weeks between the last treatment with a therapeutic antibody and the first dose of study treatment may be permitted following discussion with the medical monitor.
4. The subject has received radioimmunotherapy within 6 weeks of the first dose of study treatment.
5. The subject has received radiation therapy within 14 days of the first dose of study treatment.

6. The subject has received prior treatment with a small-molecule kinase inhibitor or other small-molecule investigational agent within 14 days or 5 half-lives of the compound or active metabolites, whichever is greater, before the first dose of study treatment.
7. Stage 2 (study candidates being considered for LAM-002A/rituximab combination therapy): Best overall response with the last regimen containing an anti-CD20 antibody (eg, rituximab, ofatumumab, obinutuzumab) was disease progression.
8. Stage 2 (study candidates being considered for LAM-002A/atezolizumab combination therapy): Prior exposure to a CD137 agonist or an immune checkpoint inhibitor, including an anti-PD1, anti-PDL1, or anti-CTLA4 therapeutic antibody.
9. Stage 2 (study candidates being considered for LAM-002A/atezolizumab combination therapy): treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the last dose of atezolizumab.
10. Stage 2 (study candidates being considered for LAM-002A/atezolizumab combination therapy): Current treatment with anti-viral therapy for hepatitis B virus (HBV).
11. Stage 2 (study candidates being considered for LAM-002A/atezolizumab combination therapy): Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment.
12. The subject is currently receiving treatment with strong inhibitors or inducers of CYP450 2C9 or 3A4 enzymes.
13. The subject is chronically receiving immunosuppressive therapy (eg, with cyclophosphamide, azathioprine, thalidomide, lenalidomide, methotrexate, or anti-TNF-α agents) within 2 weeks prior to initiation of study treatment or requires systemic or enteric corticosteroids at the time of starting study therapy. Study candidates using systemic low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency or topical, intra-articular, nasal, or inhaled corticosteroids are not excluded from study participation. ***Note: During study therapy, subjects may use systemic, enteric, topical, intraarticular, nasal, or inhaled corticosteroids as required by protocol or for treatment-emergent conditions.***
14. The subject has not recovered from toxicity due to all prior therapies (i.e., return to pre-therapy baseline or to Grade 0 or 1). Persistent > Grade 1 toxicity from prior therapy will be considered by the sponsor for inclusion if there is no evidence of an overlapping LAM-002A toxicity.
15. The subject has uncontrolled significant intercurrent illness including, but not limited to, ongoing or active infection, history of congestive heart failure within 6 months, Grade ≥3 hypertension, unstable angina pectoris within 6 months, stroke within 6 months, myocardial infarction within 6 months, or cardiac arrhythmias. (Controlled chronic atrial fibrillation will not be excluded).

16. Severe uncontrolled infection within 2 weeks prior to initiation of study treatment, including hospitalization for complications of infection, bacteremia, or severe pneumonia or treatment with therapeutic oral or IV antibiotics. ***Note: subjects receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are not excluded.***
17. Stage 2 (study candidates being considered for LAM-002A/atezolizumab combination therapy): Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (with the following exceptions: history of autoimmune-related hypothyroidism and receiving thyroid-replacement hormone; controlled Type 1 diabetes mellitus on an insulin regimen; eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations if rash covers < 10% of body surface area, disease is well controlled at baseline and requires only low-potency topical corticosteroids, there is no occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months, and the subject does not have extra-cutaneous disease [e.g., psoriatic arthritis]).
18. The subject has a history of malabsorption or other GI disease that may significantly alter the absorption of apilimod (e.g., ≥ Grade 2 nausea, vomiting or diarrhea).
19. The subject has undergone major surgery within 28 days prior to first dose of study drug.
20. The subject has a QTcF > 470 msec on screening ECG or has a history or risk factors for, or use of medications known to prolong QTc interval or that may be associated with Torsades de Pointes within 7 days of treatment start.
21. The subject has past history of tuberculosis (TB) or active infection with TB, human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV). ***Note: Subjects must have negative human immunodeficiency virus (HIV) antibody, negative hepatitis B surface antigen (HBsAg) and negative hepatitis B core (HBc) antibody or undetectable HBV deoxyribonucleic acid (DNA) by quantitative polymerase chain reaction (PCR) testing, and negative HCV antibody or negative HCV ribonucleic acid (RNA) by quantitative PCR.***
22. The subject is lactating and breast feeding.
23. The subject has a previously identified allergy or hypersensitivity to components of the study treatment formulation.
24. Stage 1 (study candidates being considered for LAM-002A intermittent administration): Known inability to tolerate the protocol-specified antiemetic and antidiarrheal supportive care regimen.
25. The subject is unable or unwilling to abide by the study protocol or cooperate fully

with the investigator or designee.

26. The subject has a history of other medical or psychiatric illness or organ dysfunction which, in the opinion of the investigator, would either compromise the subject's safety or interfere with the evaluation of the safety of the study agent.
27. The subject has a history of prior cancer (not under study) that has not been in remission for at least 3 years. The following are exempt from the 3-year limit: basal cell or squamous cell carcinoma of the skin, localized prostate cancer with normal prostate-specific antigen (PSA), cervical cancer in situ, or other in situ carcinomas.

Investigational Product, Dosage and Mode of Administration:

LAM-002A is supplied as 25 mg or 50 capsules and will be administered with a BID or TID oral dosing regimen. Subjects on a BID schedule will be advised to take the doses at the same time each day, ~12 hours apart. Subjects on a TID schedule will be advised to take the doses at the same time each day at intervals of ~6 to 8 hours. On PK days, subjects on a TID schedule should receive the morning dose and complete the blood collections through 8 hours thereafter before taking the second dose on that day. For the dose-escalation stage of the study, the dosing regimens described in Table S-1 above will be evaluated. For the cohort-expansion stage of the study, a LAM-002A starting dosing regimen of 125 mg BID will be evaluated when given as monotherapy or in combination.

Combination Therapy, Dosage and Mode of Administration:

In the expansion and extension stages (Stages 2 and 3), LAM-002A will be combined with either rituximab/rituximab hyaluronidase human or atezolizumab in cohorts of subjects as described in Table S-2 above.

For subjects allocated to LAM-002A/rituximab, the rituximab will be administered intravenously or rituximab/hyaluronidase human will be administered subcutaneously in the clinic for a total of 8 treatments:

Intravenous rituximab (Rituxan®)

- Four induction infusions of 375 mg/mg^2 will be administered weekly on Cycle 1 Day 1, Cycle 1 Day 8, Cycle 1 Day 15, and Cycle 1 Day 22.
- Four subsequent maintenance infusions of 375 mg/mg^2 will be administered every 8 weeks on Cycle 4 Day 1, Cycle 6 Day 1, Cycle 8 Day 1, and Cycle 10 Day 1.

Subcutaneous rituximab (rituximab/hyaluronidase human; Rituxan Hycela®)

- An initial dose of 375 mg/mg^2 will be administered intravenously on Cycle 1 Day1.
- Three subcutaneous injections of 1,400 mg/23,400 Units (1,400 mg rituximab and 23,400 Units hyaluronidase human) will be administered weekly on Cycle 1 Day 8, Cycle 1 Day 15, and Cycle 1 Day 22.
- Four subsequent maintenance subcutaneous injections of 1,400 mg/23,400 Units (1,400 mg rituximab and 23,400 Units hyaluronidase human) will be administered

every 8 weeks on Cycle 4 Day 1, Cycle 6 Day 1, Cycle 8 Day 1, and Cycle 10 Day 1.

For subjects allocated to LAM-002A/atezolizumab, the atezolizumab will be administered intravenously in the clinic at a dose of 1200 mg every 3 weeks.

Duration of Treatment:

Subjects may continue to receive study therapy until the earliest of subject withdrawal of informed consent, documented progression of cancer while on therapy, unacceptable study-drug-related toxicity despite appropriate dose modification, development of intercurrent illness that precludes continued study therapy, physician decision that continuation is not in the subject's best interest, treatment of the cancer with another therapeutic regimen, pregnancy or breastfeeding, substantial noncompliance with study procedures, or study discontinuation. If medically appropriate, subjects allocated to combination therapy may continue with protocol-specified therapy for the therapeutic agent (LAM-002A, rituximab, or atezolizumab) that continues to be tolerated, even if the other agent need to be discontinued due to drug-specific toxicity.

Criteria for Evaluation:

Safety:

Safety evaluations will include assessments of AEs, vital signs, ECGs, laboratory tests, and concomitant medications. Adverse event seriousness, severity grade, and relationship to study treatment will be assessed by the investigator. Severity grade will be defined using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

Pharmacokinetics:

PK assessments (for apilimod and circulating active metabolites) on Cycle Day 1, Cycle 1 Day 8, and Cycle 1 Day 15 will determine PK parameters that will be estimated using standard non-compartmental methods. Dose proportionality and drug accumulation will be assessed.

Pharmacodynamics:

Pharmacodynamic evaluations will explore the extent of PIKfyve inhibition as determined by plasma assays, changes in gene expression in PBMCs/B cells, changes in plasma cytokines (including IL-12 and IL-23), correlations between genetic alterations as determined by next generation sequencing and/or gene expression in tumor tissue, plasma or PBMCs/B-cells and anti-lymphoma activity following treatment with LAM-002A, and correlations between changes in plasma bioanalytes and anticancer activity following treatment with LAM-002A as determined by proteomic tools.

Efficacy:

Efficacy will be determined based on standard definitions of response and progression for NHL and CLL/SLL. Rates of response and time-to-event parameters will be calculated.

Statistical Methods:

Analysis Sets:

Appropriate data analysis sets will be defined. The full-analysis set will include data from all patients who receive ≥1 dose of study therapy. Other analysis sets (responder and evaluable analysis sets) will be defined, as appropriate, and will include data from patients who have the necessary baseline and on study measurements to provide interpretable results for specific parameters of interest.

Patient Disposition and Baseline Characteristics:

Based on the full-analysis set, information regarding patient disposition, demographics, disease history, tumor characteristics, and other baseline characteristics will be described.

Study Drug Exposure, Concomitant Medications, and Safety:

Study drug administration and compliance, concomitant medication use, AEs, laboratory abnormalities, vital signs, performance status, body weight, and ECOG performance status will be described and summarized. For safety analyses, AEs will be classified using the Medical Dictionary for Regulatory Activities (MedDRA). The severity of AEs will be graded by the investigator according to the CTCAE, Version 4.03. Standard regulatory definitions of seriousness will be applied to AEs. Laboratory abnormalities will be graded according to CTCAE severity grade. Concomitant medication use will be coded using the World Health Organization Drug Dictionary into Anatomical Therapeutic-Chemical classification (ATC) codes. Quantitative and qualitative ECG assessments of rhythm abnormalities, cardiac intervals, wave form abnormalities, and ectopy will be reported.

Pharmacokinetics:

Noncompartmental methods will be used to derive pharmacokinetic parameters. Drug and metabolite concentrations and derived pharmacokinetic parameters will be described and will be summarized using appropriate graphical and tabular methods. The relationship between the parameters of drug exposure and dose may be examined using the power model or similar regression techniques. Drug accumulation over time will be described.

Pharmacodynamics:

Pharmacodynamic measures will be listed and will be summarized using appropriate graphical and tabular methods. As appropriate, statistical analysis of changes from baseline in pharmacodynamic parameters will be performed using appropriate parametric or nonparametric methods.

Efficacy:

For endpoints relating to tumor control, analyses will be based on the full-analysis and responder data sets. Tumor response and progression will be assessed using standard response and progression criteria appropriate for the patient's disease type (NHL or CLL/SLL). Response rates will be presented with corresponding 95% CIs. Time-to-event endpoints will be summarized using Kaplan-Meier methods.

Other Analyses:

Using appropriate regression or stratification techniques, associations between patient characteristics (eg, sex, race, age, weight, tumor characteristics, dose) and outcome measures (eg, pharmacodynamic and pharmacokinetic parameters) may be assessed. Similarly, associations between outcome measures (eg, relationships between pharmacokinetic and pharmacodynamic parameters) may be evaluated.

Basis for the Planned Sample Size (Dose-Escalation Stage):

In the dose escalation, the cohort size allows evaluation of regimen safety using a standard definition of MTD (i.e., a dose associated with DLT in < 33% of patients during Cycle 1 of therapy). With the 3+3 dose-escalation paradigm, there is high probability of dose escalation if the true underlying proportion of DLT is low. Conversely, there is a low probability of dose escalation if the true underlying proportion of DLT is high.

Basis for the Planned Sample Sizes (Expansion Stage):

As indicated in Table S-2 above, expansion cohorts of ≥ 6 subjects will be accrued. Enrollment of 6 subjects per cohort offers the opportunity to determine if there is any antitumor activity sufficient to warrant further development in the selected tumor types. An overall response rate (ORR) of ≥ 35% is considered of potential interest in each of the selected indications. If 0/6 subjects in a cohort experience an objective response, then a population ORR of ≥ 35% for that cancer can be excluded with > 90% certainty (1-sided exact binomial 90% CI upper bound = 32%).

Based on the observation of objective responses among study subjects with FL receiving either LAM-002A monotherapy or LAM-002A/rituximab, expanded accrual of subjects with relapsed FL is planned to evaluate the level of activity with these 2 regimens. Preference will be given to enrolling subjects to receive LAM-002A monotherapy before enrolling subjects to receive LAM-002A/rituximab.

Based on historical data with other treatments, it is known that an ORR of < 20% in subjects with relapsed FL receiving LAM-002A monotherapy would be uninteresting while achieving a target ORR of ≥ 40% would suggest that further development is warranted. Sequential boundaries will be used to continuously monitor that the ORR is ≥ 40% while excluding an ORR of < 20% using a 1-sided test with a significance level of 0.05. A significant result with this testing would conclude with 95% confidence that the actual ORR is ≥ 20%. Accrual of up to ~20 evaluable subjects will be considered with the potential to stop accrual early if the boundary is crossed. Thus, accrual can be considered sufficient if the following n/N values are observed: 4/5, 4/6, 4/7, 5/8, 5/9, 5/10, 5/11, 6/11, 6/12, 6/13, 6/14, 7/15, 7/16, 7/17, 8/18, 8/19, 8/20. For all these values, the ORR is ≥ 40% with a lower 1-sided binomial confidence bound of ≥ 20%.

As noted above, the target ORR with LAM-002A alone is ~40%. Adding rituximab or rituximab hyaluronidase human to LAM-002A would be expected to enhance the ORR over that associated with single-agent LAM-002A. Thus, the combination of LAM-002A/rituximab could warrant further development if an ORR of ≥ 60% could be targeted in preference to an ORR of < 40%. Accordingly, for combination therapy, sequential boundaries will be used to continuously monitor that the ORR is ≥ 60% while excluding an ORR of 39% using a 1-sided test with a significance level of 0.05. A significant result with this testing would conclude with 95% confidence that the actual ORR is > 39%.

Accrual of up to ~20 evaluable subjects will be considered with the potential to stop accrual early if the boundary is crossed. Thus, accrual can be considered sufficient if the following n/N values are observed: 7/10, 8/11, 8/12, 9/13, 9/14, 10/15, 10/16, 11/17, 11/18, 12/19, 12/20. For all these values, the ORR is ≥ 60% with a lower 1-sided binomial confidence bound of ≥ 39%.

Experience indicates the rates of discontinuations from rituximab or atezolizumab therapy are < 5%. A rate of AE discontinuations of therapy due to adverse events of ≥ 25% in the 2 combination therapy groups of LAM-002A/rituximab (N = 12) or LAM-002A/atezolizumab (N = 12) would suggest a potential adverse interaction among the components of the combination therapy. Sequential Pocock-type boundaries will be used to continuously monitor the rate of AE discontinuations and to test the null hypothesis, after each subject, that the event rate is ≥ 0.25 using a 1-sided significance test of ~ 0.05. AE discontinuation rates will be considered excessive if the following n/N values are observed: -/1, -/2, 3/3, 3/4, 4/5, 4/6, 5/7, 5/8, 5/9, 6/10, 6/11, 7/12. With this method, the probability of detecting an AE discontinuation safety signal ranges from 0.091 to >0.820 for true discontinuation rates of 25% to ≥ 60%. If excessive levels of AE discontinuation are observed, the sponsor, working in collaboration with the investigators, will take appropriate actions (eg, continuation of the cohort with modifications in design or monitoring plan, interruption of cohort accrual, cohort therapy discontinuation).

***Basis for the Planned Sample Sizes (Extension Stage)*:** The sample size in the extension stage of the study will be no higher than the total number of subjects on study therapy on the data cutoff date that concludes the dose-escalation and expansion stages of the clinical trial.

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations and specialist terms used in this study protocol are provided in Table 1.

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
%CV	percent coefficient of variation
5PS	5-point scale
ABC	activated B-cell lymphoma
AE	adverse event
ALC	absolute lymphocyte count
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
ASCT	autologous stem-cell transplantation
AST	aspartate aminotransferase
AUC	area under the concentration curve
AUC_{0-t}	area under the plasma concentration versus time curve, as determined by a trapezoidal method, from time zero to t hours post-dose
AUC_t	area under the concentration-time curve calculated to the last observable concentration at time t
BID	twice daily (or 2 times a day) (“bis in die”)
BL	Burkitt lymphoma
BUN	blood urea nitrogen
CAP	College of American Pathologists
CFR	Code of Federal Regulations
CLL	chronic lymphocytic leukemia
CLL/SLL	chronic lymphocytic leukemia/small lymphocytic lymphoma
C_{max}	peak (maximum) plasma concentration
CNS	central nervous system
CR	complete response or complete remission
CRO	contract research organization
CT scan	computerized tomography scan
DAT	direct antiglobulin test
DLBCL	diffuse large B-cell lymphoma

Table 1: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
DLT	dose-limiting toxicity
ECG	electrocardiogram
eCRF	electronic case report form
EC	ethics committee
EC_{50}	half maximal effective concentration
ECOG	Eastern cooperative oncology group
EDC	electronic data capture
EOT	end of treatment
FAS	full analysis set
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FISH	fluorescence *in Situ* hybridization
FL	follicular lymphoma
FSH	follicle stimulating hormone
GCB	germinal center B-cell lymphoma
GCP	good clinical practice
GI	gastrointestinal
HIV	human immunodeficiency virus
IB	investigator brochure
ICH	International Conference on Harmonisation
ID	identification
IHC	immunohistochemistry
IL-12	interleukin-12
IL-23	interleukin-23
IND	investigational new drug
IRB	institutional review board
LAM-002A	apilimod dimesylate, (E)-4-(6-(2-(3-methylbenzylidene)hydrazinyl)-2-(2-(pyridin-2-yl)ethoxy)pyrimidin-4-yl)morpholine dimesylate capsules
LDH	lactate dehydrogenase
LD	longest dimension
LDi	longest transverse diameter of a lesion
LPD	longest perpendicular dimension

Table 1: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
MCL	mantle cell lymphoma
MedDRA	medical dictionary for regulatory activities
mg/kg/day	milligram/kilogram/day
mL	milliliter
MRD	minimal residual disease
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MZL	marginal zone lymphoma
NCI CTCAE	National Cancer Institute common terminology criteria for adverse events
NHL	Non-Hodgkin's lymphoma
nM	nanomolar
NOEL	no observed effect level
PBMC	peripheral blood mononuclear cells
PD	progressive disease
PDs	pharmacodynamics
PE	physical examination
PET	positron emission tomography
PFS	progression-free survival
PI	phosphatidyl inositol
PIKfyve	phosphatidylinositol-3-phosphate- 5 kinase
PK	pharmacokinetics
PPD	cross product of the longest transverse diameter of a lesion and perpendicular diameter
PR	partial remission
PSA	prostate specific antigen
QD	once daily ("quaque die")
QRS	combination of 3 of the graphical deflections seen on a typical electrocardiogram (ECG)
QT	time of start of Q wave until end of T wave in the heart's electrical cycle
QTc	corrected QT interval
QTcF	Fridericia correction formula
R	accumulation ratio

Table 1: Abbreviations and Specialist Terms (Continued)

R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
RBC	red blood cell
RNA	ribonucleic acid
RNAi	RNA interference
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SAS	statistical analysis system
SD	stable disease
SDi	shortest axis perpendicular to the LDi
SLL	small lymphocytic lymphoma
SOP	standard operating procedure
SPD	sum of the product of the perpendicular diameters for multiple lesions
$t_{½}$	terminal elimination half-life
TB	tuberculosis
T-CLL	T-cell chronic lymphocytic leukemia
Th1	T-helper cell phenotype
TID	thrice per day
TLS	tumor lysis syndrome
t_{max}	time to maximum concentration
ULN	upper limit of normal
WBC	white blood cell
WCBP	women of child bearing potential
WHO	World Health Organization
WHODD	World Health Organization drug dictionary

4. INTRODUCTION

AI Therapeutics is developing LAM-002A (apilimod dimesylate capsules) for the treatment of patients with malignancies including recurrent B-cell non-Hodgkin lymphoma (NHL). Initially, apilimod dimesylate, and apilimod, the free base (LAM-002), were under development by Synta Pharmaceuticals, Inc (Synta) for the treatment of psoriasis (IND # 62,112) and Crohn's Disease (IND # 70,204). Under these INDs, over 700 subjects were exposed to total daily doses up to 200 mg dimesylate and 210 mg free base (the equivalent of 294 mg apilimod dimesylate) for time periods ranging from a single day to 12 weeks.

4.1. Product Summary

LAM-002A is intended for oral administration. Each capsule will contain 25 mg or 50 of apilimod dimesylate (equivalent to 17.1 mg or 34.3 mg of apilimod free base, respectively). The 25-mg capsule is Swedish orange and the 50-mg capsule is white. Both the 25- and 50-mg capsules are Size 0 and both have a total fill weight of 175 mg.

Inactive components in active capsules are microcrystalline cellulose, silicified microcrystalline cellulose, anhydrous lactose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate.

4.1.1. Pharmacology

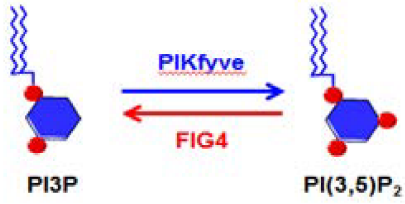
Apilimod and apilimod dimesylate were originally introduced into clinical trials based on apilimod's immunomodulatory properties (Wada 2007; Wada 2012). Apilimod inhibits the production of interleukin-12 (IL-12) and interleukin-23 (IL-23), and was effective in preclinical animal models of various autoimmune diseases that are mediated by the inappropriate expression of T-helper cell phenotype (Th1) cytokines (Wada 2007).

Recently published data have shown that apilimod is a potent and highly selective first-in-class phosphatidylinositol-3-phosphate- 5 kinase (PIKfyve) inhibitor (Cai 2013, Gayle 2017). In total, AI Therapeutics has tested 456 kinases, including disease-relevant kinases, for their ability to bind to apilimod. The screening concentration of apilimod was 1 μM, a concentration that is > 12,000 times greater than the K_d (81 picomolar) for apilimod against PIKfyve. The results showed that apilimod did not bind to any of the 456 kinases tested.

Inhibition of PIKfyve by pharmacological methods as well as RNA interference (RNAi) produces swollen vacuoles and disruption of endomembrane dynamics. In cell culture, the pharmacological disruption of PIKfyve with apilimod induces selective lethality of specific cancer cell lines, presumably through disruption of intracellular trafficking that leads to noncanonical cell death (Gayle 2017).

PIKfyve kinase is a 240-kDa endosomal phosphatidyl inositol (PI) 5 lipid kinase that catalyzes the phosphorylation of PI3 phosphate to PI (3, 5) P2 as shown in Figure 1.

Figure 1: PIKfyve Kinase



Abbreviations: FIG4: FIG4 phosphoinositide 5-phosphatase; PI3P: Phosphatidylinositol 3-phosphate; $PI(3,5)P_2$: Phosphatidylinositol 3,5-bisphosphate; PIKfyve: Phosphatidylinositol-3-phosphate-5 kinase

PIKfyve kinase is associated with the cytosolic leaflet of early endosomes and its activity is required for endomembrane homeostasis, endolysosomal function and proper retrograde transport from the endosome to the trans-Golgi network (Rutherford 2006). Introduction of catalytically inactive kinase mutant into cells induces a swollen vacuole phenotype that can be rescued by microinjection of PI(3, 5)P2 (Ikonomov 2001). Inhibition of PIKfyve by pharmacological methods or RNAi produces swollen vacuoles and disruption of endomembrane dynamics (Cai 2013, de Lartigue 2009; Rutherford 2006). In cell culture, the pharmacological disruption of PIKfyve with apilimod induces selective lethality of specific cancer cell lines presumably through disruption of intracellular trafficking that leads to apoptosis (AI Therapeutics, unpublished data).

The *in vitro* cytotoxic activity of apilimod was evaluated in 3-day assays on 139 human cancer cell lines. A cell line was designated apilimod-sensitive if the half maximal effective concentration (EC_{50}) was less than 500 nanomolar (nM). Forty cell lines were identified as sensitive to apilimod. Apilimod was shown to be highly selective for cancer cells compared to normal cells; i.e., apilimod was 20- to 200-fold more potent based on EC_{50} values in cancer cells (which included cells derived from several different cancers including NHL, Hodgkin lymphoma, colorectal cancer, and lung cancer) compared to normal human cells. The most sensitive of those cancer cell lines tested were B-cell NHL lines. Apilimod also has demonstrated *in vivo* activity in multiple mouse xenograft models using human DLBCL or Burkitt lymphoma (BL) cancer lines. *In vivo* testing of apilimod together with other chemoimmunotherapeutic drugs used in the therapy of NHL has demonstrated enhanced antitumor activity, most notably when apilimod was administered in combination with the anti-CD20 antibody rituximab in a murine xenograft model of human DLBCL and in combination with an anti-programmed death ligand (PDL1) antibody in a syngeneic immunocompetent murine lymphoma model (Gayle 2017).

AI Therapeutics has also performed research into the mechanism of action of apilimod cytotoxicity in cancer cells. Putative genes that confer sensitivity / resistance to apilimod have been identified and will be evaluated as potential biomarkers for predicting apilimod efficacy.

4.1.2. Absorption, Distribution, Metabolism, and Excretion

A number of studies were conducted to determine the pharmacokinetics of apilimod in plasma after intravenous or oral administration to mice, rats, dogs, mini-pigs and monkeys. Systemic exposure to apilimod following oral administration generally increased as the dose level increased in both species. Increases in peak (maximum) plasma concentration (C_{max}) and area

under the curve (AUC) were, in general, less than proportional to the increase in the dose. After oral administration, apilimod was rapidly absorbed. The time to maximum concentration (t_{max}) generally occurred within 1 to 2 hours after oral dosing and the terminal elimination half-life ($t_{½}$) ranged from 1 to 4 hours. Apilimod is highly protein bound (≥ 99%) to rat, dog, and human plasma proteins.

Six primary metabolites were identified *in vitro* (rat and human) and *in vivo* (rat and dog). Human, rat, rabbit and dog studies showed a qualitatively similar metabolic profile. Reaction phenotyping studies indicated that CYP3A4, and to a lesser extent CYP1A2 and/or CYP2D6, contribute to the metabolism of apilimod. The primary metabolites were STA-5864 (CYP1A2/2D6), STA-5908 (CYP3A4) and STA-5944 (CYP3A4). STA-5864 is further metabolized via CYP3A4 to STA-5919. STA-5908 undergoes CYP3A4-mediated metabolism to STA-5919 and STA-6048. Further CYP3A4 mediated metabolism of STA-5944 results in STA-6035 and STA-6048. As with the parent compound, the primary metabolites of apilimod are similarly short-lived in circulation. Generally, t_{max} occurred within 1 or 2 hours after the oral dose of apilimod, consistent with the rapid elimination of this compound from the circulation.

The distribution of [^{14}C]-apilimod derived radioactivity was widespread after a single oral administration to rats. The tissues with the highest activity were liver, kidney, stomach, adrenal gland, Harderian gland, brown fat, preputial gland, spleen, and esophagus. Most tissues reached C_{max} 1 hour after dosing. Approximately 60% of the total dosed radioactivity was recovered in bile from bile duct cannulated rats. Concentrations were generally high in the gastrointestinal (GI) tract, consistent with biliary excretion. Renal clearance was a minor route of elimination accounting for approximately 20% of the total dosed radioactivity.

The tissue distribution of apilimod and its metabolites was further evaluated in a study in rats using material that was not radiolabeled. In this study it was determined that the rank order for plasma AUC and C_{max} was STA-5944 > STA-5908 > STA-5326 (apilimod). Brain to plasma AUC ratios were highest for STA-5326 (apilimod) > STA-5908 >STA-5944, ranging from 3.1 for STA-5326 (apilimod) to 0.19 for STA-5944. Tissue to plasma AUC ratios of each analyte were greater than 4.6 for intestine, kidneys, and liver. The exception was STA-5944 which generally had low liver concentrations.

4.1.3. Toxicology

A series of nonclinical safety assessment studies was conducted using apilimod and apilimod dimesylate in the CD-1 mouse, Sprague-Dawley rat, the beagle dog, and Cynomolgus monkey. Studies included safety pharmacology, general toxicology up to 6 to 9 months in duration, and fertility and developmental toxicology studies. Assessments of genotoxicity and carcinogenicity were also performed.

Single- and repeat-dose toxicology studies were conducted in the mouse (up to 90 days), rat (up to 6 months), dog (up to 9 months) and monkey (up to 9 months). In the mouse, rat and dog, clinical signs at toxic doses included GI findings (emesis and soft stools in rats and dogs; diarrhea in the dog only), central nervous system (convulsions, tremors, ataxia), hypoactivity, ptosis, and hunched posture, decreased weight gain, and reduced food consumption.

Relevant clinical pathology findings at toxic doses included increases in blood urea nitrogen (BUN), creatinine, potassium, inorganic phosphorous, and decreases in total protein and

albumin. These increases were attributed to dehydration (pre-renal) as well as decreased glomerular filtration (renal).

Histopathology findings attributed to the investigational drug were intracellular vacuolation in the cervix, uterus, liver, spleen, thymus, bone marrow, intestinal tract, adrenal cortex, urinary bladder, chief cells in the parathyroid gland, renal tubular epithelium and tubule regeneration/degeneration with excess tubular cell mitotic cell figures and the vacuolation of epidermal cells in the distal caput and corpus region of the epididymis. Upon cessation of drug administration, all histology findings, with the exception of the epididymis, had returned to normal. These data strongly suggest the kidney is the target organ of toxicity.

In an immunotoxicology study in the rat, there were no biologically significant changes in spleen or thymus weights or adverse anatomic pathology findings. Additionally, there were no significant changes in peripheral blood lymphocyte subsets or immunologically adverse findings in splenic antibody-forming cells. In a chronic monkey study in virally infected monkeys, apilimod dimesylate did not elicit lymphomas, or compromise T-cell mediated antibody responses.

In a combined male and female fertility and general reproduction toxicity study, oral administration of apilimod dimesylate had no effects on libido, mating, fertility and estrus. The reproductive no-observed-effect level (NOEL) for male and female rats is 38.38 mg/kg/day. Administration of apilimod dimesylate to gravid rats and rabbits during the period of organogenesis (implantation to closure of the hard palate) demonstrated that it is a non-selective developmental toxicant in the rat. There were no fetal effects in the rabbit.

Apilimod and apilimod dimesylate were not demonstrated to be mutagenic, clastogenic, or aneugenic. In 2-year carcinogenicity studies in rodents, apilimod dimesylate was not carcinogenic.

4.1.4. Pharmacokinetics, Clinical Efficacy and Safety

4.1.4.1. Pharmacokinetics

In humans, apilimod is orally bioavailable, rapidly absorbed, and extensively metabolized. Pharmacokinetic studies revealed generally dose-dependent increases in both C_{max} and AUC. t_{max} following oral administration was 1 hour in the absence of food and 2 to 3 hours when taken with food; in normal healthy volunteers and subjects with psoriasis, t_{max} ranged from 2 to 4 hours. Approximately 90% or more of the absorbed drug was cleared from circulation within 8 to 10 hours following administration, after which any remaining drug was eliminated with a terminal half-life of 5 to 10 hours following administration on the first day, increasing to 12 to 21 hours on Day 14. These findings suggest that either daily (QD) or BID dosing regimens may be appropriate. A small food effect was observed but is not deemed to be clinically significant.

The 2 dosage forms (apilimod dimesylate and apilimod formulations) used to date in clinical trials are bioequivalent. The 50-mg dose of apilimod dimesylate provides the same amount of active ingredient as the previously used 35-mg capsule of apilimod. Similarly, a 100-mg dose of apilimod dimesylate is equivalent to 70 mg apilimod. Future studies will utilize apilimod dimesylate capsules (LAM-002A).

4.1.4.2. Efficacy

In Study LAM-002A-NHL-CLN01, efficacy has been assessed in subjects with NHL. Decreases in tumor metabolic activity were noted in 3 subjects with relapsed DLBCL receiving LAM-002A monotherapy but these changes did not meet formal criteria for objective response. Nine subjects with FL treated with LAM-002A monotherapy, LAM-002A in combination with rituximab, or LAM-002A in combination with atezolizumab have had substantial tumor regressions compromising 2 complete responses (CRs) and 7 partial responses (PRs). The responses have been long-lasting, with durations exceeding 12 months among several subjects with mature data. One subject with MZL receiving LAM-002A/rituximab also experienced a durable PR.

4.1.4.3. Safety

Apilimod dimesylate has been generally well tolerated in humans. In patient populations with Crohn's disease or psoriasis, more frequent (> 10%) AEs experienced to date included headache, upper respiratory tract infection, and nausea; less frequent (> 5% to 10%) AEs included dizziness, fatigue, and nasopharyngitis; and rare (2% to 5%) AEs included diarrhea, arthralgia, fever, abdominal pain, peripheral edema, and vomiting. In general, most AEs were assessed as mild in severity.

In the ongoing trial of LAM-002A in patients with hematological cancers, dose-dependent gastrointestinal events of nausea, vomiting, and diarrhea have been observed. One patient with DLBCL developed acute transient elevations in serum creatinine and blood-urea nitrogen (BUN) due to tumor lysis syndrome (TLS) shortly after starting LAM-002A at a dose of 125 mg BID. One patient with a hematological malignancy receiving the drug at 150 mg BID developed asymptomatic Grade 3 hyponatremia that was attributed to the combined effects of LAM-002A-induced diarrhea and hydrochlorothiazide administration. No other clinically significant safety signals in laboratory, physical examination, or vital sign findings have been noted.

Cardiac monitoring in clinical studies to date has not revealed any major issues. However, in a thorough QT/QTc study, apilimod dimesylate at doses of 50 mg and 150 mg was associated with repolarization findings in excess of those deemed negative by International Conference on Harmonisation (ICH) E14 guidance. The magnitude of the change was modest (~8.5 msec) and the root-mean-square based analyses did not demonstrate as large an increase in cardiac repolarization time (≤ 1.22 msec) as that identified using the Fridericia method. Therefore, the significance of this finding is unclear. Preliminary QTc observations in the ongoing study in patients with hematological malignancies suggest the potential for dose- and exposure-dependent Grade 1 or 2 QT prolongation.

4.1.5. Overview of Indication

Non-Hodgkin's lymphoma (NHL) is a collective term for a heterogeneous group of lymphoproliferative malignancies with differing severities, ranging from slow growing to aggressive subtypes, and varying responses to treatment. In 2015, it is estimated that there will be 71,850 new cases of NHL and an estimated 19,790 people will die of this disease (National Cancer Institute SEER webpage). The two most common types, diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL), will account for about half of these (Martelli 2013). Other relatively common lymphomas include chronic lymphocytic leukemia/ small lymphocytic lymphoma (CLL/SLL) (6%), mantle cell lymphoma (MCL, 6%),

and marginal zone lymphoma (MZL, 6%). DLBCL is further divided into two subtypes, "GCB" and "ABC" (also called "non-GCB"), based on resemblance to normal stages of B-cell development by gene expression profiling (Alizadeh 2000, Rosenwald 2002). The GCB (germinal center B-cell) type arises from malignant transformation of normal germinal center B-cells, and the ABC (activated B-cell) type arises from post-germinal center B-cells in the process of differentiating into plasma cells. ABC DLBCLs have an inferior prognosis compared to GCB DLBCLs, but several novel agents are in development with unique activity in ABC disease (Hans 2004, Cultrera 2012).

The median age at diagnosis of NHL is the seventh decade of life, though they can occur at any age. The prognosis of NHL depends on the histologic type, stage, and treatment.

Management of NHL varies widely depending upon histology. NHL patients are usually treated with chemotherapy, with or without radiation. Virtually all B-cell lymphomas are treated with chemotherapy in combination with the anti-CD20 monoclonal antibody rituximab (Zelenetz 2014). If NHL persists or recurs after standard treatment, autologous stem-cell transplantation (ASCT) may be a potentially curative option for patients with DLBCL (Raut 2014), though the cure rate for ASCT is low for patients relapsing after standard R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone).

Patients with DLBCL who relapse after, or who are not candidates for ASCT, as well as patients with relapsed MCL, MZL, FL, and CLL/SLL are not considered curable with conventional therapies. Patients with recurrent disease are commonly given sequential regimens of chemotherapeutic, immunotherapeutic, or investigational agents in an attempt to control disease manifestations. Rituximab is commonly employed in combination with other agents (Zelenetz 2014). Newer immunopotentiating approaches using anti-PD1/PDL1 inhibitors (including atezolizumab [https://clinicaltrials.gov/ct2/show/NCT031206761]) are being explored and have shown evidence of activity in patients with recurrent NHL (Ilcus 2017). However, despite use of agents with differing mechanisms of action, progressive resistance to treatment typically develops. Patients with refractory or multiply relapsed progressive disease have poor prognoses and are ultimately likely to die of their cancers. Novel mechanisms of action are needed that can be administered alone or in combination with existing chemoimmunotherapeutic approaches to offer additional treatment options for patients with hematological cancers who have experienced disease progression.

4.1.6. Previous Clinical Experience with Apilimod and Apilimod Dimesylate in Nonmalignant Conditions

There is substantial experience administering apilimod or apilimod dimesylate to human subjects. Clinical trials in normal healthy volunteers were initiated in May 2003 by a previous pharmaceutical sponsor. These were followed by studies in patients with Crohn's disease, psoriasis and rheumatoid arthritis. To date, more than 700 individuals have participated in clinical studies that evaluated apilimod/apilimod dimesylate. Clinical experience has been generated in 255 subjects dosed with total daily doses of apilimod dimesylate 100 mg or the equivalent apilimod dose of 70 mg free base.

The starting dose for this Phase 1 clinical study in B-cell NHL is based on 2 Phase 2, randomized, double-blind placebo-controlled trials conducted in subjects with Crohn's disease or plaque psoriasis. Study 5326-07 enrolled 220 subjects with Crohn's disease. Subjects were

randomized to once daily placebo or apilimod dimesylate at doses of 50 or 100 mg. Of the 147 subjects who received any dose of apilimod dimesylate, 46% were dosed for durations between 4 and 6 weeks (53% at 50 mg; 38% at 100 mg) while 12% were dosed for more than 20 weeks. No deaths occurred on study. The most common treatment-emergent AEs reported as related to study drug during the blinded portion of the study were nausea (14%), headache (7%), and dizziness (5%). The incidence of related nausea was more than double in the 100-mg group (20%) compared with the 50-mg group (8%) while the incidence of headache and dizziness was identical in the 2 groups. Adverse events of Grade 3 or higher severity were reported for 15% of subjects during the blinded portion of the study. A total of 7 subjects discontinued due to an AE.

Study 5326-04 was a randomized, placebo-controlled, double-blind, study. A total of 212 subjects with chronic moderate to severe plaque psoriasis were randomized to placebo or to apilimod at 7, 21 or 35 mg (equivalent to apilimod dimesylate at 10, 30, 50 mg, respectively) twice daily (BID) for 12 weeks. Treatment groups were balanced: 60% of subjects completed the study with roughly 30 completers in each treatment group. There were no deaths. Slight trends toward increased frequency of AEs (i.e., dizziness, upper respiratory infections) were observed in the highest dose group (35 mg BID) though no trends were observed in the most common treatment-related AEs (headache and fatigue). A total of 16 (8%) patients discontinued from the study due to an AE: 8% in the placebo group, 4% in the 7 mg BID group, 6% in the 21 mg BID group, and 12% in the 35 mg BID group.

4.1.7. Starting Dose

As noted in Studies 5326-04 and 5326-07, apilimod was found to be safe and well-tolerated at daily doses up to 100 mg/day as a single daily dose of apilimod dimesylate or BID at a total dose of 70 mg of apilimod (equivalent to apilimod dimesylate 100 mg). The starting dose selected for this Phase 1 dose escalation trial is LAM-002A 50 mg BID. This dose is expected to achieve a C_{max} of ~ 70-80 ng/mL, or 180 nM, with predicted plasma half-life of 5 - 10 hours. Concentrations required for 90% inhibition of highly sensitive NHL subtypes in *in vitro* assays is ~50 nM. It is acknowledged that this starting dose level will likely result in plasma levels over a 24-hour period that are lower than the *in vitro* concentrations cited; however, the LAM-002A 50-mg-BID dose for the first cohort is chosen to minimize the risk of potential toxicities in this highly pre-treated NHL population.

Dose escalation will proceed by a modified Fibonacci schema as outlined in Table 3. If additional dose exploration beyond the highest dose shown in Table 3 is required to define the maximum tolerated dose (MTD), then dose escalation may proceed at increments ≤ 33%.

The subject population in this study will be comprised of subjects with B-cell NHL who have relapsed or were refractory to previous therapy (including at least one prior chemoimmunotherapy regimen), and failed or were ineligible or unwilling to undergo ASCT in the setting of DLBCL.

5. TRIAL OBJECTIVES AND PURPOSE

The overall purpose of this Phase 1 study is to explore the safety and tolerability of LAM-002A when given alone and in combination for the treatment of subjects with relapsed or refractory B-cell NHL.

5.1. Primary Objectives

- To determine the maximum tolerated dose (MTD) of daily oral administration of LAM-002A in subjects with relapsed or refractory B-cell NHL

5.2. Secondary Objectives

- To evaluate the plasma pharmacokinetics (PK) of apilimod, and its active metabolites, administered orally in subjects with relapsed or refractory B-cell NHL
- To evaluate the safety and tolerability of daily oral administration of LAM-002A in subjects with relapsed or refractory B-cell NHL
- To evaluate the preliminary anti-tumor activity of LAM-002A

5.3. Exploratory Objectives

- To evaluate the pharmacodynamic effects of LAM-002A, administered orally, in plasma assays and surrogate tissue (gene expression in peripheral blood mononuclear cells [PBMCs]/B cells, and plasma cytokines [including (IL)-12 and IL-23]).
- To evaluate tumor and/or plasma for gene expression and genetic alterations (with saliva and/or B-cell-depleted PBMC collection for germ-line control) and surrogate tissue (PBMC/B cells) for gene expression that may predict anti-lymphoma activity.
- To evaluate plasma for changes in analytes or tumor for protein expression that may predict anti-lymphoma activity

5.4. Primary Endpoints

- Frequency of dose-limiting toxicities (DLTs) as a function of the dose of LAM-002A during the first cycle of treatment

5.5. Secondary Endpoints

- Standard PK parameters including but not limited to AUC, $t_{½}$ and C_{max}
- The type and frequency of AEs, serious adverse events (SAEs) using National Cancer Institute (NCI) CTCAE v4.0 (Common Toxicity Criteria for Adverse Events, version 4.0) as well as changes in clinical laboratory values, electrocardiogram (ECG) parameters and vital sign measurements
- Response as assessed by the investigator according to modified Lugano Response Criteria for NHL (Cheson 2014) and revised guidelines for the diagnosis and treatment of CLL (Hallek 2008, Cheson 2012)

5.6. Exploratory Endpoints

- Extent of PIKfyve inhibition as determined by plasma inhibitory assays
- Changes in gene expression in PBMCs
- Changes in plasma cytokines (including IL-12 and IL-23)
- Correlation between genetic alterations as determined by next generation sequencing and/or gene expression in tumor tissue, plasma (circulating tumor DNA), or PBMCs/B cells and anti-lymphoma activity following treatment with LAM-002A
- Correlation between changes in plasma bioanalytes or tumor protein expression and anti-lymphoma activity following treatment with LAM-002A as determined by proteomic tools

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This is a Phase 1, single-arm, open-label, dose-escalation study of safety and PK of apilimod administered to subjects with refractory or relapsed B-cell NHL. This study will be conducted in 3 stages.

6.1.1. LAM-002A Dose Escalation Stage (Stage 1)

The maximum tolerated dose (MTD) will be determined during the dose-escalation stage, evaluating both continuous and intermittent dosing regimens. Subjects will accrue using a 3 + 3 design. During this stage, the decision to open a new cohort at a higher or lower dose level will be made by the participating clinical investigators and sponsor when all subjects in the current cohort have been treated through at least Week 4 or once 2 DLTs have occurred in that dose cohort. All available safety and PK data will be considered in a decision by the medical monitor in collaboration with the investigators to dose escalate, de-escalate, expand the current cohort or explore alternate regimens of drug administration. The MTD will be determined based primarily on DLTs observed through Week 4 in ≥ 6 subjects.

6.1.2. Expansion Stage (Stage 2)

Once the MTD and/or recommended phase 2 dose (RP2D) and schedule is determined, the study will enter the expansion stage, in which cohorts of subjects will be accrued in order to obtain additional information on safety, tolerability, preliminary anti-tumor activity, PK, and pharmacodynamic data at the RP2D and schedule when LAM-002A is administered alone or in combination with rituximab/rituximab hyaluronidase or atezolizumab. Expansion-stage cohorts will comprise groups of subjects with specific types of previously treated, relapsed, progressive, and measurable NHL who will receive LAM-002A monotherapy or LAM-002A-containing combination therapy as shown in Table 2. For both monotherapy and combination cohorts, the starting dose of LAM-002A will be 125 mg BID administered continuously.

Table 2: Expansion Stage Disease Types and Therapies

Cohort Number	NHL Type	Investigational Drug	Combination Drug	Evaluable Subjects, n
1	FL	LAM-002A	--	Up to ~20
2	MZL	LAM-002A	--	6
3	DLBCL-GCB	LAM-002A	--	6
4	DLBCL-ABC	LAM-002A	--	6
5	FL or MZL	LAM-002A	Rituximab or rituximab hyaluronidase human	Up to ~20 with FL
6	DLBCL-GCB or DLBCL-ABC	LAM-002A	Rituximab or rituximab hyaluronidase human	6
7	FL or MZL	LAM-002A	Atezolizumab	6
8	DLBCL-GCB or DLBCL-ABC	LAM-002A	Atezolizumab	6

Abbreviations: ABC: activated B-cell (subtype); DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; GCB: germinal center B-cell (subtype); MZL: marginal zone lymphoma; NHL: non-Hodgkin lymphoma

6.1.3. Extension Stage (Stage 3)

The extension stage (Stage 3) can begin once the last study subject has completed at least 8 cycles of study treatment. At this time, the study sponsor will conclude the dose-escalation and expansion stages of the study, will collate and verify all study data through an appropriate data cutoff date, and will lock the study database for preparation of a study report. Subjects who are still safely benefiting from Stage 1 or Stage 2 study therapy as of the data cutoff date may electively continue their current regimen of study therapy in Stage 3, receiving clinical care and diagnostic testing consistent with conventional practice standards as deemed appropriate by the treating investigator. Therapy in Stage 3 may continue in the absence of protocol-defined reasons to discontinue therapy. During Stage 3, collection of clinical data by the sponsor will be limited to serious adverse event (SAE) reports. Study drug accountability will be managed per site procedures; relevant pharmacy records may be collected by the sponsor to document study drug disposition.

6.1.4. Subject Allocation (Stage 1 and Stage 2)

Subjects will be allocated to the cohorts by the study sponsor working in collaboration with each investigator considering the availability of openings for enrollment in Stage 1 or 2, disease type (i.e., FL, MZL, DLBCL-GCB, DLBCL-ABC, or other indications), therapy history (e.g., prior use of anti-CD20 or anti-PD1/PDL1 antibodies), and current disease status (e.g., potential to benefit from rituximab treatment based on past responses to anti-CD20 antibody therapy).

During Stage 1 dose ranging with LAM-002A monotherapy, allocation will be performed according to a 3+3 dose-escalation procedure with the requirement that each cohort of 3 subjects be observed for ≥4 weeks before another cohort is enrolled (as detailed in Section 6.6). During Stage 2 cohort expansion evaluating LAM-002A monotherapy, allocation will be performed as subjects present to the accruing clinics and there will be no specific restrictions on the cadence of enrollment. During Stage 2 cohort-expansion of LAM-002A combinations with rituximab and

atezolizumab, enrollment of the first 3 subjects in each combination cohort will be restricted such that each subject must be enrolled sequentially and observed for ≥3 weeks before the next subject is enrolled. Beginning with the 4th patient in each combination group, further enrollment may proceed without restriction as long as the continuous reassessment boundaries for toxic drug discontinuations are not met (as detailed in Section 6.8.4.4 and Section 14.1.2).

6.1.5. Subject Evaluability

A Stage 1 subject will be considered evaluable if the subject meets the definition for evaluability of Cycle 1 DLT as described in Section 6.6. A Stage 2 subject will be considered evaluable if the subject has both baseline and ≥1 on-study tumor assessments sufficient to allow a determination of response to study therapy.

6.2. Number of Subjects

As many as 145 subjects will be enrolled, assuming that:

- In the dose-escalation stage of the study, the total number of subjects will depend upon the numbers of subjects accrued to each dose level and the number of dose levels evaluated. If 6 subjects are enrolled at all open starting dose levels (Dose Levels 5, 6, 7, and 8) and 6 additional subjects are enrolled at the MTD or RD, as many as 30 subjects could be enrolled. To allow for the possibility that some subjects may not be fully evaluable for DLT or that an intermediate dose level might be evaluated, up to ~45 subjects may be enrolled.
- In the expansion stage of the study, if all 8 potential expansion cohorts are accrued, as many as ~76 subjects could be enrolled. To allow for the possibility that some subjects may not be fully evaluable for efficacy or to establish bounds on efficacy estimates with greater confidence, up to ~100 subjects may be enrolled.
- In the extension stage of the study, the total number of subjects will include ≤4 subjects who have participated in the expansion stage of the study and are still receiving study therapy on the data cutoff date that concludes the dose-escalation and expansion stages of the clinical trial.

6.3. Randomization and Blinding

This is an open-label study and there is no randomization of subjects.

6.4. Treatment Assignment

Inclusion and exclusion criteria will be reviewed for each potential subject by the investigator. If the consented subject is eligible for study participation, the site will send the eligibility form to Ce3 (see Study Manual).

Ce3 will review the subject's eligibility form to confirm each subject's eligibility and will complete the enrollment form with treatment cohort, treatment dose and frequency. The enrollment form will be signed and a copy sent to the study site. Once the site receives the completed enrollment form, the subject will begin treatment accordingly. The treatment will be conducted in an open-label manner. Study sites cannot start dosing the subject without receiving the assigned dose on the returned Subject Enrollment and Eligibility Form.

Subject identification (ID) will be in the format of Site XXX-Subject XXX, for example, 001-001 is for Site 001 first subject. Site ID will be assigned consecutively and subject ID will be sequential per site.

Subject replacement is described in Section 6.13

6.5. Overall Treatment Periods

6.5.1. Pre-Treatment Period

The subject is consented and undergoes screening assessments to be qualified for the study. The Schedule of Assessments can be found in Section 8.7.

6.5.2. Treatment Period

The subject is treated and monitored for safety (including assessments of AEs, vital signs, ECGs, laboratory tests and concomitant medications). Additionally, preliminary anti-tumor activity will be assessed and PK and biomarker samples will be collected.

6.5.3. Post-Treatment Period

Subjects should be followed until the later of either 30 days after the last dose of study treatment or until resolution/stabilization of any ongoing drug-related AEs and/or SAEs. For subjects with events that require follow-up, information regarding concomitant medications should be collected. Any necessary follow-up may be obtained in person or by telephone contact.

Subjects who have discontinued study treatment for reasons other than PD will be assessed per Revised Response Criteria for NHL or Guidelines for the diagnosis and treatment of CLL at a minimum of every 12 weeks until documentation of PD, start of new anti-cancer therapy or for up to 1 year from the last enrolled subject's first treatment (Cycle 1 Day 1) whichever comes first.

Long-term follow-up survival information will be obtained in all surviving subjects who permanently discontinue study therapy. Such information may be collected at ~3- to 6-month intervals at the sponsor's discretion through 3 years. This long-term follow-up information will be gathered during routine clinic visits, other study site contact with the subjects, or via telephone or e-mail with the subjects/caregivers or referring physician offices.

6.6. LAM-002A Dose-Escalation Procedures

LAM-002A will be administered on a twice daily (BID), or thrice daily (TID) oral dosing regimen with a cycle length of 28 days. Subjects on a BID schedule will be advised to take the doses at the same time each day, ~12 hours apart. Subjects on a TID schedule will be advised to take the doses at the same time each day at intervals of ~6 to 8 hours. On PK days, subjects on a TID schedule should receive the morning dose and complete the blood collections through 8 hours thereafter before taking the second dose on that day.

Other drug administration schedules may be considered if the initial BID or TID regimen's safety, PK and/or pharmacodynamics suggest that a different schedule would be better tolerated and might allow for serum exposures required for anti-lymphoma activity. This might include a treatment break such as 3 weeks on/1 week off treatment or 5 days on/2 days off over a 4-week

cycle or an asymmetric (AM dosing > PM dosing) or once-daily dosing schedule. If another treatment regimen is evaluated, then the initial dose tested on this schedule will be no higher than the total daily dose that has been previously evaluated and tolerated.

Cohorts of 3 to 6 subjects will be sequentially enrolled at progressively higher starting dose levels of LAM-002A, as indicated in Table 3. The initial cohort of subjects will be prescribed LAM-002A at Dose Level 0 (50 mg BID). Dose level -1 (25 mg BID) is provided to permit a dose decrement in subjects experiencing DLT at Dose Level 0.

Table 3: LAM-002A Provisional Starting Dose Levels

Continuous Administration		
Dose Level	**LAM-002A Dose and Schedule**	**LAM-002A Total Daily Dose**
-1	25 mg BID	50 mg
0 (Initial Dose Level)	50 mg BID	100 mg
1	100 mg BID	200 mg
1a	125 mg BID	250 mg
1b	75 mg TID	225 mg
1c	100 mg TID	300 mg
1d	125 mg TID	375 mg
2	150 mg BID	300 mg
3	200 mg BID	400 mg
4	275 mg BID	550 mg
Intermittent Administration		
Dose Level	**LAM-002A Dose and Schedule**	**LAM-002A Total Daily Dose**
5	150 mg BID	300 mg
6	200 mg BID	400 mg
7	250 mg BID	500 mg
8	300 mg BID	600 mg

Abbreviations: BID: Twice daily (or 2 times per day); TID: Thrice daily (or 3 times per day)

A 3 + 3 design will be utilized to define an MTD. For cohorts consisting of 3 subjects, dose escalation to the next higher dose may proceed if no DLT is observed within the first cycle of the 3 evaluable subjects accrued to a cohort (See Section 6.1.1). If 1 of 3 subjects in the cohort experiences a DLT, up to a total of 6 evaluable subjects will be enrolled. If 2 or more of the 3-6 evaluable subjects in a cohort experience a DLT, dose escalation will cease, and additional subjects will be treated at a lower dose level or with another schedule. If de-escalation to the previous dose cohort is undertaken, this cohort may be expanded to ≥6 subjects. Additional subjects (up to 12 total per cohort) may be evaluated to refine the estimation of the MTD and RP2D at the planned dose levels or at an intermediate dose level between the highest previously tolerated total dose and the next planned total daily dose. The MTD is defined as the highest dose at which < 33% of subjects experience a DLT in the total dose cohort.

Dose escalation decisions will be evaluated in a DLT-evaluable population. The DLT-evaluable population will include subjects who complete Cycle 1 dosing or who are withdrawn from study due to a DLT in Cycle 1. A subject will be deemed non-evaluable for determining DLTs and will not be counted toward the total cohort size if the subject did not experience a DLT, did not

receive at least 75% (42/56 BID schedule; 63/84 TID schedule, 18/24 intermittent schedule) of the planned first-cycle doses or discontinued from the study prior to completing necessary safety evaluations through the first 28 days of study treatment. These subjects may be replaced unless accrual to the cohort has stopped due to DLT.

Following the above guidelines, the participating investigators and sponsor will review available data including toxicity, PK and anti-tumor activity data to reach consensus on dose levels and determination of the MTD. This group will review available safety data for each cohort and will determine whether the MTD has been reached and decide upon further subject enrollment. Any detected cumulative toxicity may require later dose reductions or other action as appropriate, and may be evaluated in determining the RP2D and schedule.

The RP2D and schedule will be determined in discussion between the sponsor and participating investigators. Observations related to PK, pharmacodynamics and any drug-related toxicities may be included in the rationale supporting the RP2D and schedule.

6.7. Definition of LAM-002A Dose-Limiting Toxicity (DLT)

A DLT will be defined as an AE or abnormal laboratory value meeting the criteria in Table 4 and that is assessed as unrelated to disease, a comorbid condition, intercurrent illness, or concomitant medications). For the purposes of dose escalation and determination of the LAM-002A MTDs, DLTs that occur within the first cycle of treatment must be included in decisions regarding dose escalation. DLTs or other clinically significant toxicities that occur after Cycle 1 may also be considered when determining the RP2D.

Table 4: Criteria for Defining Dose-Limiting Toxicities (DLTs)

Toxicity	**Criteria**
Hematology	CTCAE Grade 4 neutropenia lasting ≥ 7 days CTCAE Grade 4 febrile neutropenia CTCAE Grade 3 thrombocytopenia with bleeding that requires transfusion therapy CTCAE Grade 4 thrombocytopenia
Toxicity	**Criteria**
Gastrointestinal	≥ CTCAE Grade 3 vomiting or nausea despite the use of optimal anti-emetic treatments ≥ CTCAE Grade 3 diarrhea despite the use of optimal anti-diarrheal treatments
Renal	Serum creatinine > 3.0 x ULN
Hepatic	Total bilirubin ≥ CTCAE Grade 3 Total bilirubin ≥ CTCAE Grade 2 and ALT or AST ≥ CTCAE Grade 2 or, for subjects with liver metastases at baseline, total bilirubin ≥ 2.0 x ULN and ALT or AST ≥ CTCAE Grade 3

Toxicity	Criteria
Treatment interruption/delays	Inability to administer ≥28/56 (BID schedule) or ≥42/84 (TID schedule) or ≥12/24 (intermittent schedule) planned LAM-002A doses in a treatment cycle due to drug-related AEs or Failure to recover from LAM-002A-related toxicities to baseline within 14 days from the last dose of LAM-002A in a cycle
Other adverse events not listed above	Non-hematologic toxicities of CTCAE ≥ Grade 3 except for the following. • Alopecia • CTCAE Grade 3 fatigue for < 72 hours • Asymptomatic Grade 3 elevations in biochemistry laboratory values that last for ≤ 7 days that are not deemed to be clinically relevant. This includes electrolyte abnormalities that respond to medical intervention. Any LAM-002A-related adverse event that, in the opinion of the investigator, requires a dose reduction or discontinuation of treatment.

Abbreviations: ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CTCAE: Common terminology criteria for adverse events; DLT: Dose-limiting toxicity; ECG: Electrocardiogram; NHL: Non-Hodgkin lymphoma; ULN: Upper limit of normal

6.8. Treatment Guidelines

6.8.1. Tumor Lysis Syndrome Prophylaxis and Therapy

The risk for TLS must be considered based on established algorithms (Cairo 2010, MDACC 2013, Roberts 2016):

- Low-risk: Serum LDH ≤ ULN, all measurable lymph nodes < 5 cm, and absolute lymphocyte count (ALC) < 25×10^9/L
- Intermediate risk: Serum LDH > 1 to ≤ 2 × ULN, ≥ 1 measurable lymph node with an LD of ≥ 5 but < 10 cm, or ALC ≥ 25×10^9/L
- High risk: Serum LDH > 2 × ULN, ≥ 1 measurable lymph node with a LD of ≥ 10 cm, or both ≥ 1 measurable lymph node with an LD of ≥ 5 but < 10 cm and ALC ≥ 25×10^9/L

Subjects who are at intermediate or high risk of TLS must receive medical prophylaxis according to the following prophylaxis regimens or similar institutional regimens:

- Intermediate Risk of TLS: These subjects should receive allopurinol, 100 to 300 mg orally every 8 hours starting ≥ 24 to 48 hours before the initial administration of LAM-002A on Cycle 1-Day 1 of therapy; of note, the maximum daily allopurinol dose is 800 mg, doses ≤ 300 mg need not be divided (but may be insufficient for high-risk subjects), and doses should be reduced by ≥ 50% in subjects with renal insufficiency. In addition, subjects who develop hyperuricemia should receive rasburicase, 0.2 mg/kg.
- High Risk of TLS: These subjects should receive allopurinol, 100 to 300 mg orally every 8 hours starting ≥ 24 to 48 hours before the initial administration of LAM-002A on Cycle 1-Day 1 of therapy; of note, the maximum daily allopurinol dose is 800 mg, doses ≤ 300 mg need not be divided (but may be insufficient for high-risk subjects), and doses should

be reduced by ≥ 50% in subjects with renal insufficiency. In addition, high-risk subjects should receive rasburicase, 0.2 mg/kg, administered 3 to 4 hours prior to the first dose of LAM-002A.

In addition, subjects who are at high risk of TLS should be considered for in-hospital monitoring during the first 24 to 48 hours of LAM-002A administration.

Subjects who develop TLS may experience hyperkalemia, hypocalcemia, hyperuricemia, hyperphosphatemia, cardiac dysrhythmias, and acute renal failure; thus, close monitoring of electrolytes is important after initial therapy.

Subjects with TLS should receive intravenous hydration, rapid reversal of hyperkalemia, antihyperuricemic agents, and appropriate cardiac and renal support, including dialysis as indicated. Upon recovery to baseline functioning and as medically appropriate, such subjects should continue with protocol therapy to maintain tumor control.

6.8.2. LAM-002A

6.8.2.1. Premedications

Subjects taking LAM-002A by continuous administration may be offered antiemetics and antidiarrheals as necessary to control gastrointestinal symptoms as described in Section 6.8.2.6.1. For subject who do develop such adverse effects, sites should consider providing study participants with antiemetics and antidiarrheals so that these supportive care medications are readily available in case gastrointestinal symptoms related to LAM-002A recur or persist.

Subjects taking LAM-002A by intermittent administration are required to receive prophylactic antiemetic supportive care as described in Section 6.8.2.6.2.

6.8.2.2. In-Clinic LAM-002A Administration

For subjects receiving the continuous LAM-002A regimen, the morning dose of LAM-002A should be orally administered on Cycle 1 Day 1 and Cycle 1 Day 8 (after a minimum fast of 6 hours) by site staff after the collection of the biomarker samples and pre-dose PK sample. Subjects are allowed to eat after PK Sample #4 (Hour 2) has been collected. On Cycle 1 Day 15, the morning dose of LAM-002A should be orally administered (after a minimum fast of 6 hours) by site staff immediately after collection of the pre-dose PK and biomarker samples.

For subjects receiving the intermittent LAM-002A regimen, prophylactic antiemetics are a required component of the regimen as described in Section 6.8.2.6.2. After initiation of the antiemetic regimen, the morning dose of LAM-002A should be orally administered on Cycle 1 Day 1 and Cycle 1 Day 10 (after a minimum fast of 6 hours) by site staff after the collection of the biomarker samples and pre-dose PK sample. Subjects are allowed to eat after PK Sample #4 (Hour 2) has been collected. Similarly, on Cycle 1 Day 8 and Cycle 1 Day 15, the antiemetic regimen should be initiated and the morning dose of LAM-002A should be orally administered (after a minimum fast of 6 hours) by site staff immediately after collection of the pre-dose samples.

When given as a component of combination therapy with rituximab, LAM-002A will be started on Cycle 1 Day 1 with a BID schedule. LAM-002A will be administered after administration of premedications (see Section 6.8.3.1) and ~15 to 30 minutes prior to the start of the initial

rituximab infusion. On Cycle 1 Day 8, the morning dose of LAM-002A will be administered after premedications (see Section 6.8.3.1) and ~15 to 30 minutes prior to the rituximab infusion/injection.

When given as a component of combination therapy with atezolizumab, LAM-002A will be started on Cycle 1 Day 1 with a BID schedule. LAM-002A will be administered ~15 to 30 minutes prior to the start of the initial atezolizumab infusion. On Cycle 1 Day 8, the morning dose of LAM-002A will be administered in the clinic.

6.8.2.3. LAM-002A Self-Administration

Except for the days where treatment is administered in the clinic, LAM-002A will be self-administered orally, BID or TID of each 28-day cycle until disease progression or other discontinuation criteria are met. When taking the drug at home, subjects should be advised to take LAM-002A with ≥ 4 oz. (~160 mL) of water at the same times each day. Subjects on a BID schedule will be advised to take the doses at ~12 hours apart (e.g., 8:00 AM and 8:00 PM) (+/- 1-hour window). Subjects on a TID schedule will be advised to take the doses at intervals of ~6 to 8 hours. When self-administering LAM-002A at home, subjects may take the drug in the fed or fasted state. On PK days, subjects should come to clinic fasted (a minimum fasting state of 6 to 8 hours) and take the dose at the site under supervision. All subjects will be required to complete a dosing diary, which must be returned to the site for review at each site visit.

For those subjects taking LAM-002A with continuous administration, the drug should be taken according the prescribed BID or TID schedule without interruption unless toxicity or intercurrent illness requires a modification to the dosing regimen (see Section 6.8.2.5).

For those subjects taking LAM-002A with intermittent administration, the drug should be taken in repeated 7-day sequences comprising BID self-administration for 3 days (6 doses) followed by 4 days without dosing. If the cadence of the on-off periods is interrupted due to toxicity, intercurrent illness, or other reasons, the medical monitor should be consulted regarding the timing of therapy resumption and dose modification (see Section 6.8.2.5).

6.8.2.4. LAM-002A Dose Schedule Interruptions and Vomited Doses

Subjects on a BID schedule who have a delay in administration of a dose of LAM-002A of < 6 hours should take the planned dose as soon as possible after the intended time of administration. For subjects who have a delay in administration of LAM-002A of ≥ 6 hours, the dose should not be taken. The planned timing of subsequent LAM-002A dosing should not be altered.

Subjects on a TID schedule who inadvertently have a delay in administration of a dose LAM-002A of ≤ 1 hour, the planned dose should be taken with no changes to the subsequent dose schedule. For subjects who have a delay of > 1 hour but ≤ 4 hours, the planned dose should be taken; however, all future doses for that day should be shifted later by a corresponding amount. It is recommended that subjects take the last dose of study medication no later than 12:00 midnight on any study treatment day. For example, if the 7:00 AM dose is taken at 10:00 AM, the next dose should be taken ≥ 6 hours later (after 5:00 PM), and the last dose should be taken ≥ 6 hours thereafter (between 11:00 PM and 12:00 midnight). For subjects on a TID schedule who have a delay in administration of LAM-002A of > 4 hours, the dose should

not be taken. LAM-002A administration may continue but the missed dose should not be made up and the planned timing of subsequent LAM-002A dosing should not be altered.

For subjects who vomit shortly after taking LAM-002A, the vomited dose should not be replaced. The planned timing of subsequent LAM-002A dosing should not be altered.

6.8.2.5. LAM-002A Dose Modifications

The AEs associated with LAM-002A administration have included gastrointestinal toxicities of nausea, vomiting, and diarrhea, typically beginning shortly after initiation of drug administration.

If a subject experiences an AE that is suspected to be related to LAM-002A, appropriate supportive care (e.g., antiemetics, antidiarrheals, therapy for tumor lysis syndrome [TLS]) should be instituted consistent with the nature of the event.

If a subject experiences an LAM-002A-related DLT (reference Table 4) or other AE requiring a dose modification, then the LAM-002A administration should be interrupted until the toxicity recovers to Grade ≤ 1 or baseline. Upon resumption of LAM-002A, the total daily dose of LAM-002A should be reduced using an appropriate dose level or schedule (reference Table 3) as agreed between the investigator and medical monitor. Successive adjustments to progressively lower total daily dose levels can be made. If the subject cannot tolerate LAM-002A after a decrease to Dose Level -1 (25 mg BID), then the subject should be discontinued from LAM-002A therapy unless continued treatment is permitted by the medical monitor.

After the LAM-002A dose is reduced, the dose can be maintained at that dose level or schedule, even if there is minimal or no toxicity with the reduced dosing regimen. However, if the subject tolerates a reduced total daily dose of LAM-002A for ≥ 4 weeks then the LAM-002A dosing regimen may be reescalated to a higher total daily dose level at the discretion of the investigator and with the concurrence of the medical monitor. Such reescalation may be particularly warranted if the AE comprised TLS or if further evaluation reveals that the AE that led to the dose reduction was not related to LAM-002A. Successive adjustments to progressively higher total daily dose levels can be made. However, the escalated dose cannot exceed the total daily starting dose level for that subject during the first 2 cycles of therapy.

Individual subjects who initiated treatment at a total daily dose level at or below the lower of the currently established MTD or the RP2D and who have not experienced a DLT after ≥ 2 cycles of treatment may have the LAM-002A total daily dose escalated to the next higher dose level if both the principal investigator and the medical monitor agree that a dose escalation is medically warranted (e.g., for a subject with stable disease who is tolerating the current dose level of LAM-002A therapy). In such subjects, successive adjustments to progressively higher total daily dose levels can be made at intervals of ≥ 4 weeks with the condition that the escalated total daily dose level cannot exceed a LAM-002A dose of 150 mg BID when administered continuously or the lower of the currently established MTD or RP2D of LAM-002A when given intermittently.

In a subject who experiences a DLT precluding resumption of LAM-002A therapy during a cycle, a new cycle of treatment may begin at the later of Day 29 or when AEs or laboratory abnormalities related to LAM-002A have returned to baseline levels. If drug-related AEs or laboratory abnormalities precluding further administration of study drug are not resolved to

baseline by Day 29, week-by-week delays in initiating the new cycle of treatment should be instituted. When all drug-related AEs and laboratory abnormalities have returned to baseline, the next cycle of therapy can be initiated. Upon initiation of a new cycle of therapy, the prior cycle of therapy will be considered completed.

Investigators are to discuss modifications in the dosing regimen with the medical monitor. The appropriate clinic staff should dispense the LAM-002A for the new dose level or schedule and instruct the subject/caregiver about the change in the dosing regimen.

6.8.2.6. LAM-002A Supportive Care

6.8.2.6.1. Antiemetics for Subjects Taking LAM-002A by Continuous Administration

For subjects taking LAM-002A via continuous administration, sites should consider providing study participants with antiemetics and antidiarrheals so that these supportive care medications are readily available in case gastrointestinal symptoms related to LAM-002A develop.

For subjects taking LAM-002A via continuous administration, it is recommended that, if prophylactic or therapeutic antiemetics are required, subjects be offered 2 mg of the serotonin antagonist, granisetron (Kytril®, Granisol®), as an oral tablet or solution every 6 hours as needed. If subjects have persistent nausea or vomiting, consideration can be given to a 10-mg subcutaneous injection of the extended release form of granisetron (Sustol®). Alternatively, application of a 31.3 mg granisetron transdermal patch (Sancuso®) every 3 to 7 days can be offered. For transdermal prophylaxis, 24 to 48 hours may be necessary to allow a sufficient period to achieve effective granisetron systemic concentrations. Use of the serotonin antagonists, ondansetron (Zofran®, Zuplenz®) or dolasetron (Anzemet®), is discouraged due to the possibility that such agents could prolong the cardiac QT interval.

The dopamine antagonist, olanzapine (Zyprexa®), at doses of 2.5 to 10 mg, may be considered alone or in conjunction with serotonin antagonists or other types of antiemetic agents. Olanzapine doses of 10 mg may be sedating, which could be helpful for certain subjects, but may represent a concern for others, particularly for those who are elderly.

Based on currently available information regarding LAM-002A metabolism, the neurokinin 1 receptor antagonist, rolapitant (Varubi®), can be considered, but aprepitant (Emend®) or netupitant+palonosetron (Akynzeo®) should be avoided because these drugs may inhibit CYP3A4 and/or CYP2C9 activity.

Other classes of antiemetic medications that may be employed include dopamine antagonists or benzodiazepines if such drugs do not pose risks of QT prolongation or drug-drug interactions. Given the possibility that LAM-002A may alter immunological mechanisms, use of systemic corticosteroids (e.g., dexamethasone) should be minimized (particularly when coadministered with atezolizumab) to avoid immunocompromise; however, corticosteroids can be introduced if other types of antiemetic agents are not sufficiently effective.

6.8.2.6.2. Antiemetics for Subjects Taking LAM-002A by Intermittent Administration

Because LAM-002A induces dose-dependent nausea and vomiting, subjects who are taking LAM-002A by intermittent administration are required to receive antiemetic supportive care.

The following prophylaxis regimen should be started ≥30 minutes before initiation of each LAM-002A 3-day treatment sequence:

- Dexamethasone 12 mg PO on Day 1 and then 8 mg PO on Day 2 and Day 3
- Granisetron 2 mg PO on Day 1 and then 1 mg PO BID on Days 2 and 3
- Olanzapine, 10 mg PO on Day 1 and then 10 mg PO on Days 2 and 3

The study subject must be sent home from the clinic with sufficient dexamethasone, granisetron, and olanzapine to ensure that the supportive care medications are readily available to the subject for each of the four 3-day courses of LAM-002A therapy during each 28-day cycle.

Doses of dexamethasone and olanzapine may be adjusted to tolerance. Other antiemetic drugs (eg, neurokinin 1 receptor antagonists, dopamine antagonists, or benzodiazepines) may be considered in consultation with the medical monitor.

6.8.2.6.3. Antidiarrheals

For management of diarrhea related to LAM-002A, it is recommended that subjects take loperamide, 4 mg, at the occurrence of the first loose stool and then 2 mg every 2 hours until they are diarrhea-free for at least 12 hours. More aggressive loperamide prophylactic or therapeutic administration and titration of loperamide dosing for each loose bowel movement may be considered. During the night, subjects may take 4 mg of loperamide every 4 hours. Subjects should be advised to avoid dehydration through adequate fluid intake. Drugs such as 5HT3 antagonists or octreotide may be considered for their anti-secretory effects. For subjects who develop diarrhea while also receiving atezolizumab, the possibility of atezolizumab-induced colitis should be considered (see Section 6.8.4.4).

6.8.3. Rituximab or Rituximab/Hyaluronidase Human

6.8.3.1. Premedications

In accordance with rituximab/rituximab hyaluronidase human prescribing information (Genentech 2016, Genentech 2018), subjects should be premedicated with an antipyretic and an antihistamine to reduce the incidence and severity of infusion/injection reactions. A recommended regimen is diphenhydramine, 25 mg orally, and acetaminophen (paracetamol), 650 mg orally, both given ~30 minutes prior to each rituximab administration. Intravenous corticosteroids may also be administered as a premedication. Local practices and guidelines may be followed.

6.8.3.2. Rituximab Administration

Based on past experience with this regimen (Ghielmini 2004, Martinelli 2010), rituximab will be administered intravenously or rituximab/hyaluronidase human will be administered subcutaneously in the clinic for a total of 8 treatments:

Intravenous rituximab (Rituxan®)

- Four induction infusions of 375 mg/m^2 will be administered weekly on Cycle 1 Day 1, Cycle 1 Day 8, Cycle 1 Day 15, and Cycle 1 Day 22.

- Four subsequent maintenance infusions of 375 mg/m^2 will be administered every 8 weeks on Cycle 4 Day 1, Cycle 6 Day 1, Cycle 8 Day 1, and Cycle 10 Day 1.

Subcutaneous rituximab (rituximab/hyaluronidase human; Rituxan Hycela®)

- An initial dose of 375 mg/mg^2 will be administered intravenously on Cycle 1 Day1.
- Three subcutaneous injections of 1,400 mg/23,400 Units (1,400 mg rituximab and 23,400 Units hyaluronidase human) will be administered weekly on Cycle 1 Day 8, Cycle 1 Day 15, and Cycle 1 Day 22.
- Four subsequent maintenance subcutaneous injections of 1,400 mg/23,400 Units (1,400 mg rituximab and 23,400 Units hyaluronidase human) will be administered every 8 weeks on Cycle 4 Day 1, Cycle 6 Day 1, Cycle 8 Day 1, and Cycle 10 Day 1.

The dose calculation of body surface area for infused rituximab will be based on the subject's height and actual body weight prior to therapy. Once established based on the pretreatment body weight, the total dose of rituximab for the subject should not be altered during therapy based on fluctuations in body weight unless required by institutional policy.

At Cycle 1 Day 1, ~30 minutes after administration of the required antipyretic and antihistamine premedications and ~15 to 30 minutes after administration of the first dose of LAM-002A, the first infusion of rituximab will be administered via an infusion pump. For the initial infusion, the recommended infusion rate is 50 mg/hour. In the absence of infusion toxicity, the infusion rate can be increased in 50-mg/hour increments every 30 minutes, to a maximum of 400 mg/hour.

For subsequent rituximab infusions, the required antipyretic and antihistamine premedications will be given and the rituximab will be infused via an infusion pump. For these infusions, the infusion can be initiated at 100 mg/hour. In the absence of infusion toxicity, the infusion rate can be increased in 100-mg/hour increments every 30 minutes, to a maximum of 400 mg/hour. Alternatively, for subjects who tolerate the first infusion with Grade ≤3 infusion toxicity, subsequent infusions can be administered over a planned infusion time of 90 minutes, with ~20% of the total dose administered in the first 30 minutes and the remaining 80% of the total protein dose administered in the subsequent 60 minutes (Dakhil 2014, Genentech 2016).

For subsequent rituximab/hyaluronidase human injections, the required antipyretic and antihistamine premedications will be given and the rituximab/hyaluronidase human will be injected into the subcutaneous tissue of the abdomen over ~5 minutes. Areas where the skin is red, bruised, tender or hard, or areas where there are moles or scars should be avoided. No data are available on performing the injection at other sites of the body. If administration of rituximab/hyaluronidase human is interrupted, drug administration can continue at the same site or at a different site but restricted to the abdomen. Patients should be observed for ≥15 minutes following the completion of injection. During treatment with rituximab/hyaluronidase human, do not administer other medications for subcutaneous use at the same sites.

6.8.3.3. Management of Rituximab Infusion/Injection Toxicity

Rituximab can cause severe, including fatal, infusion reactions (Genentech 2016). Patients with pre-existing cardiac or pulmonary conditions, those who experienced prior cardiopulmonary adverse reactions to rituximab, and those with high numbers of circulating malignant cells ($\geq 25 \times 10^9$/L) may be at particular risk. Severe reactions typically occur during the first infusion and are generally less frequent and less severe with subsequent infusions. The time to onset of infusion toxicity ranges from 30 to 120 minutes. Rituximab-induced infusion reactions and sequelae include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, and/or anaphylactoid events.

Rituximab infusions/injections should be interrupted or slowed in subjects experiencing Grade ≥3 rituximab-related infusion reactions. Medical management (eg, oxygen, epinephrine, bronchodilators, and/or glucocorticoids) should be instituted, as needed. Upon improvement of symptoms, the infusion may be continued at 50% of the previous rate. At the discretion of the investigator, rituximab therapy may be permanently discontinued in subjects with Grade 4 infusion/injection reactions or with reactions requiring substantial intervention.

6.8.3.4. Rituximab/Rituximab Hyaluronidase Human Dose Modifications and Supportive Care

Rituximab-related noninfectious pneumonitis has been described (Subramanian 2010) with an incidence of ~4.3% (Salmasi 2010). In patients developing rituximab-associated pneumonitis, the mean time from the first rituximab infusion to the onset of respiratory symptoms was 3 months, with a peak incidence after administration of a mean cumulative dosage of 1600 mg/m2 (Lioté 2010).

Severe, including fatal, mucocutaneous reactions can occur in patients receiving rituximab during infusion or at later timepoints. Non-infusion related events have included paraneoplastic pemphigus, Stevens Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis (Genentech 2016). The onset of these reactions has varied from 1 to 13 weeks following initiation of rituximab exposure.

Among patients receiving rituximab in combination with chemotherapy, rare instances of life-threatening bowel obstruction or perforation has been observed (Ram 2009), primarily in patients with NHL. In post-marketing reports, the mean time to documented gastrointestinal perforation was 6 (range 1–77) days from start of chemoimmunotherapy.

Fulminate and fatal HBV infection and reactivation can occur during or after treatment with rituximab (Genentech 2016). The risk is very low among patients with negative anti-HBc serology (Matsue 2010) and/or undetectable HBV DNA as assessed by quantitative PCR. Because subjects with such evidence of persistent HBV infection are excluded from this study, reactivation is not anticipated. Other serious bacterial, fungal, and new or reactivated viral infections have also occurred during and for ~1 year following rituximab-based therapy (Gea-Banacloche 2010). Other new or reactivated viral infections in patients receiving rituximab have included CMV, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile

virus, and HCV. Progressive multifocal leukoencephalopathy (PML) due to polyomavirus JC has been observed in patients who have received rituximab therapy for hematologic malignancies (Carson 2009).

No dose reductions of rituximab/rituximab hyaluronidase human are recommended. If a subject experiences an AE that is suspected to be related to rituximab/rituximab hyaluronidase human and is of sufficient severity to warrant modification of therapy, administration of the drug should be interrupted or discontinued. Protocol-recommended management of selected adverse events and appropriate supportive care is described in Table 5.

Table 5: Recommended Rituximab or Rituximab/Hyaluronidase Modifications and Supportive Care

Adverse Event	Rituximab Interruption and Resumption	Rituximab Permanent Discontinuation	Supportive Care
Pneumonitis	Interrupt for Grade 2; resume when Grade ≤ 1	Grade ≥3	For Grade ≥2, corticosteroids, 1-2 mg/kg of prednisone equivalents
Rash	Interrupt for Grade 3; resume when Grade ≤ 1	Grade 4	For Grade 2, topical corticosteroids. For Grade ≥ 3, corticosteroids, 1-2 mg/kg of prednisone equivalents
Hepatitis	Grade ≥3 elevations of serum AST or ALT (> 5 x ULN); resume when Grade ≤ 1	--	Evaluate for HBV positivity; if HBV reactivation, treat with appropriate antiviral considering any potential for drug-drug interaction with LAM-002A.
Bowel obstruction or perforation	--	Any grade	Provide appropriate antibiotic therapy and surgical supportive care.
Infection	Grade ≥3; resume when control of infection achieved	--	Treat with appropriate systemic antibiotics for suspected or confirmed infections

Abbreviations: ALT=alanine aminotransferase, AST=aspirate aminotransferase, ULN=upper limits of normal

6.8.4. Atezolizumab

6.8.4.1. Premedications

No specific premedications are recommended for administration prior to atezolizumab administration. Given the potential for interference with desired atezolizumab immunopotentiation, systemic corticosteroid administration should be avoided.

6.8.4.2. Atezolizumab Administration

Atezolizumab will be administered intravenously in the clinic every 3 weeks. The dose for each infusion will be 1200 mg.

Using an infusion pump, atezolizumab should be administered through an intravenous line with or without a sterile, non-pyrogenic, low-protein binding in-line filter (pore size of 0.2 to 0.22 μm). Other drugs should not be coadministered with atezolizumab through the same intravenous line.

At Cycle 1 Day 1, ~15 to 30 minutes after administration of the first dose of LAM-002A, the first infusion of atezolizumab will be administered over 60 minutes. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes. Atezolizumab should not be administered as an intravenous push or bolus.

6.8.4.3. Management of Atezolizumab Infusion Toxicity

While infrequent (incident <2%), severe infusion reactions have occurred in clinical trial subjects receiving atezolizumab. For subjects with Grade 1 or 2 infusion reactions, the atezolizumab infusion should be interrupted or slowed. For subjects with Grade ≥3 infusion reactions, atezolizumab therapy should be permanently discontinued.

6.8.4.4. Atezolizumab Dose Modifications and Supportive Care

In clinical trials supporting its approval as therapy for patients with previously treated advanced non-small cell lung cancer and metastatic bladder cancer (Weinstock 2017, Ning 2017), atezolizumab administration has been associated with immune-related AEs of pneumonitis, hepatitis, pancreatitis, colitis, endocrinopathies (hypophysitis, thyroiditis, adrenal insufficiency, diabetes mellitus), and neurological toxicity (meningitis/encephalitis, motor/sensory neuropathies, myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome). Immune-related AEs can be observed within days to months after starting atezolizumab therapy (Genentech 2017).

Severe infections, including pneumonias, urinary tract infections, sepsis, herpes encephalitis, and mycobacterial infection have occurred.

Systemic immune activation is a rare condition characterized by an excessive immune response. Given the mechanism of action of atezolizumab, systemic immune activation is considered a potential risk when atezolizumab is given in combination with other immunomodulating agents. Systemic immune activation should be included in the differential diagnosis for study subjects who, in the absence of an alternative etiology, develop a sepsis-like syndrome after administration of atezolizumab. The initial evaluation should include:

- CBC with peripheral smear

- PT, PTT, fibrinogen, and D-dimer
- Ferritin
- Triglycerides
- AST, ALT, and total bilirubin
- LDH
- Complete neurologic and abdominal examination (assessing for hepatosplenomegaly)

If systemic immune activation is suspected after the initial evaluation, the medical monitor should be contacted in consultation.

Reference should be made to Section 6 of the atezolizumab investigator brochure for a detailed description of anticipated safety risks for atezolizumab.

No dose reductions of atezolizumab are recommended. If a subject experiences an AE that is suspected to be related to atezolizumab and is of sufficient severity to warrant modification of therapy, administration of the drug should be interrupted or discontinued. Protocol-recommended management of selected adverse events is described in Table 6.

Table 6: Recommended Atezolizumab Modifications and Supportive Care

Adverse Event	Atezolizumab Interruption and Resumption	Atezolizumab Permanent Discontinuation	Supportive Care
Pneumonitis	Interrupt for Grade 2; resume when Grade ≤ 1	Grade ≥3	For Grade ≥2, corticosteroids, 1-2 mg/kg of prednisone equivalents
Hepatitis	Interrupt for Grade 2 elevations of serum AST or ALT (> 3-5 x ULN) or total bilirubin (> 1.5-3 x ULN); resume when Grade ≤ 1	Grade ≥3 elevations of serum AST or ALT (> 5 x ULN) or total bilirubin (> 3 x ULN)	For Grade ≥2, corticosteroids, 1-2 mg/kg of prednisone equivalents
Colitis	Interrupt for Grade 2 or 3; resume if Grade ≤ 1 within 12 weeks on ≤ 10 mg oral prednisone equivalents	Grade 4	For Grade 2 recurrent or persistent (> 5 days), corticosteroids, 1-2 mg/kg of prednisone equivalents; For Grade ≥3, methylprednisolone 1-2 mg/kg intravenous → oral corticosteroid taper over ≥ 1 month

Adverse Event	Atezolizumab Interruption and Resumption	Atezolizumab Permanent Discontinuation	Supportive Care
Pancreatitis	Interrupt for Grade 2 or 3 pancreatitis or Grade ≥3 increases in serum amylase or lipase levels (>2 x ULN); resume if Grade ≤ 1 within 12 weeks on ≤ 10 mg oral prednisone equivalents	Grade 4 pancreatitis or any grade of recurrent pancreatitis	For Grade ≥2, methylprednisolone 1-2 mg/kg intravenous → oral corticosteroid taper over ≥ 1 month
Hypophysitis	Interrupt for symptoms; resume when Grade ≤ 1	--	Administer corticosteroids and hormone replacement as clinically indicated
Thyroid disorders	Interrupt for symptoms; resume when Grade ≤ 1	--	For symptomatic hypo- or hyperthyroidism, initiate hormone replacement or anti-thyroid drug, as needed
Adrenal insufficiency	Interrupt for symptoms; resume if Grade ≤ 1 within 12 weeks on ≤ 10 mg oral prednisone equivalents	--	For symptoms, methylprednisolone 1-2 mg/kg intravenous → oral corticosteroid taper over ≥ 1 month
Diabetes mellitus	Interrupt for Grade ≥3 hyperglycemia (serum glucose ≥ 250 mg/dL; resume when blood sugar control achieved	--	Insulin for Type 1 diabetes mellitus
Meningitis, encephalitis, myasthenic syndrome, myasthenia gravis, or Guillain-Barré syndrome	--	Any grade	Methylprednisolone 1-2 mg/kg intravenous → oral corticosteroid taper over ≥ 1 month
Rash	Interrupt for Grade 3; resume when Grade ≤ 1	Grade 4	For Grade 2, topical corticosteroids. For Grade ≥ 3, corticosteroids, 1-2 mg/kg of prednisone equivalents

Adverse Event	Atezolizumab Interruption and Resumption	Atezolizumab Permanent Discontinuation	Supportive Care
Infection	Grade 3 or 4; resume when control of infection achieved	--	Treat with appropriate systemic antibiotics for suspected or confirmed infections

Abbreviations: ALT=alanine aminotransferase, AST=aspirate aminotransferase, ULN=upper limits of normal

6.9. Other Supportive Care Recommendations

Consistent with subject safety and comfort, administration of any prescription or over-the-counter drug products other than study medication will be minimized during the study period. Subjects should be discouraged from use of herbal remedies, self-prescribed drugs, tobacco products, or street drugs during their participation in the clinical study and should be counseled to minimize use of alcohol or nonmedical marijuana.

If considered necessary for the subject's well-being, drugs for concomitant medical conditions or for symptom management may be given at the discretion of the investigator. The investigator's decision to authorize the use of any drug other than study drug will take into account subject safety, the medical need, the potential for drug interactions, the possibility for masking symptoms of a more significant underlying event, and whether use of the drug will compromise the outcome or integrity of the study.

Subjects will be instructed about the importance of the need to inform the clinic staff of the use of any drugs or remedies (whether prescribed, over-the-counter, or illicit) before and during the study.

Recommendations regarding specific types of concomitant therapies, supportive care, diet, and other interventions are provided below. To minimize variations in supportive care, the recommended supportive care agents (eg, loperamide, granisetron) should be used unless there is a medical rationale in a specific subject for use of an alternative product.

6.9.1. Antibiotics, Antifungals, and Antivirals

Care should be taken to avoid or minimize concomitant administration of prophylactic or therapeutic antibacterial, antifungal, or antiviral, agents that are moderate or strong CYP3A4 or CY2C9 inhibitors or inducers (see Section 6.9.6 and Appendix 3).

For subjects with a history of recurrent infections, prophylaxis with intravenous gamma-globulin may be offered and consideration may be given to initiation of antibiotic prophylaxis against pneumocystis infection (eg, with trimethoprim-sulfamethoxazole, dapsone, aerosolized pentamidine, or atovaquone) beginning prior to study drug administration. Such support also offers the benefit of reducing the risk for other bacterial infections (Stern 2014). Local practices or guidelines regarding infection prophylaxis may be followed.

Subjects developing an intercurrent infection during study drug treatment may receive therapeutic antibacterial, antiviral, or antifungal drugs for intercurrent infections as needed. Continuation of study therapy during treatment for an intercurrent infection is at the discretion of

the investigator but guidance in Section 6.8.3.4 and Section 6.8.4.4 should be considered in subjects receiving combination therapy.

6.9.2. Anticancer Therapies Other than the Study Drugs

No systemic anticancer therapies (including chemotherapy, antibody therapy, hormonal therapy, immunotherapy, or other experimental therapies) for the subject's cancer are permitted while the subject is receiving study treatment. Subjects are not allowed to participate concurrently in any other therapeutic clinical or imaging study.

The use of palliative radiotherapy should be minimized given the potential of such treatment to confuse assessments of study drug safety or therapeutic effect. However, administration of limited-fraction radiotherapy is permitted to control local tumor-related symptoms if irradiation is unlikely to induce major organ toxicity or affect target lesions being followed for tumor response and progression.

If required to maintain disease control, study drugs may be continued with caution during radiotherapy administration.

6.9.3. Anticoagulants

Use of local anticoagulation or antithrombotic agents to maintain a venous access catheter is permitted. While not prohibited, use of systemic anticoagulants (eg, unfractionated heparin, low-molecular-weight heparin, fractionated heparin, warfarin or other oral anticoagulants, aspirin) after a subject is on study should be avoided unless necessary for development of a serious intercurrent thrombotic or embolic condition. Subjects who develop conditions that require anticoagulant therapy are permitted to receive such drugs and are not required to discontinue study participation if they appear to be safely benefiting from study therapy. Subjects should be closely monitored for bleeding events when on systemic anticoagulant therapy.

6.9.4. Antihistamine, Antiinflammatory, or Antipyretic, Drugs

Antihistamines (eg, cetirizine, diphenhydramine), and antiinflammatory/antipyretic drugs (eg, acetaminophen [paracetamol], nonsteroidal anti-inflammatory drugs [NSAIDs]), may be used during the study, as medically warranted. The potential for adverse hepatic effects with acetaminophen and platelet inhibitory effects with NSAIDs should be considered in the selection of the appropriate drug for the clinical situation.

6.9.5. Corticosteroids

At study entry, subjects may not be using systemic or enteric corticosteroids but may be receiving inhaled or topical corticosteroids. During study therapy, subjects may use systemic, enteric, topical or enteric corticosteroids as required by protocol or for treatment-emergent conditions. Use of systemic or enteric corticosteroids as premedications or for other reasons should be minimized but can be considered after consultation with the medical monitor.

6.9.6. Drugs with Potential for Drug-Drug Interactions with LAM-002A

No information is available regarding interactions of LAM-002A with therapeutic agents or other substances in humans. *In vitro* data suggest that concomitant administration of potent inhibitors or inducers of CYP3A4 or CYP2C9 might alter LAM-002A clearance and lead to clinically

significant increases or decreases in LAM-002A exposure. Consequently, the concomitant use of strong inhibitors or inducers of CYP3A4 or CYP2C9 (see Table 15) should be avoided when possible.

Based on these considerations, protocol candidates who require therapy with strong CYP3A4 or CYP2C9 inhibitors or inducers listed in Table 15 should not be enrolled into the study.

During study participation, coadministration of LAM-002A with CYP3A4 or CYP2C9 inhibitors or inducers (see Table 15) should be avoided, if possible. However, a subject who develops a condition that may require use of such drugs is not required to permanently discontinue LAM-002A if the subject is experiencing clinical benefit and other options for treating the subject's cancer are limited. If medically appropriate, investigators may wish to use a therapeutic alternative that would not be expected to affect these enzymes. For subjects who require temporary use of a drug that does affect these enzymes (e.g., treatment with a systemic antifungal agent), LAM-002A can be interrupted (or the doses reduced) during use of the other medication and then resumed after completion of the other drug. For subjects who require initiation of chronic therapy with a drug that potently affects these enzymes, investigators must consult with the medical monitor to consider the best course of action.

6.9.7. Drugs Known to Prolong the QT Interval

In a thorough QTc study, apilimod dimesylate at doses of 50 mg and 150 mg was associated with repolarization findings in excess of those deemed negative by regulatory guidance. The magnitude of the change was modest (~8.5 msec), peaked at 4 hours and did not demonstrate a dose trend. Preliminary QTc observations in the ongoing study in patients with hematological malignancies suggest the potential for dose- and exposure dependent Grade 1 or 2 QT prolongation.

As a precaution, the clinical potential of LAM-002A to prolong the QT interval will be assessed in this study. Accordingly, co-administration of LAM-002A and known QT-prolonging drugs is to be minimized because use of such drugs might confound interpretation of QT data from the trial.

Based on these considerations, protocol candidates who require therapy with drugs known to prolong the QT interval (as listed in Table 16) should not be enrolled into the study. If medically justified, protocol candidates may be enrolled if such drugs can be discontinued or alternative drugs that do not affect QT can be substituted >7 days before the first dose of study drug.

After the subject is enrolled to the protocol, use of drugs known to prolong the QT interval should be minimized but is not prohibited if administration of such drug is necessary and the subject appears to be benefiting from protocol therapy.

6.9.8. Hematopoietic Support

Granulocyte colony-stimulating factor (G-CSF) (eg, filgrastim, filgrastim snd, pegfilgrastim, lenograstim) may be administered in response to Grade ≥3 neutropenia or neutropenic complications.

Granulocyte-macrophage colony-stimulating factor (GM-CSF) should not be administered given the potential for GM-CSF-related inflammatory symptoms.

Use of erythropoietic agents (eg, erythropoietin or darbepoetin) is not recommended.

Red blood cell or platelet transfusions may be administered as medically indicated.

6.9.9. Immunization

There is no information regarding the effects of LAM-002A or atezolizumab on the safety or response to immunization against infectious pathogens.

In randomized clinical trials, rituximab has been shown to reduce the antibody response to pneumococcal vaccination (a T-cell-independent antigen) or to anti-keyhole limpet hemocyanin antibodies (a novel protein antigen) (Genentech 2016). Response to tetanus toxoid vaccine (a T-cell-dependent antigen with existing immunity) or maintenance of a positive Candida skin test (as a measure of T-cell-mediated delayed-type hypersensitivity) was not altered. The specific clinical relevance of these findings is unknown.

For subjects who are at substantial risk of an infection (eg, influenza) that might be prevented by immunization, consideration should be given to providing the vaccine prior to initiation of study therapy. Vaccination with live virus vaccines during study treatment is not recommended.

6.9.10. Procedures/Surgery

The extent to which LAM-002A or other study drugs may affect wound healing or the risk of would infection is unknown. Investigators may use clinical discretion in deciding whether to interrupt protocol therapy before and after surgery or other invasive procedures.

6.9.11. Skeletal Event Prophylaxis

Bisphosphonates or denosumab are permitted if a subject was receiving such therapy at the time of screening and will continue on a stable regimen throughout protocol therapy. The need to start such drugs while on therapy may be an indication of disease progression and should be discussed with the sponsor prior to implementation.

6.10. Study Restrictions

6.10.1. Breast Feeding

There is no information regarding the presence of LAM-002A or its metabolites in animal or human breast milk and the effects of the drug on the breastfed infant or on milk production are unknown.

Rituximab is secreted in the milk of lactating cynomolgus monkeys, but it is not specifically known whether rituximab is secreted into human milk (Genentech 2016). There is similarly no information regarding the presence of atezolizumab in human milk (Genentech 2017). However, because human IgG is excreted in human milk, there is a hypothetical potential for absorption and harm to an infant from administration of these types of therapeutic antibodies.

For these reasons, women who are nursing are not eligible to participate in this study. Lactating women who do participate in this clinical trial must discontinue nursing during protocol therapy and should avoid nursing for ≥2 months after LAM-002A and for ≥5 months after the last dose of rituximab or atezolizumab.

6.10.2. Contraception

Animal studies have been conducted to assess the effects of apilimod on fertility and organogenesis. In studies conducted to date, apilimod or apilimod dimesylate did not affect fertility or cause reproductive harm. One patient receiving the drug for Crohn disease conceived during therapy; a normal pregnancy was carried to term and a healthy infant was born. However, no other experience is available with the drug in pregnant patients.

Reproduction studies of rituximab in cynomolgus monkeys at maternal exposures similar to human therapeutic exposures have shown no teratogenic effects (Genentech 2016). However, B-cell lymphoid tissue was reduced in the offspring of these animals; B-cell counts returned to normal levels and immunologic function was restored within 6 months of birth. In humans, B-cell lymphocytopenia generally lasting <6 months can occur postnatally in infants exposed to rituximab in utero.

Animal reproduction studies have not been conducted with atezolizumab to evaluate its effect on reproduction and fetal development. A literature-based assessment of the effects on reproduction demonstrated that a central function of the PD-L1/PD-1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to a fetus (Genentech 2017). Blockage of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to a fetus and to result in an increase in fetal loss; therefore, potential risks of administering atezolizumab during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-L1/PD-1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-L1 and PD-1 knockout mice. Based on its mechanism of action, fetal exposure to atezolizumab may increase the risk of developing immune-mediated disorders or altering the normal immune response.

Accordingly, sexually active females of childbearing potential must agree to use a protocol-recommended method of contraception during heterosexual intercourse from the start of the screening period until ≥5 months days after the final dose of study therapy.

In the context of this protocol, a female subject is considered to be of childbearing potential unless she has had a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy; has medically documented ovarian failure (with serum follicle stimulating hormone (FSH) level > 35 mIU/mL and a negative serum or urine beta βHCG); or is menopausal (amenorrhea for ≥12 months).

Sexually active male subjects who can father a child and are having intercourse with females of childbearing potential who are not using adequate contraception must agree to use a protocol-recommended method of contraception from the start of study therapy until ≥5 months days after the final dose of the study therapy and to refrain from sperm donation from the start of study therapy until ≥5 months after administration of the final dose of study therapy.

In the context of this protocol, a male subject is considered able to father a child unless he has had a bilateral vasectomy with documented aspermia or a bilateral orchiectomy.

Protocol-recommended contraceptive methods are described in Table 7.

Table 7: Protocol-Recommended Contraceptive Methods

Individual Methods	Combination Methods	
	Hormonal Methods (One method to be used with a barrier method)	**Barrier Methods (Both methods to be used OR one method to be used with one hormonal method)**
IUD (eg, Copper T380A, LNg20)	Estrogen and progesterone	Diaphragm with spermicide
Tubal sterilization	Oral contraceptives	Male condom (with spermicide)
Hysterectomy	Transdermal patch	
Vasectomy	Vaginal ring	
	Progesterone injection or implant	

Abbreviation: IUD=intrauterine device

6.10.3. Diet

Because LAM-002A is a substrate of CYP3A4, subjects should be advised to avoid ingestion of grapefruit, grapefruit juice, or Seville oranges (which contains a potent CYP3A4 inhibitor) and should not use St. John's wort, which is a potent CYP3A4 inducer. No other specific dietary restrictions are required.

6.11. Duration of Subject Participation

Subjects may continue receiving LAM-0002A until the occurrence of any events requiring treatment discontinuation as defined in Section 6.8.2.5 and Section 6.12.

Subjects allocated to LAM-0002A/rituximab may continue to receive rituximab or rituximab hyaluronidase human until the earliest of a maximum of 8 infusions or the occurrence of any events requiring treatment discontinuation as defined in Section 6.8.3.4 and Section 6.12.

Subjects allocated to LAM-0002A/atezolizumab may continue to receive atezolizumab until the earliest of any events requiring treatment discontinuation as defined in Section 6.8.4.4 or Section 6.12.

Note: If medically appropriate, subjects allocated to combination doublet therapy may continue with protocol-specified therapy for the therapeutic agent (LAM-002A, rituximab, rituximab hyaluronidase human, or atezolizumab) that continues to be tolerated, even if the other agent need to be discontinued due to drug-specific toxicity.

Subjects who have discontinued study treatment for reasons other than PD will be assessed per Revised Response Criteria for NHL or Guidelines for the diagnosis and treatment of CLL at a minimum of every 12 weeks until documentation of PD, start of new anti-cancer therapy or for up to 1 year from the last enrolled subject's first treatment (Cycle 1 Day 1), whichever comes first. Long-term follow-up survival information will be obtained in all surviving subjects who permanently discontinue study therapy. Such information may be collected at ~3- to 6-month intervals at the sponsor's discretion through 3 years. This long-term follow-up information will be gathered during routine clinic visits, other study site contact with the subjects, or via telephone or e-mail with the subjects/caregivers or referring physician offices.

6.12. Criteria for Subject Withdrawal from Study Treatment or Study Participation

Subjects may be withdrawn from further study treatment for any of the following reasons:

- Subject withdrawal of informed consent
- Disease progression of cancer while receiving study therapy ***Note: Apparent worsening of disease during temporary interruption of study therapy (e.g., for drug-related toxicity or intercurrent illness) may not indicate true cancer progression. Study subjects undergoing PET for lymphoma assessment can experience transient disease flare on imaging before having subsequent therapy-induced tumor regression. Worsening of constitutional symptoms or performance status in the absence of objective evidence of worsening lymphoma (e.g., due to infection) may not represent definitive disease progression. For these reasons, if there is uncertainty regarding whether there is true disease progression and if medically appropriate, the subject may continue or resume study treatment and remain under close observation (e.g., evaluated at 4- to 8-week intervals) while relevant radiographic, clinical, and/or laboratory assessments are performed to document whether tumor control can be maintained or whether disease progression has truly occurred. If subsequent evaluations suggest that the subject has experienced persistent definitive disease progression, then the date of progression will be the timepoint at which progression was first objectively documented.***
- Unacceptable study-drug-related toxicity despite appropriate dose modification
- Development of intercurrent illness that precludes continued study therapy
- Physician decision that continuation is not in the subject's best interest
- Treatment of the cancer with another therapeutic regimen
- Subject becomes pregnant or begins breastfeeding
- Substantial noncompliance with study drug administration, study procedures, or study requirements in circumstances that increase risk or substantially compromise the interpretation of study results
- Termination of the study by the sponsor, relevant regulatory agencies, or the IRB/IEC

The investigator must determine the primary reason for a subject's withdrawal from the study and record this information on the electronic case report form (eCRF).

Unless they withdraw consent for further follow-up, subjects who discontinue study therapy will continue on study for acquisition of safety information through ≥30 days after the last dose of study treatment, and for further collection of long-term information regarding survival.

6.13. Replacement of Subjects

Subjects not meeting the criteria for evaluability defined in Section 6.1.5 may be replaced at the discretion of the sponsor. If a subject needs to be replaced, the associated subject ID will not be used again.

7. SELECTION OF SUBJECTS

7.1. Subject Inclusion Criteria

1. The subject is capable of understanding and complying with the protocol requirements and has signed the informed consent document. The subject is able to provide signed and dated informed consent prior to initiation of any study-specific procedures.
2. Subjects must have a histologically confirmed diagnosis of B-cell NHL limited to FL, DLBCL, MCL, MZL, primary mediastinal B-cell lymphoma (PMBL), or CLL/SLL according to the World Health Organization (WHO) classification, that has progressed and for which standard curative measures do not exist or are no longer effective.
3. Subjects with DLBCL must have progressed after transplant, or be unwilling, unable or not an appropriate candidate for an autologous stem cell or bone marrow transplant.
4. Subjects must have radiographically measurable lymphadenopathy or extranodal lymphoid malignancy (defined as the presence of ≥ 1 lesion that measures ≥ 2.0 cm in the longest dimension [LD] and ≥ 1.0 cm in the longest perpendicular dimension [LPD] as assessed radiographically).
5. The subject is ≥ 18 years old.
6. The subject has an Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 2.
7. The subject has organ and marrow function as follows:
   a. Absolute neutrophil count (ANC) ≥ 1.0×10^9/L ($1{,}000/mm^3$) without hematopoietic-stimulating factor support
   b. Platelets ≥ 50×10^9/L ($50{,}000/mm^3$)
   c. Total bilirubin ≤ 1.5 x the upper limit of normal (ULN) except for subjects with known Gilbert disease (total bilirubin ≤ 3 x ULN permitted)
   d. Serum creatinine ≤ 1.5 x ULN or calculated creatinine clearance ≥ 60 mL/min (based on the Cockcroft-Gault formula)
   e. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x ULN if no liver involvement, or ≤ 5 x ULN with liver involvement
   f. Albumin ≥ 2 g/dL
   g. ***Note: Grade ≥ 3 neutropenia or thrombocytopenia is permitted if the abnormality is related to bone marrow involvement with hematological malignancy (as documented by bone marrow biopsy/aspirate obtained since the last prior therapy).***
8. The subject has the ability to swallow oral capsules without difficulty.
9. Sexually active subjects (men and women), even if on oral contraceptives, must agree to remain abstinent (refrain from heterosexual intercourse) or use appropriate contraceptive methods (see Section 6.10.2) during the treatment period and for 5 months after the last dose of study therapy.
10. Women of childbearing potential (WCBP) must have a negative serum or urine pregnancy test at screening. WCBP include any woman who has experienced menarche

and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal. Postmenopausal is defined as:

a. Amenorrhea ≥ 12 consecutive months without another cause or
b. For women with irregular menstrual periods and on hormone replacement therapy, a documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL

11. For subjects with lymphoma: The subject is willing to undergo a pretreatment core needle, excisional, or incisional biopsy of a lymphoma nodal lesion (preferred); or is willing to undergo a pretreatment bone marrow aspirate if there is known bone marrow involvement (≥ 50% NHL cells). If a biopsy or bone marrow aspirate is not possible, archived tumor tissue that was obtained within 4 months prior to the start of screening can be used, provided adequate quantities are available.
12. For subjects with CLL/SLL: The subject has sufficient circulating cells in the peripheral blood (e.g., ALC ≥ 10 x 10^9/L) or is willing to undergo a pretreatment bone marrow aspirate to obtain CLL cells.

7.2. Subject Exclusion Criteria

1. Subjects with central nervous system (CNS) lymphoma are not eligible for the trial unless the disease had been treated and the subject remained asymptomatic (for at least 6 months) with no active CNS lymphoma, as determined by lumbar puncture, computed tomography scan (CT), or magnetic resonance imaging (MRI).
2. The subject has received cytotoxic chemotherapy (including investigational cytotoxic chemotherapy) within 3 weeks, or nitrosoureas/ mitomycin C within 6 weeks before the first dose of study treatment.
3. The subject has received treatment with a therapeutic antibody less than 4 weeks before the first dose of study treatment. For subjects with rapidly progressive or aggressive subtypes of lymphoma, a minimum period of 2 weeks between the last treatment with a therapeutic antibody and the first dose of study treatment may be permitted following discussion with the medical monitor.
4. The subject has received radioimmunotherapy within 6 weeks of the first dose of study treatment.
5. The subject has received radiation therapy within 14 days of the first dose of study treatment.
6. The subject has received prior treatment with a small-molecule kinase inhibitor or other small-molecule investigational agent within 14 days or 5 half-lives of the compound or active metabolites, whichever is greater, before the first dose of study treatment.
7. Stage 2 (study candidates being considered for LAM-002A/rituximab combination therapy): Best overall response with the last regimen containing an anti-CD20 antibody (eg, rituximab, ofatumumab, obinutuzumab) was disease progression.

8. Stage 2 (study candidates being considered for LAM-002A/atezolizumab combination therapy): Prior exposure to a CD137 agonist or an immune checkpoint inhibitor, including an anti-PD1, anti-PDL1, or anti-CTLA4 therapeutic antibody.
9. Stage 2 (study candidates being considered for LAM-002A/atezolizumab combination therapy): treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the last dose of atezolizumab.
10. Stage 2 (study candidates being considered for LAM-002A/atezolizumab combination therapy): Current treatment with anti-viral therapy for hepatitis B virus (HBV).
11. Stage 2 (study candidates being considered for LAM-002A/atezolizumab combination therapy): Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment.
12. The subject is currently receiving treatment with strong inhibitors or inducers of CYP450 2C9 or 3A4 enzymes.
13. The subject is chronically receiving immunosuppressive therapy (eg, with cyclophosphamide, azathioprine, thalidomide, lenalidomide, methotrexate, or anti-TNF-α agents) within 2 weeks prior to initiation of study treatment or requires systemic or enteric corticosteroids at the time of starting study therapy. Study candidates using systemic low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency or topical, intra-articular, nasal, or inhaled corticosteroids are not excluded from study participation. Note: During study therapy, subjects may use systemic, enteric, topical, intraarticular, nasal, or inhaled corticosteroids as required by protocol or for treatment-emergent conditions.
14. The subject has not recovered from toxicity due to all prior therapies (i.e., return to pre-therapy baseline or to Grade 0 or 1). Persistent > Grade 1 toxicity from prior therapy will be considered by the sponsor for inclusion if there is no evidence of an overlapping apilimod toxicity.
15. The subject has uncontrolled significant intercurrent illness including, but not limited to, ongoing or active infection, history of congestive heart failure within 6 months, Grade ≥3 hypertension, unstable angina pectoris within 6 months, stroke within 6 months, myocardial infarction within 6 months, or cardiac arrhythmias. (Controlled chronic atrial fibrillation will not be excluded).
16. Severe uncontrolled infection within 2 weeks prior to initiation of study treatment, including hospitalization for complications of infection, bacteremia, or severe pneumonia or treatment with therapeutic oral or IV antibiotics. ***Note: subjects receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are not excluded.***
17. Stage 2 (study candidates being considered for LAM-002A/atezolizumab combination therapy): Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid

antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (with the following exceptions: history of autoimmune-related hypothyroidism and receiving thyroid-replacement hormone; controlled Type 1 diabetes mellitus on an insulin regimen; eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations if rash covers < 10% of body surface area, disease is well controlled at baseline and requires only low-potency topical corticosteroids, there is no occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months, and the subject does not have extra-cutaneous disease [e.g., psoriatic arthritis]).

18. The subject has a history of malabsorption or other GI disease that may significantly alter the absorption of apilimod (e.g., ≥ Grade 2 nausea, vomiting or diarrhea).
19. The subject has undergone major surgery within 28 days prior to first dose of study drug.
20. The subject has a QTcF > 470 msec on screening ECG or has a history or risk factors for, or use of medications known to prolong QTc interval or that may be associated with Torsades de Pointes within 7 days of treatment start.
21. The subject has past history of tuberculosis (TB) or active infection with TB, human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV). ***Note: Subjects must have negative human immunodeficiency virus (HIV) antibody, negative hepatitis B surface antigen (HBsAg) and negative hepatitis B core (HBc) antibody or undetectable HBV deoxyribonucleic acid (DNA) by quantitative polymerase chain reaction (PCR) testing, and negative HCV antibody or negative HCV ribonucleic acid (RNA) by quantitative PCR.***
22. The subject is lactating and breast feeding.
23. The subject has a previously identified allergy or hypersensitivity to components of the study treatment formulation.
24. Stage 1 (study candidates being considered for LAM-002A intermittent administration): Known inability to tolerate the protocol-specified antiemetic and antidiarrheal supportive care regimen.
25. The subject is unable or unwilling to abide by the study protocol or cooperate fully with the investigator or designee.
26. The subject has a history of other medical or psychiatric illness or organ dysfunction which, in the opinion of the investigator, would either compromise the subject's safety or interfere with the evaluation of the safety of the study agent.
27. The subject has a history of prior cancer (not under study) that has not been in remission for at least 3 years. The following are exempt from the 3-year limit: basal cell or squamous cell carcinoma of the skin, localized prostate cancer with normal Prostate Specific Antigen (PSA), cervical cancer in situ or other in situ carcinomas.

8. METHODS OF ASSESSMENT AND ENDPOINTS

All trial data during the dose-escalation stage (Stage 1) and expansion stage (Stage 2) will be recorded on the eCRFs. Timing of study procedures for the dose-escalation stage (Stage 1) and expansion stage (Stage 2) are listed in schedules of assessments tables – Table 8: Schedule of Assessments (LAM-002A Continuous Monotherapy Administration), Table 9: Schedule of Assessments (LAM-002A Intermittent Monotherapy Administration), Table 10: Schedule of Assessments (LAM-002A/Rituximab Combination Therapy), and Table 11: Schedule of Assessments (LAM-002A/Atezolizumab Combination Therapy) – in Section 8.7. During the extension stage (Stage 3), collection of clinical data by the sponsor will be limited to serious adverse event (SAE) reports. Study drug accountability will be managed per site procedures; relevant pharmacy records may be collected by the sponsor to document study drug disposition.

8.1. Screening/Baseline Evaluations Only

8.1.1. Informed Consent

Each potential subject must sign a written informed consent form (ICF) prior to performing any study-specific procedure. Principal investigators (PIs) at each site are responsible for maintaining a record of all subjects screened, including both those who enter the study and those who are excluded.

8.1.2. Inclusion and Exclusion Criteria

During Screening, inclusion and exclusion criteria will be reviewed for each potential subject and confirmed by Day 1 of Cycle 1.

8.1.3. Medical History

At Screening, a complete medical history will be obtained from each subject, including relevant medical history, current primary cancer diagnosis, pathology reports (including corresponding flow cytometry and cytogenetic reports), prior cancer treatments (chemo- and immunotherapies, radiation therapy, surgeries), and disease-specific characteristics, such as tumor stage and histology.

8.1.4. Demography

At Screening, subject demographic data will be collected, including date of birth, gender, race, and ethnicity.

8.1.5. Disease Status Assessment for Subjects with NHL

Pretreatment tumor assessments will be performed within 30 days of the first dose of study treatment and will include diagnostic CT scans (with intravenous contrast) or Positron Emission Tomography (PET)/Computerized Tomography Scans (CT scan) for patients with lymphoma, bone marrow aspirate/biopsy, complete blood counts and physical examination. It is anticipated that in most cases the PET/CT scans will be conducted using a single instrument, i.e., as a PET/CT scan (CT scans should be performed using a contiguous reconstruction algorithm of ≤ 5 mm). However, MRI is an acceptable alternative method for assessing disease in subjects

who cannot receive intravenous contrast with CT scans. In such subjects MRI and PET scans will have to be obtained separately.

Suitable scans performed prior to screening and within 30 days before first dose may be used for baseline tumor assessments. Similarly bone marrow biopsies/aspirates performed within 2 months prior to first dose may be used for baseline assessments. For subjects with NHL, baseline bone marrow biopsies/aspirates may be omitted if not deemed essential for response assessment or patient management and there is another source of tumor tissue for pretreatment evaluation of gene expression and prognosis. For subjects with CLL/SLL, a baseline bone marrow aspirate is required unless the presence of sufficient circulating cells in the peripheral blood (e.g., ALC $\geq 10 \times 10^9$/L) permits assessment of baseline parameters for gene expression and prognosis. Details of assessments will be collected on the eCRF and must be filed in the subject's medical record.

Fresh tumor tissue (preferred) or archival tumor tissue that was obtained within 4 months prior to the start of screening (provided adequate quantities are available) must be obtained pretreatment for nucleic acid extraction. For subjects undergoing a biopsy, adequate tumor tissue should be acquired via excisional biopsy, incisional biopsy or core needle biopsy (e.g., ≥ 3 passes using a 16-gauge core needle). Confirmation of tumor in biopsy with fine needle aspirate, touch prep, or FFPE processing is requested when possible. The tumor lesion selected should not have been previously irradiated and should not be an index lesion that is followed for response assessment. Alternatively, cells from a bone marrow aspirate may be obtained in subjects with bone marrow involvement due to NHL (≥50% of cells). Tissue will be submitted for evaluation of the percentage of tumor cells and analysis of genetic alterations and/or gene expression that may predict anti-lymphoma activity and/or pharmacodynamics activity.

In addition, tumor tissue from the fresh biopsy or most recently availably biopsy or surgery will be evaluated for known prognostic characteristics (e.g., for DLBCL: ABC or GCB subtype; expression of BCL2, BCL6, Ki-67, CD20, and MYC; other mutational status), for PDL1 status, and for immune infiltration. The baseline biopsy procedure (if required) should ideally be performed after the study candidate has undergone the baseline radiology examination and is otherwise considered eligible for study participation.

8.1.6. Disease Status Assessments for Subjects with CLL/SLL

All subjects with CLL must have baseline imaging (with CT scans [preferred] or MRI scans).

Subjects with CLL/SLL must provide either a fresh blood sample containing circulating tumor cells or a bone marrow aspirate sample pretreatment. Tissue will be submitted for evaluation of the percentage of tumor cells and analysis of genetic alterations and/or gene expression that may predict anticancer activity and/or pharmacodynamic activity. In addition, for subjects with CLL/SLL, the sponsor may arrange for a portion of the sample to be evaluated at a sponsor-specified laboratory for known prognostic markers (e.g., quantitative immunoglobulins, FISH panel [chromosome 11q deletion, 13q deletion, 17p deletion and 12 trisomy], DNA mutational analysis for p53, IgHV [including IgHV3-21], and other genes of interest in CLL [e.g., Notch]; flow cytometry [for CD5, CD10, CD11c, CD19, CD20, CD23, CD38, CD45, kappa and lambda light chains and ZAP-70], and/or β2-microglobulin). The baseline bone marrow aspiration procedure (if required) should ideally be performed after the study candidate has undergone the baseline radiology examination and is otherwise considered eligible for study participation.

8.2. Baseline Assessment for All Subjects

8.2.1. Physical Examination and ECOG Performance Status

Complete physical examination (PE) will be performed at Screening and may include evaluation of head, ears, eyes, nose, and throat, dermatological, respiratory, cardiovascular, gastrointestinal, endocrine/metabolic, neurological, lymphatic, and musculoskeletal systems. A directed PE, including weight, will be performed within 72 hours prior to the start of each cycle and at End of Treatment.

ECOG Performance Status will be assessed at the same time points as PEs (See Appendix 1).

8.2.2. Pregnancy Test

Serum or urine pregnancy test will be performed for WCBP at Screening, within 72 hours of Day 1 of each treatment cycle, and at the EOT visits. The test does not need to be repeated at Cycle 1 Day 1 if baseline testing was performed within 72 hours of first dose. However, the result must be negative for the subject to be enrolled in the study and to continue participation.

8.2.3. Urinalysis

A urine sample will be obtained at Screening, within 72 hours of Day 1 of each treatment cycle, and at the EOT visit. Analysis will include assessment of appearance, specific gravity and pH as well as a semi-quantitative “dipstick” evaluation of glucose, protein, bilirubin, ketones, leukocytes and blood. Microscopic examination of sediment will be performed if urinalysis is positive for white blood cells (WBCs), proteins, or blood.

8.2.4. Electrocardiogram

A 12-lead ECG with subject resting for 5 minutes will be done at Screening. Additional ECGs will be conducted according to Table 8: Schedule of Assessments (LAM-002A Continuous Monotherapy Administration), Table 9: Schedule of Assessments (LAM-002A Intermittent Monotherapy Administration), Table 10: Schedule of Assessments (LAM-002A/Rituximab Combination Therapy), and Table 11: Schedule of Assessments (LAM-002A/Atezolizumab Combination Therapy) – in Section 8.7 and more often if clinically indicated. Parameters measured will include heart rate, PR, QRS, QT, and QTc intervals (calculated by the Fridericia correction formula. Bazett’s correction is acceptable if institutional policy). See Section 12 for PK time points. The ECGs will be reviewed and signed by the investigator.

8.2.5. Vital Signs

Vital signs including temperature (°C), blood pressure, pulse, and respiration rate will be measured at each indicated visit including screening, prior to the start of each cycle, prior to each PK time point, at the End of Treatment, and more often if clinically indicated.

8.3. Screening/Baseline, Day 1, 8, 10, 15 (Cycles 1 and 2 Only) and Prior to Each Subsequent Cycle and End of Treatment

8.3.1. Clinical Laboratory Tests

Clinical laboratory tests during the first 2 cycles will be performed by the investigative site's local laboratory. Samples will be collected from subjects at scheduled study visits before the administration of study drug unless otherwise noted, and more frequently if clinically indicated. Clinical laboratory tests may be performed up to 72 hours prior to the scheduled visits (see Section 8.7 for Schedules of Assessments). Upon completion of Cycle 2, subjects may use the investigative site's laboratory or their local laboratory for clinical laboratory assessments. Accredited certification, such as College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendments (CLIA), and valid reference ranges must be collected for all clinical laboratories used by subjects.

The following clinical laboratory tests will be collected: Hematology, Coagulation, Blood Chemistry and PK Assessments.

8.3.1.1. Hematology

Hemoglobin, hematocrit, WBC count with differential, red blood cell (RBC) count, and platelet count will be collected according to the relevant schedule of events; see Table 8: Schedule of Assessments (LAM-002A Continuous Monotherapy Administration), Table 9: Schedule of Assessments (LAM-002A Intermittent Monotherapy Administration), Table 10: Schedule of Assessments (LAM-002A/Rituximab Combination Therapy), and Table 11: Schedule of Assessments (LAM-002A/Atezolizumab Combination Therapy) in Section 8.7.

Coagulation parameters (aPTT [or PTT] and INR) should be performed at Screening.

8.3.1.2. Blood Chemistry

Albumin, alkaline phosphatase (ALP), total bilirubin, calcium, carbon dioxide, chloride, creatinine, glucose, inorganic phosphorus, potassium, total protein, ALT, AST, lactate dehydrogenase (LDH), sodium, BUN, and uric acid will be collected according to the relevant schedule of events; see Table 8: Schedule of Assessments (LAM-002A Continuous Monotherapy Administration), Table 9: Schedule of Assessments (LAM-002A Intermittent Monotherapy Administration), Table 10: Schedule of Assessments (LAM-002A/Rituximab Combination Therapy), and Table 11: Schedule of Assessments (LAM-002A/Atezolizumab Combination Therapy) in Section 8.7. If the total bilirubin concentration is > 1.5 times the upper normal limit, total bilirubin should be differentiated and the total and direct bilirubin should be reported.

8.3.1.3. PK and Biomarker Assessments

Pharmacokinetic samples will be collected for determination of apilimod and metabolite concentrations in plasma at the time points indicated in Section 12. All subjects must participate in PK assessments. Fasting status must be recorded at the time of each PK blood draw. Comprehensive information on blood sample acquisition, handling, storage and sample shipments can be found in the laboratory manual "Procedures for Processing and Shipping PK and Biomarker Samples."

Biomarker samples will be obtained at time points indicated in Section 13. Comprehensive information on tissue acquisition, handling, storage, and sample shipments can be found in the laboratory manual "Procedures for Processing and Shipping PK and Biomarker Samples."

8.4. Disease Assessment

The type of assessment and schedule is defined by the subject's disease. Therefore, the type and schedule of assessments is presented in Appendix 2 for subjects with relapsed or refractory B-cell NHL and CLL/SLL.

8.5. Adverse Events

Adverse Events will be assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI 2010). AEs, including SAEs, will be captured on the eCRFs from Cycle 1 Day 1 through 30 days after the last dose of study treatment. Study treatment related AEs/SAEs that are ongoing 30 days after the last dose of study treatment should continue to be followed until resolution or stabilization. AE assessment will be done at a minimum at each scheduled visit. For the weeks that the subject is not required to come to the study site, the investigator will monitor each subject for possible AEs via telephone contact as needed.

8.6. Treatment Compliance

The investigator will dispense the study medication only for use by subjects enrolled in the study as described in this protocol. The study medication is not to be used for reasons other than those described in this protocol.

The investigator or other study staff will supervise LAM-002A treatment given at the site and instruct the subject on study medication self-administration. Subjects will be asked to bring their dosing diary with them at each visit. Compliance with protocol-defined LAM-002A intake will be checked by pill count at the end of each cycle and compliance decisions will be made by the investigator.

A subject is considered to be DLT-evaluable if he/she has taken at least 75% (42/56 BID schedule; 63/84 TID schedule, 18/24 intermittent schedule) of the planned first-cycle doses and has sufficient safety data, or has experienced a DLT in the first cycle.

8.7. Schedules of Assessments

Table 8: Schedule of Assessments (LAM-002A Continuous Monotherapy Administration)

Assessment	Screening	Cycle 1					Cycle 2		Cycle ≥ 3		End of Treatment (EOT)	Long-Term F/U
		Day					Day		Day			
	-28 to -1	1	2	3	8	15	1	15-28	1	15-28		
Informed consent	X											
Inclusion/exclusion criteria	X	X[a]										
Demographics	X											
Medical history	X											
Signs and symptoms, PE[b]	X	X[c]					X		X		X	
ECOG performance status	X	X[c]					X		X		X	
Vital signs	X	X[d]			X[d]	X[d]	X		X		X	
ECG	X	X[d]			X[d]	X[d]	X		X		X	
HIV, HBV, and HCV serology	X											
Hematology[e, f]	X	X			X	X	X		X		X	
Serum chemistry[f, g]	X	X	X[f]	X[f]	X	X	X		X		X	
Coagulation	X											
Urinalysis[h]	X	X[c]					X		X		X	
Pregnancy testing[i]	X	X[i]					X		X		X	
PET/CT or CT (or MRI) scans (based on indication) for response assessment	X[j]							X[k]		X[k]	X[l]	
CLL baseline assessments[m]	X											
PK/PD plasma sampling[n]		X			X	X						
Bone marrow aspirate/biopsy	X[o]							X[p]		X[p]		
Biomarker – tumor tissue[q]	X											
Biomarker – plasma tumor DNA[r]		X				X					X	
Biomarker – plasma cytokines[s]		X			X	X					X	
Biomarker – PBMC/B cell[t]	X											
Biomarker – saliva[u]	X											
LAM-002A administration in clinic[v]		X			X	X						
Adverse events		Throughout Study										
Concomitant medications[w]		Throughout Study										
Long-term follow-up (F/U)[x]												X

A Eligibility will be confirmed by C1D1.
B Complete physical examination (PE) will be performed at screening. A directed PE, including weight, will be performed within 72 hours prior to the start of each cycle and EOT.
C Assessment/test does not need to be repeated on C1D1 if baseline was within normal limits and conducted within 72 hours of first dose.
D Obtained on Day 1 for all cycles. For C1D1 and C1D8 obtained prior to dosing and 1 hour (± 15 minutes after dosing), 2 hours (± 30 minutes), 4 hours (± 1 hour), and 8 hours (± 1 hour) postdose. For C1D15, obtained prior to dosing.
E Hematology includes hemoglobin, hematocrit, RBC count, platelet count, WBC and differential.
F All hematology and chemistry laboratory parameters should be assessed at Screening and at C1D1, C1D8, C1D15, C≥2D1 (all subsequent cycles), and then at least once prior to the start of all subsequent cycles and at EOT. Obtaining a chemistry laboratory parameter on Days 2 and Day 3 of Cycle 1 is only required in subjects with intermediate or high risk of TLS (per the risk definition in Section 6.8.1). Except for Days 1, 2, and 3 of Cycle 1, these parameters may be obtained within 72 hours prior to the planned day of collection. Abnormal test values should be monitored per protocol guidance.
G Chemistry includes albumin, alkaline phosphatase, total bilirubin, BUN, calcium, carbon dioxide, chloride, creatinine, glucose, inorganic phosphorus, potassium, total protein, LDH, ALT, AST, sodium, and uric acid.
H Urinalysis includes appearance, specific gravity and pH as well as a semi-quantitative "dipstick" evaluation of glucose, protein, bilirubin, ketones, leukocytes, and blood. Microscopic examination of sediment will be performed if urinalysis is positive for WBC, proteins or blood. Urinalysis may be obtained within 72 hours prior to the planned day of collection.
I Pregnancy testing (serum or urine) will be required for women of childbearing potential (WCBP) only. Testing is required at Screening; within 72 hours of Day 1 of each cycle and at EOT. Test does not need to be repeated on C1D1 if baseline was negative and conducted within 72 hours of first dose.
J Imaging as appropriate for disease indication will be conducted within 30 days of the first dose of study treatment. Suitable scans performed prior to screening and within 30 days before first dose may be used for baseline tumor assessments.
K Assessment of disease status will be conducted with standard clinical measurements: PE, CBCs, bone marrow aspirates/biopsies, and imaging as appropriate for indication. During treatment, scans will be repeated for tumor assessment within 7 days of Day 1, Cycles 3, 5, and 7 then every 3 months until PD or use of alternative antineoplastic therapy. For subjects still in response after 1 year, intervals for radiographic surveillance may be every 6 months. Subjects with CLL who achieve CR will require assessment of MRD by flow cytometry of bone marrow and peripheral blood.
L Imaging at EOT is not required if PD has already been radiographically documented or last imaging was within 30 days of EOT visit.
M Subjects with CLL/SLL must provide either a fresh blood sample containing circulating tumor cells or a bone marrow aspirate sample pretreatment. Tissue will be submitted for evaluation of the percentage of tumor cells and analysis of genetic alterations and/or gene expression that may predict anticancer activity and/or pharmacodynamic activity. In addition, for subjects with CLL/SLL, the sponsor may arrange for a portion of the sample to be evaluated at a sponsor-specified laboratory for known prognostic markers (e.g., quantitative immunoglobulins, FISH panel [chromosome 11q deletion, 13q deletion, 17p deletion and 12 trisomy], DNA mutational analysis for p53, IgHV [including IgHV3-21], and other genes of interest in CLL [e.g., Notch]; flow cytometry [for CD5, CD10, CD11c, CD19, CD20, CD23, CD38, CD45, kappa and lambda light chains and ZAP-70], and/or β2-microglobulin). The baseline bone marrow aspiration procedure (if required) should be performed after the study candidate has undergone the baseline radiology examination and is otherwise considered eligible for study participation. All subjects with CLL/SLL must have baseline imaging (with CT scans [preferred] or MRI scans).
N Blood sampling for determination of the plasma concentrations and activity of LAM-002A and metabolites will be performed on C1D1 and C1D8 as follows: pre-dose, 30 minutes, 1, 2, 4, 6, 8 hours post-first dose of the day. Sampling on C1D15 will be pre-dose only. Subjects are required to come to the study site in a fasting state prior to the collection of certain PK samples.

O Bone marrow aspirates/biopsies performed within 2 months prior to first dose may be used for clinical baseline assessments. For subjects with NHL, baseline bone marrow biopsies/aspirates may be omitted if not deemed essential for response assessment or patient management and there is another source of tumor tissue for pretreatment evaluation of gene expression and prognosis. For subjects with CLL/SLL, a baseline bone marrow aspirate is required unless the presence of sufficient circulating cells in the peripheral blood (e.g., absolute lymphocyte count [ALC] ≥ 10 x 10^9/L) permits assessment of baseline parameters as described in Footnote m, above.

P If necessary per applicable response criteria, a repeat bone marrow biopsy or aspirate will be required for subjects who have a CR by imaging and physical examination.

Q Fresh tumor tissue (preferred) or archival tissue from the most recent available biopsy or surgery (within 4 months prior to the start of screening) must be obtained pretreatment for nucleic acid extraction. For subjects undergoing a biopsy, adequate tumor tissue should be acquired via excisional biopsy, incisional biopsy or core needle biopsy (e.g., ≥ 3 passes using a 16-gauge core needle). Confirmation of tumor in biopsy with fine needle aspirate, touch prep, or FFPE processing is requested when possible. The tumor lesion selected should not have been previously irradiated and should not be an index lesion that is followed for response assessment. Alternatively, cells from a bone marrow aspirate may be obtained in subjects with bone marrow involvement due to NHL (≥50% of cells). Tissue will be submitted for evaluation of the percentage of tumor cells and analysis of genetic alterations and/or gene expression that may predict anti-lymphoma activity and/or pharmacodynamics activity. In addition, the fresh biopsy or tumor tissue from the most recently availably biopsy or surgery will be evaluated for known prognostic characteristics (e.g., for DLBCL: ABC or GCB subtype; expression of BCL2, BCL6, Ki-67, CD20, and MYC; other mutational status), for PDL1 status, and for immune infiltration. The baseline biopsy procedure (if required) should ideally be performed after the study candidate has undergone the baseline radiology examination and is otherwise considered eligible for study participation.

R Plasma will be collected on C1D1 pretreatment, on C1D15 pretreatment, and at EOT visit for evaluation of circulating tumor DNA to measure tumor burden and mutational changes.

S Plasma will be collected for evaluation of circulating cytokines (including IL-12 and IL-23) predose on each of C1D1, C1D8, and C1D15 and at EOT.

T PBMCs/B-cells will be collected during Screening for determination of changes in gene expression that may predict or correlate with anti-lymphoma activity and/or pharmacodynamic activity and will also serve as normal-tissue controls for gene mutation studies in tumors.

U Saliva will be obtained during Screening as a normal-tissue control for gene mutation studies in tumors.

V LAM-002A to be administered to the subject in clinic (with recording of the date and actual clock time of the LAM-002A administration).

W Information on concomitant medications and other treatments will be collected from 14 days prior to informed consent through 30-37 days after the last dose of study drug.

X Subjects who have discontinued study treatment for reasons other than PD will be assessed per Revised Response Criteria for NHL or Guidelines for the diagnosis and treatment of CLL at a minimum of every 12 weeks until documentation of PD, start of new anti-cancer therapy or for up to 1 year from the last enrolled subject's first treatment (C1D1) whichever comes first. Long-term follow-up survival information will be obtained in all surviving subjects who permanently discontinue study therapy. Such information may be collected at ~3- to 6-month intervals at the sponsor's discretion through 3 years. This long-term follow-up information will be gathered during routine clinic visits, other study site contact with the subjects, or via telephone or e-mail with the subjects/caregivers or referring physician offices.

Abbreviations: ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BID, twice per day; BUN: Blood urea nitrogen; CBCs: Complete blood counts; CD: Cluster of differentiation; CLL: Chronic lymphocytic leukemia; CR: Complete response; CT: Computerized tomography; ECG: Electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOT: End of treatment; FISH: Fluorescence *in situ* hybridization; h: Hour; hrs: Hours; LDH: Lactate dehydrogenase; min: Minutes; MRD: Minimal residual disease; MRI: Magnetic Resonance Imaging; PBMC: Peripheral blood mononuclear cell; PD: Progressive disease; PE: Physical exam; PET: Positron emission tomography; PK: Pharmacokinetics; QTc: Corrected QT interval; RBC: Red blood cell; SAE: Serious adverse event; TLS: tumor lysis syndrome; WBC: White blood cell; WCBP: Women of child bearing potential

Table 9: Schedule of Assessments (LAM-002A Intermittent Monotherapy Administration)

Assessment	Screening	Cycle 1						Cycle 2		Cycle ≥ 3		End of Treatment (EOT)	Long-Term F/U
		Day						Day		Day			
	-28 to -1	1	2	3	8	10	15	1	15-28	1	15-28		
Informed consent	X												
Inclusion/exclusion criteria	X	X[a]											
Demographics	X												
Medical history	X												
Signs and symptoms, PE[b]	X	X[c]						X		X		X	
ECOG performance status	X	X[c]						X		X		X	
Vital signs	X	X[d]			X	X[d]	X[d]	X		X		X	
ECG	X	X[d]			X	X[d]		X		X		X	
HIV, HBV, and HCV serology	X												
Hematology[e, f]	X	X			X		X	X		X		X	
Serum chemistry[f, g]	X	X	X[f]	X[f]	X		X	X		X		X	
Coagulation	X												
Urinalysis[h]	X	X[c]						X		X		X	
Pregnancy testing[i]	X	X[i]						X		X		X	
PET/CT or CT (or MRI) scans (based on indication) for response assessment	X[j]								X[k]		X[k]	X[l]	
CLL baseline assessments[m]	X												
PK/PD plasma sampling[n]		X			X	X	X						
Bone marrow aspirate/biopsy	X[o]								X[p]		X[p]		
Biomarker – tumor tissue[q]	X												
Biomarker – plasma tumor DNA[r]		X					X					X	
Biomarker – plasma cytokines[s]		X			X	X	X					X	
Biomarker – PBMC/B cell[t]	X												
Biomarker – saliva[u]	X												
LAM-002A administration in clinic[v]		X			X	X	X						
Adverse events		Throughout Study											
Concomitant medications[w]		Throughout Study											
Long-term follow-up (F/U)[x]													X

A Eligibility will be confirmed by C1D1.
B Complete physical examination (PE) will be performed at screening. A directed PE, including weight, will be performed within 72 hours prior to the start of each cycle and EOT.
C Assessment/test does not need to be repeated on C1D1 if baseline was within normal limits and conducted within 72 hours of first dose.
D Obtained on Day 1 for all cycles. For C1D1 and C1D10 obtained prior to dosing and 1 hour (± 15 minutes after dosing), 2 hours (± 30 minutes), 4 hours (± 1 hour), and 8 hours (± 1 hour) postdose. For C1D8 and C1D15, obtained prior to dosing.
E Hematology includes hemoglobin, hematocrit, RBC count, platelet count, WBC and differential.
F All hematology and chemistry laboratory parameters should be assessed at Screening and C1D1, C1D8, C1D15, C≥2D1 (all subsequent cycles), and then at least once prior to the start of all subsequent cycles and at EOT. Obtaining a chemistry laboratory parameter on Days 2 and Day 3 of Cycle 1 is only required in subjects with intermediate or high risk of TLS (per the risk definition in Section 6.8.1). Except for Days 1, 2, and 3 of Cycle 1, these parameters may be obtained within 72 hours prior to the planned day of collection. Abnormal test values should be monitored per protocol guidance.
G Chemistry includes albumin, alkaline phosphatase, total bilirubin, BUN, calcium, carbon dioxide, chloride, creatinine, glucose, inorganic phosphorus, potassium, total protein, LDH, ALT, AST, sodium, and uric acid.
H Urinalysis includes appearance, specific gravity and pH as well as a semi-quantitative “dipstick” evaluation of glucose, protein, bilirubin, ketones, leukocytes, and blood. Microscopic examination of sediment will be performed if urinalysis is positive for WBC, proteins or blood. Urinalysis may be obtained within 72 hours prior to the planned day of collection.
I Pregnancy testing (serum or urine) will be required for women of childbearing potential (WCBP) only. Testing is required at Screening; within 72 hours of Day 1 of each cycle and at EOT. Test does not need to be repeated on C1D1 if baseline was negative and conducted within 72 hours of first dose.
J Imaging as appropriate for disease indication will be conducted within 30 days of the first dose of study treatment. Suitable scans performed prior to screening and within 30 days before first dose may be used for baseline tumor assessments.
K Assessment of disease status will be conducted with standard clinical measurements: PE, CBCs, bone marrow aspirates/biopsies, and imaging as appropriate for indication. During treatment, scans will be repeated for tumor assessment within 7 days of Day 1, Cycles 3, 5, and 7 then every 3 months until PD or use of alternative antineoplastic therapy. For subjects still in response after 1 year, intervals for radiographic surveillance may be every 6 months. Subjects with CLL who achieve CR will require assessment of MRD by flow cytometry of bone marrow and peripheral blood.
L Imaging at EOT is not required if PD has already been radiographically documented or last imaging was within 30 days of EOT visit.
M Subjects with CLL/SLL must provide either a fresh blood sample containing circulating tumor cells or a bone marrow aspirate sample pretreatment. Tissue will be submitted for evaluation of the percentage of tumor cells and analysis of genetic alterations and/or gene expression that may predict anticancer activity and/or pharmacodynamic activity. In addition, for subjects with CLL/SLL, the sponsor may arrange for a portion of the sample to be evaluated at a sponsor-specified laboratory for known prognostic markers (e.g., quantitative immunoglobulins, FISH panel [chromosome 11q deletion, 13q deletion, 17p deletion and 12 trisomy], DNA mutational analysis for p53, IgHV [including IgHV3-21], and other genes of interest in CLL [e.g., Notch]; flow cytometry [for CD5, CD10, CD11c, CD19, CD20, CD23, CD38, CD45, kappa and lambda light chains and ZAP-70], and/or β2-microglobulin). The baseline bone marrow aspiration procedure (if required) should be performed after the study candidate has undergone the baseline radiology examination and is otherwise considered eligible for study participation. All subjects with CLL/SLL must have baseline imaging (with CT scans [preferred] or MRI scans).
N Blood sampling for determination of the plasma concentrations and activity of LAM-002A and metabolites will be performed on C1D1 and C1D10 as follows: pre-dose, 30 minutes, 1, 2, 4, 6, 8 hours post-first dose of the day. Sampling on C1D8 and C1D15 will be pre-dose only. Subjects are required to come to the study site in a fasting state prior to the collection of certain PK samples.

O Bone marrow aspirates/biopsies performed within 2 months prior to first dose may be used for clinical baseline assessments. For subjects with NHL, baseline bone marrow biopsies/aspirates may be omitted if not deemed essential for response assessment or patient management and there is another source of tumor tissue for pretreatment evaluation of gene expression and prognosis. For subjects with CLL/SLL, a baseline bone marrow aspirate is required unless the presence of sufficient circulating cells in the peripheral blood (e.g., absolute lymphocyte count [ALC] ≥ 10 x 10^9/L) permits assessment of baseline parameters as described in Footnote m, above.

P If necessary per applicable response criteria, a repeat bone marrow biopsy or aspirate will be required for subjects who have a CR by imaging and physical examination.

Q Fresh tumor tissue (preferred) or archival tissue from the most recent available biopsy or surgery (within 4 months prior to the start of screening) must be obtained pretreatment for nucleic acid extraction. For subjects undergoing a biopsy, adequate tumor tissue should be acquired via excisional biopsy, incisional biopsy or core needle biopsy (e.g., ≥ 3 passes using a 16-gauge core needle). Confirmation of tumor in biopsy with fine needle aspirate, touch prep, or FFPE processing is requested when possible. The tumor lesion selected should not have been previously irradiated and should not be an index lesion that is followed for response assessment. Alternatively, cells from a bone marrow aspirate may be obtained in subjects with bone marrow involvement due to NHL (≥50% of cells). Tissue will be submitted for evaluation of the percentage of tumor cells and analysis of genetic alterations and/or gene expression that may predict anti-lymphoma activity and/or pharmacodynamics activity. In addition, the fresh biopsy or tumor tissue from the most recently availably biopsy or surgery will be evaluated for known prognostic characteristics (e.g., for DLBCL: ABC or GCB subtype; expression of BCL2, BCL6, Ki-67, CD20, and MYC; other mutational status), for PDL1 status, and for immune infiltration. The baseline biopsy procedure (if required) should ideally be performed after the study candidate has undergone the baseline radiology examination and is otherwise considered eligible for study participation.

R Plasma will be collected on C1D1 (predose), on C1D15 (predose), and at EOT visit for evaluation of circulating tumor DNA to measure tumor burden and mutational changes.

S Plasma will be collected for evaluation of circulating cytokines (including IL-12 and IL-23) on C1D1 (predose), C1D8 (predose), C1D10 (predose), and C1D15 (predose) and at EOT.

T PBMCs/B-cells will be collected during Screening for determination of changes in gene expression that may predict or correlate with anti-lymphoma activity and/or pharmacodynamic activity and will also serve as normal-tissue controls for gene mutation studies in tumors.

U Saliva will be obtained during Screening as a normal-tissue control for gene mutation studies in tumors.

V LAM-002A to be administered with antiemetic prophylaxis according to intermittent schedule (see Section 6.8.2.1, Section 6.8.2.2, and Section 6.8.2.3). On the designated days the subject will take LAM-002A in the clinic (with recording of the date and actual clock time of the LAM-002A administration).

W Information on concomitant medications and other treatments will be collected from 14 days prior to informed consent through 30-37 days after the last dose of study drug.

X Subjects who have discontinued study treatment for reasons other than PD will be assessed per Revised Response Criteria for NHL or Guidelines for the diagnosis and treatment of CLL at a minimum of every 12 weeks until documentation of PD, start of new anti-cancer therapy or for up to 1 year from the last enrolled subject's first treatment (C1D1) whichever comes first. Long-term follow-up survival information will be obtained in all surviving subjects who permanently discontinue study therapy. Such information may be collected at ~3- to 6-month intervals at the sponsor's discretion through 3 years. This long-term follow-up information will be gathered during routine clinic visits, other study site contact with the subjects, or via telephone or e-mail with the subjects/caregivers or referring physician offices.

Abbreviations: ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BID, twice per day; BUN: Blood urea nitrogen; CBCs: Complete blood counts; CD: Cluster of differentiation; CLL: Chronic lymphocytic leukemia; CR: Complete response; CT: Computerized tomography; ECG: Electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOT: End of treatment; FISH: Fluorescence in situ hybridization; h: Hour; hrs: Hours; LDH: Lactate dehydrogenase; min: Minutes; MRD: Minimal residual disease; MRI: Magnetic Resonance Imaging; PBMC: Peripheral blood mononuclear cell; PD: Progressive disease; PE: Physical exam; PET: Positron emission tomography; PK: Pharmacokinetics; QTc: Corrected QT interval; RBC: Red blood cell; SAE: Serious adverse event; TLS: tumor lysis syndrome; WBC: White blood cell; WCBP: Women of child bearing potential

Table 10: Schedule of Assessments (LAM-002A/Rituximab Combination Therapy)

Assessment	Screening	Cycle 1						Cycles ≥2		End of Treatment (EOT)	Long-Term F/U
		Day						Day			
	-28 to -1	1	2	3	8	15	22	1	22-28		
Informed consent	X										
Inclusion/exclusion criteria	X	X[a]									
Demographics	X										
Medical history	X										
Signs and symptoms, PE[b]	X	X[c]						X		X	
ECOG performance Status	X	X[c]						X		X	
Vital signs	X	X[d]			X[d]	X[d]		X		X	
ECG	X	X[d]			X[d]	X[d]		X		X	
HIV, HBV, and HCV serology	X										
Hematology[e, f]	X	X			X	X	X	X		X	
Serum chemistry[f, g]	X	X	X[f]	X[f]	X	X	X	X		X	
Coagulation	X										
Urinalysis[h]	X	X[c]						X		X	
Pregnancy testing[i]	X	X[i]						X		X	
PET/CT or CT (or MRI) scans (based on indication) for response assessment	X[j]								X[k]	X[l]	
PK/PD sampling[m]		X			X	X					
Bone marrow aspirate/biopsy	X[n]								X[o]		
Biomarker – tumor tissue[p]	X										
Biomarker – plasma tumor DNA[q]		X				X				X	
Biomarker – plasma cytokines[r]		X			X	X				X	
Biomarker – PBMC/B cell[s]	X										
Biomarker – saliva[t]	X										
Premedication[u]		X			X	X	X	X[u]			
LAM-002A administration in clinic[v]		X			X	X					
Rituximab infusion/injection[w]		X			X	X	X	X[w]			
Adverse events		Throughout study									
Concomitant medications[x]		Throughout study									
Long-term F/U[y]											X

A Eligibility will be confirmed by C1D1.
B Complete PE will be performed at Screening. A directed PE, including weight, will be performed within 72 hours prior to the start of each cycle and EOT.
C Assessment/test does not need to be repeated on C1D1 if baseline was within normal limits and conducted within 72 hours of first dose.
D Obtained on Day 1 for all cycles. For C1D1 and C1D8 obtained prior to dosing and 1 hour (± 15 minutes after dosing), 2 hours (± 30 minutes), 4 hours (± 1 hour), and 8 hours (± 1 hour) postdose. For C1D15, obtained prior to dosing.
E Hematology includes hemoglobin, hematocrit, RBC count, platelet count, WBC and differential.
F All hematology and chemistry laboratory parameters should be assessed at Screening, on C1D1, C1D8, C1D15, C≥2D1 (all subsequent cycles), and at EOT. Obtaining a chemistry laboratory parameter on C1D2 and C1D3 is only required in subjects with intermediate or high risk of TLS (per the risk definition in Section 6.8.1). Except for C1D1, C1D2, and C1D3, these parameters may be obtained within 72 hours prior to the planned day of collection.
G Serum chemistry includes albumin, alkaline phosphatase, total bilirubin, BUN, calcium, carbon dioxide, chloride, creatinine, glucose, inorganic phosphorus, potassium, total protein, LDH, ALT, AST, sodium, and uric acid.
H Urinalysis includes appearance, specific gravity and pH as well as a semi-quantitative "dipstick" evaluation of glucose, protein, bilirubin, ketones, leukocytes, and blood. Microscopic examination of sediment will be performed if urinalysis is positive for WBC, proteins or blood. Urinalysis may be obtained within 72 hours prior to the planned day of collection.
I Pregnancy testing (serum or urine) will be required for women of childbearing potential (WCBP) only. Testing is required at Screening; within 72 hours of Day 1 of each cycle and at EOT. Test does not need to be repeated on C1D1 if baseline was negative and conducted within 72 hours of first dose.
J Imaging as appropriate for disease indication will be conducted within 30 days before C1D1. Suitable scans performed prior to Screening and within 30 days before first dose may be used for baseline tumor assessments.
K Assessment of disease status will be conducted with standard imaging as appropriate for indication. During treatment, scans will be repeated for tumor assessment within 7 days before C3D1, C5D1, C7D1, and then every 3 cycles (12 weeks) until PD or use of alternative antineoplastic therapy.
L Imaging at EOT is not required if PD has already been radiographically documented or last imaging was within 4 weeks of EOT visit.
M Blood sampling for determination of the plasma concentrations and activity of LAM-002A and metabolites will be performed on C1D1 and C1D8 as follows: pre-dose, 30 minutes, 1, 2, 4, 6, 8 hours post-first dose of the day. Sampling on C1D15 will be pre-dose only. Subjects are required to come to the study site in a fasting state prior to the collection of certain PK samples.
N Bone marrow aspirates/biopsies performed within 2 months prior to first dose may be used for clinical baseline assessments. Baseline bone marrow biopsies/aspirates may be omitted if not deemed essential for response assessment or patient management and there is another source of tumor tissue for pretreatment evaluation of gene expression and prognosis.
O If necessary per applicable response criteria, a repeat bone marrow biopsy or aspirate will be required for subjects who have a CR by imaging and PE
p Fresh tumor tissue (preferred) or archival tissue from the most recent available biopsy or surgery (within 4 months prior to the start of screening) must be obtained pretreatment for nucleic acid extraction. For subjects undergoing a biopsy, adequate tumor tissue should be acquired via excisional biopsy, incisional biopsy or core needle biopsy (e.g., ≥ 3 passes using a 16-gauge core needle). Confirmation of tumor in biopsy with fine needle aspirate, touch prep, or FFPE processing is requested when possible. The tumor lesion selected should not have been previously irradiated and should not be an index lesion that is followed for response assessment. Alternatively, cells from a bone marrow aspirate may be obtained in subjects with bone marrow involvement due to NHL (≥50% of cells). Tissue will be submitted for evaluation of the percentage of tumor cells and analysis of genetic alterations and/or gene expression that may predict anti-lymphoma activity and/or pharmacodynamics activity. In addition, the fresh biopsy or tumor tissue from the most recently availably biopsy or surgery will be evaluated for known prognostic characteristics (e.g., for DLBCL: ABC or GCB subtype; expression of BCL2, BCL6, Ki-67, CD20, and MYC; other mutational status), for PDL1 status, and for immune infiltration. The baseline biopsy procedure (if required) should ideally be performed after the study candidate has undergone the baseline radiology examination and is otherwise considered eligible for study participation.
Q Plasma will be collected on C1D1 (predose), on C1D15 (predose), and at EOT visit for evaluation of circulating tumor DNA to measure tumor burden and mutational changes.

R Plasma will be collected for evaluation of circulating cytokines (including IL-12 and IL-23) on C1D1 (predose), C1D8 (predose), and C1D15 (predose) and at EOT.

S PBMCs/B-cells will be collected during Screening for determination of changes in gene expression that may predict or correlate with anti-lymphoma activity and/or pharmacodynamic activity and will also serve as normal-tissue controls for gene mutation studies in tumors.

T Saliva will be obtained during Screening as a normal-tissue control for gene mutation studies in tumors.

U Oral antipyretic, oral or intravenous antihistamine, and intravenous corticosteroid (at investigator discretion) (see Section 6.8.3.1) to be administered to the subject ~30 minutes prior to each rituximab infusion/injection (see Footnote w).

v LAM-002A to be administered to the subject in clinic (with recording of the date and actual clock time of the LAM-002A administration). On C1D1, LAM-002A will be started on a BID schedule after administration of premedications (see Section 6.8.3.1) and ~15 to 30 minutes prior to the start of the initial rituximab infusion. On C1D8, the morning dose of LAM-002A will be administered after premedications (see Section 6.8.3.1) and ~15 to 30 minutes prior to the rituximab infusion/injection.

W Rituximab, 375 mg/m^2, will be administered by intravenous infusion ~30 minutes after premedication weekly on C1D1, C1D8, C1D15, and C1D22 and then every 8 weeks on C4D1, C6D1, C8D1, and C10D1 for a total of 8 infusions. Alternatively, rituximab, 375 mg/m^2, will be administered by intravenous infusion ~30 minutes after premedication weekly on C1D1 and then rituximab hyaluronidase human, 1,400 mg rituximab and 23,400 Units hyaluronidase human per 11.7 mL, will be administered by subcutaneous injection on C1D8, C1D15, and C1D22 and then every 8 weeks on C4D1, C6D1, C8D1, and C10D1 for a total of 8 treatments.

X Information on concomitant medications and other treatments will be collected from 14 days prior to informed consent through 30-37 days after the last dose of study drug.

Y Subjects who have discontinued study treatment for reasons other than PD will be assessed at a minimum of every 12 weeks until documentation of PD, start of new anti-cancer therapy or for up to 1 year from the last enrolled subject's first treatment (C1D1) whichever comes first. Long-term follow-up survival information will be obtained in all surviving subjects who permanently discontinue study therapy. Such information may be collected at ~3- to 6-month intervals at the sponsor's discretion through 3 years. This long-term follow-up information will be gathered during routine clinic visits, other study site contact with the subjects, or via telephone or e-mail with the subjects/caregivers or referring physician offices.

Abbreviations: ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BID: twice per day; BUN: Blood urea nitrogen; CBCs: Complete blood counts; CD: Cluster of differentiation; CLL: Chronic lymphocytic leukemia; CR: Complete response; CT: Computerized tomography; ECG: Electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOT: End of treatment; FISH: Fluorescence *in situ* hybridization; F/U: Follow-up; LDH: Lactate dehydrogenase; MRI: Magnetic Resonance Imaging; PBMC: Peripheral blood mononuclear cell; PD: Progressive disease; PDL1: programmed death ligand-1; PE: Physical exam; PET: Positron emission tomography; PK: Pharmacokinetics; QTc: Corrected QT interval; RBC: Red blood cell; SAE: Serious adverse event; TLS: tumor lysis syndrome; WBC: White blood cell; WCBP: Women of child-bearing potential

Table 11: Schedule of Assessments (LAM-002A/Atezolizumab Combination Therapy)

Assessment	Screening	Cycle 1 Day					Cycles ≥2 Day		End of Treatment (EOT)	Long-Term F/U
	-28 to -1	1	2	3	8	15	1	15-22		
Informed consent	X									
Inclusion/exclusion criteria	X	X[a]								
Demographics	X									
Medical history	X									
Signs and symptoms, PE[b]	X	X[c]					X		X	
ECOG performance Status	X	X[c]					X		X	
Vital signs	X	X[d]			X[d]	X[d]	X		X	
ECG	X	X[d]			X[d]	X[d]	X		X	
HIV, HBV, and HCV serology	X									
Hematology[e, f]	X	X			X	X	X		X	
Serum chemistry[f, g]	X	X	X[f]	X[f]	X	X	X		X	
Serum thyroid function[h]	X						X			
Coagulation	X									
Urinalysis[i]	X	X[c]					X		X	
Pregnancy testing	X	X[j]					X		X	
PET/CT or CT (or MRI) scans (based on indication) for response assessment	X[k]							X[l]	X[m]	
PK/PD sampling[n]		X			X	X				
Bone marrow aspirate/biopsy	X[o]							X[p]		
Biomarker – tumor tissue[q]	X									
Biomarker – plasma tumor DNA[r]		X				X			X	
Biomarker – plasma cytokines[s]		X			X	X	X		X	
Biomarker – PBMC/B cells[t]	X									
Biomarker – saliva[u]	X									
LAM-002A administration in clinic[v]		X			X	X				
Atezolizumab infusion[w]		X					X[w]			
Adverse events		Throughout study								
Concomitant medications[x]		Throughout study								
Long-term F/U[y]										X

A Eligibility will be confirmed by C1D1.
B Complete PE will be performed at Screening. A directed PE, including weight, will be performed within 72 hours prior to the start of each cycle and EOT.
C Assessment/test does not need to be repeated on C1D1 if baseline was within normal limits and conducted within 72 hours of first dose.
D Obtained on Day 1 for all cycles. For C1D1 and C1D8 obtained prior to dosing and 1 hour (± 15 minutes after dosing), 2 hours (± 30 minutes), 4 hours (± 1 hour), and 8 hours (± 1 hour) postdose. For C1D15, obtained prior to dosing.
E Hematology includes hemoglobin, hematocrit, RBC count, platelet count, WBC and differential.
F All hematology and chemistry laboratory parameters should be assessed at Screening, on C1D1, C1D8, C1D15, C≥2D1 (all subsequent cycles), and at EOT. Obtaining a chemistry laboratory parameter on C1D2 and C1D3 is only required in subjects with intermediate or high risk of TLS (per the risk definition in Section 6.8.1). Except for C1D1, C1D2, and C1D3, these parameters may be obtained within 72 hours prior to the planned day of collection.
G Serum chemistry includes albumin, alkaline phosphatase, total bilirubin, BUN, calcium, carbon dioxide, chloride, creatinine, glucose, inorganic phosphorus, potassium, total protein, LDH, ALT, AST, sodium, and uric acid.
H Serum thyroid function tests include TSH, free T3, and free T4 at C3D1, C5D1, C7D1, C9D1, and then every 4 cycles (12 weeks)..
i Urinalysis includes appearance, specific gravity and pH as well as a semi-quantitative "dipstick" evaluation of glucose, protein, bilirubin, ketones, leukocytes, and blood. Microscopic examination of sediment will be performed if urinalysis is positive for WBC, proteins or blood. Urinalysis may be obtained within 72 hours prior to the planned day of collection.
J Pregnancy testing (serum or urine) will be required for women of childbearing potential (WCBP) only. Testing is required at Screening; within 72 hours of Day 1 of each cycle and at EOT. Test does not need to be repeated on C1D1 if baseline was negative and conducted within 72 hours of first dose.
K Imaging as appropriate for disease indication will be conducted within 30 days before C1D1. Suitable scans performed prior to Screening and within 30 days before first dose may be used for baseline tumor assessments.
L Assessment of disease status will be conducted with standard imaging as appropriate for indication. During treatment, scans will be repeated for tumor assessment within 7 days before C3D1, C5D1, C7D1, C9D1, and then every 4 cycles (12 weeks) until PD or use of alternative antineoplastic therapy.
M Imaging at EOT is not required if PD has already been radiographically documented or last imaging was within 4 weeks of EOT visit.
N Blood sampling for determination of the plasma concentrations and activity of LAM-002A and metabolites will be performed on C1D1 and C1D8 as follows: pre-dose, 30 minutes, 1, 2, 4, 6, 8 hours post-first dose of the day. Sampling on C1D15 will be pre-dose only. Subjects are required to come to the study site in a fasting state prior to the collection of certain PK samples.
O Bone marrow aspirates/biopsies performed within 2 months prior to first dose may be used for clinical baseline assessments. Baseline bone marrow biopsies/aspirates may be omitted if not deemed essential for response assessment or patient management and there is another source of tumor tissue for pretreatment evaluation of gene expression and prognosis.
P If necessary per applicable response criteria, a repeat bone marrow biopsy or aspirate will be required for subjects who have a CR by imaging and PE.
Q Fresh tumor tissue (preferred) or archival tissue from the most recent available biopsy or surgery (within 4 months prior to the start of screening) must be obtained pretreatment for nucleic acid extraction. For subjects undergoing a biopsy, adequate tumor tissue should be acquired via excisional biopsy, incisional biopsy or core needle biopsy (e.g., ≥ 3 passes using a 16-gauge core needle). Confirmation of tumor in biopsy with fine needle aspirate, touch prep, or FFPE processing is requested when possible. The tumor lesion selected should not have been previously irradiated and should not be an index lesion that is followed for response assessment. Alternatively, cells from a bone marrow aspirate may be obtained in subjects with bone marrow involvement due to NHL (≥50% of cells). Tissue will be submitted for evaluation of the percentage of tumor cells and analysis of genetic alterations and/or gene expression that may predict anti-lymphoma activity and/or pharmacodynamics activity. In addition, the fresh biopsy or tumor tissue from the most recently availably biopsy or surgery will be evaluated for known prognostic characteristics (e.g., for DLBCL: ABC or GCB subtype; expression of BCL2, BCL6, Ki-67, CD20, and MYC; other mutational status), for PDL1 status, and for immune infiltration. The baseline biopsy procedure (if required) should ideally be performed after the study candidate has undergone the baseline radiology examination and is otherwise considered eligible for study participation.

R Plasma will be collected on C1D1 (predose), on C1D15 (predose), and at EOT visit for evaluation of circulating tumor DNA to measure tumor burden and mutational changes.

S Plasma will be collected for evaluation of circulating cytokines (including IL-12 and IL-23) on C1D1 (predose), C1D8 (predose), C1D15 (predose), C2D1, and at EOT.

T PBMCs/B-cells will be collected during Screening for determination of changes in gene expression that may predict or correlate with anti-lymphoma activity and/or pharmacodynamic activity and will also serve as normal-tissue controls for gene mutation studies in tumors.

U Saliva will be obtained during Screening as a normal-tissue control for gene mutation studies in tumors.

V LAM-002A to be administered to the subject in clinic (with recording of the date and actual clock time of the LAM-002A administration). On C1D1, LAM-002A will be started on a BID schedule after administration of premedications (see Section 6.8.3.1) and ~15 to 30 minutes prior to the start of the initial atezolizumab infusion. On C1D8, the morning dose of LAM-002A will be administered after premedications (see Section 6.8.3.1) and ~15 to 30 minutes prior to the atezolizumab infusion

w Atezolizumab, 1200 mg, will be administered by intravenous infusion over ~30 minutes every 3 weeks.

X Information on concomitant medications and other treatments will be collected from 14 days prior to informed consent through 30-37 days after the last dose of study drug.

Y Subjects who have discontinued study treatment for reasons other than PD will be assessed at a minimum of every 12 weeks until documentation of PD, start of new anti-cancer therapy or for up to 1 year from the last enrolled subject's first treatment (C1D1) whichever comes first. Long-term follow-up survival information will be obtained in all surviving subjects who permanently discontinue study therapy. Such information may be collected at ~3- to 6-month intervals at the sponsor's discretion through 3 years. This long-term follow-up information will be gathered during routine clinic visits, other study site contact with the subjects, or via telephone or e-mail with the subjects/caregivers or referring physician offices.

Abbreviations: ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BID: twice per day; BUN: Blood urea nitrogen; CBCs: Complete blood counts; CD: Cluster of differentiation; CLL: Chronic lymphocytic leukemia; CR: Complete response; CT: Computerized tomography; ECG: Electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOT: End of treatment; FISH: Fluorescence *in situ* hybridization; F/U: Follow-up; LDH: Lactate dehydrogenase; MRI: Magnetic Resonance Imaging; PBMC: Peripheral blood mononuclear cell; PD: Progressive disease; PE: Physical exam; PET: Positron emission tomography; PK: Pharmacokinetics; QTc: Corrected QT interval; RBC: Red blood cell; SAE: Serious adverse event; T3: triiodothyronine; T4: thyroxine; TLS: tumor lysis syndrome; TSH: thyroid-stimulating hormone; WBC: White blood cell; WCBP: Women of child-bearing potential

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. LAM-002A

9.1.1. Description

LAM-002A drug description is provided in Table 12.

Table 12: LAM-002A Drug Description

Product Name:	LAM-002A
Dosage Form:	Capsule
Unit Dose	25 mg or 50 mg
Route of Administration	Oral
Physical Description	Each capsule will contain 25 mg or 50 of apilimod dimesylate (equivalent to 17.1 mg or 34.3 mg of apilimod free base, respectively). The 25-mg capsule is Swedish orange and the 50-mg capsule is white. Both the 25- and 50-mg capsules are Size 0 and both have a total fill weight of 175 mg. Inactive components in active capsules are microcrystalline cellulose, silicified microcrystalline cellulose, anhydrous lactose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate.
Manufacturer	Patheon

9.1.2. LAM-002A Packaging and Labeling

LAM-002A will be provided in bulk bottles to each investigational pharmacy for dispensing. The pharmacist will dispense capsules into bottles for each subject (based on Cohort assignment) following applicable state and federal laws and site policies. Details on the labeling, dispensing, and administration of LAM-002A are provided in the Pharmacy Manual.

9.1.3. Source

LAM-002A will be provided by the sponsor.

9.1.4. Storage

The LAM-002A must be stored in a secure storage area, with limited access, under environmental conditions appropriate for the product. LAM-002A capsules should be stored at 2 to 8°C.

9.1.5. Accountability

LAM-002A will be dispensed to subjects in labeled bottles at the beginning of each cycle. Subjects should be instructed to bring all bottles, including empty bottles, to each Day 1 or End of Treatment study visit for a compliance and product accountability check. Returned LAM-002A should be retained for monitor review prior to destruction at the site, unless contraindicated by site standard operating procedures (SOPs). If contraindicated by the site SOP,

approval of site process by the sponsor must be obtained and filed in the pharmacy file and/or regulatory binder. The investigational pharmacy must maintain contemporary and accurate records on product receipt, storage temperature, stock, dispensation, return and disposal. These records should be available for review during monitoring visits and copies available for retrieval for the Trial Master File.

9.1.6. Handling and Disposal

LAM-002A accountability and inventory records will be inspected by the sponsor prior to final disposition. Instructions will be provided by the sponsor for shipment to and destruction of unused LAM-002A product by the designated packaging depot, to include unopened bulk bottles at the end of the study and expired product. Unused product returned by study subjects or opened bulk bottles will be destroyed by each site per site SOPs. LAM-002A should only be shipped or destroyed upon written authorization from the sponsor. Documentation of return of shipment, including a packing list and copy of the tracking label, should be retained in the Pharmacy and/or regulatory files.

9.2. Rituximab (for Intravenous Administration)

9.2.1. Description

Rituximab (Rituxan®, MabThera®) is a genetically engineered chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen found on pre-B and mature B cells (Genentech 2016). Rituximab is produced by mammalian Chinese hamster ovary cells. The protein has an approximate molecular weight of 145 kD.

The drug is provided as a clear, colorless, preservative-free liquid concentrate containing 10 mg/mL of rituximab. The product is formulated in 9 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dihydrate, 0.7 mg/mL polysorbate 80, and water for injection with a pH of 6.5.

9.2.2. Packaging

Rituximab is supplied in 100-mg (10-mL) or 500-mg (50-mL) single-use vials.

9.2.3. Source

Unless otherwise instructed by the sponsor, the rituximab to be used in this study may be obtained from available commercial supplies.

9.2.4. Storage and Stability

Rituximab vials are stable at 2°C–8°C (36°F–46°F). Vials should be protected from direct sunlight and should not be frozen or shaken.

Diluted rituximab solutions for infusion may be stored at 2°C–8°C (36°F–46°F) for 24 hours and are known to be stable for an additional 24 hours at room temperature. However, since rituximab solutions do not contain a preservative, diluted solutions should be stored refrigerated (2°C–8°C).

No incompatibilities between rituximab and polyvinylchloride or polyethylene bags have been observed.

9.2.5. Solution Preparation

Before use, the rituximab vials should be inspected for particulate matter or discoloration. Any vial with evidence of particulates or discoloration should not be used.

Using aseptic technique, the necessary amount of rituximab should be withdrawn from the vial and diluted to a final concentration of 1 to 4 mg/mL in an infusion bag containing either 0.9% Sodium Chloride, USP or 5% Dextrose in Water, USP. The bag should be gently inverted to mix the solution. The infusion solution should not be mixed or diluted with other drugs. Any unused portion of rituximab remaining in the vial should be discarded.

9.2.6. Accountability

Acquisition, storage, control, and disposal of rituximab used in the study should be performed according to institutional procedures and policies.

The investigator and/or the responsible site personnel must maintain accurate records of the source, dates of administration, quantities of administration, and lot numbers of the rituximab dispensed for this study.

9.3. Rituximab/Hyaluronidase Human (For Subcutaneous Administration)

9.3.1. Description

Rituximab/hyaluronidase human (Rituxan Hycela®) is a genetically engineered chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen found on pre-B and mature B cells. In this formulation, it is combined with hyaluronidase human, an endoglycosidase (Genentech 2018). Rituximab is produced by mammalian Chinese hamster ovary cells. The protein has an approximate molecular weight of 145 kD. Hyaluronidase human increases permeability of the subcutaneous tissue by temporarily depolymerizing hyaluronan.

The drug is provided as a colorless to yellowish, clear to opalescent, preservative-free liquid solution. Each mL of solution contains rituximab (120 mg), hyaluronidase human (2,000 Units), L-histidine (0.53 mg), L-histidine hydrochloride monohydrate (3.47 mg), L-methionine (1.49 mg), polysorbate 80 (0.6 mg), α,α-trehalose dihydrate (79.45 mg), and Water for Injection.

9.3.2. Packaging

For use in patients with FL/DLBCL, rituximab/hyaluronidase human is supplied in single-dose vials containing 1,400 mg rituximab and 23,400 Units hyaluronidase human per 11.7 mL of solution.

9.3.3. Source

Unless otherwise instructed by the sponsor, the rituximab/hyaluronidase human to be used in this study may be obtained from available commercial supplies.

9.3.4. Storage and Stability

Rituximab/hyaluronidase human vials are stable at 2°C-8°C (36°F-46°F). Vials should be protected from direct sunlight and should not be frozen or shaken.

Diluted rituximab/hyaluronidase human solutions for injection may be stored at 2°C-8°C (36°F-46°F) for 48 hours and are known to be stable for an additional 8 hours at room temperatures up to 30°C (86°F) in diffuse light. However, since rituximab solutions do not contain a preservative, solutions should be used as soon as possible after withdrawal from the vial.

Rituximab/hyaluronidase is compatible with polypropylene and polycarbonate syringe material and stainless-steel transfer and injection needles.

9.3.5. Preparation

Before use, the rituximab/hyaluronidase human vials should be inspected for particulate matter or discoloration. Any vial with evidence of particulates or discoloration should not be used.

Using aseptic technique, the entire 11.7 mL of rituximab/hyaluronidase human should be withdrawn from the vial via a hypodermic needle into a syringe and the vial should be discarded.

9.3.6. Accountability

Acquisition, storage, control, and disposal of rituximab/hyaluronidase used in the study should be performed according to institutional procedures and policies.

The investigator and/or the responsible site personnel must maintain accurate records of the source, dates of administration, quantities of administration, and lot numbers of the rituximab/hyaluronidase dispensed for this study.

9.4. Atezolizumab

9.4.1. Description

Atezolizumab (TECENTRIQ®) is an Fc-engineered, humanized, monoclonal antibody that binds to PD-L1 and blocks interactions with the PD-1 and B7.1 receptors (Genentech 2017). Atezolizumab is a non-glycosylated IgG1 kappa immunoglobulin that has a calculated molecular mass of 145 kDa.

The drug is provided as a sterile, preservative-free, colorless to slightly yellow solution in single-dose vials. Each mL of TECENTRIQ contains 60 mg of atezolizumab and is formulated in glacial acetic acid (16.5 mg), L-histidine (62 mg), sucrose (821.6 mg), polysorbate 20 (8 mg). The solution has a pH of 5.8.

9.4.2. Packaging

Atezolizumab is supplied in a carton containing one 1200-mg/20-mL single-dose vial.

9.4.3. Source

The atezolizumab to be used in this study will be supplied by Genentech, Inc. via the study sponsor (AI Therapeutics, Inc.).

9.4.4. Storage and Stability

Atezolizumab vials are stable at 2°C–8°C (36°F–46°F). Vials should be stored in the original cartons protected from light and should not be frozen or shaken.

Atezolizumab does not contain a preservative; thus, diluted solutions should be administered as soon as possible after preparation. If the diluted atezolizumab solution is not used immediately, it may be stored or maintained at room temperature (e.g., 20°C–25°C; 68°F–77°F). for ≤6 hours from the time of preparation, including time for administration of the infusion. Alternatively, it may be stored under refrigeration at 2°C–8°C (36°F–46°F) for ≤24 hours.

9.4.5. Solution Preparation

Before use, the atezolizumab vials should be inspected for particulate matter or discoloration. Any vial with evidence of particulates or discoloration should not be used. The vial should not be shaken.

Using aseptic technique, 20 mL of atezolizumab should be withdrawn from the vial and diluted into a 250-mL polyvinyl chloride, polyethylene, or polyolefin infusion bag containing 0.9% Sodium Chloride Injection, USP. The bag should be gently inverted to mix the solution. Shaking of the bag must be avoided. The infusion solution should not be mixed or diluted with other drugs. Used or empty vials of atezolizumab should be discarded.

The intravenous solution should be prepared and dispensed by the study center pharmacist and should be infused by a qualified nurse with experience in monitoring the administration of chemotherapeutic agents.

9.4.6. Accountability

Acquisition, storage, control, and disposal of atezolizumab used in the study should be performed according to institutional procedures and policies.

The investigator and/or the responsible site personnel must maintain accurate records of the source, dates of administration, quantities of administration, and lot numbers of the atezolizumab dispensed for this study.

10. ASSESSMENT OF SAFETY

10.1. Adverse Events

The investigator is responsible for the detection and documentation of events meeting the definition of an AE or SAE as provided in this protocol. Monitoring of AEs will be initiated upon treatment with LAM-002A .

10.1.1. Definitions

10.1.1.1. Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE (also referred to as an adverse experience) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality (i.e., whether or not considered related to the drug). An AE can arise with any use of the drug (e.g., use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

Note that progressive disease should not be reported as an AE. In cases of SAEs, sites can use progressive disease if there are no alternative terms that can be satisfactorily substituted. In those cases, the AE can match the SAE.

10.1.1.2. Suspected Adverse Reaction

Suspected adverse reactions are a subset of all AEs for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility means that there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

The investigator is responsible for determining whether there is a reasonable possibility that the drug caused the AE, and will capture the causality assessment in the eCRF.

10.1.1.3. Adverse Reaction

An adverse reaction means any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude the drug caused the event.

10.1.1.3.1. Unexpected

An AE or suspected adverse reaction is considered “unexpected” if it is not listed in the investigator brochure (IB) or is not listed at the specificity or severity that has been observed. The sponsor is responsible for determining whether an event meets the definition of “unexpected,” based on adverse reactions listed in the Apilimod IB.

10.1.1.3.2. Serious

An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening AE
  - Note: An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization is a hospital admission that lasts more than 24 hours or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Leads to congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and/or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

10.1.1.4. Adverse Events of Special Interest

Adverse events of special interest (AESIs) comprise TLS occurring in any study subject. Among study subjects receiving atezolizumab the following treatment-emergent AEs will be considered AESIs:

- AE suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, influenza-like illness, systemic inflammatory response syndrome, or systemic immune activation
- Autoimmune hemolytic anemia
- Cardiac disorders Grade ≥ 2: atrial fibrillation, myocarditis, pericarditis
- Colitis
- Cutaneous reactions: Stevens-Johnson syndrome, bullous dermatitis, toxic epidermal necrolysis
- Drug-induced liver injury (Grade ≥ 3 serum ALT or AST increase in combination with a Grade ≥ 2 serum total bilirubin)
- Endocrinopathy: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, or hypophysitis

- Hepatitis (Grade ≥3 serum ALT or AST increase)
- Muscular disorders: myositis, myopathy, rhabdomyolysis
- Nephritis
- Neurological disorders: Guillain-Barre syndrome, myasthenic syndrome or myasthenia gravis, or meningoencephalitis
- Ocular toxicities: uveitis, retinitis, optic neuritis
- Pneumonitis
- Systemic lupus erythematosus
- Transmission of an infectious agent due to contamination of atezolizumab
- Vasculitis

AESIs will be described in narratives as indicated in Section 10.6.

10.2. Study Drug Related AE or SAE

A study drug-related AE or SAE is defined as an AE or SAE that is related to the treatment with study drug.

10.3. Further AE and SAE Definitions

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the investigator, it should be recorded as a separate AE. Laboratory data are to be collected as stipulated in this protocol. Clinical syndromes associated with laboratory abnormalities are to be recorded as appropriate (e.g., diabetes mellitus rather than hyperglycemia).

Scheduled hospitalizations or elective surgical procedures will not be considered as AEs or SAEs. Prolongation of a scheduled hospitalization can be considered an SAE as discussed in Section 10.1.1.3.2. Complications associated with scheduled procedures are considered AEs or SAEs.

An abnormal test finding will be classified as an AE if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy. Note: simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an AE
- The test finding leads to a change in study drug dosing or discontinuation of subject participation in the clinical research study
- The test finding is considered an AE by the investigator

10.4. AE and SAE Assessment Criteria

AEs and SAEs are evaluated and severity determined by the investigator.

10.4.1. Assessment of Causality

The relationship between an AE and the study product will be determined by the investigator on the basis or his/her clinical judgment and the following definitions:

10.4.1.1. Related

The AE follows a reasonable temporal sequence from study drug administration, and cannot be reasonably explained by the subject's clinical state or other factors (e.g., disease under study, comorbid diseases, concomitant medications) or is a known reaction to the drug under study or its chemical group, or is predicted by known pharmacology, or a known reaction to agent or chemical group.

10.4.1.2. Not Related

The AE does not follow a reasonable sequence from study drug administration, or can be reasonably explained by the subject's clinical state or other factors (e.g., disease under study, comorbid diseases, and concomitant medications).

10.4.2. Grading of Severity

Each AE or SAE will be graded for severity using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0. (NCI 2010) However for those events not listed in the NCI CTCAE, the following scale should be used:

- Mild: Minor awareness of signs and symptoms that are easily tolerated without specific medical intervention
- Moderate: Discomfort that interferes with usual activities and may require minimal intervention
- Severe: Significant signs or symptoms that are incapacitating with an inability to work or perform routine activities and/or that require medical intervention

- Life threatening: immediate risk of death from the reaction

10.5. Responsibilities and Procedures

The responsibility for the safety of an individual subject lies in all cases with the investigator. This includes the timely review of all safety data obtained during the course of the study. An investigator must instruct his/her subjects to report any AE and SAEs they experience. Investigators capture, evaluate, and document all AEs and SAEs occurring during a subject's enrollment in the study, commencing with first treatment up to 30 days after the last dose of study drug on source documents and on designated eCRF pages.

Investigators should assess AEs at each scheduled and non-scheduled visit, by the use of open-ended questioning, physical examination, and review of laboratory results.

Note: It is important to record all AEs and SAEs that result in temporary and permanent discontinuation of study drug, regardless of severity.

Investigators are required to promptly report all events to the Institutional Review Board (IRB) according to the IRB's reporting requirements.

10.6. SAE and AESI Reporting

- The investigator is obligated to immediately report to AI Therapeutics each SAE and each AESI that occurs during this investigation, within 24 hours from knowledge of the event, whether or not it is considered study-drug related.
- All requested supplementary documents (e.g., discharge summary, autopsy report) and relevant data (e.g., ECGs, laboratory tests, discharge summaries, post mortem results) must be faxed or emailed within 24 hours to [redacted]

The information provided in a SAE or AESI report should be as complete as possible, but contain a minimum of the following:

- A short description of the AE (diagnosis) and the reason why the AE was categorized as an SAE or AESI
- Subject identification and treatment
- Investigator's name and telephone number (if applicable)
- Name of the suspect medicinal product and dates of administration
- Assessment of causality.

If any questions or considerations regarding SAE or AESI report requirements or report completion arise, the principal investigator/site staff should contact AI Therapeutics. Medically related questions or concerns regarding treatment should be directed to the sponsor's medical monitor.

If all information about the SAE or AESI is not yet known, the investigator will be required to report any additional information within 24 hours as it becomes available. SAEs and AESIs must be followed and reported upon until the event has completely resolved to Grade 0 or baseline or until the event becomes a new stable baseline condition for a subject.

All SAEs and AESIs will be evaluated by the sponsor's medical monitor or designee.

The investigators must notify their governing IRB of any SAEs in accordance with Section 18.1.

For any suspected adverse reaction that is both serious and unexpected (not documented in the IB or package insert), an Investigational New Drug (IND) safety report or revision to the IB may be issued to inform all investigators involved in any study with LAM-002A.

10.6.1. Post-treatment Safety Follow-up

In this study, all AEs occurring after first treatment will be captured on the eCRF. All subjects should be instructed to report AEs or SAEs occurring up to 30 days after the last dose of study drug. Unresolved study drug-related AEs and SAEs at the time of treatment discontinuation or new study-drug related AEs and SAEs that occur during the 30-day post dose time frame will be followed until they have, in the opinion of the investigator, resolved to baseline, have stabilized, or are deemed to be irreversible.

10.7. Pregnancy Reporting

Pregnancy occurring in a subject is not considered an AE. However, the investigator must capture pregnancy information for subject and/or subject's partner (as applicable) on a pregnancy report form within 24 hours of learning of the pregnancy. Then the site

- Completes the pregnancy form with as much information as possible; however, at a minimum the subject identification number, name of product, and name of reporter is required;
- Signs Pregnancy Notification form; and
- FAX the form to AI Therapeutics at [redacted].

Subjects determined to be pregnant must be immediately removed from treatment and will be followed by the investigator until termination of the pregnancy or delivery of the child. Additional information on the course of the pregnancy should be supplied on follow-up forms as it becomes available and at minimum at termination or birth.

11. ASSESSMENT OF EFFICACY

Tumor response will be assessed in the Dose Escalation Stage and Expansion Stage using modified Lugano Response Criteria for NHL (Cheson 2014) and revised guidelines for the diagnosis and treatment of CLL (Hallek 2008, Cheson 2012) (see Appendix 2).

Pretreatment tumor assessments will be performed within 30 days of the first dose (bone marrow assessment may be performed within 2 months prior to first dose) and will include diagnostic CT scans (with intravenous contract) or PET/CT for subjects with lymphoma (CT only for subjects with CLL/SLL), bone marrow aspirate/biopsy, complete blood counts and physical examination. It is anticipated that in most cases the PET and CT scans will be conducted using a single instrument, i.e., as a PET/CT scan (CT scans should be performed using a contiguous reconstruction algorithm of ≤ 5 mm). However, MRI is an acceptable alternative method for assessing disease in subjects who cannot receive intravenous contrast with CT scans. In such subjects MRI and PET scans will have to be obtained separately. Baseline bone marrow biopsies/aspirates may be omitted if not deemed essential for response assessment or patient management.

During treatment, radiology studies will be performed for tumor assessments as indicated in Table 8: Schedule of Assessments (LAM-002A Continuous Monotherapy Administration), Table 9: Schedule of Assessments (LAM-002A Intermittent Monotherapy Administration), Table 10: Schedule of Assessments (LAM-002A/Rituximab Combination Therapy), and Table 11: Schedule of Assessments (LAM-002A/Atezolizumab Combination Therapy) in Section 8.7 until PD or use of alternative antineoplastic therapy. If necessary per applicable response criteria, a repeat bone marrow biopsy or aspirate will be required for subjects who have a Complete Response (CR) by imaging and physical examination. Subjects with CLL/SLL who achieve CR will require assessment of minimal residual disease (MRD) by flow cytometry of bone marrow and peripheral blood.

12. PHARMOCOKINETIC ASSESSMENTS

Plasma concentration levels of apilimod and the active metabolites will be measured in the dose-escalation and dose-expansion stages at each of the specified time points; Table 8: Schedule of Assessments (LAM-002A Continuous Monotherapy Administration), Table 9: Schedule of Assessments (LAM-002A Intermittent Monotherapy Administration), Table 10: Schedule of Assessments (LAM-002A/Rituximab Combination Therapy), and Table 11: Schedule of Assessments (LAM-002A/Atezolizumab Combination Therapy) in Section 8.7. The analytical laboratory will measure plasma concentrations of apilimod using a validated analytic method. PK parameters will be estimated using standard non-compartmental methods will include: C_{max}, t_{max}, AUC_{0-t}, AUC_{τ}; $t_{½}$, trough concentrations on Days 8 and 15, and a comparison of AUC_{0-t} from Days 1 and 8 or Days 1 and Day 10 (as appropriate); additional parameters may be determined based on the available data. Accumulation will be assessed by calculating the accumulation ratios I for C_{max} and AUC when comparing Day 8 to Day 1 for all continuous LAM-002A regimens (whether given as monotherapy or in combination) or when comparing Day 10 to Day 1 for the intermittent LAM-002A regimen. Dose proportionality for C_{max} and AUC_{0-t} will be assessed by applying an appropriate power model to the data. Descriptive statistics of PK parameters will include minimum, maximum, mean, standard deviation, percent coefficient of variation (%CV), and range.

Pharmacokinetic samples will be collected for determination of plasma apilimod and active metabolite concentrations at the time points indicated in Table 13. All subjects must participate in PK assessments. Fasting status must be recorded at the time of each PK blood draw.

Table 13: Pharmacokinetic Sampling Time Points

Sample	Study Day	PK Sampling Time Points[a]
1[b]	1	Pre-dose (within 30 min prior to dose of LAM-002A)
2	1	0.5 hour (± 10 min) after dosing with LAM-002A
3	1	1 hour (± 10 min) after dosing with LAM-002A
4	1	2 hours (± 10 min) after dosing with LAM-002A
5	1	4 hours (± 10 min) after dosing with LAM-002A
6	1	6 hours (± 10 min) after dosing with LAM-002A
7	1	8 hours (± 10 min) after dosing with LAM-002A
8[b]	8 or 10[c]	Pre-dose (within 30 min prior to dose of LAM-002A)
9	8 or 10[c]	0.5 hour (± 10 min) after dosing with LAM-002A
10	8 or 10[c]	1 hour (± 10 min) after dosing with LAM-002A
11	8 or 10[c]	2 hours (± 10 min) after dosing with LAM-002A
12	8 or 10[c]	4 hours (± 10 min) after dosing with LAM-002A
13	8 or 10[c]	6 hours (± 10 min) after dosing with LAM-002A
14	8 or 10[c]	8 hours (± 10 min) after dosing with LAM-002A
15[b]	15	Pre-dose (within 30 min prior to dose of LAM-002A)

[a] Applies to first dose of the day
[b] Dosing with LAM-002A should occur after the PK sample has been drawn
[c] Sampling to be performed on Day 8 for all continuous LAM-002A regimens (whether given as monotherapy or in combination) or on Day 10 for the intermittent LAM-002A dosing regimen
Abbreviation: PK: Pharmacokinetic

Comprehensive information on blood sample acquisition, handling, storage and sample shipments can be found in the laboratory manual “Procedures for Processing and Shipping PK and Biomarker Samples.”.

On Cycle 1 Day 1, and Cycle 1 Day 8 the dose of LAM-002A should be orally administered (a minimum fasting state of 6 to 8 hours) by staff in the clinic immediately after the collection of the biomarker samples and after the collection of the first PK sample. Subjects are allowed to eat after PK Sample #4 (hour 2) has been collected. Subjects may consume clear liquids during fasting periods.

On Cycle 1 Day 15, the dose of LAM-002A should be orally administered (a minimum fasting state of 6 to 8 hours) by staff in the clinic immediately after collection of the pre-dose PK and biomarker samples.

13. BIOMARKER ASSESSMENTS

Plasma will be obtained for pharmacodynamics biomarker analysis on C1D1, C1D15, and at the EOT visit. Samples will be analyzed circulating tumor DNA to measure tumor burden and mutational changes.

Plasma pharmacodynamic samples will also be collected for determination of plasma apilimod and active metabolite activity at the PK time points indicated in Table 13. The plasma will be used in an ex vivo cathepsin activity assay or equivalent to determine level of PIKfyve inhibition.

Plasma will also be collected for evaluation of circulating cytokines (including IL-12 and IL-23) predose on each of Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 1 Day 15 and at the EOT visit. Samples will be analyzed using appropriate immune-detection assays.

For all subjects, PBMCs/B cells will be collected during the prescreening period for determination of changes in gene expression that may predict or correlate with anti-lymphoma activity and/or pharmacodynamic activity and will also serve as normal-tissue controls for gene mutation studies in tumors.

For subjects with NHL, fresh tumor tissue (preferred) or archival tissue from the most recent available biopsy or surgery (within 4 months prior to the start of screening) must be obtained pretreatment. For subjects undergoing a biopsy, adequate tumor tissue should be acquired via excisional biopsy, incisional biopsy or core needle biopsy (e.g., ≥ 3 passes using a 16-gauge core needle). Confirmation of tumor in biopsy with fine needle aspirate, touch prep, or FFPE processing is requested when possible. The tumor lesion selected should not have been previously irradiated and should not be an index lesion that is followed for response assessment. Alternatively, cells from a bone marrow aspirate may be obtained in subjects with bone marrow involvement due to NHL (>50% NHL cells). Tissue will be submitted for evaluation of the percentage of tumor cells and analysis of genetic alterations and/or gene expression that may predict anti-lymphoma activity and/or pharmacodynamics activity. In addition, tumor may be evaluated for known prognostic characteristics (e.g., for DLBCL: ABC or GCB subtype; expression of BCL2, BCL6, Ki-67, CD20, and MYC; other mutational status), for PDL1 status, and for immune infiltration.

Subjects with CLL/SLL must provide either a fresh blood sample containing circulating tumor cells or a bone marrow aspirate sample pretreatment. Tissue will be submitted for evaluation of the percentage of tumor cells and analysis of genetic alterations and/or gene expression that may predict anticancer activity and/or pharmacodynamic activity. In addition, for subjects with CLL/SLL, the sponsor may arrange for a portion of the sample to be evaluated at a sponsor-specified laboratory for known prognostic markers (e.g., quantitative immunoglobulins, FISH panel [chromosome 11q deletion, 13q deletion, 17p deletion and 12 trisomy], DNA mutational analysis for p53, IgHV [including IgHV3-21], and other genes of interest in CLL [e.g., Notch]; flow cytometry [for CD5, CD10, CD11c, CD19, CD20, CD23, CD38, CD45, kappa and lambda light chains and ZAP-70], and/or β2-microglobulin).

A saliva sample will be obtained during Screening as a normal-tissue control for gene mutation studies in tumors.

Comprehensive information on tissue acquisition, handling, storage and sample shipments can be found in the laboratory manual “Procedures for Processing and Shipping PK and Biomarker Samples.”

14. STATISTICS

14.1. Determination of Sample Size

14.1.1. Dose Escalation Stage (Stage 1)

The planned sample size for the dose-escalation is not based on a specific statistical hypothesis but on experience in the conduct of similar trials in subjects with cancer.

In the dose escalation, the cohort sizes of 3 to 6 subjects allow evaluation of regimen safety using a standard definition of MTD (ie, a starting dose associated with DLT in <33% of subjects during the first cycle of therapy). Based on the planned 3+3 dose-escalation scheme, Table 14 shows the probability of escalating to the next dose level or proceeding to the next stage, based on the true rate of DLT at the current dose level.

Table 14: Statistical Basis for 3+3 Dose-Escalation Paradigm

True Incidence of DLT	Probability of Escalating
10%	0.91
20%	0.71
30%	0.49
40%	0.31
50%	0.17
60%	0.08

Abbreviation: DLT=dose-limiting toxicity

Thus, if the true underlying proportion of DLT is low (eg, ≤10% at the current dose level, there is a high probability (≥0.91) of dose escalation to the next dose level. Conversely, if the true underlying proportion of DLT is high (eg, ≥60%) at the current dose level, there is a low probability (≤0.08) of escalation to the next dose level.

14.1.2. Cohort Expansion Stage (Stage 2)

As indicated in Section 6.1.2, expansion cohorts of 6 subjects will be accrued. Enrollment of 6 subjects per cohort offers the opportunity to determine if there is any antitumor activity sufficient to warrant further development in the selected tumor types. An ORR of ≥ 35% is considered of potential interest in each of the selected indications. If 0/6 subjects in a cohort experience an objective response, then a population ORR of ≥ 35% for that cancer can be excluded with > 90% certainty (1-sided exact binomial 90% CI upper bound = 32%).

Based on the observation of objective responses among study subjects with FL receiving either LAM-002A monotherapy or LAM-002A/rituximab, expanded accrual of subjects with relapsed FL is planned to evaluate the level of activity with these 2 regimens. Preference will be given to enrolling subjects to receive LAM-002A monotherapy before enrolling subjects to receive LAM-002A/rituximab.

Based on historical data with other treatments (Zelenetz 2014), it is known that an ORR of < 20% in subjects with relapsed FL receiving LAM-002A monotherapy would be uninteresting while achieving a target ORR of ≥ 40% would suggest that further development is warranted. Sequential boundaries will be used to continuously monitor that the ORR is ≥ 40% while

excluding an ORR of < 20% using a 1-sided test with a significance level of 0.05. A significant result with this testing would conclude with 95% confidence that the actual ORR is ≥ 20%. Accrual of up to ~20 evaluable subjects will be considered with the potential to stop accrual early if the boundary is crossed. Thus, accrual can be considered sufficient if the following n/N values are observed: 4/5, 4/6, 4/7, 5/8, 5/9, 5/10, 5/11, 6/11, 6/12, 6/13, 6/14, 7/15, 7/16, 7/17, 8/18, 8/19, 8/20. For all these values, the ORR is ≥ 40% with a lower 1-sided binomial confidence bound of ≥ 20%.

As noted above, the target ORR with LAM-002A alone is ~40%. Adding rituximab or rituximab hyaluronidase human to LAM-002A would be expected to enhance the ORR over that associated with single-agent LAM-002A. Thus, the combination of LAM-002A/rituximab could warrant further development if an ORR of ≥ 60% could be targeted in preference to an ORR of < 40%. Accordingly, for combination therapy, sequential boundaries will be used to continuously monitor that the ORR is ≥ 60% while excluding an ORR of 39% using a 1-sided test with a significance level of 0.05. A significant result with this testing would conclude with 95% confidence that the actual ORR is > 39%. Accrual of up to ~20 evaluable subjects will be considered with the potential to stop accrual early if the boundary is crossed. Thus, accrual can be considered sufficient if the following n/N values are observed: 7/10, 8/11, 8/12, 9/13, 9/14, 10/15, 10/16, 11/17, 11/18, 12/19, 12/20. For all these values, the ORR is ≥ 60% with a lower 1-sided binomial confidence bound of ≥ 39%.

Experience indicates the rates of discontinuations from rituximab or atezolizumab therapy are < 5% (Genentech 2016, Genentech 2017). A rate of AE discontinuations of therapy due to adverse events of ≥25% in the 2 combination therapy groups of LAM-002A/rituximab (N = 12) or LAM-002A/atezolizumab (N = 12) would suggest a potential adverse interaction among the components of the combination therapy. Sequential Pocock-type boundaries will be used to continuously monitor the rate of AE discontinuations and to test the null hypothesis, after each subject, that the event rate is ≥ 0.25 using a 1-sided significance test of ~ 0.05. AE discontinuation rates will be considered excessive if the following n/N values are observed: -/1, -/2, 3/3, 3/4, 4/5, 4/6, 5/7, 5/8, 5/9, 6/10, 6/11, 7/12. With this method, the probability of detecting an AE discontinuation safety signal ranges from 0.091 to >0.820 for true discontinuation rates of 25% to ≥ 60%. If excessive levels of AE discontinuation are observed, the sponsor, working in collaboration with the cooperating companies and investigators, will take appropriate actions (eg, continuation of the cohort with modifications in design or monitoring plan, interruption of cohort accrual, cohort therapy discontinuation).

14.1.3. Extension Stage (Stage 3)

The sample size in the extension stage of the study will be no higher than the total number of subjects on study therapy on the data cutoff date that concludes the dose-escalation and expansion stages of the clinical trial.

14.2. Statistical and Analytical Plans

Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a statistical analysis plan (SAP). The SAP may modify the plans outlined in the protocol; any major modifications of the primary endpoint definition and/or its analysis will be described in the SAP and the final clinical study report. Additional statistical analyses other

than those described in this section may be performed if deemed appropriate and will be described in the SAP. Where individual data points are missing because of insufficient samples, dropouts, or other reasons, the data will be analyzed based on reduced denominators.

Results will be summarized by dose cohorts.

14.3. Analysis Sets

14.3.1. Full Analysis Set

The full analysis set includes all subjects who receive ≥ 1 dose of study drug. This analysis set will be used in the analyses of subject characteristics, study drug administration and compliance, safety, and categorical and time-to-event efficacy outcomes. In analyses of response rates in the full analysis set, subjects who do not have sufficient baseline and on-study tumor assessments to characterize response (i.e., have a best overall response of NE) will be counted as failures.

14.3.2. Responding Analysis Set

The responding analysis set includes subjects in the full analysis set who have measurable disease, who can be evaluated for tumor response with both baseline and on-study tumor evaluations, and who achieve a CR, CRi, or PR. This analysis set will be used in the analyses of time to response and duration of response.

14.3.3. Evaluable Analysis Sets

The evaluable analysis sets include subjects in the full analysis set who have the necessary baseline and on-study measurements to provide interpretable results for specific parameters of interest. These analysis sets will be used in the analyses of changes in tumor dimensions, PK parameters, and pharmacodynamic parameters.

14.4. Demographics and Baseline Disease Characteristics

Demographics and other baseline characteristics will be summarized by dose escalation cohorts and expanded cohorts.

14.5. Study Drug Exposure

Study drug exposure information will be summarized using descriptive statistics such as number of treatment cycles and total dose.

14.6. Concomitant Medications

Medications under use at the time of or initiated after enrollment will be summarized by cohorts.

14.7. Safety and Tolerability

Safety and tolerability of LAM-002A will be assessed based on the following:

- Incidence, severity of treatment-emergent AEs, SAEs, AEs resulting in permanent discontinuation of study drug, and deaths on treatment through approximately 30 days from

the last dose of study drug (or immediately before the administration of another anti-cancer treatment)

- Changes in laboratory test results
- Changes in vital signs including blood pressure, pulse, and temperature
- Changes in electrocardiogram results

Adverse events will be coded using the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs are defined as AEs that start on or after the first dose of study drug and within approximately 30 days of the last administration of study drug. Adverse events will be summarized by the number and percentage of subjects who experienced the event, according to system organ class and preferred term. A subject reporting multiple cases of the same AE will be counted once within each system organ class and similarly counted once within each preferred term.

Unless specified otherwise, the denominator for these calculations will be based on the number of subjects in each cohort who received at least one administration of LAM-002A irrespective of the total number of doses or treatment cycles administered. These conventions will be appropriately modified to calculate AE incidence rates separately for each cycle that study therapy is administered.

AEs will also be summarized by NCI-CTCAE Version 4.0 severity grade and by relationship to each study drug. Additional summaries may also be provided for SAEs, and events resulting in the permanent discontinuation of therapy. All AEs will be included in individual subject listings.

The changes in hematology, chemistry, and other laboratory values will be summarized descriptively for each scheduled and unscheduled protocol assessment time point. Changes will be calculated relative to the values collected at baseline and on the first day of each cycle of treatment.

The incidence of DLT will be provided by treatment cycle and across all treatment cycles. The toxicity grades for laboratory tests will be based on NCI-CTCAE Version 4.0 criteria. Subject listings of all laboratory data collected during the study will be presented. Laboratory values outside normal limits will be identified in the subject listings and will include flags for high and low values.

Vital sign results (blood pressure, pulse, respirations, and temperature) will be summarized descriptively for each scheduled and unscheduled protocol time point. Changes will be calculated relative to the assessments at baseline and on the first day of each cycle of therapy.

14.8. Biomarkers

Descriptive statistics will be primarily used to summarize the biomarker and other laboratory data generated in this study. For continuous variables, the number of subjects with non-missing data, mean, either the standard error or standard deviation, median, 25th percentile (first quartile), 75th percentile (third quartile), minimum, and maximum will be presented. For discrete data, the frequency and percent distribution will be presented.

The Wilcoxon signed rank test may be used to identify any statistically significant ($p < 0.05$) changes in biomarker levels. Additionally, correlations may be assessed by calculating Spearman's correlation coefficient between pairs of biomarkers or other parameters.

14.9. Efficacy Analysis

The tumor response will be assessed by the modified criteria for NHL (Cheson 2014) and revised guidelines for the diagnosis and treatment of CLL (Hallek 2008, Cheson 2012) (see Appendix 2).

The objective response rate will be estimated for each dose escalation cohort and each expanded cohort. The estimate of the objective response rate will be calculated based on the maximum likelihood estimator (i.e., crude proportion of subjects whose best overall response is CR or partial remission [PR]). The estimate of the objective response rate will be accompanied by 2-sided 95% exact binomial confidence intervals.

The duration of objective response will be calculated for subjects who achieve CR or PR. For such subjects, the duration of objective response is defined as the number of days from the start date of PR or CR (whichever response is achieved first) to the first date that progressive disease is objectively documented. The duration of objective response will be right-censored for subjects who achieve CR or PR and meet 1 of the following conditions: 1) non-protocol anticancer treatment started before documentation of disease progression, 2) death or documented disease progression after more than 1 missed disease assessment visit, or 3) alive and does not have documentation of disease progression before a data analysis cutoff date.

The duration of objective response will be summarized descriptively using the Kaplan-Meier method. The 50th percentile of the Kaplan-Meier distribution will be used to estimate the median response duration.

Progression-free survival (PFS) will be measured as from the date of enrollment to the date of documented progression or death (whatever the cause). Subjects who are alive and progression free at last follow-up (up to a year from first treatment at Cycle 1 day 1) will be censored. Those who start another anticancer treatment without evidence of progression will be censored at start date of the new therapy.

The PFS will be summarized descriptively using the Kaplan-Meier method. The 50th percentile of the Kaplan-Meier distribution will be used to estimate the median PFS of each cohort of subjects.

14.10. Interim Analysis

Dose escalation decision will be made as outlined based on available safety and available PK/pharmacodynamic information. No statistical analyses are planned to aid the dose escalation decision.

14.11. Missing Data and Imputation

Missing data generally will not be imputed except those defined in the SAP.

14.12. Protocol Deviations

By-subject listings will be generated for all enrolled subjects' inclusion and exclusion criteria; this includes those subjects who do not meet one or more inclusion criteria, and those subjects who meet one or more exclusion criteria. A list of all protocol deviations will be maintained by the clinical team and will be included in the clinical study report. The impact of the protocol deviation on the efficacy analysis will be evaluated.

15. DIRECT ACESS TO SOURCE DATA/DOCUMENTS

A representative of AI Therapeutics will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

16. STUDY MONITORING

Before an investigational site can enter a subject into the study, a representative of AI Therapeutics will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the investigator and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of AI Therapeutics or its representatives. This will be documented in a Clinical Study Agreement between AI Therapeutics and the investigator.

During the study, a monitor from AI Therapeutics or its representative will have regular contacts with the investigational site for the following:

- Provide information and support to the investigator
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol that data are being accurately recorded in the eCRFs, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the CRFs with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (e.g., clinic charts)
- Record and report any protocol deviations not previously sent to AI Therapeutics
- Confirm AEs and SAEs have been properly documented on eCRFs, and confirm any SAEs have been forwarded to AI Therapeutics and those SAEs that met criteria for reporting have been forwarded to the IRB

The monitor will be available between visits if the investigator or other staff members need information or advice.

Upon conclusion of the Dose-Escalation (Stage 1) and Expansion (Stage 2) stages of the study, routine site monitoring by AI Therapeutics or its representatives will be discontinued.

16.1. Audits and Inspections

Authorized representatives of AI Therapeutics, a regulatory authority, and/or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of a AI Therapeutics audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP) Guidelines of the International Conference on Harmonisation, and any applicable regulatory requirements. The investigator should contact AI Therapeutics immediately if contacted by a regulatory agency about an inspection.

16.2. Institutional Review Board

The investigator must obtain IRB or Ethics Committee (EC) approval for the investigation. Initial IRB/EC approval, and all materials approved by the IRB/EC for this study, including the subject consent form and recruitment materials, must be maintained by the investigator and made available for inspection.

17. QUALITY CONTROL AND QUALITY ASSURANCE

Qualified staff of AI Therapeutics or its representative will conduct independent monitoring of the clinical study for protocol and GCP compliance periodically.

The investigator will permit direct access of the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of this data.

18. ETHICS

18.1. Ethics Review

The investigator will obtain IRB/EC approval of the clinical protocol and corresponding informed consent form(s); modifications to the clinical protocol and corresponding informed consent forms; and advertisements (i.e., directed at potential research subjects) for study recruitment prior to study implementation. The investigator must submit written approval to AI Therapeutics or designee before enrolling any subject into the study.

The only circumstance in which a deviation from the current IRB/EC approved clinical protocol/consent form(s) may be initiated in the absence of prospective IRB/EC approval is to eliminate an apparent immediate hazard to the research subject(s). In such circumstances, the investigator will promptly notify the IRB/EC of the deviation.

The investigator is also responsible for providing the IRB/EC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. AI Therapeutics will provide this information to the investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB/EC according to local regulations and guidelines.

18.2. Ethical Conduct of the Study

The clinical research study will be conducted in accordance with the current IRB/EC approved clinical protocol, ICH GCP Guidelines, relevant policies, and requirements of the national regulations and laws.

18.3. Written Informed Consent

The investigator will make certain that an appropriate informed consent process is in place to ensure that potential research subjects, or their authorized representatives, are fully informed about the nature and objectives of the clinical study, the potential risks and benefits of study participation, and their rights as research subjects. The investigator, or a sub-investigator(s) designated by the investigator, will obtain the written, signed informed consent of each subject, or the subject's authorized representative, prior to performing any study-specific procedures on the subject. Subjects must also be notified that they are free to discontinue from the study at any time. The subject (or authorized representative) should be given the opportunity to ask questions and allowed time to consider the information provided. The date and time that the subject or the subject's authorized representative signs the informed consent form and a narrative of the issues discussed during the informed consent process will be documented in the subject's case history. The investigator will retain the original copy of the signed informed consent form, and a copy will be provided to the subject, or to the subject's authorized representative.

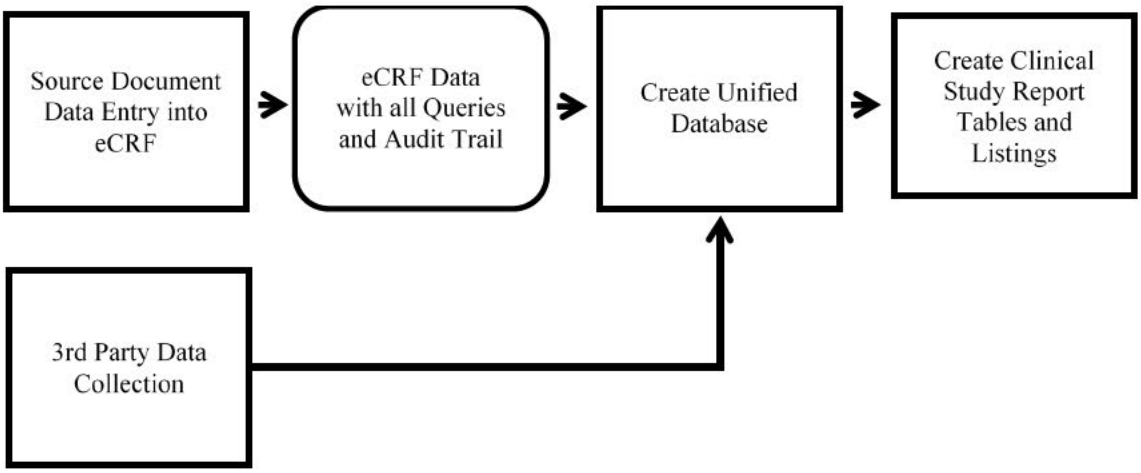
The investigator will make certain that appropriate processes and procedures are in place to ensure that ongoing questions and concerns of enrolled subjects are adequately addressed and that subjects are informed of any new information that may affect their decision to continue participation in the clinical study. In the event of substantial changes to the clinical study or the

benefit: risk ratio of study participation, the investigator will obtain the informed consent of enrolled subjects for continued participation in the clinical study.

19. DATA COLLECTION, REPORTING AND PROCESSING

The standard flow of the clinical study data from collection to clinical study report is illustrated in Figure 2.

Figure 2: Transmission of Electronic Data



Abbreviations: eCRF = electronic case report form

Data will be transcribed from source into a validated 21 Code of Federal Regulations (CFR) Part 11 compliant, electronic data capture (EDC) system using single data entry. External data will also be imported into the system. Medical Coding (MedDRA and World Health Organization Drug Dictionary [WHODD]) and pharmacokinetic raw and parameter data, for example, will be merged into the database using Statistical Analysis System (SAS) or Excel transfers. Data originators, as well as system administrators, will be trained, authorized, and each assigned an individual identifier (user name and password). Electronic tools (prompts), as well as data review and query, will be used to alert users to and correct for missing data, data inconsistencies, inadmissible values, entries out of range, and to request additional data as applicable. An audit trail will be maintained to record data entries and edits. Data originators will have access to their data during study conduct and will be provided a read-only copy of the final data, audit trail, and queries in a human readable file suitable for long term storage.

The investigator and any vendors will permit study-related monitoring, audits, IRB review, and regulatory inspection(s) by providing direct access to source data/documents. Data entered into the eCRF will be available to the parties responsible for study data management (sponsor, contract research organization [CRO]) as it is entered and can be exported into files compatible with SAS and Excel, among other data formats.

Subject data necessary for analysis and reporting of this study will be transferred via a validated procedure into a validated database or data system (e.g., SAS), to enable the data to be restructured into Industry standards. Clinical data management will be performed in accordance with applicable AI Therapeutics or designee's standards and data cleaning procedures. This is applicable for data recorded on eCRF as well as for data from other sources. Examples of other data would be the medical glossary coding (e.g., AEs, medication) that will be performed with

internationally recognized and accepted dictionaries. Additional details are recorded in the monitoring and data management documentation.

19.1. Inspection of Records

AI Therapeutics will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

19.2. Retention of Records

The investigator will maintain records in accordance with GCP guidelines; to include:

- Food and Drug Administration (FDA) correspondence related to the IND and clinical protocol, including copies of submitted Safety Reports and Annual Reports
- IRB correspondence (including approval notifications) related to the clinical protocol, including copies of AE reports and annual or interim reports
- Current and past versions of the IRB-approved clinical protocol and corresponding IRB-approved consent form(s) and, if applicable, subject recruitment advertisements
- Signed FDA Form 1572 Statement of the investigator
- Financial disclosure information (i.e., for the investigator and for sub-investigators who will be involved in the administration of the study drugs and/or the evaluation of research subjects [i.e., who will contribute significantly to the research study data])
- Curriculum vitae (i.e., for the investigator)
- Certificates of required training, e.g., human subject protections, GCP, and so on (i.e., for the investigator and for all sub-investigators who will be involved in the administration of the study drugs and/or the evaluation of research subjects [i.e., who will contribute significantly to the study data])
- Listing of printed names/signatures. (i.e., for the investigator and for all sub-investigators who will be involved in the administration of the study drugs and/or the evaluation of research subjects [i.e., who will contribute significantly to the study data])
- Normal value(s)/range(s) for medical/laboratory/technical procedures or tests included in the clinical protocol
- Laboratory certification information
- Instructions for on-site preparation and handling of the investigational drug(s), study treatment(s), and other study-related materials (i.e., if not addressed in the clinical protocol)
- Responsibility delegation log
- Signed informed consent forms
- Completed eCRFs, signed and dated by the investigator
- Source Documents or certified copies of Source Documents

- Monitoring visit reports
- Copies of investigator correspondence (including notifications of safety information) to sub-investigators
- Subject screening and enrollment logs
- Subject identification code list
- Investigational drug accountability records, including documentation of drug disposal.
- Final clinical study report.

The investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuance of the test article for investigation. If it becomes necessary for AI Therapeutics or the Regulatory Authority to review any documentation relating to the study, the investigator must permit access to such records.

19.3. Data Recording/Case Report Forms

An eCRF will be completed for each subject enrolled into the clinical study. The investigator will review, approve, and sign/date each completed eCRF; the investigator's signature serves as attestation of the investigator's responsibility for ensuring that all clinical and laboratory data entered on the eCRF are complete, accurate, and authentic.

Source data are the clinical findings and observations, laboratory and test data, and other information contained in source documents. Source documents are the original records (and certified copies of original records) including, but not limited to, hospital medical records, physician or office charts, physician or nursing notes, subject diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, x-rays, and so on. When applicable, information recorded on the eCRF shall match the source data recorded on the source documents.

20. PUBLICATION POLICY

It is the intent of the sponsor to publish the complete study results in a timely manner that is appropriate to the project. Contribution to the project will be reflected in authorship. Separate publication of a portion of the study results (a sub-study) is discouraged.

21. STUDY DISCONTINUATION

Both the investigator and AI Therapeutics reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures. The investigator will be responsible for notifying the relevant study center IRB. AI Therapeutics will be responsible for notifying the appropriate regulatory authorities. In terminating the study, the investigator and AI Therapeutics will assure that adequate consideration is given to the protection of the subjects' interests. As directed by AI, Therapeutics all study materials must be collected and all eCRFs completed to the greatest extent possible.

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Appendix 1. Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken 1982.

Appendix 2. Criteria for Response Assessment

1. LYMPHOMA

1.1. Tumor Assessment Criteria

The determination of response and progression for subject with NHL will be based on standardized criteria (Cheson 2014).

1.2. Method of Assessment

Imaging-based evaluation will be used in this study as the primary basis of lymphoma assessment. CT scan is the preferred method for radiographic tumor assessment. Contrast-enhanced scanning is preferred, but contrast material may be omitted in subjects for whom use of a contrast agent becomes medically contraindicated or if CT scanning is done in conjunction with PET. If available, PET scan data will be considered in response and progression assessment; however, PET scanning will not be a required component of assessment in this study. As necessary, bone marrow aspirate/biopsy (e.g., for confirmation of CR) or cytological/histological evaluation of lymph nodes, effusions, ascites, or other organ abnormalities) will be also be considered. Clinical palpation, chest x-ray, ultrasound, endoscopy, laparoscopy, radionuclide scan, or tumor markers will not be considered for response assessment. MRI scanning is not advised but may be used at the investigator's discretion in subjects for whom this becomes a necessary alternative to CT scanning.

For radiographic assessments, the same method of assessment and the same technique (e.g., scan type, scanner, subject position, dose of contrast, injection/scan interval) should be used to characterize each identified and reported lesion at baseline and during study treatment and follow-up. CT of the neck, chest, abdomen, and pelvis should be performed with cuts of ≤ 0.5 mm in slice thickness contiguously. If performed, whole-body FDG PET-CT scanning should be extended from the base of the skull to mid-thigh.

All relevant radiographic and clinical information required to make each tumor status assessment must be made available for source verification as requested by the study sponsor.

1.3. Timing of Assessments

During screening, clinical and imaging-based tumor assessments should be performed within the specified screening period. On-study tumor assessments should be performed as stipulated in Section 8.7. An end-of-therapy tumor assessment should be performed unless the subject already has radiographic confirmation of disease progression ≤ 4 weeks prior to study drug discontinuation. If a subject permanently discontinues treatment prior to objective documentation of lymphoma progression, investigators should ideally continue further follow-up of tumor status with assessments at ~12-week intervals until disease progression is documented or until the initiation of a new post-study therapy for the subject's lymphoma.

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1.4. Identification and Follow-up of Tumor Lesions and Organomegaly

1.4.1. Index Lesions

Up to 6 lesions (e.g., lymph nodes, liver or spleen nodules, and/or other circumscribed extranodal masses) should be selected as index lesions that will be used to quantitate the status of the disease during study treatment. Ideally, the index lesions should be located in disparate regions of the body and include mediastinal, abdominal, and retroperitoneal areas of disease whenever these sites are involved. For subjects with FDG-avid lymphomas undergoing PET, selection of FDG-avid lesions is preferred.

Index lesions will be measured and recorded at baseline and at the stipulated intervals during treatment. The largest cross-sectional dimensions (i.e., the LD × LPD will be recorded (in cm) for each index lesion. Using the LD and LPD, the product of the perpendicular diameters (PPD) for each index lesion will be calculated. The PPDs and the SPDs for all index lesions will be calculated and recorded. The baseline and nadir PPDs of individual lesions and the baseline and nadir SPDs will be used as references by which objective tumor response and progression will be characterized during treatment. All PPD and SPD measurements will be reported in centimeters squared.

1.4.2. Nodal Index Lesions

A nodal mass may be selected as a nodal index lesion if it is both abnormal and measurable at baseline. A lymph node lesion is considered abnormal if it has a single diameter that is > 1.0 cm and is considered measurable if it has 2 perpendicular diameters that can be accurately measured in cross section with the LD being ≥ 1.0 cm and the LPD also being ≥ 1.0 cm.

Abnormal, measurable nodal lesions will be subcategorized as either large or small.

- Large nodal lesions have an LD that is > 1.5 cm and an LPD that is ≥ 1.0 cm.
- Small nodal lesions have an LD that is > 1.0 cm and ≤ 1.5 cm and an LPD that is > 1.0 cm.

Index lesions measuring > 1.5 cm in the LD, regardless of the measurement of the LPD, will be prioritized during baseline index lesion selection.

At follow-up timepoints, the PPDs for individual nodal lesions and the SPD of all nodal index lesions will be considered. Because nodal index lesions that have one or both diameters > 0 cm and < 1.0 cm cannot be reliably measured, a default value of 1.0 cm will be assigned for each diameter that meets these criteria and the resulting PPD will be used in SPD calculations. Based on this convention, a CR may be achieved even if an SPD value is > 0 cm^2 (i.e., if all lymph nodes measure < 1.0 cm^2).

New or enlarging nodal lesions that are still ≤ 1.0 cm by ≤ 1.0 cm will not be considered to represent recurrent or PD. A new node that measures > 1.5 cm in any diameter or a new node that measures > 1.0 cm to ≤ 1.5 cm in the LD and measures > 1.0 cm in the LPD will be considered PD.

In cases in which a large lymph node mass has split into multiple components, only those elements that are > 1.0 cm in ≥ 1 diameter will be considered abnormal and used in calculating

the SPD. Components that are ≤ 1.0 cm in the LD are assumed to be normal lymph node structures. PD will not be based on the growth of a lesion sub-component until it meets the criteria for abnormal. Lesion sub-components that are abnormal (> 1.0 cm in ≥ 1 diameter) will have the true PPDs calculated with the result used only for calculating an accurate nadir. Lesion subcomponents that are normal (≤ 1.0 cm in the LD) will have the default PPD of 1.0 cm^2 (1.0 cm x 1.0 cm) stored only for the purposes of calculating the nadir value.

If lesions merge, a boundary between the lesions will be established so the LD of each individual lesion can continue to be measured. If the lesions have merged in a way that they can no longer be separated by this boundary, the newly merged lesion will be measured bidimensionally.

1.4.3. Extranodal Index Lesions

An extranodal mass may be selected as an index lesion if it is both abnormal and measurable at baseline. An extranodal mass of any size is considered abnormal. It is considered measurable at baseline if it has 2 perpendicular diameters that can be accurately measured in cross section with the LD being ≥ 1.0 cm and the LPD also being ≥ 1.0 cm.

At follow-up timepoints, the PPD of each single extranodal index lesion and the SPD of all extranodal index lesions will be considered. Because extranodal index lesions that have one or both diameters < 0.5 cm and > 0 cm cannot be reliably measured, a default value of 0.5 cm will be assigned for each diameter that meets these criteria and the resulting PPD will be used in SPD calculations. If an extranodal lesion is no longer clearly visible, it will be considered resolved and its PPD will be defined as 0 cm^2.

If an extranodal lesion that had resolved (i.e., had a PPD of 0 cm^2) subsequently reappears, the subject will be considered to have PD. A new extranodal lesion of any size that appears at a site that was not previously involved with lymphoma and is discernible to the radiologist by CT scan will be considered PD.

1.4.4. Non-Index Lesions

Any other measurable and abnormal nodal or extranodal lesions not selected for quantitation as index lesions may be considered non-index lesions. In addition, non-measurable evidence of lymphoma such as abnormal, non-measurable nodal lesions, extranodal lesions with both diameters < 1.0 cm, bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusions, lymphangitis of the skin or lung, abdominal masses that are not confirmed and followed by imaging techniques, cystic lesions, previously irradiated lesions, or lesions with artifacts may be considered as non-index disease.

If present at baseline, up to 6 non-index lesions should be recorded. Measurements are not required.

Non-index disease will be used as a general reference to further characterize regression or progression of lymphoma during assessments of the objective tumor response during treatment. These lesions should be followed as “present” or “absent”.

1.4.5. Spleen and Liver

Qualitative assessments of the sizes of the spleen and liver will be performed. In addition, the presence or absence of splenic nodules will be recorded.

At baseline and follow-up timepoints, the spleen and liver size will be reported as normal, enlarged not due to lymphoma (no nodules present), enlarged due to lymphoma (≥ 1 nodule present), unequivocal increase not due to lymphoma (no nodules present), or unequivocal progression (≥ 1 nodule present). For subjects with splenomegaly or hepatomegaly at baseline or at the nadirs for assessments of spleen and liver, evaluations will consider only changes relative to the enlargement of the organ (i.e., the portion of the LVD that is > 12 cm by imaging for the spleen and > 18 cm in LVD for the liver) at baseline or nadir, not changes relative to the total splenic LVD.

By imaging, the spleen will be considered enlarged if it is > 12 cm in LVD (Bezerra 2005, Asghar 2011), with the LVD being obtained by multiplying the number of sections on which the spleen is visualized by the thickness of the sections (e.g., if the spleen is seen in 14 contiguous cross-sectional images with 0.5-cm thickness, the LVD is recorded as 7 cm). An increase in splenic enlargement by ≥ 50% (minimum increase of 2 cm) from nadir and the presence of ≥ 1 splenic nodule is required for declaration of splenic progression. Subjects with a normal spleen LVD (i.e., a LVD of ≤ 0 cm by physical examination or ≤ 12 cm by imaging) at nadir will only be considered to have progressed if the spleen attains a LVD of > 14 cm by imaging and there is ≥ 1 splenic nodule.

By imaging, the liver will be considered enlarged if it is > 18 cm in LVD (Erturk 2006). An increase in liver enlargement by ≥ 50% (minimum increase of 2 cm) from nadir and the presence of ≥ 1 hepatic nodule is required for declaration of hepatic progression. Subjects with a normal liver LVD (i.e., a LVD of ≤ 18 cm by imaging) at nadir will only be considered to have progressed if the liver attains a LVD of > 20 cm by imaging and there is ≥ 1 hepatic nodule.

1.4.6. Bone Marrow

Bone marrow assessments will be based on morphologic evaluation of bone marrow biopsies. Immunohistochemistry may be used to assess response if the sample is indeterminate by morphology.

In a subject who has a baseline bone marrow biopsy showing bone marrow lymphoma or does not have a baseline bone marrow examination, declaration of an on-study CR requires bone marrow biopsy documentation of the absence of bone marrow lymphoma. In a subject who has a baseline bone marrow biopsy showing no evidence of lymphoma, declaration of an on-study CR does not require bone marrow examination as long as other criteria for CR are met. Of note, in subjects with an FDG-PET avid lymphoma, declaration of an on-study CR can be based on FDG-PET documentation of the absence of bone marrow involvement, even if a bone marrow biopsy is not performed or not available.

1.4.7. Lymph Node Biopsy

Lymph node biopsy is not required in the determination of subject eligibility.

During study participation, a subject with a more indolent type of disease (e.g., CLL/SLL, FL) who has a lymph node biopsy indicating transformation to an aggressive lymphoma will be considered to have PD even in the absence of other evidence of PD. If the subject has no earlier objective documentation of PD, the date of the lymph node biopsy will be considered the date of PD.

1.5. Definitions of Tumor Response and Progression

Responses will be categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). In addition, a response category of nonevaluable (NE) is provided for situations in which there is inadequate information to otherwise categorize response status.

The best overall response will be determined. The best overall response is the best on-treatment response from baseline recorded from the start of treatment until PD/recurrence. The baseline measurement will be taken as a reference for determinations of response. The nadir measurement will be taken as a reference for PD; this measurement constitutes the smallest measurement recorded, including the baseline measurement if this is the smallest measurement. For FDG-avid tumors, metabolic criteria for response by PET-CT will take precedence over anatomic criteria for response by contrast CT when assessing CR.

1.5.1. Complete Response

To satisfy criteria for CR, all of the following conditions must be attained:

- No evidence of new disease
- Regression of all index nodal lesions to normal size (≤ 1.5 cm in the LD for nodes that were considered large at baseline and ≤ 1.0 cm in the LPD for nodes that were considered small at baseline) (see Section 1.4.2 for definitions of large and small nodes)
- Regression to normal of all nodal non-index disease
- Disappearance of all detectable extranodal index and non-index disease
- Normal spleen and liver size by imaging studies, no hepatic or splenic lymphoma nodules, and no new liver or spleen enlargement
- Morphologically negative bone marrow based on an adequate unilateral core biopsy (> 20 mm unilateral core); if the sample is indeterminate by morphology, it should be negative by immunohistochemistry
- If PET performed, no evidence of residual disease – i.e., score of 1 (no uptake above background), 2 (uptake ≤ mediastinum), or 3 (uptake > mediastinum but ≤ liver) on the Deauville 5-point scale.
- Negative for bone marrow involvement by PET for a PET-avid tumor or by an adequate unilateral core biopsy (> 20 mm unilateral core); if the bone marrow biopsy is indeterminate by morphology, it should be negative by immunohistochemistry.

1.5.2. Partial Response

To satisfy criteria for PR, all of the following conditions must be attained:

- No evidence of new disease
- A ≥ 50% decrease from baseline in the SPD of the index nodal and extranodal lesions
- No increase from the nadir in the size of non-index disease
- No increase from the nadir in the size of the liver or spleen and no new liver or spleen enlargement
- If PET performed:
  - Typically FDG-avid lymphoma: if no baseline PET scan or if the PET scan was positive before therapy, the on-treatment PET is positive in ≥ 1 previously involved site– i.e., score of 4 (uptake moderately > liver) or score of 5 (uptake markedly > liver) on the Deauville 5-point scale but with reduced uptake compared with baseline. If baseline PET was performed and was negative, there is no new PET evidence of disease.
  - Variably FDG-avid lymphoma/FDG-avidity unknown: if no pretreatment PET scan or if the pretreatment PET scan was negative for lymphoma, CT criteria should be used in assessing the tumor during treatment. If the PET scan was positive before therapy, the on-treatment PET is positive in ≥ 1 previously involved site.
- Persistence of bone marrow involvement in a subject who meets other criteria for CR based on the disappearance of all nodal and extranodal masses

1.5.3. Stable Disease

To satisfy criteria for SD, all of the following conditions must be attained:

- No evidence of new disease
- Neither sufficient tumor shrinkage from baseline to qualify for PR nor sufficient evidence of tumor growth to qualify for PD
- If PET-CT performed, the results show a score of 4 (uptake moderately > liver) or score of 5 (uptake markedly > liver) on the Deauville 5-point scale with no significant change in uptake compared with baseline.

1.5.4. Progressive Disease

The occurrence of any of the following events indicates progressive disease (PD):

- Evidence of any new disease that was not present at baseline:
  - A new node that measures > 1.5 cm in any diameter
  - A new node that measures > 1.0 cm to ≤ 1.5 cm in the LD and > 1.0 cm in the LPD

- Reappearance of an extranodal lesion that had resolved (i.e., had previously been assigned a PPD of 0 cm^2)
- A new extranodal lesion of any size
- New non-index disease (e.g., effusions, ascites, or other organ abnormalities) of any size unequivocally attributable to lymphoma (usually requires PET, biopsy, cytology, or other non-radiologic confirmation to confirm disease attributable to lymphoma). ***Note: Isolated new effusions, ascites, or bone lesions are not sufficient evidence alone of PD unless histologically confirmed. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are usually benign. Thus, a declaration of PD should not be made if this is the only manifestation of an apparently new lesion.***
- New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If there is uncertainty regarding the etiology of new lesions, biopsy or interval scan may be considered.
- New or recurrent bone marrow involvement with lymphoma by PET-CT or by bone marrow biopsy if prior PET-CT or bone marrow biopsy performed as part of the study was negative for lymphoma.

- Evidence of worsening of nodal or extranodal index lesions:
  - Increase from the nadir by ≥ 50% in the SPD of index lesions
  - Evidence of worsening of individual index lymph nodes or nodal masses:
    - Increase from the nadir by ≥ 50% in the PPD for any individual node if the node now has an LD of > 1.5 cm and there is an absolute change from the nadir of ≥ 0.5 cm in the LD or LPD and to an absolute dimension of ≥ 2.0 cm.
    - Increase from the nadir by ≥ 50% in the LD for any individual node if the node now has an LD of > 1.5 cm and there is an absolute change from the nadir of ≥ 0.5 cm in the LD
    - Increase from the nadir by ≥ 50% in the LPD for any individual node if the node now has an LPD of > 1.5 cm and there is an absolute change from the nadir of ≥ 0.5 cm in the LPD
    - If a lesion had been classified as a small lymph node, there is an additional requirement that the lesion has an LD of > 1.0 cm and an LPD of > 1.0 cm
  - Unequivocal increase in the size of non-index disease
  - Unequivocal worsening in the size of the liver or spleen (with the additional condition that there must be ≥ 1 nodule present in the enlarging organ)
- Transformation to a more aggressive NHL histology as established by lymph node biopsy

- If PET performed, there is a score of 4 (uptake moderately > liver) or score of 5 (uptake markedly >liver) on the Deauville 5-point scale with an increase in uptake compared with the nadir in conjunction with an anatomic increase in lesion size consistent with PD.

Note: Study subjects undergoing PET for lymphoma assessment can experience transient disease flare on imaging before having subsequent therapy-induced tumor regression. Worsening of constitutional symptoms or performance status in the absence of objective evidence of worsening lymphoma (e.g., due to infection) may not represent definitive disease progression. Further, transient worsening of disease during temporary interruptions of study therapy (e.g., for drug-related toxicity or inter-current illness) may not indicate definitive progressive lymphoma. If there is uncertainty regarding whether there is true lymphoma progression and if medically appropriate, the subject may continue or resume study treatment and remain under close observation (e.g., evaluated at 3- to 6-week intervals) while relevant radiographic, clinical, and/or laboratory assessments are performed to document whether tumor control can be maintained or whether disease progression has truly occurred. If subsequent evaluations suggest that the subject has experienced persistent definitive disease progression, then the date of progression will be the timepoint at which progression was first objectively documented.

1.5.5. Nonevaluable

In a subject who does not have evidence of PD, the occurrence of any of the following conditions indicates a response status of NE:

- There are no images or inadequate or missing images, defined as the inability to visualize > 25% of index disease and > 50% of non-index disease.

2. CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA

2.1. Tumor Assessment Criteria

The determination of CLL/SLL response and progression will be based on standardized criteria (Hallek 2008), as recently updated (Cheson 2012).

2.2. Method of Assessment

In addition to clinical examination, imaging-based evaluation will be used in this study in all subjects enrolled. CT scan is the preferred method for radiographic tumor assessment. MRI scanning may be used at the investigator's discretion in subjects for whom this may be a preferred alternative to CT scanning; however, if MRI is performed, a non-contrast CT of the chest should be performed. Contrast-enhanced scanning is preferred, but iodine-containing or gadolinium contrast material may be omitted in subjects for whom use of a contrast agent would be medically contraindicated. Chest x-ray, ultrasound, endoscopy, laparoscopy, PET, radionuclide scans, or tumor markers will not be considered for response assessment.

For radiographic evaluations, the same method of assessment and the same technique (e.g., scan type, scanner, subject position, dose of contrast, injection/scan interval) should be used to characterize each identified and reported lesion at baseline and during study treatment and follow-up. However, if a subject is imaged without contrast at baseline, subsequent assessments should be performed with contrast, unless the subject cannot tolerate the contrast.

All relevant clinical and radiographic information required to make each tumor status assessment must be made available for source verification as requested by the study sponsor.

2.3. Timing of Assessments

During screening, clinical, laboratory, and imaging-based tumor assessments should be performed within the specified screening period. Clinical tumor assessments should be performed at each designated clinical visit. On-study CT/MRI tumor assessments should be performed as indicated in Section 8.7. An end-of-study CT/MRI tumor assessment should be performed unless the subject already has radiographic confirmation of disease progression ≤ 4 weeks prior. If a subject permanently discontinues study drug prior to objective documentation of CLL/SLL progression, investigators should optimally attempt to obtain further follow-up at ~12-week intervals until CLL/SLL progression is documented or until the initiation of a new post-study therapy for the subject's CLL/SLL.

2.4. Identification and Measurement of Tumor Lesions and Organomegaly

2.4.1. Index Lesions

At baseline, up to 6 lymph nodes should be selected as index lesions that will be used to quantitate the status of the disease during study treatment. Ideally, the index lesions should be located in disparate regions of the body. Only peripheral nodes need be selected as index lesions. However, it is optimal if mediastinal and retroperitoneal areas of disease are assessed whenever these sites are involved.

Index lesions will be measured and recorded at baseline and at the stipulated intervals. The cross-sectional dimensions (the largest cross-sectional diameter, i.e., the LD × LPD) will be recorded (in cm) for each index lesion. The product of the perpendicular diameters (PPD) (in cm^2) for each index lesion and SPD (in cm^2) for all index lesions will be calculated and recorded. The baseline SPD will be used as references by which objective tumor response will be characterized during treatment. The nadir LD of individual lesions and the nadir SPD will be used as references by which CLL/SLL progression will be characterized. All LD and LPD diameters will be reported in centimeters and all PPDs and SPDs will be reported in centimeters squared.

A nodal mass may be selected as a nodal index lesion if it is both abnormal and measurable at baseline. A lymph node lesion is considered abnormal if it has a single diameter that is > 1.5 cm and is considered measurable if it has 2 perpendicular diameters that can be accurately measured in cross section with the LD being ≥ 1.0 cm and the LPD also being ≥ 1.0 cm.

Index lesions measuring > 1.5 cm in the LD, regardless of the measurement of the LPD, will be prioritized during baseline index lesion selection.

At follow-up timepoints, the LDs for individual lesions and the SPD of all nodal index lesions will be considered. Because nodal index lesions that have one or both diameters > 0 cm and < 1.0 cm cannot be reliably measured, a default value of 1.0 cm will be assigned for each diameter that meets these criteria and the resulting PPD will be used in SPD calculations. Based on this convention, a CR may be achieved even if an SPD value is > 0 cm^2, (i.e., if all lymph nodes measure < 1.0 cm^2).

A new node that measures > 1.5 cm in any diameter or a new node that measures > 1.0 cm to ≤ 1.5 cm in the LD and measures > 1.0 cm in the LPD will be considered progressive disease.

In cases in which a large lymph node mass has split into multiple components, only those elements that are > 1.0 cm in ≥ 1 diameter will be considered abnormal and used in calculating the SPD. Progression of the lesion can only be based on the SPD of abnormal sub-components. Lesion sub-components that are considered normal but measurable will have the true PPDs calculated, with the result used only for calculating an accurate nadir. Similarly, lesion sub-components that are visible but neither abnormal nor measurable will have the default PPD of 1.0 cm^2 (1.0 cm × 1.0 cm) stored only for the purposes of calculating the nadir SPD value.

If lesions merge, a boundary between the lesions will be established so the LD of each individual lesion can continue to be measured. If the lesions have merged in a way that they can no longer be separated by this boundary, the newly merged lesion will be measured bi-dimensionally.

2.4.2. Spleen and Liver

Both the spleen and liver will be assessed by CT/MRI scan and by physical examination at baseline and at the stipulated intervals during treatment. The baseline and nadir values for the longest vertical dimension (LVD) of each organ will be used as reference to further characterize the objective tumor response of the measurable dimensions of the CLL/SLL during treatment. All spleen and liver LVD measurements should be recorded in centimeters.

Physical examination of the spleen should comprise assessment of its LVD below the left costal margin by palpation. By physical examination, the spleen will be considered enlarged if it is palpable below the left costal margin. If the spleen is not palpable below the left costal margin, it should be assigned a value of 0 cm for physical examination assessment. By imaging, the spleen will be considered enlarged if it is > 12 cm in LVD (Bezerra 2005, Asghar 2011), with the LVD being obtained by multiplying the number of sections on which the spleen is visualized by the thickness of the sections (e.g., if the spleen is seen in 14 contiguous cross-sectional images with 0.5-cm thickness, the LVD is recorded as 7 cm).

For subjects with splenomegaly at baseline or at the splenic LVD nadir, respective response and progression evaluations of the spleen will consider only changes relative to the enlargement of the spleen (i.e., the portion of the LVD that is > 0 cm by physical examination or > 12 cm by imaging) at baseline or nadir, not changes relative to the total splenic LVD.

A 50% decrease from baseline (minimum decrease of 2 cm) in the enlargement of the spleen in its LVD or to ≤ 12 cm by imaging, or regression to a spleen LVD of ≤ 0 cm by physical examination, is required for declaration of a splenomegaly response. Conversely, an increase in splenic enlargement by ≥ 50% (minimum increase of 2 cm) from nadir is required for declaration of splenic progression. Subjects with a normal spleen LVD (i.e., a LVD of ≤ 0 cm by physical

examination or ≤ 12 cm by imaging) at nadir will only be considered to have progressed if the spleen attains a LVD of > 14 cm by imaging or > 2 cm by physical exam.

Physical examination of the liver should comprise assessment of its LVD at the right midclavicular line by percussion. By physical examination, the liver will be considered enlarged if it is > 15 cm in LVD as assessed by percussion (Walker 1990). By imaging, the liver will be considered enlarged if it is > 18 cm in LVD (Erturk 2006).

A 50% decrease (minimum decrease of 2 cm) from baseline in the enlargement of the liver in its LVD or to ≤ 18 cm by imaging, or regression to a liver LVD of ≤ 15 cm by physical examination, is required for declaration of a hepatomegaly response. Conversely, an increase in liver enlargement by ≥ 50% (minimum increase of 2 cm) from nadir is required for declaration of hepatic progression. Subjects with a normal liver LVD (i.e., a LVD of ≤ 15 cm by physical examination or ≤ 18 cm by imaging) at nadir will only be considered to have progressed if the liver attains a LVD of > 20 cm by imaging or > 17 cm by physical exam.

2.4.3. Non-Index Lesions

Any other measurable and abnormal nodal lesions not selected for quantitation as index lesions may be considered non-index lesions. In addition, non-measurable evidence of CLL/SLL such as nodal lesions with both diameters < 1.0 cm, extranodal lesions, bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusions, lymphangitis of the skin or lung, abdominal masses that are not confirmed and followed by imaging techniques, cystic lesions, previously irradiated lesions, and lesions with artifacts may be considered as non-index disease.

The presence or absence of non-index disease should be recorded at baseline and at the stipulated intervals during treatment. If present at baseline, up to 6 non-index lesions should be recorded. The non-index disease at baseline will be used as a general reference to further characterize regression or progression of CLL/SLL during assessments of the objective tumor response during treatment. Measurements are not required and these lesions should be followed as "present" or "absent".

2.5. Definitions of Tumor Response and Progression

Responses will be categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). In addition, a response category of nonevaluable (NE) is provided for situations in which there is inadequate information to otherwise categorize response status.

The best overall response will be determined. The best overall response is the best response recorded from the start of treatment until disease/recurrence progression (taking as a reference for disease progression the smallest measurements recorded since treatment started). Subjects with a best overall response of NE or ND will be counted in the denominators in calculations of tumor response rates. Where imaging data are available, these data will supersede physical examination data in determining tumor status.

2.5.1. Complete Response and Complete Response with Incomplete Blood Count Recovery

To satisfy criteria for CR or CRi, all of the following conditions must be attained:

- No evidence of new disease
- ALC in peripheral blood of $< 4 \times 10^9$/L
- Regression of all index nodal masses to normal size ≤ 1.5 cm in the LD
- Normal spleen and liver size
- Regression to normal of all nodal non-index disease and disappearance of all detectable non-nodal, non-index disease
- Morphologically negative bone marrow defined as < 30% of nucleated cells being lymphoid cells and no lymphoid nodules in a bone marrow sample that is normocellular for age
- Peripheral blood meeting all of the following criteria:
  - ANC $\geq 1.5 \times 10^9$/L without need for exogenous growth factors (e.g., G-CSF)
  - Platelet count $\geq 100 \times 10^9$/L without need for exogenous growth factors
  - Hemoglobin ≥ 110 g/L (11.0 g/dL) without red blood cell transfusions or need for exogenous growth factors (e.g., erythropoietin)

Note: Subjects who fulfill all the criteria for a CR (including bone marrow criteria) but who have a persistent anemia, thrombocytopenia, or neutropenia or a hypocellular bone marrow that is related to prior or ongoing drug toxicity (and not to CLL/SLL) will be considered as a CR with incomplete marrow recovery (CRi).

2.5.2. Partial Response

To satisfy criteria for a PR, all of the following conditions must be attained:

- No evidence of new disease
- A change in disease status meeting ≥ 2 of the following criteria, with 2 exceptions in which only 1 criterion is needed: (1) Only lymphadenopathy is present at baseline; or (2) only lymphadenopathy and lymphocytosis are present at baseline; in these 2 cases, only lymphadenopathy must improve to the extent specified below:
  - Decrease in peripheral blood ALC by ≥ 50% from baseline
  - A decrease by ≥ 50% from the baseline in the SPD of the index nodal lesions
  - In a subject with enlargement of the spleen at baseline, a splenomegaly response as defined in Section 2.4.2
  - In a subject with enlargement of the liver at baseline, a hepatomegaly response as defined in Section 2.4.2

  - A decrease by ≥ 50% from baseline in the CLL/SLL marrow infiltrate or in B-lymphoid nodules

- No index, splenic, liver, or non-index disease with worsening that meets the criteria for definitive PD
- Peripheral blood meeting ≥ 1 of the following criteria:
  - ANC ≥ 1.5 x 10^9/L or ≥ 50% increase over baseline without need for exogenous growth factors (e.g., G-CSF)
  - Platelet count ≥ 100 x 10^9/L or ≥ 50% increase over baseline without need for exogenous growth factors
  - Hemoglobin ≥ 110 g/L (11.0 g/dL) or ≥ 50% increase over baseline without red blood cell transfusions or need for exogenous growth factors (e.g., erythropoietin)

2.5.3. Stable Disease

To satisfy criteria for SD, the following conditions must be attained:

- No evidence of new disease
- There is neither sufficient evidence of tumor shrinkage to qualify for PR nor sufficient evidence of tumor growth to qualify for definitive PD

2.5.4. Progressive Disease

The occurrence of any of the following events indicates PD:

- Evidence of any new disease:
  - A new node that measures > 1.5 cm in any diameter
  - New splenomegaly as defined in Section 2.4.2
  - New hepatomegaly as defined in Section 2.4.2
  - New non-index disease (e.g., effusions, ascites, or other organ abnormalities related to CLL/SLL)

Note: Isolated new effusions, ascites, or other organ abnormalities are not sufficient evidence alone of PD unless histologically confirmed. Thus, a declaration of PD should not be made if this is the only manifestation of apparently new disease.

- Evidence of worsening of index lesions, spleen or liver, or non-index disease:
  - Increase from the nadir by ≥ 50% from the nadir in the SPD of index lesions
  - Increase from the nadir by ≥ 50% in the LD of an individual node or extranodal mass that now has an LD of > 1.5 cm and an LPD of > 1.0 cm
  - Splenic progression as defined in Section 2.4.2
  - Hepatic progression as defined in Section 2.4.2

  - Unequivocal increase in the size of non-index disease (e.g., effusions, ascites, or other organ abnormalities related to CLL/SLL)
  - Transformation to a more aggressive histology (e.g., Richter syndrome) as established by lymph node biopsy (with the date of the lymph node biopsy being considered the date of CLL/SLL progression if the subject has no earlier objective documentation of CLL/SLL progression)

- Decrease in platelet count or hemoglobin that is attributable to CLL/SLL, is not attributable to an autoimmune phenomenon, and is confirmed by bone marrow biopsy showing an infiltrate of clonal CLL/SLL cells
  - The current platelet count is < 100 x 10^9/L and there has been a decrease by > 50% from the highest on-study platelet count
  - The current hemoglobin is < 110 g/L (11.0 g/dL) and there has been a decrease by > 20 g/L (2 g/dL) from the highest on-study hemoglobin

Note: If there is uncertainty regarding whether there is true progression, the subject should continue study treatment and remain under close observation (e.g., evaluated at 4-week intervals) pending confirmation of progression status. In particular, worsening of constitutional symptoms in the absence of objective evidence of worsening CLL/SLL will not be considered definitive disease progression; in such subjects, both CLL/SLL-related and non-CLL/SLL-related causes for the constitutional symptoms should be considered. Worsening of disease during temporary interruption of study treatment (e.g., for intercurrent illness) is not necessarily indicative of resistance to study treatment. In these instances, CT/MRI or other relevant evaluations should be considered in order to document whether definitive disease progression has occurred. If subsequent evaluations suggest that the subject has experienced persistent definitive CLL/SLL progression, then the date of progression should be the timepoint at which progression was first objectively documented.

2.5.5. Nonevaluable

In a subject who does not have evidence of PD, the occurrence of any of the following conditions indicates a response status of NE:

- There are no images or inadequate or missing images
- Images of the liver and spleen are missing at that timepoint (with the exception that absence of splenic images will not result in an NE designation in a subject known to have undergone splenectomy).

2.5.6. Lymphocytosis during Therapy

Lymphocytosis early in therapy may not represent disease progression in subjects who have persistent control of other CLL/SLL-related signs and symptoms. ***In the absence of other objective evidence of disease progression, lymphocytosis alone will not preclude subjects from meeting the criteria for PR if other criteria for PR are met and will not be considered evidence of disease progression if occurring in isolation.*** Subjects with lymphocytosis should be continued on study drug until the occurrence of definitive disease progression (i.e., disease

progression that is manifest by worsening CLL/SLL-related signs other than lymphocytosis alone), or the occurrence of another reason to discontinue study therapy.

Appendix 3. Potential Drug Interactions with LAM-002A

Table 15: CYP2C9 and CYP3A Inhibitors and Inducers

CYP2C9 Inhibitors Z			
Strong	**Moderate**	**Weak**	**Other**
fluconazole	amiodarone		efavirenz isoniazid metronidazole paroxetine sulfamethoxazole voriconazole
CYP2C9 Inducers			
Strong	**Moderate**	**Weak**	**Other**
			carbamazepine nevirapine phenobarbital rifampin St. John's Wort
CYP3A Inhibitors			
Strong	**Moderate**	**Weak**	**Other**
Boceprevir Clarithromycin Cobicistat Conivaptan Fluvoxamine Grapefruit Juice (in large amounts, > 1 liter a day, and in high concentrations) Indinavir Itraconazole Ketoconazole Lopinavir and Ritonavir Nefazodone Nelfinavir Posaconazole Quinupristin Ritonavir	Aprepitant Atazanavir Ciprofloxacin Darunavir Diltiazem Dronedarone Erythromycin Fluconazole Fosamprenavir Grapefruit Juice (in lower concentrations and smaller amounts) Imatinib Verapamil	Alprazolam Amiodarone Amlodipine Atorvastatin Bicalutamide Cilostazol Cimetidine Cyclosporine Fluoxetine Ginkgo Goldenseal Imipramine Isoniazid Nilotinib Oral contraceptives Ranitidine Ranolazine	Azithromycin Bromocriptine Chloramphenicol Delavirdine Desipramine Danazol Felodipine Iloperidone Linagliptin Nicardipine Nifedipine Quinidine Simeprevir Zafirlukast

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Table 15: CYP2C9 and CYP3A Inhibitors and Inducers (Continued)

CYP3A Inhibitors			
Strong	**Moderate**	**Weak**	**Other**
Saquinavir Telaprevir Telithromycin Voriconazole		Tipranavir Zileuton	
CYP3A Inducers			
Strong	**Moderate**	**Weak**	**Other**
Carbamazepine Phenobarbital Phenytoin Rifampin St. John's Wort	Bosentan Efavirenz Etravirine Modafinil Nafcillin	Aprepitant Armodafinil Echinacea Pioglitazone Prednisone Rufinamide Topiramate	Dexamethasone Felbamate Fosamprenavir Griseofulvin Nevirapine Oxcarbazepine Rifabutin Rifapentine Tocilizumab Tumor Necrosis Factor inhibitors

Source: Flockhart 2007

Table 16: Drugs Known to Prolong the QT Interval and/or Cause Torsades De Pointes (TDP)

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Amiodarone	Cordarone®, Pacerone®, Nexterone®	Antiarrhythmic	Abnormal heart rhythm
Anagrelide	Agrylin®, Xagrid®	Phosphodiesterase 3 inhibitor	Thrombocythemia
Arsenic trioxide	Trisenox®	Anticancer	Cancer (leukemia)
Astemizole (removed from market)	Hismanal®	Antihistamine	Allergic rhinitis
Azithromycin	Zithromax®, Zmax®	Antibiotic	Bacterial infection
Bepridil (removed from market)	Vascor®	Antianginal	Angina Pectoris (heart pain)
Chloroquine	Aralen®	Antimalarial	Malaria
Chlorpromazine	Thorazine®, Largactil®, Megaphen®	Antipsychotic / Antiemetic	Schizophrenia, nausea, many others
Cilostazol	Pletal®	Phosphodiesterase 3 inhibitor	Intermittent claudication
Ciprofloxacin	Cipro®, Cipro-XR®, Neofloxin®	Antibiotic	Bacterial infection
Cisapride (removed from market)	Propulsid®	Gastrointestinal stimulant	Increase gastrointestinal motility
Citalopram	Celexa®, Cipramil®	Antidepressant, selective serotonin reuptake inhibitor	Depression
Clarithromycin	Biaxin®, Prevpac®	Antibiotic	Bacterial infection
Cocaine	Cocaine	Local anesthetic	Anesthesia (topical)
Disopyramide	Norpace®	Antiarrhythmic	Abnormal heart rhythm
Dofetilide	Tikosyn®	Antiarrhythmic	Abnormal heart rhythm
Domperidone (only on non-US market)	Motilium®, Motillium®, Motinorm Costi®, Nomit®	Antinausea	Nausea, vomiting
Donepezil	Aricept®	Cholinesterase inhibitor	Dementia (Alzheimer's Disease)
Dronedarone	Multaq®	Antiarrhythmic	Abnormal heart rhythm
Droperidol	Inapsine®, Droleptan®, Dridol®, Xomolix®	Antipsychotic / Antiemetic	Anesthesia (adjunct), nausea
Erythromycin	E.E.S.®, Robimycin®, Emycin®, Erymax®, Ery-Tab®, Eryc Ranbaxy®, Erypar®, Eryped®, Erythrocin Stearate Filmtab®, Erythrocot®, E-Base®, Erythroped®, Ilosone®, MY-E®, Pediamycin®, Zineryt®, Abboticin®, Abboticin-ES®, Erycin®, PCE	Antibiotic	Bacterial infection, increase gastrointestinal motility

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
	Dispertab®, Stiemycine®, Acnasol®, Tiloryth®		
Escitalopram	Cipralex®, Lexapro®, Nexito®, Anxiset-E® (India), Exodus® (Brazil), Esto® (Israel), Seroplex®, Elicea®, Lexamil®, Lexam®, Entact® (Greece), Losita® (Bangladesh), Reposil® (Chile), Animaxen® (Colombia), Esitalo® (Australia), Lexamil® (South Africa)	Antidepressant, selective serotonin reuptake inhibitor	Depression (major), anxiety disorders
Flecainide	Tambocor®, Almarytm®, Apocard®, Ecrinal®, Flécaine®	Antiarrhythmic	Abnormal heart rhythm
Fluconazole	Diflucan®, Trican®	Antifungal	Fungal infection
Gatifloxacin (removed from market)	Tequin®	Antibiotic	Bacterial infection
Grepafloxacin	Raxar®	Antibiotic	Bacterial infection
Halofantrine	Halfan®	Antimalarial	Malaria
Haloperidol	Haldol® (US & UK), Aloperidin®, Bioperidolo®, Brotopon®, Dozic®, Duraperidol® (Germany), Einalon S®, Eukystol®, Halosten®, Keselan®, Linton®, Peluces®, Serenace®, Serenase®, Sigaperidol®	Antipsychotic	Schizophrenia, agitation
Ibogaine (only on non-US market)	None	Psychedelic	Narcotic addiction, unproven
Ibutilide	Corvert®	Antiarrhythmic	Abnormal heart rhythm
Levofloxacin	Levaquin®, Tavanic®	Antibiotic	Bacterial infection
Levomepromazine (methotrimeprazine) only on non-US market)	Nosinan®, Nozinan®, Levoprome®	Antipsychotic	Schizophrenia
Levosulpiride (only on non-US market)	Lesuride®, Levazeo®. Enliva® (with rabeprazole)	Antipsychotic	Schizophrenia
Levomethadyl acetate (removed from market)	Orlaam®	Opioid agonist	Narcotic dependence
Mesoridazine (removed from market)	Serentil®	Antipsychotic	Schizophrenia
Methadone	Dolophine®, Symoron®, Amidone®, Methadose®,	Opioid agonist	Narcotic dependence, pain

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
	Physeptone®, Heptadon®		
Moxifloxacin	Avelox®, Avalox®, Avelon®	Antibiotic	Bacterial infection
Ondansetron	Zofran®, Anset®, Ondemet®, Zuplenz®, Emetron®, Ondavell®, Emeset®, Ondisolv®, Setronax®	Antiemetic	Nausea, vomiting
Oxaliplatin	Eloxatin®	Antineoplastic Agent	Cancer
Papaverine HCl	none	Vasodilator, Coronary	Diagnostic adjunct
Pentamidine	Pentam®	Antifungal	Fungal infection (Pneumocystis pneumonia)
Pimozide	Orap®	Antipsychotic	Tourette's Disorder
Probucol (removed from market)	Lorelco®	Antilipemic	Hypercholesterolemia
Procainamide	Pronestyl®, Procan®	Antiarrhythmic	Abnormal heart rhythm
Propofol	Diprivan®, Propoven®	Anesthetic, general	Anesthesia
Quinidine	Quinaglute®, Duraquin®, Quinact®, Quinidex®, Cin-Quin®, Quinora®	Antiarrhythmic	Abnormal heart rhythm
Roxithromycin (only on non-US market)	Rulide®, Xthrocin®, Roxl-150®, Roxo®, Surlid®, Rulide®, Biaxsig®, Roxar®, Roximycinv®, Roxomycin®, Rulid®, Tirabicin®, Coroxin®	Antibiotic	Bacterial infection
Sevoflurane	Ulane®, Sojourn®	Anesthetic, general	Anesthesia
Sotalol	Betapace®, Sotalex®, Sotacor®	Antiarrhythmic	Abnormal heart rhythm
Sparfloxacin (removed from market)	Zagam®	Antibiotic	Bacterial infection
Sulpiride (only on non-US market)	Dogmatil®, Dolmatil®, Eglonyl®, Espiride®, Modal®, Sulpor®	Antipsychotic, atypical	Schizophrenia
Sultopride (only on non-US market)	Barnetil®, Barnotil®, Topral®	Antipsychotic, atypical	Schizophrenia
Terfenadine (removed from market)	Seldane®	Antihistamine	Allergic rhinitis
Terlipressin (only on non-US market)	Teripress®, Glypressin®, Terlipin®, Remestyp®, Tresil®, Teriss®, and others	Vasoconstrictor	Septic shock
Terodiline (only on non-US market)	Micturin®, Mictrol® (not bethanechol)	Muscle relaxant	Bladder spasm

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Thioridazine	Mellaril®, Novoridazine®, Thioril®	Antipsychotic	Schizophrenia
Vandetanib	Caprelsa®	Anticancer	Cancer (thyroid)

Note: Includes those drugs known to prolong the cardiac QT interval or cause TdP (Woosley 2018).

Abbreviation: QT: Time of start of Q wave until end of T wave in the heart's electrical cycle; TdP: Torsades de Pointes; UK: United Kingdom; US: United States

Appendix 4. Summary of Protocol Changes

Changes made in Amendment 1 (17 Jul 2015)

The primary purpose of this amendment is to reflect a change in manufacturing of Investigational Product from a tablet to capsule. Wording throughout the protocol as well as the description of the Investigational Product has been amended accordingly. Additional changes have been made to provide clarity and consistency and include the following:

- Provisional Dose Levels Table 2 was revised to correctly reflect the percent increase from 200 mg to 275mg (37.5%).
- A statement has been added to prohibit administration of live vaccines during the study due to the potential immunomodulatory effect of apilimod dimesylate.
- Schedule of Assessments Table 4 has been revised to delete the Day 8 column for Cycle 3 and Beyond as there are no assessments, other than at home dosing, on this day.
- Statement(s) regarding self-administered dosing have been amended to clarify that subjects must fast for 2 hours prior to and 2 hours after dose administration.
- Protocol section 12 has been revised to indicate that blood samples for plasma concentration (PK) levels of product and metabolites will be collected during Dose Expansion as well as Dose Escalation.
- The PK sample collection window was revised in Table 6 from +/- 1 hr to +/- 10 minutes for the 6 hr collection time points on Day 1 and Day 8.

Changes made in Amendment 2 (14 Oct 2015)

The primary purpose of this amendment is to update the biomarker / tumor tissue analysis and associated time points. Blood smears from treated subjects will be analyzed by microscopy for changes in the extent of vacuolation in white blood cells as a phenotypic marker of PIKfyve inhibition. Tumor tissue will be examined for the presence of infiltrating immune cells (e.g., tumor infiltrating lymphocytes, tumor associated macrophages) as a means to understand the potential immunomodulatory effect of LAM-002A. Additionally plasma will be assayed by proteomic technology for analytes that may predict anti-lymphoma activity.

Changes made in Amendment 3 (21 Mar2016)

This amendment documented a change in the medical monitor for the study. Information regarding acquisition of data for exploratory endpoints was clarified or updated. Methods of efficacy analysis were updated and were made more complete. Eligibility criteria were updated regarding tumor measurability in patients with CLL/SLL, allowed concomitant medications, and acquisition of tumor, surrogate, and control samples at baseline. Treatment guidelines and dose-modification provisions were simplified and clarified. The reasons for discontinuing a subject from study therapy were made more specific. Information regarding the disposition and destruction of study drug was clarified.

Changes made in Amendment 4 (07 Nov 2016)

In this amendment, the description of the drug product was updated with information relating to newly introduced 50-mg capsules. Descriptions of emerging safety and efficacy data were

provided. Intermediate BID dose levels were added and TID dosing regimens were introduced. The maximum number of subjects was increased to accommodate the larger number of dosing regimens to be evaluated. Post-treatment follow-up methods were clarified. The types of archival or fresh tissue to be collected during screening were clarified. Recommendations regarding management of gastrointestinal AEs were updated to reflect the evolving safety profile of the study drug. The definitions of analysis sets to be evaluated were clarified.

Changes made in Amendment 5 (14 Apr 2017)

In this amendment, medical prophylaxis has been mandated for subjects at intermediate to high risk of TLS and a recommendation has been included that subjects at high risk of TLS be monitored as inpatients during the first 24 to 48 hours of LAM-002A administration. In addition, TLS has been removed as a DLT exclusion. Serum chemistry laboratory monitoring for TLS has now been included on Days 2 and 3 of Cycle 1 for subjects at intermediate to high risk of TLS (as defined in Section 6.8.1 of the protocol).

Changes made in Amendment 6 (25 Oct 2017)

This amendment modified the protocol to evaluate the safety and tolerability of LAM-002A when given alone and in combination with rituximab or atezolizumab for the treatment of subjects with relapsed or refractory B-cell non-Hodgkin's lymphoma. In support of the addition of combination therapy to the protocol:

- Additional information was added to support the rationale for combination therapy with LAM-002A and rituximab or atezolizumab.
- The trial objectives and endpoints were revised to indicate that LAM-002A will be evaluated alone and in combination with other drugs and to indicate changes in the types of pharmacodynamic assays that were to be performed as a result of evolving experience with these exploratory assays.
- The study design was modified to:
  - include further dose exploration using an intermittent LAM-002A dosing regimen with antiemetic and antidiarrheal support as a result of previous findings that nausea, vomiting, and diarrhea were treatment-limiting when LAM-002A was given continuously at doses ≥150 mg twice per day (BID),
  - identify the disease indications and combination regimens to be administered in the expansion stage,
  - include additional information on subject allocation given the plan to explore monotherapy and combination therapy and place restrictions of Stage 1 and 2 enrollment,
  - clarify subject evaluability criteria for the dose-ranging and cohort-expansion portions of the study, and
  - revise the number of subjects participating in each portion of the trial.
- The LAM-002A dose-escalation procedures were revised consistent with the new dose-escalation and cohort-expansion portions of the study, and additional information on

premedications, administration of LAM-002A in the clinic and on an outpatient basis, dose modifications, and supportive care was added.

- Information (including description, packaging, source, storage and stability, solution preparation, and accountability) was added for rituximab and atezolizumab. Instructions were added regarding administration, dose modifications, and supportive care for rituximab and atezolizumab.
- A section on study restrictions was added to provide guidance for the investigators with regard to breast feeding, contraception, and diet.
- The duration of study participation was revised to include instructions for administration of LAM-002A as monotherapy and as combination therapy. Consistent with intention-to-treat principles designed to maximize collection of safety and efficacy data, subjects were allowed to continue on either of the combination agents even if the other agent were to be discontinued due to toxicity.
- The subject inclusion/exclusion criteria were revised as follows:
  - On mechanistic grounds, primary mediastinal B-cell lymphoma (PMBL) might respond to LAM-002A therapy; for this reason, patients with this type of lymphoma could be accrued to the dose-ranging portion of the trial.
  - A requirement for prior rituximab therapy was no longer mandated given that some patients (eg, those with chronic lymphocytic leukemia/small lymphocytic leukemia [CLL/SLL]) might not have received rituximab as prior therapy based on changing standards of care.
  - Organ function criteria for hematological function, hepatic function, and renal function were updated based on the evolving safety profile of LAM-002A showing that the drug is unlikely to adversely alter these organ systems.
  - The contraception enrollment criteria were made more specific.
  - The requirements for baseline bone marrow collection in patients with lymphoma were clarified.
  - Prior therapy prohibitions were now included for study candidates under consideration for combination therapy to minimize the likelihood that they would have disease that is totally resistant to rituximab or atezolizumab.
  - Restrictions on use of live-virus vaccines, ongoing therapy for hepatitis B virus, recent therapy with immunostimulatory agents, ongoing use of immunosuppressive therapies, recent serious infection, a history of autoimmunity, or inability to tolerate required supportive care were included; these exclusions were intended to enhance subject safety and to avoid comorbid conditions that could confuse interpretation of safety findings.
  - The requirements relating to baseline serological testing for chronic viral infections were clarified.
- Separate schedules of activities were prepared for LAM-002A continuous monotherapy administration, LAM-002A intermittent monotherapy administration,

LAM-002A/rituximab combination therapy, and LAM-002A/atezolizumab combination therapy.

- Additional information regarding collection of samples for pharmacokinetic and biomarker determinations was added.
- The statistical section was revised to provide:
  - more detailed information on the statistical basis for the Stage 1 dose-ranging approach, and
  - the statistical basis for the planned Stage 2 cohort size.

In addition to the above, administrative changes in section ordering were made to enhance the organization of information in the protocol.

Changes made in Amendment 7 (14 Jan 2019)

The following substantive changes were made to the protocol in this amendment:

- Introductory information regarding LAM-002A efficacy and safety was updated.
- Information regarding the total potential accrual to the study was updated consistent with modifications to the protocol to evaluate single-agent LAM-002A or the LAM-002A/rituximab combination in additional patients with FL.
- A statistical justification for accrual of additional patients with FL to receive LAM-002A monotherapy or LAM-002A/rituximab was included.
- In subjects receiving the LAM-002A/rituximab, combination use of either intravenously administered rituximab or subcutaneously administered rituximab hyaluronidase human was permitted. Relevant changes were made throughout the protocol to provide necessary dosing, administration, and drug product information for rituximab hyaluronidase human.

The following clarifying changes were made to the protocol in this amendment:

- The exploratory objectives and endpoints were updated to reflect changes to the substrates and parameters being analyzed.
- Biopsy procedures were clarified.
- The severity of hypertension warranting exclusion from protocol therapy was clarified.
- The text was clarified to indicate that past pathology data should be collected as part of each subject's medical history.
- In the schedules of activities, text regarding the timing of laboratory assessments was clarified.
- Information regarding pharmacovigilance reporting of pregnancies was corrected.
- Information regarding drugs with known risk of QT prolongation or torsades de pointes was updated and the relevant reference was revised accordingly.

Changes made in Amendment 8 (18 Feb 2020)

The following changes were made to the protocol in this amendment:

- Changes to the company name (from LAM Therapeutics, Inc. to AI Therapeutics, Inc.) and modifications to the protocol version and date (from Version 8, dated 14 Jan 2019 to Version 9, dated 19 February 2020) were made throughout the document without specific notation.
- Information regarding AI Therapeutics signatories to the protocol was updated.
- Information regarding LAM-002A efficacy in NHL was updated in the protocol introduction.
- Text was included throughout the protocol consistent with addition of an extension stage to the study.
- In the context of transitioning to the extension stage of the study, site monitoring by the contract research organization, Ce3, was discontinued.
- In the context of transitioning to the extension stage of the study, pharmacovigilance monitoring of SAEs and pregnancy was transitioned from the contract research organization, Pharmalex, Inc. to the study sponsor, AI Therapeutics.

Appendix 5. Detailed Protocol Changes

Changes made in Amendment 1 (17 Jul 2015)

Changes from Original Protocol (16 Jun 2015) to Amendment 1 (17 Jul 2015)

Changed to (**changes in red**): [added text **bold**, deleted text as ~~strikethrough~~]

Throughout protocol, all references — Replaced the word tablets with capsules

~~Tablet(s)~~ amended to **Capsules**

Page 27, 4.1 Product Summary; Page 56, Table 5 Physical Description — Changed the physical description of investigational product

Physical description of product including size, weight, composition and inactive ingredients amended from tablet material to capsule material.

Page 38, 6.5 Dose Escalation Procedures — Amended the percent increase on dose level 4 from 27 to 37.5

Table 2: Provisional Dose Levels

	Daily LAM-002A Dose	Percent Increase	Initial Cohort Size
-1	25 mg BID	-50	3
0	50 mg BID	Starting dose	3
1	100 mg BID	100	3
2	150 mg BID	50	3
3	200 mg BID	33	3
4	275 mg BID	~~27~~37.5	3

Page 44, Table 4 Schedule of Assessments — Removed Day 8 column from Cycle 3 and Beyond

Column deleted from table

Page 11, synopsis on investigational product and dose administration; Page 48, 7.3.3 LAM002A Self-Administration Dosing Diary; Page 57, 9.4 Study Drug Administration — Amended the language with regard to fasting around dosing

~~**They may eat 2 hours before or 2 hours after dose administration**~~

Subjects should fast for 2 hours before and 2 hours after dose administration, with no dietary restrictions otherwise.

Page 54, 8.6.4 Other Concomitant Medications — Added statement about use of live vaccines during study

Vaccines: Administration of live vaccines is prohibited during the study.

Page 64, Section 12 Pharmacokinetic Assessments — Added statement about testing in dose expansion and changed window for hr 6 assessments

Plasma concentration levels of apilimod and the active metabolites will be measured in the Dose Escalation **and Dose Expansion Stages** at each of the specified time points.

Table 6: Pharmacokinetic Sampling Time Points

Sample	Study Day	PK Sampling Time Points*
1**	1	Pre-dose (within 30 min prior to dose of LAM-002A)
2	1	0.5 hour (± 10 min) after dosing with LAM-002A
3	1	1 hour (± 10 min) after dosing with LAM-002A
4	1	2 hours (± 10 min) after dosing with LAM-002A
5	1	4 hours (± 10 min) after dosing with LAM-002A
6	1	6 hours (± ~~1 hr~~ 10 min) after dosing with LAM-002A
7	1	8 hours (± 10 min) after dosing with LAM-002A
8**	8	Pre-dose (within 30 min prior to dose of LAM-002A)
9	8	0.5 hour (± 10 min) after dosing with LAM-002A
10	8	1 hour (± 10 min) after dosing with LAM-002A
11	8	2 hours (± 10 min) after dosing with LAM-002A
12	8	4 hours (± 10 min) after dosing with LAM-002A
13	8	6 hours (± ~~1 hr~~ 10 min) after dosing with LAM-002A
14	8	8 hours (± 10 min) after dosing with LAM-002A
15**	15	Pre-dose (within 30 min prior to dose of LAM-002A)

Changes made in Amendment 2 (14 Oct 2015)

Synopsis: updated dates for accrual

Estimated date first subject enrolled: ~~Sep~~ **Nov** 2015

Estimated date last subject completed: ~~Jan~~ **Mar** 2018

Synopsis, Exploratory Objectives: Removed reference to PBMCs and added blood smear analysis. Added two exploratory objectives.

To evaluate the pharmacodynamic effects of LAM-002A (apilimod dimesylate capsules), administered orally, on tumor samples and surrogate tissue (e.g., **white blood cells in** peripheral blood **smears** ~~mononuclear cells [PBMC]~~).

To evaluate tumor tissue for infiltrating immune cells in order to determine if LAM-002A has potential positive benefit through immune modulation

To evaluate plasma for changes in analytes that may predict anti-lymphoma activity.

Synopsis, Pharmacokinetic Assessment: updated for addition of analyte analysis by proteomic methods.

Pharmacokinetic **and Analyte** Assessment:

- Blood sampling for determination of the plasma concentrations of apilimod and its metabolites will be performed on Cycle 1 Day 1 and Cycle 1 Day 8 as follows: pre-dose, 30 minutes, 1, 2, 4, 6, 8 hours post-dose. Cycle 1 Day 15 pre-dose only. **For analyte determination, pharmacokinetic back-up sample will be used from time points: Cycle 1 Day 1 and Cycle 1 Day 8 pre-dose.**

Synopsis, Biomarker Assessment: Removed reference to PBMCs and added blood smear analysis.

• Blood smears will be obtained for biomarker analysis on Cycle 1 Day 1 and Cycle 1 Day 8 as follows: pre-dose, 4 and 8 hours post-dose; and Cycle 1 Day 15 pre-dose only. Samples will be analyzed by microscopy for changes in the extent of vacuolation in white blood cells as a phenotypic marker of phosphatidylinositol-3-phosphate- 5 kinase (PIKfyve) inhibition. ~~PBMCs will be collected for biomarker analysis prior to the first dose, at the time of tumor assessment and at the EOT visit. Samples will be analyzed for Phosphatidylinositol-3-phosphate-5-kinase (PIKfyve) inhibition by an immunohistochemistry assay and/or extent of vacuolation by microscopy.~~

• Tissue from the most recent available biopsy or surgery prior to first dose will be submitted for biomarker analysis **and determination of immune cell infiltration** to determine genetic alterations, ~~or~~ gene expression **or immune markers** that may predict response to apilimod. Although tumor samples are not required for enrollment of subjects, obtaining and submitting fresh or archival samples is strongly encouraged.

• A bone marrow aspirate (if positive at baseline) and core tumor biopsy will be obtained at the time of the first scheduled tumor assessment (end of Cycle 2). However, the requirement for core tumor biopsy may be waived for subjects whose tumor cannot be safely biopsied or for whom the investigator deems the procedure inappropriate. These tissues will be analyzed for inhibition of PIKfyve~~by an immunohistochemistry assay and~~ **measuring** extent of vacuolation by microscopy. **The biopsy tissue will also be submitted for immunohistochemistry to examine for presence of infiltrating immune cells (e.g., tumor infiltrating lymphocytes and tumor associated macrophages).** Additionally, ribonucleic acid (RNA) will be collected from fresh samples for gene expression analysis.

Synopsis, Investigational product, dosage and mode of administration: provide clarity on consumption of liquids

Subjects will be advised to take the doses at the same time each day, approximately 12 hours apart on an empty stomach (no food within 2 hours prior to dose, or within 2 hours after dose, **only clear liquids allowed in this time window**).

Section 4.1.1 Pharmacology: Updated with references for immunomodulatory properties of LAM-002A.

Apilimod and apilimod dimesylate were originally introduced into clinical trials based on apilimod's immunomodulatory properties (**Wada 2007; Wada 2012**). Apilimod inhibits the production of interleukin-12 (IL-12) and interleukin-23 (IL-23), and was effective in preclinical animal models of various autoimmune diseases that are mediated by the inappropriate expression of T-helper cell phenotype (Th1) cytokines (**Wada 2007**).

Section 5.3, Exploratory Objectives: Updated for change in biomarker assessment. Added exploratory objectives.

To evaluate the pharmacodynamic effects of LAM-002A (apilimod dimesylate capsules), administered orally on tumor samples and surrogate tissue (e.g., **white blood cells in** peripheral blood **smears** ~~mononuclear cells~~).

To evaluate tumor tissue for infiltrating immune cells in order to determine if LAM-002A has potential positive benefit through immune modulation.

To evaluate plasma for changes in analytes that may predict anti-lymphoma activity.

Section 5.6, Exploratory Endpoints: Updated for change in biomarker assessment

Extent of PIKfyve inhibition ~~and~~ **as determined by the extent of** vacuole formation in tumor tissue and **white blood cells in** peripheral blood **smears** ~~mononuclear cells (PBMCs)~~ by ~~immunohistochemical and~~ microscopic **evaluation.** ~~Assay, respectively~~

Extent of immune cell infiltration as determined by immunohistochemistry in tumor tissue.

Correlation between changes in plasma bioanalytes and antilymphoma activity following treatment with LAM-002A as determined by proteomic tools.

Section 6.9, Schedule of Assessments: time points updated and exploratory biomarkers added in table and footnote n, q, r

[n] **For analyte determination, PK back-up sample will be used from time points: Cycle 1 Day 1 and Cycle 1 Day 8 pre-dose.**

[q] **The biopsy tissue will also be examined for presence of infiltrating immune cells.**

[r] ~~PBMCs~~ **Blood smears** will be collected for ~~biomarker analysis~~**microscopic evaluation of vacuole formation on C1D1 and C1D8 as follows: pre-dose, 4 hrs and 8 hrs post first dose of the day. C1D15 pre-dose only.** ~~Prior to the first dose, at the time of tumor assessment and at the end of treatment visit.~~

Section 7.3.3., LAM-002A (Apilimod Dimesylate Capsules) Self-Administration Dosing Diary: added details regarding pre- and post-dose liquid consumption.

Subjects should not eat within 2 hours prior to taking their dose or within 2 hours after taking their dose, with no **solid** diet~~ary~~ restrictions otherwise. **Clear liquids are allowed within the +/- 2 hour fasting window.**

Section 8.8, Treatment Compliance

Subjects will be asked to bring their ~~study medication container and~~ dosing diary with them at each visit. Compliance with protocol-defined study drug intake will be checked by pill count **at the end of each cycle** and compliance decisions will be made by the investigator.

Section 9.4, Study Drug Administration: provide clarity regarding consumption of liquids

Subjects should not eat within 2 hours of or within 2 hours after dose administration; no **solid** diet~~ary~~ restrictions otherwise. **Subjects may consume clear liquids in the 2-hour pre- and post-dose window.**

Section 9.5, Study Drug Accountability: provide clarity on return of study drug

Subjects should be instructed to bring all bottles, including empty bottles, to each ~~subsequent~~ **Day 1 or End of Treatment** study visit for a compliance and product accountability check.

Section 12, Pharmacokinetic Assessments: provide clarity regarding consumption of liquids

Subjects are allowed to eat after PK Sample #4 (hour 2) has been collected. **Subjects may consume clear liquids during fasting periods.**

Section 13, Biomarker Assessments: updated with exploratory biomarker information.

Blood smears will be obtained for biomarker analysis on C1D1 and C1D8 as follows: pre-dose, 4 and 8 hours post-first dose of the day and C1D15 pre-dose only. Samples will be analyzed for PIKfyve inhibition as determined by the extent of vacuolation by microscopy. ~~PBMCs will be collected for biomarker analysis prior to the first dose, at the time of tumor assessment and at the EOT visit. Samples will be analyzed for PIKfyve inhibition by an immunohistochemistry assay and/or extent of vacuolation by microscopy.~~

Tissue from the most recent available biopsy or surgery prior to first dose will be submitted for biomarker analysis to determine genetic alterations or gene expression **and determination of immune cell infiltration** that may predict response to LAM-002A (apilimod dimesylate capsules). Although tumor samples are not required for enrollment of subjects, obtaining and submitting fresh or archival samples is strongly encouraged. **Plasma bioanalytes will be examined by proteomic technology at Cycle 1 Day 1 and Cycle 1 Day 8 to determine changes that may predict response to LAM-002A.**

These tissues will be analyzed for inhibition of PIKfyve by ~~an immunohistochemistry assay and~~ **measuring** the extent of vacuolation by microscopy. **Tissue will also be analyzed by immunohistochemistry for determination of the extent of immune cell infiltration (tumor infiltrating lymphocytes, tumor associated macrophages).**

Section 21, List of References: References added.

Wada Y, Lu R, Zhou D, Chu J, Przewloka T et al. Selective abrogation of Th1 response by STA-5326, a potent IL-12/IL-23 inhibitor. Blood 2007;109:1156-1164.

Wada Y, Cardinale I, Khatcherian A, Chu J et al. Apilimod inhibits the production of IL-12 and IL-23 and reduces dendritic cell infiltration in psoriasis. 2012; PloS ONE 7(4): e35069.

Changes made in Amendment 3 (21 March 2016)

Title Page

Change: The protocol version and date have been updated.

Protocol Version and Date: **Version 4.0, 21 Mar 2016** ~~Version 3.0; 14 October 2015~~

Signature Page

Change: Updated medical monitor name.

Name: Title:	[redacted] Clinical Consultant to LAM Therapeutics	Date

Investigator's Agreement

Change: The date has been updated.

I have read the attached Protocol entitled "A Phase 1 Dose Escalation Study of the Safety and Pharmacokinetics of LAM-002A (apilimod dimesylate capsules) Administered Orally in Subjects with Relapsed or Refractory B-cell Non-Hodgkin's Lymphoma" dated **21 March 2016**~~14 Oct 2015~~.

Procedures in Case of Emergency

Change: The monitor name and contact information have been updated.

Prior to initiation of the study, the sponsor (or its designee) will provide a study roster with contact information for applicable study personnel.

The medical monitor, [redacted], can be reached by telephone at [redacted] and by email at [redacted]

Synopsis

Changes: All of the changes to the synopsis also occur in the body of the protocol. Thus, changes to the synopsis are not described; instead, changes to the body of the protocol are described.

Abbreviations

Change: Abbreviations have been added.

ALC	**Absolute lymphocyte count**
LD	**Longest dimension**
LPD	**Longest perpendicular dimension**

Section 4.1.1 Pharmacology

Change: A paragraph has been added justifying the scientific basis for collection of pre-treatment tumor biopsy material.

LAM Therapeutics has also performed research into the mechanism of action of apilimod cytotoxicity in cancer cells. Putative genes that confer sensitivity / resistance to apilimod have been identified and will be evaluated as potential biomarkers for predicting apilimod efficacy.

Section 5.3 Exploratory Objectives

Change: The objectives have been updated to reflect discontinuation of the plan for on-treatment tumor biopsies and to clarify the types of assessments that will be done in surrogate and normal tissues and plasma to assess drug effects.

- To evaluate the pharmacodynamic effects of LAM-002A (apilimod dimesylate capsules), administered orally, on surrogate tissue (e.g., vacuoles in peripheral blood smears, gene expression in peripheral blood mononuclear cells [PBMCs], and plasma cytokines [including (IL)-12 and IL-23]).
- To evaluate tumor for gene expression and genetic alterations (with saliva collection for germ-line control); and surrogate tissue (PBMC) for gene expression that may predict anti-lymphoma activity.
- To evaluate the pharmacodynamic effects of LAM-002A (apilimod dimesylate capsules), administered orally, on tumor samples and surrogate tissue (e.g., white blood cells in peripheral blood smears).
- To evaluate tumor tissue for genetic alterations and/or gene expression that may predict anti-lymphoma activity.
- To evaluate tumor tissue for infiltrating immune cells in order to determine if LAM-002A has potential positive benefit through immune modulation

Section 5.5 Secondary Endpoints

Change: A additional citation for a reference describing changes to the Hallek criteria has been included

- Response as assessed by the investigator according to modified Lugano Response Criteria for NHL (*Cheson 2014*) and revised guidelines for the diagnosis and treatment of CLL (*Hallek 2008*, ***Cheson 2012***).

Section 5.6 Exploratory Endpoints

Change: The exploratory endpoints have been updated to match the updated exploratory objectives.

- Extent of PIKfyve inhibition as determined by the extent of vacuole formation in ~~tumor tissue and~~ white blood cells in peripheral blood smears by microscopic evaluation.
- Changes in gene expression in PBMCs

- Changes in plasma cytokines (including IL-12 and IL-23).
- Correlation between genetic alterations as determined by next generation sequencing and/or gene expression in tumor tissue **or PBMCs** and anti-lymphoma activity following treatment with LAM-002A (apilimod dimesylate capsules).
- Extent of immune cell infiltration as determined by immunohistochemistry in tumor tissue.
- Correlation between changes in plasma bioanalytes and antilymphoma activity following treatment with LAM-002A as determined by proteomic tools.

Section 6.2 Number of Subjects

Change: The text has been altered for consistency with amendments to the definitions of evaluability in other sections of the protocol document.

Approximately 75 evaluable subjects (evaluable subjects include those who complete Cycle 1 dosing [administered at least **75**~~80~~% of doses] and have sufficient safety data, or who are withdrawn from the study due to a DLT in Cycle 1) will be enrolled, assuming that:

Section 6.4 Treatment Assignment

Change: The description of the enrollment procedures has been updated consistent with current study procedures.

Ce3 will ~~conduct a preliminary~~ review ~~of~~ the subject's eligibility **form to** ~~and in consultation with the medical monitor~~ confirm each subject's eligibility and will complete the enrollment form w**ith** treatment cohort, treatment dose and frequency~~)~~. The enrollment form will be signed and a copy sent to the study site. Once the site receives the completed enrollment form, the subject will begin treatment accordingly. The treatment will be conducted in an open-label manner. Study sites cannot start dosing the subject without receiving the assigned **dose on the returned Subject Enrollment and Eligibility Form**~~subject number first~~.

Section 6.4.1.2 Treatment Period

Change: The text has been updated for consistency with other sections of the protocol that now indicate the full list of reasons for treatment discontinuation.

The subject is treated and monitored for safety (including assessments of AEs, vital signs, ECGs, laboratory tests and concomitant medications). Additionally, preliminary anti-tumor activity will be assessed and PK and biomarker samples will be collected. In the absence of ~~progressive disease (PD) and/or intolerable toxicity~~**protocol-defined reasons to discontinue therapy,** subjects may continue to receive study treatment for up to 1 year at the discretion of the investigator and beyond 1 year with the agreement of the investigator and the sponsor.

Section 6.4.1.3 Post-Treatment Period

Change: The text has been clarified to separate the end-of-treatment (EOT) visit from the post-treatment period and to specify the nature of the follow-up required in the post-treatment period.

Subjects should be followed until the later of either 30 days after the last dose of study treatment or until resolution/stabilization of any ongoing drug-related AEs and/or SAEs.

For subjects with events that require follow-up, information regarding concomitant medications should be collected. Any necessary follow-up may be obtained in person or by telephone contact.

~~The subject returns to the study site 30-37 days after the last dose of LAM-002A (apilimod dimesylate capsules) for an EOT assessment. All serious treatment-emergent AEs and those AEs assessed by the investigator as related to study drug should continue to be followed until they resolve or stabilize, whichever comes first.~~

Section 6.5 Dose Escalation Procedures

Changes: The text has been reorganized so as to use a consistent approach in both the synopsis and body of the protocol in presenting dose escalation information.

For clarity, additional information regarding the dose levels to be studied is now provided.

The DLT criterion relating to the required amount of first-cycle therapy has been made more specific to enhance interpretability.

~~Subject enrollment will proceed according to a 3 + 3 design. The starting dose of LAM-002A (apilimod dimesylate capsules) will be 50 mg administered orally BID. In the absence of DLT, subsequent dose levels will increase sequentially according to Table 3, adjusted to accommodate available capsule strengths.~~

Apilimod dimesylate will be administered on a twice daily (BID) oral dosing regimen with a cycle length of 28 days. Subjects will be advised to take the doses at the same time each day, approximately 12 hours apart. Less dose intensive schedules may be considered if the initial BID regimen's safety, PK and/or pharmacodynamics suggest that a different schedule would be better tolerated and might allow for serum exposures required for anti-lymphoma activity. This might include a treatment break such as 3 weeks on/1 week off treatment or 5 days on/2 days off over a 4 week cycle or an asymmetric (AM dosing > PM dosing) or once-daily dosing schedule. If a less dose-intensive treatment regimen is evaluated, then the initial dose tested on this schedule will be a daily dose that has been previously evaluated and tolerated on the more dose-intensive, BID schedule.

Cohorts of 3 to 6 subjects will be sequentially enrolled at progressively higher starting dose levels of apilimod dimesylate, as indicated in Table 2.The initial cohort of subjects will be prescribed apilimod dimesylate at Dose Level 0 (50 mg BID). Dose level -1 (25 mg BID) is provided to permit a dose decrement in subjects experiencing DLT at Dose Level 0.

Table 2: Provisional Dose Levels

	Daily LAM-002A Dose	Percent Increase	Initial Cohort Size
-1	25 mg BID	-50	3
0	50 mg BID	Starting dose	3
1	100 mg BID	100	3
2	150 mg BID	50	3
3	200 mg BID	33	3
4	275 mg BID	37.5	3

Abbreviations: BID: Twice daily (or 2 times a day)

A 3 + 3 design will be utilized to define an MTD. For cohorts consisting of 3 subjects, dose escalation to the next higher dose may proceed if no DLT is observed within the first cycle of the 3 evaluable subjects accrued to a cohort (See Section 6.1.1). If 1 of 3 subjects in the cohort experiences a DLT, up to a total of 6 evaluable subjects will be enrolled. If 2 or more of the 3-6 evaluable subjects in a cohort experience a DLT, dose escalation will cease, and additional subjects will be treated at a lower dose level. If de-escalation to the previous dose cohort is undertaken, this cohort will be expanded to 6 subjects. The MTD is defined as the highest dose at which no more than 1 of 6 subjects (i.e., < 33%) experiences a DLT in the dose cohort.

Dose escalation decisions will be evaluated in a DLT evaluable population. The DLT evaluable population will include subjects who complete Cycle 1 dosing or who are withdrawn from study due to a DLT in Cycle 1. A subject will be deemed non-evaluable for determining DLTs and will not be counted toward the total cohort size if the subject did not experience a DLT, did not receive at least **75% (42/56) of the** ~~80% of their assigned~~**planned first-cycle** dose**s** or discontinued from the study prior to completing necessary safety evaluations through the first 28 days of study treatment. These subjects may be replaced unless accrual to the cohort has stopped due to DLT.

Section 6.6. Treatment Guidelines

Changes: Instructions for TLS prophylaxis have been included as a safeguard should this appear as a drug-related adverse event.

Information regarding study drug administration has been moved from a later section of the protocol to consolidate instructions regarding study treatment in one section of the protocol.

Because food does not appreciably influence study drug absorption, subjects will not be limited to ingestion of the drug under fasting conditions except on specified days of intensive PK monitoring.

Information regarding management of interruptions in scheduling and vomited doses is provided in more detail.

The dose modification criteria for the protocol have been clarified. In particular, the dose modification rules have been updated to provide consistent practice relating to dose modification for DLT in both Cycle 1 and later cycles. This approach permits patients the maximal opportunity to derive clinical benefit.

Mandatory discontinuation criteria are removed consistent with other changes to the dose modification criteria. These intent is to allow the investigators and medical monitor to judge the clinical significance of each event relative to the potential clinical benefit being experienced by the patient in determining whether continued therapy is appropriate.

Typographical errors in the DLT criteria have been corrected, the criterion for neutropenic DLT has been made more stringent by the omission of growth factors from the definition, and the hepatic DLT criteria have been made more stringent by the addition of substantial elevations in AST as a laboratory event of potential concern.

Criteria regarding required durations of first-cycle exposure as components of DLT have been made more specific for clarity and interpretability.

6.6.1. Tumor Lysis Syndrome (TLS) Prophylaxis

The risk for TLS should be considered based on established algorithms (*Cairo 2010, MDACC 2013, Roberts 2016*):

- **Low-risk: Serum LDH ≤ ULN, all measurable lymph nodes < 5 cm, and absolute lymphocyte count (ALC) < 25 × 10^9/L**
- **Intermediate risk: Serum LDH > 1 to ≤ 2 × ULN, ≥ 1 measurable lymph node with an LD of ≥ 5 but < 10 cm, or ALC ≥ 25 × 10^9/L**
- **High risk: Serum LDH > 2 × ULN, ≥ 1 measurable lymph node with a LD of ≥ 10 cm, or both ≥ 1 measurable lymph node with an LD of ≥ 5 but < 10 cm and ALC ≥ 25 × 10^9/L**

If, during the dose escalation it is observed that the study drug appears to induce TLS, subsequent subjects who are at risk should be considered for medical prophylaxis of TLS and according to local prevention paradigms. Alternatively, investigators may wish to consider the following regimens for prophylaxis in subjects at intermediate or high risk of TLS:

- **Intermediate Risk of TLS: These subjects can receive allopurinol, 100 to 300 mg orally every 8 hours starting ≥ 24 to 48 hours before the initial administration of apilimod dimesylate on Cycle 1-Day 1 of therapy; in addition, subjects who develop hyperuricemia should receive rasburicase, 0.2 mg/kg.**
- **High Risk of TLS: These subjects can receive allopurinol, 100 to 300 mg orally every 8 hours starting ≥ 24 to 48 hours before the initial administration of apilimod dimesylate on Cycle 1-Day 1 of therapy; in addition, high-risk subjects can receive rasburicase, 0.2 mg/kg, administered 3 to 4 hours prior to the first dose of apilimod dimesylate.**

Information regarding the management of TLS is provided in Section 8.6.1.

6.6.2 Description of Study Drug

LAM-002A (apilimod dimesylate capsule) is intended for oral administration. Each capsule will contain 25 mg of apilimod dimesylate (equivalent to 17.1 mg apilimod free base) and the total fill weight of each capsule will be 175 mg. LAM-002A is formulated as a blend with excipients in Size 0 Swedish Orange gelatin capsules. For additional information, see Section 9.1.

6.6.3 In-Clinic LAM-002A (Apilimod Dimesylate Capsules) Administration

On Cycle 1 Day 1, and Cycle 1 Day 8 the dose of LAM-002A (apilimod dimesylate capsules) should be orally administered (a minimum fasting state of 6 to 8 hours) by site staff immediately after the collection of the biomarker samples and pre-dose PK sample. Subjects are allowed to eat after PK Sample #4 (hour 2) has been collected. On Cycle 1 Day 15, the dose of LAM-002A (apilimod dimesylate capsules) should be orally administered (a

minimum fasting state of 6 to 8 hours) by site staff immediately after collection of the pre-dose PK and biomarker samples.

6.6.4 LAM-002A (Apilimod Dimesylate Capsules) Self-Administration

Except for the days where treatment is administered in the clinic, LAM-002A (apilimod dimesylate capsules) will be self-administered orally, BID of each 28-day cycle until disease progression or other discontinuation criteria are met. Subjects should be advised to take study drug with ≥ 4 oz. (~160 mL) of water at the same time each day, 12 hours apart (e.g., 8 AM and 8 PM) (+/- 1 hour window). When self-administering the study drug at home, subjects may take the drug in the fed or fasted state. On PK days, subjects should come to clinic fasted (a minimum fasting state of 6 to 8 hours) and take the dose at the site under supervision. All subjects will be required to complete a Dosing Diary, which must be returned to the site for review at each site visit.

6.6.5 Dose Schedule Interruptions and Vomited Doses

Subjects who have a delay in administration of a dose of apilimod dimesylate of <6 hours should take the planned dose as soon as possible after the intended time of administration. For subjects who have a delay in administration of apilimod dimesylate of ≥ 6 hours, the dose should not be taken. The planned timing of subsequent apilimod dimesylate dosing should not be altered.

For subjects who vomit shortly after taking apilimod dimesylate, the vomited dose should not be replaced. The planned timing of subsequent apilimod dimesylate dosing should not be altered.

6.6.6. Dose Modifications

If a subject experiences an AE that is suspected to be related to apilimod dimesylate, appropriate supportive care (e.g., antiemetics, antidiarrheals, therapy for tumor lysis syndrome [TLS]) should be instituted consistent with the nature of the event.

If a subject experiences an apilimod dimesylate-related DLT (reference Table 3), then the study drug administration should be interrupted until the toxicity recovers to Grade ≤ 1 or baseline. Upon resumption of study drug, the dose of apilimod dimesylate should be reduced by 1 dose level (reference Table 3). Successive adjustments to progressively lower dose levels can be made. If the subject cannot tolerate apilimod dimesylate after a decrease to Dose Level -1 (25 mg BID), then the subject should be discontinued from apilimod dimesylate therapy unless continued treatment is permitted by the medical monitor.

After the apilimod dimesylate dose is reduced, the dose can be maintained at that dose level, even if there is minimal or no toxicity with the reduced dose. However, if the subject tolerates a reduced dose of apilimod dimesylate for ≥ 4 weeks then the apilimod dimesylate dosing regimen may be reescalated to the next higher dose level at the discretion of the investigator. Such reescalation may be particularly warranted if the AE comprised TLS or if further evaluation reveals that the AE that led to the dose reduction was not related to apilimod dimesylate. Successive adjustments to progressively higher dose levels can be made. However, the escalated dose cannot exceed the starting dose level for that subject during the first 4 cycles of therapy.

Individual subjects who initiated treatment at a dose level below the lower of the currently established MTD or the RP2D and who have not experienced a DLT after ≥ 4 cycles of treatment may have the apilimod dimesylate dose escalated to the next higher dose level if both the principal investigator and the medical monitor agree that a dose escalation is medically warranted (e.g., for a subject with stable disease who is tolerating the current dose level of apilimod dimesylate therapy). In such subjects, successive adjustments to progressively higher dose levels can be made at intervals of ≥ 4 weeks with the condition that the escalated dose level cannot exceed the lower of the currently established MTD or RP2D.

In a subject who experiences a DLT precluding resumption of apilimod dimesylate therapy during a cycle, a new cycle of treatment may begin at the later of Day 29 or when AEs or laboratory abnormalities related to apilimod dimesylate have returned to baseline levels. If drug-related AEs or laboratory abnormalities precluding further administration of study drug are not resolved to baseline by Day 29, week-by-week delays in initiating the new cycle of treatment should be instituted. When all drug-related AEs and laboratory abnormalities have returned to baseline, the next cycle of therapy can be initiated. Upon initiation of a new cycle of therapy, the prior cycle of therapy will be considered completed.

Investigators are to discuss modifications in the dosing regimen with the medical monitor. The appropriate clinic staff should dispense the study drug for the new dose level and instruct the subject/caregiver about the change in dose level.

~~During a cycle of treatment, study drug should continue to be administered as planned unless a DLT has occurred.~~

~~**6.6.2 New Cycle of Therapy Guidelines**~~

~~In the absence of otherwise dose-limiting toxicity (DLT), in order for a subject to begin a new cycle of therapy, the following criteria must be met on Day 1 of the new cycle.~~

- Absolute neutrophil count (ANC) must be ≥ 1.0 x10^9/L (1,000/mm^3)
- Platelet count must be ≥ 75 x 10^9/L (75,000/mm^3)
- All non-hematologic toxicities considered related to study treatment must be ≤ Grade 1 (except alopecia) or returned to baseline.

~~If the subject does not meet these criteria, dosing will be delayed and the subject should be re-evaluated within 48 – 72 hours. Dosing may resume if these criteria have been met. However, if the next cycle is delayed by > 14 days because of insufficient recovery from a treatment related toxicity, this will be considered a dose-limiting event (See Section Deleted). If the next cycle is delayed due to treatment-related toxicity by > 21 days, then the subject must be removed from study treatment.~~

~~6.6.3~~ 6.6.7 Definition of Dose-Limiting Toxicity (DLT)

A DLT will be defined as an AE or abnormal laboratory value meeting the criteria in Table 3 and that is assessed as unrelated to disease, **a comorbid condition,** intercurrent illness, or concomitant medications. For the purposes of dose escalation and determination of the MTD, DLTs that occur within the first cycle of treatment must be included in decisions regarding dose

escalation. DLTs or other clinically significant toxicities that occur after Cycle 1 may also be considered when determining the MTD/RP2D.

~~If at any time during the study a subject experiences a DLT, the study treatment must be stopped and the toxicity in question must be followed until resolution or stabilization. If treatment is to be resumed then re-initiation criteria must be met and administration must be resumed at a lower dose (Section 6.6.4).~~

Table 3: Criteria for Defining Dose Limiting Toxicities (DLTs)

Toxicity	**Criteria**
Hematology	CTCAE Grade 4 neutropenia lasting ~~> 5~~**≥ 7** days ~~despite growth factor support~~ CTCAE Grade 4 febrile neutropenia CTCAE Grade 3 thrombocytopenia with bleeding that requires transfusion therapy CTCAE Grade 4 thrombocytopenia
Gastrointestinal	≥ CTCAE Grade 3 vomiting or nausea despite the use of optimal anti-emetic treatments ≥ CTCAE Grade 3 diarrhea despite the use of optimal anti-diarrheal treatments
Renal	Serum creatinine > 3.0 x ULN
Hepatic*	**Total b**~~B~~ilirubin ≥ CTCAE Grade 3~~.0~~ **Total b**~~B~~ilirubin ≥ CTCAE Grade 2~~.0~~ and ALT **or AST** ≥ CTCAE Grade 2 or, for subjects with liver metastases at baseline, **total b**~~B~~~~ilirubin~~ ≥ 2.0 x ULN and ALT **or AST** ≥ CTCAE Grade 3
Treatment interruption/delays	**Inability to administer ≥ 28/56 planned apilimod dimesylate doses in a treatment cycle due to drug-related AEs** **or** **Failure to recover from apilimod-dimesylate-related toxicities to baseline within 14 days from the last dose of study drug in a** ~~**cycle**~~**Treatment** ~~interruption caused by LAM-002A (apilimod dimesylate capsules) related toxicity causing > 14 days of missed dosing during a cycle~~ ~~or~~ ~~Treatment delays by LAM-002A (apilimod dimesylate capsules) related toxicity causing > 14 days in the start of a subsequent cycle of treatment~~
Other adverse events not listed above	Non-hematologic toxicities of CTCAE ≥ Grade 3 except for the following. • alopecia • CTCAE Grade 3 fatigue for < 72 hours • Asymptomatic Grade 3 elevations in biochemistry laboratory values that last for ≤ 7 days that are not deemed to be clinically relevant. This includes electrolyte abnormalities that respond to medical intervention Any LAM-002A (apilimod dimesylate capsules)-related adverse event that, in the opinion of the investigator, requires a dose reduction or discontinuation of treatment.

* For any dose-limiting hepatic toxicity that does not resolve within 7 days to baseline, an abdominal CT scan must be performed to assess whether it is related to disease progression.

Repeat testing of a blood sample or procedure (e.g., ECG) is required to confirm any laboratory abnormality that meets the definition of a DLT.

Note: Known oncologic emergencies from NHL (e.g., tumor lysis syndrome, spinal cord compression, ureteric obstruction, lymphomatous meningitis, and superior vena cava syndrome) will not be considered as dose-limiting toxicities.

Abbreviations: ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CTCAE: Common terminology criteria for adverse events; DLT: Dose-limiting toxicity; ECG: Electrocardiogram; NHL: Non-Hodgkin's lymphoma; ULN: Upper limit of normal

~~6.6.4~~ 6.6.8 Follow-up for DLTs and AEs Leading to Discontinuation

Subjects who experience a non-laboratory DLT must be evaluated weekly, at a minimum, for 4 weeks until resolution to ≤ Grade 1 or baseline and then at least monthly until return to baseline or stabilization of the event, whichever comes first. For abnormal laboratory values that qualify as a DLT, subjects will initially be followed at least twice weekly until values resolve to ≤ Grade 2 or return to baseline. If not resolved or stabilized within 2 weeks then subjects should be followed at least weekly until return to baseline or stabilization, whichever comes first.

Subjects who discontinue the study for a study-related AE or an abnormal laboratory value must be followed at least once a week for 4 weeks, and subsequently at 4-week intervals until resolution or stabilization of the AE or laboratory abnormality, whichever comes first.

QTc: An immediate evaluation by a qualified site physician should be conducted for any subject with a new Fridericia correction formula (QTcF) > 500 msec. Following the event, the subject should be monitored by the investigator with hourly ECGs until the QTcF is ≤ 500 msec and the QTcF has returned to < 30 msec from baseline. A blood sample should be obtained as soon as possible following the observation of a QTc > 500 msec to determine levels of potassium and magnesium as well as evaluation of circulating apilimod. Management of abnormal potassium and magnesium levels as well as other clinical factors such as oxygenation should be addressed immediately.

Upon resolution of the QTc event, the decision to continue treatment at a reduced dose requires discussion between the investigator and the subject, and the investigator and the sponsor.

~~6.6.5 Criteria for Re-initiation of Therapy Following Occurrence of a DLT After Cycle 1~~

~~Study treatment will be stopped if a subject experiences a DLT (See Section Deleted) at any time during the study. Additional AE management is provided in Section 8.6.1. Study treatment may resume, except as noted under "Discontinuation of therapy due to treatment-related toxicity", with applicable dose adjustments if the following criteria are met:~~

- ANC must be ≥ 1.0 x10^9/L (1,000/mm^3)
- Platelet count must be ≥ 75 x 10^9/L (75,000/mm^3)
- All other non-hematologic treatment-related toxicities must be ≤ Grade 1 (except alopecia) or returned to baseline.

~~6.6.6 Dose Modification Guidelines~~

~~6.6.6.1 Dose Reductions Following DLTs~~

~~Subjects who experience a DLT (See Section Deleted) in Cycle 1 will be discontinued from treatment. However, subjects who develop a DLT in subsequent cycles of treatment may continue treatment at a reduced dose level (a minimum reduction of at least one dose level) if the following criteria are met:~~

- the AE reverts to baseline or ≤ Grade 1 within 21 days,
- the subject is clearly deriving clinical benefit, and
- the subject has an otherwise favorable risk/benefit profile

~~The decision to continue treatment at a reduced dose requires discussion between the investigator and the subject, and the investigator and the sponsor.~~

~~Once a dose level reduction has occurred, subjects will continue to receive this reduced dose. See Section 8.6.1 for the management of toxicities.~~

~~6.6.6.2 Discontinuation of Therapy Due to Treatment-related Toxicity~~

~~Study treatment should not be resumed in the case of the following treatment-related events:~~

- Occurrence of a DLT in Cycle 1 (including > 14 day dose delay secondary to insufficient recovery from a treatment-related toxicity)
- ≥ Grade 3 cardiac event
- Non-hematologic events of Grade 4 severity
- > 21 day dose delay due to a treatment-related event in Cycle 2 and beyond.

~~See Section Deleted for the management of toxicities~~

~~6.6.7~~ 6.6.9 Duration of Subject Participation

All subjects will be treated for at least 1 cycle unless there is evidence of unacceptable toxicity or PD. Although subjects may continue to receive study treatment until experiencing unacceptable toxicity or disease progression, it is estimated that each subject will participate for an average of 6 months of treatment and an additional 1 month of follow-up. Subjects who have discontinued study treatment for reasons other than PD will be assessed per Revised Response Criteria for NHL or Guidelines for the diagnosis and treatment of CLL at a minimum of every 12 weeks until documentation of PD, start of new anti-cancer therapy or for up to 1 year from the last enrolled subject's first treatment (Cycle 1 Day 1), whichever comes first.

Section 6.7. Criteria for Study Termination

Change: Treatment withdrawal criteria have been updated for clarity and interpretability.

The sponsor may terminate this study at any time, provided a written notice is submitted at a reasonable time in advance of the intended termination.

Subjects may be withdrawn from further study treatment for any of the following reasons:

- Subject withdrawal of informed consent

- Disease progression of cancer while receiving study therapy Note: Apparent worsening of disease during temporary interruption of study therapy (e.g., for drug-related toxicity or intercurrent illness) may not indicate true cancer progression. Study subjects undergoing PET for lymphoma assessment can experience transient disease flare on imaging before having subsequent therapy-induced tumor regression. Worsening of constitutional symptoms or performance status in the absence of objective evidence of worsening lymphoma (e.g., due to infection) may not represent definitive disease progression. For these reasons, if there is uncertainty regarding whether there is true disease progression and if medically appropriate, the subject may continue or resume study treatment and remain under close observation (e.g., evaluated at 4- to 8-week intervals) while relevant radiographic, clinical, and/or laboratory assessments are performed to document whether tumor control can be maintained or whether disease progression has truly occurred. If subsequent evaluations suggest that the subject has experienced persistent definitive disease progression, then the date of progression will be the timepoint at which progression was first objectively documented.
- Unacceptable study-drug-related toxicity despite appropriate dose modification
- Development of intercurrent illness that precludes continued study therapy
- Physician decision ~~if~~ **that** continuation is not in the subject's best interest
- Treatment of the cancer with another therapeutic regimen
- Subject becomes pregnant **or begins breastfeeding**
- Substantial noncompliance with study drug administration, study procedures, or study requirements in circumstances that increase risk or substantially compromise the interpretation of study results
- Termination of the study by the sponsor, relevant regulatory agencies, or the IRB/IEC

The investigator must determine the primary reason for a subject's withdrawal from the study and record this information on the electronic case report form (eCRF).

Section 6.9. Schedule of Assessment

Changes: The table has been corrected to include screening viral serology.

The request for an on-study tumor biopsy has been removed.

Confirmation of eligibility need not occur precisely on Day 1; thus, the relevant footnote has been changed to indicated that it must occur by Day 1.

The enrollment criteria have been modified to only include subjects with measurable lymphadenopathy and so caveats relating to subjects with CLL without adenopathy have been removed because they are no longer applicable.

Greater specificity have been provided in the baseline peripheral blood or bone marrow aspirate assessments required for subjects with CLL/SLL in order to ensure clarity regarding the studies to be performed.

The requirements for baseline and follow-up bone marrow analyses have been clarified.

The procedures for baseline acquisition of tumor tissue in study candidates have been updated and clarified. The request for an on-study tumor biopsy has been removed.

Assessment of changes in circulating cytokines has been added.

One-time, baseline collection of blood or saliva has now been included to obtain a normal-tissue control for mutation studies in tumors.

6.9 Schedule of Assessments

Table 4: Schedule of Assessments

Assessment	Screening	Cycle 1			Cycle 2			Cycle 3 and Beyond		End of Treatment (EOT)
		Day			Day			Day		
	-28 to -1	1	8	15	1	8	15-28	1	15-28	
Informed consent	X									
Inclusion/exclusion criteria	X	X[a]								
Demographics	X									
Medical history	X									
Signs and Symptoms, PE[b]	X	X[c]			X			X		X
ECOG Performance Status	X	X[c]			X			X		X
Vital signs	X	X[d]	X[d]	X[d]	X			X		X
ECG	X	X[d]	X[d]	X[d]	X			X		X
HIV, HBV, and HCV serology	**X**									
Hematology[e, f]	X	X	X	X	X	X	X	X		X
Serum chemistry[f, g]	X	X	X	X	X	X	X	X		X
Coagulation	X	X[c]								
Urinalysis[h]	X	X[c]			X			X		X
Pregnancy testing[i]	X	X[i]			X			X		X
PET/CT or CT (or MRI) scans (based on indication) **for Response Assessment**	X[j]						X[k]		X[k]	X[l]
CLL baseline assessments[m]	X									
PK sampling[n] + Analyte		X	X	X						
Bone marrow aspirate/biopsy	X[o]						X[p, q]		X[p]	
Biomarker – tumor tissue	X[q]						~~X~~[q]			
Biomarker – blood smears[r]		X	X	X						
Biomarker – plasma cytokines[s]		**X**	**X**	**X**						
Biomarker – PBMC[t]		**X**	**X**							
Biomarker – saliva[u]		**X**								
~~Response Assessment~~							~~X~~[k]		~~X~~[k]	
LAM-002A administration		X	X	X	X	X	X	X	X	
Adverse events		Throughout Study								
Concomitant medications[v]		Throughout Study								

a Eligibility will be confirmed **by**~~on~~ Cycle 1 Day 1.

B Complete physical examination (PE) will be performed at screening. A directed PE, including weight, will be performed within 72 hours prior to the start of each cycle and EOT.

C Assessment/test does not need to be repeated on C1D1 if baseline was within normal limits and conducted within 72 hours of first dose.

D Obtained on Day 1 prior to dosing for all Cycles. For C1D1 and C1D8 obtained prior to dosing and 1 h (± 15 min after dosing), 2 hrs (± 30 min), 4 hrs (± 1h), and 8 hrs (± 1h) postdose. For C1D15, obtained prior to dosing.

E Hematology includes hemoglobin, hematocrit, RBC count, platelet count, WBC and differential.

F All hematology and chemistry lab**oratory parameters** should be assessed at Screening and Days 1, 8, and 15 of Cycles 1 and 2 and then at least once prior to the start of all subsequent cycles (within 72 hrs) and at EOT. **These parameters may be obtained within 72 hours prior to the planned day of collection.** Abnormal test values should be monitored per protocol guidance.

G Chemistry includes albumin, alkaline phosphatase, total bilirubin, BUN, calcium, carbon dioxide, chloride, creatinine, glucose, inorganic phosphorus, potassium, total protein, LDH, ALT, AST, sodium, and uric acid.

H Urinalysis includes appearance, specific gravity and pH as well as a semi-quantitative "dipstick" evaluation of glucose, protein, bilirubin, ketones, leukocytes, and blood. Microscopic examination of sediment will be performed if urinalysis is positive for WBC, proteins or blood. **Urinalysis may be obtained within 72 hours prior to the planned day of collection.**

I Pregnancy testing (serum or urine) will be required for women of childbearing potential (WCBP) only. Testing is required at Screening; within 72 hours of Day 1 of each cycle and at EOT. Test does not need to be repeated on C1D1 if baseline was negative and conducted within 72 hours of first dose.

J Imaging as appropriate for disease indication will be conducted within 30 days of the first dose of study treatment. Suitable scans performed prior to screening and within 30 days before first dose may be used for baseline tumor assessments

k Assessment of disease status will be conducted with standard clinical measurements: PE, CBCs, bone marrow aspirates/biopsies, and imaging as appropriate for indication. During treatment, scans will be repeated for tumor assessment within 7 days of Day 1, Cycles 3, 5, and 7 then every 3 months until PD or use of alternative antineoplastic therapy. For subjects still in response after 1 year, intervals for radiographic surveillance may be every 6 months. ~~For subjects with CLL without nodal disease, splenomegaly or masses on baseline imaging, CT surveillance will not be required except for confirmation of CR. Also s~~Subjects with CLL who achieve CR will require assessment of MRD by flow cytometry of bone marrow and peripheral blood.

L Imaging at EOT is not required if PD has already been radiographically documented or last imaging was within 30 days of EOT visit.

M **Subjects with CLL/SLL must provide either a fresh blood sample containing circulating tumor cells or a bone marrow aspirate sample pretreatment. Tissue will be submitted for evaluation of the percentage of tumor cells and analysis of genetic alterations and/or gene expression that may predict anticancer activity and/or pharmacodynamic activity. In addition, for subjects with CLL/SLL, the sponsor may arrange for a portion of the sample to be evaluated at a sponsor-specified laboratory for known prognostic markers (e.g., quantitative immunoglobulins, FISH panel [chromosome 11q deletion, 13q deletion, 17p deletion and 12 trisomy], DNA mutational analysis for p53, IgHV [including IgHV3-21], and other genes of interest in CLL [e.g., Notch]; flow cytometry [for CD5, CD10, CD11c, CD19, CD20, CD23, CD38, CD45, kappa and lambda light chains and ZAP-70], and/or β2-microglobulin).** ~~Baseline assessments for subjects with CLL include DAT, quantitative immunoglobulins, FISH panel, flow cytometry, and β2-microglobulin.~~ **All subjects with CLL/SLL must have baseline i~~I~~**maging (**with** CT scans **[preferred] or MRI scans)** ~~and bone marrow biopsy will be performed as indicated~~.

N Blood sampling for determination of the plasma concentrations of apilimod and metabolites will be performed on C1D1 and C1D8 as follows: pre-dose, 30 minutes, 1, 2, 4, 6, 8 hours post-first dose of the day. C1D15 pre-dose only. Additional PK samples will be collected, if possible, whenever a subject has a study treatment-related SAE or QTc > 500 msec. Subjects are required to come to the study site in a fasting state prior to the collection of certain PK samples. For analyte determination, PK back-up sample will be used from time points: Cycle 1 Day 1 and Cycle 1 Day 8 pre-dose.

O Bone marrow aspirates/biopsies performed within 2 months prior to first dose may be used for **clinical** baseline assessments. **For subjects with NHL, b~~B~~**aseline bone marrow biopsies/aspirates may be omitted if not deemed essential for response assessment or patient management. **For subjects with**

CLL/SLL, a baseline bone marrow aspirate is required unless the presence of sufficient circulating cells in the peripheral blood (e.g., ALC ≥ 10 x 10^9/L) permits assessment of baseline parameters as described in Footnote m, above.

P **If necessary per applicable response criteria, a repeat bone marrow biopsy or aspirate will be required for subjects who have a CR by imaging and physical examination.** ~~Repeat bone marrow aspirate/biopsy is only required to confirm response as applicable~~.

Q **Archival or fresh tumor tissue from the most recent available biopsy or surgery prior to first dose in subjects with NHL must be obtained pretreatment. For subjects undergoing a biopsy, adequate tumor tissue should be acquired via excisional biopsy, incisional biopsy or core needle biopsy (e.g., ≥ 3 passes using a 16-gauge core needle). Tissue will be submitted for evaluation of the percentage of tumor cells and analysis of genetic alterations and/or gene expression that may predict anti-lymphoma activity and/or pharmacodynamics activity. In addition, for subjects with NHL, tumor may be evaluated for known prognostic characteristics (e.g., for DLBCL: ABC or GCB subtype; expression of BCL2, BCL6, Ki-67, CD20, and MYC; other mutational status). The baseline biopsy procedure (if required) should be performed after the study candidate has undergone the baseline radiology examination and is otherwise considered eligible for study participation.**

R Blood smears will be collected for microscopic evaluation of vacuole formation on C1D1 and C1D8 as follows: pre-dose, 4 hrs and 8 hrs post first dose of the day. C1D15 pre-dose only.

S **Plasma will be collected for evaluation of circulating cytokines (including IL-12 and IL-23) predose on each of Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 1 Day 15.**

T **PBMCs will be collected on Cycle 1, Day 1 pre-treatment; on Cycle 1, Day 1 at 8 hours post-dose; and on Cycle 1, Day 1 at 8 hours post-dose for determination of changes in gene expression that may predict or correlate with anti-lymphoma activity and/or pharmacodynamic activity.**

U **Saliva will be obtained pre-dose on Cycle 1 Day 1 as a normal-tissue control for gene mutation studies in tumors.**

V Information on concomitant medications and other treatments will be collected from 14 days prior to informed consent through 30-37 days after the last dose of study drug.

Abbreviations: ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; CBCs: Complete blood counts; CD: Cluster of differentiation; CLL: Chronic lymphocytic leukemia; CR: Complete response; CT: Computerized tomography; DAT: Direct antiglobulin test; ECG: Electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOT: End of treatment; FISH: Fluorescence *in situ* hybridization; h: Hour; hrs: Hours; LDH: Lactate dehydrogenase; min: Minutes; MRD: Minimal residual disease; MRI: Magnetic Resonance Imaging; PBMC: Peripheral blood mononuclear cell; PD: Progressive disease; PE: Physical exam; PET: Positron emission tomography; PK: Pharmacokinetics; QTc: Corrected QT interval; RBC: Red blood cell; SAE: Serious adverse event; WBC: White blood cell; WCBP: Women of child bearing potential

Section 7.1 Subject Inclusion Criteria

Changes: Inclusion criteria have been updated to indicate that all study subjects must have measurable lymphadenopathy.

In view of the fact that the study drug is not expected to be substantially myelosuppressive and that study therapy has the hypothetical potential to improve disease-related cytopenias, study candidates who have Grade ≥3 neutropenia or thrombocytopenia due to disease infiltration of the bone marrow are permitted to enroll.

The study will require that candidates with NHL be willing to provide archival or fresh tissue prior to enrollment.

The study will require that candidates with CLL/SLL be willing to provide CLL cells from peripheral blood or bone marrow prior to enrollment.

4. **Subjects must have radiographically measurable lymphadenopathy or extranodal lymphoid malignancy (defined as the presence of ≥ 1 lesion that measures ≥ 2.0 cm in the longest dimension [LD] and ≥ 1.0 cm in the longest perpendicular dimension [LPD] as assessed radiographically).** ~~Subjects may have measurable or non-measurable disease but to be eligible their disease must be clinically evaluable for improvement or progression.~~

7. The subject has organ and marrow function as follows:

   c. Absolute neutrophil count (ANC) ≥ 1.0×10^9/L (1,000/mm^3).
   d. Platelets ≥ 75×10^9/L (75,000/mm^3).
   e. Total bilirubin ≤ 1.5 x the upper limit of normal (ULN).
   f. Serum creatinine ≤ 1.5 x ULN or calculated creatinine clearance ≥ 60 mL/min.
   g. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x ULN if no liver involvement, or ≤ 5 x ULN with liver involvement.
   h. **Note: Grade ≥3 neutropenia or thrombocytopenia is permitted if the abnormality is related to bone marrow involvement with hematological malignancy (as documented by bone marrow biopsy/aspirate obtained since the last prior therapy).**

11. **For subjects with lymphoma: The subject has archived tumor tissue for analysis or is willing to undergo a pretreatment core needle, excisional, or incisional biopsy of a lymphoma nodal lesion.**

12. **For subjects with CLL/SLL: The subject has sufficient circulating cells in the peripheral blood (e.g., ALC ≥ 10 x 10^9/L) or is willing to undergo a pretreatment bone marrow aspirate to obtain CLL cells.**

Section 7.2 Subject Exclusion Criteria

Changes: Restrictions on immunosuppressive therapy and corticosteroid use have been clarified.

The text in Exclusion Criterion 19 was corrected for consistency with other criteria.

8. The subject is chronically receiving **immunosuppressive therapy, is receiving** > 10 mg/day of prednisone (or the corticosteroid equivalent**), or is using enteric corticosteroids. Study candidates using** ~~Acute (short-term) systemic steroid treatment as indicated by standard clinical practice at higher doses will be allowed upon agreement between the investigator and sponsor. T~~topical, intra-articular, nasal, and inhaled corticosteroids ~~are also allowed~~**are not excluded from study participation. During study therapy, subjects may use systemic, enteric, topical, intra-articular, nasal, or inhaled corticosteroids as required for treatment-emergent conditions.**

19. **The subject has a h**~~H~~history of prior cancer (not under study) that has not been in remission for at least 3 years. The following are exempt from the 3-year limit: basal cell or squamous cell carcinoma of the skin, localized prostate cancer with normal Prostate Specific Antigen (PSA), cervical cancer in situ or other in situ carcinomas.

Section 7.3 Treatment of Subjects

Changes: This information was moved from this section and consolidated with other drug administration information earlier in the protocol document.

Because food does not appreciably influence study drug absorption, subjects will not be limited to ingestion of the drug under fasting conditions except on specified days of intensive PK monitoring.

Further information regarding management of interruptions in scheduling is now provided in more detail in other sections of the study protocol document.

~~**7.3.1 Description of Study Drug**~~

~~LAM-002A (apilimod dimesylate capsule) is intended for oral administration. Each capsule will contain 25 mg of apilimod dimesylate (equivalent to 17.1 mg apilimod free base) and the total fill weight of each capsule will be 175 mg. LAM-002A is formulated as a blend with excipients in Size 0 Swedish Orange gelatin capsules. For additional information, see Section 9.1.~~

~~**7.3.2 In-Clinic LAM-002A (Apilimod Dimesylate Capsules) Administration**~~

~~On Cycle 1 Day 1, and Cycle 1 Day 8 the dose of LAM-002A (apilimod dimesylate capsules) should be orally administered (a minimum fasting state of 6 to 8 hours) by site staff immediately after the collection of the biomarker samples and pre-dose PK sample. Subjects are allowed to eat after PK Sample #4 (hour 2) has been collected. On Cycle 1 Day 15, the dose of LAM-002A (apilimod dimesylate capsules) should be orally administered (a minimum fasting state of 6 to 8 hours) by site staff immediately after collection of the pre-dose PK and biomarker samples.~~

~~**7.3.3 LAM-002A (Apilimod Dimesylate Capsules) Self-Administration Dosing Diary**~~

~~Except for the days where treatment is administered in the clinic, LAM-002A (apilimod dimesylate capsules) will be self-administered orally, BID every 12 hours (e.g., 8 AM and 8 PM) of each 28-day cycle until disease progression or other discontinuation criteria are met.~~

~~Administration guidelines: Subjects should be advised to take study drug with 12 oz. water at the same time each day, 12 hours apart +/- 1 hour window. Subjects should not take drug if > 3 hours from scheduled dose and the +/- window. Subjects should not eat within 2 hours prior to taking their dose or within 2 hours after taking their dose, with no solid diet restrictions otherwise. Clear liquids are allowed within the +/- 2 hour fasting window. On PK days, subjects~~

~~should come to clinic fasted (a minimum fasting state of 6 to 8 hours) and take the dose at the site under supervision. If the subject forgets to take a dose by > 3 hours then the dose should not be taken and will be reported as 'missed' in the subject's dosing diary. If the subject vomits after taking a dose, that dose should not be taken again.~~

~~Dosing should occur at the same time each day whenever possible. All subjects will be required to complete a Dosing Diary, which must be returned to the site for review at each site visit.~~

Section 8.1.2 Inclusion and Exclusion Criteria

Changes: Confirmation of eligibility need not occur precisely on Day 1; thus this provision has been changed.

~~At~~ **During** Screening, inclusion and exclusion criteria will be reviewed for each potential subject and confirmed ~~on~~ **by** Day 1 of Cycle 1.

Section 8.1.5 Disease Status Assessment for Subjects with NHL

Changes: The requirements for baseline imaging and bone marrow analyses have been clarified.

The procedures for baseline acquisition of tumor tissue in study candidates with lymphoma have been updated and clarified.

Pretreatment tumor assessments will be performed within 30 days of the first dose of study treatment and will include **diagnostic CT scans (with intravenous contrast) or** Positron Emission Tomography (PET)/Computerized Tomography Scans (CT scan) **for patients with lymphoma** ~~(CT for subjects with CLL/SLL)~~, bone marrow aspirate/biopsy, complete blood counts and physical examination. It is anticipated that in most cases the PET~~/ and (~~CT scans~~)~~ will be conducted using a single instrument, i.e., as a PET/CT scan (CT scans should be performed using a contiguous reconstruction algorithm of ≤ 5 mm). However, MRI is an acceptable alternative method for assessing disease in subjects who cannot receive intravenous contrast with CT scans. In such subjects MRI and PET scans will have to be obtained separately.

Suitable scans performed prior to screening and within 30 days before first dose may be used for baseline tumor assessments. Similarly bone marrow biopsies/aspirates performed within 2 months prior to first dose may be used for baseline assessments. **For subjects with NHL, baseline bone marrow biopsies/aspirates may be omitted if not deemed essential for response assessment or patient management. For subjects with CLL/SLL, a baseline bone marrow aspirate is required unless the presence of sufficient circulating cells in the peripheral blood (e.g., ALC ≥ 10 x 10^9/L) permits assessment of baseline parameters for gene expression and prognosis.** ~~Baseline bone marrow biopsies/aspirates may be omitted if not deemed essential for response assessment or patient management.~~ Details of assessments will be collected on the eCRF and must be filed in the subject's medical record.

Archival tissue from the most recent available biopsy or surgery or fresh tumor tissue must be obtained pretreatment. For subjects undergoing a biopsy, adequate tumor tissue should be acquired via excisional biopsy, incisional biopsy or core needle biopsy (e.g., ≥ 3 passes using a 16-gauge core needle). Tissue will be submitted for evaluation of the percentage of tumor cells and analysis of genetic alterations and/or gene expression that may predict anti-lymphoma activity and/or pharmacodynamics activity. In addition, tumor may be evaluated for known prognostic characteristics (e.g., for DLBCL: ABC or GCB subtype;

expression of BCL2, BCL6, Ki-67, CD20, and MYC; other mutational status). The baseline biopsy procedure (if required) should ideally be performed after the study candidate has undergone the baseline radiology examination and is otherwise considered eligible for study participation.

Section 8.1.6. Disease Status ~~Baseline~~ Assessments for Subjects with CLL/SLL

Changes: Greater specificity have been provided in the baseline imaging and peripheral blood assessments for subjects with CLL/SLL in order to ensure clarity regarding the studies to be performed.

All subjects with CLL must have baseline imaging (with CT scans [preferred] or MRI scans).

Subjects with CLL/SLL must provide either a fresh blood sample containing circulating tumor cells or a bone marrow aspirate sample pretreatment. Tissue will be submitted for evaluation of the percentage of tumor cells and analysis of genetic alterations and/or gene expression that may predict anticancer activity and/or pharmacodynamic activity. In addition, for subjects with CLL/SLL, the sponsor may arrange for a portion of the sample to be evaluated at a sponsor-specified laboratory for known prognostic markers (e.g., quantitative immunoglobulins, FISH panel [chromosome 11q deletion, 13q deletion, 17p deletion and 12 trisomy], DNA mutational analysis for p53, IgHV [including IgHV3-21], and other genes of interest in CLL [e.g., Notch]; flow cytometry [for CD5, CD10, CD11c, CD19, CD20, CD23, CD38, CD45, kappa and lambda light chains and ZAP-70], and/or β2-microglobulin). ~~Subjects with CLL will have the following baseline assessments performed direct antiglobulin test (DAT), quantitative immunoglobulins, Fluorescence *in Situ* Hybridization (FISH) panel, flow cytometry and β2 microglobulin. Imaging and bone marrow aspirate/biopsy will be conducted as above at Screening/Baseline, Each Cycle and End of Treatment.~~

Section 8.3.1 Clinical Laboratory Tests

Change: Information regarding the locations for clinical laboratory testing has been clarified.

Clinical laboratory tests **during the first 2 cycles** will be performed by the investigative site's local laboratory. Samples will be collected from subjects at scheduled study visits before the administration of study drug unless otherwise noted, and more frequently if clinically indicated. Clinical laboratory tests may be performed up to 72 hours prior to the scheduled visits (See ~~Section Deleted~~ for Schedule of Assessments). Upon completion of Cycle 2, subjects may use **the investigative site's laboratory or** their local laboratory for clinical lab**oratory** assessments. Accredited certification, such as College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendments (CLIA), and valid reference ranges must be collected for all clinical lab**oratorie**s used by subjects.

Section 8.3.1.1 Hematology

Change: The text has been edited to allow reporting of either aPTT or PTT depending upon the type of test done at the site. Text regarding on-study tumor biopsies is no longer applicable because the on-study tumor biopsies have been removed as components of this study.

Hemoglobin, hematocrit, WBC count with differential, red blood cell (RBC) count, and platelet count will be collected at Screening and Days 1, 8, and 15 of Cycles 1 and 2 then at least once prior to start of all subsequent cycles and at EOT.

Coagulation parameters (aPTT **[or PTT]** and INR) should be performed at Screening. ~~Additionally these labs should be repeated per institutional guidelines prior to any on-study tumor biopsies.~~

Section 8.3.1.2 Blood Chemistry

Change: The text has been edited to match the plan for reporting of bilirubin on the case report forms. Total bilirubin should be recorded and direct bilirubin should be reported if available. If necessary, the indirect bilirubin will be calculated programmatically.

Albumin, alkaline phosphatase (ALP), total bilirubin, calcium, carbon dioxide, chloride, creatinine, glucose, inorganic phosphorus, potassium, total protein, ALT, AST, lactate dehydrogenase (LDH), sodium, BUN, and uric acid will be collected at Screening and Days 1, 8, and 15 of Cycles 1 and 2 then at least once prior to start of all subsequent cycles and at EOT. If the total bilirubin concentration is > 1.5 times the upper normal limit, total bilirubin should be differentiated **and the total and direct bilirubin should be reported.**~~into the direct and indirect reacting bilirubin.~~

Section 8.3.1.3 PK and Biomarker Assessments

Change: The text has been edited for accuracy.

Biomarker samples will be obtained at time points indicated in Section 13. Comprehensive information on tissue acquisition, handling, storage, and sample shipments can be found in the biomarker **sample process documents.** ~~Laboratory manual.~~

Section 8.5 Adverse Events

Change: Information that is already described in other sections of the protocol has been deleted in order to avoid redundancy and/or inconsistency.

~~The frequency of AE monitoring increases for subjects who experience a DLT as outlined below and in Section Deleted. See Section 6.6.5 for dosing adjustment/termination criteria. Subjects who experience a DLT (See Section Deleted) in Cycle 1 will be discontinued from treatment.~~

~~If at any time during the study a subject experiences a DLT, the study treatment must be stopped and the toxicity in question must be followed until resolution or stabilization. Subjects who experience a non-laboratory DLT must be evaluated weekly, at a minimum, for 4 weeks until resolution to ≤ Grade 1 or baseline and then at least monthly until return to baseline or stabilization of the event, whichever comes first. For abnormal laboratory values that qualify as a DLT, subjects will initially be followed at least twice weekly until values resolve to ≤ Grade 2 or return to baseline. If not resolved or stabilized within 2 weeks then subjects should be followed at least weekly until return to baseline or stabilization, whichever comes first.~~

~~For patients who discontinue study treatment due to a study related AE, the reporting time period may be extended. These patients must be followed at least once a week for 4 weeks, and subsequently at 4-week intervals until resolution or stabilization of the AE or laboratory abnormality, whichever comes first.~~

Section 8.6. Concomitant Medications and Supportive Care and Section 8.6.1 TLS Management

Change: Recommendations for TLS management have been included for completeness.

Information regarding TLS prophylaxis is provided in Section 6.8.1.

Subjects who develop TLS may experience hyperkalemia, hypocalcemia, hyperuricemia, hyperphosphatemia, cardiac dysrhythmias, and acute renal failure; thus, close monitoring of electrolytes is important after initial therapy.

Subjects with TLS should receive intravenous hydration, rapid reversal of hyperkalemia, antihyperuricemic agents, and appropriate cardiac and renal support, including dialysis as indicated. Upon recovery to baseline functioning and as medically appropriate, such subjects should continue with protocol therapy to maintain tumor control.

Section ~~8.6.4~~ 8.6.5 Other Concomitant Medications

Change: The text has been changed to allow more latitude regarding the implementation of bisphosphonates under circumstances in which the occurrence of disease progression is not certain.

Instructions on the concomitant administration of corticosteroids during study therapy are now provided.

Bisphosphonates: Bisphosphonates are permitted if a subject was receiving ongoing bisphosphonate therapy at time of screening and will continue on a stable regimen throughout protocol therapy. The need to start bisphosphonates while on therapy **may be an indication of disease progression and should be discussed with the sponsor prior to implementation**~~will be seen as an indication of disease progression and the subject should be withdrawn from therapy~~.

Corticosteroids: Subjects may be using topical, intra-articular, nasal, or inhaled corticosteroids at study entry and may use such drugs during therapy. The use of systemic or enteric corticosteroids is precluded at study entry because such drugs may confound interpretation of pharmacodynamic, immunological, or toxic responses in subjects on this study. However, such drugs are permitted if a subject develops intercurrent conditions that require corticosteroid therapy.

Section 8.7 Drug Interactions

Change: Restrictions on coadministration of drugs that may alter apilimod dimesylate disposition have been updated.

Drug Interactions: No information is available regarding interactions of LAM-002A (apilimod dimesylate capsules) with therapeutic agents or other substances in humans**. *In vitro* data suggest that concomitant administration of potent inhibitors or inducers of CYP3A4 or CYP2C9 might alter apilimod dimesylate clearance and lead to clinically significant increases or decreases in apilimod dimesylate exposure. Consequently, the concomitant use of strong inhibitors or inducers of CYP3A4 or CYP2C9 (see Table 15) should be avoided when possible.**

Based on these considerations, protocol candidates who require therapy with CYP3A4 or CYP2C9 inhibitors or inducers listed in Table 15 should not be enrolled into the study.

During study participation, coadministration of apilimod dimesylate with CYP3A4 or CYP2C9 inhibitors or inducers (see Table 15) should be avoided, if possible. However, a subject who develops a condition that may require use of such drugs is not required to permanently discontinue apilimod dimesylate if the subject is experiencing clinical benefit and other options for treating the subject's cancer are limited. If medically appropriate, investigators may wish to use a therapeutic alternative that would not be expected to affect these enzymes. For subjects who require temporary use of a drug that does affect these enzymes (e.g., treatment with a systemic antifungal agent), apilimod dimesylate can be interrupted (or the doses reduced) during use of the other medication and then resumed after completion of the other drug. For subjects who require initiation of chronic therapy with a drug that potently affects these enzymes, investigators must consult with the medical monitor to consider the best course of action. ~~However, theoretically interactions may occur with medications metabolized in the following pathways: CYP3A4 and CYP2C9. Subjects will be excluded from concomitantly receiving strong inducers or inhibitors of CYP2C9 and CYP3A4 (Table 15). Investigators are also advised that subjects should not be treated with moderate inducers/inhibitors of these enzymes if alternative treatment is available. If such treatments are required, concomitant medications should be started at the lowest effective dose level.~~

Section 8.8 Treatment Compliance

Change: Consistent with other sections of the protocol document, this DLT criterion has been made more specific to enhance interpretability.

A subject is considered to be DLT-evaluable if he/she has taken ~~80%~~ **at least 75% (42/56)** of **the planned** first-cycle doses and has sufficient safety data, or has experienced a DLT in **the** first cycle.

Section 9 Study Drug Materials and Management

Changes: The text has been clarified to indicate that drug dispensing must conform to legal, regulatory, or site requirements.

Information that is already described in other sections of the protocol has been deleted in order to avoid redundancy and/or inconsistency.

Information regarding disposition of study drug has been updated and clarified.

9.1 Study Drug

LAM-002A drug description is provided in Table 12.

Table 5: LAM-002A Drug Description

Product Name:	LAM-002A
Dosage Form:	Capsule
Unit Dose	25 mg (50 mg pending future development)
Route of Administration	Oral

Product Name:	LAM-002A
Physical Description	Each capsule will contain 25 mg of apilimod dimesylate (equivalent to 17.1 mg of apilimod free base) and the total fill weight of each capsule will be 175 mg. The claimed dosage strength of the active ingredient will be expressed in the free base form of apilimod. Manufacture of a 50 mg capsule is planned as part of the ongoing development program. Inactive components in active capsules are microcrystalline cellulose Avicell PH102, silicified microcrystalline cellulose, anhydrous lactose, croscarmellose sodium (Ac-Di-Sol), colloidal silicon dioxide, and magnesium stearate.
Manufacturer	Patheon

Abbreviation: mg: Milligram

9.2 Study Drug Packaging and Labeling

Study drug will be provided in bulk bottles to each investigational pharmacy for dispensing. The pharmacist will dispense capsules into bottles for each subject (based on Cohort assignment) **following applicable state and federal laws and site policies**. Details on the labeling, dispensing, and administration of study drug are provided in the Pharmacy Manual.

~~**9.4 Study Drug Administration**~~

~~Except for the days where treatment is administered in the clinic, LAM-002A will be self-administered orally, BID every 12 hours (e.g., 8 AM and 8 PM) of each 28-day cycle until disease progression or other discontinuation criteria are met.~~

~~Administration guidelines: Subjects should be advised to take study drug with 12 oz. water at the same time each day, 12 hours apart +/- 1 hour window. Subjects should not eat within 2 hours of or within 2 hours after dose administration; no solid diet restrictions otherwise. Subjects may consume clear liquids in the 2 hour pre- and post-dose window. On PK days, subjects should come to clinic fasted and take dose in the clinic under supervision.~~

~~Missed Dose: Dosing should occur at the same time each day whenever possible. If the subject forgets to take a dose by > 3 hours then the dose should not be taken and will be reported as 'missed' in the subject's diary. The next dose should be taken on schedule.~~

~~If the subject vomits after taking a dose, that dose should not be taken again.~~

~~Dosing Diary: All subjects will be required to complete a Dosing Diary, which must be returned to the clinic for review at each clinic visit.~~

~~9.5~~ 9.4 Study Drug Accountability

Study drug will be dispensed to subjects in labeled bottles at the beginning of each cycle. Subjects should be instructed to bring all bottles, including empty bottles, to each Day 1 or End of Treatment study visit for a compliance and product accountability check. Returned study drug should be retained for monitor review prior to **destruction at the site**~~return to the drug depot~~, unless contraindicated by site standard operating procedures (SOPs). If contraindicated by the site SOP, approval of site process by the sponsor must be obtained and filed in the pharmacy file

and/or regulatory binder. The investigational pharmacy must maintain contemporary and accurate records on product receipt, storage temperature, stock, dispensation, return and disposal. These records should be available for review during monitoring visits and copies available for retrieval for the Trial Master File.

~~9.6~~ 9.5 Study Drug Handling and Disposal

Study drug accountability and inventory records will be inspected by the sponsor/Ce3 prior to final disposition. Instructions will be provided by the sponsor/Ce3 for shipment to and destruction of unused study drug product by the designated packaging depot, to include **unopened bulk bottles**~~unused product returned by study subjects, unused stock product~~ at the end of the study and expired product. **Unused product returned by study subjects or opened bulk bottles will be destroyed by each site per site SOPs.** Study drug should only be shipped or destroyed upon written authorization from the sponsor/Ce3. Documentation of return of shipment, including a packing list and copy of the tracking label, should be retained in the Pharmacy and/or regulatory files.

Section 11 Assessment of Efficacy

Changes: *Citations have been updated and associated references in the bibliography have been corrected.*

Following subjects with diagnostic CT scans to evaluate efficacy is now also permitted.

Patients with CLL must have lymphadenopathy to be enrolled in the study.

Tumor response will be assessed in the Dose Escalation Stage and Expansion Stage using modified Lugano Response Criteria for NHL (***Cheson 2014*** ~~NCCN 1 2015~~) and revised g~~G~~uidelines for the diagnosis and treatment of CLL (***Hallek****~~Blood~~ 2008****, Cheson 2012***) (See Appendix 2).

Pretreatment tumor assessments will be performed within 30 days of the first dose (bone marrow assessment may be performed within 2 months prior to first dose) and will include **diagnostic CT scans (with intravenous contract) or** PET/CT **for subjects with lymphoma** (CT **only** for subjects with CLL/SLL), bone marrow aspirate/biopsy, complete blood counts and physical examination. It is anticipated that in most cases the PET and CT scans will be conducted using a single instrument, i.e., as a PET/CT scan (CT scans should be performed using a contiguous reconstruction algorithm of ≤ 5 mm). However, MRI is an acceptable alternative method for assessing disease in subjects who cannot receive intravenous contrast with CT scans. In such subjects MRI and PET scans will have to be obtained separately. Baseline bone marrow biopsies/aspirates may be omitted if not deemed essential for response assessment or patient management.

During treatment, **radiology studies** ~~PET/CT scans~~ will be performed for tumor assessments within 7 days prior to Day 1 of Cycles 3, 5, 7 and then every 3 months thereafter until PD or use of alternative antineoplastic therapy. **If necessary per applicable response criteria**~~Additionally~~, a repeat bone marrow biopsy or aspirate will be required for subjects ~~with bone marrow infiltration at baseline~~ who have a Complete Response (CR) by imaging and physical examination. ~~For subjects with CLL without nodal disease, splenomegaly or masses on baseline imaging, CT surveillance will not be required except for confirmation of CR. Also s~~subjects with

CLL/SLL who achieve CR will require assessment of minimal residual disease (MRD) by flow cytometry of bone marrow and peripheral blood.

Section 13 Biomarker Assessments

Changes: Assessments of changes in circulating cytokines have been added to the study.

The procedures for baseline acquisition of tumor tissue in study candidates with lymphoma have been updated and clarified.

Greater specificity has been provided in the baseline peripheral blood assessments for subjects with CLL/SLL in order to ensure clarity regarding the studies to be performed.

One-time, baseline collection of a saliva sample has now been included to obtain a normal-tissue control for mutation studies in tumors.

Obtaining pre-treatment histopathological material is now mandatory.

The resource for information regarding biomarker sample processing has been clarified.

Blood smears will be obtained for pharmacodynamics biomarker analysis on C1D1 and C1D8 as follows: pre-dose, 4 and 8 hours post-first dose of the day and C1D15 pre-dose only. Samples will be analyzed for PIKfyve inhibition as determined by the extent of vacuolation by microscopy.

Plasma will be collected for evaluation of circulating cytokines (including IL-12 and IL-23) predose on each of Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 1 Day 15. Samples will be analyzed using appropriate □mmune-detection assays.

For all subjects, PBMCs will be collected on Cycle 1, Day 1 pre-treatment; on Cycle 1, Day 1 at 8 hours post-dose; and on Cycle 1, Day 8 at 8 hours post-dose for determination of changes in gene expression that may predict or correlate with anti-lymphoma activity and/or pharmacodynamic activity.

For subjects with NHL, archival tissue from the most recent available biopsy or surgery or fresh tumor tissue must be obtained pretreatment. For subjects undergoing a biopsy, adequate tumor tissue should be acquired via excisional biopsy, incisional biopsy or core needle biopsy (e.g., ≥ 3 passes using a 16-gauge core needle). Tissue will be submitted for evaluation of the percentage of tumor cells and analysis of genetic alterations and/or gene expression that may predict anti-lymphoma activity and/or pharmacodynamics activity. In addition, tumor may be evaluated for known prognostic characteristics (e.g., for DLBCL: ABC or GCB subtype; expression of BCL2, BCL6, Ki-67, CD20, and MYC; other mutational status).

Subjects with CLL/SLL must provide a fresh blood sample containing tumor cells or a bone marrow aspirate sample pretreatment. Tissue will be submitted for evaluation of the percentage of tumor cells and analysis of genetic alterations and/or gene expression that may predict anti-lymphoma activity and/or pharmacodynamics activity. In addition, for subjects with CLL/SLL, tumor may be evaluated for known prognostic characteristics (e.g., quantitative immunoglobulins, FISH panel [chromosome 11q deletion, 13q deletion, 17p deletion and 12 trisomy], DNA mutational analysis for p53, IgHV [(including

IgHV3-21], and other genes of interest in CLL [e.g., Notch]; flow cytometry [for CD5, CD10, CD11c, CD19, CD20, CD23, CD38, CD45, kappa and lambda light chains and ZAP-70]), and serum β2-microglobulin.

A saliva sample will be obtained on Cycle 1 Day 1 as a normal-tissue control for gene mutation studies in tumors.

~~Tissue from the most recent available biopsy or surgery prior to first dose will be submitted for biomarker analysis to determine genetic alterations or gene expression and determination of immune cell infiltration that may predict response to LAM-002A (apilimod dimesylate capsules). Although tumor samples are not required for enrollment of subjects, obtaining and submitting fresh or archival samples is strongly encouraged. Plasma bioanalytes will be examined by proteomic technology at Cycle 1 Day 1 and Cycle 1 Day 8 to determine changes that may predict response to LAM-002A.~~

~~Additionally, a bone marrow aspirate (if positive at baseline) and core tumor biopsy will be obtained at the time of the first scheduled tumor assessment (end of Cycle 2). However, the requirement for core tumor biopsy may be waived for subjects whose tumor cannot be safely biopsied or for whom the investigator deems the procedure inappropriate. These tissues will be analyzed for inhibition of PIKfyve by measuring the extent of vacuolation by microscopy. Tissue will also be analyzed by immunohistochemistry for determination of the extent of immune cell infiltration (tumor infiltrating lymphocytes, tumor associated macrophages). Additionally, ribonucleic acid (RNA) will be collected from fresh samples for gene expression analysis.~~

Comprehensive information on tissue acquisition, handling, storage and sample shipments can be found in the biomarker **sample process documents** ~~laboratory manual~~.

Section 14.3.4 DLT Evaluable Population

Change: The text has been altered for consistency with amendments to the definitions of DLT evaluability in other sections of the protocol document

Dose escalation decisions will be evaluated in DLT evaluable population. The DLT evaluable population will include subjects who complete Cycle 1 dosing (administered at least **75**~~80~~% of doses) and have sufficient safety data, or who are withdrawn from study due to a DLT in Cycle 1.

Section 14.9 Efficacy Analysis

Change: Citations and references in the bibliography have been corrected.

The tumor response will be assessed by the modified ~~Lugano Response C~~**c**riteria for NHL (~~*NCCN 1 2015*~~ ***Cheson 2014***) and revised **g**~~G~~uidelines for the diagnosis and treatment of CLL (*Hallek 2008*, ***Cheson 2012***) (See Appendix 2).

Section 21 List of References

Change: References in the bibliography have been updated consistent with other additions or changes to the protocol document.

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Appendix 2. Criteria for Response Assessment

Changes: A more comprehensive description of the criteria for response assessment in lymphoma has been provided to ensure appropriate evaluation of patients with both FDG-avid and FDG-non-avid lymphoma subtypes and patients who are followed by PET/CT or by diagnostic CT. The criteria are consistent with Cheson 2014.

The criteria for response assessment in CLL have been updated and clarified consistent with both the Hallek 2008 and Cheson 2012 references.

~~**Table 7: 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)~~
~~Lymph nodes and extralymphatic sites~~	~~Score 1, 2, or 3~~[*] ~~with or without a residual mass on 5PS~~[‡] ~~It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., 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~~	~~Target nodes/nodal masses must regress to ≤ 1.5 cm in Ldi~~ ~~No extralymphatic sites of disease~~

Response and Site	PET-CT-Based Response	CT-Based Response
	physiologic uptake	
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)
Lymph nodes and extralymphatic sites	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
-	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
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 (e.g., a 15-cm spleen must increase to > 16

Response and Site	PET-CT-Based Response	CT-Based Response
		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 (e.g., 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

* 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 under-treatment). Measured dominant lesions: Up to 6 of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in 2 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 (e.g., 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 (e.g.,, 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 (e.g., 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.
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.

Source: *Cheson 2014*.

Response Assessment of CLL (Source: *Hallek 2008*)

The World Health Organization (WHO) classification of hematopoietic neoplasias describes CLL as leukemic, lymphocytic lymphoma, being only distinguishable from small lymphocytic lymphoma (SLL) by its leukemic appearance. In the World Health Organization classification, CLL is always a disease of neoplastic B cells, whereas the entity formerly described as T-cell chronic lymphocytic leukemia (T-CLL) is now called T-cell prolymphocytic leukemia.

It is important to verify that the subject has CLL and not some other lymphoproliferative disease that can masquerade as CLL, such as hairy cell leukemia, or leukemic manifestations of mantle cell lymphoma, marginal zone lymphoma, splenic marginal zone lymphoma with circulating

~~villous lymphocytes, or follicular lymphoma. To achieve this, it is essential to evaluate the blood count, blood smear, and the immune phenotype of the circulating lymphoid cells.~~

~~Definition of Response~~

~~Assessment of response should include a careful physical examination and evaluation of the blood and marrow (See **). To define a CR, the marrow sample must be at least normocellular for age, with less than 30% of nucleated cells being lymphocytes. Lymphoid nodules should be absent.~~

~~Complete remission (CR)~~

~~CR requires all of the following criteria as assessed at least 2 months after completion of therapy:~~

- ~~Peripheral blood lymphocytes (evaluated by blood and differential count) below 4×10^9/L (4,000/μL).~~

13. ~~In clinical trials, the presence of MRD after therapy should be assessed. The sensitivity of the method used to evaluate for MRD should be reported.~~
14. ~~Absence of significant lymphadenopathy (e.g, lymph nodes > 1.5 cm in diameter) by physical examination. In clinical trials, a CT scan of the abdomen, pelvis, and thorax is desirable if previously abnormal. Lymph nodes should not be larger than 1.5 cm in diameter.~~
15. ~~No hepatomegaly or splenomegaly by physical examination. In clinical trials, a CT scan of the abdomen should be performed at response assessment if found to be abnormal before therapy or if physical examination is inconclusive at the time of evaluation.~~
16. ~~Absence of constitutional symptoms.~~
17. ~~Blood counts above the following values:~~
    - Neutrophils More Than 1.5×10^9/L (1500/μL) without need for Exogenous Growth Factors.
    - Platelets More Than 100×10^9/L (100,000/μL) without need for Exogenous Growth Factors.
    - Hemoglobin More Than 110 G/L (11.0 g/dL) without Red Blood Cell Transfusion or need for Exogenous Erythropoietin.
    - For subjects in clinical trials a marrow aspirate and biopsy should be performed at least 2 months after the last treatment and if clinical and laboratory results above demonstrate that a CR has been achieved

~~Partial remission (PR)~~

~~PR is defined by the criteria described in Sections 1, 2, or 3 below (if abnormal before therapy), as well as one or more of the features listed in Section 4. To define a PR, these parameters need to be documented for a minimal duration of 2 months (See Table 8). Constitutional symptoms persisting for more than 1 month should be recorded.~~

1. ~~A decrease in the number of blood lymphocytes by 50% or more from the value before therapy.~~

18. ~~Reduction in lymphadenopathy (by CT scans in clinical trials or by palpation in general practice) as defined by the following:~~

    - A decrease in lymph node size by 50% or more either in the sum products of up to 6 lymph nodes, or in the largest diameter of the enlarged lymph node(s) detected prior to therapy.
    - No increase in any lymph node, and no new enlarged lymph node. In small lymph nodes (< 2 cm), an increase of less than 25% is not considered to be significant.

19. ~~A reduction in the noted pretreatment enlargement of the spleen or liver by 50% or more, as detected by CT scan (in clinical trials) or palpation (in general practice).~~

20. ~~The blood count should show one of the following results:~~

    - Neutrophils more than 1.5 x 10^9/L (1,500/µL) without need for exogenous growth factors.
    - Platelet counts greater than 100 × 10^9/L (100,000/µL) or 50% improvement over baseline without need for exogenous growth factors.
    - Hemoglobin greater than 110 g/L (11.0 g/dL) or 50% improvement over baseline without requiring red blood cell transfusions or exogenous erythropoietin.

~~Stable disease (SD)~~

~~Patients who have not achieved a CR or a PR, and who have not exhibited progressive disease, will be considered to have stable disease (which is equivalent to a nonresponse).~~

~~Progressive Disease~~

~~Progressive disease during or after therapy is characterized by at least one of the following:~~

1. ~~Lymphadenopathy.~~
   ~~Progression of lymphadenopathy is often discovered by physical examination and should be recorded. In CLL, the use of CT scans usually does not add much information for the detection of progression or relapse. Therefore, the use of imaging methods to follow CLL progression is at the discretion of the treating physician. Disease progression occurs if one of the following events is observed:~~
   ~~Appearance of any new lesion, such as enlarged lymph nodes (> 1.5 cm), splenomegaly, hepatomegaly, or other organ infiltrates.~~
   ~~An increase by 50% or more in greatest determined diameter of any previous site.~~

21. ~~An increase in the previously noted enlargement of the liver or spleen by 50% or more or the de novo appearance of hepatomegaly or splenomegaly.~~

22. ~~An increase in the number of blood lymphocytes by 50% or more with at least 5,000 B lymphocytes per microliter.~~

23. ~~Transformation to a more aggressive histology (e.g., Richter syndrome). Whenever possible, this diagnosis should be established by lymph node biopsy.~~

~~**Table 8: Response Definition After Chronic Lymphocytic Leukemia Treatment**~~

~~Parameter~~	~~CR*~~	~~PR*~~	~~PD*~~
~~Group A~~	-	-	-
~~Lymphadenopathy†~~	~~None > 1.5 cm~~	~~Decrease ≥ 50%~~	~~Increase ≥ 50%~~
~~Hepatomegaly~~	~~None~~	~~Decrease ≥ 50%~~	~~Increase ≥ 50%~~
~~Splenomegaly~~	~~None~~	~~Decrease ≥ 50%~~	~~Increase ≥ 50%~~
~~Blood lymphocytes~~	~~< 4000/µL~~	~~Decrease ≥ 50% from baseline~~	~~Increase ≥ 50% over baseline~~
~~Marrow‡~~	~~Normocellular, < 30% lymphocytes, no B-lymphoid nodules. Hypocellular marrow defines CRi.~~	~~50% reduction in marrow infiltrate, or B-lymphoid nodules~~	-
~~Group B~~	-	-	-
~~Platelet count~~	~~> 100 000/µL~~	~~> 100 000/µL or increase ≥ 50% over baseline~~	~~Decrease of ≥ 50% from baseline secondary to CLL~~
~~Hemoglobin~~	~~> 11.0 g/dL~~	~~> 11 g/dL or increase ≥ 50% over baseline~~	~~Decrease of > 2 g/dL from baseline secondary to CLL~~
~~Neutrophils‡~~	~~> 1500/µL~~	~~> 1500/µL or > 50% improvement over baseline~~	-

- ~~Note: Group A criteria define the tumor load, Group B criteria define the function of the hematopoietic system (or marrow).~~

~~* CR (complete remission): all of the criteria have to be met, and patients have to lack disease related constitutional symptoms; PR (partial remission): at least 2 of the criteria of group A plus one of the criteria of group B have to be met; SD is absence of progressive disease (PD) and failure to achieve at least a PR; PD: at least one of the above criteria of group A or group B has to be met.~~
~~† Sum of the products of multiple lymph nodes (as evaluated by CT scans in clinical trials, or by physical examination in general practice).~~
~~‡ These parameters are irrelevant for some response categories.~~
~~Abbreviations: cm: Centimeter; Cri: CR with incomplete marrow recovery; dL: Deciliter; g: Gram; µL: Microliter~~
~~Source: *Hallek 2008*.~~

1 LYMPHOMA

1.1 Tumor Assessment Criteria

The determination of response and progression for subject with NHL will be based on standardized criteria [Cheson 2014].

1.2 Method of Assessment

Imaging-based evaluation will be used in this study as the primary basis of lymphoma assessment. CT scan is the preferred method for radiographic tumor assessment. Contrast-

enhanced scanning is preferred, but contrast material may be omitted in subjects for whom use of a contrast agent becomes medically contraindicated or if CT scanning is done in conjunction with PET. If available, PET scan data will be considered in response and progression assessment; however, PET scanning will not be a required component of assessment in this study. As necessary, bone marrow aspirate/biopsy (e.g., for confirmation of CR) or cytological/histological evaluation of lymph nodes, effusions, ascites, or other organ abnormalities) will be also be considered. Clinical palpation, chest x-ray, ultrasound, endoscopy, laparoscopy, radionuclide scan, or tumor markers will not be considered for response assessment. MRI scanning is not advised but may be used at the investigator's discretion in subjects for whom this becomes a necessary alternative to CT scanning.

For radiographic assessments, the same method of assessment and the same technique (e.g., scan type, scanner, subject position, dose of contrast, injection/scan interval) should be used to characterize each identified and reported lesion at baseline and during study treatment and follow-up. CT of the neck, chest, abdomen, and pelvis should be performed with cuts of ≤ 0.5 mm in slice thickness contiguously. If performed, whole-body FDG PET-CT scanning should be extended from the base of the skull to mid-thigh.

All relevant radiographic and clinical information required to make each tumor status assessment must be made available for source verification as requested by the study sponsor.

1.3 Timing of Assessments

During screening, clinical and imaging-based tumor assessments should be performed within the specified screening period. On-study tumor assessments should be performed as stipulated in Section Changed. An end-of-therapy tumor assessment should be performed unless the subject already has radiographic confirmation of disease progression ≤ 4 weeks prior to study drug discontinuation. If a subject permanently discontinues treatment prior to objective documentation of lymphoma progression, investigators should ideally continue further follow-up of tumor status with assessments at ~12-week intervals until disease progression is documented or until the initiation of a new post-study therapy for the subject's lymphoma.

1.4 Identification and Follow-up of Tumor Lesions and Organomegaly

1.4.1 Index Lesions

Up to 6 lesions (e.g., lymph nodes, liver or spleen nodules, and/or other circumscribed extranodal masses) should be selected as index lesions that will be used to quantitate the status of the disease during study treatment. Ideally, the index lesions should be located in disparate regions of the body and include mediastinal, abdominal, and retroperitoneal areas of disease whenever these sites are involved. For subjects with FDG-avid lymphomas undergoing PET, selection of FDG-avid lesions is preferred.

Index lesions will be measured and recorded at baseline and at the stipulated intervals during treatment. The largest cross-sectional dimensions (i.e., the LD × LPD will be recorded (in cm) for each index lesion. Using the LD and LPD, the product of the perpendicular diameters (PPD) for each index lesion will be calculated. The PPDs and the SPDs for all index lesions will be calculated and recorded. The baseline and nadir PPDs of individual lesions and the baseline and nadir SPDs will be used as references by which

objective tumor response and progression will be characterized during treatment. All PPD and SPD measurements will be reported in centimeters squared.

1.4.2 Nodal Index Lesions

A nodal mass may be selected as a nodal index lesion if it is both abnormal and measurable at baseline. A lymph node lesion is considered abnormal if it has a single diameter that is > 1.0 cm and is considered measurable if it has 2 perpendicular diameters that can be accurately measured in cross section with the LD being ≥ 1.0 cm and the LPD also being ≥ 1.0 cm.

Abnormal, measurable nodal lesions will be subcategorized as either large or small.

- **Large nodal lesions have an LD that is > 1.5 cm and an LPD that is ≥ 1.0 cm.**
- **Small nodal lesions have an LD that is > 1.0 cm and ≤ 1.5 cm and an LPD that is > 1.0 cm.**

Index lesions measuring > 1.5 cm in the LD, regardless of the measurement of the LPD, will be prioritized during baseline index lesion selection.

At follow-up timepoints, the PPDs for individual nodal lesions and the SPD of all nodal index lesions will be considered. Because nodal index lesions that have one or both diameters > 0 cm and < 1.0 cm cannot be reliably measured, a default value of 1.0 cm will be assigned for each diameter that meets these criteria and the resulting PPD will be used in SPD calculations. Based on this convention, a CR may be achieved even if an SPD value is > 0 cm^2 (i.e., if all lymph nodes measure < 1.0 cm^2).

New or enlarging nodal lesions that are still ≤ 1.0 cm by ≤ 1.0 cm will not be considered to represent recurrent or PD. A new node that measures > 1.5 cm in any diameter or a new node that measures > 1.0 cm to ≤ 1.5 cm in the LD and measures > 1.0 cm in the LPD will be considered PD.

In cases in which a large lymph node mass has split into multiple components, only those elements that are > 1.0 cm in ≥ 1 diameter will be considered abnormal and used in calculating the SPD. Components that are ≤ 1.0 cm in the LD are assumed to be normal lymph node structures. PD will not be based on the growth of a lesion sub-component until it meets the criteria for abnormal. Lesion sub-components that are abnormal (> 1.0 cm in ≥ 1 diameter) will have the true PPDs calculated with the result used only for calculating an accurate nadir. Lesion subcomponents that are normal (≤ 1.0 cm in the LD) will have the default PPD of 1.0 cm^2 (1.0 cm x 1.0 cm) stored only for the purposes of calculating the nadir value.

If lesions merge, a boundary between the lesions will be established so the LD of each individual lesion can continue to be measured. If the lesions have merged in a way that they can no longer be separated by this boundary, the newly merged lesion will be measured bidimensionally.

1.4.3 Extranodal Index Lesions

An extranodal mass may be selected as an index lesion if it is both abnormal and measurable at baseline. An extranodal mass of any size is considered abnormal. It is considered measurable at baseline if it has 2 perpendicular diameters that can be

accurately measured in cross section with the LD being ≥ 1.0 cm and the LPD also being ≥ 1.0 cm.

At follow-up timepoints, the PPD of each single extranodal index lesion and the SPD of all extranodal index lesions will be considered. Because extranodal index lesions that have one or both diameters < 0.5 cm and > 0 cm cannot be reliably measured, a default value of 0.5 cm will be assigned for each diameter that meets these criteria and the resulting PPD will be used in SPD calculations. If an extranodal lesion is no longer clearly visible, it will be considered resolved and its PPD will be defined as 0 cm^2.

If an extranodal lesion that had resolved (i.e., had a PPD of 0 cm^2) subsequently reappears, the subject will be considered to have PD. A new extranodal lesion of any size that appears at a site that was not previously involved with lymphoma and is discernible to the radiologist by CT scan will be considered PD.

1.4.4 Non-Index Lesions

Any other measurable and abnormal nodal or extranodal lesions not selected for quantitation as index lesions may be considered non-index lesions. In addition, non-measurable evidence of lymphoma such as abnormal, non-measurable nodal lesions, extranodal lesions with both diameters < 1.0 cm, bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusions, lymphangitis of the skin or lung, abdominal masses that are not confirmed and followed by imaging techniques, cystic lesions, previously irradiated lesions, or lesions with artifacts may be considered as non-index disease.

If present at baseline, up to 6 non-index lesions should be recorded. Measurements are not required.

Non-index disease will be used as a general reference to further characterize regression or progression of lymphoma during assessments of the objective tumor response during treatment. These lesions should be followed as "present" or "absent".

1.4.5 Spleen and Liver

Qualitative assessments of the sizes of the spleen and liver will be performed. In addition, the presence or absence of splenic nodules will be recorded.

At baseline and follow-up timepoints, the spleen and liver size will be reported as normal, enlarged not due to lymphoma (no nodules present), enlarged due to lymphoma (≥ 1 nodule present), unequivocal increase not due to lymphoma (no nodules present), or unequivocal progression (≥ 1 nodule present). For subjects with splenomegaly or hepatomegaly at baseline or at the nadirs for assessments of spleen and liver, evaluations will consider only changes relative to the enlargement of the organ (i.e., the portion of the LVD that is > 12 cm by imaging for the spleen and > 18 cm in LVD for the liver) at baseline or nadir, not changes relative to the total splenic LVD.

By imaging, the spleen will be considered enlarged if it is > 12 cm in LVD [Bezerra 2005, Asghar 2011], with the LVD being obtained by multiplying the number of sections on which the spleen is visualized by the thickness of the sections (e.g., if the spleen is seen in 14 contiguous cross-sectional images with 0.5-cm thickness, the LVD is recorded as 7 cm). An increase in splenic enlargement by ≥ 50% (minimum increase of 2 cm) from nadir and the presence of ≥ 1 splenic nodule is required for declaration of splenic progression.

Subjects with a normal spleen LVD (i.e., a LVD of ≤ 0 cm by physical examination or ≤ 12 cm by imaging) at nadir will only be considered to have progressed if the spleen attains a LVD of > 14 cm by imaging and there is ≥ 1 splenic nodule.

By imaging, the liver will be considered enlarged if it is > 18 cm in LVD [Erturk 2006]. An increase in liver enlargement by ≥ 50% (minimum increase of 2 cm) from nadir and the presence of ≥ 1 hepatic nodule is required for declaration of hepatic progression. Subjects with a normal liver LVD (i.e., a LVD of ≤ 18 cm by imaging) at nadir will only be considered to have progressed if the liver attains a LVD of > 20 cm by imaging and there is ≥ 1 hepatic nodule.

1.4.6 Bone Marrow

Bone marrow assessments will be based on morphologic evaluation of bone marrow biopsies. Immunohistochemistry may be used to assess response if the sample is indeterminate by morphology.

In a subject who has a baseline bone marrow biopsy showing bone marrow lymphoma or does not have a baseline bone marrow examination, declaration of an on-study CR requires bone marrow biopsy documentation of the absence of bone marrow lymphoma. In a subject who has a baseline bone marrow biopsy showing no evidence of lymphoma, declaration of an on-study CR does not require bone marrow examination as long as other criteria for CR are met. Of note, in subjects with an FDG-PET avid lymphoma, declaration of an on-study CR can be based on FDG-PET documentation of the absence of bone marrow involvement, even if a bone marrow biopsy is not performed or not available.

1.4.7 Lymph Node Biopsy

Lymph node biopsy is not required in the determination of subject eligibility.

During study participation, a subject with a more indolent type of disease (e.g., CLL/SLL, FL) who has a lymph node biopsy indicating transformation to an aggressive lymphoma will be considered to have PD even in the absence of other evidence of PD. If the subject has no earlier objective documentation of PD, the date of the lymph node biopsy will be considered the date of PD.

1.5 Definitions of Tumor Response and Progression

Responses will be categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). In addition, a response category of nonevaluable (NE) is provided for situations in which there is inadequate information to otherwise categorize response status.

The best overall response will be determined. The best overall response is the best on-treatment response from baseline recorded from the start of treatment until PD/recurrence. The baseline measurement will be taken as a reference for determinations of response. The nadir measurement will be taken as a reference for PD; this measurement constitutes the smallest measurement recorded, including the baseline measurement if this is the smallest measurement. For FDG-avid tumors, metabolic criteria for response by PET-CT will take precedence over anatomic criteria for response by contrast CT when assessing CR.

1.5.1 Complete Response

To satisfy criteria for CR, all of the following conditions must be attained:

- **No evidence of new disease**
- **Regression of all index nodal lesions to normal size (≤ 1.5 cm in the LD for nodes that were considered large at baseline and ≤ 1.0 cm in the LPD for nodes that were considered small at baseline) (see Section 1.4.2 for definitions of large and small nodes)**
- **Regression to normal of all nodal non-index disease**
- **Disappearance of all detectable extranodal index and non-index disease**
- **Normal spleen and liver size by imaging studies, no hepatic or splenic lymphoma nodules, and no new liver or spleen enlargement**
- **Morphologically negative bone marrow based on an adequate unilateral core biopsy (> 20 mm unilateral core); if the sample is indeterminate by morphology, it should be negative by immunohistochemistry**
- **If PET performed, no evidence of residual disease – i.e., score of 1 (no uptake above background), 2 (uptake ≤ mediastinum), or 3 (uptake > mediastinum but ≤ liver) on the Deauville 5-point scale.**
- **Negative for bone marrow involvement by PET for a PET-avid tumor or by an adequate unilateral core biopsy (> 20 mm unilateral core); if the bone marrow biopsy is indeterminate by morphology, it should be negative by immunohistochemistry.**

1.5.2 Partial Response

To satisfy criteria for PR, all of the following conditions must be attained:

- **No evidence of new disease**
- **A ≥ 50% decrease from baseline in the SPD of the index nodal and extranodal lesions**
- **No increase from the nadir in the size of non-index disease**
- **No increase from the nadir in the size of the liver or spleen and no new liver or spleen enlargement**
- **If PET performed:**
  - **Typically FDG-avid lymphoma: if no baseline PET scan or if the PET scan was positive before therapy, the on-treatment PET is positive in ≥ 1 previously involved site– i.e., score of 4 (uptake moderately > liver) or score of 5 (uptake markedly > liver) on the Deauville 5-point scale but with reduced uptake compared with baseline. If baseline PET was performed and was negative, there is no new PET evidence of disease.**
  - **Variably FDG-avid lymphoma/FDG-avidity unknown: if no pretreatment PET scan or if the pretreatment PET scan was negative for lymphoma, CT criteria should be used in assessing the tumor during treatment. If the PET scan was positive before therapy, the on-treatment PET is positive in ≥ 1 previously involved site.**

- **Persistence of bone marrow involvement in a subject who meets other criteria for CR based on the disappearance of all nodal and extranodal masses**

1.5.3 Stable Disease

To satisfy criteria for SD, all of the following conditions must be attained:

- **No evidence of new disease**
- **Neither sufficient tumor shrinkage from baseline to qualify for PR nor sufficient evidence of tumor growth to qualify for PD**
- **If PET-CT performed, the results show a score of 4 (uptake moderately > liver) or score of 5 (uptake markedly > liver) on the Deauville 5-point scale with no significant change in uptake compared with baseline.**

1.5.4 Progressive Disease

The occurrence of any of the following events indicates progressive disease (PD):

- **Evidence of any new disease that was not present at baseline:**
  - **A new node that measures > 1.5 cm in any diameter**
  - **A new node that measures > 1.0 cm to ≤ 1.5 cm in the LD and > 1.0 cm in the LPD**
  - **Reappearance of an extranodal lesion that had resolved (i.e., had previously been assigned a PPD of 0 cm^2)**
  - **A new extranodal lesion of any size**
  - **New non-index disease (e.g., effusions, ascites, or other organ abnormalities) of any size unequivocally attributable to lymphoma (usually requires PET, biopsy, cytology, or other non-radiologic confirmation to confirm disease attributable to lymphoma). *Note: Isolated new effusions, ascites, or bone lesions are not sufficient evidence alone of PD unless histologically confirmed. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are usually benign. Thus, a declaration of PD should not be made if this is the only manifestation of an apparently new lesion.***
  - **New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If there is uncertainty regarding the etiology of new lesions, biopsy or interval scan may be considered.**
  - **New or recurrent bone marrow involvement with lymphoma by PET-CT or by bone marrow biopsy if prior PET-CT or bone marrow biopsy performed as part of the study was negative for lymphoma.**
- **Evidence of worsening of nodal or extranodal index lesions:**
  - **Increase from the nadir by ≥ 50% in the SPD of index lesions**
  - **Evidence of worsening of individual index lymph nodes or nodal masses:**
    - **Increase from the nadir by ≥ 50% in the PPD for any individual node if the node now has an LD of > 1.5 cm and there is an absolute change from the nadir of ≥ 0.5 cm in the LD or LPD and to an absolute dimension of ≥ 2.0 cm.**

- **Increase from the nadir by ≥ 50% in the LD for any individual node if the node now has an LD of > 1.5 cm and there is an absolute change from the nadir of ≥ 0.5 cm in the LD**
- **Increase from the nadir by ≥ 50% in the LPD for any individual node if the node now has an LPD of > 1.5 cm and there is an absolute change from the nadir of ≥ 0.5 cm in the LPD**
- **If a lesion had been classified as a small lymph node, there is an additional requirement that the lesion has an LD of > 1.0 cm and an LPD of > 1.0 cm**

- **Unequivocal increase in the size of non-index disease**
- **Unequivocal worsening in the size of the liver or spleen (with the additional condition that there must be ≥ 1 nodule present in the enlarging organ)**

- **Transformation to a more aggressive NHL histology as established by lymph node biopsy**
- **If PET performed, there is a score of 4 (uptake moderately > liver) or score of 5 (uptake markedly > liver) on the Deauville 5-point scale with an increase in uptake compared with the nadir in conjunction with an anatomic increase in lesion size consistent with PD.**

Note: Study subjects undergoing PET for lymphoma assessment can experience transient disease flare on imaging before having subsequent therapy-induced tumor regression. Worsening of constitutional symptoms or performance status in the absence of objective evidence of worsening lymphoma (e.g., due to infection) may not represent definitive disease progression. Further, transient worsening of disease during temporary interruptions of study therapy (e.g., for drug-related toxicity or inter-current illness) may not indicate definitive progressive lymphoma. If there is uncertainty regarding whether there is true lymphoma progression and if medically appropriate, the subject may continue or resume study treatment and remain under close observation (e.g., evaluated at 3- to 6-week intervals) while relevant radiographic, clinical, and/or laboratory assessments are performed to document whether tumor control can be maintained or whether disease progression has truly occurred. If subsequent evaluations suggest that the subject has experienced persistent definitive disease progression, then the date of progression will be the timepoint at which progression was first objectively documented.

1.5.5 Nonevaluable

In a subject who does not have evidence of PD, the occurrence of any of the following conditions indicates a response status of NE:

- **There are no images or inadequate or missing images, defined as the inability to visualize > 25% of index disease and > 50% of non-index disease.**

2 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

2.1 Tumor Assessment Criteria

The determination of CLL/SLL response and progression will be based on standardized criteria [Hallek 2008], as recently updated [Cheson 2012].

2.2 Method of Assessment

In addition to clinical examination, imaging-based evaluation will be used in this study in all subjects enrolled. CT scan is the preferred method for radiographic tumor assessment. MRI scanning may be used at the investigator's discretion in subjects for whom this may be a preferred alternative to CT scanning; however, if MRI is performed, a non-contrast CT of the chest should be performed. Contrast-enhanced scanning is preferred, but iodine-containing or gadolinium contrast material may be omitted in subjects for whom use of a contrast agent would be medically contraindicated. Chest x-ray, ultrasound, endoscopy, laparoscopy, PET, radionuclide scans, or tumor markers will not be considered for response assessment.

For radiographic evaluations, the same method of assessment and the same technique (e.g., scan type, scanner, subject position, dose of contrast, injection/scan interval) should be used to characterize each identified and reported lesion at baseline and during study treatment and follow-up. However, if a subject is imaged without contrast at baseline, subsequent assessments should be performed with contrast, unless the subject cannot tolerate the contrast.

All relevant clinical and radiographic information required to make each tumor status assessment must be made available for source verification as requested by the study sponsor.

2.3 Timing of Assessments

During screening, clinical, laboratory, and imaging-based tumor assessments should be performed within the specified screening period. Clinical tumor assessments should be performed at each designated clinical visit. On-study CT/MRI tumor assessments should be performed as indicated in Section Changed. An end-of-study CT/MRI tumor assessment should be performed unless the subject already has radiographic confirmation of disease progression ≤ 4 weeks prior. If a subject permanently discontinues study drug prior to objective documentation of CLL/SLL progression, investigators should optimally attempt to obtain further follow-up at ~12-week intervals until CLL/SLL progression is documented or until the initiation of a new post-study therapy for the subject's CLL/SLL.

2.4 Identification and Measurement of Tumor Lesions and Organomegaly

2.4.1 Index Lesions

At baseline, up to 6 lymph nodes should be selected as index lesions that will be used to quantitate the status of the disease during study treatment. Ideally, the index lesions should be located in disparate regions of the body. Only peripheral nodes need be selected as index lesions. However, it is optimal if mediastinal and retroperitoneal areas of disease are assessed whenever these sites are involved.

Index lesions will be measured and recorded at baseline and at the stipulated intervals. The cross-sectional dimensions (the largest cross-sectional diameter, i.e., the LD × LPD) will be recorded (in cm) for each index lesion. The product of the perpendicular diameters (PPD) (in cm^2) for each index lesion and SPD (in cm^2) for all index lesions will be calculated and recorded. The baseline SPD will be used as references by which objective tumor response will be characterized during treatment. The nadir LD of individual lesions and the nadir

SPD will be used as references by which CLL/SLL progression will be characterized. All LD and LPD diameters will be reported in centimeters and all PPDs and SPDs will be reported in centimeters squared.

A nodal mass may be selected as a nodal index lesion if it is both abnormal and measurable at baseline. A lymph node lesion is considered abnormal if it has a single diameter that is > 1.5 cm and is considered measurable if it has 2 perpendicular diameters that can be accurately measured in cross section with the LD being ≥ 1.0 cm and the LPD also being ≥ 1.0 cm.

Index lesions measuring > 1.5 cm in the LD, regardless of the measurement of the LPD, will be prioritized during baseline index lesion selection.

At follow-up timepoints, the LDs for individual lesions and the SPD of all nodal index lesions will be considered. Because nodal index lesions that have one or both diameters > 0 cm and < 1.0 cm cannot be reliably measured, a default value of 1.0 cm will be assigned for each diameter that meets these criteria and the resulting PPD will be used in SPD calculations. Based on this convention, a CR may be achieved even if an SPD value is > 0 cm^2, (i.e., if all lymph nodes measure < 1.0 cm^2).

A new node that measures > 1.5 cm in any diameter or a new node that measures > 1.0 cm to ≤ 1.5 cm in the LD and measures > 1.0 cm in the LPD will be considered progressive disease.

In cases in which a large lymph node mass has split into multiple components, only those elements that are > 1.0 cm in ≥ 1 diameter will be considered abnormal and used in calculating the SPD. Progression of the lesion can only be based on the SPD of abnormal sub-components. Lesion sub-components that are considered normal but measurable will have the true PPDs calculated, with the result used only for calculating an accurate nadir. Similarly, lesion sub-components that are visible but neither abnormal nor measurable will have the default PPD of 1.0 cm^2 (1.0 cm × 1.0 cm) stored only for the purposes of calculating the nadir SPD value.

If lesions merge, a boundary between the lesions will be established so the LD of each individual lesion can continue to be measured. If the lesions have merged in a way that they can no longer be separated by this boundary, the newly merged lesion will be measured bi-dimensionally.

2.4.2 Spleen and Liver

Both the spleen and liver will be assessed by CT/MRI scan and by physical examination at baseline and at the stipulated intervals during treatment. The baseline and nadir values for the longest vertical dimension (LVD) of each organ will be used as reference to further characterize the objective tumor response of the measurable dimensions of the CLL/SLL during treatment. All spleen and liver LVD measurements should be recorded in centimeters.

Physical examination of the spleen should comprise assessment of its LVD below the left costal margin by palpation. By physical examination, the spleen will be considered enlarged if it is palpable below the left costal margin. If the spleen is not palpable below the left costal margin, it should be assigned a value of 0 cm for physical examination

assessment. By imaging, the spleen will be considered enlarged if it is > 12 cm in LVD [Bezerra 2005, Asghar 2011], with the LVD being obtained by multiplying the number of sections on which the spleen is visualized by the thickness of the sections (e.g., if the spleen is seen in 14 contiguous cross-sectional images with 0.5-cm thickness, the LVD is recorded as 7 cm).

For subjects with splenomegaly at baseline or at the splenic LVD nadir, respective response and progression evaluations of the spleen will consider only changes relative to the enlargement of the spleen (i.e., the portion of the LVD that is > 0 cm by physical examination or > 12 cm by imaging) at baseline or nadir, not changes relative to the total splenic LVD.

A 50% decrease from baseline (minimum decrease of 2 cm) in the enlargement of the spleen in its LVD or to ≤ 12 cm by imaging, or regression to a spleen LVD of ≤ 0 cm by physical examination, is required for declaration of a splenomegaly response. Conversely, an increase in splenic enlargement by ≥ 50% (minimum increase of 2 cm) from nadir is required for declaration of splenic progression. Subjects with a normal spleen LVD (i.e., a LVD of ≤ 0 cm by physical examination or ≤ 12 cm by imaging) at nadir will only be considered to have progressed if the spleen attains a LVD of > 14 cm by imaging or > 2 cm by physical exam.

Physical examination of the liver should comprise assessment of its LVD at the right midclavicular line by percussion. By physical examination, the liver will be considered enlarged if it is > 15 cm in LVD as assessed by percussion [Walker 1990]. By imaging, the liver will be considered enlarged if it is > 18 cm in LVD [Erturk 2006].

A 50% decrease (minimum decrease of 2 cm) from baseline in the enlargement of the liver in its LVD or to ≤ 18 cm by imaging, or regression to a liver LVD of ≤ 15 cm by physical examination, is required for declaration of a hepatomegaly response. Conversely, an increase in liver enlargement by ≥ 50% (minimum increase of 2 cm) from nadir is required for declaration of hepatic progression. Subjects with a normal liver LVD (i.e., a LVD of ≤ 15 cm by physical examination or ≤ 18 cm by imaging) at nadir will only be considered to have progressed if the liver attains a LVD of > 20 cm by imaging or > 17 cm by physical exam.

2.4.3 Non-Index Lesions

Any other measurable and abnormal nodal lesions not selected for quantitation as index lesions may be considered non-index lesions. In addition, non-measurable evidence of CLL/SLL such as nodal lesions with both diameters < 1.0 cm, extranodal lesions, bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusions, lymphangitis of the skin or lung, abdominal masses that are not confirmed and followed by imaging techniques, cystic lesions, previously irradiated lesions, and lesions with artifacts may be considered as non-index disease.

The presence or absence of non-index disease should be recorded at baseline and at the stipulated intervals during treatment. If present at baseline, up to 6 non-index lesions should be recorded. The non-index disease at baseline will be used as a general reference to further characterize regression or progression of CLL/SLL during assessments of the

objective tumor response during treatment. Measurements are not required and these lesions should be followed as "present" or "absent".

2.5 Definitions of Tumor Response and Progression

Responses will be categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). In addition, a response category of nonevaluable (NE) is provided for situations in which there is inadequate information to otherwise categorize response status.

The best overall response will be determined. The best overall response is the best response recorded from the start of treatment until disease/recurrence progression (taking as a reference for disease progression the smallest measurements recorded since treatment started). Subjects with a best overall response of NE or ND will be counted in the denominators in calculations of tumor response rates. Where imaging data are available, these data will supersede physical examination data in determining tumor status.

2.5.2 Complete Response and Complete Response with Incomplete Blood Count Recovery

To satisfy criteria for CR or CRi, all of the following conditions must be attained:

- **No evidence of new disease**
- **Absolute lymphocyte count (ALC) in peripheral blood of $< 4 \times 10^9$/L**
- **Regression of all index nodal masses to normal size ≤ 1.5 cm in the LD**
- **Normal spleen and liver size**
- **Regression to normal of all nodal non-index disease and disappearance of all detectable non-nodal, non-index disease**
- **Morphologically negative bone marrow defined as < 30% of nucleated cells being lymphoid cells and no lymphoid nodules in a bone marrow sample that is normocellular for age**
- **Peripheral blood meeting all of the following criteria:**
  - **ANC ≥ 1.5×10^9/L without need for exogenous growth factors (e.g., G-CSF)**
  - **Platelet count ≥ 100×10^9/L without need for exogenous growth factors**
  - **Hemoglobin ≥ 110 g/L (11.0 g/dL) without red blood cell transfusions or need for exogenous growth factors (e.g., erythropoietin)**

Note: Subjects who fulfill all the criteria for a CR (including bone marrow criteria) but who have a persistent anemia, thrombocytopenia, or neutropenia or a hypocellular bone marrow that is related to prior or ongoing drug toxicity (and not to CLL/SLL) will be considered as a CR with incomplete marrow recovery (CRi).

2.5.3 Partial Response

To satisfy criteria for a PR, all of the following conditions must be attained:

- **No evidence of new disease**

- **A change in disease status meeting ≥ 2 of the following criteria, with 2 exceptions in which only 1 criterion is needed: (1) Only lymphadenopathy is present at baseline; or (2) only lymphadenopathy and lymphocytosis are present at baseline; in these 2 cases, only lymphadenopathy must improve to the extent specified below:**
  - **Decrease in peripheral blood ALC by ≥ 50% from baseline**
  - **A decrease by ≥ 50% from the baseline in the SPD of the index nodal lesions**
  - **In a subject with enlargement of the spleen at baseline, a splenomegaly response as defined in Section 2.4.2**
  - **In a subject with enlargement of the liver at baseline, a hepatomegaly response as defined in Section 2.4.2**
  - **A decrease by ≥ 50% from baseline in the CLL/SLL marrow infiltrate or in B-lymphoid nodules**
- **No index, splenic, liver, or non-index disease with worsening that meets the criteria for definitive PD**
- **Peripheral blood meeting ≥ 1 of the following criteria:**
  - **ANC ≥ 1.5 x 10^9/L or ≥ 50% increase over baseline without need for exogenous growth factors (e.g., G-CSF)**
  - **Platelet count ≥ 100 x 10^9/L or ≥ 50% increase over baseline without need for exogenous growth factors**
  - **Hemoglobin ≥ 10 g/L (11.0 g/dL) or ≥ 50% increase over baseline without red blood cell transfusions or need for exogenous growth factors (e.g., erythropoietin)**

2.5.3 Stable Disease

To satisfy criteria for SD, the following conditions must be attained:

- **No evidence of new disease**
- **There is neither sufficient evidence of tumor shrinkage to qualify for PR nor sufficient evidence of tumor growth to qualify for definitive PD**

2.5.4 Progressive Disease

The occurrence of any of the following events indicates PD:

- **Evidence of any new disease:**
  - **A new node that measures > 1.5 cm in any diameter**
  - **New splenomegaly as defined in Section 2.4.2**
  - **New hepatomegaly as defined in Section 2.4.2**
  - **New non-index disease (e.g., effusions, ascites, or other organ abnormalities related to CLL/SLL)**

    Note: Isolated new effusions, ascites, or other organ abnormalities are not sufficient evidence alone of PD unless histologically confirmed. Thus, a declaration of PD should not be made if this is the only manifestation of apparently new disease.
- **Evidence of worsening of index lesions, spleen or liver, or non-index disease:**

- **Increase from the nadir by ≥ 50% from the nadir in the SPD of index lesions**
- **Increase from the nadir by ≥ 50% in the LD of an individual node or extranodal mass that now has an LD of > 1.5 cm and an LPD of > 1.0 cm**
- **Splenic progression as defined in Section 2.4.2**
- **Hepatic progression as defined in Section 2.4.2**
- **Unequivocal increase in the size of non-index disease (e.g., effusions, ascites, or other organ abnormalities related to CLL/SLL)**
- **Transformation to a more aggressive histology (e.g., Richter syndrome) as established by lymph node biopsy (with the date of the lymph node biopsy being considered the date of CLL/SLL progression if the subject has no earlier objective documentation of CLL/SLL progression)**

- **Decrease in platelet count or hemoglobin that is attributable to CLL/SLL, is not attributable to an autoimmune phenomenon, and is confirmed by bone marrow biopsy showing an infiltrate of clonal CLL/SLL cells**
  - **The current platelet count is < 100 x 10^9/L and there has been a decrease by > 50% from the highest on-study platelet count**
  - **The current hemoglobin is < 110 g/L (11.0 g/dL) and there has been a decrease by > 20 g/L (2 g/dL) from the highest on-study hemoglobin**

Note: If there is uncertainty regarding whether there is true progression, the subject should continue study treatment and remain under close observation (e.g., evaluated at 4-week intervals) pending confirmation of progression status. In particular, worsening of constitutional symptoms in the absence of objective evidence of worsening CLL/SLL will not be considered definitive disease progression; in such subjects, both CLL/SLL-related and non-CLL/SLL-related causes for the constitutional symptoms should be considered. Worsening of disease during temporary interruption of study treatment (e.g., for intercurrent illness) is not necessarily indicative of resistance to study treatment. In these instances, CT/MRI or other relevant evaluations should be considered in order to document whether definitive disease progression has occurred. If subsequent evaluations suggest that the subject has experienced persistent definitive CLL/SLL progression, then the date of progression should be the timepoint at which progression was first objectively documented.

2.5.5 Nonevaluable

In a subject who does not have evidence of PD, the occurrence of any of the following conditions indicates a response status of NE:

- **There are no images or inadequate or missing images**
- **Images of the liver and spleen are missing at that timepoint (with the exception that absence of splenic images will not result in an NE designation in a subject known to have undergone splenectomy).**

2.5.6 Lymphocytosis during Therapy

Lymphocytosis early in therapy may not represent disease progression in subjects who have persistent control of other CLL/SLL-related signs and symptoms. *In the absence of other objective evidence of disease progression, lymphocytosis alone will not preclude subjects*

from meeting the criteria for PR if other criteria for PR are met and will not be considered evidence of disease progression if occurring in isolation. **Subjects with lymphocytosis should be continued on study drug until the occurrence of definitive disease progression (i.e., disease progression that is manifest by worsening CLL/SLL-related signs other than lymphocytosis alone), or the occurrence of another reason to discontinue study therapy.**

Changes made in Amendment 4 (07 Nov 2016)

Title Page

Change: The protocol version and date have been updated.

Protocol Version and Date:	**Version 5.0, 07 Nov 2016** ~~Version 4.0; 21 Mar 2016~~

Investigator's Agreement

Change: The date has been updated.

I have read the attached Protocol entitled "A Phase 1 Dose Escalation Study of the Safety and Pharmacokinetics of LAM-002A (apilimod dimesylate capsules) Administered Orally in Subjects with Relapsed or Refractory B-cell Non-Hodgkin's Lymphoma" dated **07 Nov 2016**~~21 Mar 2016~~.

Synopsis

Changes: All changes to the synopsis also occur in the body of the protocol. Thus, changes to the synopsis are not described; instead, changes to the body of the protocol are described.

Abbreviations

Change: An abbreviation has been added.

TID	**Thrice per day**

Section 4.1 Product Summary

Change: The description of the drug product has been updated with information relating to the newly introduced 50-mg capsule.

LAM-002A (apilimod dimesylate capsule) is intended for oral administration. Each capsule will contain 25 mg or 50 of apilimod dimesylate (equivalent to 17.1 mg or 34.3 mg of apilimod free base, respectively). The 25-mg capsule is Swedish orange and the 50-mg capsule is white. Both the 25- and 50-mg capsules are Size 0 and both have a total fill weight of 175 mg.

Inactive components in active capsules are microcrystalline cellulose Avicell PH102, silicified microcrystalline cellulose, anhydrous lactose, croscarmellose sodium (Ac-Di-Sol), colloidal silicon dioxide, and magnesium stearate.

~~LAM-002A (apilimod dimesylate capsule) is intended for oral administration. LAM-002A is formulated as a blend with excipients in Size 0 Swedish Orange gelatin capsules. Each capsule will contain 25 mg of apilimod dimesylate (equivalent to 17.1 mg of apilimod free base) and the~~

~~total fill weight of each capsule will be 175 mg. The claimed dosage strength of the active ingredient will be expressed in the free base form of apilimod. Manufacture of a 50 mg capsule is planned as part of the ongoing development program.~~

~~Inactive components in active capsules are anticipated to be microcrystalline cellulose Avicell PH102, silicified microcrystalline cellulose, anhydrous lactose, croscarmellose sodium (Ac-Di-Sol), colloidal silicon dioxide and magnesium stearate.~~

Section 4.1.4.2 Efficacy

Change: The description of drug efficacy has been updated.

Efficacy data in patients with hematological malignancies are pending. One patient, a 60-year-old male with GCB-DLBCL who was had experienced minimal or no response to multiple prior chemoimmunotherapy regimens (including R-CHOP), received apilimod dimesylate at 100 mg/dose BID for 6 weeks before enlarging right axillary lymphadenopathy required cessation of study drug and intervention with local radiation therapy. A follow-up PET-CT, obtained approximately 2 weeks later, showed a substantial systemic decrease in DLBCL lesions in non-irradiated lymph nodes, liver, spleen, and bone (C4 vertebra); these improvements in disease burden were attributed by the investigator to the study drug. ~~There is no efficacy data in patients with NHL or other malignancies.~~

Section 4.1.4.3 Safety

Change: The description of drug safety has been updated.

Apilimod dimesylate has been **generally** well tolerated in humans. In patient populations with Crohn's disease or psoriasis, more frequent (> 10%) AEs experienced to date included headache, upper respiratory tract infection, and nausea; less frequent (> 5% to 10%) AEs included dizziness, fatigue, and nasopharyngitis; and rare (2% to 5%) AEs included diarrhea, arthralgia, fever, abdominal pain, peripheral edema, and vomiting. In general, most AEs were assessed as mild in severity**. In the ongoing trial of apilimod dimesylate in patients with hematological cancers, dose-dependent gastrointestinal events of nausea, vomiting, and diarrhea have been observed.**

No renal insufficiency has been observed in completed clinical trials to date and no clinically significant safety signals in laboratory, physical examination, or vital sign findings have been noted. **One patient with a hematological malignancy receiving the drug at 150 mg BID developed asymptomatic Grade 3 hyponatremia that was attributed to the combined effects of a apilimod-dimesylate-induced diarrhea and hydrochlorothiazide administration.**

Cardiac monitoring in clinical studies to date has not revealed any major issues. However in a thorough QT/QTc study, apilimod dimesylate at doses of 50 mg and 150 mg was associated with repolarization findings in excess of those deemed negative by International Conference on Harmonisation (ICH) E14 guidance. The magnitude of the change was modest (~8.5 msec) and the root-mean-square based analyses did not demonstrate as large an increase in cardiac repolarization time (≤ 1.22 msec) as that identified using the Fridericia method. Therefore the significance of this finding is unclear. **Preliminary QTc observations in the ongoing study in patients with hematological malignancies suggest the potential for dose- and exposure-dependent Grade 1 or 2 QT prolongation.**

~~In totality, the nonclinical and clinical data collected to date support the exploration of apilimod dimesylate in patients with NHL.~~

Section 4.1.6. Previous Clinical Experience with Apilimod and Apilimod Dimesylate in Nonmalignant Conditions

Change: The title of the section has been clarified, as noted above.

SECTION 6 INVESTIGATIONAL PLAN

Changes: Information in Subsections 6.1, 6.2, and 6.5 regarding the dose-escalation and sample sizes has been updated to reflection inclusion of additional dose levels and schedules.

Subsection 6.4.3,1 has been clarified to indicate that all subjects will be followed for survival and to provide additional information regarding out how that follow-up will be performed.

6.1 Overall Study Design

This is a Phase 1, single-arm, open-label, dose-escalation study of safety and PK of apilimod administered to subjects with refractory or relapsed B-cell NHL. This study consists of 2 stages:

6.1.1 Dose Escalation Stage

The maximum tolerated dose (MTD) will be determined during the Dose Escalation Stage. Subjects will accrue using a 3 + 3 design. During this stage, the decision to open a new cohort at a higher **or lower** dose level will be made by the participating clinical investigators and sponsor when all subjects in the current cohort have been treated through at least Week 4 or once 2 DLTs have occurred in that dose cohort. All available safety and PK data will be considered in a decision **by the medical monitor in collaboration with the investigators** to dose escalate, de-escalate, ~~or~~ expand the current cohort **or explore an alternate schedule of drug administration**. The MTD will be determined based primarily on DLTs observed through Week 4 in at least 6 subjects.

6.1.2 Expansion Stage

Once the MTD and/or Recommended Phase 2 Dose (RP2D) **and schedule** is determined, the study will enter the Expansion Stage, in which 3 cohorts of 15 subjects each will be accrued in order to obtain additional information on safety, tolerability, preliminary anti-tumor activity, PK, and pharmacodynamic data at the RP2D and schedule. The eligibility criteria will remain the same as in escalation but each cohort will be specific to subjects with DLBCL, FL, and CLL/SLL, respectively. The treatment regimen in each of the expansion cohorts will be single agent LAM-002A (apilimod dimesylate capsules) according to the RP2D and schedule.

6.2 Number of Subjects

Approximately **115** ~~75~~ evaluable subjects (evaluable subjects include those who complete Cycle 1 dosing [administered at least 75% of doses] and have sufficient safety data, or who are withdrawn from the study due to a DLT in Cycle 1) will be enrolled, assuming that:

- In the Dose Escalation Stage of the study, the total number of subjects will depend upon the numbers of subjects accrued to each dose level and the number of dose

levels evaluated. If 6 subjects are enrolled at all 9 possible starting dose levels and 6 additional subjects are enrolled at the MTD or RD, as many as 60 subjects could be enrolled. To allow for the possibility that some subjects may not be fully evaluable for DLT or that an intermediate dose level might be evaluated, up to ~70 subjects may be enrolled~~5 dose levels will be studied and a maximum of 6 subjects will be enrolled per dose level, for an estimated total of 18 to 30 evaluable subjects~~.

- In the Expansion Stage of the study, if all 3 potential expansion cohorts of 15 evaluable subjects are accrued, as many as 45 subjects could be enrolled. To allow for the possibility that some subjects may not be fully evaluable for efficacy, up to ~55 subjects may be enrolled. ~~Up to an additional 45 evaluable subjects (3 cohorts of 15 subjects) will be enrolled in the Expansion Stage of the study.~~ Subjects will be treated at the RP2D and schedule determined in the Dose Escalation Stage of the study.

6.4.3.1 Post-Treatment Period

Subjects should be followed until the later of either 30 days after the last dose of study treatment or until resolution/stabilization of any ongoing drug-related AEs and/or SAEs. For subjects with events that require follow-up, information regarding concomitant medications should be collected. Any necessary follow-up may be obtained in person or by telephone contact.

Subjects who have discontinued study treatment for reasons other than PD will be assessed per Revised Response Criteria for NHL or Guidelines for the diagnosis and treatment of CLL at a minimum of every 12 weeks until documentation of PD, start of new anti-cancer therapy or for up to 1 year from the last enrolled subject's first treatment (Cycle 1 Day 1) whichever comes first. **Long-term follow-up survival information will be obtained in all surviving subjects who permanently discontinue study therapy. Such information may be collected at ~3- to 6-month intervals at the sponsor's discretion through 3 years. This long-term follow-up information will be gathered during routine clinic visits, other study site contact with the subjects, or via telephone or e-mail with the subjects/caregivers or referring physician offices.**~~Survival of all subjects will be followed by the investigator via telephone contact every 3 months.~~

6.5 Dose Escalation Procedures

Apilimod dimesylate will be administered on a twice daily (BID) **or thrice daily (TID)** oral dosing regimen with a cycle length of 28 days. Subjects **on a BID schedule** will be advised to take the doses at the same time each day, ~~approximately~~ ~12 hours apart. **Subjects on a TID schedule will be advised to take the doses at the same time each day at intervals of ~6 to 8 hours. On PK days, subjects on a TID schedule should receive the morning dose and complete the blood collections through 8 hours thereafter before taking the second dose on that day.**

Other drug administration ~~Less dose intensive~~ schedules may be considered if the initial BID **or TID** regimen's safety, PK and/or pharmacodynamics suggest that a different schedule would be better tolerated and might allow for serum exposures required for anti-lymphoma activity. This might include a treatment break such as 3 weeks on/1 week off treatment or 5 days on/2 days off over a 4-week cycle or an asymmetric (AM dosing > PM dosing) or once-daily dosing schedule. If ~~a less dose intensive~~**another** treatment regimen is evaluated, then the initial dose

tested on this schedule will be **no higher than the total** ~~a~~ daily dose that has been previously evaluated and tolerated ~~on the more dose-intensive, BID schedule~~.

Cohorts of 3 to 6 subjects will be sequentially enrolled at progressively higher starting dose levels of apilimod dimesylate, as indicated in Table 2. The initial cohort of subjects will be prescribed apilimod dimesylate at Dose Level 0 (50 mg BID). Dose level -1 (25 mg BID) is provided to permit a dose decrement in subjects experiencing DLT at Dose Level 0.

Table 2: LAM-002A Provisional Starting Dose Levels

Dose Level	Apilimod Dimesylate Dose mg/dose	Apilimod Dimesylate Dose mg/day
-1	25 mg BID	50
0 (Initial Dose Level)	50 mg BID	100
1	100 mg BID	200
1a	125 mg BID	250
1b	75 mg TID	225
1c	100 mg TID	300
1d	125 mg TID	375
2	150 mg BID	300
3	200 mg BID	400
4	275 mg BID	550

Abbreviations: BID: Twice daily (or 2 times per day); TID: Thrice daily (or 3 times per day)

	~~Daily LAM-002A Dose~~	~~Percent Increase~~	~~Initial Cohort Size~~
~~-1~~	~~25 mg BID~~	~~-50~~	~~3~~
~~0~~	~~50 mg BID~~	~~Starting dose~~	~~3~~
~~1~~	~~100 mg BID~~	~~100~~	~~3~~
~~2~~	~~150 mg BID~~	~~50~~	~~3~~
~~3~~	~~200 mg BID~~	~~33~~	~~3~~
~~4~~	~~275 mg BID~~	~~37.5~~	~~3~~

~~Abbreviations: BID: Twice daily (or 2 times a day)~~

A 3 + 3 design will be utilized to define an MTD. For cohorts consisting of 3 subjects, dose escalation to the next higher dose may proceed if no DLT is observed within the first cycle of the 3 evaluable subjects accrued to a cohort (See Section 6.1.1). If 1 of 3 subjects in the cohort experiences a DLT, up to a total of 6 evaluable subjects will be enrolled. If 2 or more of the 3-6 evaluable subjects in a cohort experience a DLT, dose escalation will cease, and additional subjects will be treated at a lower dose level **or with another schedule**. If de-escalation to the previous dose cohort is undertaken, this cohort will be expanded to ≥6 subjects. **Additional subjects (up to 12 total per cohort) may be evaluated to refine the estimation of the MTD and RP2D at the planned dose levels or at an intermediate dose level between the highest previously tolerated total dose and the next planned total daily dose.** The MTD is defined as the highest dose at which ~~no more than 1 of 6 subjects (i.e.,~~ < 33% **of subjects)** experience~~s~~ a DLT in the **total** dose cohort.

Dose escalation decisions will be evaluated in a DLT evaluable population. The DLT evaluable population will include subjects who complete Cycle 1 dosing or who are withdrawn from study

due to a DLT in Cycle 1. A subject will be deemed non-evaluable for determining DLTs and will not be counted toward the total cohort size if the subject did not experience a DLT, did not receive at least 75% (42/56 **BID schedule; 63/84 TID schedule**) of the planned first-cycle doses or discontinued from the study prior to completing necessary safety evaluations through the first 28 days of study treatment. These subjects may be replaced unless accrual to the cohort has stopped due to DLT.

Following the above guidelines, the participating investigators and sponsor will review available data including toxicity, PK and anti-tumor activity data to reach consensus on dose levels and determination of the MTD. This group will review available safety data for each cohort and will determine whether the MTD has been reached and decide upon further subject enrollment. Any detected cumulative toxicity may require later dose reductions or other action as appropriate, and may ~~also have an effect on~~**be evaluated in determining** the RP2D and schedule.

The RP2D and schedule will be determined in discussion between the sponsor and participating investigators. Observations related to PK, pharmacodynamics and any drug-related toxicities may be included in the rationale supporting the RP2D and schedule.

Once the RP2D and schedule are established, additional subjects will be treated in 3 histologically distinct dose expansion cohorts designed to better characterize the safety, tolerability, preliminary anti-tumor activity, PK, and pharmacodynamics of the study drug when provided at the MTD (or lower dose per agreement of the investigators and sponsor) in a specific B-cell NHL subtype. Up to 15 subjects will be treated in each expansion cohort.

Section 6.6.2 Description of Study Drug

Change: The description of the drug product has been updated with information relating to the newly introduced 50-mg capsule.

LAM-002A (apilimod dimesylate capsule) is intended for oral administration. Each capsule will contain 25 mg or 50 of apilimod dimesylate (equivalent to 17.1 mg or 34.3 mg of apilimod free base, respectively). The 25-mg capsule is Swedish orange and the 50-mg capsule is white. Both the 25- and 50-mg capsules are Size 0 and both have a total fill weight of 175 mg. ~~LAM-002A (apilimod dimesylate capsule) is intended for oral administration. Each capsule will contain 25 mg of apilimod dimesylate (equivalent to 17.1 mg apilimod free base) and the total fill weight of each capsule will be 175 mg. LAM-002A is formulated as a blend with excipients in Size 0 Swedish Orange gelatin capsules.~~ For additional information, see Section 9.1.

Section 6.6.4 LAM-002A (Apilimod Dimesylate Capsules) Self-Administration

Change: Information has been updated to reflection inclusion of additional dose levels and schedules.

Except for the days where treatment is administered in the clinic, LAM-002A (apilimod dimesylate capsules) will be self-administered orally, BID **or TID** of each 28-day cycle until disease progression or other discontinuation criteria are met. **When taking the drug at home, s**~~S~~ubjects should be advised to take study drug with ≥ 4 oz. (~160 mL) of water at the same time**s** each day~~.~~**. Subjects on a BID schedule will be advised to take the doses at approximately** 12 hours apart (e.g., 8 AM and 8 PM) (+/- 1 hour window**). Subjects on a TID schedule will be advised to take the doses at intervals of ~6 to 8 hours.** When self-administering the study drug

at home, subjects may take the drug in the fed or fasted state. On PK days, subjects should come to clinic fasted (a minimum fasting state of 6 to 8 hours) and take the dose at the site under supervision. All subjects will be required to complete a Dosing Diary, which must be returned to the site for review at each site visit.

Section 6.6.5 Dose Schedule Interruptions and Vomited Doses

Change: Information has been updated to reflection inclusion of additional dose levels and schedules.

Subjects **on a BID schedule** who have a delay in administration of a dose of apilimod dimesylate of <6 hours should take the planned dose as soon as possible after the intended time of administration. For subjects who have a delay in administration of apilimod dimesylate of ≥6 hours, the dose should not be taken. The planned timing of subsequent apilimod dimesylate dosing should not be altered.

Subjects on a TID schedule who inadvertently have a delay in administration of a dose of the study drug of ≤1 hour, the planned dose should be taken with no changes to the subsequent dose schedule. For subjects who have a delay of >1 hour but ≤4 hours, the planned dose should be taken; however, all future doses for that day should be shifted later by a corresponding amount. It is recommended that subjects take the last dose of study medication no later than 12:00 midnight on any study treatment day. For example, if the 07:00 AM dose is taken at 10:00 AM, the next dose should be taken ≥6 hours later (after 5:00 PM), and the last dose should be taken ≥6 hours thereafter (between 11:00PM and 12:00 midnight). For subjects on a TID schedule who have a delay in administration of study drug of >4 hours, the dose should not be taken. Study drug administration may continue but the missed dose should not be made up and the planned timing of subsequent study drug dosing should not be altered.

For subjects who vomit shortly after taking apilimod dimesylate, the vomited dose should not be replaced. The planned timing of subsequent apilimod dimesylate dosing should not be altered.

Section 6.6.6 Dose Modifications

Change: Information has been updated to reflection inclusion of additional dose levels and schedules.

If a subject experiences an AE that is suspected to be related to apilimod dimesylate, appropriate supportive care (e.g., antiemetics, antidiarrheals, therapy for tumor lysis syndrome [TLS]) should be instituted consistent with the nature of the event.

If a subject experiences an apilimod dimesylate-related DLT (reference ~~Section Deleted~~) **or other AE requiring a dose modification**, then the study drug administration should be interrupted until the toxicity recovers to Grade ≤ 1 or baseline. Upon resumption of study drug, the **total daily** dose of apilimod dimesylate should be reduced **using an appropriate** ~~by 1~~ dose level **or schedule** (reference ~~Section Deleted~~) **as agreed between the investigator and medical monitor**. Successive adjustments to progressively lower **total daily** dose levels can be made. If the subject cannot tolerate apilimod dimesylate after a decrease to Dose Level -1 (25 mg BID), then the subject should be discontinued from apilimod dimesylate therapy unless continued treatment is permitted by the medical monitor.

After the apilimod dimesylate dose is reduced, the dose can be maintained at that dose level **or schedule**, even if there is minimal or no toxicity with the reduced dos**ing regimen**. However, if the subject tolerates a reduced **total daily** dose of apilimod dimesylate for ≥ 4 weeks then the apilimod dimesylate dosing regimen may be reescalated to ~~the next~~**a** higher **total daily** dose level at the discretion of the investigator **and with the concurrence of the medical monitor**. Such reescalation may be particularly warranted if the AE comprised TLS or if further evaluation reveals that the AE that led to the dose reduction was not related to apilimod dimesylate. Successive adjustments to progressively higher **total daily** dose levels can be made. However, the escalated dose cannot exceed the **total daily** starting dose level for that subject during the first 4 cycles of therapy.

Individual subjects who initiated treatment at a **total daily** dose level below the lower of the currently established MTD or the RP2D and who have not experienced a DLT after ≥ 4 cycles of treatment may have the apilimod dimesylate **total daily** dose escalated to the next higher dose level if both the principal investigator and the medical monitor agree that a dose escalation is medically warranted (e.g., for a subject with stable disease who is tolerating the current dose level of apilimod dimesylate therapy). In such subjects, successive adjustments to progressively higher **total daily** dose levels can be made at intervals of ≥ 4 weeks with the condition that the escalated **total daily** dose level cannot exceed the lower of the currently established MTD or RP2D.

In a subject who experiences a DLT precluding resumption of apilimod dimesylate therapy during a cycle, a new cycle of treatment may begin at the later of Day 29 or when AEs or laboratory abnormalities related to apilimod dimesylate have returned to baseline levels. If drug-related AEs or laboratory abnormalities precluding further administration of study drug are not resolved to baseline by Day 29, week-by-week delays in initiating the new cycle of treatment should be instituted. When all drug-related AEs and laboratory abnormalities have returned to baseline, the next cycle of therapy can be initiated. Upon initiation of a new cycle of therapy, the prior cycle of therapy will be considered completed.

Investigators are to discuss modifications in the dosing regimen with the medical monitor. The appropriate clinic staff should dispense the study drug for the new dose level **or schedule** and instruct the subject/caregiver about the change in ~~dose level~~**the dosing regimen**.

Section 6.6.7 Definition of Dose-Limiting Toxicity (DLT)

Change: Information has been updated to reflection inclusion of additional schedules.

Table 3: Criteria for Defining Dose-Limiting Toxicities (DLTs)

Toxicity	**Criteria**
Treatment interruption/delays	Inability to administer ≥28/56 **(BID schedule) or ≥42/84 (TID schedule)** planned apilimod dimesylate doses in a treatment cycle due to drug-related AEs or Failure to recover from apilimod-dimesylate-related toxicities to baseline within 14 days from the last dose of study drug in a cycle

Section 6.6.9 Duration of Subject Participation

Change: The section has been clarified to indicate that all subjects will be followed for survival and to provide additional information regarding out how that follow-up will be performed.

All subjects will be treated for at least 1 cycle unless there is evidence of unacceptable toxicity or PD. Although subjects may continue to receive study treatment until experiencing unacceptable toxicity or disease progression, it is estimated that each subject will participate for an average of 6 months of treatment and an additional 1 month of follow-up. Subjects who have discontinued study treatment for reasons other than PD will be assessed per Revised Response Criteria for NHL or Guidelines for the diagnosis and treatment of CLL at a minimum of every 12 weeks until documentation of PD, start of new anti-cancer therapy or for up to 1 year from the last enrolled subject's first treatment (Cycle 1 Day 1), whichever comes first. **Long-term follow-up survival information will be obtained in all surviving subjects who permanently discontinue study therapy. Such information may be collected at ~3- to 6-month intervals at the sponsor's discretion through 3 years. This long-term follow-up information will be gathered during routine clinic visits, other study site contact with the subjects, or via telephone or e-mail with the subjects/caregivers or referring physician offices.**

Section 6.9 Schedule of Assessments

Changes: In Table 4 (Schedule of Assessments), it has been clarified that the pretherapy collection of blood for coagulation parameters is only required during Screening. This clarification removes an inconsistency with protocol text.

An extra column and extra row have been added consistent with existing instructions in protocol indicating that long-term follow-up is requested. In an addition, an explanatory footnote (Footnote w) has now been included to indicate how that follow-up will be performed.

In Footnote q, information has been included to note that a bone marrow aspirate may be substituted for archival or fresh biopsy tissues in subjects with bone marrow involvement due to NHL.

Assessment	Screening	Cycle 1 Day			Cycle 2 Day			Cycle ≥3 Day		End of Treatment (EOT)	Long-Term F/U
	-28 to -1	1	8	15	1	8	15-28	1	15-28		
Coagulation	X	~~X~~[e]									
Long-term follow-up (F/U)[w]											**X**

q Archival or fresh tumor tissue from the most recent available biopsy or surgery prior to first dose in subjects with NHL must be obtained pretreatment. For subjects undergoing a biopsy, adequate tumor tissue should be acquired via excisional biopsy, incisional biopsy or core needle biopsy (e.g., ≥ 3 passes using a 16-gauge core needle). **Alternatively, cells from a bone marrow aspirate may be obtained in subjects with bone marrow involvement due to NHL.** Tissue will be submitted for evaluation of the percentage of tumor cells and analysis of genetic alterations and/or gene expression that may predict anti-lymphoma activity and/or pharmacodynamics activity. In addition, for subjects with NHL, tumor may be evaluated for known prognostic characteristics (e.g., for DLBCL: ABC or GCB subtype; expression of BCL2, BCL6, Ki-67, CD20, and MYC; other mutational status). The baseline biopsy procedure (if required) should be performed after the study candidate has undergone the baseline radiology examination and is otherwise considered eligible for study participation.

W Subjects who have discontinued study treatment for reasons other than PD will be assessed per Revised Response Criteria for NHL or Guidelines for the diagnosis and treatment of CLL at a minimum of every 12

weeks until documentation of PD, start of new anti-cancer therapy or for up to 1 year from the last enrolled subject's first treatment (Cycle 1 Day 1) whichever comes first. Long-term follow-up survival information will be obtained in all surviving subjects who permanently discontinue study therapy. Such information may be collected at ~3- to 6-month intervals at the sponsor's discretion through 3 years. This long-term follow-up information will be gathered during routine clinic visits, other study site contact with the subjects, or via telephone or e-mail with the subjects/caregivers or referring physician offices.

Section 8.1.5. Disease Status Assessment for Subjects with NHL

Change: Information has been included to note that a bone marrow aspirate may be substituted for archival or fresh biopsy tissues in subjects with bone marrow involvement due to NHL.

Archival tissue from the most recent available biopsy or surgery or fresh tumor tissue must be obtained pretreatment. For subjects undergoing a biopsy, adequate tumor tissue should be acquired via excisional biopsy, incisional biopsy or core needle biopsy (e.g., ≥ 3 passes using a 16-gauge core needle). **Alternatively, cells from a bone marrow aspirate may be obtained in subjects with bone marrow involvement due to NHL.** Tissue will be submitted for evaluation of the percentage of tumor cells and analysis of genetic alterations and/or gene expression that may predict anti-lymphoma activity and/or pharmacodynamics activity. In addition, tumor may be evaluated for known prognostic characteristics (e.g., for DLBCL: ABC or GCB subtype; expression of BCL2, BCL6, Ki-67, CD20, and MYC; other mutational status). The baseline biopsy procedure (if required) should ideally be performed after the study candidate has undergone the baseline radiology examination and is otherwise considered eligible for study participation.

Section 8.6.2 Medications for AE Management – Gastrointestinal AEs

Change: Recommendations regarding management of gastrointestinal AEs have been updated to reflect the evolving safety profile of the study drug.

While prophylactic antiemetics can be considered, it is preferred that antiemetics not be given prophylactically before initial study drug administration on Cycle 1, Day 1.

It is recommended that, if prophylactic or therapeutic antiemetics are required, subjects be offered 2 mg of the serotonin antagonist, granisetron (Kytril®, Granisol®), as an oral tablet or solution every 6 hours as needed. If subjects have persistent nausea or vomiting, consideration can be given to application of a 31.3 mg granisetron transdermal patch (Sancuso®) every 3 to 7 days. For transdermal prophylaxis, 24 to 48 hours may be necessary to allow a sufficient period to achieve effective granisetron systemic concentrations. Use of the serotonin antagonists, ondansetron (Zofran®, Zuplenz®) or dolasetron (Anzemet®), is discouraged due to the possibility that such agents could prolong the cardiac QT interval.

Based on currently available information regarding LAM-002A metabolism, the neurokinin 1 receptor antagonist, rolapitant (Varubi®), can be considered, but aprepitant (Emend®) or netupitant+palonosetron (Akynzeo®) should be avoided because these drugs may inhibit CYP3A4 and/or CYP2C9 activity.

Other classes of antiemetic medications that may be employed include dopamine antagonists or benzodiazepines if such drugs do not pose risks of QT prolongation or drug-drug interactions. Given the possibility that LAM-002A may alter immunological

mechanisms, use of systemic corticosteroids (e.g., dexamethasone) should be minimized to avoid immunocompromise; however, corticosteroids can be introduced if other types of antiemetic agents are not sufficiently effective.

~~Management of nausea and/or vomiting: Prophylactic anti-emetic therapy will not be used in this study. However, it may be implemented if it is demonstrated that LAM-002A (apilimod dimesylate capsules) clearly causes acute nausea and vomiting. If prophylactic anti-emetic therapy is needed, 5-HT$_3$ receptor antagonists and benzodiazepines should be tried first. Additionally, anti-emetic therapy may be used as needed in the individual management of subjects who develop nausea and/or vomiting.~~

For m~~M~~anagement of diarrhea**, it is recommended that s**~~: S~~ubjects ~~should be instructed to~~ take loperamide, 4 mg, at the occurrence of the first loose stool and then 2 mg every 2 hours until they are diarrhea-free for at least 12 hours. **More aggressive loperamide administration or titration of loperamide dosing for each loose bowel movement may be considered.** During the night, subjects may take 4 mg of loperamide every 4 hours. Subjects should be advised to avoid dehydration through adequate fluid intake**. Drugs such as 5HT3 antagonists or octreotide may be considered for their anti-secretory effects:**

~~As with any AE, s~~**Sites should consider providing study participants with antiemetics and antidiarrheals so that these supportive care medications are readily available in case gastrointestinal symptoms develop. S**ubjects who develop nausea, vomiting or diarrhea should be monitored closely until the event is resolved/stabilized.

Section 8.8 Treatment Compliance

Change: Information has been updated to reflection inclusion of additional schedules.

The investigator will dispense the study medication only for use by subjects enrolled in the study as described in this protocol. The study medication is not to be used for reasons other than those described in this protocol.

The investigator or other study staff will supervise study drug treatment given at the site and instruct the subject on study medication self-administration. Subjects will be asked to bring their dosing diary with them at each visit. Compliance with protocol-defined study drug intake will be checked by pill count at the end of each cycle and compliance decisions will be made by the investigator.

A subject is considered to be DLT-evaluable if he/she has taken at least 75% (42/56 **BID schedule; 63/84 TID schedule**) of the planned first-cycle doses and has sufficient safety data, or has experienced a DLT in the first cycle.

Section 9.1 Study Drug

Change: The description of the drug product has been updated with information relating to the newly introduced 50-mg capsule.

LAM-002A drug description is provided in Table 5.

Table5: LAM-002A Drug Description

Product Name:	LAM-002A

Product Name:	LAM-002A
Dosage Form:	Capsule
Unit Dose	25 mg **or** ~~(~~50 mg ~~pending future development)~~
Route of Administration	Oral
Physical Description	**Each capsule will contain 25 mg or 50 of apilimod dimesylate (equivalent to 17.1 mg or 34.3 mg of apilimod free base, respectively). The 25-mg capsule is Swedish orange and the 50-mg capsule is white. Both the 25- and 50-mg capsules are Size 0 and both have a total fill weight of 175 mg.** **Inactive components in active capsules are microcrystalline cellulose Avicell PH102, silicified microcrystalline cellulose, anhydrous lactose, croscarmellose sodium (Ac-Di-Sol), colloidal silicon dioxide, and magnesium stearate.** ~~Each capsule will contain 25 mg of apilimod dimesylate (equivalent to 17.1 mg of apilimod free base) and the total fill weight of each capsule will be 175 mg. The claimed dosage strength of the active ingredient will be expressed in the free base form of apilimod. Manufacture of a 50 mg capsule is planned as part of the ongoing development program.~~ ~~Inactive components in active capsules are microcrystalline cellulose Avicell PH102, silicified microcrystalline cellulose, anhydrous lactose, croscarmellose sodium (Ac-Di-Sol), colloidal silicon dioxide, and magnesium stearate.~~
Manufacturer	Patheon

Abbreviation: mg: Milligram

Section 14.1 Determination of Sample Size

Change: Information regarding the sample sizes has been updated to reflect inclusion of additional dose levels and schedules.

This Phase 1 trial is being conducted primarily to assess the safety and tolerability of LAM-002A (apilimod dimesylate capsules) when administered in subjects with relapsed or refractory B-cell NHL and to determine the MTD and RP2D of LAM-002A. No formal sample-size estimation was performed. The choice of the number of subjects was based on the standard 3 + 3 design that is commonly used in Phase 1 trials of anti-cancer investigational drugs. For the Dose Escalation Stage of the study, the maximum sample size will be **approximately 60**~~30~~ subjects if 6 subjects are assigned ~~at~~ **to each of the 9 potential** dose levels ~~0 to 4~~ **and an additional 6 patients are accrued at the RP2D**. However, additional subjects may be added if exploration of intermediate dose level(s) of LAM-002A is warranted.

Up to 45 additional **evaluable** subjects (3 cohorts of 15 subjects) may be enrolled at the RP2D and schedule in the Expansion Stage of the study. The safety population will consist of all subjects receiving at least 1 dose of LAM-002A. The assessment of DLT and MTD will involve only those subjects completing the first cycle of therapy, unless the subject discontinuation in first cycle was due to a DLT.

Section 14.3 Analysis Sets

Change: The definitions of the analysis sets have been clarified and simplified.

14.3.1 Full Analysis Sets

The full analysis set includes all subjects who receive ≥1 dose of study drug. This analysis set will be used in the analyses of subject characteristics, study drug administration and compliance, safety, and categorical and time-to-event efficacy outcomes. In analyses of response rates in the full analysis set, subjects who do not have sufficient baseline and on-study tumor assessments to characterize response (i.e., have a best overall response of NE) will be counted as failures.

14.3.2 Responding Analysis Set

The responding analysis set includes subjects in the full analysis set who have measurable disease, who can be evaluated for tumor response with both baseline and on-study tumor evaluations, and who achieve a CR, CRi, or PR. This analysis set will be used in the analyses of time to response and duration of response.

14.3.3 Evaluable Sets

The evaluable analysis sets include subjects in the full analysis set who have the necessary baseline and on-study measurements to provide interpretable results for specific parameters of interest. These analysis sets will be used in the analyses of changes in tumor dimensions, PK parameters, and pharmacodynamic parameters.

~~**14.3.1 Pharmacokinetic Evaluable Population**~~

~~The primary analysis of PK will use the PK Evaluable Population, which consists of enrolled subjects who have all of their PK samples collected in Cycle 1, who did not have any major protocol deviations and who are evaluable for C_{max} or AUC_{0-t} analysis.~~

~~**14.3.2 Pharmacodynamic Evaluable Population**~~

~~The population of subjects evaluable for pharmacodynamics will include all subjects who have tissue or PBMCs available for analysis at baseline and during treatment, and for which an assessment of changes (e.g., gene expression, vacuolation, PIKfyve inhibition) is technically feasible.~~

~~**14.3.3 Safety Population**~~

~~For safety analyses, the Safety Population will be used. This population consists of subjects who have taken at least one dose of LAM-002A.~~

~~**14.3.4 DLT Evaluable Population**~~

~~Dose escalation decisions will be evaluated in DLT evaluable population. The DLT evaluable population will include subjects who complete Cycle 1 dosing (administered at least 75% of doses) and have sufficient safety data, or who are withdrawn from study due to a DLT in Cycle 1.~~

~~**14.3.5 Full Analysis Data Set**~~

~~The Full Analysis Set (FAS) will serve as the primary population for the analysis of tumor response and other efficacy-related data. Subjects will be excluded from the FAS for the following reasons:~~

- No baseline data
- Failure to receive at least one dose of LAM-002A
- No post-baseline endpoint data subsequent to at least 1 dose of study drug.

Changes made in Amendment 5 (14 Apr 2017)

Title Page

Change: The protocol version and date have been updated.

Protocol Version and Date: **Version 6.0, 14 Apr 2017** ~~Version 5.0; 07 Nov 2016~~

Investigator's Agreement

Change: The date has been updated.

I have read the attached Protocol entitled "A Phase 1 Dose Escalation Study of the Safety and Pharmacokinetics of LAM-002A (apilimod dimesylate capsules) Administered Orally in Subjects with Relapsed or Refractory B-cell Non-Hodgkin's Lymphoma" dated **14 Apr 2017** ~~07 Nov 2016~~.

Section 6.6.1 Tumor Lysis Syndrome (TLS) Prophylaxis

Change: Medical prophylaxis has been mandated for subjects at intermediate to high risk of TLS and a recommendation has been included that subjects at high risk of TLS be monitored as inpatients during the first 24 to 48 hours of LAM-002A administration.

The risk for TLS ~~should~~ **must** be considered based on established algorithms (*Cairo 2010, MDACC 2013, Roberts 2016*):

- Low-risk: Serum LDH ≤ ULN, all measurable lymph nodes < 5 cm, and absolute lymphocyte count (ALC) < 25×10^9/L
- Intermediate risk: Serum LDH > 1 to ≤ 2 × ULN, ≥ 1 measurable lymph node with an LD of ≥ 5 but < 10 cm, or ALC ≥ 25×10^9/L
- High risk: Serum LDH > 2 × ULN, ≥ 1 measurable lymph node with a LD of ≥ 10 cm, or both ≥ 1 measurable lymph node with an LD of ≥ 5 but < 10 cm and ALC ≥ 25×10^9/L

Subjects who are at intermediate or high risk of TLS must receive medical prophylaxis according to the following prophylaxis regimens or similar institutional regimens:

~~If, during the dose escalation it is observed that the study drug appears to induce TLS, subsequent subjects who are at risk should be considered for medical prophylaxis of TLS and according to local prevention paradigms. Alternatively, investigators may wish to consider the following regimens for prophylaxis in subjects at intermediate or high risk of TLS:~~

- Intermediate Risk of TLS: These subjects **should**~~can~~ receive allopurinol, 100 to 300 mg orally every 8 hours starting ≥ 24 to 48 hours before the initial administration of ~~apilimod dimesylate~~**LAM-002A** on Cycle 1-Day 1 of therapy; **of note, the maximum daily allopurinol dose is 800 mg, doses ≤ 300 mg need not be divided**

(but may be insufficient for high-risk subjects), and doses should be reduced by ≥ 50% in subjects with renal insufficiency. In addition, subjects who develop hyperuricemia should receive rasburicase, 0.2 mg/kg.

- High Risk of TLS: These subjects ~~can~~ **should** receive allopurinol, 100 to 300 mg orally every 8 hours starting ≥ 24 to 48 hours before the initial administration of ~~apilimod dimesylate~~**LAM-002A** on Cycle 1-Day 1 of therapy; **of note, the maximum daily allopurinol dose is 800 mg, doses ≤ 300 mg need not be divided (but may be insufficient for high-risk subjects), and doses should be reduced by ≥ 50% in subjects with renal insufficiency.** In addition, high-risk subjects ~~can~~ **should** receive rasburicase, 0.2 mg/kg, administered 3 to 4 hours prior to the first dose of apilimod dimesylate.

In addition, subjects who are at high risk of TLS should be considered for in-hospital monitoring during the first 24 to 48 hours of LAM-002A administration.

Section 6.6.7 Definition of Dose-Limiting Toxicity (DLT) – Footnote to Table 3. Criteria for Defining Dose Limiting Toxicities (DLTs)

Change: TLS has been removed as a DLT exclusion.

Note: Known oncologic emergencies from NHL (e.g., ~~tumor lysis syndrome,~~ spinal cord compression, ureteric obstruction, lymphomatous meningitis, and superior vena cava syndrome) will not be considered as dose-limiting toxicities.

Section 6.9 Schedule of Assessments – Table 4 Schedule of Assessments

Change: Serum chemistry laboratory monitoring for TLS has now been included on Days 2 and 3 of Cycle 1 for subjects at intermediate to high risk of TLS (as defined in Section 6.8.1 of the protocol).

Table 4: Schedule of Assessments

Assessment	Screening	Cycle 1					Cycle 2			Cycle ≥ 3		End of Treatment (EOT)	Long-Term F/U
		Day					Day			Day			
	-28 to -1	1	2	3	8	15	1	8	15-28	1	15-28		
Informed consent	X												
Inclusion/exclusion criteria	X	X[a]											
Demographics	X												
Medical history	X												
Signs and Symptoms, PE[b]	X	X[c]					X			X		X	
ECOG Performance Status	X	X[c]					X			X		X	
Vital signs	X	X[d]			X[d]	X[d]	X			X		X	
ECG	X	X[d]			X[d]	X[d]	X			X		X	
HIV, HBV, and HCV serology	X												
Hematology[e, f]	X	X			X	X	X	X	X	X		X	
Serum chemistry[f, g]	X	X	X[f]	X[f]	X	X	X	X	X	X		X	
Coagulation	X	-											
Urinalysis[h]	X	X[c]					X			X		X	
Pregnancy testing[i]	X	X[i]					X			X		X	
PET/CT or CT (or MRI) scans (based on indication) for response assessment	X[j]								X[k]		X[k]	X[l]	
CLL baseline assessments[m]	X												
PK sampling[n] + Analyte		X			X	X							

Table 4: Schedule of Assessments (Continued)

Assessment	Screening	Cycle 1					Cycle 2			Cycle ≥ 3		End of Treatment (EOT)	Long-Term F/U
		Day					Day			Day			
	-28 to -1	1	2	3	8	15	1	8	15-28	1	15-28		
Bone marrow aspirate/biopsy	X[o]								X[p, q]		X[p]		
Biomarker – tumor tissue	X[q]												
Biomarker – blood smears[r]		X			X	X							
Biomarker – plasma cytokines[s]		X			X	X							
Biomarker – PBMC[t]		X			X								
Biomarker – saliva[u]		X											
LAM-002A administration		X	X	X	X	X	X	X	X	X	X		
Adverse events		Throughout Study											
Concomitant medications[v]		Throughout Study											
Long-term follow-up (F/U)[w]													X

a Eligibility will be confirmed by Cycle 1 Day 1.

B Complete physical examination (PE) will be performed at screening. A directed PE, including weight, will be performed within 72 hours prior to the start of each cycle and EOT.

C Assessment/test does not need to be repeated on C1D1 if baseline was within normal limits and conducted within 72 hours of first dose.

D Obtained on Day 1 prior to dosing for all Cycles. For C1D1 and C1D8 obtained prior to dosing and 1 h (± 15 min after dosing), 2 hrs (± 30 min), 4 hrs (± 1h), and 8 hrs (± 1h) postdose. For C1D15, obtained prior to dosing.

E Hematology includes hemoglobin, hematocrit, RBC count, platelet count, WBC and differential.

F All hematology and chemistry laboratory parameters should be assessed at Screening and Days 1, 8, and 15 of Cycles 1 and 2, and then at least once prior to the start of all subsequent cycles and at EOT. **Obtaining a chemistry laboratory parameter on Days 2 and Day 3 of Cycle 1 is only required in subjects with intermediate or high risk of TLS (per the risk definition in Section 6.8.1). Except for Days 1, 2, and 3 of Cycle 1, t~~T~~hese parameters may be obtained within 72 hours prior to the planned day of collection. Abnormal test values should be monitored per protocol guidance.

G Chemistry includes albumin, alkaline phosphatase, total bilirubin, BUN, calcium, carbon dioxide, chloride, creatinine, glucose, inorganic phosphorus, potassium, total protein, LDH, ALT, AST, sodium, and uric acid.

H Urinalysis includes appearance, specific gravity and pH as well as a semi-quantitative “dipstick” evaluation of glucose, protein, bilirubin, ketones, leukocytes, and blood. Microscopic examination of sediment will be performed if urinalysis is positive for WBC, proteins or blood. Urinalysis may be obtained within 72 hours prior to the planned day of collection.

I Pregnancy testing (serum or urine) will be required for women of childbearing potential (WCBP) only. Testing is required at Screening; within 72 hours of Day 1 of each cycle and at EOT. Test does not need to be repeated on C1D1 if baseline was negative and conducted within 72 hours of first dose.

J Imaging as appropriate for disease indication will be conducted within 30 days of the first dose of study treatment. Suitable scans performed prior to screening and within 30 days before first dose may be used for baseline tumor assessments.

K Assessment of disease status will be conducted with standard clinical measurements: PE, CBCs, bone marrow aspirates/biopsies, and imaging as appropriate for indication. During treatment, scans will be repeated for tumor assessment within 7 days of Day 1, Cycles 3, 5, and 7 then every 3 months until PD or use of alternative antineoplastic therapy. For subjects still in response after 1 year, intervals for radiographic surveillance may be every 6 months. Subjects with CLL who achieve CR will require assessment of MRD by flow cytometry of bone marrow and peripheral blood.

L Imaging at EOT is not required if PD has already been radiographically documented or last imaging was within 30 days of EOT visit.

M Subjects with CLL/SLL must provide either a fresh blood sample containing circulating tumor cells or a bone marrow aspirate sample pretreatment. Tissue will be submitted for evaluation of the percentage of tumor cells and analysis of genetic alterations and/or gene expression that may predict anticancer activity and/or pharmacodynamic activity. In addition, for subjects with CLL/SLL, the sponsor may arrange for a portion of the sample to be evaluated at a sponsor-specified laboratory for known prognostic markers (e.g., quantitative immunoglobulins, FISH panel [chromosome 11q deletion, 13q deletion, 17p deletion and 12 trisomy], DNA mutational analysis for p53, IgHV [including IgHV3-21], and other genes of interest in CLL [e.g., Notch]; flow cytometry [for CD5, CD10, CD11c, CD19, CD20, CD23, CD38, CD45, kappa and lambda light chains and ZAP-70], and/or β2-microglobulin). The baseline bone marrow aspiration procedure (if required) should be performed after the study candidate has undergone the baseline radiology examination and is otherwise considered eligible for study participation. All subjects with CLL/SLL must have baseline imaging (with CT scans [preferred] or MRI scans).

N Blood sampling for determination of the plasma concentrations of apilimod and metabolites will be performed on C1D1 and C1D8 as follows: pre-dose, 30 minutes, 1, 2, 4, 6, 8 hours post-first dose of the day. C1D15 pre-dose only. Additional PK samples will be collected, if possible, whenever a subject has a study treatment-related SAE or QTc > 500 msec. Subjects are required to come to the study site in a fasting state prior to the collection of certain PK samples. For analyte determination, PK back-up sample will be used from time points: Cycle 1 Day 1 and Cycle 1 Day 8 pre-dose.

O Bone marrow aspirates/biopsies performed within 2 months prior to first dose may be used for clinical baseline assessments. For subjects with NHL, baseline bone marrow biopsies/aspirates may be omitted if not deemed essential for response assessment or patient management. For subjects with CLL/SLL, a baseline bone marrow aspirate is required unless the presence of sufficient circulating cells in the peripheral blood (e.g., absolute lymphocyte count [ALC] ≥ 10 x 10^9/L) permits assessment of baseline parameters as described in Footnote m, above.

P If necessary per applicable response criteria, a repeat bone marrow biopsy or aspirate will be required for subjects who have a CR by imaging and physical examination.

Q Archival or fresh tumor tissue from the most recent available biopsy or surgery prior to first dose in subjects with NHL must be obtained pretreatment. For subjects undergoing a biopsy, adequate tumor tissue should be acquired via excisional biopsy, incisional biopsy or core needle biopsy (e.g., ≥ 3 passes using a 16-gauge core needle). Alternatively, cells from a bone marrow aspirate may be obtained in subjects with bone marrow involvement due to NHL. Tissue will be submitted for evaluation of the percentage of tumor cells and analysis of genetic alterations and/or gene expression that may predict anti-lymphoma activity and/or pharmacodynamics activity. In addition, for subjects with NHL, tumor may be evaluated for known prognostic characteristics (e.g., for DLBCL: ABC or GCB subtype; expression of BCL2, BCL6, Ki-67, CD20, and MYC; other mutational status). The baseline biopsy procedure (if required) should be performed after the study candidate has undergone the baseline radiology examination and is otherwise considered eligible for study participation.

R Blood smears will be collected for microscopic evaluation of vacuole formation on C1D1 and C1D8 as follows: pre-dose, 4 hrs and 8 hrs post first dose of the day. C1D15 pre-dose only.

S Plasma will be collected for evaluation of circulating cytokines (including IL-12 and IL-23) predose on each of Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 1 Day 15.

T PBMCs will be collected on Cycle 1, Day 1 pre-treatment; on Cycle 1, Day 1 at 8 hours post-dose; and on Cycle 1, Day 8 at 8 hours post-dose for determination of changes in gene expression that may predict or correlate with anti-lymphoma activity and/or pharmacodynamic activity.

U Saliva will be obtained pre-dose on Cycle 1 Day 1 as a normal-tissue control for gene mutation studies in tumors.

V Information on concomitant medications and other treatments will be collected from 14 days prior to informed consent through 30-37 days after the last dose of study drug.

W Subjects who have discontinued study treatment for reasons other than PD will be assessed per Revised Response Criteria for NHL or Guidelines for the diagnosis and treatment of CLL at a minimum of every 12 weeks until documentation of PD, start of new anti-cancer therapy or for up to 1 year from the last enrolled subject's first treatment (Cycle 1 Day 1) whichever comes first. Long-term follow-up survival information will be obtained in all surviving subjects who permanently discontinue study therapy. Such information may be collected at ~3- to 6-month intervals at the sponsor's discretion through 3 years. This long-term follow-up information will be gathered during routine clinic visits, other study site contact with the subjects, or via telephone or e-mail with the subjects/caregivers or referring physician offices.

Abbreviations: ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; CBCs: Complete blood counts; CD: Cluster of differentiation; CLL: Chronic lymphocytic leukemia; CR: Complete response; CT: Computerized tomography; DAT: Direct antiglobulin test; ECG: Electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOT: End of treatment; FISH: Fluorescence *in situ* hybridization; h: Hour; hrs: Hours; LDH: Lactate dehydrogenase; min: Minutes; MRD: Minimal residual disease; MRI: Magnetic Resonance Imaging; PBMC: Peripheral blood mononuclear cell; PD: Progressive disease; PE: Physical exam; PET: Positron emission tomography; PK: Pharmacokinetics; QTc: Corrected QT interval; RBC: Red blood cell; SAE: Serious adverse event; WBC: White blood cell; WCBP: Women of child bearing potential

Changes made in Amendment 6 (25 Oct 2017)

In preparing this amendment of the protocol document, the following changes were made. Explanations of the changes are provided in italics as "*Changes*." Inserted text is indicated by **red bold font**. Deleted text is indicated by ~~red strikeout font~~. Changes to the synopsis also appear in the body of the protocol; thus, changes to the synopsis are not described and only changes to the body of the protocol are described.

General Change

Change: Where applicable and as appropriate for the context, the name "apilimod dimesylate" was redesignated as LAM-002A. Similarly, to provide clarity, the term "study drug" was modified to "LAM-002A," when appropriate.

Title Page

Change: The protocol version and date were updated.

Protocol Version and Date: **Version 7.0, 25 Oct 2017** ~~Version 6.0; 14 Apr 2017~~

Investigator's Agreement

Change: The date was updated.

I have read the attached Protocol entitled "A Phase 1 Dose Escalation Study of the Safety and Pharmacokinetics of LAM-002A (apilimod dimesylate capsules) Administered Orally in Subjects with Relapsed or Refractory B-cell Non-Hodgkin's Lymphoma" dated **25 Oct 2017** ~~14 Apr 2017~~.

Section 4.1.1. Pharmacology

Change: An additional reference was added to replace a former reference to unpublished data, and all references were hyperlinked to the bibliography.

Apilimod and apilimod dimesylate were originally introduced into clinical trials based on apilimod's immunomodulatory properties (Wada 2007; Wada 2012). Apilimod inhibits the production of interleukin-12 (IL-12) and interleukin-23 (IL-23), and was effective in preclinical animal models of various autoimmune diseases that are mediated by the inappropriate expression of T-helper cell phenotype (Th1) cytokines (Wada 2007).

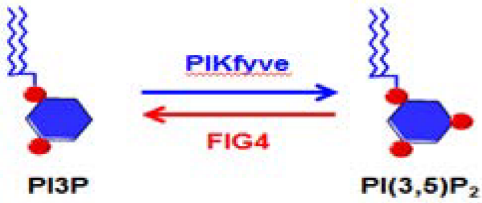
Recent**ly** published data ~~(and LAM Therapeutics unpublished data in cancer cells)~~ have shown that apilimod is a potent and highly selective first-in-class phosphatidylinositol-3-phosphate- 5 kinase (PIKfyve) inhibitor (Cai 2013, **Gayle 2017**). In total, LAM has tested 456 kinases, including disease-relevant kinases, for their ability to bind to apilimod. The screening concentration of apilimod was 1 µM, a concentration that is > 12,000 times greater than the K_d (81 picomolar) for apilimod against PIKfyve. The results showed that apilimod did not bind to any of the 456 kinases tested.

Inhibition of PIKfyve by pharmacological methods as well as RNA interference (RNAi) produces swollen vacuoles and disruption of endomembrane dynamics. In cell culture, the pharmacological disruption of PIKfyve with apilimod induces selective lethality of specific

cancer cell lines, presumably through disruption of intracellular trafficking that leads to **noncanonical cell death (Gayle 2017)**~~apoptosis (LAM Therapeutics, unpublished data)~~.

PIKfyve kinase is a 240-kDa endosomal phosphatidyl inositol (PI) 5 lipid kinase that catalyzes the phosphorylation of PI3 phosphate to PI (3, 5) P2 as shown in Figure 1.

Figure 1: PIKfyve Kinase



Abbreviations: FIG4: FIG4 phosphoinositide 5-phosphatase; PI3P: Phosphatidylinositol 3-phosphate; $PI(3,5)P_2$: Phosphatidylinositol 3,5-bisphosphate; PIKfyve: Phosphatidylinositol-3-phosphate-5 kinase

PIKfyve kinase is associated with the cytosolic leaflet of early endosomes and its activity is required for endomembrane homeostasis, endolysosomal function and proper retrograde transport from the endosome to the trans-Golgi network (Rutherford 2006). Introduction of catalytically inactive kinase mutant into cells induces a swollen vacuole phenotype that can be rescued by microinjection of PI (3, 5) P2 (Ikonomov 2001). Inhibition of PIKfyve by pharmacological methods or RNAi produces swollen vacuoles and disruption of endomembrane dynamics (Cai 2013, de Lartigue 2009; Rutherford 2006). In cell culture, the pharmacological disruption of PIKfyve with apilimod induces selective lethality of specific cancer cell lines presumably through disruption of intracellular trafficking that leads to apoptosis (LAM Therapeutics, unpublished data).

The *in vitro* cytotoxic activity of apilimod was evaluated in 3-day assays on 139 human cancer cell lines. A cell line was designated apilimod-sensitive if the half maximal effective concentration (EC_{50}) was less than 500 nanomolar (nM). Forty cell lines were identified as sensitive to apilimod. Apilimod was shown to be highly selective for cancer cells compared to normal cells; i.e., apilimod was 20- to 200-fold more potent based on EC_{50} values in cancer cells (which included cells derived from several different cancers including NHL, Hodgkin lymphoma, colorectal cancer, and lung cancer) compared to normal human cells. The most sensitive of those cancer cell lines tested were B-cell NHL lines. Apilimod also has demonstrated *in vivo* activity in multiple mouse xenograft models using human DLBCL or Burkitt lymphoma (BL) cancer lines. ***In vivo* testing of apilimod together with other chemoimmunotherapeutic drugs used in the therapy of NHL has demonstrated enhanced antitumor activity, most notably when apilimod was administered in combination with the anti-CD20 antibody rituximab in a murine xenograft model of human DLBCL and in combination with an anti-programmed death ligand (PDL1) antibody in a syngeneic immunocompetent murine lymphoma model (Gayle 2017).**

LAM Therapeutics has also performed research into the mechanism of action of apilimod cytotoxicity in cancer cells. Putative genes that confer sensitivity / resistance to apilimod have been identified and will be evaluated as potential biomarkers for predicting apilimod efficacy.

Section 4.1.4.2. Efficacy

Change: Efficacy information from the study in patients with hematological malignancies was updated to reflect data as of 30 Sep 2017.

Efficacy data in patients with hematological malignancies are **evolving**~~pending~~. **As of 30 Sep 2017, positron emission tomography (PET) demonstrated systemic partial metabolic responses in nodal and extranodal lesions in 3 patients with refractory DLBCL (treated at 100 mg BID, 75 mg TID, and 125 mg BID) (1 of whom also received radiation for bulky axillary adenopathy); concomitant computed tomography (CT) demonstrated anatomic shrinkage of many lesions. One additional subject with transformed, refractory DLBCL (treated at 125 mg BID) experienced tumor lysis syndrome (TLS). One patient with marginal zone lymphoma (MZL) (treated at 125 mg BID) has had a metabolic response by PET together with a 43% decrease in the sum of the products of the perpendicular diameters (SPD) of index lesions by CT. Another patient with MZL and a patient with chronic lymphocytic leukemia (CLL) (both receiving 100 mg BID) experienced prolonged stable disease through 11+ and 14 cycles, respectively.** ~~One patient, a 60-year-old male with GCB-DLBCL who was had experienced minimal or no response to multiple prior chemoimmunotherapy regimens (including R-CHOP), received apilimod dimesylate at 100 mg/dose BID for 6 weeks before enlarging right axillary lymphadenopathy required cessation of study drug and intervention with local radiation therapy. A follow-up PET-CT, obtained approximately 2 weeks later, showed a substantial systemic decrease in DLBCL lesions in non-irradiated lymph nodes, liver, spleen, and bone (C4 vertebra); these improvements in disease burden were attributed by the investigator to the study drug.~~

Section 4.1.4.3. Safety

Change: Safety data in the second paragraph were updated.

No renal insufficiency has been observed in ~~completed~~ clinical trials to date **except in 1 patient with DLBCL who acutely developed transient elevations in serum creatinine and blood-urea nitrogen (BUN) due to tumor lysis syndrome (TLS) shortly after starting LAM-002A at a dose of 125 mg BID.** ~~And no clinically significant safety signals in laboratory, physical examination, or vital sign findings have been noted~~One patient with a hematological malignancy receiving the drug at 150 mg BID developed asymptomatic Grade 3 hyponatremia that was attributed to the combined effects of ~~a apilimod dimesylate-induced~~ **LAM-002A-induced** diarrhea and hydrochlorothiazide administration. **No other clinically significant safety signals in laboratory, physical examination, or vital sign findings have been noted.**

Section 4.1.5. Overview of Indication

Change: Background information was added to the fourth paragraph to support the combination of LAM-002A with rituximab or atezolizumab.

Patients with DLBCL who relapse after, or who are not candidates for ASCT, as well as patients with relapsed MCL, MZL, FL, and CLL/SLL are not considered ~~curative~~ **curable** with conventional therapies. ~~Therefore, management of relapsed and refractory NHL remains an unmet medical need~~. **Patients with recurrent disease are commonly given sequential regimens of chemotherapeutic, immunotherapeutic, or investigational agents in an attempt to control disease manifestations. Rituximab is commonly employed in combination with**

other agents (Zelentz 2014). Newer immunopotentiating approaches using anti-PD1/PDL1 inhibitors (including atezolizumab [https://clinicaltrials.gov/ct2/show/NCT031206761]) are being explored and have shown evidence of activity in patients with recurrent NHL (Ilcus 2017). However, despite use of agents with differing mechanisms of action, progressive resistance to treatment typically develops. Patients with refractory or multiply relapsed progressive disease have poor prognoses and are ultimately likely to die of their cancers. Novel mechanisms of action are needed that can be administered alone or in combination with existing chemoimmunotherapeutic approaches to offer additional treatment options for patients with hematological cancers who have experienced disease progression.

Section 5. TRIAL OBJECTIVES AND PURPOSE

Change: The section was updated to indicate that LAM-002A will be evaluated alone and in combination with other drugs and to indicate changes in the types of pharmacodynamic assays that will be performed based on evolving experience with these exploratory endpoints. ***Only the sections in which changes were made are shown.***

5. TRIAL OBJECTIVES AND PURPOSE

The overall purpose of this Phase 1 study is to explore the safety and tolerability of LAM-002A **when given alone and in combination** for the treatment of subjects with relapsed or refractory B-cell NHL.

5.3. Exploratory Objectives

- To evaluate the pharmacodynamic effects of LAM-002A, administered orally, **in plasma assays and** ~~on~~ surrogate tissue (~~e.g., vacuoles in peripheral blood smears,~~ gene expression in peripheral blood mononuclear cells [PBMCs]**/B cells**, and plasma cytokines [including (IL)-12 and IL-23]).
- To evaluate tumor for gene expression and genetic alterations (with saliva **and/or B-cell-depleted PBMC** collection for germ-line control) and surrogate tissue (PBMC**/B cells**) for gene expression that may predict anti-lymphoma activity.
- To evaluate plasma for changes in analytes **or tumor for protein expression** that may predict anti-lymphoma activity.

5.6. Exploratory Endpoints

- Extent of PIKfyve inhibition as determined by **plasma inhibitory** ~~assaysthe extent of vacuole formation in white blood cells in peripheral blood smears by microscopic evaluation~~
- Changes in gene expression in PBMCs
- Changes in plasma cytokines (including IL-12 and IL-23)
- Correlation between genetic alterations as determined by next generation sequencing and/or gene expression in tumor tissue**, circulating tumor DNA,** or PBMCs**/B cells** and anti-lymphoma activity following treatment with LAM-002A

- Correlation between changes in plasma bioanalytes **or tumor protein expression** and anti-lymphoma activity following treatment with LAM-002A as determined by proteomic tools

Section 6.1.1. LAM-002A Dose Escalation Stage

Change: Based on findings that nausea, vomiting, and diarrhea were treatment-limiting when LAM-002A was given continuously at a dose ≥150 mg twice per day (BID), a plan for further dose exploration using an intermittent LAM-002A dosing regimen with antiemetic and antidiarrheal support was defined (see also Section 6.6). The section was modified accordingly.

The maximum tolerated dose (MTD) will be determined during the dose-escalation stage**, evaluating both continuous and intermittent dosing regimens.** Subjects will accrue using a 3 + 3 design. During this stage, the decision to open a new cohort at a higher or lower dose level will be made by the participating clinical investigators and sponsor when all subjects in the current cohort have been treated through at least Week 4 or once 2 DLTs have occurred in that dose cohort. All available safety and PK data will be considered in a decision by the medical monitor in collaboration with the investigators to dose escalate, de-escalate, expand the current cohort or explore ~~an~~ alternate **regimens** ~~schedule~~of drug administration. The MTD will be determined based primarily on DLTs observed through Week 4 in ~~at least~~≥ 6 subjects.

Section 6.1.2. Expansion Stage

Change: Based on emerging clinical data, the disease indications to be evaluated in the expansion stage of the study were established. In addition, based on emerging nonclinical data, the combination regimens to be evaluated in the expansion stage were defined. The section was modified accordingly.

Once the MTD and/or recommended phase 2 dose (RP2D) and schedule is determined, the study will enter the expansion stage, in which ~~3~~ cohorts of ~~15~~ subjects ~~each~~ will be accrued in order to obtain additional information on safety, tolerability, preliminary anti-tumor activity, PK, and pharmacodynamic data at the RP2D and schedule **when LAM-002A is administered alone or in combination with rituximab or atezolizumab. Expansion-stage cohorts will comprise groups of subjects with specific types of previously treated, relapsed, progressive, and measurable NHL who will receive LAM-002A monotherapy or LAM-002A-containing combination therapy as shown in Table 2. For both monotherapy and combination cohorts, the starting dose of LAM-002A will be 125 mg BID administered continuously.** ~~The eligibility criteria will remain the same as in escalation but each cohort will be specific to subjects with DLBCL, FL, and CLL/SLL, respectively. The treatment regimen in each of the expansion cohorts will be single agent LAM-002A (apilimod dimesylate capsules) according to the RP2D and schedule.~~

Table 2: Expansion Stage Disease Types and Therapies

Cohort Number	NHL Type	Investigational Drug	Combination Drug	Evaluable Subjects, n
1	FL	LAM-002A	--	6
2	MZL	LAM-002A	--	6
3	DLBCL-GCB	LAM-002A	--	6
4	DLBCL-ABC	LAM-002A	--	6
5	FL or MZL	LAM-002A	Rituximab	6
6	DLBCL-GCB or DLBCL-ABC	LAM-002A	Rituximab	6
7	FL or MZL	LAM-002A	Atezolizumab	6
8	DLBCL-GCB or DLBCL-ABC	LAM-002A	Atezolizumab	6

Abbreviations: ABC: activated B-cell (subtype); DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; GCB: germinal center B-cell (subtype); MZL: marginal zone lymphoma; NHL: non-Hodgkin lymphoma

Section 6.1.3. Subject Allocation (Stages 1 and 2)

Change: Consistent with the plan to perform dose-ranging evaluation of intermittent LAM-002A administration and to assess monotherapy and combination therapy cohorts using continuous LAM-002A administration, this section was added to provide information on subject allocation and to describe restrictions to enrollment in Stage 1 and Stage 2 enrollment to enhance study safety.

Subjects will be allocated to the cohorts by the study sponsor working in collaboration with each investigator considering the availability of openings for enrollment in Stage 1 or 2, disease type (i.e., FL, MZL, DLBCL-GCB, DLBCL-ABC, or other indications), therapy history (e.g., prior use of anti-CD20 or anti-PD1/PDL1 antibodies), and current disease status (e.g., potential to benefit from rituximab treatment based on past responses to anti-CD20 antibody therapy).

During Stage 1 dose ranging with LAM-002A monotherapy, allocation will be performed according to a 3+3 dose-escalation procedure with the requirement that each cohort of 3 subjects be observed for ≥4 weeks before another cohort is enrolled (as detailed in Section 6.6). During Stage 2 cohort expansion evaluating LAM-002A monotherapy, allocation will be performed as subjects present to the accruing clinics and there will be no specific restrictions on the cadence of enrollment. During Stage 2 cohort-expansion of LAM-002A combinations with rituximab and atezolizumab, enrollment of the first 3 subjects in each combination cohort will be restricted such that each subject must be enrolled sequentially and observed for ≥3 weeks before the next subject is enrolled. Beginning with the 4th patient in each combination group, further enrollment may proceed without restriction as long as the continuous reassessment boundaries for toxic drug discontinuations are not met (as detailed in Section 6.8.2.5 and Section 6.12).

Section 6.1.4 Subject Evaluability

Change: This section was added to clarify subject evaluability for the dose-ranging and cohort-expansion portions of the study.

A Stage 1 subject will be considered evaluable if the subject meets the definition for evaluability of Cycle 1 DLT as described in Section 6.6. A Stage 2 subject will be considered evaluable if the subject has both baseline and ≥1 on-study tumor assessments sufficient to allow a determination of response to study therapy.

Section 6.2. Number of Subjects

Change: The number of subjects was updated to reflect the new dose-escalation and cohort-expansion plans.

As many as 110 ~~Approximately 115 evaluable~~ subjects ~~(evaluable subjects include those who complete Cycle 1 dosing [administered at least 75% of doses] and have sufficient safety data, or who are withdrawn from the study due to a DLT in Cycle 1)~~ will be enrolled, assuming that:

- In the dose-escalation stage of the study, the total number of subjects will depend upon the numbers of subjects accrued to each dose level and the number of dose levels evaluated. If 6 subjects are enrolled at all ~~9 possible~~ **open** starting dose levels **(Dose Levels 5, 6, 7, and 8)** and 6 additional subjects are enrolled at the MTD or RD, as many as ~~60~~ **30** subjects could be enrolled. To allow for the possibility that some subjects may not be fully evaluable for DLT or that an intermediate dose level might be evaluated, up to ~~70~~ **45** subjects may be enrolled.
- In the expansion stage of the study, if all ~~3~~ **8** potential expansion cohorts of ~~15~~ **6** evaluable subjects are accrued, as many as ~~45~~ **48** subjects could be enrolled. To allow for the possibility that some subjects may not be fully evaluable for efficacy, up to ~~55~~ **65** subjects may be enrolled. ~~Subjects will be treated at the RP2D and schedule determined in the Dose Escalation Stage of the study.~~

Section 6.6. LAM-002A Dose-Escalation Procedures

Change: Table 3 was updated consistent with the new dose-escalation and cohort-expansion plans. The initial dose level of the 150 mg BID to be explored with intermittent dosing represented a modest increment over the recommended Phase 2 continuous dosing regimen of 125 mg BID. The text definition of "DLT evaluable" was updated to include the minimum required dosing.

Table 3: LAM-002A Provisional Starting Dose Levels

Continuous Administration		
Dose Level	**LAM-002A Dose and Schedule ~~Apilimod Dimesylate Dose mg/dose~~**	**LAM-002A Total Daily Dose ~~Apilimod Dimesylate Dose mg/day~~**
-1	25 mg BID	50 mg
0 (Initial Dose Level)	50 mg BID	100 mg
1	100 mg BID	200 mg
1a	125 mg BID	250 mg
1b	75 mg TID	225 mg
1c	100 mg TID	300 mg
1d	125 mg TID	375 mg
2	150 mg BID	300 mg
3	200 mg BID	400 mg
4	275 mg BID	550 mg
Intermittent Administration		
Dose Level	**LAM-002A Dose and Schedule**	**LAM-002A Total Daily Dose**
5	**150 mg BID**	**300 mg**
6	**200 mg BID**	**400 mg**
7	**250 mg BID**	**500 mg**
8	**300 mg BID**	**600 mg**

Abbreviations: BID: Twice daily (or 2 times per day); TID: Thrice daily (or 3 times per day)

Dose escalation decisions will be evaluated in a DLT-evaluable population. The DLT-evaluable population will include subjects who complete Cycle 1 dosing or who are withdrawn from study due to a DLT in Cycle 1. A subject will be deemed non-evaluable for determining DLTs and will not be counted toward the total cohort size if the subject did not experience a DLT, did not receive at least 75% (42/56 BID schedule; 63/84 TID schedule**, 18/24 intermittent schedule**) of the planned first-cycle doses or discontinued from the study prior to completing necessary safety evaluations through the first 28 days of study treatment. These subjects may be replaced unless accrual to the cohort has stopped due to DLT.

Section 6.7. Definition of LAM-002A Dose-Limiting Toxicity (DLT)

Change: Information regarding DLT definitions was moved to this section (previously in Section 6.7.2.5) to provide an easier flow of concepts. No changes to the substance of the DLT definitions were made except that the inability to administer the required minimum number of doses on the intermittent schedule due to drug-related AEs was added as a necessary new DLT criterion.

A DLT will be defined as an AE or abnormal laboratory value meeting the criteria in Table 3 and that is assessed as unrelated to disease, a comorbid condition, intercurrent illness, or concomitant medications (see Table 4). For the purposes of dose escalation and determination of the LAM-002A MTDs, DLTs that occur within the first cycle of treatment must be included in decisions regarding dose escalation. DLTs or other clinically significant toxicities that occur after Cycle 1 may also be considered when determining the RP2D.

Table 4: Criteria for Defining Dose-Limiting Toxicities (DLTs)

Toxicity	Criteria
Hematology	CTCAE Grade 4 neutropenia lasting ≥ 7 days CTCAE Grade 4 febrile neutropenia CTCAE Grade 3 thrombocytopenia with bleeding that requires transfusion therapy CTCAE Grade 4 thrombocytopenia
Toxicity	Criteria
Gastrointestinal	≥ CTCAE Grade 3 vomiting or nausea despite the use of optimal anti-emetic treatments ≥ CTCAE Grade 3 diarrhea despite the use of optimal anti-diarrheal treatments
Renal	Serum creatinine > 3.0 x ULN
Hepatic[a]	Total bilirubin ≥ CTCAE Grade 3 Total bilirubin ≥ CTCAE Grade 2 and ALT or AST ≥ CTCAE Grade 2 or, for subjects with liver metastases at baseline, total bilirubin ≥ 2.0 x ULN and ALT or AST ≥ CTCAE Grade 3
Treatment interruption/delays	Inability to administer ≥28/56 (BID schedule) or ≥42/84 (TID schedule) or ≥12/24 (intermittent schedule) planned LAM-002A doses in a treatment cycle due to drug-related AEs or Failure to recover from apilimod-dimesylate-related toxicities to baseline within 14 days from the last dose of LAM-002A in a cycle
Other adverse events not listed above	Non-hematologic toxicities of CTCAE ≥ Grade 3 except for the following. • alopecia • CTCAE Grade 3 fatigue for < 72 hours • Asymptomatic Grade 3 elevations in biochemistry laboratory values that last for ≤ 7 days that are not deemed to be clinically relevant. This includes electrolyte abnormalities that respond to medical intervention. Any LAM-002A-related adverse event that, in the opinion of the investigator, requires a dose reduction or discontinuation of treatment.

Abbreviations: ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CTCAE: Common terminology criteria for adverse events; DLT: Dose-limiting toxicity; ECG: Electrocardiogram; NHL: Non-Hodgkin lymphoma; ULN: Upper limit of normal

~~Once the RP2D and schedule are established, additional subjects will be treated in 3 histologically distinct dose expansion cohorts designed to better characterize the safety, tolerability, preliminary anti-tumor activity, PK, and pharmacodynamics of the study drug when provided at the MTD (or lower dose per agreement of the Investigators and Sponsor) in a specific B-cell NHL subtype. Up to 15 subjects will be treated in each expansion cohort.~~

Section 6.8.1. Tumor Lysis Syndrome Prophylaxis and Therapy

Change: The heading of the section was changed, as shown above, and information on TLS management was condensed under a single section within the protocol document.

~~**6.8.2 TLS Management**~~

~~Information regarding TLS prophylaxis is provided in Section 6.6.1.~~

Subjects who develop TLS may experience hyperkalemia, hypocalcemia, hyperuricemia, hyperphosphatemia, cardiac dysrhythmias, and acute renal failure; thus, close monitoring of electrolytes is important after initial therapy.

Subjects with TLS should receive intravenous hydration, rapid reversal of hyperkalemia, antihyperuricemic agents, and appropriate cardiac and renal support, including dialysis as indicated. Upon recovery to baseline functioning and as medically appropriate, such subjects should continue with protocol therapy to maintain tumor control.

Section 6.8.2. LAM-002A

Change: Information regarding LAM-002A administration, dose modifications, and supportive care was consolidated in one location in the protocol text, and this section was updated consistent with the new dose-escalation and cohort-expansion plans. The description of the study drug was removed from Section 6.8 and consolidated in a single location in Section 9.1 to avoid redundancy. The types of adverse events typically requiring LAM-002A dose modification were described. Given that LAM-002A has no obvious cumulative toxicity, allowance was made for dose escalation after Cycle 2 of therapy if such an escalation might be medically appropriate considering subject tolerance and antitumor efficacy. More detailed and protocol-specific guidelines for antiemetic prophylaxis and antidiarrheal prophylaxis were included based on current ASCO guidelines.

6.8.2.1. Premedications

Subjects taking LAM-002A by continuous administration may be offered antiemetics and antidiarrheals as necessary to control gastrointestinal symptoms as described in Section 6.8.2.6.1 For subject who do develop such adverse effects, sites should consider providing study participants with antiemetics and antidiarrheals so that these supportive care medications are readily available in case gastrointestinal symptoms related to LAM-002A recur or persist.

Subjects taking LAM-002A by intermittent administration are required to receive prophylactic antiemetic supportive care as described in Section 6.8.2.6.2.

~~6.7.2. Description of Study Drug~~

~~LAM-002A (apilimod dimesylate capsule) is intended for oral administration. Each capsule will contain 25 mg or 50 of apilimod dimesylate (equivalent to 17.1 mg or 34.3 mg of apilimod free base, respectively). The 25-mg capsule is Swedish orange and the 50-mg capsule is white. Both~~

~~the 25- and 50-mg capsules are Size 0 and both have a total fill weight of 175 mg. For additional information, see Section 9.1~~

6.8.2.2. In-Clinic LAM-002A Administration

For subjects receiving the continuous LAM-002A regimen, ~~On Cycle 1 Day 1, and Cycle 1 Day 8~~ the **morning** dose of LAM-002A should be orally administered **on Cycle 1 Day 1 and Cycle 1 Day 8** (a**fter a** minimum fast~~ing state~~ of 6 ~~to 8~~ hours) by site staff ~~immediately~~ after the collection of the biomarker samples and pre-dose PK sample. Subjects are allowed to eat after PK Sample #4 (Hour 2) has been collected. On Cycle 1 Day 15, the **morning** dose of LAM-002A should be orally administered (**after** a minimum fast~~ing state~~ of 6 ~~to 8~~ hours) by site staff immediately after collection of the pre-dose PK and biomarker samples.

For subjects receiving the intermittent LAM-002A regimen, prophylactic antiemetics are a required component of the regimen as described in Section 6.8.2.5.2. After initiation of the antiemetic regimen, the morning dose of LAM-002A should be orally administered on Cycle 1 Day 1 and Cycle 1 Day 10 (after a minimum fast of 6 hours) by site staff after the collection of the biomarker samples and pre-dose PK sample. Subjects are allowed to eat after PK Sample #4 (Hour 2) has been collected. Similarly, on Cycle 1 Day 8 and Cycle 1 Day 15, the antiemetic regimen should be initiated and the morning dose of LAM-002A should be orally administered (after a minimum fast of 6 hours) by site staff immediately after collection of the pre-dose samples.

When given as a component of combination therapy with rituximab, LAM-002A will be started on Cycle 1 Day 1 with a BID schedule. LAM-002A will be administered after administration of premedications (see Section 6.8.3.1) and ~15 to 30 minutes prior to the start of the initial rituximab infusion. On Cycle 1 Day 8, the morning dose of LAM-002A will be administered after premedications (see Section 6.8.3.1) and ~15 to 30 minutes prior to the rituximab infusion.

When given as a component of combination therapy with atezolizumab, LAM-002A will be started on Cycle 1 Day 1 with a BID schedule. LAM-002A will be administered ~15 to 30 minutes prior to the start of the initial atezolizumab infusion. On Cycle 1 Day 8, the morning dose of LAM-002A will be administered ~15 to 30 minutes prior to the atezolizumab infusion.

6.8.2.3. LAM-002A Self-Administration

Except for the days where treatment is administered in the clinic, LAM-002A will be self-administered orally, BID or TID of each 28-day cycle until disease progression or other discontinuation criteria are met. When taking the drug at home, subjects should be advised to take LAM-002A with ≥ 4 oz. (~160 mL) of water at the same times each day. Subjects on a BID schedule will be advised to take the doses at ~12 hours apart (e.g., 8:00 AM and 8:00 PM) (+/- 1-hour window). Subjects on a TID schedule will be advised to take the doses at intervals of ~6 to 8 hours. When self-administering LAM-002A at home, subjects may take the drug in the fed or fasted state. On PK days, subjects should come to clinic fasted (a minimum fasting state of 6 to 8 hours) and take the dose at the site under supervision. All subjects will be required to complete a dosing diary, which must be returned to the site for review at each site visit.

For those subjects taking LAM-002A with continuous administration, the drug should be taken according the prescribed BID or TID schedule without interruption unless toxicity or intercurrent illness requires a modification to the dosing regimen (see Section 6.8.2.5).

For those subjects taking LAM-002A with intermittent administration, the drug should be taken in repeated 7-day sequences comprising BID self-administration for 3 days (6 doses) followed by 4 days without dosing. If the cadence of the on-off periods is interrupted due to toxicity, intercurrent illness, or other reasons, the medical monitor should be consulted regarding the timing of therapy resumption and dose modification (see Section 6.8.2.5).

6.8.2.4. LAM-002A Dose Schedule Interruptions and Vomited Doses

No changes were made to this section.

6.8.2.5. LAM-002A Dose Modifications

The AEs associated with LAM-002A administration have included gastrointestinal toxicities of nausea, vomiting, and diarrhea, typically beginning shortly after initiation of drug administration.

If a subject experiences an AE that is suspected to be related to LAM-002A, appropriate supportive care (e.g., antiemetics, antidiarrheals, therapy for tumor lysis syndrome [TLS]) should be instituted consistent with the nature of the event.

If a subject experiences an LAM-002A-related DLT (reference Table 3) or other AE requiring a dose modification, then the LAM-002A administration should be interrupted until the toxicity recovers to Grade ≤ 1 or baseline. Upon resumption of LAM-002A, the total daily dose of LAM-002A should be reduced using an appropriate dose level or schedule (reference Table 3) as agreed between the investigator and medical monitor. Successive adjustments to progressively lower total daily dose levels can be made. If the subject cannot tolerate LAM-002A after a decrease to Dose Level -1 (25 mg BID), then the subject should be discontinued from LAM-002A therapy unless continued treatment is permitted by the medical monitor.

After the LAM-002A dose is reduced, the dose can be maintained at that dose level or schedule, even if there is minimal or no toxicity with the reduced dosing regimen. However, if the subject tolerates a reduced total daily dose of LAM-002A for ≥ 4 weeks then the LAM-002A dosing regimen may be reescalated to a higher total daily dose level at the discretion of the investigator and with the concurrence of the medical monitor. Such reescalation may be particularly warranted if the AE comprised TLS or if further evaluation reveals that the AE that led to the dose reduction was not related to LAM-002A. Successive adjustments to progressively higher total daily dose levels can be made. However, the escalated dose cannot exceed the total daily starting dose level for that subject during the first ~~4~~ **2** cycles of therapy.

Individual subjects who initiated treatment at a total daily dose level **at or** below the lower of the currently established MTD or the RP2D and who have not experienced a DLT after ≥ ~~4~~ **2** cycles of treatment may have the LAM-002A total daily dose escalated to the next higher dose level if both the principal investigator and the medical monitor agree that a dose escalation is medically warranted (e.g., for a subject with stable disease who is tolerating the current dose level of LAM-002A therapy). In such subjects, successive adjustments to progressively higher total daily dose levels can be made at intervals of ≥ 4 weeks with the condition that the escalated total daily

dose level cannot exceed **a LAM-002A dose of 150 mg BID when administered continuously or** the lower of the currently established MTD or RP2D **of LAM-002A when given intermittently**.

In a subject who experiences a DLT precluding resumption of LAM-002A therapy during a cycle, a new cycle of treatment may begin at the later of Day 29 or when AEs or laboratory abnormalities related to LAM-002A have returned to baseline levels. If drug-related AEs or laboratory abnormalities precluding further administration of study drug are not resolved to baseline by Day 29, week-by-week delays in initiating the new cycle of treatment should be instituted. When all drug-related AEs and laboratory abnormalities have returned to baseline, the next cycle of therapy can be initiated. Upon initiation of a new cycle of therapy, the prior cycle of therapy will be considered completed.

Investigators are to discuss modifications in the dosing regimen with the medical monitor. The appropriate clinic staff should dispense the LAM-002A for the new dose level or schedule and instruct the subject/caregiver about the change in the dosing regimen.

6.6.2.6. LAM-002A Supportive Care

6.8.2.6.1. Antiemetics for Subjects Taking LAM-002A by Continuous Administration

For subjects taking LAM-002A via continuous administration, sites should consider providing study participants with antiemetics and antidiarrheals so that these supportive care medications are readily available in case gastrointestinal symptoms related to LAM-002A develop.

For subjects taking LAM-002A via continuous administration, it is recommended that, if prophylactic or therapeutic antiemetics are required, subjects be offered 2 mg of the serotonin antagonist, granisetron (Kytril®, Granisol®), as an oral tablet or solution every 6 hours as needed. If subjects have persistent nausea or vomiting, consideration can be given to a 10-mg subcutaneous injection of the extended release form of granisetron (Sustol®). Alternatively, application of a 31.3 mg granisetron transdermal patch (Sancuso®) every 3 to 7 days can be offered. For transdermal prophylaxis, 24 to 48 hours may be necessary to allow a sufficient period to achieve effective granisetron systemic concentrations. Use of the serotonin antagonists, ondansetron (Zofran®, Zuplenz®) or dolasetron (Anzemet®), is discouraged due to the possibility that such agents could prolong the cardiac QT interval.

The dopamine antagonist, olanzapine (Zyprexa®), at doses of 2.5 to 10 mg, may be considered alone or in conjunction with serotonin antagonists or other types of antiemetic agents. Olanzapine doses of 10 mg may be sedating, which could be helpful for certain subjects, but may represent a concern for others, particularly for those who are elderly.

Based on currently available information regarding LAM-002A metabolism, the neurokinin 1 receptor antagonist, rolapitant (Varubi®), can be considered, but aprepitant (Emend®) or netupitant+palonosetron (Akynzeo®) should be avoided because these drugs may inhibit CYP3A4 and/or CYP2C9 activity.

Other classes of antiemetic medications that may be employed include dopamine antagonists or benzodiazepines if such drugs do not pose risks of QT prolongation or drug-drug interactions. Given the possibility that LAM-002A may alter immunological

mechanisms, use of systemic corticosteroids (e.g., dexamethasone) should be minimized (particularly when coadministered with atezolizumab) to avoid immunocompromise; however, corticosteroids can be introduced if other types of antiemetic agents are not sufficiently effective.

6.8.2.6.2. Antiemetics for Subjects Taking LAM-002A by Intermittent Administration

Because LAM-002A induces dose-dependent nausea and vomiting, subjects who are taking LAM-002A by intermittent administration are required to receive antiemetic supportive care. The following prophylaxis regimen should be started ≥30 minutes before initiation of each LAM-002A 3-day treatment sequence:

- **Dexamethasone 12 mg PO on Day 1 and then 8 mg PO on Day 2 and Day 3**
- **Granisetron 2 mg PO on Day 1 and then 1 mg PO BID on Days 2 and 3**
- **Olanzapine, 10 mg PO on Day 1 and then 10 mg PO on Days 2 and 3**

The study subject must be sent home from the clinic with sufficient dexamethasone, granisetron, and olanzapine to ensure that the supportive care medications are readily available to the subject for each of the four 3-day courses of LAM-002A therapy during each 28-day cycle.

Doses of dexamethasone and olanzapine may be adjusted to tolerance. Other antiemetic drugs (eg, neurokinin 1 receptor antagonists, dopamine antagonists, or benzodiazepines) may be considered in consultation with the medical monitor.

6.8.2.6.3. Antidiarrheals

For management of diarrhea related to LAM-002A, it is recommended that subjects take loperamide, 4 mg, at the occurrence of the first loose stool and then 2 mg every 2 hours until they are diarrhea-free for at least 12 hours. More aggressive loperamide prophylactic or therapeutic administration and titration of loperamide dosing for each loose bowel movement may be considered. During the night, subjects may take 4 mg of loperamide every 4 hours. Subjects should be advised to avoid dehydration through adequate fluid intake. Drugs such as 5HT3 antagonists or octreotide may be considered for their anti-secretory effects. For subjects who develop diarrhea while also receiving atezolizumab, the possibility of atezolizumab-induced colitis should be considered (see Section 6.8.4.4).

Section 6.8.3. Rituximab

Change: Consistent with the plan to evaluate the combination of LAM-002A and rituximab in this study, instructions for administration, dose modifications, and supportive care relating to rituximab were added to the protocol.

6.8.3.1. Premedications

In accordance with rituximab prescribing information (Genentech 2016), subjects should be premedicated with an antipyretic and an antihistamine to reduce the incidence and severity of infusion reactions. A recommended regimen is diphenhydramine, 25 mg orally, and acetaminophen (paracetamol), 650 mg orally, both given ~30 minutes prior to each

rituximab administration. Intravenous corticosteroids may also be administered as a premedication. Local practices and guidelines may be followed.

6.8.3.2. Rituximab Administration

Based on past experience with this regimen (Ghielmini 2004, Martinelli 2010), rituximab will be administered intravenously in the clinic for a total of 8 infusions:

- **Four induction infusions will be administered weekly on Cycle 1 Day 1, Cycle 1 Day 8, Cycle 1 Day 15, and Cycle 1 Day 22.**
- **Four subsequent maintenance infusions will be administered every 8 weeks on Cycle 4 Day 1, Cycle 6 Day 1, Cycle 8 Day 1, and Cycle 10 Day 1.**

The dose for each infusion will be 375 mg/m^2 of body surface area. The dose calculation of body surface area will be based on the subject's height and actual body weight prior to therapy. Once established based on the pretreatment body weight, the total dose of rituximab for the subject should not be altered during therapy based on fluctuations in body weight unless required by institutional policy.

At Cycle 1 Day 1, ~30 minutes after administration of the required antipyretic and antihistamine premedications and ~15 to 30 minutes after administration of the first dose of LAM-002A, the first infusion of rituximab will be administered via an infusion pump. For the initial infusion, the recommended infusion rate is 50 mg/hour. In the absence of infusion toxicity, the infusion rate can be increased in 50-mg/hour increments every 30 minutes, to a maximum of 400 mg/hour.

For subsequent infusions, the required antipyretic and antihistamine premedications will be given and the rituximab will be infused via an infusion pump. For these infusions, the infusion can be initiated at 100 mg/hour. In the absence of infusion toxicity, the infusion rate can be increased in 100-mg/hour increments every 30 minutes, to a maximum of 400 mg/hour. Alternatively, for subjects who tolerate the first infusion with Grade ≤3 infusion toxicity, subsequent infusions can be administered over a planned infusion time of 90 minutes, with ~20% of the total dose administered in the first 30 minutes and the remaining 80% of the total protein dose administered in the subsequent 60 minutes (Dakhil 2014, Genentech 2016).

6.8.3.3. Management of Rituximab Infusion Toxicity

Rituximab can cause severe, including fatal, infusion reactions (Genentech 2016). Patients with pre-existing cardiac or pulmonary conditions, those who experienced prior cardiopulmonary adverse reactions to rituximab, and those with high numbers of circulating malignant cells (≥25 x 10^9/L) may be at particular risk. Severe reactions typically occur during the first infusion and are generally less frequent and less severe with subsequent infusions. The time to onset of infusion toxicity ranges from 30 to 120 minutes. Rituximab-induced infusion reactions and sequelae include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, and/or anaphylactoid events.

Rituximab infusions should be interrupted or slowed in subjects experiencing Grade ≥3 rituximab-related infusion reactions. Medical management (eg, oxygen, epinephrine, bronchodilators, and/or glucocorticoids) should be instituted, as needed. Upon improvement of symptoms, the infusion may be continued at 50% of the previous rate. At the discretion of the investigator, rituximab therapy may be permanently discontinued in subjects with Grade 4 infusion reactions or with reactions requiring substantial intervention.

6.8.3.4. Rituximab Dose Modifications and Supportive Care

Rituximab-related noninfectious pneumonitis has been described (Subramanian 2010) with an incidence of ~4.3% (Salmasi 2010). In patients developing rituximab-associated pneumonitis, the mean time from the first rituximab infusion to the onset of respiratory symptoms was 3 months, with a peak incidence after administration of a mean cumulative dosage of 1600 mg/m2 (Lioté 2010).

Severe, including fatal, mucocutaneous reactions can occur in patients receiving rituximab during infusion or at later timepoints. Non-infusion related events have included paraneoplastic pemphigus, Stevens Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis (Genentech 2016). The onset of these reactions has varied from 1 to 13 weeks following initiation of rituximab exposure.

Among patients receiving rituximab in combination with chemotherapy, rare instances of life-threatening bowel obstruction or perforation has been observed [Ram 2009], primarily in patients with NHL. In post-marketing reports, the mean time to documented gastrointestinal perforation was 6 (range 1–77) days from start of chemoimmunotherapy.

Fulminate and fatal HBV infection and reactivation can occur during or after treatment with rituximab (Genentech 2016). The risk is very low among patients with negative anti-HBc serology (Matsue 2010) and/or undetectable HBV DNA as assessed by quantitative PCR. Because subjects with such evidence of persistent HBV infection are excluded from this study, reactivation is not anticipated. Other serious bacterial, fungal, and new or reactivated viral infections have also occurred during and for ~1 year following rituximab-based therapy (Gea-Banacloche 2010). Other new or reactivated viral infections in patients receiving rituximab have included CMV, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and HCV. Progressive multifocal leukoencephalopathy (PML) due to polyomavirus JC has been observed in patients who have received rituximab therapy for hematologic malignancies (Carson 2009).

No dose reductions of rituximab are recommended. If a subject experiences an AE that is suspected to be related to rituximab and is of sufficient severity to warrant modification of therapy, administration of the drug should be interrupted or discontinued. Protocol-recommended management of selected adverse events and appropriate supportive care is described in Table 5.

Table 5: Recommended Rituximab Modifications and Supportive Care

Adverse Event	Rituximab Interuption and Resumption	Rituximab Permanent Discontinuation	Supportive Care
Pneumonitis	Interrupt for Grade 2; resume when Grade ≤ 1	Grade ≥3	For Grade ≥2, corticosteroids, 1-2 mg/kg of prednisone equivalents
Rash	Interrupt for Grade 3; resume when Grade ≤ 1	Grade 4	For Grade 2, topical corticosteroids. For Grade ≥ 3, corticosteroids, 1-2 mg/kg of prednisone equivalents
Hepatitis	Grade ≥3 elevations of serum AST or ALT (> 5 x ULN); resume when Grade ≤ 1	--	Evaluate for HBV positivity; if HBV reactivation, treat with appropriate antiviral considering any potential for drug-drug interaction with LAM-002A.
Bowel obstruction or perforation	--	Any grade	Provide appropriate antibiotic therapy and surgical supportive care.
Infection	Grade ≥3; resume when control of infection achieved	--	Treat with appropriate systemic antibiotics for suspected or confirmed infections

Abbreviations: ALT=alanine aminotransferase, AST=aspirate aminotransferase, ULN=upper limits of normal

Section 6.8.4. Atezolizumab

Change: Consistent with the plan to evaluate the combination of LAM-002A and atezolizumab in this study, instructions for administration, dose modifications, and supportive care relating to atezolizumab were added to the protocol.

6.8.4.1. Premedications

No specific premedications are recommended for administration prior to atezolizumab administration. Given the potential for interference with desired atezolizumab immunopotentiation, systemic corticosteroid administration should be avoided.

6.8.4.2. Atezolizumab Administration

Atezolizumab will be administered intravenously in the clinic every 3 weeks. The dose for each infusion will be 1200 mg.

Using an infusion pump, atezolizumab should be administered through an intravenous line with or without a sterile, non-pyrogenic, low-protein binding in-line filter (pore size of 0.2 to 0.22 µm). Other drugs should not be coadministered with atezolizumab through the same intravenous line.

At Cycle 1 Day 1, ~15 to 30 minutes after administration of the first dose of LAM-002A, the first infusion of atezolizumab will be administered over 60 minutes. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes. Atezolizumab should not be administered as an intravenous push or bolus.

6.8.4.3. Management of Atezolizumab Infusion Toxicity

While infrequent (incident <2%), severe infusion reactions have occurred in clinical trial subjects receiving atezolizumab. For subjects with Grade 1 or 2 infusion reactions, the atezolizumab infusion should be interrupted or slowed. For subjects with Grade ≥3 infusion reactions, atezolizumab therapy should be permanently discontinued.

6.8.4.4. Atezolizumab Dose Modifications and Supportive Care

In clinical trials supporting its approval as therapy for patients with previously treated advanced non-small cell lung cancer and metastatic bladder cancer (Weinstock 2017, Ning 2017), atezolizumab administration has been associated with immune-related AEs of pneumonitis, hepatitis, pancreatitis, colitis, endocrinopathies (hypophysitis, thyroiditis, adrenal insufficiency, diabetes mellitus), and neurological toxicity (meningitis/encephalitis, motor/sensory neuropathies, myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome). Immune-related AEs can be observed within days to months after starting atezolizumab therapy (Genentech 2017).

Severe infections, including pneumonias, urinary tract infections, sepsis, herpes encephalitis, and mycobacterial infection have occurred.

Systemic immune activation is a rare condition characterized by an excessive immune response. Given the mechanism of action of atezolizumab, systemic immune activation is considered a potential risk when atezolizumab is given in combination with other immunomodulating agents. Systemic immune activation should be included in the differential diagnosis for study subjects who, in the absence of an alternative etiology, develop a sepsis-like syndrome after administration of atezolizumab. The initial evaluation should include:

- **CBC with peripheral smear**
- **PT, PTT, fibrinogen, and D-dimer**
- **Ferritin**
- **Triglycerides**
- **AST, ALT, and total bilirubin**

- **LDH**
- **Complete neurologic and abdominal examination (assessing for hepatosplenomegaly)**

If systemic immune activation is suspected after the initial evaluation, the medical monitor should be contacted in consultation.

Reference should be made to Section 6 of the atezolizumab investigator brochure for a detailed description of anticipated safety risks for atezolizumab.

No dose reductions of atezolizumab are recommended. If a subject experiences an AE that is suspected to be related to atezolizumab and is of sufficient severity to warrant modification of therapy, administration of the drug should be interrupted or discontinued. Protocol-recommended management of selected adverse events is described in Table 6.

Table 6: Recommended Atezolizumab Modifications and Supportive Care

Adverse Event	Atezolizumab Interruption and Resumption	Atezolizumab Permanent Discontinuation	Supportive Care
Pneumonitis	Interrupt for Grade 2; resume when Grade ≤ 1	Grade ≥3	For Grade ≥2, corticosteroids, 1-2 mg/kg of prednisone equivalents
Hepatitis	Interrupt for Grade 2 elevations of serum AST or ALT (> 3-5 x ULN) or total bilirubin (> 1.5-3 x ULN); resume when Grade ≤ 1	Grade ≥3 elevations of serum AST or ALT (> 5 x ULN) or total bilirubin (> 3 x ULN)	For Grade ≥2, corticosteroids, 1-2 mg/kg of prednisone equivalents
Colitis	Interrupt for Grade 2 or 3; resume if Grade ≤ 1 within 12 weeks on ≤ 10 mg oral prednisone equivalents	Grade 4	For Grade 2 recurrent or persistent (> 5 days), corticosteroids, 1-2 mg/kg of prednisone equivalents; For Grade ≥3, methylprednisolone 1-2 mg/kg intravenous → oral corticosteroid taper over ≥ 1 month

Pancreatitis	**Interrupt for Grade 2 or 3 pancreatitis or Grade ≥3 increases in serum amylase or lipase levels (>2 x ULN); resume if Grade ≤ 1 within 12 weeks on ≤ 10 mg oral prednisone equivalents**	**Grade 4 pancreatitis or any grade of recurrent pancreatitis**	**For Grade ≥2, methylprednisolone 1-2 mg/kg intravenous → oral corticosteroid taper over ≥ 1 month**
Hypophysitis	**Interrupt for symptoms; resume when Grade ≤ 1**	**--**	**Administer corticosteroids and hormone replacement as clinically indicated**
Thyroid disorders	**Interrupt for symptoms; resume when Grade ≤ 1**	**--**	**For symptomatic hypo- or hyperthyroidism, initiate hormone replacement or anti-thyroid drug, as needed**
Adrenal insufficiency	**Interrupt for symptoms; resume if Grade ≤ 1 within 12 weeks on ≤ 10 mg oral prednisone equivalents**	**--**	**For symptoms, methylprednisolone 1-2 mg/kg intravenous → oral corticosteroid taper over ≥ 1 month**
Diabetes mellitus	**Interrupt for Grade ≥3 hyperglycemia (serum glucose ≥ 250 mg/dL; resume when blood sugar control achieved**	**--**	**Insulin for Type 1 diabetes mellitus**
Meningitis, encephalitis, myasthenic syndrome, myasthenia gravis, or Guillain-Barré syndrome	**--**	**Any grade**	**Methylprednisolone 1-2 mg/kg intravenous → oral corticosteroid taper over ≥ 1 month**
Rash	**Interrupt for Grade 3; resume when Grade ≤ 1**	**Grade 4**	**For Grade 2, topical corticosteroids. For Grade ≥ 3, corticosteroids, 1-2 mg/kg of prednisone equivalents**

Infection	**Grade 3 or 4; resume when control of infection achieved**	**--**	**Treat with appropriate systemic antibiotics for suspected or confirmed infections**

Abbreviations: ALT=alanine aminotransferase, AST=aspirate aminotransferase, ULN=upper limits of normal

Section 6.9 Other Supportive Care Recommendations

Change: General supportive care recommendations were updated and consolidated in this section of the protocol.

6.9 Other Supportive Care Recommendations

Consistent with subject safety and comfort, administration of any prescription or over-the-counter drug products other than study medication will be minimized during the study period. Subjects should be discouraged from use of herbal remedies, self-prescribed drugs, tobacco products, or street drugs during their participation in the clinical study and should be counseled to minimize use of alcohol or nonmedical marijuana.

If considered necessary for the subject's well-being, drugs for concomitant medical conditions or for symptom management may be given at the discretion of the investigator. The investigator's decision to authorize the use of any drug other than study drug will take into account subject safety, the medical need, the potential for drug interactions, the possibility for masking symptoms of a more significant underlying event, and whether use of the drug will compromise the outcome or integrity of the study.

Subjects will be instructed about the importance of the need to inform the clinic staff of the use of any drugs or remedies (whether prescribed, over-the-counter, or illicit) before and during the study.

Recommendations regarding specific types of concomitant therapies, supportive care, diet, and other interventions are provided below. To minimize variations in supportive care, the recommended supportive care agents (eg, loperamide, granisetron) should be used unless there is a medical rationale in a specific subject for use of an alternative product.

6.9.1. Antibiotics, Antifungals, and Antivirals

Care should be taken to avoid or minimize concomitant administration of prophylactic or therapeutic antibacterial, antifungal, or antiviral, agents that are moderate or strong CYP3A4 or CY2C9 inhibitors or inducers (see Section 6.96 and Appendix 3).

For subjects with a history of recurrent infections, prophylaxis with intravenous gammglobulin may be offered and consideration may be given to initiation of antibiotic prophylaxis against pneumocystis infection (eg, with trimethoprim-sulfamethoxazole, dapsone, aerosolized pentamidine, or atovaquone) beginning prior to study drug administration. Such support also offers the benefit of reducing the risk for other bacterial infections (Stern 2014). Local practices or guidelines regarding infection prophylaxis may be followed.

Subjects developing an intercurrent infection during study drug treatment may receive therapeutic antibacterial, antiviral, or antifungal drugs for intercurrent infections as needed. Continuation of study therapy during treatment for an intercurrent infection is at the discretion of the investigator but guidance in Section 6.8.3.4 and Section 6.8.4.4 should be considered in subjects receiving combination therapy.

6.9.2. Anticancer Therapies Other than the Study Drugs

No systemic anticancer therapies (including chemotherapy, antibody therapy, hormonal therapy, immunotherapy, or other experimental therapies) for the subject's cancer are permitted while the subject is receiving study treatment. Subjects are not allowed to participate concurrently in any other therapeutic clinical or imaging study.

The use of palliative radiotherapy should be minimized given the potential of such treatment to confuse assessments of study drug safety or therapeutic effect. However, administration of limited-fraction radiotherapy is permitted to control local tumor-related symptoms if irradiation is unlikely to induce major organ toxicity or affect target lesions being followed for tumor response and progression.

If required to maintain disease control, study drugs may be continued with caution during radiotherapy administration.

6.9.3. Anticoagulants

Use of local anticoagulation or antithrombotic agents to maintain a venous access catheter is permitted. While not prohibited, use of systemic anticoagulants (eg, unfractionated heparin, low-molecular-weight heparin, fractionated heparin, warfarin or other oral anticoagulants, aspirin) after a subject is on study should be avoided unless necessary for development of a serious intercurrent thrombotic or embolic condition. Subjects who develop conditions that require anticoagulant therapy are permitted to receive such drugs and are not required to discontinue study participation if they appear to be safely benefiting from study therapy. Subjects should be closely monitored for bleeding events when on systemic anticoagulant therapy.

6.9.4. Antihistamine, Antiinflammatory, or Antipyretic, Drugs

Antihistamines (eg, cetirizine, diphenhydramine), and antiinflammatory/antipyretic drugs (eg, acetaminophen [paracetamol], nonsteroidal anti-inflammatory drugs [NSAIDs]), may be used during the study, as medically warranted. The potential for adverse hepatic effects with acetaminophen and platelet inhibitory effects with NSAIDs should be considered in the selection of the appropriate drug for the clinical situation.

6.9.5. Corticosteroids

At study entry, subjects may not be using systemic or enteric corticosteroids but may be receiving inhaled or topical corticosteroids. During study therapy, subjects may use systemic, enteric, topical or enteric corticosteroids as required by protocol or for treatment-emergent conditions. Use of systemic or enteric corticosteroids as premedications or for other reasons should be minimized but can be considered after consultation with the medical monitor.

6.9.6. Drugs with Potential for Drug-Drug Interactions with LAM-002A

No information is available regarding interactions of LAM-002A with therapeutic agents or other substances in humans. *In vitro* data suggest that concomitant administration of potent inhibitors or inducers of CYP3A4 or CYP2C9 might alter LAM-002A clearance and lead to clinically significant increases or decreases in LAM-002A exposure. Consequently, the concomitant use of strong inhibitors or inducers of CYP3A4 or CYP2C9 (see Table 14) should be avoided when possible.

Based on these considerations, protocol candidates who require therapy with strong CYP3A4 or CYP2C9 inhibitors or inducers listed in Table 14 should not be enrolled into the study.

During study participation, coadministration of LAM-002A with CYP3A4 or CYP2C9 inhibitors or inducers (see Table 14) should be avoided, if possible. However, a subject who develops a condition that may require use of such drugs is not required to permanently discontinue LAM-002A if the subject is experiencing clinical benefit and other options for treating the subject's cancer are limited. If medically appropriate, investigators may wish to use a therapeutic alternative that would not be expected to affect these enzymes. For subjects who require temporary use of a drug that does affect these enzymes (e.g., treatment with a systemic antifungal agent), LAM-002A can be interrupted (or the doses reduced) during use of the other medication and then resumed after completion of the other drug. For subjects who require initiation of chronic therapy with a drug that potently affects these enzymes, investigators must consult with the medical monitor to consider the best course of action.

6.9.7. Drugs Known to Prolong the QT Interval

In a thorough QTc study, apilimod dimesylate at doses of 50 mg and 150 mg was associated with repolarization findings in excess of those deemed negative by regulatory guidance. The magnitude of the change was modest (~8.5 msec), peaked at 4 hours and did not demonstrate a dose trend. Preliminary QTc observations in the ongoing study in patients with hematological malignancies suggest the potential for dose- and exposure dependent Grade 1 or 2 QT prolongation.

As a precaution, the clinical potential of LAM-002A to prolong the QT interval will be assessed in this study. Accordingly, co-administration of LAM-002A and known QT-prolonging drugs is to be minimized because use of such drugs might confound interpretation of QT data from the trial.

Based on these considerations, protocol candidates who require therapy with drugs known to prolong the QT interval (as listed in Table 15) should not be enrolled into the study. If medically justified, protocol candidates may be enrolled if such drugs can be discontinued or alternative drugs that do not affect QT can be substituted >7 days before the first dose of study drug.

After the subject is enrolled to the protocol, use of drugs known to prolong the QT interval should be minimized but is not prohibited if administration of such drug is necessary and the subject appears to be benefiting from protocol therapy.

6.9.8. Hematopoietic Support

Granulocyte colony-stimulating factor (G-CSF) (eg, filgrastim, filgrastim snd, pegfilgrastim, lenograstim) may be administered in response to Grade ≥3 neutropenia or neutropenic complications.

Granulocyte-macrophage colony-stimulating factor (GM-CSF) should not be administered given the potential for GM-CSF-related inflammatory symptoms.

Use of erythropoietic agents (eg, erythropoietin or darbepoetin) is not recommended.

Red blood cell or platelet transfusions may be administered as medically indicated.

6.9.9. Immunization

There is no information regarding the effects of LAM-002A or atezolizumab on the safety or response to immunization against infectious pathogens.

In randomized clinical trials, rituximab has been shown to reduce the antibody response to pneumococcal vaccination (a T-cell-independent antigen) or to anti-keyhole limpet hemocyanin antibodies (a novel protein antigen) (Genentech 2016). Response to tetanus toxoid vaccine (a T-cell-dependent antigen with existing immunity) or maintenance of a positive Candida skin test (as a measure of T-cell-mediated delayed-type hypersensitivity) was not altered. The specific clinical relevance of these findings is unknown.

For subjects who are at substantial risk of an infection (eg, influenza) that might be prevented by immunization, consideration should be given to providing the vaccine prior to initiation of study therapy. Vaccination with live virus vaccines during study treatment is not recommended.

6.9.10. Procedures/Surgery

The extent to which LAM-002A or other study drugs may affect wound healing or the risk of would infection is unknown. Investigators may use clinical discretion in deciding whether to interrupt protocol therapy before and after surgery or other invasive procedures.

6.9.11. Skeletal Event Prophylaxis

Bisphosphonates or denosumab are permitted if a subject was receiving such therapy at the time of screening and will continue on a stable regimen throughout protocol therapy. The need to start such drugs while on therapy may be an indication of disease progression and should be discussed with the sponsor prior to implementation.

Section 6.10. Study Restrictions

Change: A study restrictions section was added to provide guidance to the investigator.

6.10.1. Breast Feeding

There is no information regarding the presence of LAM-002A or its metabolites in animal or human breast milk and the effects of the drug on the breastfed infant or on milk production are unknown.

Rituximab is secreted in the milk of lactating cynomolgus monkeys, but it is not specifically known whether rituximab is secreted into human milk (Genentech 2016). There is similarly no information regarding the presence of atezolizumab in human milk (Genentech 2017). However, because human IgG is excreted in human milk, there is a hypothetical potential for absorption and harm to an infant from administration of these types of therapeutic antibodies.

For these reasons, women who are nursing are not eligible to participate in this study. Lactating women who do participate in this clinical trial must discontinue nursing during protocol therapy and should avoid nursing for ≥2 months after LAM-002A and for ≥5 months after the last dose of rituximab or atezolizumab.

6.10.2. Contraception

Animal studies have been conducted to assess the effects of apilimod on fertility and organogenesis. In studies conducted to date, apilimod or apilimod dimesylate did not affect fertility or cause reproductive harm. One patient receiving the drug for Crohn disease conceived during therapy; a normal pregnancy was carried to term and a healthy infant was born. However, no other experience is available with the drug in pregnant patients.

Reproduction studies of rituximab in cynomolgus monkeys at maternal exposures similar to human therapeutic exposures have shown no teratogenic effects (Genentech 2016). However, B-cell lymphoid tissue was reduced in the offspring of these animals; B-cell counts returned to normal levels and immunologic function was restored within 6 months of birth. In humans, B-cell lymphocytopenia generally lasting <6 months can occur postnatally in infants exposed to rituximab in utero.

Animal reproduction studies have not been conducted with atezolizumab to evaluate its effect on reproduction and fetal development. A literature-based assessment of the effects on reproduction demonstrated that a central function of the PD-L1/PD-1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to a fetus (Genentech 2017). Blockage of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to a fetus and to result in an increase in fetal loss; therefore, potential risks of administering atezolizumab during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-L1/PD-1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-L1 and PD-1 knockout mice. Based on its mechanism of action, fetal exposure to atezolizumab may increase the risk of developing immune-mediated disorders or altering the normal immune response.

Accordingly, sexually active females of childbearing potential must agree to use a protocol-recommended method of contraception during heterosexual intercourse from the start of the screening period until ≥5 months days after the final dose of study therapy.

In the context of this protocol, a female subject is considered to be of childbearing potential unless she has had a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy; has medically documented ovarian failure (with serum follicle stimulating hormone (FSH) level > 35 mIU/mL and a negative serum or urine beta βHCG); or is menopausal (amenorrhea for ≥12 months).

Sexually active male subjects who can father a child and are having intercourse with females of childbearing potential who are not using adequate contraception must agree to use a protocol-recommended method of contraception from the start of study therapy until ≥5 months days after the final dose of the study therapy and to refrain from sperm donation from the start of study therapy until ≥5 months after administration of the final dose of study therapy.

In the context of this protocol, a male subject is considered able to father a child unless he has had a bilateral vasectomy with documented aspermia or a bilateral orchiectomy.

Protocol-recommended contraceptive methods are described in Table 7.

Table 7: Protocol-Recommended Contraceptive Methods

Individual Methods	Combination Methods	
	Hormonal Methods (One method to be used with a barrier method)	Barrier Methods (Both methods to be used OR one method to be used with one hormonal method)
IUD (eg, Copper T380A, LNg20)	Estrogen and progesterone	Diaphragm with spermicide
Tubal sterilization	Oral contraceptives	Male condom (with spermicide)
Hysterectomy	Transdermal patch	
Vasectomy	Vaginal ring	
	Progesterone injection or implant	

Abbreviation: IUD=intrauterine device

6.10.3. Diet

Because LAM-002A is a substrate of CYP3A4, subjects should be advised to avoid ingestion of grapefruit, grapefruit juice, or Seville oranges (which contains a potent CYP3A4 inhibitor) and should not use St. John's wort, which is a potent CYP3A4 inducer. No other specific dietary restrictions are required.

Section 6.11. Duration of Subject Participation

Change: Information regarding the duration of subject participation was updated to include instructions for administration of both LAM-002A monotherapy and LAM-002A-based combination therapy. Consistent with intention-to-treat principles designed to maximize collection of safety and efficacy data, it was noted that subjects could continue on either of the combination agents even if the other agent were to be discontinued due to toxicity.

~~All subjects will be treated for at least 1 cycle unless there is evidence of unacceptable toxicity or PD. Although subjects may continue to receive study treatment until experiencing unacceptable toxicity or disease progression, it is estimated that each subject will participate for an average of 6 months of treatment and an additional 1 month of follow up.~~

Subjects may continue receiving LAM-0002A until the occurrence of any events requiring treatment discontinuation as defined in Section 6.8.2.5 and Section 6.12.

Subjects allocated to LAM-0002A/rituximab may continue to receive rituximab until the earliest of a maximum of 8 infusions or the occurrence of any events requiring treatment discontinuation as defined in Section 6.8.3.4 and Section 6.12.

Subjects allocated to LAM-0002A/atezolizumab may continue to receive atezolizumab until the earliest of any events requiring treatment discontinuation as defined in Section 6.8.4.4 or Section 6.12.

Note: If medically appropriate, subjects allocated to combination doublet therapy may continue with protocol-specified therapy for the therapeutic agent (LAM-002A, rituximab, or atezolizumab) that continues to be tolerated, even if the other agent need to be discontinued due to drug-specific toxicity.

Subjects who have discontinued study treatment for reasons other than PD will be assessed per Revised Response Criteria for NHL or Guidelines for the diagnosis and treatment of CLL at a minimum of every 12 weeks until documentation of PD, start of new anti-cancer therapy or for up to 1 year from the last enrolled subject's first treatment (Cycle 1 Day 1), whichever comes first. Long-term follow-up survival information will be obtained in all surviving subjects who permanently discontinue study therapy. Such information may be collected at ~3- to 6-month intervals at the sponsor's discretion through 3 years. This long-term follow-up information will be gathered during routine clinic visits, other study site contact with the subjects, or via telephone or e-mail with the subjects/caregivers or referring physician offices.

Section 6.12. Criteria for Subject Withdrawal from Study Treatment or Study Participation ~~Study Termination~~

Change: This section of the protocol was modified to focus on potential reasons for subject withdrawal from study treatment or study participation. A later section dealing with potential study termination was updated.

~~The sponsor may terminate this study at any time, provided a written notice is submitted at a reasonable time in advance of the intended termination.~~

Subjects may be withdrawn from further study treatment for any of the following reasons:

- Subject withdrawal of informed consent
- Disease progression of cancer while receiving study therapy ***Note: Apparent worsening of disease during temporary interruption of study therapy (e.g., for drug-related toxicity or intercurrent illness) may not indicate true cancer progression. Study subjects undergoing PET for lymphoma assessment can experience transient disease flare on imaging before having subsequent therapy-induced tumor regression. Worsening of constitutional symptoms or performance status in the absence of objective evidence of worsening lymphoma (e.g., due to infection) may not represent definitive disease progression. For these reasons, if there is uncertainty regarding whether there is true disease progression and if medically appropriate, the subject may continue or resume study treatment and remain under close observation (e.g., evaluated at 4- to 8-week intervals) while relevant radiographic, clinical, and/or laboratory assessments are performed to document whether tumor control can be maintained or whether disease***

progression has truly occurred. If subsequent evaluations suggest that the subject has experienced persistent definitive disease progression, then the date of progression will be the timepoint at which progression was first objectively documented.

- Unacceptable study-drug-related toxicity despite appropriate dose modification
- Development of intercurrent illness that precludes continued study therapy
- Physician decision that continuation is not in the subject's best interest
- Treatment of the cancer with another therapeutic regimen
- Subject becomes pregnant or begins breastfeeding
- Substantial noncompliance with study drug administration, study procedures, or study requirements in circumstances that increase risk or substantially compromise the interpretation of study results
- Termination of the study by the sponsor, relevant regulatory agencies, or the IRB/IEC

The investigator must determine the primary reason for a subject's withdrawal from the study and record this information on the electronic case report form (eCRF).

Unless they withdraw consent for further follow-up, subjects who discontinue study therapy will continue on study for acquisition of safety information through ≥30 days after the last dose of study treatment, and for further collection of long-term information regarding survival.

Section 6.13. Replacement of Subjects

Change: Because Stage 1 focuses on DLT evaluability and Stage 2 focuses on efficacy evaluability, the information in this section was updated and cross-referenced to relevant sections of the protocol.

6.13. Replacement of Subjects

Subjects not meeting the criteria for evaluability defined in Section 6.1.3 may be replaced at the discretion of the sponsor. ~~Subjects who are withdrawn from study treatment prior to completing Cycle 1 dosing for reasons other than DLT will be replaced so that a full cohort of subjects completes Cycle 1 safety evaluations.~~ If a subject needs to be replaced, ~~the site will notify the Sponsor for the need of a replacement;~~ the associated subject ID will not be used.

Section 7. SELECTION ~~AND WITHDRAWAL~~ OF SUBJECTS

Changes: The description of withdrawal of subjects was moved to Section 6.12. Subject selection criteria were updated as follows:

- *On mechanistic grounds, PMBL may respond to LAM-002A therapy; for this reason, patients with this type of lymphoma were permitted to be accrued to the dose-ranging portion of the trial.*

- *A requirement for prior rituximab therapy was no longer mandated given that some patients (eg, those with CLL/SLL) may not have received rituximab as prior therapy based on changing standards of care.*
- *Organ function criteria for hematological function, hepatic function, and renal function were updated based on the evolving safety profile of LAM-002A showing that the drug is unlikely to adversely alter these organ systems.*
- *The contraception enrollment criteria were made more specific, referencing protocol-recommended contraceptive measures now described in Section 6.10.2.*
- *The requirements for disease biopsy timing and baseline bone marrow collection in patients with lymphoma were clarified.*
- *Prior therapy prohibitions were included for study candidates under consideration for combination therapy to minimize the likelihood that they have disease that might be totally resistant to rituximab or atezolizumab.*
- *Included were restrictions on use of live virus vaccines, ongoing therapy for HBV, recent therapy with immunostimulatory agents, ongoing use of immunosuppressive therapies, recent serious infection, a history of autoimmunity, or inability to tolerate required supportive care; these exclusions were intended to enhance subject safety and to avoid comorbid conditions that could confuse interpretation of safety findings.*
- *The requirements relating to baseline serological testing for chronic viral infections were clarified.*

7.1. Subject Inclusion Criteria

1. The subject is capable of understanding and complying with the protocol requirements and has signed the informed consent document. The subject is able to provide signed and dated informed consent prior to initiation of any study-specific procedures.
2. Subjects must have a histologically confirmed diagnosis of B-cell NHL limited to FL, DLBCL, MCL, MZL, **primary mediastinal B-cell lymphoma (PMBL),** or CLL/SLL according to the World Health Organization (WHO) classification, that has progressed and for which standard curative measures do not exist or are no longer effective~~. Prior therapy must have included a rituximab-based chemoimmunotherapy regimen.~~
3. Subjects with DLBCL must have progressed after transplant, or be unwilling, unable or not an appropriate candidate for an autologous stem cell or bone marrow transplant.
4. Subjects must have radiographically measurable lymphadenopathy or extranodal lymphoid malignancy (defined as the presence of ≥ 1 lesion that measures ≥ 2.0 cm in the longest dimension [LD] and ≥ 1.0 cm in the longest perpendicular dimension [LPD] as assessed radiographically).
5. The subject is ≥ 18 years old.
6. The subject has an Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 2.

7. The subject has organ and marrow function as follows:
   a. Absolute neutrophil count (ANC) ≥ 1.0 × 10^9/L (1,000/mm^3) **without hematopoietic-stimulating factor support**
   b. Platelets ≥ ~~75~~ **50** × 10^9/L (**50**~~75~~,000/mm^3)
   c. Total bilirubin ≤ 1.5 x the upper limit of normal (ULN**) except for subjects with known Gilbert disease (total bilirubin ≤ 3 x ULN permitted)**
   d. Serum creatinine ≤ 1.5 x ULN or calculated creatinine clearance ≥ 60 mL/**min (based on the Cockcroft-Gault formula)**
   e. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x ULN if no liver involvement, or ≤ 5 x ULN with liver involvement
   f. Albumin ≥ 2 g/dL

   Note: Grade ≥ 3 neutropenia or thrombocytopenia is permitted if the abnormality is related to bone marrow involvement with hematological malignancy (as documented by bone marrow biopsy/aspirate obtained since the last prior therapy).
8. The subject has the ability to swallow oral capsules without difficulty.
9. Sexually active subjects (men and women), even if on oral contraceptives, must agree to **remain abstinent (refrain from heterosexual intercourse) or use appropriate contraceptive methods (see Section 6.10.2) during the treatment period and for 5 months after the last dose of study therapy** ~~use medically-accepted barrier methods of contraception (e.g., male condom, female condom, or diaphragm with spermicidal gel) during the course of the study and for 3 months after the last dose of study drug~~.
10. Women of childbearing potential (WCBP) must have a negative serum or urine pregnancy test at screening. WCBP include any woman who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal. Postmenopausal is defined as:
    a. Amenorrhea ≥ 12 consecutive months without another cause or
    b. For women with irregular menstrual periods and on hormone replacement therapy, a documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL
11. <u>For subjects with lymphoma</u>: The subject has archived tumor tissue for analysis **that was obtained within 4 months prior to the start of screening;** ~~or~~ is willing to undergo a pretreatment core needle, excisional, or incisional biopsy of a lymphoma nodal lesion; **or is willing to undergo a pretreatment bone marrow aspirate if there is known bone marrow involvement (≥ 50% NHL cells)**.
12. <u>For subjects with CLL/SLL</u>: The subject has sufficient circulating cells in the peripheral blood (e.g., ALC ≥ 10 x 10^9/L) or is willing to undergo a pretreatment bone marrow aspirate to obtain CLL cells.

7.2 Subject Exclusion Criteria

1. Subjects with central nervous system (CNS) lymphoma are not eligible for the trial unless the disease had been treated and the subject remained asymptomatic (for at least 6 months) with no active CNS lymphoma, as determined by lumbar puncture, computed tomography scan (CT), or magnetic resonance imaging (MRI).
2. The subject has received cytotoxic chemotherapy (including investigational cytotoxic chemotherapy) within 3 weeks, or nitrosoureas/ mitomycin C within 6 weeks before the first dose of study treatment.
3. The subject has received treatment with a therapeutic antibody less than 4 weeks before the first dose of study treatment. For subjects with rapidly progressive or aggressive subtypes of lymphoma, a minimum period of 2 weeks between the last treatment with a therapeutic antibody and the first dose of study treatment may be permitted following discussion with the medical monitor.
4. The subject has received radioimmunotherapy within 6 weeks of the first dose of study treatment.
5. The subject has received radiation therapy within 14 days of the first dose of study treatment.
6. The subject has received prior treatment with a small-molecule kinase inhibitor or other small-molecule investigational agent within 14 days or 5 half-lives of the compound or active metabolites, whichever is greater, before the first dose of study treatment.
7. **Stage 2 (study candidates being considered for LAM-002A/rituximab combination therapy): Best overall response with the last regimen containing an anti-CD20 antibody (eg, rituximab, ofatumumab, obinutuzumab) was disease progression.**
8. **Stage 2 (study candidates being considered for LAM-002A/atezolizumab combination therapy): Prior exposure to a CD137 agonist or an immune checkpoint inhibitor, including an anti-PD1, anti-PDL1, or anti-CTLA4 therapeutic antibody.**
9. **Stage 2 (study candidates being considered for LAM-002A/atezolizumab combination therapy): treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the last dose of atezolizumab.**
10. **Stage 2 (study candidates being considered for LAM-002A/atezolizumab combination therapy): Current treatment with anti-viral therapy for hepatitis B virus (HBV).**
11. **Stage 2 (study candidates being considered for LAM-002A/atezolizumab combination therapy): Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks**

or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment.

12. The subject is currently receiving treatment with strong inhibitors or inducers of CYP450 2C9 or 3A4 enzymes.

13. The subject is chronically receiving immunosuppressive therapy **(eg, with cyclophosphamide, azathioprine, thalidomide, lenalidomide, methotrexate, or anti-TNF-α agents) within 2 weeks prior to initiation of study treatment** or requires systemic or enteric corticosteroids**at the time of starting study therapy.** Study candidates using **systemic low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency or** topical, intra-articular, nasal, or inhaled corticosteroids are not excluded from study participation. ***Note: During study therapy, subjects may use systemic, enteric, topical, intraarticular, nasal, or inhaled corticosteroids as required*** *by protocol or* ***for treatment-emergent conditions***.

14. The subject has not recovered from toxicity due to all prior therapies (i.e., return to pre-therapy baseline or to Grade 0 or 1). Persistent > Grade 1 toxicity from prior therapy will be considered by the sponsor for inclusion if there is no evidence of an overlapping apilimod toxicity.

15. The subject has uncontrolled significant intercurrent illness including, but not limited to, ongoing or active infection, history of congestive heart failure within 6 months, hypertension, unstable angina pectoris within 6 months, stroke within 6 months, myocardial infarction within 6 months, or cardiac arrhythmias. (Controlled chronic atrial fibrillation will not be excluded).

16. Severe uncontrolled infection within 2 weeks prior to initiation of study treatment, including hospitalization for complications of infection, bacteremia, or severe pneumonia or treatment with therapeutic oral or IV antibiotics. ***Note: subjects receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are not excluded***.

17. **Stage 2 (study candidates being considered for LAM-002A/atezolizumab combination therapy): Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (with the following exceptions: history of autoimmune-related hypothyroidism and receiving thyroid-replacement hormone; controlled Type 1 diabetes mellitus on an insulin regimen; eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations if rash covers covers < 10% of body surface area, disease is well controlled at baseline and requires only low-potency topical corticosteroids, there is no occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months, and the subject does not have extra-cutaneous disease [e.g., psoriatic arthritis]).**

18. The subject has a history of malabsorption or other GI disease that may significantly alter the absorption of apilimod (e.g., ≥ Grade 2 nausea, vomiting or diarrhea).
19. The subject has undergone major surgery within 28 days prior to first dose of study drug.
20. The subject has a QTcF > 470 msec on screening ECG or has a history or risk factors for, or use of medications known to prolong QTc interval or that may be associated with Torsades de Pointes within 7 days of treatment start.
21. The subject has past history of tuberculosis (TB) or active infection with TB, human immunodeficiency virus (HIV), hepatitis B **virus (HBV)** or hepatitis C **virus (HCV).** ***Note:* Subjects must have *negative human immunodeficiency virus (HIV) antibody, negative hepatitis B surface antigen (HbsAg) and negative hepatitis B core (HBc) antibody or undetectable HBV deoxyribonucleic acid (DNA) by quantitative polymerase chain reaction (PCR) testing, and negative HCV antibody or negative HCV ribonucleic acid (RNA) by quantitative PCR.***
22. The subject is lactating and breast feeding.
23. The subject has a previously identified allergy or hypersensitivity to components of the study treatment formulation.
24. **Stage 1 (study candidates being considered for LAM-002A intermittent administration): Known inability to tolerate the protocol-specified antiemetic and antidiarrheal supportive care regimen.**
25. The subject is unable or unwilling to abide by the study protocol or cooperate fully with the investigator or designee.
26. The subject has a history of other medical or psychiatric illness or organ dysfunction which, in the opinion of the investigator, would either compromise the subject's safety or interfere with the evaluation of the safety of the study agent.
27. The subject has a history of prior cancer (not under study) that has not been in remission for at least 3 years. The following are exempt from the 3-year limit: basal cell or squamous cell carcinoma of the skin, localized prostate cancer with normal Prostate Specific Antigen (PSA), cervical cancer in situ or other in situ carcinomas.

Section 8. METHODS OF ASSESSMENT AND ENDPOINTS

Change: The following changes were made:

- *Information regarding pretreatment tumor tissue assessment was updated.*
- *All schedules of assessment tables were consolidated into Section 8.*
- *Methods of assessment were updated in text, tables, and table footnotes to enhance clarity and to ensure consistency with the updated exploratory endpoints described in Section 5. Schedules of assessment specific for LAM-002A continuous monotherapy, LAM-002A intermittent monotherapy, LAM-002A/rituximab combination therapy, and LAM-002A/atezolizumab combination therapy were included.*

- *Information regarding concomitant medications and supportive care was removed from Section 8 and updated and consolidated in Section 6.9.*

Only the sections in which changes were made are displayed below.

8. METHODS OF ASSESSMENT AND ENDPOINTS

~~All trial data will be recorded on the eCRFs. Timing of study procedures are listed in Section Deleted: Schedule of Assessments.~~ **All trial data will be recorded on the eCRFs. Timing of study procedures are listed in schedules of assessments tables – Table 8: Schedule of Assessments (LAM-002A Continuous Monotherapy Administration), Table 9: Schedule of Assessments (LAM-002A Intermittent Monotherapy Administration), Table 10: Schedule of Assessments (LAM-002A/Rituximab Combination Therapy), and Table 11: Schedule of Assessments (LAM-002A/Atezolizumab Combination Therapy) in Section 8.7.**

8.1.5. Disease Status Assessment for Subjects with NHL

Pretreatment tumor assessments will be performed within 30 days of the first dose of study treatment and will include diagnostic CT scans (with intravenous contrast) or Positron Emission Tomography (PET)/Computerized Tomography Scans (CT scan) for patients with lymphoma, bone marrow aspirate/biopsy, complete blood counts and physical examination. It is anticipated that in most cases the PET/CT scans will be conducted using a single instrument, i.e., as a PET/CT scan (CT scans should be performed using a contiguous reconstruction algorithm of ≤ 5 mm). However, MRI is an acceptable alternative method for assessing disease in subjects who cannot receive intravenous contrast with CT scans. In such subjects MRI and PET scans will have to be obtained separately.

Suitable scans performed prior to screening and within 30 days before first dose may be used for baseline tumor assessments. Similarly bone marrow biopsies/aspirates performed within 2 months prior to first dose may be used for baseline assessments. For subjects with NHL, baseline bone marrow biopsies/aspirates may be omitted if not deemed essential for response assessment or patient management **and there is another source of tumor tissue for pretreatment evaluation of gene expression and prognosis.** For subjects with CLL/SLL, a baseline bone marrow aspirate is required unless the presence of sufficient circulating cells in the peripheral blood (e.g., ALC ≥ 10 x 10^9/L) permits assessment of baseline parameters for gene expression and prognosis. Details of assessments will be collected on the eCRF and must be filed in the subject's medical record.

Archival tissue from the most recent available biopsy or surgery or fresh tumor tissue **(preferred)** must be obtained pretreatment **for nucleic acid extraction**. For subjects undergoing a biopsy, adequate tumor tissue should be acquired via excisional biopsy, incisional biopsy or core needle biopsy (e.g., ≥ 3 passes using a 16-gauge core needle). Alternatively, cells from a bone marrow aspirate may be obtained in subjects with bone marrow involvement due to NHL **(≥50% of cells)**. Tissue will be submitted for evaluation of the percentage of tumor cells and analysis of genetic alterations and/or gene expression that may predict anti-lymphoma activity and/or pharmacodynamics activity.

In addition, tumor **tissue from the most recently availably biopsy or surgery will**~~may~~ be evaluated for known prognostic characteristics (e.g., for DLBCL: ABC or GCB subtype; expression of BCL2, BCL6, Ki-67, CD20, and MYC; other mutational status)**, for PDL1 status,**

and for immune infiltration. The baseline biopsy procedure (if required) should ideally be performed after the study candidate has undergone the baseline radiology examination and is otherwise considered eligible for study participation..

8.2.4. Electrocardiogram

A 12-lead ECG with subject resting for 5 minutes will be done at Screening. Additional ECGs will be conducted **Table 8: Schedule of Assessments (LAM-002A Continuous Monotherapy Administration), Table 9: Schedule of Assessments (LAM-002A Intermittent Monotherapy Administration), Table 10: Schedule of Assessments (LAM-002A/Rituximab Combination Therapy), and Table 11: Schedule of Assessments (LAM-002A/Atezolizumab Combination Therapy) in Section 8.7** ~~prior to the start of each cycle, prior to each PK time point (except for 30 minutes and 6 hours) on Day 1 and Day 8, at the End of Treatment,~~ and more often if clinically indicated. Parameters measured will include heart rate, PR, QRS, QT, and QTc intervals (calculated by the Fridericia correction formula. Bazett's correction is acceptable if institutional policy). See Section 12 for PK time points. The ECGs will be reviewed and signed by the investigator.

8.3.1.1 Hematology

Hemoglobin, hematocrit, WBC count with differential, red blood cell (RBC) count, and platelet count will be collected ~~at Screening and Days 1, 8, and 15 of Cycles 1 and 2 then at least once prior to start of all subsequent cycles and at **EOT**~~**according to the relevant schedule of events; see Table 8: Schedule of Assessments (LAM-002A Continuous Monotherapy Administration), Table 9: Schedule of Assessments (LAM-002A Intermittent Monotherapy Administration), Table 10: Schedule of Assessments (LAM-002A/Rituximab Combination Therapy), and Table 11: Schedule of Assessments (LAM-002A/Atezolizumab Combination Therapy) in Section 8.7.**

Coagulation parameters (aPTT [or PTT] and INR) should be performed at Screening.

8.3.1.2 Blood Chemistry

Albumin, alkaline phosphatase (ALP), total bilirubin, calcium, carbon dioxide, chloride, creatinine, glucose, inorganic phosphorus, potassium, total protein, ALT, AST, lactate dehydrogenase (LDH), sodium, BUN, and uric acid will be collected **according to the relevant schedule of events; see Table 8: Schedule of Assessments (LAM-002A Continuous Monotherapy Administration), Table 9: Schedule of Assessments (LAM-002A Intermittent Monotherapy Administration), Table 10: Schedule of Assessments (LAM-002A/Rituximab Combination Therapy), and Table 11: Schedule of Assessments (LAM-002A/Atezolizumab Combination Therapy) in Section 8.7.** ~~at Screening and Days 1, 8, and 15 of Cycles 1 and 2 then at least once prior to start of all subsequent cycles and at EOT.~~ If the total bilirubin concentration is > 1.5 times the upper normal limit, total bilirubin should be differentiated and the total and direct bilirubin should be reported.

~~8.6 Concomitant Medications and Supportive Care~~

~~Information on concomitant medications and other treatments will be collected from 14 days prior to informed consent through 30 37 days after the last dose of study drug.~~

~~8.6.1. Antineoplastic Medications/Therapy~~

~~Antineoplastic Therapy: Other chemotherapy, investigational agents or biologic therapy will not be permitted during the study.~~

~~Palliative radiotherapy for local peripheral metastases not being used as target lesions is allowed. However, the need for such therapy may be an indication of disease progression and should be discussed with the Sponsor prior to implementation. Radiotherapy for central metastases (e.g., vertebral, mediastinal) will not be allowed; the need for such radiotherapy while on therapy will be seen as an indication of disease progression and the subject should be withdrawn from therapy.~~

~~8.6.2. Growth Factors~~

~~Hematopoietic Growth Factors: Subjects receiving hematopoietic growth factors such as erythropoietin prior to study start may continue to receive pre-treatment doses.~~

~~The use of erythropoietic and granulocyte growth factors in accordance with American Society of Clinical Oncology (ASCO) guidelines may be implemented during study treatment at the discretion of the treating physician.~~

~~8.6.3. Other Concomitant Medications~~

~~Bisphosphonates: Bisphosphonates are permitted if a subject was receiving ongoing bisphosphonate therapy at time of screening and will continue on a stable regimen throughout protocol therapy. The need to start bisphosphonates while on therapy may be an indication of disease progression and should be discussed with the Sponsor prior to implementation.~~

~~Anticoagulants: Apilimod is highly protein bound; therefore, the Investigator is cautioned about the use of therapeutic doses of sodium warfarin.~~

~~Corticosteroids: Subjects may be using topical, intra-articular, nasal, or inhaled corticosteroids at study entry and may use such drugs during therapy. The use of systemic or enteric corticosteroids is precluded at study entry because such drugs may confound interpretation of pharmacodynamic, immunological, or toxic responses in subjects on this study. However, such drugs are permitted if a subject develops intercurrent conditions that require corticosteroid therapy.~~

~~Medications for the treatment of AEs or cancer symptoms, e.g., packed red blood cells and pain medications, are allowed. Measures to prevent potential tumor lysis syndrome are allowed per institutional guidelines. Additionally, medications (not addressed above) used to treat underlying medical conditions at study entry (including anti-emetics and anti-diarrheals) will be allowed to continue.~~

~~Vaccines: Administration of live vaccines is prohibited during the study.~~

~~8.7. Drug Interactions~~

~~Drug Interactions: No information is available regarding interactions of LAM-002A (apilimod dimesylate capsules) with therapeutic agents or other substances in humans. *In vitro* data suggest that concomitant administration of potent inhibitors or inducers of CYP3A4 or CYP2C9 might alter apilimod dimesylate clearance and lead to clinically significant increases or decreases in~~

~~apilimod dimesylate exposure. Consequently, the concomitant use of strong inhibitors or inducers of CYP3A4 or CYP2C9 (see Table 7) should be avoided when possible.~~

~~Based on these considerations, protocol candidates who require therapy with strong CYP3A4 or CYP2C9 inhibitors or inducers listed in Table 7 should not be enrolled into the study.~~

~~During study participation, coadministration of apilimod dimesylate with CYP3A4 or CYP2C9 inhibitors or inducers (see Table 7) should be avoided, if possible. However, a subject who develops a condition that may require use of such drugs is not required to permanently discontinue apilimod dimesylate if the subject is experiencing clinical benefit and other options for treating the subject's cancer are limited. If medically appropriate, investigators may wish to use a therapeutic alternative that would not be expected to affect these enzymes. For subjects who require temporary use of a drug that does affect these enzymes (e.g., treatment with a systemic antifungal agent), apilimod dimesylate can be interrupted (or the doses reduced) during use of the other medication and then resumed after completion of the other drug. For subjects who require initiation of chronic therapy with a drug that potently affects these enzymes, investigators must consult with the medical monitor to consider the best course of action.~~

~~Medications that prolong QT_C and/or cause Torsades de pointes should be avoided (See Table 8).~~

~~See Appendix 3 for additional information.~~

8.6. Treatment Compliance

Change: The minimum requirement for DLT evaluability was included for subjects taking LAM-002A on the intermittent schedule.

The investigator will dispense the study medication only for use by subjects enrolled in the study as described in this protocol. The study medication is not to be used for reasons other than those described in this protocol.

The investigator or other study staff will supervise LAM-002A treatment given at the site and instruct the subject on study medication self-administration. Subjects will be asked to bring their dosing diary with them at each visit. Compliance with protocol-defined LAM-002A intake will be checked by pill count at the end of each cycle and compliance decisions will be made by the investigator.

A subject is considered to be DLT-evaluable if he/she has taken at least 75% (42/56 BID schedule; 63/84 TID schedule**, 18/24 intermittent schedule**) of the planned first cycle doses and has sufficient safety data, or has experienced a DLT in the first cycle.

Section 8.7 Schedules of Assessments

Change: Previous schedule of assessments (Table 6, previously in Section 6) was deleted and separate tables were included that were specific for LAM-002A continuous monotherapy, LAM-002A intermittent monotherapy, LAM-002A/rituximab combination therapy, and LAM-002A/atezolizumab.

Table 6: Schedule of Assessments

Assessment	Screening	Cycle 1					Cycle 2			Cycle ≥ 3		End of Treatment (EOT)	Long Term F/U
		Day					Day			Day			
	28 to 1	1	2	3	8	15	1	8	15 28	1	15 28		
Informed consent	X												
Inclusion/exclusion criteria	X	X[a]											
Demographics	X												
Medical history	X												
Signs and Symptoms, PE[b]	X	X[e]					X			X		X	
ECOG Performance Status	X	X[e]					X			X		X	
Vital signs	X	X[d]			X[d]	X[d]	X			X		X	
ECG	X	X[d]			X[d]	X[d]	X			X		X	
HIV, HBV, and HCV serology	X												
Hematology[e, f]	X	X			X	X	X	X	X	X		X	
Serum chemistry[f, g]	X	X	X[f]	X[f]	X	X	X	X	X	X		X	
Coagulation	X	–											
Urinalysis[h]	X	X[e]					X			X		X	
Pregnancy testing[i]	X	X[i]					X			X		X	
PET/CT or CT (or MRI) scans (based on indication) for response assessment	X[j]								X[k]		X[k]	X[l]	
CLL baseline assessments[m]	X												
PK sampling[n] + Analyte		X			X	X							

Table 6:: Schedule of Assessments (Continued)

Assessment	Screening	Cycle 1					Cycle 2			Cycle ≥ 3		End of Treatment (EOT)	Long-Term F/U
		Day					Day			Day			
	-28 to -1	1	2	3	8	15	1	8	15-28	1	15-28		
Bone marrow aspirate/biopsy	X[o]								X[p, q]		X[p]		
Biomarker – tumor tissue	X[q]												
Biomarker – blood smears[r]		X			X	X							
Biomarker – plasma cytokines[s]		X			X	X							
Biomarker – PBMC[t]		X			X								
Biomarker – saliva[u]		X											
LAM-002A administration		X	X	X	X	X	X	X	X	X	X		
Adverse events		Throughout Study											
Concomitant medications[v]		Throughout Study											
Long-term follow-up (F/U)[w]													X

a Eligibility will be confirmed by Cycle 1 Day 1.

BComplete physical examination (PE) will be performed at screening. A directed PE, including weight, will be performed within 72 hours prior to the start of each cycle and EOT.

CAssessment/test does not need to be repeated on C1D1 if baseline was within normal limits and conducted within 72 hours of first dose.

D Obtained on Day 1 prior to dosing for all Cycles. For C1D1 and C1D8 obtained prior to dosing and 1 hour (± 15 min after dosing), 2 hours (± 30 min), 4 hours (± 1h), and 8 hours (± 1h) postdose. For C1D15, obtained prior to dosing.

E Hematology includes hemoglobin, hematocrit, RBC count, platelet count, WBC and differential.

F All hematology and chemistry laboratory parameters should be assessed at Screening and Days 1, 8, and 15 of Cycles 1 and 2, and then at least once prior to the start of all subsequent cycles and at EOT. Obtaining a chemistry laboratory parameter on Days 2 and Day 3 of Cycle 1 is only required in subjects with intermediate or high risk of TLS (per the risk definition in Section 6.8.1). Except for Days 1, 2, and 3 of Cycle 1, these parameters may be obtained within 72 hours prior to the planned day of collection. Abnormal test values should be monitored per protocol guidance.

G Chemistry includes albumin, alkaline phosphatase, total bilirubin, BUN, calcium, carbon dioxide, chloride, creatinine, glucose, inorganic phosphorus, potassium, total protein, LDH, ALT, AST, sodium, and uric acid.

H Urinalysis includes appearance, specific gravity and pH as well as a semi-quantitative "dipstick" evaluation of glucose, protein, bilirubin, ketones, leukocytes, and blood. Microscopic examination of sediment will be performed if urinalysis is positive for WBC, proteins or blood. Urinalysis may be obtained within 72 hours prior to the planned day of collection.

I Pregnancy testing (serum or urine) will be required for women of childbearing potential (WCBP) only. Testing is required at Screening; within 72 hours of Day 1 of each Cycle and at EOT. Test does not need to be repeated on C1D1 if baseline was negative and conducted within 72 hours of first dose.

J Imaging as appropriate for disease indication will be conducted within 30 days of the first dose of study treatment. Suitable scans performed prior to screening and within 30 days before first dose may be used for baseline tumor assessments.

K Assessment of disease status will be conducted with standard clinical measurements: PE, CBCs, bone marrow aspirates/biopsies, and imaging as appropriate for indication. During treatment, scans will be repeated for tumor assessment within 7 days of Day 1, Cycles 3, 5, and 7 then every 3 months until PD or use of alternative antineoplastic therapy. For subjects still in response after 1 year, intervals for radiographic surveillance may be every 6 months. Subjects with CLL who achieve CR will require assessment of MRD by flow cytometry of bone marrow and peripheral blood.

L Imaging at EOT is not required if PD has already been radiographically documented or last imaging was within 30 days of EOT visit.

M Subjects with CLL/SLL must provide either a fresh blood sample containing circulating tumor cells or a bone marrow aspirate sample pretreatment. Tissue will be submitted for evaluation of the percentage of tumor cells and analysis of genetic alterations and/or gene expression that may predict anticancer activity and/or pharmacodynamic activity. In addition, for subjects with CLL/SLL, the sponsor may arrange for a portion of the sample to be evaluated at a sponsor-specified laboratory for known prognostic markers (e.g., quantitative immunoglobulins, FISH panel [chromosome 11q deletion, 13q deletion, 17p deletion and 12 trisomy], DNA mutational analysis for p53, IgHV [including IgHV3-21], and other genes of interest in CLL [e.g., Notch]; flow cytometry [for CD5, CD10, CD11c, CD19, CD20, CD23, CD38, CD45, kappa and lambda light chains and ZAP-70], and/or β2-microglobulin). The baseline bone marrow aspiration procedure (if required) should be performed after the study candidate has undergone the baseline radiology examination and is otherwise considered eligible for study participation. All subjects with CLL/SLL must have baseline imaging (with CT scans [preferred] or MRI scans).

N Blood sampling for determination of the plasma concentrations of apilimod and metabolites will be performed on C1D1 and C1D8 as follows: pre-dose, 30 minutes, 1, 2, 4, 6, 8 hours post-first dose of the day. C1D15 pre-dose only. Additional PK samples will be collected, if possible, whenever a subject has a study treatment-related SAE or QTc > 500 msec. Subjects are required to come to the study site in a fasting state prior to the collection of certain PK samples. For analyte determination, PK back-up sample will be used from time points: Cycle 1 Day 1 and Cycle 1 Day 8 pre-dose.

O Bone marrow aspirates/biopsies performed within 2 months prior to first dose may be used for clinical baseline assessments. For subjects with NHL, baseline bone marrow biopsies/aspirates may be omitted if not deemed essential for response assessment or patient management. For subjects with CLL/SLL, a baseline bone marrow aspirate is required unless the presence of sufficient circulating cells in the peripheral blood (e.g., absolute lymphocyte count [ALC] ≥ 10 x 109/L) permits assessment of baseline parameters as described in Footnote m, above.

P If necessary per applicable response criteria, a repeat bone marrow biopsy or aspirate will be required for subjects who have a CR by imaging and physical examination.

Q Archival or fresh tumor tissue from the most recent available biopsy or surgery prior to first dose in subjects with NHL must be obtained pretreatment. For subjects undergoing a biopsy, adequate tumor tissue should be acquired via excisional biopsy, incisional biopsy or core needle biopsy (e.g., ≥ 3 passes using a 16-gauge core needle). Alternatively, cells from a bone marrow aspirate may be obtained in subjects with bone marrow involvement due to NHL. Tissue will be submitted for evaluation of the percentage of tumor cells and analysis of genetic alterations and/or gene expression that may predict anti-lymphoma activity and/or pharmacodynamics activity. In addition, for subjects with NHL, tumor may be evaluated for known prognostic characteristics (e.g., for DLBCL: ABC or GCB subtype; expression of BCL2, BCL6, Ki-67, CD20, and MYC; other mutational status). The baseline biopsy procedure (if required) should be performed after the study candidate has undergone the baseline radiology examination and is otherwise considered eligible for study participation.

R Blood smears will be collected for microscopic evaluation of vacuole formation on C1D1 and C1D8 as follows: pre-dose, 4 hours and 8 hours post-first dose of the day. C1D15 pre-dose only.

S Plasma will be collected for evaluation of circulating cytokines (including IL-12 and IL-23) predose on each of Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 1 Day 15.

T PBMCs will be collected on Cycle 1, Day 1 pre-treatment; on Cycle 1, Day 1 at 8 hours post-dose; and on Cycle 1, Day 8 at 8 hours post-dose for determination of changes in gene expression that may predict or correlate with anti-lymphoma activity and/or pharmacodynamic activity.

U. Saliva will be obtained pre-dose on Cycle 1 Day 1 as a normal tissue control for gene mutation studies in tumors.

V. Information on concomitant medications and other treatments will be collected from 14 days prior to informed consent through 30-37 days after the last dose of study drug.

W. Subjects who have discontinued study treatment for reasons other than PD will be assessed per Revised Response Criteria for NHL or Guidelines for the diagnosis and treatment of CLL at a minimum of every 12 weeks until documentation of PD, start of new anti-cancer therapy or for up to 1 year from the last enrolled subject's first treatment (Cycle 1 Day 1) whichever comes first. Long-term follow-up survival information will be obtained in all surviving subjects who permanently discontinue study therapy. Such information may be collected at ~3- to 6-month intervals at the sponsor's discretion through 3 years. This long-term follow-up information will be gathered during routine clinic visits, other study site contact with the subjects, or via telephone or e-mail with the subjects/caregivers or referring physician offices.

Abbreviations: ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; CBCs: Complete blood counts; CD: Cluster of differentiation; CLL: Chronic lymphocytic leukemia; CR: Complete response; CT: Computerized tomography; ECG: Electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOT: End of treatment; FISH: Fluorescence *in situ* hybridization; h: Hour; hrs: Hours; LDH: Lactate dehydrogenase; min: Minutes; MRD: Minimal residual disease; MRI: Magnetic Resonance Imaging; PBMC: Peripheral blood mononuclear cell; PD: Progressive disease; PE: Physical exam; PET: Positron emission tomography; PK: Pharmacokinetics; QTc: Corrected QT interval; RBC: Red blood cell; SAE: Serious adverse event; WBC: White blood cell; WCBP: Women of child bearing potential

Table 8: Schedule of Assessments (LAM-002A Continuous Monotherapy Administration)

Assessment	Screening	Cycle 1 Day					Cycle 2 Day		Cycle ≥ 3 Day		End of Treatment (EOT)	Long-Term F/U
	-28 to -1	1	2	3	8	15	1~~8~~	15-28	1	15-28		
Informed consent	X											
Inclusion/exclusion criteria	X	X[a]										
Demographics	X											
Medical history	X											
Signs and symptoms, PE[b]	X	X[c]					X		X		X	
ECOG performance status	X	X[c]					X		X		X	
Vital signs	X	X[d]			X[d]	X[d]	X		X		X	
ECG	X	X[d]			X[d]	X[d]	X		X		X	
HIV, HBV, and HCV serology	X											
Hematology[e, f]	X	X			X	X	X~~X~~	~~X~~	X		X	
Serum chemistry[f, g]	X	X	X[f]	X[f]	X	X	X~~X~~	~~X~~	X		X	
Coagulation	X											
Urinalysis[h]	X	X[c]					X		X		X	
Pregnancy testing[i]	X	X[i]					X		X		X	
PET/CT or CT (or MRI) scans (based on indication) for response assessment	X[j]							X[k]		X[k]	X[l]	
CLL baseline assessments[m]	X											
PK/**PD plasma** sampling[n] ~~+ analyte~~		X			X	X						
Bone marrow aspirate/biopsy	X[o]							X[p, ~~q~~]		X[p]		
Biomarker – tumor tissue	X[q]											
Biomarker – **plasma tumor DNA**~~blood smears~~ [r]		X			~~X~~	X					**X**	
Biomarker – plasma cytokines[s]		X			X	X						
Biomarker – PBMC/**B cell**[t]	**X**	~~X~~			~~X~~							
Biomarker – saliva[u]	**X**	~~X~~										
LAM-002A administration **in clinic**[v]		X	~~X~~	~~X~~	X	X	~~XX~~	~~X~~	~~X~~	~~X~~		
Adverse events		Throughout Study										
Concomitant medications[w]		Throughout Study										
Long-term follow-up (F/U)[x]												X

a Eligibility will be confirmed by C1D1.

B Complete physical examination (PE) will be performed at screening. A directed PE, including weight, will be performed within 72 hours prior to the start of each cycle and EOT.

C Assessment/test does not need to be repeated on C1D1 if baseline was within normal limits and conducted within 72 hours of first dose.

D Obtained on Day 1 ~~prior to dosing~~ for all cycles. For C1D1 and C1D8 obtained prior to dosing and 1 hour (± 15 minutes after dosing), 2 hours (± 30 minutes), 4 hours (± 1 hour), and 8 hours (± 1 hour) postdose. For C1D15, obtained prior to dosing.

E Hematology includes hemoglobin, hematocrit, RBC count, platelet count, WBC and differential.

F All hematology and chemistry laboratory parameters should be assessed at Screening and Days 1, 8, and 15 of Cycles 1 and 2, and then at least once prior to the start of all subsequent cycles and at EOT. Obtaining a chemistry laboratory parameter on Days 2 and Day 3 of Cycle 1 is only required in subjects with intermediate or high risk of TLS (per the risk definition in Section 6.8.1). Except for Days 1, 2, and 3 of Cycle 1, these parameters may be obtained within 72 hours prior to the planned day of collection. Abnormal test values should be monitored per protocol guidance.

G Chemistry includes albumin, alkaline phosphatase, total bilirubin, BUN, calcium, carbon dioxide, chloride, creatinine, glucose, inorganic phosphorus, potassium, total protein, LDH, ALT, AST, sodium, and uric acid.

H Urinalysis includes appearance, specific gravity and pH as well as a semi-quantitative "dipstick" evaluation of glucose, protein, bilirubin, ketones, leukocytes, and blood. Microscopic examination of sediment will be performed if urinalysis is positive for WBC, proteins or blood. Urinalysis may be obtained within 72 hours prior to the planned day of collection.

I Pregnancy testing (serum or urine) will be required for women of childbearing potential (WCBP) only. Testing is required at Screening; within 72 hours of Day 1 of each cycle and at EOT. Test does not need to be repeated on C1D1 if baseline was negative and conducted within 72 hours of first dose.

J Imaging as appropriate for disease indication will be conducted within 30 days of the first dose of study treatment. Suitable scans performed prior to screening and within 30 days before first dose may be used for baseline tumor assessments.

K Assessment of disease status will be conducted with standard clinical measurements: PE, CBCs, bone marrow aspirates/biopsies, and imaging as appropriate for indication. During treatment, scans will be repeated for tumor assessment within 7 days of Day 1, Cycles 3, 5, and 7 then every 3 months until PD or use of alternative antineoplastic therapy. For subjects still in response after 1 year, intervals for radiographic surveillance may be every 6 months. Subjects with CLL who achieve CR will require assessment of MRD by flow cytometry of bone marrow and peripheral blood.

L Imaging at EOT is not required if PD has already been radiographically documented or last imaging was within 30 days of EOT visit.

M Subjects with CLL/SLL must provide either a fresh blood sample containing circulating tumor cells or a bone marrow aspirate sample pretreatment. Tissue will be submitted for evaluation of the percentage of tumor cells and analysis of genetic alterations and/or gene expression that may predict anticancer activity and/or pharmacodynamic activity. In addition, for subjects with CLL/SLL, the sponsor may arrange for a portion of the sample to be evaluated at a sponsor-specified laboratory for known prognostic markers (e.g., quantitative immunoglobulins, FISH panel [chromosome 11q deletion, 13q deletion, 17p deletion and 12 trisomy], DNA mutational analysis for p53, IgHV [including IgHV3-21], and other genes of interest in CLL [e.g., Notch]; flow cytometry [for CD5, CD10, CD11c, CD19, CD20, CD23, CD38, CD45, kappa and lambda light chains and ZAP-70], and/or β2-microglobulin). The baseline bone marrow aspiration procedure (if required) should be performed after the study candidate has undergone the baseline radiology examination and is otherwise considered eligible for study participation. All subjects with CLL/SLL must have baseline imaging (with CT scans [preferred] or MRI scans).

N Blood sampling for determination of the plasma concentrations **and activity** of ~~apilimod~~ **LAM-002A** and metabolites will be performed on C1D1 and C1D8 as follows: pre-dose, 30 minutes, 1, 2, 4, 6, 8 hours post-first dose of the day. **Sampling on** C1D15 **will be** pre-dose only. ~~Additional PK samples will be collected, if possible, whenever a subject has a study treatment related SAE or QTc > 500 msec.~~ Subjects are required to come to the study site in a fasting state prior to the collection of certain PK samples. ~~For analyte determination, PK back-up sample will be used from time points: Cycle 1 Day 1 and Cycle 1 Day 8 pre-dose.~~

O Bone marrow aspirates/biopsies performed within 2 months prior to first dose may be used for clinical baseline assessments. For subjects with NHL, baseline bone marrow biopsies/aspirates may be omitted if not deemed essential for response assessment or patient management **and there is another source of tumor tissue for pretreatment evaluation of gene expression and prognosis.** For subjects with CLL/SLL, a baseline bone marrow aspirate is required unless the presence of sufficient circulating cells in the peripheral blood (e.g., absolute lymphocyte count [ALC] ≥ 10 x 10^9/L) permits assessment of baseline parameters as described in Footnote m, above.

P If necessary per applicable response criteria, a repeat bone marrow biopsy or aspirate will be required for subjects who have a CR by imaging and physical examination.

Q Archival tissue from the most recent available biopsy or surgery or fresh tumor tissue **(preferred)** must be obtained pretreatment **for nucleic acid extraction**. For subjects undergoing a biopsy, adequate tumor tissue should be acquired via excisional biopsy, incisional biopsy or core needle biopsy (e.g., ≥ 3 passes using a 16-gauge core needle). Alternatively, cells from a bone marrow aspirate may be obtained in subjects with bone marrow involvement due to NHL **(≥50% of cells)**. Tissue will be submitted for evaluation of the percentage of tumor cells and analysis of genetic alterations and/or gene expression that may predict anti-lymphoma activity and/or pharmacodynamics activity. **In addition,** tumor **tissue from the most recently availably biopsy or surgery will** ~~may~~ be evaluated for known prognostic characteristics (e.g., for DLBCL: ABC or GCB subtype; expression of BCL2, BCL6, Ki-67, CD20, and MYC; other mutational status)**, for PDL1 status, and for immune infiltration**. The baseline biopsy procedure (if required) should ideally be performed after the study candidate has undergone the baseline radiology examination and is otherwise considered eligible for study participation.

R **Plasma will be collected on C1D1 pretreatment, on C1D15 pretreatment, and at EOT visit for evaluation of circulating tumor DNA to measure tumor burden and mutational changes.** ~~Blood smears will be collected for microscopic evaluation of vacuole formation on C1D1 and C1D8 as follows: pre-dose, 4 hours and 8 hours post first dose of the day. C1D15 pre-dose only.~~

S Plasma will be collected for evaluation of circulating cytokines (including IL-12 and IL-23) predose on each of C1D1, C1D8, and C1D15 **and at EOT**.

T PBMCs**/B-cells** will be collected **during Screening,** ~~on C1D1 pre-treatment; on C1D1 at 8 hours post-dose; and on C1D8 at 8 hours post-dose~~ for determination of changes in gene expression that may predict or correlate with anti-lymphoma activity and/or pharmacodynamic activity **and will also serve as normal-tissue controls for gene mutation studies in tumors.**

U Saliva will be obtained during **Screening** ~~pre-dose on C1D1~~ as a normal-tissue control for gene mutation studies in tumors.

V **LAM-002A to be administered to the subject in clinic (with recording of the date and actual clock time of the LAM-002A administration).**

W Information on concomitant medications and other treatments will be collected from 14 days prior to informed consent through 30-37 days after the last dose of study drug.

X Subjects who have discontinued study treatment for reasons other than PD will be assessed per Revised Response Criteria for NHL or Guidelines for the diagnosis and treatment of CLL at a minimum of every 12 weeks until documentation of PD, start of new anti-cancer therapy or for up to 1 year from the last enrolled subject's first treatment (C1D1) whichever comes first. Long-term follow-up survival information will be obtained in all surviving subjects who permanently discontinue study therapy. Such information may be collected at ~3- to 6-month intervals at the sponsor's discretion through 3 years. This long-term follow-up information will be gathered during routine clinic visits, other study site contact with the subjects, or via telephone or e-mail with the subjects/caregivers or referring physician offices.

Abbreviations: ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BID, twice per day; BUN: Blood urea nitrogen; CBCs: Complete blood counts; CD: Cluster of differentiation; CLL: Chronic lymphocytic leukemia; CR: Complete response; CT: Computerized tomography; ECG: Electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOT: End of treatment; FISH: Fluorescence *in situ* hybridization; h: Hour; hrs: Hours; LDH: Lactate dehydrogenase; min: Minutes; MRD: Minimal residual disease; MRI: Magnetic Resonance Imaging; PBMC: Peripheral blood mononuclear cell; PD: Progressive disease; PE: Physical exam; PET: Positron emission tomography; PK: Pharmacokinetics; QTc: Corrected QT interval; RBC: Red blood cell; SAE: Serious adverse event; TLS: tumor lysis syndrome; WBC: White blood cell; WCBP: Women of child bearing potential

Table 9: Schedule of Assessments (LAM-002A Intermittent Monotherapy Administration)

Assessment	Screening	Cycle 1						Cycle 2		Cycle ≥ 3		End of Treatment (EOT)	Long-Term F/U
		Day						Day		Day			
	-28 to -1	1	2	3	8	10	15	1	15-28	1	15-28		
Informed consent	X												
Inclusion/exclusion criteria	X	X[a]											
Demographics	X												
Medical history	X												
Signs and symptoms, PE[b]	X	X[c]						X		X		X	
ECOG performance status	X	X[c]						X		X		X	
Vital signs	X	X[d]			X	X[d]	X[d]	X		X		X	
ECG	X	X[d]			X	X[d]		X		X		X	
HIV, HBV, and HCV serology	X												
Hematology[e, f]	X	X			X		X	X		X		X	
Serum chemistry[f, g]	X	X	X[f]	X[f]	X		X	X		X		X	
Coagulation	X												
Urinalysis[h]	X	X[c]						X		X		X	
Pregnancy testing[i]	X	X[i]						X		X		X	
PET/CT or CT (or MRI) scans (based on indication) for response assessment	X[j]								X[k]		X[k]	X[l]	
CLL baseline assessments[m]	X												
PK/PD plasma sampling[n]		X			X	X	X						
Bone marrow aspirate/biopsy	X[o]								X[p]		X[p]		
Biomarker – tumor tissue[q]	X												
Biomarker – plasma tumor DNA[r]		X					X					X	
Biomarker – plasma cytokines[s]		X			X	X	X					X	
Biomarker – PBMC/B cell[t]	X												
Biomarker – saliva[u]	X												
LAM-002A administration in clinic[v]		X			X	X	X						
Adverse events		Throughout Study											
Concomitant medications[w]		Throughout Study											
Long-term follow-up (F/U)[x]													X

a Eligibility will be confirmed by C1D1.

B Complete physical examination (PE) will be performed at screening. A directed PE, including weight, will be performed within 72 hours prior to the start of each cycle and EOT.

C Assessment/test does not need to be repeated on C1D1 if baseline was within normal limits and conducted within 72 hours of first dose.

D Obtained on Day 1 for all cycles. For C1D1 and C1D10 obtained prior to dosing and 1 hour (± 15 minutes after dosing), 2 hours (± 30 minutes), 4 hours (± 1 hour), and 8 hours (± 1 hour) postdose. For C1D8 and C1D15, obtained prior to dosing.

E Hematology includes hemoglobin, hematocrit, RBC count, platelet count, WBC and differential.

F All hematology and chemistry laboratory parameters should be assessed at Screening and Days 1, 8, and 15 of Cycles 1 and 2, and then at least once prior to the start of all subsequent cycles and at EOT. Obtaining a chemistry laboratory parameter on Days 2 and Day 3 of Cycle 1 is only required in subjects with intermediate or high risk of TLS (per the risk definition in Section 6.8.1). Except for Days 1, 2, and 3 of Cycle 1, these parameters may be obtained within 72 hours prior to the planned day of collection. Abnormal test values should be monitored per protocol guidance.

G Chemistry includes albumin, alkaline phosphatase, total bilirubin, BUN, calcium, carbon dioxide, chloride, creatinine, glucose, inorganic phosphorus, potassium, total protein, LDH, ALT, AST, sodium, and uric acid.

H Urinalysis includes appearance, specific gravity and pH as well as a semi-quantitative "dipstick" evaluation of glucose, protein, bilirubin, ketones, leukocytes, and blood. Microscopic examination of sediment will be performed if urinalysis is positive for WBC, proteins or blood. Urinalysis may be obtained within 72 hours prior to the planned day of collection.

I Pregnancy testing (serum or urine) will be required for women of childbearing potential (WCBP) only. Testing is required at Screening; within 72 hours of Day 1 of each cycle and at EOT. Test does not need to be repeated on C1D1 if baseline was negative and conducted within 72 hours of first dose.

J Imaging as appropriate for disease indication will be conducted within 30 days of the first dose of study treatment. Suitable scans performed prior to screening and within 30 days before first dose may be used for baseline tumor assessments.

K Assessment of disease status will be conducted with standard clinical measurements: PE, CBCs, bone marrow aspirates/biopsies, and imaging as appropriate for indication. During treatment, scans will be repeated for tumor assessment within 7 days of Day 1, Cycles 3, 5, and 7 then every 3 months until PD or use of alternative antineoplastic therapy. For subjects still in response after 1 year, intervals for radiographic surveillance may be every 6 months. Subjects with CLL who achieve CR will require assessment of MRD by flow cytometry of bone marrow and peripheral blood.

L Imaging at EOT is not required if PD has already been radiographically documented or last imaging was within 30 days of EOT visit.

M Subjects with CLL/SLL must provide either a fresh blood sample containing circulating tumor cells or a bone marrow aspirate sample pretreatment. Tissue will be submitted for evaluation of the percentage of tumor cells and analysis of genetic alterations and/or gene expression that may predict anticancer activity and/or pharmacodynamic activity. In addition, for subjects with CLL/SLL, the sponsor may arrange for a portion of the sample to be evaluated at a sponsor-specified laboratory for known prognostic markers (e.g., quantitative immunoglobulins, FISH panel [chromosome 11q deletion, 13q deletion, 17p deletion and 12 trisomy], DNA mutational analysis for p53, IgHV [including IgHV3-21], and other genes of interest in CLL [e.g., Notch]; flow cytometry [for CD5, CD10, CD11c, CD19, CD20, CD23, CD38, CD45, kappa and lambda light chains and ZAP-70], and/or β2-microglobulin). The baseline bone marrow aspiration procedure (if required) should be performed after the study candidate has undergone the baseline radiology examination and is otherwise considered eligible for study participation. All subjects with CLL/SLL must have baseline imaging (with CT scans [preferred] or MRI scans).

N Blood sampling for determination of the plasma concentrations and activity of LAM-002A and metabolites will be performed on C1D1 and C1D10 as follows: pre-dose, 30 minutes, 1, 2, 4, 6, 8 hours post-first dose of the day. Sampling on C1D8 and C1D15 will be pre-dose only. Subjects are required to come to the study site in a fasting state prior to the collection of certain PK samples.

O Bone marrow aspirates/biopsies performed within 2 months prior to first dose may be used for clinical baseline assessments. For subjects with NHL, baseline bone marrow biopsies/aspirates may be omitted if not deemed essential for response assessment or patient management and there is another source of tumor tissue for pretreatment evaluation of gene expression and prognosis. For subjects with CLL/SLL, a baseline bone marrow aspirate is required unless the presence of sufficient circulating cells in the peripheral blood (e.g., absolute lymphocyte count [ALC] $\geq 10 \times 10^9$/L) permits assessment of baseline parameters as described in Footnote m, above.

P If necessary per applicable response criteria, a repeat bone marrow biopsy or aspirate will be required for subjects who have a CR by imaging and physical examination.

Q Archival tissue from the most recent available biopsy or surgery or fresh tumor tissue (preferred) must be obtained pretreatment for nucleic acid extraction. For subjects undergoing a biopsy, adequate tumor tissue should be acquired via excisional biopsy, incisional biopsy or core needle biopsy (e.g., ≥ 3 passes using a 16-gauge core needle). Alternatively, cells from a bone marrow aspirate may be obtained in subjects with bone marrow involvement due to NHL (≥50% of cells). Tissue will be submitted for evaluation of the percentage of tumor cells and analysis of genetic alterations and/or gene expression that may predict anti-lymphoma activity and/or pharmacodynamics activity. In addition, tumor tissue from the most recently availably biopsy or surgery will be evaluated for known prognostic characteristics (e.g., for DLBCL: ABC or GCB subtype; expression of BCL2, BCL6, Ki-67, CD20, and MYC; other mutational status), for PDL1 status, and for immune infiltration. The baseline biopsy procedure (if required) should ideally be performed after the study candidate has undergone the baseline radiology examination and is otherwise considered eligible for study participation.

R Plasma will be collected on C1D1 (predose), on C1D15 (predose), and at EOT visit for evaluation of circulating tumor DNA to measure tumor burden and mutational changes.

S Plasma will be collected for evaluation of circulating cytokines (including IL-12 and IL-23) on C1D1 (predose), C1D8 (predose), C1D10 (predose), and C1D15 (predose) and at EOT.

T PBMCs/B-cells will be collected during Screeningfor determination of changes in gene expression that may predict or correlate with anti-lymphoma activity and/or pharmacodynamic activity and will also serve as normal-tissue controls for gene mutation studies in tumors.

U Saliva will be obtained during Screening as a normal-tissue control for gene mutation studies in tumors.

V LAM-002A to be administered to the subject in clinic (with recording of the date and actual clock time of the LAM-002A administration).

W Information on concomitant medications and other treatments will be collected from 14 days prior to informed consent through 30-37 days after the last dose of study drug.

X Subjects who have discontinued study treatment for reasons other than PD will be assessed per Revised Response Criteria for NHL or Guidelines for the diagnosis and treatment of CLL at a minimum of every 12 weeks until documentation of PD, start of new anti-cancer therapy or for up to 1 year from the last enrolled subject's first treatment (C1D1) whichever comes first. Long-term follow-up survival information will be obtained in all surviving subjects who permanently discontinue study therapy. Such information may be collected at ~3- to 6-month intervals at the sponsor's discretion through 3 years. This long-term follow-up information will be gathered during routine clinic visits, other study site contact with the subjects, or via telephone or e-mail with the subjects/caregivers or referring physician offices.

Abbreviations: ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BID, twice per day; BUN: Blood urea nitrogen; CBCs: Complete blood counts; CD: Cluster of differentiation; CLL: Chronic lymphocytic leukemia; CR: Complete response; CT: Computerized tomography; ECG: Electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOT: End of treatment; FISH: Fluorescence in situ hybridization; h: Hour; hrs: Hours; LDH: Lactate dehydrogenase; min: Minutes; MRD: Minimal residual disease; MRI: Magnetic Resonance Imaging; PBMC: Peripheral blood mononuclear cell; PD: Progressive disease; PE: Physical exam; PET: Positron emission tomography; PK: Pharmacokinetics; QTc: Corrected QT interval; RBC: Red blood cell; SAE: Serious adverse event; TLS: tumor lysis syndrome; WBC: White blood cell; WCBP: Women of child bearing potential

Table 10: Schedule of Assessments (LAM-002A/Rituximab Combination Therapy)

Assessment	Screening	Cycle 1 Day						Cycles ≥2 Day		End of Treatment (EOT)	Long-Term F/U
	-28 to -1	1	2	3	8	15	22	1	22-28		
Informed consent	X										
Inclusion/exclusion criteria	X	X[a]									
Demographics	X										
Medical history	X										
Signs and symptoms, PE[b]	X	X[c]						X		X	
ECOG performance Status	X	X[c]						X		X	
Vital signs	X	X[d]			X[d]	X[d]		X		X	
ECG	X	X[d]			X[d]	X[d]		X		X	
HIV, HBV, and HCV serology	X										
Hematology[e, f]	X	X			X	X	X	X		X	
Serum chemistry[f, g]	X	X	X[f]	X[f]	X	X	X	X		X	
Coagulation	X										
Urinalysis[h]	X	X[c]						X		X	
Pregnancy testing[i]	X	X[i]						X		X	
PET/CT or CT (or MRI) scans (based on indication) for response assessment	X[j]								X[k]	X[l]	
PK/PD sampling[m]		X			X	X					
Bone marrow aspirate/biopsy	X[n]								X[o]		
Biomarker – tumor tissue[p]	X										
Biomarker – plasma tumor DNA[q]		X				X				X	
Biomarker – plasma cytokines[r]		X			X	X				X	
Biomarker – PBMC/B cell[s]	X										
Biomarker – saliva[t]	X										
Premedication[u]		X			X	X	X	X[u]			
LAM-002A administration in clinic[v]		X			X	X					
Rituximab infusion[w]		X			X	X	X	X[w]			
Adverse events		Throughout study									
Concomitant medications[x]		Throughout study									
Long-term F/U[y]											X

a Eligibility will be confirmed by C1D1.
B Complete PE will be performed at Screening. A directed PE, including weight, will be performed within 72 hours prior to the start of each cycle and EOT.
C Assessment/test does not need to be repeated on C1D1 if baseline was within normal limits and conducted within 72 hours of first dose.
D Obtained on Day 1 for all cycles. For C1D1 and C1D8 obtained prior to dosing and 1 hour (± 15 minutes after dosing), 2 hours (± 30 minutes), 4 hours (± 1 hour), and 8 hours (± 1 hour) postdose. For C1D15, obtained prior to dosing.
E Hematology includes hemoglobin, hematocrit, RBC count, platelet count, WBC and differential.
F All hematology and chemistry laboratory parameters should be assessed at Screening, on C1D1, C1D8, C1D15, C≥2D1 (all subsequent cycles), and at EOT. Obtaining a chemistry laboratory parameter on C1D2 and C1D3 is only required in subjects with intermediate or high risk of TLS (per the risk definition in Section 6.8.1). Except for C1D1, C1D2, and C1D3, these parameters may be obtained within 72 hours prior to the planned day of collection.
G Serum chemistry includes albumin, alkaline phosphatase, total bilirubin, BUN, calcium, carbon dioxide, chloride, creatinine, glucose, inorganic phosphorus, potassium, total protein, LDH, ALT, AST, sodium, and uric acid.
H Urinalysis includes appearance, specific gravity and pH as well as a semi-quantitative "dipstick" evaluation of glucose, protein, bilirubin, ketones, leukocytes, and blood. Microscopic examination of sediment will be performed if urinalysis is positive for WBC, proteins or blood. Urinalysis may be obtained within 72 hours prior to the planned day of collection.
I Pregnancy testing (serum or urine) will be required for women of childbearing potential (WCBP) only. Testing is required at Screening; within 72 hours of Day 1 of each cycle and at EOT. Test does not need to be repeated on C1D1 if baseline was negative and conducted within 72 hours of first dose.
J Imaging as appropriate for disease indication will be conducted within 30 days before C1D1. Suitable scans performed prior to Screening and within 30 days before first dose may be used for baseline tumor assessments.
K Assessment of disease status will be conducted with standard imaging as appropriate for indication. During treatment, scans will be repeated for tumor assessment within 7 days before C3D1, C5D1, C7D1, and then every 3 cycles (12 weeks) until PD or use of alternative antineoplastic therapy.
L Imaging at EOT is not required if PD has already been radiographically documented or last imaging was within 4 weeks of EOT visit.
M Blood sampling for determination of the plasma concentrations and activity of LAM-002A and metabolites will be performed on C1D1 and C1D8 as follows: pre-dose, 30 minutes, 1, 2, 4, 6, 8 hours post-first dose of the day. Sampling on C1D15 will be pre-dose only. Subjects are required to come to the study site in a fasting state prior to the collection of certain PK samples.
N Bone marrow aspirates/biopsies performed within 2 months prior to first dose may be used for clinical baseline assessments. Baseline bone marrow biopsies/aspirates may be omitted if not deemed essential for response assessment or patient management and there is another source of tumor tissue for pretreatment evaluation of gene expression and prognosis.
O If necessary per applicable response criteria, a repeat bone marrow biopsy or aspirate will be required for subjects who have a CR by imaging and PE.

P **Archival tissue from the most recent available biopsy or surgery or fresh tumor tissue (preferred) must be obtained pretreatment for nucleic acid extraction. For subjects undergoing a biopsy, adequate tumor tissue should be acquired via excisional biopsy, incisional biopsy or core needle biopsy (e.g., ≥ 3 passes using a 16-gauge core needle). Alternatively, cells from a bone marrow aspirate may be obtained in subjects with bone marrow involvement due to NHL (≥50% of cells). Tissue will be submitted for evaluation of the percentage of tumor cells and analysis of genetic alterations and/or gene expression that may predict anti-lymphoma activity and/or pharmacodynamics activity. In addition, tumor tissue from the most recently availably biopsy or surgery will be evaluated for known prognostic characteristics (e.g., for DLBCL: ABC or GCB subtype; expression of BCL2, BCL6, Ki-67, CD20, and MYC; other mutational status), for PDL1 status, and for immune infiltration. The baseline biopsy procedure (if required) should ideally be performed after the study candidate has undergone the baseline radiology examination and is otherwise considered eligible for study participation.**

Q **Plasma will be collected on C1D1 (predose), on C1D15 (predose), and at EOT visit for evaluation of circulating tumor DNA to measure tumor burden and mutational changes.**

R **Plasma will be collected for evaluation of circulating cytokines (including IL-12 and IL-23) on C1D1 (predose), C1D8 (predose), C1D15 (predose), C2D1, and at EOT.**

S **PBMCs/B-cells will be collected during Screening for determination of changes in gene expression that may predict or correlate with anti-lymphoma activity and/or pharmacodynamic activity and will also serve as normal-tissue controls for gene mutation studies in tumors.**

T **Saliva will be obtained during Screening as a normal-tissue control for gene mutation studies in tumors.**

U **Oral antipyretic, oral or intravenous antihistamine, and intravenous corticosteroid (at investigator discretion) (see Section 6.8.3.1) to be administered to the subject ~30 minutes prior to each rituximab infusion (see Footnote w).**

v **LAM-002A to be administered to the subject in clinic (with recording of the date and actual clock time of the LAM-002A administration). On C1D1, LAM-002A will be started on a BID schedule after administration of premedications (see Section 6.8.3.1) and ~15 to 30 minutes prior to the start of the initial rituximab infusion. On C1D8, the morning dose of LAM-002A will be administered after premedications (see Section 6.8.3.1) and ~15 to 30 minutes prior to the rituximab infusion**

w **Rituximab, 375 mg/m^2, will be administered by intravenous infusion ~30 after premedication weekly on C1D1, C1D8, C1D15, and C1D22 and then every 8 weeks on C4D1, C6D1, C8D1, and C10D1 for a total of 8 infusions.**

X **Information on concomitant medications and other treatments will be collected from 14 days prior to informed consent through 30-37 days after the last dose of study drug.**

Y **Subjects who have discontinued study treatment for reasons other than PD will be assessed at a minimum of every 12 weeks until documentation of PD, start of new anti-cancer therapy or for up to 1 year from the last enrolled subject's first treatment (C1D1) whichever comes first. Long-term follow-up survival information will be obtained in all surviving subjects who permanently discontinue study therapy. Such information may be collected at ~3- to 6-month intervals at the sponsor's discretion through 3 years. This long-term follow-up information will be gathered during routine clinic visits, other study site contact with the subjects, or via telephone or e-mail with the subjects/caregivers or referring physician offices.**

Abbreviations: ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BID: twice per day; BUN: Blood urea nitrogen; CBCs: Complete blood counts; CD: Cluster of differentiation; CLL: Chronic lymphocytic leukemia; CR: Complete response; CT: Computerized tomography; ECG: Electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOT: End of treatment; FISH: Fluorescence *in situ* hybridization; F/U: Follow-up; LDH: Lactate dehydrogenase; MRI: Magnetic Resonance Imaging; PBMC: Peripheral blood mononuclear cell; PD: Progressive disease; PDL1: programmed death ligand-1; PE: Physical exam; PET: Positron emission tomography; PK: Pharmacokinetics; QTc: Corrected QT interval; RBC: Red blood cell; SAE: Serious adverse event; TLS: tumor lysis syndrome; WBC: White blood cell; WCBP: Women of child-bearing potential.

Table 11: Schedule of Assessments (LAM-002A/Atezolizumab Combination Therapy)

Assessment	Screening	Cycle 1 Day					Cycles ≥2 Day		End of Treatment (EOT)	Long-Term F/U
	-28 to -1	1	2	3	8	15	1	15-22		
Informed consent	X									
Inclusion/exclusion criteria	X	X[a]								
Demographics	X									
Medical history	X									
Signs and symptoms, PE[b]	X	X[c]					X		X	
ECOG performance Status	X	X[c]					X		X	
Vital signs	X	X[d]			X[d]	X[d]	X		X	
ECG	X	X[d]			X[d]	X[d]	X		X	
HIV, HBV, and HCV serology	X									
Hematology[e, f]	X	X			X	X	X		X	
Serum chemistry[f, g]	X	X	X[f]	X[f]	X	X	X		X	
Serum thyroid function[h]	X						X			
Coagulation	X									
Urinalysis[i]	X	X[c]					X		X	
Pregnancy testing	X	X[j]					X		X	
PET/CT or CT (or MRI) scans (based on indication) for response assessment	X[k]							X[l]	X[m]	
PK/PD sampling[n]		X			X	X				
Bone marrow aspirate/biopsy	X[o]							X[p]		
Biomarker – tumor tissue[q]	X									
Biomarker – plasma tumor DNA[r]		X				X			X	
Biomarker – plasma cytokines[s]		X			X	X	X		X	
Biomarker – PBMC/B cells[t]	X									
Biomarker – saliva[u]	X									
LAM-002A administration in clinic[v]		X			X	X				
Atezolizumab infusion[w]		X					X[w]			
Adverse events		Throughout study								
Concomitant medications[x]		Throughout study								
Long-term F/U[y]										X

a Eligibility will be confirmed by C1D1.
B Complete PE will be performed at Screening. A directed PE, including weight, will be performed within 72 hours prior to the start of each cycle and EOT.
C Assessment/test does not need to be repeated on C1D1 if baseline was within normal limits and conducted within 72 hours of first dose.

D Obtained on Day 1 for all cycles. For C1D1 and C1D8 obtained prior to dosing and 1 hour (± 15 minutes after dosing), 2 hours (± 30 minutes), 4 hours (± 1 hour), and 8 hours (± 1 hour) postdose. For C1D15, obtained prior to dosing.

E Hematology includes hemoglobin, hematocrit, RBC count, platelet count, WBC and differential.

F All hematology and chemistry laboratory parameters should be assessed at Screening, on C1D1, C1D8, C1D15, C≥2D1 (all subsequent cycles), and at EOT. Obtaining a chemistry laboratory parameter on C1D2 and C1D3 is only required in subjects with intermediate or high risk of TLS (per the risk definition in Section 68.1). Except for C1D1, C1D2, and C1D3, these parameters may be obtained within 72 hours prior to the planned day of collection.

G Serum chemistry includes albumin, alkaline phosphatase, total bilirubin, BUN, calcium, carbon dioxide, chloride, creatinine, glucose, inorganic phosphorus, potassium, total protein, LDH, ALT, AST, sodium, and uric acid.

H Serum thyroid function tests include TSH, free T3, and free T4 at C3D1, C5D1, C7D1, C9D1, and then every 4 cycles (12 weeks).

I Urinalysis includes appearance, specific gravity and pH as well as a semi-quantitative "dipstick" evaluation of glucose, protein, bilirubin, ketones, leukocytes, and blood. Microscopic examination of sediment will be performed if urinalysis is positive for WBC, proteins or blood. Urinalysis may be obtained within 72 hours prior to the planned day of collection.

J Pregnancy testing (serum or urine) will be required for women of childbearing potential (WCBP) only. Testing is required at Screening; within 72 hours of Day 1 of each cycle and at EOT. Test does not need to be repeated on C1D1 if baseline was negative and conducted within 72 hours of first dose.

K Imaging as appropriate for disease indication will be conducted within 30 days before C1D1. Suitable scans performed prior to Screening and within 30 days before first dose may be used for baseline tumor assessments.

L Assessment of disease status will be conducted with standard imaging as appropriate for indication. During treatment, scans will be repeated for tumor assessment within 7 days before C3D1, C5D1, C7D1, C9D1, and then every 4 cycles (12 weeks) until PD or use of alternative antineoplastic therapy.

M Imaging at EOT is not required if PD has already been radiographically documented or last imaging was within 4 weeks of EOT visit.

N Blood sampling for determination of the plasma concentrations and activity of LAM-002A and metabolites will be performed on C1D1 and C1D8 as follows: pre-dose, 30 minutes, 1, 2, 4, 6, 8 hours post-first dose of the day. Sampling on C1D15 will be pre-dose only. Subjects are required to come to the study site in a fasting state prior to the collection of certain PK samples.

O Bone marrow aspirates/biopsies performed within 2 months prior to first dose may be used for clinical baseline assessments. Baseline bone marrow biopsies/aspirates may be omitted if not deemed essential for response assessment or patient management and there is another source of tumor tissue for pretreatment evaluation of gene expression and prognosis.

P If necessary per applicable response criteria, a repeat bone marrow biopsy or aspirate will be required for subjects who have a CR by imaging and PE.

Q Archival tissue from the most recent available biopsy or surgery or fresh tumor tissue (preferred) must be obtained pretreatment for nucleic acid extraction. For subjects undergoing a biopsy, adequate tumor tissue should be acquired via excisional biopsy, incisional biopsy or core needle biopsy (e.g., ≥ 3 passes using a 16-gauge core needle). Alternatively, cells from a bone marrow aspirate may be obtained in subjects with bone marrow involvement due to NHL (≥50% of cells). Tissue will be submitted for evaluation of the percentage of tumor cells and analysis of genetic alterations and/or gene expression that may predict anti-lymphoma activity and/or pharmacodynamics activity. In addition, tumor tissue from the most recently availably biopsy or surgery will be evaluated for known prognostic characteristics (e.g., for DLBCL: ABC or GCB subtype; expression of BCL2, BCL6, Ki-67, CD20, and MYC; other mutational status), for PDL1 status, and for immune infiltration. The baseline biopsy procedure (if required) should ideally be performed after the study candidate has undergone the baseline radiology examination and is otherwise considered eligible for study participation.

R Plasma will be collected on C1D1 (predose), on C1D15 (predose), and at EOT visit for evaluation of circulating tumor DNA to measure tumor burden and mutational changes.

S Plasma will be collected for evaluation of circulating cytokines (including IL-12 and IL-23) on C1D1 (predose), C1D8 (predose), and C1D15 (predose) and at EOT.

T PBMCs/B-cells will be collected during Screening for determination of changes in gene expression that may predict or correlate with anti-lymphoma activity and/or pharmacodynamic activity and will also serve as normal-tissue controls for gene mutation studies in tumors.

U Saliva will be obtained during Screening as a normal-tissue control for gene mutation studies in tumors.

V LAM-002A to be administered to the subject in clinic (with recording of the date and actual clock time of the LAM-002A administration). On C1D1, LAM-002A will be started on a BID schedule after administration of premedications (see Section 6.8.3.1) and ~15 to 30 minutes prior to the start of the initial atezolizumab infusion. On C1D8, the morning dose of LAM-002A will be administered after premedications (see Section 6.8.3.1) and ~15 to 30 minutes prior to the atezolizumab infusion

w Atezolizumab, 1200 mg, will be administered by intravenous infusion ~30 every 3 weeks.

X Information on concomitant medications and other treatments will be collected from 14 days prior to informed consent through 30-37 days after the last dose of study drug.

Y Subjects who have discontinued study treatment for reasons other than PD will be assessed at a minimum of every 12 weeks until documentation of PD, start of new anti-cancer therapy or for up to 1 year from the last enrolled subject's first treatment (C1D1) whichever comes first. Long-term follow-up survival information will be obtained in all surviving subjects who permanently discontinue study therapy. Such information may be collected at ~3- to 6-month intervals at the sponsor's discretion through 3 years. This long-term follow-up information will be gathered during routine clinic visits, other study site contact with the subjects, or via telephone or e-mail with the subjects/caregivers or referring physician offices.

Abbreviations: ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BID: twice per day; BUN: Blood urea nitrogen; CBCs: Complete blood counts; CD: Cluster of differentiation; CLL: Chronic lymphocytic leukemia; CR: Complete response; CT: Computerized tomography; ECG: Electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOT: End of treatment; FISH: Fluorescence *in situ* hybridization; F/U: Follow-up; LDH: Lactate dehydrogenase; MRI: Magnetic Resonance Imaging; PBMC: Peripheral blood mononuclear cell; PD: Progressive disease; PE: Physical exam; PET: Positron emission tomography; PK: Pharmacokinetics; QTc: Corrected QT interval; RBC: Red blood cell; SAE: Serious adverse event; T3: triiodothyronine; T4: thyroxine; TLS: tumor lysis syndrome; TSH: thyroid-stimulating hormone; WBC: White blood cell; WCBP: Women of child-bearing potential

Section 9. STUDY DRUG MATERIALS AND MANAGEMENT

Change: Pharmaceutical information regarding LAM-002A was updated and information for rituximab and atezolizumab was added.

9.1. LAM-002A

9.1.1. Description

LAM-002A drug description is provided in Table 12.

Table 12: LAM-002A Drug Description

Product Name:	LAM-002A
Dosage Form:	Capsule
Unit Dose	25 mg or 50 mg
Route of Administration	Oral
Physical Description	Each capsule will contain 25 mg or 50 of apilimod dimesylate (equivalent to 17.1 mg or 34.3 mg of apilimod free base, respectively). The 25-mg capsule is Swedish orange and the 50-mg capsule is white. Both the 25- and 50-mg capsules are Size 0 and both have a total fill weight of 175 mg. Inactive components in active capsules are microcrystalline cellulose Avicell PH102, silicified microcrystalline cellulose, anhydrous lactose, croscarmellose sodium (Ac-Di-Sol), colloidal silicon dioxide, and magnesium stearate.
Manufacturer	Patheon

Abbreviation: mg: Milligram

9.1.2. LAM-002A Packaging and Labeling

LAM-002 will be provided in bulk bottles to each investigational pharmacy for dispensing. The pharmacist will dispense capsules into bottles for each subject (based on Cohort assignment) following applicable state and federal laws and site policies. Details on the labeling, dispensing, and administration of LAM-002A are provided in the Pharmacy Manual.

9.1.3. Source

LAM-002A will be provided by the sponsor.

9.1.4. Storage

The LAM-002A must be stored in a secure storage area, with limited access, under environmental conditions appropriate for the product. LAM-002A capsules should be stored at 2 to 8°C.

9.1.5. Accountability

LAM-002A will be dispensed to subjects in labeled bottles at the beginning of each cycle. Subjects should be instructed to bring all bottles, including empty bottles, to each Day 1 or End of Treatment study visit for a compliance and product accountability check. Returned ~~study~~LAM-002A should be retained for monitor review prior to destruction at the site, unless contraindicated by site standard operating procedures (SOPs). If contraindicated by the site SOP,

approval of site process by the sponsor must be obtained and filed in the pharmacy file and/or regulatory binder. The investigational pharmacy must maintain contemporary and accurate records on product receipt, storage temperature, stock, dispensation, return and disposal. These records should be available for review during monitoring visits and copies available for retrieval for the Trial Master File.

9.1.6. Handling and Disposal

LAM-002A accountability and inventory records will be inspected by the sponsor/Ce^3 prior to final disposition. Instructions will be provided by the sponsor/Ce^3 for shipment to and destruction of unused LAM-002A product by the designated packaging depot, to include unopened bulk bottles at the end of the study and expired product. Unused product returned by study subjects or opened bulk bottles will be destroyed by each site per site SOPs. LAM-002A should only be shipped or destroyed upon written authorization from the sponsor/Ce^3. Documentation of return of shipment, including a packing list and copy of the tracking label, should be retained in the Pharmacy and/or regulatory files.

9.2. Rituximab

9.2.1. Description

Rituximab (Rituxan®, MabThera®) is a genetically engineered chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen found on pre-B and mature B cells (Genentech 2016). Rituximab is produced by mammalian Chinese hamster ovary cells. The protein has an approximate molecular weight of 145 kD.

The drug is provided as a clear, colorless, preservative-free liquid concentrate containing 10 mg/mL of rituximab. The product is formulated in 9 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dihydrate, 0.7 mg/mL polysorbate 80, and water for injection with a pH of 6.5.

9.2.2. Packaging

Rituximab is supplied in 100-mg (10-mL) or 500-mg (50-mL) single-use vials.

9.2.3. Source

Unless otherwise instructed by the sponsor, the rituximab to be used in this study may be obtained from available commercial supplies.

9.2.4. Storage and Stability

Rituximab vials are stable at 2°C–8°C (36°F–46°F). Vials should be protected from direct sunlight and should not be frozen or shaken.

Diluted rituximab solutions for infusion may be stored at 2°C–8°C (36°F–46°F) for 24 hours and are known to be stable for an additional 24 hours at room temperature. However, since rituximab solutions do not contain a preservative, diluted solutions should be stored refrigerated (2°C–8°C).

No incompatibilities between rituximab and polyvinylchloride or polyethylene bags have been observed.

9.2.6. Solution Preparation

Before use, the rituximab vials should be inspected for particulate matter or discoloration. Any vial with evidence of particulates or discoloration should not be used.

Using aseptic technique, the necessary amount of rituximab should be withdrawn from the vial and diluted to a final concentration of 1 to 4 mg/mL in an infusion bag containing either 0.9% Sodium Chloride, USP or 5% Dextrose in Water, USP. The bag should be gently inverted to mix the solution. The infusion solution should not be mixed or diluted with other drugs. Any unused portion of rituximab remaining in the vial should be discarded.

9.2.7. Accountability

Acquisition, storage, control, and disposal of rituximab used in the study should be performed according to institutional procedures and policies.

The investigator and/or the responsible site personnel must maintain accurate records of the source, dates of administration, quantities of administration, and lot numbers of the rituximab dispensed for this study.

9.3. Atezolizumab

9.3.1. Description

Atezolizumab (TECENTRIQ®) is an Fc-engineered, humanized, monoclonal antibody that binds to PD-L1 and blocks interactions with the PD-1 and B7.1 receptors (Genentech 2017). Atezolizumab is a non-glycosylated IgG1 kappa immunoglobulin that has a calculated molecular mass of 145 kDa.

The drug is provided as a sterile, preservative-free, colorless to slightly yellow solution in single-dose vials. Each mL of TECENTRIQ contains 60 mg of atezolizumab and is formulated in glacial acetic acid (16.5 mg), L-histidine (62 mg), sucrose (821.6 mg), polysorbate 20 (8 mg). The solution has a pH of 5.8.

9.3.2. Packaging

Atezolizumab is supplied in a carton containing one 1200-mg/20-mL single-dose vial.

9.3.3. Source

The atezolizumab to be used in this study will be supplied by Genentech, Inc. via the study sponsor (LAM Therapeutics, Inc.).

9.3.4. Storage and Stability

Atezolizumab vials are stable at 2°C–8°C (36°F–46°F). Vials should be stored in the original cartons protected from light and should not be frozen or shaken.

Atezolizumab does not contain a preservative; thus, diluted solutions should be administered as soon as possible after preparation. If the diluted atezolizumab solution is not used immediately, it may be stored or maintained at room temperature (e.g., 20°C–25°C; 68°F–77°F). for ≤6 hours from the time of preparation, including time for administration of the infusion. Alternatively, it may be stored under refrigeration at 2°C–8°C (36°F–46°F) for ≤24 hours.

9.3.5. Solution Preparation

Before use, the atezolizumab vials should be inspected for particulate matter or discoloration. Any vial with evidence of particulates or discoloration should not be used. The vial should not be shaken.

Using aseptic technique, 20 mL of atezolizumab should be withdrawn from the vial and diluted into a 250-mL polyvinyl chloride, polyethylene, or polyolefin infusion bag containing 0.9% Sodium Chloride Injection, USP. The bag should be gently inverted to mix the solution. Shaking of the bag must be avoided. The infusion solution should not be mixed or diluted with other drugs. Used or empty vials of atezolizumab should be discarded.

The intravenous solution should be prepared and dispensed by the study center pharmacist and should be infused by a qualified nurse with experience in monitoring the administration of chemotherapeutic agents.

9.3.6 Accountability

Acquisition, storage, control, and disposal of atezolizumab used in the study should be performed according to institutional procedures and policies.

The investigator and/or the responsible site personnel must maintain accurate records of the source, dates of administration, quantities of administration, and lot numbers of the atezolizumab dispensed for this study.

Section 10.1.1.4 Adverse Event of Special Interest

Change: A definition of adverse events of special interest has now been added.

Adverse events of special interest (AESIs) comprise TLS occurring in any study subject. Among study subjects receiving atezolizumab the following treatment-emergent AEs will be considered AESIs:

- **AE suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, influenza-like illness, systemic inflammatory response syndrome, or systemic immune activation**
- **Autoimmune hemolytic anemia**
- **Cardiac disorders Grade ≥ 2: atrial fibrillation, myocarditis, pericarditis**
- **Colitis**
- **Cutaneous reactions: Stevens-Johnson syndrome, bullous dermatitis, toxic epidermal necrolysis**
- **Drug-induced liver injury (Grade ≥ 3 serum ALT or AST increase in combination with a Grade ≥ 2 serum total bilirubin)**
- **Endocrinopathy: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, or hypophysitis**
- **Hepatitis (Grade ≥3 serum ALT or AST increase)**

- **Muscular disorders: myositis, myopathy, rhabdomyolysis**
- **Nephritis**
- **Neurological disorders: Guillain-Barre syndrome, myasthenic syndrome or myasthenia gravis, or meningoencephalitis**
- **Ocular toxicities: uveitis, retinitis, optic neuritis**
- **Pneumonitis**
- **Systemic lupus erythematosus**
- **Transmission of an infectious agent due to contamination of atezolizumab**
- **Vasculitis**

AESIs will be described in narratives as indicated in Section 10.6.

Section 10.6 SAE and AESI Reporting

Change: Reporting requirements for SAEs have been updated and reporting requirements for AESIs have now been added.

The investigator is obligated to immediately report to **Pharmalex** ~~Data Safety Solutions~~, Inc. ~~(DSS)~~ each SAE **and each AESI** that occurs during this investigation, within 24 hours from knowledge of the event, whether or not it is considered study-drug related. All requested supplementary documents (e.g., discharge summary, autopsy report) and relevant data (e.g., ECGs, laboratory tests, discharge summaries, post mortem results) must be faxed or emailed within 24 hours to ~~DSS at~~ the contact below:

- FAX to [redacted]
  email a copy to [redacted]

The information provided in a SAE **or AESI** report ~~to DSS~~ should be as complete as possible, but contain a minimum of the following:

- A short description of the AE (diagnosis) and the reason why the AE was categorized as ~~serious~~ **an SAE or AESI**
- Subject identification and treatment
- Investigator's name and telephone number (if applicable)
- Name of the suspect medicinal product and dates of administration
- Assessment of causality.

If any questions or considerations regarding SAE **or AESI** report requirements or report completion arise, the principal investigator/site staff should contact ~~DSS~~ **PharmaLex**. Medically related questions or concerns regarding treatment should be directed to the sponsor's medical monitor.

If all information about the SAE **or AESI** is not yet known, the investigator will be required to report any additional information within 24 hours as it becomes available. SAEs **and AESIs**

must be followed and reported upon until the event has completely resolved to Grade 0 or baseline or until the event becomes a new stable baseline condition for a subject.

All SAEs **and AESIs** will be evaluated by the sponsor's medical monitor or designee.

The investigators must notify their governing IRB of any SAEs in accordance with Section 18.1.

For any suspected adverse reaction that is both serious and unexpected (not documented in the IB or package insert), an Investigational New Drug (IND) safety report or revision to the IB may be issued to inform all investigators involved in any study with LAM-002A.

Section 11. ASSESSMENT OF EFFICACY

Changes: References to the schedules of assessment tables were included to clarify where information regarding the timing of efficacy assessments could be found.

11. ASSESSMENT OF EFFICACY

Tumor response will be assessed in the Dose Escalation Stage and Expansion Stage using modified Lugano Response Criteria for NHL (Cheson 2014) and revised guidelines for the diagnosis and treatment of CLL (Hallek 2008, Cheson 2012) (see Appendix 2).

Pretreatment tumor assessments will be performed within 30 days of the first dose (bone marrow assessment may be performed within 2 months prior to first dose) and will include diagnostic CT scans (with intravenous contract) or PET/CT for subjects with lymphoma (CT only for subjects with CLL/SLL), bone marrow aspirate/biopsy, complete blood counts and physical examination. It is anticipated that in most cases the PET and CT scans will be conducted using a single instrument, i.e., as a PET/CT scan (CT scans should be performed using a contiguous reconstruction algorithm of ≤ 5 mm). However, MRI is an acceptable alternative method for assessing disease in subjects who cannot receive intravenous contrast with CT scans. In such subjects MRI and PET scans will have to be obtained separately. Baseline bone marrow biopsies/aspirates may be omitted if not deemed essential for response assessment or patient management.

During treatment, radiology studies will be performed for tumor assessments ~~within 7 days prior to Day 1 of Cycles 3, 5, 7 and then every 3 months thereafter~~ **as indicated** in **Table 8: Schedule of Assessments (LAM-002A Continuous Monotherapy Administration), Table 9: Schedule of Assessments (LAM-002A Intermittent Monotherapy Administration), Table 10: Schedule of Assessments (LAM-002A/Rituximab Combination Therapy), and Table 11: Schedule of Assessments (LAM-002A/Atezolizumab Combination Therapy) in Section 8.7.** until PD or use of alternative antineoplastic therapy. If necessary per applicable response criteria, a repeat bone marrow biopsy or aspirate will be required for subjects who have a Complete Response (CR) by imaging and physical examination. Subjects with CLL/SLL who achieve CR will require assessment of minimal residual disease (MRD) by flow cytometry of bone marrow and peripheral blood.

Section 12. PHARMACOKINETIC ASSESSMENTS

Changes: Additional information regarding the timing of pharmacokinetic assessments was provided, and references to the schedules of assessment tables were included to clarify where information regarding the timing of pharmacokinetic assessments can be found. Collection of unscheduled pharmacokinetic samples was removed because it is difficult to manage and provided little incremental information over the frequent pharmacokinetic samples that were already planned.

12. PHARMACOKINETIC ASSESSMENTS

Plasma concentration levels of apilimod and the active metabolites will be measured in the dose-escalation and dose-expansion stages at each of the specified time points; **Table 8: Schedule of Assessments (LAM-002A Continuous Monotherapy Administration), Table 9: Schedule of Assessments (LAM-002A Intermittent Monotherapy Administration), Table 10: Schedule of Assessments (LAM-002A/Rituximab Combination Therapy), and Table 11: Schedule of Assessments (LAM-002A/Atezolizumab Combination Therapy) in Section 8.7** The analytical laboratory will measure plasma concentrations of apilimod using a validated analytic method. PK parameters ~~that~~ will be estimated ~~on Day 1 and Day 8~~ using standard non-compartmental methods ~~as follows~~ **will include**: C_{max}, t_{max}, AUC_{0-t}, AUC_{τ}; $t_{½}$, trough concentrations on Days 8 and 15, and a comparison of AUC_{0-t} from Days 1 and 8 **or Days 1 and Day 10 (as appropriate)**; additional parameters may be determined based on the available data. Accumulation will be assessed by calculating the ~~Day 15/Day 1~~ accumulation ratios I for C_{max} and AUC **when comparing Day 8 to Day 1 for all continuous LAM-002A regimens (whether given as monotherapy or in combination) or when comparing Day 10 to Day 1 for the intermittent LAM-002A regimen**. Dose proportionality for C_{max} and AUC_{0-t} will be assessed by applying an appropriate power model to the data. Descriptive statistics of PK parameters will include minimum, maximum, mean, standard deviation, percent coefficient of variation (%CV), and range.

Metabolite concentrations at the time points indicated in Table 13. All subjects must participate in PK assessments. Fasting status must be recorded at the time of each PK blood draw.

Table 13: Pharmacokinetic Sampling Time Points

Sample	Study Day	PK Sampling Time Points[a]
1[b]	1	Pre-dose (within 30 min prior to dose of LAM-002A)
2	1	0.5 hour (± 10 min) after dosing with LAM-002A
3	1	1 hour (± 10 min) after dosing with LAM-002A
4	1	2 hours (± 10 min) after dosing with LAM-002A
5	1	4 hours (± 10 min) after dosing with LAM-002A
6	1	6 hours (± 10 min) after dosing with LAM-002A
7	1	8 hours (± 10 min) after dosing with LAM-002A
8[b]	8 **or 10**[c]	Pre-dose (within 30 min prior to dose of LAM-002A)
9	8 **or 10**[c]	0.5 hour (± 10 min) after dosing with LAM-002A
10	8 **or 10**[c]	1 hour (± 10 min) after dosing with LAM-002A
11	8 **or 10**[c]	2 hours (± 10 min) after dosing with LAM-002A
12	8 **or 10**[c]	4 hours (± 10 min) after dosing with LAM-002A
13	8 **or 10**[c]	6 hours (± 10 min) after dosing with LAM-002A
14	8 **or 10**[c]	8 hours (± 10 min) after dosing with LAM-002A
15[b]	15	Pre-dose (within 30 min prior to dose of LAM-002A)

[a] Applies to first dose of the day
[b] Dosing with LAM-002A should occur after the PK sample has been drawn.
[c] Sampling to be performed on Day 8 for all continuous LAM-002A regimens (whether given as monotherapy or in combination) or on Day 10 for the intermittent LAM-002A dosing regimen.
Abbreviations: min: Minutes; PK: Pharmacokinetic

Comprehensive information on blood sample acquisition, handling, storage and sample shipments can be found in the pharmacokinetic laboratory manual.

On Cycle 1 Day 1, and Cycle 1 Day 8 the dose of LAM-002A should be orally administered (a minimum fasting state of 6 to 8 hours) by staff in the clinic immediately after the collection of the biomarker samples and after the collection of the first PK sample. Subjects are allowed to eat after PK Sample #4 (hour 2) has been collected. Subjects may consume clear liquids during fasting periods.

On Cycle 1 Day 15, the dose of LAM-002A should be orally administered (a minimum fasting state of 6 to 8 hours) by staff in the clinic immediately after collection of the pre-dose PK and biomarker samples.

~~In addition, PK samples may be collected, if possible and deemed appropriate by the Investigator and Sponsor, whenever a subject has a study treatment-related SAE or QTc > 500 msec.~~

Section 13. BIOMARKER ASSESSMENTS

Changes: Biomarkers were clarified and updated consistent with emerging data and methods and the modified study therapy plan.

13. BIOMARKER ASSESSMENTS

Plasma ~~Blood smears~~ will be obtained for pharmacodynamics biomarker analysis on C1D1, ~~and~~ C1D**15**, **and at the EOT visit** ~~8 as follows: pre-dose, 4 and 8 hours post-first dose of the day and C1D15 pre-dose only~~. Samples will be analyzed for **circulating tumor DNA to measure tumor burden and mutational changes.**~~PIKfyve inhibition as determined by the extent of vacuolation by microscopy.~~

Plasma pharmacodynamic samples will also be collected for determination of plasma apilimod and active metabolite activity at the PK time points indicated in Table 13. The plasma will be used in an ex vivo cathepsin activity assay or equivalent to determine level of PIKfyve inhibition.

Plasma will **also** be collected for evaluation of circulating cytokines (including IL-12 and IL-23) predose on each of Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 1 Day 15 **and at the EOT visit**. Samples will be analyzed using appropriate □mmune-detection assays.

For all subjects, PBMCs**/B cells** will be collected ~~on~~ **during the prescreening period**~~, Cycle 1, Day 1 pre-treatment; on Cycle 1, Day 1 at 8 hours post-dose; and on Cycle 1, Day 8 at 8 hours post-dose~~ for determination of changes in gene expression that may predict or correlate with anti-lymphoma activity and/or pharmacodynamic activity **and will also serve as normal-tissue controls for gene mutation studies in tumors**.

For subjects with NHL, archival tissue from the most recent available biopsy or surgery or fresh tumor tissue **(preferred)** must be obtained pretreatment. Alternatively, cells from a bone marrow aspirate may be obtained in subjects with bone marrow involvement due to NHL **(>50% NHL cells).** For subjects undergoing a biopsy, adequate tumor tissue should be acquired via excisional biopsy, incisional **biopsy or core needle biopsy (e.g.,** ≥3 passes using a 16-gauge core needle). Tissue will be submitted for evaluation of the percentage of tumor cells and analysis of genetic alterations and/or gene expression that may predict anti-lymphoma activity and/or pharmacodynamics activity. In addition, tumor may be evaluated for known prognostic characteristics (e.g., for DLBCL: ABC or GCB subtype; expression of BCL2, BCL6, Ki-67, CD20, and MYC; other mutational status)**, for PDL1 status, and for immune infiltration**.

Subjects with CLL/SLL must provide either a fresh blood sample containing circulating tumor cells or a bone marrow aspirate sample pretreatment. Tissue will be submitted for evaluation of the percentage of tumor cells and analysis of genetic alterations and/or gene expression that may predict anticancer activity and/or pharmacodynamic activity. In addition, for subjects with CLL/SLL, the sponsor may arrange for a portion of the sample to be evaluated at a sponsor-specified laboratory for known prognostic markers (e.g., quantitative immunoglobulins, FISH panel [chromosome 11q deletion, 13q deletion, 17p deletion and 12 trisomy], DNA mutational analysis for p53, IgHV [including IgHV3-21], and other genes of interest in CLL [e.g., Notch]; flow cytometry [for CD5, CD10, CD11c, CD19, CD20, CD23, CD38, CD45, kappa and lambda light chains and ZAP-70], **and/or** β2-microglobulin).

A saliva sample will be obtained ~~on Cycle 1 Day 1~~ **during Screening** as a normal-tissue control for gene mutation studies in tumors.

Comprehensive information on tissue acquisition, handling, storage and sample shipments can be found in the biomarker sample process documents.

Section 14. STATISTICS

Changes: The Stage 1 dose-ranging approach and a statistical basis for the planned Stage 2 cohort sizes were provided. A method for continuous reassessment of safety created a framework for risk assessments associated with the investigational combination therapies to be explored in the study. This safety method complemented the restrictions on the pace of Stage 2 combination therapy enrollment detailed in Section 6.1.3 of the protocol.

14.1. Determination of Sample Size

14.1.1. Stage 1 (Dose Escalation)

The planned sample size for the dose-escalation is not based on a specific statistical hypothesis but on experience in the conduct of similar trials in subjects with cancer.

In the dose escalation, the cohort sizes of 3 to 6 subjects allow evaluation of regimen safety using a standard definition of MTD (ie, a starting dose associated with DLT in <33% of subjects during the first cycle of therapy). Based on the planned 3+3 dose-escalation scheme, Table 14 shows the probability of escalating to the next dose level or proceeding to the next stage, based on the true rate of DLT at the current dose level.

Table 14: Statistical Basis for 3+3 Dose-Escalation Paradigm

True Incidence of DLT	Probability of Escalating
10%	0.91
20%	0.71
30%	0.49
40%	0.31
50%	0.17
60%	0.08

Abbreviation: DLT=dose-limiting toxicity

Thus, if the true underlying proportion of DLT is low (eg, ≤10% at the current dose level, there is a high probability (≥0.91) of dose escalation to the next dose level. Conversely, if the true underlying proportion of DLT is high (eg, ≥60%) at the current dose level, there is a low probability (≤0.08) of escalation to the next dose level.

14.1.2. Stage 2 (Cohort Expansion)

As indicated in Section 6.1.2, expansion cohorts of 6 subjects will be accrued. Enrollment of 6 subjects per cohort offers the opportunity to determine if there is any antitumor activity sufficient to warrant further development in the selected tumor types. An ORR of ≥ 35% is considered of potential interest in each of the selected indications. If 0/6 subjects in a cohort experience an objective response, then a population ORR of ≥ 35% for that cancer can be excluded with > 90% certainty (1-sided exact binomial 90% CI upper bound = 32%).

Experience indicates the rates of discontinuations from rituximab or atezolizumab therapy are < 5% (Genentech 2016, Genentech 2017). A rate of AE discontinuations of therapy due to adverse events of ≥25% in the 2 combination therapy groups of LAM-002A/rituximab (N = 12) or LAM-002A/atezolizumab (N = 12) would suggest a potential adverse interaction among the components of the combination therapy. Sequential Pocock-type boundaries will be used to continuously monitor the rate of AE discontinuations and to test the null hypothesis, after each subject, that the event rate is ≥ 0.25 using a 1-sided significance test of ~ 0.05. AE discontinuation rates will be considered excessive if the following n/N values are observed: -/1, -/2, 3/3, 3/4, 4/5, 4/6, 5/7, 5/8, 5/9, 6/10, 6/11, 7/12. With this method, the probability of detecting an AE discontinuation safety signal ranges from 0.091 to >0.820 for true discontinuation rates of 25% to ≥ 60%. If excessive levels of AE discontinuation are observed, the sponsor, working in collaboration with the cooperating companies and investigators, will take appropriate actions (eg, continuation of the cohort with modifications in design or monitoring plan, interruption of cohort accrual, cohort therapy discontinuation).

~~This Phase 1 trial is being conducted primarily to assess the safety and tolerability of LAM-002A (apilimod dimesylate capsules) when administered in subjects with relapsed or refractory B-cell NHL and to determine the MTD and RP2D of LAM-002A. No formal sample size estimation was performed. The choice of the number of subjects was based on the standard 3 + 3 design that is commonly used in Phase 1 trials of anti-cancer investigational drugs. For the Dose Escalation Stage of the study, the maximum sample size will be approximately 60 subjects if 6 subjects are assigned to each of the 9 potential dose levels and an additional 6 patients are accrued at the RP2D. However, additional subjects may be added if exploration of intermediate dose level(s) of LAM-002A is warranted.~~

~~Up to 45 additional evaluable subjects (3 cohorts of 15 subjects) may be enrolled at the RP2D and schedule in the Expansion Stage of the study. The safety population will consist of all subjects receiving at least 1 dose of LAM-002A. The assessment of DLT and MTD will involve only those subjects completing the first cycle of therapy, unless the subject discontinuation in first cycle was due to a DLT.~~

Section 21. STUDY DISCONTINUATION

Change: This section was added to separate it from Sections 6.11 and 6.12, which relate to duration of therapy and discontinuation of participation for individual subjects.

12. STUDY DISCONTINUATION

Both the investigator and LAM reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures. The investigator will be responsible for notifying the relevant study center IRB. LAM will be responsible for notifying the appropriate regulatory authorities. In terminating the study, the investigator and LAM will assure that adequate consideration is given to the protection of the subjects' interests. As directed by LAM, all study materials must be collected and all eCRFs completed to the greatest extent possible.

Section 22. LIST OF REFERENCES

Change: The reference list was updated to include additional relevant references.

22. LIST OF REFERENCES

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Changes made in Amendment 7 (14 Jan 2019)

In preparing this amendment of the protocol document, the following changes were made. Explanations of the changes are provided in italics as "*Changes*." Inserted text is indicated by red double-underlined font. Deleted text is indicated by ~~red strikeout font~~. Changes to the synopsis also appear in the body of the protocol; thus, changes to the synopsis are not described and only changes to the body of the protocol are described. Modifications to the list of abbreviations and definitions of terms or minor typographical or syntax corrections are not indicated.

Title Page

Change: The protocol version and date were updated.

Protocol Version and Date: Version 8.0, 14 Jan 2019
~~Version 7.0; 25 Oct 2017~~

Investigator's Agreement

Change: The date was updated.

I have read the attached Protocol entitled "A Phase 1 Dose Escalation Study of the Safety and Pharmacokinetics of LAM-002A (apilimod dimesylate capsules) Administered Orally in Subjects with Relapsed or Refractory B-cell Non-Hodgkin's Lymphoma" dated ~~25 Oct 2017~~ 14 Jan 2019. I agree to abide by all provisions set forth herein. I agree to comply with the International Conference on Harmonisation Guidelines on Good Clinical Practice, effective in the United States from 09 May 1997, and applicable United States Food and Drug Administration regulations set forth in 21 Code of Federal Regulations (CFR) §50, 54, 56, and 312 and any applicable local regulatory requirements. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical investigation without the prior written consent of LAM Therapeutics, 530 Old Whitfield Street, Guilford CT 06437, United States.

Procedures in Case of Emergency

Change: The medical monitor's email address was updated.

Prior to initiation of the study, the sponsor (or its designee) will provide a study roster with contact information for applicable study personnel.

The medical monitor, [redacted], can be reached by telephone at [redacted] and by email at [redacted].

Section 4.1.4.2 Efficacy

Change: Introductory information regarding LAM-002A efficacy was updated.

Efficacy data in patients with hematological malignancies are evolving. As of ~~30 Sep 2017~~ 14 Jan 2019, 2/5 patients with FL receiving LAM-002A monotherapy had achieved an objective response (1 complete response [CR] and 1 partial response [PR]); 2/4 patients with FL receiving LAM-002A/rituximab had achieved PRs, and 1/1 patient with FL receiving LAM-002A/atezolizumab had achieved a PR. Among subjects with other types of NHL, positron emission tomography (PET) demonstrated systemic partial metabolic responses in nodal and extranodal lesions in 3 patients with refractory DLBCL (treated at 100 mg BID, 75 mg TID, and 125 mg BID) (1 of whom also received radiation for bulky axillary adenopathy); concomitant computed tomography (CT) demonstrated anatomic shrinkage of many lesions. One additional subject with transformed, refractory DLBCL (treated at 125 mg BID) experienced tumor lysis syndrome (TLS). One patient with marginal zone lymphoma (MZL) (treated at 125 mg BID) has had a metabolic response by PET together with a 43% decrease in the sum of the products of the perpendicular diameters (SPD) of index lesions by CT. Another patient with MZL and a patient with chronic lymphocytic leukemia (CLL) (both receiving 100 mg BID) experienced prolonged stable disease through 11+ and 14 cycles, respectively.

Section 4.1.4.3 Safety

Change: Introductory information regarding LAM-002A safety was updated.

In the ongoing trial of LAM-002A in patients with hematological cancers, dose-dependent gastrointestinal events of nausea, vomiting, and diarrhea have been observed. ~~No renal insufficiency has been observed in clinical trials to date except in 1~~ One patient with DLBCL ~~who acutely~~ developed acute transient elevations in serum creatinine and blood-urea nitrogen (BUN) due to tumor lysis syndrome (TLS) shortly after starting LAM-002A at a dose of 125 mg BID. One patient with a hematological malignancy receiving the drug at 150 mg BID developed asymptomatic Grade 3 hyponatremia that was attributed to the combined effects of LAM-002A-induced diarrhea and hydrochlorothiazide administration. No other clinically significant safety signals in laboratory, physical examination, or vital sign findings have been noted.

Section 5.3 Exploratory Objectives

Change: The exploratory objectives were updated to reflect changes to the substrates and parameters being analyzed.

- To evaluate the pharmacodynamic effects of LAM-002A, administered orally, in plasma assays and surrogate tissue (gene expression in peripheral blood mononuclear cells [PBMCs]/B cells, and plasma cytokines [including (IL)-12 and IL-23]).

- To evaluate tumor and/or plasma for gene expression and genetic alterations (with saliva and/or B-cell-depleted PBMC collection for germ-line control) and surrogate tissue (PBMC/B cells) for gene expression that may predict anti-lymphoma activity.
- To evaluate plasma for changes in analytes or tumor for protein expression that may predict anti-lymphoma activity

Section 5.6 Exploratory Endpoints

Change: The exploratory endpoints were updated to reflect changes to the substrates and parameters being analyzed.

- Extent of PIKfyve inhibition as determined by plasma inhibitory assays
- Changes in gene expression in PBMCs
- Changes in plasma cytokines (including IL-12 and IL-23)
- Correlation between genetic alterations as determined by next generation sequencing and/or gene expression in tumor tissue, plasma (circulating tumor DNA), or PBMCs/B cells and anti-lymphoma activity following treatment with LAM-002A
- Correlation between changes in plasma bioanalytes or tumor protein expression and anti-lymphoma activity following treatment with LAM-002A as determined by proteomic tools

Section 6.1.2 Expansion Stage

Change: The protocol was modified to permit evaluation of single-agent LAM-002A or the LAM-002A/rituximab combination in additional patients with FL. Use of either intravenously administered rituximab or subcutaneously administered rituximab hyaluronidase human was permitted.

Once the MTD and/or recommended phase 2 dose (RP2D) and schedule is determined, the study will enter the expansion stage, in which cohorts of subjects will be accrued in order to obtain additional information on safety, tolerability, preliminary anti-tumor activity, PK, and pharmacodynamic data at the RP2D and schedule when LAM-002A is administered alone or in combination with rituximab/rituximab hyaluronidase or atezolizumab. Expansion-stage cohorts will comprise groups of subjects with specific types of previously treated, relapsed, progressive, and measurable NHL who will receive LAM-002A monotherapy or LAM-002A-containing combination therapy as shown in Table 2. For both monotherapy and combination cohorts, the starting dose of LAM-002A will be 125 mg BID administered continuously.

Table 2: Expansion Stage Disease Types and Therapies

Cohort Number	NHL Type	Investigational Drug	Combination Drug	Evaluable Subjects, n
1	FL	LAM-002A	--	~~6~~Up to ~20
2	MZL	LAM-002A	--	6
3	DLBCL-GCB	LAM-002A	--	6
4	DLBCL-ABC	LAM-002A	--	6
5	FL or MZL	LAM-002A	Rituximab or rituximab hyaluronidase human	~~6~~Up to ~20 with FL
6	DLBCL-GCB or DLBCL-ABC	LAM-002A	Rituximab or rituximab hyaluronidase human	6
7	FL or MZL	LAM-002A	Atezolizumab	6
8	DLBCL-GCB or DLBCL-ABC	LAM-002A	Atezolizumab	6

Abbreviations: ABC: activated B-cell (subtype); DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; GCB: germinal center B-cell (subtype); MZL: marginal zone lymphoma; NHL: non-Hodgkin lymphoma

Section 6.2 Number of Subjects

Change: Information regarding the total potential accrual to the study was updated consistent with modifications to the protocol to evaluate single-agent LAM-002A or the LAM-002A/rituximab combination in additional patients with FL.

As many as 145 ~~110~~ subjects will be enrolled, assuming that:

- In the dose-escalation stage of the study, the total number of subjects will depend upon the numbers of subjects accrued to each dose level and the number of dose levels evaluated. If 6 subjects are enrolled at all open starting dose levels (Dose Levels 5, 6, 7, and 8) and 6 additional subjects are enrolled at the MTD or RD, as many as 30 subjects could be enrolled. To allow for the possibility that some subjects may not be fully evaluable for DLT or that an intermediate dose level might be evaluated, up to ~45 subjects may be enrolled.
- In the expansion stage of the study, if all 8 potential expansion cohorts ~~of 6 evaluable subjects~~ are accrued, as many as ~76~~48~~ subjects could be enrolled. To allow for the possibility that some subjects may not be fully evaluable for efficacy or to establish bounds on efficacy estimates with greater confidence, up to ~~65~~ 100 subjects may be enrolled.

Section 6.8.2.2 In-Clinic LAM-002A Administrations

Change: To 3rd paragraph only: Use of either intravenously administered rituximab or subcutaneously administered rituximab hyaluronidase human was permitted.

When given as a component of combination therapy with rituximab, LAM-002A will be started on Cycle 1 Day 1 with a BID schedule. LAM-002A will be administered after administration of premedications (see Section 6.8.3.1) and ~15 to 30 minutes prior to the start of the initial rituximab infusion. On Cycle 1 Day 8, the morning dose of LAM-002A will be administered

after premedications (see Section 6.8.3.1) and ~15 to 30 minutes prior to the rituximab infusion/injection.

Section 6.8.3 Rituximab or Rituximab/Hyaluronidase Human

Change: Use of either intravenously administered rituximab or subcutaneously administered rituximab hyaluronidase human was permitted. Relevant changes were made to provide necessary dosing and administration information.

6.8.3.1 Premedications

In accordance with rituximab/rituximab hyaluronidase human prescribing information (Genentech 2016, Genentech 2018), subjects should be premedicated with an antipyretic and an antihistamine to reduce the incidence and severity of infusion/injection reactions. A recommended regimen is diphenhydramine, 25 mg orally, and acetaminophen (paracetamol), 650 mg orally, both given ~30 minutes prior to each rituximab administration. Intravenous corticosteroids may also be administered as a premedication. Local practices and guidelines may be followed.

6.8.3.2 Rituximab Administration

Based on past experience with this regimen (Ghielmini 2004, Martinelli 2010), rituximab will be administered intravenously or rituximab/hyaluronidase human will be administered subcutaneously in the clinic for a total of 8 ~~infusions~~ treatments:

Intravenous rituximab (Rituxan®)

- Four induction infusions of 375 mg/m^2 will be administered weekly on Cycle 1 Day 1, Cycle 1 Day 8, Cycle 1 Day 15, and Cycle 1 Day 22.
- Four subsequent maintenance infusions of 375 mg/m^2 will be administered every 8 weeks on Cycle 4 Day 1, Cycle 6 Day 1, Cycle 8 Day 1, and Cycle 10 Day 1.

Subcutaneous rituximab (rituximab/hyaluronidase human; Rituxan Hycela®)

- An initial dose of 375 mg/mg^2 will be administered intravenously on Cycle 1 Day1.
- Three subcutaneous injections of 1,400 mg/23,400 Units (1,400 mg rituximab and 23,400 Units hyaluronidase human) will be administered weekly on Cycle 1 Day 8, Cycle 1 Day 15, and Cycle 1 Day 22.
- Four subsequent maintenance subcutaneous injections of 1,400 mg/23,400 Units (1,400 mg rituximab and 23,400 Units hyaluronidase human) will be administered every 8 weeks on Cycle 4 Day 1, Cycle 6 Day 1, Cycle 8 Day 1, and Cycle 10 Day 1.

~~The dose for each infusion will be 375 mg/m^2 of body surface area.~~ The dose calculation of body surface area for infused rituximab will be based on the subject's height and actual body weight prior to therapy. Once established based on the pretreatment body weight, the total dose of rituximab for the subject should not be altered during therapy based on fluctuations in body weight unless required by institutional policy.

At Cycle 1 Day 1, ~30 minutes after administration of the required antipyretic and antihistamine premedications and ~15 to 30 minutes after administration of the first dose of LAM-002A, the first infusion of rituximab will be administered via an infusion pump. For the initial infusion, the recommended infusion rate is 50 mg/hour. In the absence of infusion toxicity, the infusion rate can be increased in 50-mg/hour increments every 30 minutes, to a maximum of 400 mg/hour.

For subsequent rituximab infusions, the required antipyretic and antihistamine premedications will be given and the rituximab will be infused via an infusion pump. For these infusions, the infusion can be initiated at 100 mg/hour. In the absence of infusion toxicity, the infusion rate can be increased in 100-mg/hour increments every 30 minutes, to a maximum of 400 mg/hour. Alternatively, for subjects who tolerate the first infusion with Grade ≤3 infusion toxicity, subsequent infusions can be administered over a planned infusion time of 90 minutes, with ~20% of the total dose administered in the first 30 minutes and the remaining 80% of the total protein dose administered in the subsequent 60 minutes (Dakhil 2014, Genentech 2016).

For subsequent rituximab/hyaluronidase human injections, the required antipyretic and antihistamine premedications will be given and the rituximab/hyaluronidase human will be injected into the subcutaneous tissue of the abdomen over ~5 minutes. Areas where the skin is red, bruised, tender or hard, or areas where there are moles or scars should be avoided. No data are available on performing the injection at other sites of the body. If administration of rituximab/hyaluronidase human is interrupted, drug administration can continue at the same site or at a different site but restricted to the abdomen. Patients should be observed for ≥15 minutes following the completion of injection. During treatment with rituximab/hyaluronidase human, do not administer other medications for subcutaneous use at the same sites.

6.8.3.3 Management of Rituximab Infusion/Injection Toxicity

Rituximab can cause severe, including fatal, infusion reactions (Genentech 2016). Patients with pre-existing cardiac or pulmonary conditions, those who experienced prior cardiopulmonary adverse reactions to rituximab, and those with high numbers of circulating malignant cells ($\geq 25 \times 10^9$/L) may be at particular risk. Severe reactions typically occur during the first infusion and are generally less frequent and less severe with subsequent infusions. The time to onset of infusion toxicity ranges from 30 to 120 minutes. Rituximab-induced infusion reactions and sequelae include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, and/or anaphylactoid events.

Rituximab infusions/injections should be interrupted or slowed in subjects experiencing Grade ≥3 rituximab-related infusion reactions. Medical management (eg, oxygen, epinephrine, bronchodilators, and/or glucocorticoids) should be instituted, as needed. Upon improvement of symptoms, the infusion may be continued at 50% of the previous rate. At the discretion of the investigator, rituximab therapy may be permanently discontinued in subjects with Grade 4 infusion/injection reactions or with reactions requiring substantial intervention.

6.8.3.4 Rituximab/Rituximab Hyaluronidase Human Dose Modifications and Supportive Care

Rituximab-related noninfectious pneumonitis has been described (Subramanian 2010) with an incidence of ~4.3% (Salmasi 2010). In patients developing rituximab-associated pneumonitis, the mean time from the first rituximab infusion to the onset of respiratory symptoms was 3 months, with a peak incidence after administration of a mean cumulative dosage of 1600 mg/m2 (Lioté 2010).

Severe, including fatal, mucocutaneous reactions can occur in patients receiving rituximab during infusion or at later timepoints. Non-infusion related events have included paraneoplastic pemphigus, Stevens Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis (Genentech 2016). The onset of these reactions has varied from 1 to 13 weeks following initiation of rituximab exposure.

Among patients receiving rituximab in combination with chemotherapy, rare instances of life-threatening bowel obstruction or perforation has been observed (Ram 2009), primarily in patients with NHL. In post-marketing reports, the mean time to documented gastrointestinal perforation was 6 (range 1–77) days from start of chemoimmunotherapy.

Fulminate and fatal HBV infection and reactivation can occur during or after treatment with rituximab (Genentech 2016). The risk is very low among patients with negative anti-HBc serology (Matsue 2010) and/or undetectable HBV DNA as assessed by quantitative PCR. Because subjects with such evidence of persistent HBV infection are excluded from this study, reactivation is not anticipated. Other serious bacterial, fungal, and new or reactivated viral infections have also occurred during and for ~1 year following rituximab-based therapy (Gea-Banacloche 2010). Other new or reactivated viral infections in patients receiving rituximab have included CMV, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and HCV. Progressive multifocal leukoencephalopathy (PML) due to polyomavirus JC has been observed in patients who have received rituximab therapy for hematologic malignancies (Carson 2009).

No dose reductions of rituximab/rituximab hyaluronidase human are recommended. If a subject experiences an AE that is suspected to be related to rituximab/rituximab hyaluronidase human and is of sufficient severity to warrant modification of therapy, administration of the drug should be interrupted or discontinued. Protocol-recommended management of selected adverse events and appropriate supportive care is described in Table 5.

Table 5: Recommended Rituximab or Rituximab/Hyaluronidase Modifications and Supportive Care

Adverse Event	Rituximab Interruption and Resumption	Rituximab Permanent Discontinuation	Supportive Care
Pneumonitis	Interrupt for Grade 2; resume when Grade ≤ 1	Grade ≥3	For Grade ≥2, corticosteroids, 1-2 mg/kg of prednisone equivalents
Rash	Interrupt for Grade 3; resume when Grade ≤ 1	Grade 4	For Grade 2, topical corticosteroids. For Grade ≥ 3, corticosteroids, 1-2 mg/kg of prednisone equivalents
Hepatitis	Grade ≥3 elevations of serum AST or ALT (> 5 x ULN); resume when Grade ≤ 1	--	Evaluate for HBV positivity; if HBV reactivation, treat with appropriate antiviral considering any potential for drug-drug interaction with LAM-002A.
Bowel obstruction or perforation	--	Any grade	Provide appropriate antibiotic therapy and surgical supportive care.
Infection	Grade ≥3; resume when control of infection achieved	--	Treat with appropriate systemic antibiotics for suspected or confirmed infections

Abbreviations: ALT=alanine aminotransferase, AST=aspirate aminotransferase, ULN=upper limits of normal

Section 6.11 Duration of Subject Participation

Change: Use of either intravenously administered rituximab or subcutaneously administered rituximab hyaluronidase human was permitted.

Subjects may continue receiving LAM-0002A until the occurrence of any events requiring treatment discontinuation as defined in Section 6.8.2.5 and Section 6.12.

Subjects allocated to LAM-0002A/rituximab may continue to receive rituximab or rituximab hyaluronidase human until the earliest of a maximum of 8 infusions or the occurrence of any events requiring treatment discontinuation as defined in Section 6.8.3.4 and Section 6.12.

Subjects allocated to LAM-0002A/atezolizumab may continue to receive atezolizumab until the earliest of any events requiring treatment discontinuation as defined in Section 6.8.4.4 or Section 6.12.

Note: If medically appropriate, subjects allocated to combination doublet therapy may continue with protocol-specified therapy for the therapeutic agent (LAM-002A, rituximab, rituximab hyaluronidase human, or atezolizumab) that continues to be tolerated, even if the other agent need to be discontinued due to drug-specific toxicity.

Section 7.1 Subject Inclusion Criteria

Change: (Inclusion Criterion 11 only): Biopsy procedures were clarified.

11. For subjects with lymphoma: The subject is willing to undergo a pretreatment core needle, excisional, or incisional biopsy of a lymphoma nodal lesion (preferred); or is willing to undergo a pretreatment bone marrow aspirate if there is known bone marrow involvement (≥ 50% NHL cells). If a biopsy or bone marrow aspirate is not possible, archived tumor tissue that was obtained within 4 months prior to the start of screening can be used, provided adequate quantities are available. ~~The subject has archived tumor tissue for analysis that was obtained within 4 months prior to the start of screening; is willing to undergo a pretreatment core needle, excisional, or incisional biopsy of a lymphoma nodal lesion; or is willing to undergo a pretreatment bone marrow aspirate if there is known bone marrow involvement (≥ 50% NHL cells).~~

Section 7.2 Subject Exclusion Criteria

Change: (Exclusion Criterion 15 only): The severity of hypertension warranting exclusion from protocol therapy was clarified.

15. The subject has uncontrolled significant intercurrent illness including, but not limited to, ongoing or active infection, history of congestive heart failure within 6 months, Grade ≥3 hypertension, unstable angina pectoris within 6 months, stroke within 6 months, myocardial infarction within 6 months, or cardiac arrhythmias. (Controlled chronic atrial fibrillation will not be excluded).

Section 8.1.3 Medical History

Change: The text was clarified to indicate that past pathology data should be collected as part of each subject's medical history.

At Screening, a complete medical history will be obtained from each subject, including relevant medical history, current primary cancer diagnosis, pathology reports (including corresponding flow cytometry and cytogenetic reports), prior cancer treatments (chemo- and immunotherapies, radiation therapy, surgeries), and disease-specific characteristics, such as tumor stage and histology.

Section 8.1.5 Disease Status Assessment for Subjects with NHL

Change: (Paragraphs 3 and 4 only): Biopsy procedures were clarified.

Fresh tumor tissue (preferred) or archival tumor tissue that was obtained within 4 months prior to the start of screening (provided adequate quantities are available) ~~Archival tissue from the most recent available biopsy or surgery or fresh tumor tissue (preferred)~~ must be obtained pretreatment for nucleic acid extraction. For subjects undergoing a biopsy, adequate tumor tissue should be acquired via excisional biopsy, incisional biopsy or core needle biopsy (e.g., ≥ 3 passes using a 16-gauge core needle). Confirmation of tumor in biopsy with fine needle aspirate, touch prep, or FFPE processing is requested when possible. The tumor lesion selected

should not have been previously irradiated and should not be an index lesion that is followed for response assessment. Alternatively, cells from a bone marrow aspirate may be obtained in subjects with bone marrow involvement due to NHL (≥50% of cells). Tissue will be submitted for evaluation of the percentage of tumor cells and analysis of genetic alterations and/or gene expression that may predict anti-lymphoma activity and/or pharmacodynamics activity.

In addition, tumor tissue from the fresh biopsy or most recently availably biopsy or surgery will be evaluated for known prognostic characteristics (e.g., for DLBCL: ABC or GCB subtype; expression of BCL2, BCL6, Ki-67, CD20, and MYC; other mutational status), for PDL1 status, and for immune infiltration. The baseline biopsy procedure (if required) should ideally be performed after the study candidate has undergone the baseline radiology examination and is otherwise considered eligible for study participation.

Section 8.3.1.3 PK and Biomarker Assessments

Change: More detailed information regarding PK and biomarkers was included.

Pharmacokinetic samples will be collected for determination of apilimod and metabolite concentrations in plasma at the time points indicated in Section 12. All subjects must participate in PK assessments. Fasting status must be recorded at the time of each PK blood draw. Comprehensive information on blood sample acquisition, handling, storage and sample shipments can be found in the laboratory manual "Procedures for Processing and Shipping PK and Biomarker Samples." ~~pharmacokinetic laboratory manual.~~

Biomarker samples will be obtained at time points indicated in Section 13. Comprehensive information on tissue acquisition, handling, storage, and sample shipments can be found in the laboratory manual "Procedures for Processing and Shipping PK and Biomarker Samples."

Section 8.7 Schedules of Assessments; Table 8 Schedule of Assessments (LAM-002A Continuous Monotherapy Administration)

Changes: (Table 8, Footnotes f and q): Text regarding the timing of laboratory assessments was clarified. Information regarding biopsy procedures was clarified.

f. All hematology and chemistry laboratory parameters should be assessed at Screening and at C1D1, C1D8, C1D15, C≥2D1 (all subsequent cycles) ~~Days 1, 8, and 15 of Cycles 1 and 2~~, and then at least once prior to the start of all subsequent cycles and at EOT. Obtaining a chemistry laboratory parameter on Days 2 and Day 3 of Cycle 1 is only required in subjects with intermediate or high risk of TLS (per the risk definition in Section 6.8.1). Except for Days 1, 2, and 3 of Cycle 1, these parameters may be obtained within 72 hours prior to the planned day of collection. Abnormal test values should be monitored per protocol guidance.

q Fresh tumor tissue (preferred) or archival tissue from the most recent available biopsy or surgery (within 4 months prior to the start of screening) must be obtained pretreatment for nucleic acid extraction. For subjects undergoing a biopsy, adequate tumor tissue should be acquired via excisional biopsy, incisional biopsy or core needle biopsy (e.g., ≥ 3 passes using a 16-gauge core needle). Confirmation of tumor in biopsy with fine needle aspirate, touch prep, or FFPE processing is requested when possible. The tumor lesion selected should not have been previously irradiated and should not be an index lesion that is followed for response assessment. Alternatively, cells from a bone marrow aspirate may be obtained in subjects with bone marrow involvement due to NHL (>50% of cells). Tissue will be submitted for evaluation of the percentage of tumor cells and analysis of genetic alterations and/or gene expression that may predict anti-lymphoma activity and/or pharmacodynamics activity. In addition, the fresh biopsy or tumor tissue from the most recently availably biopsy or surgery will be evaluated for known prognostic characteristics (e.g., for DLBCL: ABC or GCB subtype; expression of BCL2, BCL6, Ki-67, CD20, and MYC; other mutational status), for PDL1 status, and for immune infiltration. The baseline biopsy procedure (if required) should ideally be performed after the study candidate has undergone the baseline radiology examination and is otherwise considered eligible for study participation~~Archival tissue from the most recent available biopsy or surgery or fresh tumor tissue (preferred) must be obtained pretreatment for nucleic acid extraction. For subjects undergoing a biopsy, adequate tumor tissue should be acquired via excisional biopsy, incisional biopsy or core needle biopsy (e.g., ≥ 3 passes using a 16-gauge core needle). Alternatively, cells from a bone marrow aspirate may be obtained in subjects with bone marrow involvement due to NHL (≥50% of cells). Tissue will be submitted for evaluation of the percentage of tumor cells and analysis of genetic alterations and/or gene expression that may predict anti-lymphoma activity and/or pharmacodynamics activity. In addition, tumor tissue from the most recently availably biopsy or surgery will be evaluated for known prognostic characteristics (e.g., for DLBCL: ABC or GCB subtype; expression of BCL2, BCL6, Ki-67, CD20, and MYC; other mutational status), for PDL1 status, and for immune infiltration. The baseline biopsy procedure (if required) should ideally be performed after the study candidate has undergone the baseline radiology examination and is otherwise considered eligible for study participation~~.

Section 8.7 Schedules of Assessments; Table 9 Schedule of Assessments (LAM-002A Intermittent Monotherapy Administration)

Changes: (Table 9, Footnotes f and q): Text regarding the timing of laboratory assessments was clarified. Information regarding biopsy procedures was clarified.

f. All hematology and chemistry laboratory parameters should be assessed at Screening and at C1D1, C1D8, C1D15, C>2D1 (all subsequent cycles) ~~Days 1, 8, and 15 of Cycles 1 and 2~~, and then at least once prior to the start of all subsequent cycles and at EOT. Obtaining a chemistry laboratory parameter on Days 2 and Day 3 of Cycle 1 is only required in subjects with intermediate or high risk of TLS (per the risk definition in Section 6.8.1). Except for Days 1, 2, and 3 of Cycle 1, these parameters may be obtained within 72 hours prior to the planned day of collection. Abnormal test values should be monitored per protocol guidance.

q Fresh tumor tissue (preferred) or archival tissue from the most recent available biopsy or surgery (within 4 months prior to the start of screening) must be obtained pretreatment for nucleic acid extraction. For subjects undergoing a biopsy, adequate tumor tissue should be acquired via excisional biopsy, incisional biopsy or core needle biopsy (e.g., ≥ 3 passes using a 16-gauge core needle). Confirmation of tumor in biopsy with fine needle aspirate, touch prep, or FFPE processing is requested when possible. The tumor lesion selected should not have been previously irradiated and should not be an index lesion that is followed for response assessment. Alternatively, cells from a bone marrow aspirate may be obtained in subjects with bone marrow involvement due to NHL (>50% of cells). Tissue will be submitted for evaluation of the percentage of tumor cells and analysis of genetic alterations and/or gene expression that may predict anti-lymphoma activity and/or pharmacodynamics activity. In addition, the fresh biopsy or tumor tissue from the most recently availably biopsy or surgery will be evaluated for known prognostic characteristics (e.g., for DLBCL: ABC or GCB subtype; expression of BCL2, BCL6, Ki-67, CD20, and MYC; other mutational status), for PDL1 status, and for immune infiltration. The baseline biopsy procedure (if required) should ideally be performed after the study candidate has undergone the baseline radiology examination and is otherwise considered eligible for study participation~~Archival tissue from the most recent available biopsy or surgery or fresh tumor tissue (preferred) must be obtained pretreatment for nucleic acid extraction. For subjects undergoing a biopsy, adequate tumor tissue should be acquired via excisional biopsy, incisional biopsy or core needle biopsy (e.g., ≥ 3 passes using a 16-gauge core needle). Alternatively, cells from a bone marrow aspirate may be obtained in subjects with bone marrow involvement due~~

~~to NHL (≥50% of cells). Tissue will be submitted for evaluation of the percentage of tumor cells and analysis of genetic alterations and/or gene expression that may predict anti-lymphoma activity and/or pharmacodynamics activity. In addition, tumor tissue from the most recently availably biopsy or surgery will be evaluated for known prognostic characteristics (e.g., for DLBCL: ABC or GCB subtype; expression of BCL2, BCL6, Ki-67, CD20, and MYC; other mutational status), for PDL1 status, and for immune infiltration. The baseline biopsy procedure (if required) should ideally be performed after the study candidate has undergone the baseline radiology examination and is otherwise considered eligible for study participation~~.

Section 8.7 Schedules of Assessments; Table 10 Schedule of Assessments (LAM-002A/Rituximab Combination Therapy)

Changes: (Table 10, Rituximab administration text, Footnotes p, u, v, w): Use of either intravenously administered rituximab or subcutaneously administered rituximab hyaluronidase human was described. Text regarding the timing of laboratory assessments was clarified.

Rituximab infusion/injection[w]

p. Fresh tumor tissue (preferred) or archival tissue from the most recent available biopsy or surgery (within 4 months prior to the start of screening) must be obtained pretreatment for nucleic acid extraction. For subjects undergoing a biopsy, adequate tumor tissue should be acquired via excisional biopsy, incisional biopsy or core needle biopsy (e.g., > 3 passes using a 16-gauge core needle). Confirmation of tumor in biopsy with fine needle aspirate, touch prep, or FFPE processing is requested when possible. The tumor lesion selected should not have been previously irradiated and should not be an index lesion that is followed for response assessment. Alternatively, cells from a bone marrow aspirate may be obtained in subjects with bone marrow involvement due to NHL (>50% of cells). Tissue will be submitted for evaluation of the percentage of tumor cells and analysis of genetic alterations and/or gene expression that may predict anti-lymphoma activity and/or pharmacodynamics activity. In addition, the fresh biopsy or tumor tissue from the most recently availably biopsy or surgery will be evaluated for known prognostic characteristics (e.g., for DLBCL: ABC or GCB subtype; expression of BCL2, BCL6, Ki-67, CD20, and MYC; other mutational status), for PDL1 status, and for immune infiltration. The baseline biopsy procedure (if required) should ideally be performed after the study candidate has undergone the baseline radiology examination and is otherwise considered eligible for study participation.~~Archival tissue from the most recent available biopsy or surgery or fresh tumor tissue (preferred) must be obtained pretreatment for nucleic acid extraction. For subjects undergoing a biopsy, adequate tumor tissue should be acquired via excisional biopsy, incisional biopsy or core needle biopsy (e.g., ≥ 3 passes using a 16-gauge core needle). Alternatively, cells from a bone marrow aspirate may be obtained in subjects with bone marrow involvement due to NHL (≥50% of cells). Tissue will be submitted for evaluation of the percentage of tumor cells and analysis of genetic alterations and/or gene expression that may predict anti-lymphoma activity and/or pharmacodynamics activity. In addition, tumor tissue from the most recently availably biopsy or surgery will be evaluated for known prognostic characteristics (e.g., for DLBCL: ABC or GCB subtype; expression of BCL2, BCL6, Ki-67, CD20, and MYC; other mutational status), for PDL1 status, and for immune infiltration. The baseline biopsy procedure (if required) should ideally be performed after the study candidate has undergone the baseline radiology examination and is otherwise considered eligible for study participation.~~

u Oral antipyretic, oral or intravenous antihistamine, and intravenous corticosteroid (at investigator discretion) (see Section 6.8.3.1) to be administered to the subject ~30 minutes prior to each rituximab infusion/injection (see Footnote w).

v LAM-002A to be administered to the subject in clinic (with recording of the date and actual clock time of the LAM-002A administration). On C1D1, LAM-002A will be started on a BID schedule after administration of premedications (see Section 6.8.3.1) and ~15 to 30 minutes prior to the start of the initial rituximab infusion. On C1D8, the morning dose of LAM-002A will be administered after premedications (see Section 6.8.3.1) and ~15 to 30 minutes prior to the rituximab infusion/injection.

w Rituximab, 375 mg/m^2, will be administered by intravenous infusion ~30 minutes after premedication weekly on C1D1, C1D8, C1D15, and C1D22 and then every 8 weeks on C4D1, C6D1, C8D1, and C10D1 for a total of 8 infusions. Alternatively, rituximab, 375 mg/m^2, will be administered by intravenous infusion ~30 minutes after premedication weekly on C1D1 and then rituximab hyaluronidase human, 1,400 mg rituximab and 23,400 Units hyaluronidase human per 11.7 mL, will be administered by subcutaneous injection on C1D8, C1D15, and C1D22 and then every 8 weeks on C4D1, C6D1, C8D1, and C10D1 for a total of 8 treatments.

Section 8.7 Schedules of Assessments; Table 11 Schedule of Assessments (LAM-002A/Atezolizumab Combination Therapy)

Changes: (Table 11, Footnote q): Information regarding biopsy procedures was clarified.

q. Fresh tumor tissue (preferred) or archival tissue from the most recent available biopsy or surgery (within 4 months prior to the start of screening) must be obtained pretreatment for nucleic acid extraction. For subjects undergoing a biopsy, adequate tumor tissue should be acquired via excisional biopsy, incisional biopsy or core needle biopsy (e.g., ≥ 3 passes using a 16-gauge core needle). Confirmation of tumor in biopsy with fine needle aspirate, touch prep, or FFPE processing is requested when possible. The tumor lesion selected should not have been previously irradiated and should not be an index lesion that is followed for response assessment. Alternatively, cells from a bone marrow aspirate may be obtained in subjects with bone marrow involvement due to NHL (≥50% of cells). Tissue will be submitted for evaluation of the percentage of tumor cells and analysis of genetic alterations and/or gene expression that may predict anti-lymphoma activity and/or pharmacodynamics activity. In addition, the fresh biopsy or tumor tissue from the most recently availably biopsy or surgery will be evaluated for known prognostic characteristics (e.g., for DLBCL: ABC or GCB subtype; expression of BCL2, BCL6, Ki-67, CD20, and MYC; other mutational status), for PDL1 status, and for immune infiltration. The baseline biopsy procedure (if required) should ideally be performed after the study candidate has undergone the baseline radiology examination and is otherwise considered eligible for study participation.~~Archival tissue from the most recent available biopsy or surgery or fresh tumor tissue (preferred) must be obtained pretreatment for nucleic acid extraction. For subjects undergoing a biopsy, adequate tumor tissue should be acquired via excisional biopsy, incisional biopsy or core needle biopsy (e.g., ≥ 3 passes using a 16-gauge core needle). Alternatively, cells from a bone marrow aspirate may be obtained in subjects with bone marrow involvement due to NHL (≥50% of cells). Tissue will be submitted for evaluation of the percentage of tumor cells and analysis of genetic alterations and/or gene expression that may predict anti-lymphoma activity and/or pharmacodynamics activity. In addition, tumor tissue from the most recently availably biopsy or surgery will be evaluated for known prognostic characteristics (e.g., for DLBCL: ABC or GCB subtype; expression of BCL2, BCL6, Ki-67, CD20, and MYC; other mutational status), for PDL1 status, and for immune infiltration. The baseline biopsy procedure (if required) should ideally be performed after the study candidate has undergone the baseline radiology examination and is otherwise considered eligible for study participation.~~

Section 9.3 Rituximab/Hyaluronidase Human (For Subcutaneous Administration)

Changes: Information regarding subcutaneously administered rituximab hyaluronidase human was included.

9.3 Rituximab/Hyaluronidase Human (For Subcutaneous Administration)

9.3.1. Description

Rituximab/hyaluronidase human (Rituxan Hycela®) is a genetically engineered chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen found on pre-B and mature B cells. In this formulation, it is combined with hyaluronidase human, an endoglycosidase (Genentech 2018). Rituximab is produced by mammalian Chinese hamster ovary cells. The protein has an approximate molecular weight of 145 kD. Hyaluronidase human increases permeability of the subcutaneous tissue by temporarily depolymerizing hyaluronan.

The drug is provided as a colorless to yellowish, clear to opalescent, preservative-free liquid solution. Each mL of solution contains rituximab (120 mg), hyaluronidase human (2,000 Units),

L-histidine (0.53 mg), L-histidine hydrochloride monohydrate (3.47 mg), L-methionine (1.49 mg), polysorbate 80 (0.6 mg), α,α-trehalose dihydrate (79.45 mg), and Water for Injection.

9.3.2 Packaging

For use in patients with FL/DLBCL, rituximab/hyaluronidase human is supplied in single-dose vials containing 1,400 mg rituximab and 23,400 Units hyaluronidase human per 11.7 mL of solution.

9.3.3 Source

Unless otherwise instructed by the sponsor, the rituximab/hyaluronidase human to be used in this study may be obtained from available commercial supplies.

9.3.4. Storage and Stability

Rituximab/hyaluronidase human vials are stable at 2°C-8°C (36°F-46°F). Vials should be protected from direct sunlight and should not be frozen or shaken.

Diluted rituximab/hyaluronidase human solutions for injection may be stored at 2°C-8°C (36°F-46°F) for 48 hours and are known to be stable for an additional 8 hours at room temperatures up to 30°C (86°F) in diffuse light. However, since rituximab solutions do not contain a preservative, solutions should be used as soon as possible after withdrawal from the vial.

Rituximab/hyaluronidase is compatible with polypropylene and polycarbonate syringe material and stainless-steel transfer and injection needles.

9.3.5 Preparation

Before use, the rituximab/hyaluronidase human vials should be inspected for particulate matter or discoloration. Any vial with evidence of particulates or discoloration should not be used.

Using aseptic technique, the entire 11.7 mL of rituximab/hyaluronidase human should be withdrawn from the vial via a hypodermic needle into a syringe and the vial should be discarded.

9.3.6 Accountability

Acquisition, storage, control, and disposal of rituximab/hyaluronidase used in the study should be performed according to institutional procedures and policies.

The investigator and/or the responsible site personnel must maintain accurate records of the source, dates of administration, quantities of administration, and lot numbers of the rituximab/hyaluronidase dispensed for this study.

Section 10. Pregnancy

Changes: Information regarding pharmacovigilance reporting of pregnancies was corrected.

Pregnancy occurring in a subject is not considered an AE. However, the investigator must capture pregnancy information for subject and/or subject's partner (as applicable) on a pregnancy report form within 24 hours of learning of the pregnancy. Then the site

- Completes the pregnancy form with as much information as possible; however, at a minimum the Subject identification number, name of product, and name of reporter is required;

- Signs Pregnancy Notification form; and
- FAX the form to [redacted] at [redacted] and email a copy to [redacted].

Subjects determined to be pregnant must be immediately removed from treatment and will be followed by the investigator until termination of the pregnancy or delivery of the child. Additional information on the course of the pregnancy should be supplied on follow-up forms as it becomes available and at minimum at termination or birth.

Section 12. Pharmacokinetic Assessments

Changes: (Paragraph 3 only): Reference to the laboratory manual was included.

Comprehensive information on blood sample acquisition, handling, storage and sample shipments can be found in the laboratory manual "Procedures for Processing and Shipping PK and Biomarker Samples." ~~pharmacokinetic laboratory manual~~.

Section 13. Biomarker Assessments

Changes: Information regarding biopsy procedures was clarified. Reference to the laboratory manual was included.

For subjects with NHL, ~~archival tissue from the most recent available biopsy or surgery or~~ fresh tumor tissue (preferred) or archival tissue from the most recent available biopsy or surgery (within 4 months prior to the start of screening) must be obtained pretreatment. For subjects undergoing a biopsy, adequate tumor tissue should be acquired via excisional biopsy, incisional biopsy or core needle biopsy (e.g., > 3 passes using a 16-gauge core needle). Confirmation of tumor in biopsy with fine needle aspirate, touch prep, or FFPE processing is requested when possible. The tumor lesion selected should not have been previously irradiated and should not be an index lesion that is followed for response assessment. Alternatively, cells from a bone marrow aspirate may be obtained in subjects with bone marrow involvement due to NHL (>50% NHL cells). ~~For subjects undergoing a biopsy, adequate tumor tissue should be acquired via excisional biopsy, incisional biopsy or core needle biopsy (e.g., ≥ 3 passes using a 16-gauge core needle).~~ Tissue will be submitted for evaluation of the percentage of tumor cells and analysis of genetic alterations and/or gene expression that may predict anti-lymphoma activity and/or pharmacodynamics activity. In addition, tumor may be evaluated for known prognostic characteristics (e.g., for DLBCL: ABC or GCB subtype; expression of BCL2, BCL6, Ki-67, CD20, and MYC; other mutational status), for PDL1 status, and for immune infiltration.

Comprehensive information on tissue acquisition, handling, storage and sample shipments can be found in the laboratory manual "Procedures for Processing and Shipping PK and Biomarker Samples." ~~biomarker sample process documents.~~

Section 14.1.2. Stage 2 (Cohort Expansion)

Changes: A statistical justification for accrual of additional patients with FL to receive LAM-002A monotherapy or LAM-002A/rituximab was included.

As indicated in Section 6.1.2, expansion cohorts of 6 subjects will be accrued. Enrollment of 6 subjects per cohort offers the opportunity to determine if there is any antitumor activity sufficient to warrant further development in the selected tumor types. An ORR of ≥ 35% is considered of potential interest in each of the selected indications. If 0/6 subjects in a cohort

experience an objective response, then a population ORR of ≥ 35% for that cancer can be excluded with > 90% certainty (1-sided exact binomial 90% CI upper bound = 32%).

Based on the observation of objective responses among study subjects with FL receiving either LAM-002A monotherapy or LAM-002A/rituximab, expanded accrual of subjects with relapsed FL is planned to evaluate the level of activity with these 2 regimens. Preference will be given to enrolling subjects to receive LAM-002A monotherapy before enrolling subjects to receive LAM-002A/rituximab.

Based on historical data with other treatments (Zelenetz 2014), it is known that an ORR of < 20% in subjects with relapsed FL receiving LAM-002A monotherapy would be uninteresting while achieving a target ORR of ≥ 40% would suggest that further development is warranted. Sequential boundaries will be used to continuously monitor that the ORR is ≥ 40% while excluding an ORR of < 20% using a 1-sided test with a significance level of 0.05. A significant result with this testing would conclude with 95% confidence that the actual ORR is ≥ 20%. Accrual of up to ~20 evaluable subjects will be considered with the potential to stop accrual early if the boundary is crossed. Thus, accrual can be considered sufficient if the following n/N values are observed: 4/5, 4/6, 4/7, 5/8, 5/9, 5/10, 5/11, 6/11, 6/12, 6/13, 6/14, 7/15, 7/16, 7/17, 8/18, 8/19, 8/20. For all these values, the ORR is ≥ 40% with a lower 1-sided binomial confidence bound of ≥ 20%.

As noted above, the target ORR with LAM-002A alone is ~40%. Adding rituximab or rituximab hyaluronidase human to LAM-002A would be expected to enhance the ORR over that associated with single-agent LAM-002A. Thus, the combination of LAM-002A/rituximab could warrant further development if an ORR of ≥ 60% could be targeted in preference to an ORR of < 40%. Accordingly, for combination therapy, sequential boundaries will be used to continuously monitor that the ORR is ≥ 60% while excluding an ORR of 39% using a 1-sided test with a significance level of 0.05. A significant result with this testing would conclude with 95% confidence that the actual ORR is > 39%. Accrual of up to ~20 evaluable subjects will be considered with the potential to stop accrual early if the boundary is crossed. Thus, accrual can be considered sufficient if the following n/N values are observed: 7/10, 8/11, 8/12, 9/13, 9/14, 10/15, 10/16, 11/17, 11/18, 12/19, 12/20. For all these values, the ORR is ≥ 60% with a lower 1-sided binomial confidence bound of ≥ 39%.

Experience indicates the rates of discontinuations from rituximab or atezolizumab therapy are < 5% (Genentech 2016, Genentech 2017). A rate of AE discontinuations of therapy due to adverse events of ≥25% in the 2 combination therapy groups of LAM-002A/rituximab (N = 12) or LAM-002A/atezolizumab (N = 12) would suggest a potential adverse interaction among the components of the combination therapy. Sequential Pocock-type boundaries will be used to continuously monitor the rate of AE discontinuations and to test the null hypothesis, after each subject, that the event rate is ≥ 0.25 using a 1-sided significance test of ~ 0.05. AE discontinuation rates will be considered excessive if the following n/N values are observed: -/1, -/2, 3/3, 3/4, 4/5, 4/6, 5/7, 5/8, 5/9, 6/10, 6/11, 7/12. With this method, the probability of detecting an AE discontinuation safety signal ranges from 0.091 to >0.820 for true discontinuation rates of 25% to ≥ 60%. If excessive levels of AE discontinuation are observed, the sponsor, working in collaboration with the cooperating companies and investigators, will take appropriate actions (eg, continuation of the cohort with modifications in design or monitoring plan, interruption of cohort accrual, cohort therapy discontinuation).

Section 22. List of References

Changes: Information regarding drugs with known risk of QT prolongation or torsades de pointes was updated and the relevant reference was revised accordingly. Use of either intravenously administered rituximab or subcutaneously administered rituximab hyaluronidase human was permitted; accordingly, reference was made to rituximab hyaluronidase human prescribing information.

~~CredibleMeds. [homepage on the Internet]. Arizona: Combined list of drugs that prolong QC and/or cause tosrades de pointes (TDP). [Updated 2014 May 32; Cited 2015 June 12]. Available from:~~ Woosley RL, Romero KA. Drugs with known risk of torsades de pointes. 2018 Oct 31. Available at: https://www.crediblemeds.org (accessed 2018 Dec 17).

Genentech. Rituxan Hycela® (rituximab and hyaluronidase human) prescribing information. 2018 Apr. Avaliable at: https://www.gene.com/download/pdf/rituxan_hycela_prescribing.pdf (acessed 2018 Dec 18).

Appendix 3. Potential Drug Interactions with LAM-002A, Table 16 Drugs Known to Prolong the QT Interval and/or Cause Torsades De Pointes (TDP)

Changes: Information regarding drugs with known risk of QT prolongation or torsades de pointes was updated. To avoid formatting problems, the former table was removed without displaying it in strikeout font.

Table 16: Drugs Known to Prolong the QT Interval and/or Cause Torsades De Pointes (TDP)

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Amiodarone	Cordarone®, Pacerone®, Nexterone®	Antiarrhythmic	Abnormal heart rhythm
Anagrelide	Agrylin®, Xagrid®	Phosphodiesterase 3 inhibitor	Thrombocythemia
Arsenic trioxide	Trisenox®	Anticancer	Cancer (leukemia)
Astemizole (removed from market)	Hismanal®	Antihistamine	Allergic rhinitis
Azithromycin	Zithromax®, Zmax®	Antibiotic	Bacterial infection
Bepridil (removed from market)	Vascor®	Antianginal	Angina Pectoris (heart pain)
Chloroquine	Aralen®	Antimalarial	Malaria
Chlorpromazine	Thorazine®, Largactil®, Megaphen®	Antipsychotic / Antiemetic	Schizophrenia, nausea, many others
Cilostazol	Pletal®	Phosphodiesterase 3 inhibitor	Intermittent claudication
Ciprofloxacin	Cipro®, Cipro-XR®, Neofloxin®	Antibiotic	Bacterial infection
Cisapride (removed from market)	Propulsid®	Gastrointestinal stimulant	Increase gastrointestinal motility
Citalopram	Celexa®, Cipramil®	Antidepressant, selective serotonin reuptake inhibitor	Depression

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Clarithromycin	Biaxin®, Prevpac®	Antibiotic	Bacterial infection
Cocaine	Cocaine	Local anesthetic	Anesthesia (topical)
Disopyramide	Norpace®	Antiarrhythmic	Abnormal heart rhythm
Dofetilide	Tikosyn®	Antiarrhythmic	Abnormal heart rhythm
Domperidone (only on non-US market)	Motilium®, Motillium®, Motinorm Costi®, Nomit®	Antinausea	Nausea, vomiting
Donepezil	Aricept®	Cholinesterase inhibitor	Dementia (Alzheimer's Disease)
Dronedarone	Multaq®	Antiarrhythmic	Abnormal heart rhythm
Droperidol	Inapsine®, Droleptan®, Dridol®, Xomolix®	Antipsychotic / Antiemetic	Anesthesia (adjunct), nausea
Erythromycin	E.E.S.®, Robimycin®, EMycin®, Erymax®, Ery-Tab®, Eryc Ranbaxy®, Erypar®, Eryped®, Erythrocin Stearate Filmtab®, Erythrocot®, E-Base®, Erythroped®, Ilosone®, MY-E®, Pediamycin®, Zineryt®, Abboticin®, Abboticin-ES®, Erycin®, PCE Dispertab®, Stiemycine®, Acnasol®, Tiloryth®	Antibiotic	Bacterial infection, increase gastrointestinal motility
Escitalopram	Cipralex®, Lexapro®, Nexito®, Anxiset-E® (India), Exodus® (Brazil), Esto® (Israel), Seroplex®, Elicea®, Lexamil®, Lexam®, Entact® (Greece), Losita® (Bangladesh), Reposil® (Chile), Animaxen® (Colombia), Esitalo® (Australia), Lexamil® (South Africa)	Antidepressant, selective serotonin reuptake inhibitor	Depression (major), anxiety disorders
Flecainide	Tambocor®, Almarytm®, Apocard®, Ecrinal®, Flécaine®	Antiarrhythmic	Abnormal heart rhythm
Fluconazole	Diflucan®, Trican®	Antifungal	Fungal infection
Gatifloxacin (removed from market)	Tequin®	Antibiotic	Bacterial infection
Grepafloxacin	Raxar®	Antibiotic	Bacterial infection
Halofantrine	Halfan®	Antimalarial	Malaria
Haloperidol	Haldol® (US & UK), Aloperidin®, Bioperidolo®, Brotopon®,	Antipsychotic	Schizophrenia, agitation

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
	Dozic®, Duraperidol® (Germany), Einalon S®, Eukystol®, Halosten®, Keselan®, Linton®, Peluces®, Serenace®, Serenase®, Sigaperidol®		
Ibogaine (only on non-US market)	None	Psychedelic	Narcotic addiction, unproven
Ibutilide	Corvert®	Antiarrhythmic	Abnormal heart rhythm
Levofloxacin	Levaquin®, Tavanic®	Antibiotic	Bacterial infection
Levomepromazine (methotrimeprazine) only on non-US market)	Nosinan®, Nozinan®, Levoprome®	Antipsychotic	Schizophrenia
Levosulpiride (only on non-US market)	Lesuride®, Levazeo®. Enliva® (with rabeprazole)	Antipsychotic	Schizophrenia
Levomethadyl acetate (removed from market)	Orlaam®	Opioid agonist	Narcotic dependence
Mesoridazine (removed from market)	Serentil®	Antipsychotic	Schizophrenia
Methadone	Dolophine®, Symoron®, Amidone®, Methadose®, Physeptone®, Heptadon®	Opioid agonist	Narcotic dependence, pain
Moxifloxacin	Avelox®, Avalox®, Avelon®	Antibiotic	Bacterial infection
Ondansetron	Zofran®, Anset®, Ondemet®, Zuplenz®, Emetron®, Ondavell®, Emeset®, Ondisolv®, Setronax®	Antiemetic	Nausea, vomiting
Oxaliplatin	Eloxatin®	Antineoplastic Agent	Cancer
Papaverine HCl	none	Vasodilator, Coronary	Diagnostic adjunct
Pentamidine	Pentam®	Antifungal	Fungal infection (Pneumocystis pneumonia)
Pimozide	Orap®	Antipsychotic	Tourette's Disorder
Probucol (removed from market)	Lorelco®	Antilipemic	Hypercholesterolemia
Procainamide	Pronestyl®, Procan®	Antiarrhythmic	Abnormal heart rhythm
Propofol	Diprivan®, Propoven®	Anesthetic, general	Anesthesia
Quinidine	Quinaglute®, Duraquin®, Quinact®, Quinidex®, Cin-Quin®, Quinora®	Antiarrhythmic	Abnormal heart rhythm
Roxithromycin (only on non-US market)	Rulide®, Xthrocin®, Roxl-150®, Roxo®, Surlid®, Rulide®,	Antibiotic	Bacterial infection

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
	Biaxsig®, Roxar®, Roximycinv®, Roxomycin®, Rulid®, Tirabicin®, Coroxin®		
Sevoflurane	Ulane®, Sojourn®	Anesthetic, general	Anesthesia
Sotalol	Betapace®, Sotalex®, Sotacor®	Antiarrhythmic	Abnormal heart rhythm
Sparfloxacin (removed from market)	Zagam®	Antibiotic	Bacterial infection
Sulpiride (only on non-US market)	Dogmatil®, Dolmatil®, Eglonyl®, Espiride®, Modal®, Sulpor®	Antipsychotic, atypical	Schizophrenia
Sultopride (only on non-US market)	Barnetil®, Barnotil®, Topral®	Antipsychotic, atypical	Schizophrenia
Terfenadine (removed from market)	Seldane®	Antihistamine	Allergic rhinitis
Terlipressin (only on non-US market)	Teripress®, Glypressin®, Terlipin®, Remestyp®, Tresil®, Teriss®, and others	Vasoconstrictor	Septic shock
Terodiline (only on non-US market)	Micturin®, Mictrol® (not bethanechol)	Muscle relaxant	Bladder spasm
Thioridazine	Mellaril®, Novoridazine®, Thioril®	Antipsychotic	Schizophrenia
Vandetanib	Caprelsa®	Anticancer	Cancer (thyroid)

Note: Includes those drugs known to prolong the cardiac QT interval or cause TdP (Woosley 2018).
Abbreviation: QT: Time of start of Q wave until end of T wave in the heart's electrical cycle; TdP: Torsades de Pointes; UK: United Kingdom; US: United States

Changes made in Amendment 8 (18 Feb 2020)

In preparing this amendment of the protocol document, the following changes were made. Explanations of the substantive changes are provided in italics as "*Changes*." Inserted text is indicated by red double-underlined font. Deleted text is indicated by ~~red strikeout font~~.

Changes to the synopsis also appear in the body of the protocol; thus, changes to the synopsis are not described and only changes to the body of the protocol are described.

Modifications to the list of abbreviations and definitions of terms or minor typographical or syntax corrections are not indicated.

Title Pages, Headers, Body of Protocol

Changes to the company name (from LAM Therapeutics, Inc. to AI Therapeutics, Inc.) and modifications to the protocol version and date (from Version 8, dated 14 Jan 2019 to Version 9, dated 19 February 2020) were made throughout the document without specific notation.

AI Therapeutics Signature Page

Change: Information regarding AI Therapeutics signatories to the protocol was updated.

AI THERAPEUTICS SIGNATURE PAGE

Name: Title:	Candace A Fuchs, PMP ~~Henri Lichenstein, PhD~~ Head, Clinical Operations/Project Management AI Therapeutics, Inc. ~~Chief Executive Officer~~ ~~AI Therapeutics, Inc.~~	Date:
Signature:	_____	18 Feb 2020
Name: Title:	Langdon L Miller, MD Clinical Consultant AI Therapeutics, Inc.	Date:
Signature:	_____	18 Feb 2020

Section 4.1.4.2 Efficacy

Change: Information regarding LAM-002A efficacy in NHL was updated in the protocol introduction.

In Study LAM-002A-NHL-CLN01, efficacy has been assessed in subjects with NHL. Decreases in tumor metabolic activity were noted in 3 subjects with relapsed DLBCL receiving LAM-002A monotherapy but these changes did not meet formal criteria for objective response. Nine subjects with FL treated with LAM-002A monotherapy, LAM-002A in combination with rituximab, or LAM-002A in combination with atezolizumab have had substantial tumor regressions compromising 2 complete responses (CRs) and 7 partial responses (PRs). The responses have been long-lasting, with durations exceeding 12 months among several subjects with mature data. One subject with MZL receiving LAM-002A/rituximab also experienced a durable PR.

~~Efficacy data in patients with hematological malignancies are evolving. As of 14 Jan 2019, 2/5 patients with FL receiving LAM-002A monotherapy had achieved an objective response (1 complete response [CR] and 1 partial response [PR]); 2/4 patients with FL receiving LAM-002A/rituximab had achieved PRs, and 1/1 patient with FL receiving LAM-002A/atezolizumab had achieved a PR. Among subjects with other types of NHL, positron emission tomography (PET) demonstrated systemic partial metabolic responses in nodal and extranodal lesions in 3 patients with refractory DLBCL (treated at 100 mg BID, 75 mg TID, and 125 mg BID) (1 of whom also received radiation for bulky axillary adenopathy); concomitant computed tomography (CT) demonstrated anatomic shrinkage of many lesions. One additional subject with transformed, refractory DLBCL (treated at 125 mg BID) experienced tumor lysis syndrome (TLS). One patient with marginal zone lymphoma (MZL) (treated at 125 mg BID) has~~

~~had a metabolic response by PET together with a 43% decrease in the sum of the products of the perpendicular diameters (SPD) of index lesions by CT. Another patient with MZL and a patient with chronic lymphocytic leukemia (CLL) (both receiving 100 mg BID) experienced prolonged stable disease through 11+ and 14 cycles, respectively.~~

Section 6.1. Overall Study Design Stage

Changes: Text was included consistent with addition of an extension stage to the study.

This is a Phase 1, single-arm, open-label, dose-escalation study of safety and PK of apilimod administered to subjects with refractory or relapsed B-cell NHL. This study will be conducted in 3 stages ~~consists of 2 stages~~.

Section 6.1.3 Extension Stage (Stage 3)

Changes: Text was included to explain the addition of an extension stage to the study.

The extension stage (Stage 3) can begin once the last study subject has completed at least 8 cycles of study treatment. At this time, the study sponsor will conclude the dose-escalation and expansion stages of the study, will collate and verify all study data through an appropriate data cutoff date, and will lock the study database for preparation of a study report. Subjects who are still safely benefiting from Stage 1 or Stage 2 study therapy as of the data cutoff date may electively continue their current regimen of study therapy in Stage 3, receiving clinical care and diagnostic testing consistent with conventional practice standards as deemed appropriate by the treating investigator. Therapy in Stage 3 may continue in the absence of protocol-defined reasons to discontinue therapy. During Stage 3, collection of clinical data by the sponsor will be limited to serious adverse event (SAE) reports. Study drug accountability will be managed per site procedures; relevant pharmacy records may be collected by the sponsor to document study drug disposition.

Section 6.2. Number of Subjects

Changes: Text was included consistent with addition of an extension stage to the study.

As many as 145 subjects will be enrolled, assuming that:

- In the dose-escalation stage of the study, the total number of subjects will depend upon the numbers of subjects accrued to each dose level and the number of dose levels evaluated. If 6 subjects are enrolled at all open starting dose levels (Dose Levels 5, 6, 7, and 8) and 6 additional subjects are enrolled at the MTD or RD, as many as 30 subjects could be enrolled. To allow for the possibility that some subjects may not be fully evaluable for DLT or that an intermediate dose level might be evaluated, up to ~45 subjects may be enrolled.
- In the expansion stage of the study, if all 8 potential expansion cohorts are accrued, as many as ~76 subjects could be enrolled. To allow for the possibility that some subjects may not be fully evaluable for efficacy or to establish bounds on efficacy estimates with greater confidence, up to ~100 subjects may be enrolled.
- In the extension stage of the study, the total number of subjects will include ≤4 subjects who have participated in the expansion stage of the study and are still receiving study therapy on the data cutoff date that concludes the dose-escalation and expansion stages of the clinical trial.

Section 6.5.2. Treatment Period

Changes: Text was removed consistent with addition of an extension stage to the study.

The subject is treated and monitored for safety (including assessments of AEs, vital signs, ECGs, laboratory tests and concomitant medications). Additionally, preliminary anti-tumor activity will be assessed and PK and biomarker samples will be collected. ~~In the absence of protocol-defined reasons to discontinue therapy, subjects may continue to receive study treatment for up to 1 year at the discretion of the investigator and beyond 1 year with the agreement of the investigator and the sponsor.~~

Section 8. Methods of Assessment and Endpoints

Changes: Text was included consistent with addition of an extension stage to the study.

All trial data during the dose-escalation stage (Stage 1) and expansion stage (Stage 2) will be recorded on the eCRFs. Timing of study procedures for the dose-escalation stage (Stage 1) and expansion stage (Stage 2) are listed in schedules of assessments tables – Table 8: Schedule of Assessments (LAM-002A Continuous Monotherapy Administration), Table 9: Schedule of Assessments (LAM-002A Intermittent Monotherapy Administration), Table 10: Schedule of Assessments (LAM-002A/Rituximab Combination Therapy), and Table 11: Schedule of Assessments (LAM-002A/Atezolizumab Combination Therapy) – in Section 8.7. During the extension stage (Stage 3), collection of clinical data by the sponsor will be limited to serious adverse event (SAE) reports. Study drug accountability will be managed per site procedures; relevant pharmacy records may be collected by the sponsor to document study drug disposition.

Section 9.1.6. Handling and Disposal

Changes: In the context of transitioning to the extension stage of the study, site monitoring of drug accountability by the contract research organization, Ce3, was discontinued.

LAM-002A accountability and inventory records will be inspected by the sponsor~~/Ce^3~~ prior to final disposition. Instructions will be provided by the sponsor~~/Ce^3~~ for shipment to and destruction of unused LAM-002A product by the designated packaging depot, to include unopened bulk bottles at the end of the study and expired product. Unused product returned by study subjects or opened bulk bottles will be destroyed by each site per site SOPs. LAM-002A should only be shipped or destroyed upon written authorization from the sponsor~~/Ce^3~~. Documentation of return of shipment, including a packing list and copy of the tracking label, should be retained in the Pharmacy and/or regulatory files.

Section 10.6. SAE and AESI Reporting

Changes: In the context of transitioning to the extension stage of the study, pharmacovigilance monitoring of SAEs was transitioned from the contract research organization, Pharmalex, Inc. to the study sponsor, AI Therapeutics.

- The investigator is obligated to immediately report to ~~Pharmalex, Inc.~~AI Therapeutics each SAE and each AESI that occurs during this investigation, within 24 hours from knowledge of the event, whether or not it is considered study-drug related.
- All requested supplementary documents (e.g., discharge summary, autopsy report) and relevant data (e.g., ECGs, laboratory tests, discharge summaries, post mortem results) must

be faxed or emailed within 24 hours to [redacted]

The information provided in a SAE or AESI report should be as complete as possible, but contain a minimum of the following:

- A short description of the AE (diagnosis) and the reason why the AE was categorized as an SAE or AESI
- Subject identification and treatment
- Investigator's name and telephone number (if applicable)
- Name of the suspect medicinal product and dates of administration
- Assessment of causality.

If any questions or considerations regarding SAE or AESI report requirements or report completion arise, the principal investigator/site staff should contact ~~PharmaLex~~AI Therapeutics. Medically related questions or concerns regarding treatment should be directed to the sponsor's medical monitor.

If all information about the SAE or AESI is not yet known, the investigator will be required to report any additional information within 24 hours as it becomes available. SAEs and AESIs must be followed and reported upon until the event has completely resolved to Grade 0 or baseline or until the event becomes a new stable baseline condition for a subject.

All SAEs and AESIs will be evaluated by the sponsor's medical monitor or designee.

The investigators must notify their governing IRB of any SAEs in accordance with Section 18.1.

For any suspected adverse reaction that is both serious and unexpected (not documented in the IB or package insert), an Investigational New Drug (IND) safety report or revision to the IB may be issued to inform all investigators involved in any study with LAM-002A.

Section 10.7. Pregnancy Reporting

Changes: In the context of transitioning to the extension stage of the study, pharmacovigilance monitoring of pregnancy was transitioned from the contract research organization, Pharmalex, Inc. to the study sponsor, AI Therapeutics.

Pregnancy occurring in a subject is not considered an AE. However, the investigator must capture pregnancy information for subject and/or subject's partner (as applicable) on a pregnancy report form within 24 hours of learning of the pregnancy. Then the site

- Completes the pregnancy form with as much information as possible; however, at a minimum the subject identification number, name of product, and name of reporter is required;
- Signs Pregnancy Notification form; and
- FAX the form to [redacted]

Subjects determined to be pregnant must be immediately removed from treatment and will be followed by the investigator until termination of the pregnancy or delivery of the child.

Additional information on the course of the pregnancy should be supplied on follow-up forms as it becomes available and at minimum at termination or birth.

Section 10.7. 14.1.3 Extension Stage (Stage 3)

Changes: Text was included in the statistical section of the protocol consistent with addition of an extension stage to the study.

The sample size in the extension stage of the study will be no higher than the total number of subjects on study therapy on the data cutoff date that concludes the dose-escalation and expansion stages of the clinical trial.

Section 16. Study Monitoring

Changes: Text was included consistent with the plan to discontinue regular monitoring of study sites during the extension stage of the study.

Before an investigational site can enter a subject into the study, a representative of AI Therapeutics will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the investigator and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of AI Therapeutics or its representatives. This will be documented in a Clinical Study Agreement between AI Therapeutics and the investigator.

During the study, a monitor from AI Therapeutics or its representative will have regular contacts with the investigational site for the following:

- Provide information and support to the investigator
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol that data are being accurately recorded in the eCRFs, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the CRFs with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (e.g., clinic charts)
- Record and report any protocol deviations not previously sent to AI Therapeutics
- Confirm AEs and SAEs have been properly documented on eCRFs, and confirm any SAEs have been forwarded to AI Therapeutics and those SAEs that met criteria for reporting have been forwarded to the IRB

The monitor will be available between visits if the investigator or other staff members need information or advice.

Upon conclusion of the Dose-Escalation (Stage 1) and Expansion (Stage 2) stages of the study, routine site monitoring by AI Therapeutics or its representatives will be discontinued.