NCT #: NCT01882803

STUDY PROTOCOL
IPI-145-06

Protocol Title	A Phase 2 Study of IPI-145 in Subjects with Refractory Indolent Non-Hodgkin Lymphoma
Protocol Number	IPI-145-06
Phase:	Phase 2
IND Number	112,486
EudraCT	2013-004008-20
Date of Protocol	30 October 2017 (Amendment 4, Global)
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Sponsor:	Verastem, Inc. 117 Kendrick Street, Suite 500 Needham, MA 02494

INVESTIGATOR PROTOCOL APPROVAL

A Phase 2 Study of IPI-145 in Subjects with Refractory Indolent Non-Hodgkin Lymphoma

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to principles of Good Clinical Practice and local regulations and requirements.

Institution/Clinic: _____

Principal Investigator _____

Print Name: _____

Signature: _____

Date (mm/dd/yyyy): _____

SPONSOR PROTOCOL APPROVAL

A Phase 2 Study of IPI-145 in Subjects with Refractory Indolent Non-Hodgkin Lymphoma

I have read this protocol and I approve the design of this study:

[redacted] [redacted]

Signature Date

[redacted]

Verastem, Inc.
117 Kendrick Street, Suite 500
Needham, MA 02494

CONTACT INFORMATION

Sponsor:	Verastem, Inc. 117 Kendrick Street, Suite 500 Needham, MA 02494

For urgent study-related questions, please call the Medical Monitor at one of the following numbers:

- US/Canada (toll free): [redacted]
- International: [redacted]

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AKT (PKB)	A serine/threonine protein kinase
aPTT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the curve
BCR	B-cell receptor
βhCG	β human chorionic gonadotropin
BID	Twice a day
BTK	Bruton's Tyrosine Kinase
ºC	Degrees Celsius
C5a	A protein fragment released from complement component C5
CAL-101 (GS-1101)	A PI3K-δ inhibitor in clinical development for patients with hematologic malignancies, also known as idelalisib or Zydelig™
CEC	Central Ethics Committee
CLL	Chronic lymphocytic leukemia
C_{max}	Maximum concentration
CNS	Central nervous system
CMV	Cytomegalovirus
COPD	Chronic obstructive pulmonary disease
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DDI	Drug-drug interaction
DNA	Deoxyribonucleic acid

Abbreviation	Definition
DOR	Duration of response
DMC	Data monitoring committee
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
eCRF	Electronic case report form
EoT	End of Treatment
EQ-5D	EuroQol – 5D (health-related QoL assessment)
FAS	Full analysis set
FCεRI	High-affinity IgE receptor
FCγRII	Fc fragment of IgG, low affinity IIa, receptor (CD32)
FDA	Food and Drug Administration
FL	Follicular lymphoma
GLP	Good laboratory practice
GPCR	G-protein coupled receptor
GRAS	Generally Regarded as Safe
h	Hour(s)
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HCV Ab	Hepatitis C virus antibodies
HIV	Human immunodeficiency virus
HSCT	Hematopoietic stem cell transplant
IC_{50}	Half maximal inhibitory concentration
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
Ig	Immunoglobulin
in	Inches
Infinity	Infinity Pharmaceuticals, Inc.
iNHL	Indolent non-Hodgkin lymphoma

Abbreviation	Definition
INR	International normalized ratio
IPI-145	(*S*)-3-(1-(9H-purin-6-ylamino)ethyl)-8-chloro-2-phenylisoquinolin-1(2H)-one, also known as duvelisib
IRB	Institutional Review Board
IV	Intravenous(ly)
IWG	International Working Group
kg	Kilogram(s)
KPS	Karnofsky Performance Status
L	Liter(s)
LC/MS/MS	Liquid chromatography-tandem mass spectrometry method.
LDH	Lactate dehydrogenase
LEC	Local Ethics Committee
m	Meter(s)
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MEOI	Medical Event of Interest
mg	Milligram(s)
mL	Milliliter(s)
MRI	Magnetic resonance imaging
µg	Microgram(s)
µM	Micromolar
MTD	Maximum tolerated dose
MZL	Marginal zone lymphoma
N	Number
NCI	National Cancer Institute
ng	Nanogram(s)
nM	Nanomolar
NK	Natural killer
ORR	Overall response rate
OS	Overall survival

Abbreviation	Definition
PCR	Polymerase chain reaction
PD	Progressive disease
PDK-1	3-phosphoinositide dependent protein kinase-1
PET	Positron emission tomography
PFS	Progression-free survival
P-gp	P-glycoprotein
PI3K	Phosphoinositide-3-kinase
PIP3	Phosphatidylinositol (3,4,5)-trisphosphate
PK	Pharmacokinetics
PO	Oral(ly)
PR	Partial response
PT	Prothrombin time
PTEN	Phosphatase and tensin homolog
QD	Once a day
QoL	Quality of life
RAS	Protein subfamily of small GTPases involved in cellular signal transduction
RBC	Red blood cell
RIT	Radioimmunotherapy
SAD	Single ascending dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCF	Stem cell factor
SD	Stable disease
SE	Standard error
SH2	Sarc homology 2
SLL	Small lymphocytic lymphoma
SOC	Standard of care
$T_{1/2}$	Terminal elimination half-life
TTR	Time to Response
ULN	Upper limit of normal

Abbreviation	Definition
TAMs	Tumor-associated macrophages
TEAE	Treatment-emergent adverse events
T_{max}	Time to maximum concentration
UV	Ultraviolet
WBC	White blood cell
WCBP	Women of child-bearing potential

PROTOCOL SYNOPSIS

Study Title:	A Phase 2 Study of IPI-145 in Subjects with Refractory Indolent Non-Hodgkin Lymphoma
Protocol Number	IPI-145-06
Study Phase	2
Investigational Agent	IPI-145 (duvelisib)
Study Objectives:	**Primary Objective:** To evaluate the antitumor activity of IPI-145 administered to subjects diagnosed with indolent non-Hodgkin lymphoma (iNHL) (defined as follicular lymphoma [FL], marginal zone lymphoma [MZL; splenic, nodal and extranodal], or small lymphocytic lymphoma [SLL]) whose disease is refractory to rituximab and to either chemotherapy or radioimmunotherapy (RIT). **Secondary Objectives:** • To evaluate the safety of IPI-145 in all subjects • To evaluate additional efficacy parameters in all subjects • To evaluate the pharmacokinetics (PK) of IPI-145 and, if applicable, its metabolite(s) **Exploratory Objectives:** • To evaluate whether baseline values or treatment-related changes in biomarkers correlate with IPI-145 clinical activity, safety and/or resistance in iNHL • To evaluate whether tumor genomic or pharmacogenomic markers correlate with IPI-145 clinical activity, safety, PK and/or resistance in iNHL • To evaluate the health-related quality of life (QoL) of subjects
Study Endpoints:	Primary Endpoint Overall Response Rate (ORR), with overall response defined as best response of complete response/remission (CR) or partial response/remission (PR), according to the revised International Working Group (IWG) Criteria[1]

	Secondary Endpoints • Treatment-emergent adverse events (TEAEs), ECG measures, and changes in safety laboratory values • Duration of response (DOR), defined as the time from the first documentation of response to the first documentation of progressive disease (PD) or death due to any cause • Progression-free survival (PFS), defined as the time from the first dose of study treatment to the first documentation of PD or death due to any cause • Overall survival (OS) defined as the time from the first dose of study treatment to the date of death • Time to response (TTR), defined as the time from the first dose of study treatment to the first documentation of response (complete or partial) • PK parameters derived from plasma IPI-145 concentrations and, if applicable, its metabolite(s) Exploratory Endpoints • Lymph node response rate (LNR rate), with LNR defined as ≥ 50% reduction in the Sum of the Products of the Perpendicular Diameters (SPD) of nodal target lesions • Serum, plasma and tissue biomarkers and blood immunophenotype • Germline DNA sequence variations • Tumor genomic features (e.g. DNA sequence variation, DNA copy number variation, and/or RNA expression) • Health-related QoL of subjects as assessed by the following subject-reported questionnaire: o EuroQol-5D (EQ-5D), a standardized instrument for use as a measure of health-related QoL
Study Treatment:	IPI-145 is administered orally as a capsule formulation. The IPI-145 drug product is supplied as 5 mg and 25 mg formulated capsules.

Study Design:	Study IPI-145-06 is a Phase 2, open-label, single arm efficacy and safety study of IPI-145 administered orally to subjects diagnosed with iNHL (FL, MZL, or SLL) whose disease is refractory to rituximab and to either chemotherapy or RIT. Schedule of Administration Subjects will be given a starting dose of 25 mg IPI-145 orally twice daily (BID) during each 28-day treatment cycle, for up to 13 cycles. To receive additional cycles of IPI-145 beyond 13 cycles, subjects must have documented evidence of response (CR or PR) or stable disease (SD) at the Cycle 14 Day 1 response assessment according to the revised IWG criteria [1]. These subjects may continue to receive IPI-145 treatment until disease progression or unacceptable toxicity.
Study Population:	This study anticipates enrolling approximately 120 subjects with a diagnosis of iNHL whose disease is refractory to rituximab and to either chemotherapy or RIT. This will include approximately 80 subjects with FL. Total enrollment may exceed 120 subjects in order to enroll a sufficient number of FL subjects.
Study Duration:	Following treatment with IPI-145, study subjects will be followed for survival for up to 3 years from the date of their first dose of study drug. It is anticipated that the entire study will accrue subjects over approximately 30 months from the enrollment of the first subject. It is anticipated that the total duration of the study will be approximately 66 months.
Study Centers:	Enrollment is anticipated at approximately 100 sites. Approximately 40 sites will be initiated in the US, with the remainder of sites outside the US.
Inclusion Criteria:	Subjects are eligible for inclusion in the study if they meet the following criteria: 1. Age 18 years or older. 2. Subjects who have been diagnosed with indolent NHL [defined as FL, MZL (splenic, nodal and extranodal), or SLL] that has progressed. a. For subjects for whom the most recent biopsy was performed >36 months before the first dose of

	IPI-145, a repeat biopsy to confirm histology should be performed, unless medically contraindicated. b. For subjects who progressed within 2 months of initiating last prior chemotherapy, a repeat biopsy to confirm histology should be performed, unless medically contraindicated. 3. Subjects must have disease that is refractory to a chemotherapy regimen or RIT. The chemotherapy regimen (with or without rituximab) must contain at least one alkylating agent or purine nucleoside antagonist. See Appendix 5 for examples of suitable prior chemotherapy. Refractory is defined as <u>either</u>: a. Lack of a CR or PR while receiving the chemotherapy regimen or RIT <u>or</u> b. PD within 6 months of the last dose of the chemotherapy regimen or RIT documented by computed tomography (CT), PET/CT or MRI obtained within 6 months after the last dose ***Note:*** Subjects exhibiting clinical progression within 6 months after the last dose of a chemotherapy regimen or RIT who are unable to undergo CT, PET/CT or MRI scans within the 6 month timeframe are allowed up to an additional 30 days to confirm radiologic progression. 4. Subjects must have disease that is refractory to rituximab. Refractory is defined as any of the following: a. Lack of a CR or PR during treatment with a full course of single-agent rituximab (≥4 doses of 375 mg/m^2, weekly) or ≥2 doses of ≥375 mg/m^2 of rituximab in combination with chemotherapy b. PD within 6 months of the last dose of a full course of single-agent rituximab or rituximab in combination with chemotherapy c. PD during, or within 6 months of the last dose of rituximab maintenance therapy 5. Measurable disease with a lymph node or tumor mass ≥1.5 cm in at least one dimension by CT, PET/CT or MRI.

	6. Eastern Cooperative Oncology Group (ECOG) performance status 0-2 (corresponds to Karnofsky Performance Status [KPS] ≥60%). 7. Adequate renal function, defined as serum creatinine ≤2 × upper limit of normal (ULN). 8. Adequate hepatic function, defined as total bilirubin ≤1.5 × ULN (unless elevated due to Gilbert's syndrome) and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels ≤3 × ULN. 9. Negative serum or urine β human chorionic gonadotropin (βhCG) pregnancy test within 1 week before first dose of study drug if the subject is a woman of childbearing potential (WCBP) (defined as a sexually mature woman who has not undergone surgical sterilization or who has not been naturally post-menopausal for at least 24 consecutive months for women ≤55 years or 12 consecutive months for women >55 years). 10. Willingness of male and female subjects who are not surgically sterile or postmenopausal to use medically acceptable methods of birth control for the duration of the study, including 30 days after the last dose of IPI-145. Sexually active men, and women using oral contraceptive pills, should also use barrier contraception. 11. Ability to adhere to the study visit schedule and all protocol requirements. 12. Signed and dated institutional review board (IRB)/independent ethics committee (IEC)-approved informed consent form before any study specific-screening procedures are performed.
Exclusion Criteria:	Subjects are to be excluded from the study if they meet any of the following criteria: 1. Candidate for potentially curative therapies at the time of informed consent, in the opinion of the investigator. 2. Prior treatment with any PI3K inhibitor or Bruton's Tyrosine Kinase (BTK) inhibitor 3. Prior history of allogeneic hematopoietic stem cell transplant (HSCT). 4. Major surgery within 28 days before the first dose of study drug.

	5. Prior chemotherapy, cancer immunosuppressive therapy, or other investigational agents within 4 weeks before first dose of study drug. 6. Ongoing treatment with chronic immunosuppressants (e.g. cyclosporine) or systemic steroids >20 mg prednisone (or equivalent) once daily (QD). 7. Grade 3B FL and/or clinical evidence of transformation to a more aggressive subtype of lymphoma. 8. Symptomatic central nervous system (CNS) NHL; a lumbar puncture is not required unless CNS involvement with NHL is clinically suspected. 9. Ongoing systemic bacterial, fungal, or viral infections at the time of initiation of study treatment (defined as requiring therapeutic dosing of an antimicrobial, antifungal or antiviral agent) a. Subjects on antimicrobial, antifungal or antiviral prophylaxis are not specifically excluded if all other inclusion/exclusion criteria are met and there is no presence of active infection. 10. Human immunodeficiency virus (HIV) infection. 11. Baseline QTcF >500 ms (average of triplicate readings). NOTE: This criterion does not apply to subjects with a right or left bundle branch block (BBB). 12. Prior, current or chronic hepatitis B or hepatitis C infection, positive result for hepatitis C virus antibodies (HCV Ab) or hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb). 13. Unable to receive prophylactic treatment for pneumocystis, herpes simplex virus (HSV) or herpes zoster (VZV) at time of initiation of study treatment. 14. History of chronic liver disease, such as cirrhosis or chronic hepatitis due to any cause, or suspicion of alcohol abuse (iNHL in the liver is not an exclusion). 15. Unstable or severe uncontrolled medical condition (e.g., unstable cardiac function, unstable pulmonary condition). Any important medical illness or abnormal laboratory finding that would, in the investigator's judgment, increase the subject's risk to participating in this study. 16. Concurrent active malignancy other than nonmelanoma skin cancer or carcinoma in situ of the cervix; bladder

	cancer or prostate cancer not requiring treatment. Subjects with previous malignancies are eligible provided that they have been disease free for 2 years or more. 17. History of stroke, unstable angina, myocardial infarction, or ventricular arrhythmia requiring medication or mechanical control within the last 6 months prior to first dose of study drug. 18. Prior surgery or gastrointestinal dysfunction that may affect absorption of study drug (e.g. gastric bypass, gastrectomy). 19. Use of live or live attenuated vaccines within 30 days prior to signing ICF. 20. Administration of medications or foods that are strong inhibitors or inducers of CYP3A within 2 weeks prior to the first dose of study drug. 21. Female subjects who are pregnant or breastfeeding.
Statistical Methodology:	<u>Sample Size Determination</u> This study will test the null hypothesis that the ORR is ≤30% against the alternative that ORR is ≥45%. Using a group sequential design with 1 interim analysis, 120 subjects will provide >90% power to achieve a one-sided overall significance level of 0.025. The interim analysis will occur approximately 4 months after at least 30 subjects (25% of the total) have initiated treatment with IPI-145. The cumulative Type II error to be spent at the interim and final analyses are 0.02 and 0.1, respectively. The interim analysis is intended for futility only and hence no Type I error will be spent. <u>Analysis Sets</u> The Full Analysis Set (FAS) will include all subjects who were treated with at least one dose of IPI-145. The FAS will be the primary analysis set for all efficacy and safety analyses. The Evaluable Analysis Set (EAS) will include all subjects who had no major protocol violations and who remained in the treatment phase of the study for at least 8 weeks with an adequate baseline tumor assessment and at least 1 adequate post baseline tumor assessment. Subjects with documented disease progression before 8 weeks of treatment should be

	considered as "early progression" subjects and, therefore, should be considered evaluable. Primary Efficacy Analysis ORR will be tested against the null (≤30%) by 1-sided exact binomial test at the 0.025 level. The estimated ORR along with the 2-sided 95% exact confidence interval will be provided. Missing data will be imputed by assuming that any subjects not exhibiting a response (CR or PR) are non-responders.

Table 1: Study Assessments for IPI-145 Monotherapy

	Screening Day -30 to -1	Cycle 1, Cycle 2 & Cycle 3 (28-Day Cycle Length) Day 1 (±4) [u]	Cycle 1, Cycle 2 & Cycle 3 (28-Day Cycle Length) Day 15 (±3)	Cycle 4, Cycle 5, Cycle 6 & Cycle 7 (28-Day Cycle Length) Day 1 (±4)	Cycle 8 and beyond – every second cycle (28-Day Cycle Length) Day 1 (±4)	End of Treatment (EoT) (within 7 days following the decision to discontinue study treatment) [s]	Safety Follow-up (30+7 days from last dose) [t]
Informed Consent	X						
Inclusion/Exclusion Criteria	X						
Histologic confirmation of indolent B-cell lymphoma (FL, MZL, or SLL)	X [a]						
Medical History, Demographics	X						
Cancer History	X						
Follicular Lymphoma International Prognostic Index (FLIPI) score at time of Screening	X						
Hepatitis Serology, CMV/EBV serology or viral load, HIV	X [b]						
Physical Examination/Vital Signs [d]	X [c]	X	X	X	X	X	
ECG (12-lead)	X	See Table 2					
Bone marrow biopsy and/or bone marrow aspiration	X [e]	See Table 3					
CT scans of the chest, abdomen and pelvis	X [f]	See Table 3					
ECOG Performance Status	X						
B symptoms	X	X		X	X		
Serum/Urine βhCG Pregnancy Test	X [g]	X [g]		X [g]	X [g]		
Blood chemistry [j]	X [c,h]	X [h]		X [h]	X [h]	X [h]	
Liver Function Tests [j]	X [c,i]	X [i]	X [i]	X [i]	X [i]	X [i]	
Hematology [j]	X [c,k]	X [k]	X [k]	X [k]	X [k]	X [k]	
Coagulation [j]	X [c,l]	X [l]					
Urinalysis [j]	X [c,m]	X [m]		X [m]			
Prior/Concomitant Medications [n]	X	X	X	X	X	X	X [t]
Prior/Concomitant Procedures [o]	X	X	X	X	X	X	X [t]
AE/SAE Assessment	X [p]	X	X	X	X	X	X [t]
Quality of Life (QoL) (EQ-5D)	X [q]	X [q]		X [q]	X [q]	X [q]	
Drug Self-administration Diary		X					
IPI-145 Administration		X [r]		X [r]	X [r]		

a. Histologic confirmation based on biopsy obtained <36 months prior to Cycle 1, Day 1 should be performed unless medically contraindicated. For subjects who progressed within 2 months of initiating most recent chemotherapy, a repeat biopsy to confirm histology should be performed.

b. All subjects will be assayed for anti-hepatitis C antibody (anti-HCV) and hepatitis B surface antigen (HBsAg) and core antibody (HBcAb) at Screening. Subjects with a positive anti-HCV or positive HBsAg or HBcAb test will be excluded from enrolling in the study. All subjects will also be assayed for cytomegalovirus and Epstein-Barr virus [CMV and EBV (Ag and Ab)] via a serology or viral load detection via polymerase chain reaction (PCR) assay at Screening. Subjects without documentation of a prior negative HIV test result (e.g. antibody, antigen or PCR-based test) are required to undergo an HIV test during Screening. Only subjects with a negative HIV result will be eligible for the study.

c. Clinically significant findings after the time of informed consent should be recorded as an AE from all subjects (excluding screen failures). Events meeting serious criteria will be reported to the Sponsor as an SAE for all subjects from time of informed consent (including screen failures).

d. Complete physical exam at Screening: includes assessment of liver/spleen size and clinical assessment of tumor masses (if evaluable by physical exam), height and weight and vital signs (including temperature, blood pressure, pulse rate and respiratory rate). At all other visits, a focused physical exam should be performed, which includes vital signs, assessment of liver/spleen size, clinical assessment of tumor masses and other clinically significant findings (new or previously noted at Screening). If physical examination at Screening is performed within 7 days of Cycle 1, Day 1, these Screening results can be used in place of the Cycle 1, Day 1 focused physical examination.

e. Bone marrow biopsy and/or bone marrow aspiration are to be performed at Screening for subjects where bone marrow biopsies and aspirates are a necessary part of the subject's clinical staging or who have ≥Grade 3 cytopenias at Screening. If a previous bone marrow biopsy and aspirate has been performed within 60 days of Cycle 1, Day 1 and frozen aspirate sample and unstained slides or blocks are available, these results can be used in place of the Screening assessment. If bone marrow aspirate and/or bone marrow biopsy is performed, the Screening and the first post-Screening bone marrow biopsies and/or aspirate samples should be sent for biomarker analysis (along with the corresponding pathology report) if available. See the IPI-145-06 Laboratory Manual for further instructions regarding the handling, shipping, and storage of the samples.

f. CT scans of the chest, abdomen and pelvis are required for all subjects. Other scans may be performed (e.g. head/neck CT) if clinically indicated or to evaluate a site of known disease. 18-FDG-PET/CT or MRIs may be used instead of CT scans, but the same method must be used throughout the study. Copies of all scans will be sent for independent review of response assessment. Please refer to complete imaging schedule per Table 3.

g. A serum/urine βhCG pregnancy test will be performed at Screening, on Day 1 of each Cycle, and when clinically indicated while receiving IPI-145 for WCBP. The test must be performed within 7 days of first dose to confirm eligibility. If the Screening test was within 7 days of first dose, it does not need to be repeated on Cycle 1 Day 1.

h. Blood chemistry laboratory parameters include: albumin, total protein, uric acid, sodium, potassium, calcium, phosphorous, chloride, bicarbonate (or CO_2), blood urea nitrogen (BUN) or urea, creatinine, lipase, amylase, magnesium, and glucose. If the Screening chemistry evaluations are performed within 7 days of Cycle 1, Day 1, these Screening results can be used in place of the Cycle 1, Day 1 blood chemistry results. All clinically significant laboratory findings, including but not limited to those findings resulting in a drug interruption/reduction/discontinuation or requiring medical intervention should be reported as an AE (see protocol Section 8.1.1 for definition of an AE).

i. Liver function tests to include lactate dehydrogenase (LDH), serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), total and direct bilirubin, and alkaline phosphatase (ALP). If the Screening liver function tests are performed within 7 days of Cycle 1, Day 1 then these Screening results can be used in place of the Cycle 1, Day 1 liver function tests results. Blood samples should be drawn and results reviewed within 72 hours prior to the clinic visit. All clinically significant laboratory findings, including but not limited to those findings resulting in a drug interruption/reduction/discontinuation or requiring medical intervention should be reported as an AE (see protocol Section 8.1.1 for definition of an AE).

j. Additional (unscheduled) assessments should be done as clinically indicated.

k. Hematology laboratory parameters to include: hemoglobin, hematocrit, platelets, and white blood cell count with 5-part differential (manual or automated) [for an absolute neutrophil count (ANC), neutrophils, lymphocytes and monocytes, eosinophils and basophils]. If the Screening hematology evaluations are performed within 7 days of Cycle 1 Day 1, then these Screening results can be used in place of the Cycle 1 Day 1 hematology results. Blood samples should be drawn and results reviewed within 72 hours prior to the clinic visit. Clinically significant laboratory findings, including but not limited to those findings resulting in a drug interruption/reduction/discontinuation or requiring medical intervention should be reported as an AE (see protocol Section 8.1.1 for definition of an AE).

l. Coagulation evaluation will occur at Screening and on Day 1 of Cycles 1, 2, and 3 for all subjects. Coagulation laboratory parameters include prothrombin time (PT), international normalized ratio (INR) and activated partial thromboplastin time (aPTT). If the screening coagulation evaluations are performed within 7 days of Cycle 1 Day 1, these Screening results can be used in place of the Cycle 1 Day 1 coagulation results. Blood samples should be drawn and results reviewed within 72 hours prior to the clinic visit. Clinically significant laboratory findings including but not limited to those findings resulting in a drug interruption/reduction/discontinuation or requiring medical intervention should be reported as an adverse event (see protocol Section 8.1.1 for definition of an AE).

m. Complete urinalysis with qualitative analysis for protein will be performed at Screening, at Cycle 3, Day 1 and at Cycle 7, Day 1. Positive results (protein >30 mg/dL) will require quantitative analysis (assessment of urine protein to creatinine ratio) if not previously noted as part of medical history. Clinically significant laboratory findings including but not limited to those resulting in a drug interruption/reduction/discontinuation or requiring medical intervention should be reported as an adverse event (see protocol Section 8.1.1 for definition of an AE).

n. For a period of 14 days prior to Cycle 1 Day 1 and throughout study treatment, subjects must avoid the concomitant use of drugs or foods that are strong inducers and inhibitors of CYP3A4. Moderate or weak inducers/inhibitors may be used with caution (See Appendix 2).

o. Prior/concomitant procedures should include all transfusions. If the subject is transfusion-dependent at Screening, transfusion history from the previous 3 months will be collected.

p. Adverse events will be collected from time of informed consent through the 30-day post-treatment visit for all subjects (excluding screen failures). SAEs will be collected from the time of informed consent (including screen failures) through 30 days after the last dose of study drug for all subjects. All AEs will be followed until resolution, return to baseline or it is determined the event is considered chronic. See Section 8.1.1 of the protocol for more information regarding AE/SAE collection and reporting.

q. Quality of life assessment includes the EQ-5D questionnaire. Conducted at Screening, and on Day 1 of Cycle 3, Cycle 5, Cycle 7, and Cycle 10, and Day 1 of every 4th cycle thereafter while on treatment (i.e. Cycle 14, 18, 22, etc.), and, when possible, at End of Treatment (EoT) (if >1 months from last administered questionnaire).

r. IPI-145 capsules will be administered twice daily (BID) in 28-day cycles. IPI-145 doses will be dispensed at a minimum monthly through Cycle 8 and every two months thereafter so the subject has enough IPI-145 doses until at least the next dispensation visit, taking into account the dispensation visit window. The ±4 day window for Day 1 in relevant Cycles does not apply to dose administration as dosing is daily. Doses should be taken every 12 hours within ±2 hours of the scheduled dose. Missed doses outside this window or vomited doses should not be taken or repeated.

s. An End of Treatment (EoT) visit is to be performed for all subjects who permanently discontinue study treatment within 7 days following the decision to discontinue study treatment. EoT assessments need not be repeated if performed within the previous 14 days, or 30 days for CT scan.

t. All subjects will have a Safety follow-up visit approximately 30 (+7) days after the last dose of study drug. If possible, this visit should occur prior to the initiation of any subsequent anticancer therapy. Assessments should include collection of AEs/SAEs and concomitant medications/procedures. This can be performed by telephone call, as long as the subject does not require laboratory and/or other procedures related to any new or ongoing AEs, in which case a clinical visit will be required.

u. Visit window does not apply to Cycle 1, Day 1.

Table 2: Pharmacokinetic and Biomarker Assessments

	Cycle 1 (28-Day Cycle Length)				Cycle 2 (28-Day Cycle Length)	Cycle 3 (28-Day Cycle Length)	Cycles 5, 7, 10 & 14 (28-Day Cycle Length)	End of Treatment (EoT) (within 7 days following the decision to discontinue study treatment)
	Day 1	Day 15 (±3)			Day 1 (±4)	Day 1 (±4)	Day 1 (±4)	
Time (hr) relative to IPI-145 administration	**Pre-dose**	**Pre-dose**	**+1**	**+4**	**Anytime during the visit**	**Anytime during the visit**	**Anytime during the visit**	
Pharmacokinetic blood sample collection [a]		X [b]	X	X	X	X		
ECG (12-lead)	X [c]	X [c]	X [c]	X [c]				
Serum and plasma biomarkers	X	X			X	X	X	X
Immunoglobulin blood levels [d]	X					X	X	X
Immunophenotyping evaluations (e.g. B/T-lymphocyte panel) [e]	X				X	X	X	X
Archival tumor tissue [f]	X							
Optional pharmacogenomics blood sample [g]	X							
Optional tumor tissue biopsy (e.g. accessible involved lymph nodes) before treatment, on study, and at progression [h]	X	X						X [i]

a. PK blood samples for IPI-145 plasma concentration determination will be collected from all subjects on Cycle 1 Day 15, Cycle 2 Day 1 and Cycle 3 Day 1. An additional blood sample for PK is requested at the start and end of any drug interruption/hold for an AE, when feasible.
b. On Cycle 1 Day 15, the morning dose of study medication will be administered in the clinic in order to accommodate PK sampling.
c. Assessment of the QT interval (for corrected QT [QTc] determination) will be performed as marked in the above table. All ECGs are to be performed in triplicate, within approximately a 5 minute time period
d. Immunoglobulin evaluation (to be done locally) includes IgA, IgG, IgM, and where routinely performed, IgE.
e. Immunophenotyping evaluation will be performed by a central lab. Samples will be collected from all subjects on Day 1 of Cycles 1, 2, 3, 5, 7, 10, 14 and at EoT. An immunophenotyping sample is also requested at the start and end of any drug hold/interruption for an AE, when feasible.
f. Tumor tissue is not required for enrollment, but should be submitted from all enrolled subjects, if available. Lymph node or other archival soft tissue that did not undergo decalcification is preferred. A fine needle aspirate cell block is also acceptable. Bone marrow biopsies are acceptable only if a soft tissue sample is not available. In cases where bone marrow biopsies and bone marrow aspirates are a necessary part of the subject's clinical care, leftover blocks or unstained slides are requested. A screening bone marrow biopsy may also serve as archival tumor tissue. Corresponding pathology reports should also be submitted, if available. See the IPI-145-06 Laboratory Manual for further instructions regarding the handling, shipping, and storage of the samples.
g. Collected on a single occasion from subjects who provide additional optional informed consent for pharmacogenomics research. It is recommended that the pharmacogenomics blood sample be collected prior to dosing on Cycle 1 Day 1. Subjects who do not wish to participate in the pharmacogenomics research may still participate in the clinical study.

h. Optional tumor tissue biopsy sample collection for subjects who provide additional informed consent. Cycle 1 Day 1 biopsy is pre-IPI-145 therapy and may be collected at any time during the Screening period. The on-treatment biopsy at Cycle 1 Day 15 may be collected at any time during the clinic visit. For subjects with measurable disease in the blood, a whole blood sample may be collected in place of tumor tissue, if applicable.

i. Optional tumor tissue biopsy sample collection only for subjects with disease progression who provide additional informed consent.

Table 3: On-Treatment iNHL Response Assessments

Assessments	On-Treatment Assessments		End of Treatment (EoT) (within 7 days following the decision to discontinue study treatment)
	Cycles 3, 5, 7 & 10 (Day -7 to Day 1 of Each Cycle)	Cycles 14 & 18 & Every 4th Cycle Thereafter (Day -7 to Day 1 of Each cycle)	
CT scans of chest, abdomen and pelvis [a, b]	X	X	X [c]
Bone marrow aspirate and/or biopsy [d]	X	X	
Focused physical examination and assessment of B symptoms	X	X	X
Response Assessment [e]	X	X	X

a. CT scans of the chest, abdomen and pelvis are required for all subjects to document measureable disease at Screening and will be performed within 7 days prior to initiating the next cycle of study treatment (i.e. Day -7 to Day 1) of Cycles 3, 5, 7, 10 and at every fourth cycle thereafter (Cycle 14, 18, 22, etc.) while on-treatment with IPI-145. Other scans may be performed (e.g. head/neck CT) if clinically indicated or to evaluate a site of known disease. Copies of all scans will be sent for independent review of response assessment.

b. 18-FDG PET/CT scan or MRI may be substituted if clinically indicated, but the modality chosen to evaluate each individual subject should be the same throughout the duration of the study. The frequency provided is the minimum required for study participation.

c. Scans will be performed at the EoT if the subject is discontinued for reasons other than radiologic disease progression and a previous assessment has not been performed within 30 days of the EoT visit.

d. Bone marrow biopsy and/or bone marrow aspirate required only for subjects who otherwise meet the criteria for a CR unless the subject had an adequate bone marrow biopsy at Screening that was negative for lymphoma or unless the subject had previously undergone a bone marrow procedure confirming the CR. If bone marrow aspirate and/or bone marrow biopsy is performed, bone marrow biopsies and/or aspirate samples (along with corresponding pathology report, if available) should be sent for biomarker analysis if available.

e. Response assessment is determined using information from objective measurements of available CT scan, focused physical exam, bone marrow biopsy as relevant, and assessment of B symptoms.

Table 4: Long-term Follow-up Assessments for IPI-145 Monotherapy

	Disease follow-up [a]		Survival Follow-up [c]
	≤ 12 months from 1st Dose of IPI-145 Every 12 weeks	**>12 months from 1st Dose of IPI-145 Every 16 weeks**	
Response assessment [b]	X		
Survival			X

a. For subjects who discontinue study treatment for reasons other than radiologic disease progression, response assessments (as shown in Table 3) will be performed during long-term follow-up. The same tumor assessments utilized during the treatment phase of the trial should be used during long-term follow-up. The first disease assessment follow-up should occur approximately 12-16 weeks after the last on-treatment/end-of-treatment tumor assessment. Response assessments following the long-term follow-up disease assessment schedule will occur for 2 years after the first dose of IPI-145 or until progression is documented or other anticancer therapy is initiated, whichever occurs first.

b. Response assessment is determined using information from objective measurements of available CT scan, focused physical exam, bone marrow biopsy as relevant, and assessment of B symptoms.

c. For all subjects who discontinue treatment from IPI-145, survival follow-up will occur every 6 months (± 4 weeks) from IPI-145 treatment discontinuation for up to 3 years after their first dose of IPI-145. This assessment can be conducted by telephone interview. Information on initiation of other anticancer therapy will also be collected and is to include start date and therapy name(s), of other subsequent therapies if applicable.

1 BACKGROUND AND RATIONALE

1.1 INTRODUCTION

IPI-145 is a potent phosphoinositide-3-kinase (PI3K)-δ,γ inhibitor being developed by Verastem, Inc. (Verastem). PI3K-δ and PI3K-γ isoforms are necessary for adaptive and innate immunity, and are important mediators in inflammatory disorders and hematologic malignancies. Therefore, IPI-145 is being developed as an orally administered potential therapeutic in hematologic malignancy and inflammatory disease indications. This study is an evaluation of IPI-145 in iNHL subjects whose disease is refractory to rituximab and to either chemotherapy or radioimmunotherapy (RIT).

1.2 BACKGROUND

1.2.1 Functions of PI3K-δ and PI3K-γ

There are four mammalian isoforms of class 1 PI3Ks: PI3K-α, β,δ (class 1a PI3Ks) and PI3K-γ (a class 1b PI3K). These PI3Ks catalyze the production of phosphatidylinositol (3,4,5)-trisphosphate (PIP3), leading to activation of the downstream effector pathways important for cellular survival, differentiation, and function. PI3K-α and PI3K-β are widely expressed, and are important mediators of signaling from cell surface receptors. PI3K-α is the isoform most often found mutated in cancers, and has a role in insulin signaling and glucose homeostasis.[2, 3] PI3K-β is activated in cancers where phosphatase and tensin homolog (PTEN) is deleted. Both isoforms are targets of small molecule therapeutics in development for cancer. PI3K-δ and P13K-γ are preferentially expressed in leukocytes, and are important in leukocyte function.

PI3K-δ is activated by cellular receptors (e.g., receptor tyrosine kinases) through interaction with the SH2 domains of the PI3K regulatory subunit (p85), or through direct interaction with RAS.

PI3K-γ is associated with G-protein coupled receptors (GPCRs), is responsible for the very rapid induction of PIP3 in response to GPCRs, and can be also activated by RAS downstream of other receptors. PIP3 produced by PI3K activates effector pathways downstream through interaction with pleckstrin homology (PH) domain containing enzymes (e.g., PDK-1 and AKT [PKB]).[4]

It is clear that both PI3K-δ and PI3K-γ isoforms are important for chemotaxis and cell migration, and have independent roles in models of inflammatory diseases.[5] The roles of PI3K-δ and PI3K-γ in different immune cell types are outlined below.

<u>B-Cells</u>

PI3K-δ is important in B-cell function including development, activation, chemotaxis, migration, and homing to lymphoid tissue, and inhibitors of PI3K-δ block these functions.[3, 4, 6-12]

T-Cells

In T-cells, PI3K-δ has demonstrated a role in receptor and cytokine signaling. PI3K-δ is important for T-cell function including proliferation, activation, and differentiation.[3, 13-21]

Neutrophils

PI3K-δ along with PI3K-γ, are important in the response to immune complexes and FCγRII signaling in neutrophils, including migration, and the neutrophil respiratory burst. PI3K-γ is also critical for the migration and function of tumor associated neutrophils, suggesting a role in tumor immunity and cancer progression.[22] As such, PI3K-δ and PI3K-γ are central mediators of autoimmune disease and cancer.[23-27]

Macrophages/Monocytes

In macrophages collected from patients with chronic obstructive pulmonary disease (COPD), glucocorticoid responsiveness can be restored by treatment of the cells with inhibitors of PI3K-δ. Macrophages rely on PI3K-δ and PI3K-γ for responses to immune complexes through the Arthus reaction (FCγR and C5a signaling).[26, 28, 29] PI3K-γ is also critical for the migration and function of tumor associated macrophages suggesting a role in tumor immunity and cancer progression.[22]

Mast Cells

In mast cells, stem cell factor- (SCF) and IL-3-dependent proliferation, differentiation and function are PI3K-δ and PI3K-γ dependent, as is chemotaxis. The allergen/IgE cross-linking of FCεR1 resulting in cytokine release and mast cell degranulation is inhibited by treatment with PI3K-δ inhibitors, suggesting a role for PI3K-δ in allergic disease.[30-32]

NK Cells

Natural killer (NK) cells are dependent on both PI3K-δ and PI3K-γ for efficient migration. NK cell activity against viral targets is impaired in PI3K-δ kinase-dead mice, while the activity against tumors is unaffected.[33-36]

1.2.2 Indolent non-Hodgkin Lymphoma

Non- Hodgkin lymphoma (NHL) is the seventh most common cancer in male and female adults in the US,[37] representing the ninth and sixth leading cause of cancer deaths for men and women, respectively. [37] In Europe, it is the eighth most commonly diagnosed cancer, and the tenth most common cause of death from cancer in adults. The majority (>90%) of NHL represents malignancies of B-lymphocyte lineage and express CD20. There are approximately 14 classes of indolent and aggressive B-cell lymphoma classified according to morphology, immunophenotyping, genetics and clinical factors.[38] The most common of the indolent B-cell lymphomas is follicular lymphoma, comprising approximately 22% of all B-cell lymphomas. Less common are small lymphocytic lymphoma (SLL, approximately 6%), and marginal zone B-cell lymphoma, malt-type or nodal-type, approximately 5% and 1% of all B-cell lymphomas, respectively.

Indolent lymphomas tend to grow slowly. Even without treatment, subjects with indolent lymphoma often live for many years without major problems from their disease. For some subjects, no treatment is recommended until symptoms develop. With treatment, the expected median survival time is approximately 8 to 10 years. Overall response rates of ≥ 80% can be

expected with initial treatment. However, indolent lymphoma is considered incurable and almost all patients relapse with the response and duration of response to subsequent therapies decreasing with each line of therapy.[39, 40]

Rituximab, an anti-CD20 therapy, is commonly used as a single agent or in combination with cytotoxic chemotherapy for the treatment of B-cell NHL. The addition of polychemotherapy regimens to rituximab treatment has resulted in greater disease responses and longer duration of response in first-, second-, and later lines of therapy. However, there is an increasing need for effective treatments for patients with iNHL who, due to the incurable nature of this disease, eventually develop disease refractory to treatment with rituximab and chemotherapy. No standard of care exists in the refractory setting, with the treatment regimen primarily being determined by prior therapies. Therapies utilized in the refractory setting include additional chemotherapy, stem cell transplantation, and RIT. However, all these therapies are associated with lower response rates in patients refractory to chemotherapy and rituximab. In addition, stem cell transplantation is associated with significant toxicity, especially in elderly patients or those patients with comorbidities. RIT is associated with significant myelosuppression. Patients whose iNHL has not responded or has progressed within 6 months of either a rituximab containing chemotherapy regimen or RIT represent a population which would benefit from the development of novel anticancer agents.

1.3 IPI-145

1.3.1 IPI-145, a Potent PI3K-δ,γ Inhibitor

PI3K-δ and PI3K-γ contribute to the development and maintenance of inflammatory and autoimmune diseases, and hematologic malignancies.[3, 4, 8, 41] IPI-145 is a potent PI3K-δ,γ inhibitor being developed as a potential therapeutic in hematologic malignancy and inflammatory disease indications.

1.3.2 Non-Clinical Summary of IPI-145

See the IPI-145 Investigator's Brochure for detailed summaries on pharmacology, toxicology, and absorption, distribution, metabolism, and excretion (ADME) of IPI-145.

1.3.3 Clinical Experience in Humans

1.3.3.1 Study IPI-145-01 (Phase 1, first in human study)

Study IPI-145-01 was a randomized, double-blind, placebo-controlled, Phase 1 study in healthy adult subjects. Study objectives were to evaluate the safety, tolerability, PK and pharmacodynamics (PD) of single and multiple ascending doses of IPI-145 and to assess the effect of food and ketoconazole on the PK of IPI-145. This study is complete and data are summarized below.

One-hundred and six (106) subjects were enrolled overall, which included 36 subjects in the single ascending dose (SAD) portion (24 active treatment; 12 placebo), 48 subjects in the multiple ascending dose (MAD) portion (36 active treatment; 12 placebo), 6 subjects in the food effect (FE) effect portion (consisting of IPI-145 dosing with sequential fed and fasting portions),

and 16 subjects in the drug-drug interaction (DDI) portion (consisting of IPI-145 dosing periods with and without ketoconazole). The total subject exposure to IPI-145 is summarized in Table 5.

Table 5: Subject Exposure (Study IPI-145-01)

PART	Treatment Exposure	Duration of Treatment	Total Exposure per Subject (mg)	Total No. of Subjects Exposed
SAD	Placebo SD	1 day	0	12
	1 mg IPI-145 SD	1 day	1	4
	2 mg IPI-145 SD	1 day	2	4
	5 mg IPI-145 SD	1 day	5	4
	10 mg IPI-145 SD	1 day	10	4
	20 mg IPI-145 SD	1 day	20	4
	30 mg IPI-145 SD	1 day	30	4
MAD	Placebo Q12h or Q24h	14 days	0	12
	1 mg IPI-145 Q12h*	14 days	26	9
	2 mg IPI-145 Q12h*	14 days	52	9
	5 mg IPI-145 Q12h*	14 days	130	9
	10 mg IPI-145 Q24h	14 days	140	9
FE	25 mg IPI-145 Fasted-Fed	2 days	50	3
	25 mg IPI-145 Fed-Fasted	2 days	50	3
DDI	10 mg IPI-145 SD	2 days	20	16

SD = single dose; Q12h = once every 12 hrs; Q24h = once every 24 hrs; SAD = single ascending dose; MAD = multiple ascending dose; FE = food effect; DDI = drug-drug interaction. *includes QD dosing on Days 1 and 14.

IPI-145 was well tolerated at the doses evaluated. There were no deaths and no serious adverse events (SAEs). Dose escalation proceeded as planned in both the SAD and MAD portions, to a pre-determined exposure limit based on the findings in the 28-day nonclinical toxicology study in rats.

No clinically significant safety laboratory or ECG abnormalities were observed during any portion of the study.

Pharmacokinetic assessments demonstrated that IPI-145 is rapidly absorbed following single and multiple dose oral administration, with the maximum plasma concentration observed typically 1 hr after dosing. Across the dose ranges evaluated, IPI-145 exposure increased proportionally to dose. The mean elimination half-life ranged from 6.5 to 11.7 hr after repeat dosing and did not depend on the dose level administered. IPI-145 accumulation was less than 2-fold following 14 days of Q12 hr oral administration.

Data from the DDI portion indicated that concomitant administration of 200 mg Q12hr ketoconazole increased exposure to IPI 145. On average, $C_{max,}$ $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ increased

by approximately 66%, 285% and 295%, respectively, in the presence of ketoconazole compared to IPI-145 administered alone.

See the IPI-145 Investigator's Brochure for further information.

1.3.3.2 Study IPI-145-02 (Phase 1, Hematologic Malignancies)

A Phase 1 dose-escalation study (IPI-145-02) to evaluate the safety, PK and biological activity of orally administered IPI-145 in subjects with advanced hematologic malignancies is currently ongoing. Sequential cohorts of subjects have been enrolled at progressively higher dose levels (ranging from 8 mg to 100 mg given orally BID continuously in 28-day cycles) with expansion cohorts of subjects with select hematologic malignancies. Dose limiting toxicities (DLTs) of Grade 3 rash and Grade 3 alanine aminotransferase (ALT])/aspartate aminotransferase (AST) elevations were experienced by two subjects receiving 100 mg BID. Therefore, the maximum tolerated dose (MTD) has been determined to be 75 mg BID.

Clinical Safety

A total of 193 subjects have been enrolled in study IPI-145-02 as of 28 October 2013. Of these, 32 (17% of enrollment) are iNHL subjects (including follicular and marginal zone lymphoma subtypes). Other populations include relapsed/refractory chronic lymphocytic leukemia/small lymphocytic leukemia (CLL/SLL), n=52 (27%), treatment-naïve CLL, n=15 (8%) and other diagnoses, n=109 (56%).

Across the population of subjects enrolled, 122 are male and 71 female with a median age of 66 years. IPI-145 doses administered include 8 mg BID (n=1), 15 mg BID (n=6), 25 mg BID (n=61), 35 mg BID (n=3), 50 mg BID (n=3), 60 mg BID (n=4) 75 mg BID (n=112), and 100 mg BID (n=3). Subjects with iNHL were enrolled at 15 mg BID (n=1), 25 mg BID (n=15), 50 mg BID (n=1) and 75 mg BID (n=15).

As of 28 October 2013, across all subjects in all dose cohorts, the median number of treatment cycles was 4.1 cycles, with 42% of subjects continuing on treatment. Subjects who received 25 mg BID had a median time on treatment of 4.7 cycles.

Subjects with iNHL (n=32) had a median 8.5 cycles of treatment (range 0.1 to 22.7 cycles) and subjects dosed with 25 mg BID had a median of 9.8 cycles of treatment (range: 0.1 to 20.7 cycles).

In all subjects across all dose cohorts, treatment-emergent adverse events (TEAEs) have occurred in 180 (93%) subjects, including 56 subjects (92%) in the 25 mg BID dose group. The most common TEAEs (≥ 20%) in all dose groups combined included fatigue (32%), ALT or AST increased (combined, 32%), diarrhea (27%), pyrexia (25%), nausea (24%), cough (22%) and neutropenia (20%). Related Grade ≥3 TEAEs occurred in 102 subjects (53%). The most common related Grade ≥3 TEAEs (≥ 5%) included ALT or AST increased (combined, 16%), neutropenia (13%) and neutrophil count decreased (5%).

Across all 32 iNHL subjects, TEAEs have occurred in 31 (97%) subjects. The most common TEAEs (≥ 20%) in all dose groups combined included: ALT or AST increased (combined, 53%), pyrexia (41%), rash (combined terms, 41%), fatigue (34%), diarrhea (34%), nausea (34%), neutropenia (31%) and cough (31%). Related Grade ≥3 TEAEs occurred in 22 subjects (69%), The most common related Grade ≥3 TEAEs (≥5%) included: ALT or AST increased (combined,

34%), neutropenia (25%), diarrhea (16%), anemia (9%), febrile neutropenia (9%), neutrophil count decreased (6%) and pneumonitis (6%).

In iNHL subjects in the 25 mg BID group, TEAEs have occurred in 15 subjects (100%). The most common TEAEs (≥ 20%) included: ALT or AST increased (combined, 53%), nausea (40%), rash (combined terms, 27%), vomiting (27%), diarrhea (27%), neutropenia (27%), pyrexia (20%), fatigue (20%) and cough (20%). Related Grade ≥3 TEAEs occurred in 11 (73%) of iNHL subjects in the 25 mg BID group. The most common related Grade ≥3 TEAEs (≥ 5%) included: ALT or AST increased (combined, 40%).

Related SAEs in subjects with iNHL occurred in 11 (34%) subjects overall, including 4 (27%) subjects in the 25 mg BID group and 6 (40%) subjects in the 75 mg BID group. Related SAEs occurring in more than one subject with iNHL (all doses) included: diarrhea (2 [6%]), pneumonitis (2 [6%]), pneumonia (2 [6%]), pyrexia (2 [6%]), and febrile neutropenia (2 [6%]). The two subjects with febrile neutropenia were in the 75 mg BID dose group. There were no related SAEs occurring in more than one subject in the 25 mg BID group.

As of 28 October 2013, two subjects with iNHL in the 75 mg BID group had fatal SAEs. One subject with marginal zone lymphoma had an SAE of colitis, which was improving, however the subject's respiratory status declined during hospitalization and the subject died of respiratory failure. The second subject, diagnosed with lymphoplasmacytic lymphoma had fatal SAEs of fungal pneumonia and disease progression with onset dates one week after discontinuing IPI-145 for neutropenia. The events were fatal approximately one month after onset and were considered related to IPI-145 by the Investigator.

Clinical Efficacy

Tumor response was evaluated in Study IPI-145-02 based on disease-specific standard criteria. Clinical activity was observed in all populations and at all dose levels evaluated.

As of 28 October 2013, 29 subjects with iNHL (including follicular and marginal zone lymphoma) have been evaluated for response. The ORR (defined as CR and PR) was 62%, including 3 CR and 15 PR. Eight (8) subjects had stable disease (SD), and 2 subjects had progressive disease (PD). The overall response rate was 67% for subjects who received ≤25 mg BID and 57% for subjects who received >25 mg BID. The median time to response was 1.8 months (range: 1.5 to 4.1), with no variation between dose groups (median 1.8 months for 25 mg BID; 1.8 for 75 mg BID).

Clinical Pharmacokinetics

Preliminary PK data from Study IPI-145-02 demonstrate IPI-145 is rapidly absorbed following oral dosing in subjects with advanced hematologic malignancies, with the maximum plasma concentration (C_{max}) generally achieved at approximately 1 hour post-dose. Steady state exposure over the dosing interval (AUC_{0-12}) is proportional to dose. Following repeat dose administration of 25 mg BID, mean C_{max} and AUC_{0-12} values are 1460 ng/mL and 8129 ng*h/mL, respectively. IPI-145 elimination half-life ($t_{1/2}$) does not appear to vary with dose and the mean $t_{1/2}$ was 4.5 hours following 25 mg BID administration.

1.4 RATIONALE FOR IPI-145 AS A POTENTIAL THERAPY FOR SUBJECTS WITH INDOLENT NHL

PI3K-δ and PI3K-γ are expressed in hematopoietic cells, and are critical for the ability of normal immune cells to respond to survival and differentiation signals in their environment. In cancer patients, where the pathways mediated by PI3K-δ,γ contribute to survival, proliferation, and differentiation of cancer cells, treatment with IPI-145 may be beneficial. The tumor microenvironment plays an important role in the development and maintenance of cancer cells.[42] Cancer cells through the expression of various cytokines, growth factors, and chemokines recruit multiple cell types including myeloid cells capable of differentiating into tumor-associated macrophages (TAMs) which promote angiogenesis and augment tumor growth.[43] Therefore, agents that target TAMs as well as other types of infiltrating leukocytes are of potential therapeutic interest in oncology.

PI3Ks play pivotal roles in cell signaling and regulate a variety of cellular functions relevant to oncogenesis. Impaired development and function of B and T lymphocytes has been demonstrated in PI3K-δ and PI3K-γ isoform knockout mice, supporting the development of PI3K-δ,γ specific inhibitors for B- and T-cell lymphoid malignancies.

1.5 DETERMINATION OF STARTING DOSE AND REGIMEN

In Study IPI-145-02, responses (CR and PR) have been observed in subjects with iNHL at doses ≤25 mg BID. Overall, as of 28 October 2013, 193 subjects have been dosed with IPI-145, including 32 subjects with iNHL. Of the 32 iNHL subjects, 15 have been dosed with IPI-145 at 25 mg BID, with a median time on treatment of 4.7 cycles.

The clinical safety data as of 28 October 2013 for patients on 25 mg BID in the overall population (n=61) and in the iNHL population (n=15) suggest this dose is well tolerated with a safety profile similar to what might be expected in patients with advanced hematologic malignancies. Frequently occurring adverse events (≥20%) in the iNHL population receiving 25 mg BID included ALT or AST increased (combined terms) (53%), nausea (40%), rash (combined terms, 27%), vomiting (27%), diarrhea (27%), neutropenia (27%), pyrexia (20%), fatigue (20%) and cough (20%). Among the 29 evaluable subjects with iNHL, the best ORR was 62% (3 CR, 15 PR) with 8 SD and 2 PD. The overall response rate was 67% for subjects who received ≤25 mg BID and 57% for subjects who received >25 mg BID. The median time to response was 1.8 months (range: 1.5 to 4.1), with no variation between dose groups.

Based on the safety and clinical activity of IPI-145 observed to date in Study IPI-145-02, a dose of 25 mg BID has been selected to evaluate in iNHL patients in the Phase 2 setting.

1.6 SUMMARY

Effective treatment for patients who have been diagnosed with iNHL who have not responded to or have progressed within 6 months of a rituximab containing chemotherapy regimen or RIT is an area of high unmet medical need. IPI-145 is a potent PI3K-δ,γ inhibitor being developed as a potential therapeutic in hematologic malignancy and inflammatory disease indications. Initial experience of IPI-145 in the treatment of patients with relapsed/refractory iNHL suggests a therapeutic potential for IPI-145 in high risk iNHL.

Therefore, Verastem, Inc. is conducting a Phase 2 clinical trial to evaluate the safety and efficacy of IPI-145 as a monotherapy in subjects with iNHL that is refractory to rituximab and to either chemotherapy or RIT.

2 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVES

The primary objective of this trial is to evaluate the antitumor activity of IPI-145 administered to subjects diagnosed with iNHL (defined as FL, MZL [splenic, nodal and extranodal], or SLL) whose disease is refractory to rituximab and to either chemotherapy or radioimmunotherapy (RIT).

2.2 SECONDARY OBJECTIVES

The secondary objectives of the study are:

- To evaluate the safety of IPI-145 in all subjects
- To evaluate additional efficacy parameters in all subjects
- To evaluate the PK of IPI-145 and, if applicable, its metabolite(s)

2.3 EXPLORATORY OBJECTIVES

The exploratory objectives of the study are:

- To evaluate whether baseline values or treatment-related changes in biomarkers correlate with IPI-145 clinical activity, safety and/or resistance in iNHL.
- To evaluate whether tumor genomic or pharmacogenomic markers correlate with IPI-145 clinical activity, safety, PK and/or resistance in iNHL
- To evaluate the health-related quality of life (QoL) of subjects

3 STUDY ENDPOINTS

3.1 PRIMARY ENDPOINT

The primary endpoint of the study is the Overall Response Rate (ORR), with overall response defined as best response of complete response/remission (CR) or partial response/remission (PR) according to the revised International Working Group (IWG) Criteria[1]

3.2 SECONDARY ENDPOINTS

The secondary endpoints of the study are:

- Treatment-emergent adverse events (TEAEs), ECG measures, and changes in safety laboratory values
- Duration of response (DOR) defined as the time from the first documentation of response to the first documentation of progressive disease (PD) or death due to any cause
- Progression-free survival (PFS) defined as the time from the first dose of study treatment to the first documentation of PD or death due to any cause
- Overall survival (OS) defined as the time from the first dose of study treatment to the date of death
- Time to response (TTR), defined as the time from the first dose of study treatment to the first documentation of response (complete or partial)
- PK parameters derived from plasma IPI-145 concentrations and, if applicable, its metabolite(s)

3.3 EXPLORATORY ENDPOINTS

The exploratory endpoints of the study are:

- Lymph node response rate (LNR rate), with LNR defined as ≥ 50% reduction in the Sum of the Products of the Perpendicular Diameters (SPD) of nodal target lesions
- Serum, plasma and tissue biomarkers, and blood immunophenotype
- Germline DNA sequence variations
- Tumor genomic features (e.g. DNA sequence variation, DNA copy number variation, and/or RNA expression)
- Health-related QoL of subjects as assessed by the following subject-reported questionnaire:
    - EuroQol-5D (EQ-5D), a standardized instrument for use as a measure of health-related QoL

4 STUDY DESIGN

This is an open-label, single arm efficacy and safety study of IPI-145 administered orally to subjects who have been diagnosed with iNHL (FL, MZL, or SLL) whose disease is refractory to rituximab and to either chemotherapy or RIT. Approximately 120 subjects will be enrolled. Enrollment is anticipated at approximately 100 sites with approximately 40 sites in the US and the remainder of sites outside of the US. It is anticipated that the entire study will accrue subjects over approximately 30 months.

4.1 SCHEDULE OF ADMINISTRATION

Subjects will receive a starting dose of 25 mg IPI-145 BID over the course of 28-day treatment cycles for up to 13 cycles.

After completing 13 treatment cycles of IPI-145, subjects who have documented evidence of response (CR or PR) or SD at the Cycle 14 Day 1 response assessment according to the revised IWG criteria[1] may continue to receive additional cycles of IPI-145until disease progression or unacceptable toxicity. Treatment continuation assessments will be made thereafter at the start of every fourth cycle according to Table 3.

4.2 DOSE INTERRUPTION/HOLD/MODIFICATION GUIDELINES

Subjects will be monitored continuously for toxicity while on study treatment. Toxicity will be assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03. If a subject has an adverse event at least possibly related to study drug, then dose interruptions/holds with possible modifications should be made according to Table 6 below. Deviations from these guidelines may occur based on the clinical judgment of the Investigator with notification to the Medical Monitor/Sponsor. There should be no attempt to make up for missed doses.

Table 6: Dose Interruption/Hold/Modifications for IPI-145-Related Toxicities

IPI-145-related Toxicities [a, b]	Dose Interruption/Hold/Modification/Recommendation for IPI-145 [c]
Non-hematologic: Grade 2 or higher Pneumonitis/Pneumonia Or Grade 3 or higher all other Nonhematologic	**First occurrence:** Withhold until return to ≤ Grade 1 or baseline level; re-challenge therapy at original dose level. **Second occurrence of same AE:** Withhold until return to ≤ Grade 1 or baseline level; re-initiate therapy at one dose level lower from current dose. **Third occurrence of same AE:** Withhold until return to ≤ Grade 1 or baseline level; re-initiate therapy at one dose level lower from current dose. **Fourth occurrence of same AE:** Discontinue subject from study drug
Hematologic: Grade 3 or higher febrile neutropenia Or New Grade 4 neutropenia >7 days duration Or Grade 3 or higher thrombocytopenia with Grade ≥2 hemorrhage Or New Grade 4 thrombocytopenia of any duration requiring transfusion support.	
Recommendations for implementation of dose interruption Immediate hold for Grade 4 or higher nonhematologic toxicities and Grade 3 or higher febrile neutropenia For all other events, reduce from BID dosing to QD for two days, then hold	

a. IPI-145 Related = possible, probable, or definite relationship to IPI-145 as defined in Section 8.2.1.
b. Toxicity grades are defined per CTCAE Version 4.03. Note if parameter is not defined by CTCAE, then AE grading criteria (Section 8.2.1) should be utilized.
c. Refer to Table 7 for IPI-145 dose levels.

Treatment Interruption for Nonhematologic Toxicity

Treatment with IPI-145 should be interrupted for the following nonhematologic toxicities:

- Grade 2 or higher pneumonitis/pneumonia, defined as symptomatic and requiring medical intervention, including oral antimicrobials and/or steroids
  - Subjects who develop new pulmonary symptoms (e.g. cough, shortness of breath, dyspnea on exertion) or new radiographic findings should have IPI-145 held and receive empiric antimicrobial coverage while undergoing evaluation. Corticosteroids for symptomatic treatment of pneumonitis is recommended (and allowed per protocol). Restarting treatment with IPI-145 is allowed after complete resolution of symptoms.
- Grade 3 or higher other nonhematologic toxicity including the following:

- Infections: Subjects who develop infections requiring IV antibiotics/antifungals/anti-virals should have IPI-145 held until infection resolves (subject may restart IPI-145 while completing a course of oral therapy). Prophylaxis to prevent recurrence/opportunistic infections will not preclude the subject from restarting treatment.
- Hepatic events: Subjects who develop Grade 3 or higher transaminase (ALT/AST) elevations with or without clinical symptoms should have IPI-145 held until return to ≤ Grade 1. Additional work-up to evaluate viral infection/re-activation, exposure to environmental toxins (e.g. alcohol/con-meds), or other causes is recommended before restarting treatment with IPI-145.
- Gastrointestinal: Subjects who develop Grade 3 or higher nausea, vomiting or diarrhea despite optimal treatment should have IPI-145 held until resolution of symptoms. Evaluation of concomitant medications, gastrointestinal infections or inflammatory bowel (via endoscopy and biopsy) should be considered with persistent diarrhea or recurrence with restarting IPI-145. Corticosteroids (budesonide) with taper are allowed if colitis is suspected/cannot be ruled out.
- Skin rash: Subjects who develop Grade 3 or higher skin rashes should have IPI-145 held until return to ≤ Grade 1. In the setting of new Grade 1-2 skin rash early intervention is recommended to ameliorate risk of worsening symptoms. Evaluation of concomitant medications, environmental exposure, infections or other contributing factors is recommended.
- Cardiac: Subjects who develop new Grade 3 or higher cardiac events should have IPI-145 held until resolution of symptoms. This includes new Grade 3 QTcF prolongation only if >20 ms increase from Baseline. A new Grade 3 QTcF prolongation (>20 ms from baseline) requires triplicate ECGs with the average measurement used and the use of Fridericia's correction method (QTcF). For subjects with a right or left BBB, a new Grade 3 QTc prolongation is defined as an increase in QTcF of >100 ms from the pre-dose ECG to any post dose ECG as the QRS interval is prolonged at Baseline (by approximately 40 ms) in subjects with a BBB

Subjects requiring treatment interruption should be re-evaluated at least weekly until the toxicity improves to ≤ Grade 1 or returns to Baseline level. IPI-145 dose will be restarted at doses described in Table 7.

Treatment Interruption for Hematologic Toxicity

Worsening or transient Grade 3 or higher neutropenia, anemia, and/or thrombocytopenia caused by the subject's existing disease or by IPI-145 are to be expected. Blood counts should be monitored as described in the protocol with the frequency increased as clinically indicated in the setting of new or worsening Grade 3 or higher cytopenias. IPI-145 dosing may be interrupted at any time, at the discretion of the treating physician.

Treatment with IPI-145 should be interrupted for the following symptomatic hematologic toxicities:

- Grade 3 or higher febrile neutropenia
- Grade 3 or higher thrombocytopenia associated with Grade 2 or higher hemorrhage

The subject should be re-evaluated at least weekly until the toxicity improves to ≤Grade 1 or returns to Baseline.

A dose may be withheld up to 42 days for toxicity. Doses withheld for >42 days due to treatment-related toxicity will result in permanent discontinuation from treatment. Any subject who requires reduction to less than 10 mg BID due to repeat occurrence of the same treatment-related toxicity will be permanently discontinued from treatment. Any subject who requires reduction to less than 5 mg BID for different treatment-related toxicities will be permanently discontinued from study treatment. Dose levels are shown in Table 7.

Table 7: IPI-145 Dosing Levels

Dose Level	Dose (mg)
1	25 BID
-1	15 BID
-2	10 BID
-3	5 BID

Subjects who have a dose reduction due to a toxicity may be eligible for a dose increase back to the dose level prior to the reduction (i.e. the starting dose or dose of previous reduction if subject was dose reduced more than one level) if the following criteria are met:

1. Subject has tolerated the lower treatment dose for >1 treatment cycle
2. Subject has recovered to baseline levels from the toxicity which caused the dose reduction

4.3 ADDITIONAL CYCLES

Subjects with documented evidence of response (CR or PR) or SD at the Cycle 14 Day 1 response assessment according to the revised IWG criteria[1] may receive continued treatment with IPI-145 beyond the initial 13 cycles until disease progression or unacceptable toxicity. Treatment discontinuation from the study is described in Section 4.4.

4.4 TREATMENT DISCONTINUATION

A subject should be withdrawn from the study treatment if, in the opinion of the investigator, it is medically necessary, or if it is the wish of the subject. However, every effort should be made to keep the subject on study treatment. Subjects will be withdrawn from study treatment in case of any of the following reasons:

- An adverse event that requires permanent discontinuation of IPI-145
- Protocol-specified disease progression
- Subject death
- Noncompliance to protocol

- Investigator decision
- Subject becomes pregnant
- Termination of the study by sponsor
- Voluntary withdrawal from treatment by subject

In addition to the above reasons, other circumstances may necessitate discontinuation of a subject from the study treatment, as judged by the investigator or sponsor.

If a subject does not return for a scheduled visit, then every effort should be made to contact the subject. In any circumstance, every effort should be made to document subject outcome.

Adverse events (AEs) and SAEs leading to the discontinuation of a subject will be followed until resolution, resolution to baseline or until the event is considered chronic.

Subjects (including subjects that withdraw consent from study treatment but not overall study participation) must attend an End of Treatment Visit (EoT) (within 7 days following the decision to permanently discontinue study treatment) and a Safety Follow up Visit (30 +7 days from last dose of IPI-145) (Refer to Section 6.5.1 for further details). Subjects who have not withdrawn consent from overall study participation will enter long-term follow-up phase of the trial (see Section 6.5.2).

4.5 STUDY DISCONTINUATION

Subjects may voluntarily withdraw from the study at any time for any reason without prejudice.

Subjects will be withdrawn from the study in case of any of the following reasons:

- Subject death
- Subject lost to follow-up
- Completion of the follow-up period
- Termination of the study by sponsor
- Voluntary withdrawal from study participation (including follow-up) by subject

If the subject withdraws consent from overall study participation (and not just study treatment), no further evaluations should be performed and no attempts should be made to collect additional data.

5 STUDY POPULATION

This study anticipates enrolling approximately 120 subjects with a diagnosis of iNHL whose disease is refractory to rituximab and to either chemotherapy or RIT. This will include approximately 80 subjects with FL. Total enrollment may exceed 120 patients in order to enroll a sufficient number of FL subjects.

5.1 ENTRY CRITERIA

5.1.1 Inclusion Criteria

Subjects must meet all of the following criteria:

1. Age 18 years or older.
2. Subjects who have been diagnosed with indolent NHL [defined as FL, MZL (splenic, nodal and extranodal), or SLL] that has progressed.
    a. For subjects for whom the most recent biopsy was performed >36 months before the first dose of IPI-145, a repeat biopsy to confirm histology should be performed, unless medically contraindicated.
    b. For subjects who progressed within 2 months of initiating last prior chemotherapy, a repeat biopsy to confirm histology should be performed, unless medically contraindicated.
3. Subjects must have disease that is refractory to a chemotherapy regimen or RIT. The chemotherapy regimen (with or without rituximab) must contain at least one alkylating agent or purine nucleoside antagonist. See Appendix 5 for examples of suitable prior chemotherapy.

    Refractory is defined as <u>either</u>:

    a. Lack of a CR or PR while receiving the chemotherapy regimen or RIT

        <u>or</u>

    b. PD within 6 months of the last dose of the chemotherapy regimen or RIT documented by CT, PET/CT or MRI obtained within 6 months after the last dose

    Note: Subjects exhibiting clinical progression within 6 months after the last dose of a chemotherapy regimen or RIT who are unable to undergo CT, PET/CT or MRI within the 6 month timeframe are allowed up to an additional 30 days to confirm radiologic progression.
4. Subjects must have disease that is refractory to rituximab. Refractory is defined as any of the following:
    a. Lack of a CR or PR during treatment with a full course of single-agent rituximab (≥4 doses of 375 mg/m^2, weekly) or ≥2 doses of ≥375 mg/m^2 of rituximab in combination with chemotherapy
    b. PD within 6 months of the last dose of a full course of single-agent rituximab or rituximab in combination with chemotherapy

c. PD during, or within 6 months of the last dose of a rituximab maintenance therapy

5. Measurable disease with a lymph node or tumor mass ≥1.5 cm in at least one dimension by CT, PET/CT or MRI.
6. Eastern Cooperative Oncology Group (ECOG) performance status 0-2 (corresponds to Karnofsky Performance Status [KPS] ≥60%).
7. Adequate renal function, defined as serum creatinine ≤2 × upper limit of normal (ULN).
8. Adequate hepatic function, defined as total bilirubin ≤1.5 × ULN (unless elevated due to Gilbert's syndrome) and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels ≤ 3× ULN.
9. Negative serum or urine β human chorionic gonadotropin (βhCG) pregnancy test within 1 week before first dose of study drug if the subject is a woman of childbearing potential (WCBP) (defined as a sexually mature woman who has not undergone surgical sterilization or who has not been naturally post-menopausal for at least 24 consecutive months for women ≤55 years or 12 consecutive months for women >55 years).
10. Willingness of male and female subjects who are not surgically sterile or postmenopausal to use medically acceptable methods of birth control for the duration of the study, including 30 days after the last dose of IPI-145. Sexually active men, and women using oral contraceptive pills, should also use barrier contraception.
11. Ability to adhere to the study visit schedule and all protocol requirements.
12. Signed and dated institutional review board (IRB)/independent ethics committee (IEC)-approved informed consent form before any study specific-screening procedures are performed.

5.1.2 Exclusion Criteria

Subjects are to be excluded from the study if they meet any of the following criteria:

1. Candidate for potentially curative therapies at the time of informed consent, in the opinion of the investigator.
2. Prior treatment with any PI3K inhibitor or BTK inhibitor.
3. Prior history of allogeneic hematopoietic stem cell transplant (HSCT).
4. Major surgery within 28 days before the first dose of study drug.
5. Prior chemotherapy, cancer immunosuppressive therapy, or other investigational agents within 4 weeks before first dose of study drug.
6. Ongoing treatment with chronic immunosuppressants (e.g. cyclosporine) or systemic steroids >20 mg prednisone (or equivalent) once daily (QD)
7. Grade 3B FL and/or clinical evidence of transformation to a more aggressive subtype of lymphoma.
8. Symptomatic central nervous system (CNS) NHL; a lumbar puncture is not required unless CNS involvement with NHL is clinically suspected.

9. Ongoing systemic bacterial, fungal, or viral infections at the time of initiation of study treatment (defined as requiring therapeutic dosing of an antimicrobial, antifungal or antiviral agent)
    a. Subjects on antimicrobial, antifungal or antiviral prophylaxis are not specifically excluded if all other inclusion/exclusion criteria are met and there is no presence of active infection.
10. Human immunodeficiency virus (HIV) infection
11. Baseline QTcF >500 ms (average of triplicate readings).
    Note: This criterion does not apply to subjects with a right or left bundle branch block (BBB).
12. Prior, current or chronic hepatitis B or hepatitis C infection, positive result for hepatitis C virus antibodies (HCV Ab) or hepatitis B surface antigen (HBsAg), or hepatitis B core antibody (HBcAb).
13. Unable to receive prophylactic treatment for pneumocystis, herpes simplex virus (HSV) or herpes zoster (VSV) at time of initiation of study treatment.
14. History of chronic liver disease, such as cirrhosis or chronic hepatitis due to any cause, or who are suspected of alcohol abuse (iNHL in the liver is not an exclusion).
15. Unstable or severe uncontrolled medical condition (e.g., unstable cardiac function, unstable pulmonary condition). Any important medical illness or abnormal laboratory finding that would, in the investigator's judgment, increase the subject's risk to participating in this study.
16. Concurrent active malignancy other than nonmelanoma skin cancer or carcinoma in situ of the cervix; bladder cancer, or prostate cancer not requiring treatment. Subjects with previous malignancies are eligible provided that they have been disease free for 2 years or more.
17. History of stroke, unstable angina, myocardial infarction, or ventricular arrhythmia requiring medication or mechanical control within the last 6 months prior to first dose of study drug.
18. Prior surgery or gastrointestinal dysfunction that may affect absorption of study drug (e.g. gastric bypass, gastrectomy)
19. Use of live or live attenuated vaccines within 30 days prior to signing informed consent.
20. Administration of medications or foods that are strong inhibitors or inducers of CYP3Awithin 2 weeks prior to the first dose of study drug treatment.
21. Female subjects who are pregnant or breastfeeding.

6 STUDY PROCEDURES AND ASSESSMENTS

The schedule of assessments are summarized in Table 1, Table 2, Table 3, and Table 4.

6.1 INFORMED CONSENT

Subjects potentially eligible for participation must sign an informed consent form (ICF) prior to initiating any study specific procedures. Results of standard of care assessments performed prior to the subject signing the informed consent form may be utilized.

6.2 SCREENING PERIOD

6.2.1 Medical History, Physical Examination, and Screening Assessments

The Investigator at the site is responsible for maintaining a record of all subjects screened and those who are enrolled into the study.

During the Screening visit, the following assessments will be performed:

- Obtain signed ICF
- Review of inclusion/exclusion criteria
- Histologic confirmation of indolent B-cell lymphoma (FL, MZL or SLL)
- A complete medical history will be obtained from each subject, including cancer history and documentation of all previous anticancer treatments and treatment results (e.g. best response to previous disease specific treatments) prior procedures, current medications, and all medications used within 30 days prior to informed consent.
- Each subject will undergo a full physical examination including liver and spleen assessment, vital signs (temperature, blood pressure, pulse rate, and respiratory rate), height, and weight.
- 12-lead ECG should be conducted following an approximate 10-minute rest period in a semi-recumbent or supine position and obtained in triplicate within approximately a 5 minute time period. QTc measurements will use the Fridericia's correction method (QTcF).
- ECOG performance status.
- Blood chemistry laboratory parameters including albumin, total protein, uric acid, sodium, potassium, calcium, phosphorous, chloride, bicarbonate (or CO_2), blood urea nitrogen (BUN) or urea, creatinine, lipase, amylase, magnesium, and glucose.
- Liver function tests including: lactate dehydrogenase (LDH), serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), total and direct bilirubin, and alkaline phosphatase (ALP).
- Hematology laboratory parameters including: hemoglobin, hematocrit, platelets, and white blood cell count with 5-part differential (manual or automated) [for an absolute neutrophil count (ANC), neutrophils, lymphocytes, monocytes, basophils and eosinophils].
- Coagulation laboratory parameters including: prothrombin time (PT), International normalized ratio (INR) and activated partial thromboplastin time (aPTT).

- Complete urinalysis with qualitative analysis for protein (dipstick). Subjects with positive result (urine protein >30 mg/dL by dipstick) will require quantitative analysis to be performed (assessment of urine protein to creatinine ratio).
- Assessment of B symptoms [fever (i.e., temperature >38°C [>100.4°F]) for 3 consecutive days, weight loss exceeding 10% of body weight in 6 months, and/or drenching night sweats]
- Follicular Lymphoma International Prognostic Index (FLIPI) score at Screening
- Hepatitis Serology including anti-hepatitis C antibody (anti-HCV), hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb)
- Assay for CMV and EBV (Ag and Ab) via serology or viral load detection via polymerase chain reaction (PCR)
- Human Immunodeficiency virus (HIV) testing (if no previous documentation of a negative test)
- Serum or urine βhCG pregnancy test for WCBP (must be performed within 7 days prior to first dose of study drug).
- Baseline disease assessments, which include:
    - Bone marrow aspirate and/or bone marrow biopsy (for subjects where bone marrow biopsies and aspirates are a necessary part of the subject's clinical staging or who have ≥Grade 3 cytopenias at screening).
    - CT scans of chest, abdomen and pelvis are required for all subjects. Other scans may be performed (e. g, head/neck CT) if clinically indicated or to evaluate a site of known disease. Copies of all imaging/radiology films will be sent to a central laboratory for independent review.

      Note: 18-FDG-PET/CT or MRI may be substituted if clinically indicated, but the modality chosen to evaluate each individual subject should be the same throughout the duration of the study.
- Quality of Life (QoL) questionnaire (EQ-5D)

6.2.2 Contraception

The effects of IPI-145 on conception, pregnancy and lactation are unknown.

At screening, all males and female subjects who are not surgically sterile or postmenopausal must agree to use medically acceptable methods of birth control for the duration of the study and for 30 days after the last dose of IPI-145. Acceptable forms of contraception for females are nonhormonal and hormonal intrauterine devices (IUD), hormonal birth control pills, hormonal birth control patches, hormonal birth control injections or hormonal birth control implants. Sexually active men, and women using contraceptive methods described above, should also use barrier contraception with spermicide. Acceptable barrier forms of contraception are condoms or diaphragm.

6.3 TREATMENT PERIOD

6.3.1 Physical Examination and Vital signs

A focused physical exam should be performed at all clinic visits indicated in Table 1 and is to include assessment of liver/spleen size, clinical assessment of tumor masses (if evaluable by physical exam), other clinically significant findings (new or previously noted at screening). Vital signs (including temperature, blood pressure, pulse rate, respiratory rate) and weight should also be assessed. Results from the focused physical exams as outlined above will be utilized for disease response assessments at time points specific in Table 3. Any new clinically significant abnormality, or worsening changes from Baseline should be recorded on the AE CRF. If the Screening physical exam was performed within 7 days of the Cycle 1 Day 1 visit, then these results may be used in place of the Cycle 1 Day 1 physical exam results.

6.3.2 ECOG Performance Status

If the Screening ECOG performance evaluation was performed within 7 days of Cycle 1, Day 1 visit, these results can be used in place of the Cycle 1, Day 1 ECOG performance results. ECOG performance status will be assessed on each Day 1 clinic visit as indicated in Table 1.

6.3.3 B symptoms

B symptoms [fever (i.e., temperature >38°C [>100.4°F]) for 3 consecutive days, weight loss exceeding 10% of body weight in 6 months, and/or drenching night sweats] will be assessed on each Day 1 clinic visit indicated in Table 1.

6.3.4 12-Lead ECG

Assessment of the QT interval via ECGs will be performed at visits as indicated in Table 1. All ECGs should be conducted following an approximate 10-minute rest period in a semi-recumbent or supine position and obtained in triplicate within approximately a 5 minute time period. QTc measurements will use the Fridericia's correction method (QTcF).

Any clinically significant change from baseline in ECG parameters will be captured as an AE, per Section 8.2.1.

6.3.5 Clinical Laboratory Tests

The following laboratory parameters will be evaluated according to Table 1:

- Liver function tests including: lactate dehydrogenase (LDH), serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), total and direct bilirubin, and alkaline phosphatase (ALP).
- Hematology laboratory parameters including: hemoglobin, hematocrit, platelets, and white blood cell count with 5-part differential (manual or automated) [for an absolute neutrophil count (ANC), neutrophils, lymphocytes, monocytes, basophils and eosinophils].

- Blood chemistry laboratory parameters including: albumin, total protein, uric acid, sodium, potassium, calcium, phosphorous, chloride, bicarbonate (or CO_2), BUN or urea, creatinine, lipase, amylase, magnesium, and glucose.
- Coagulation laboratory parameters include: prothrombin time (PT), International normalized ratio (INR) and activated partial thromboplastin time (aPTT).
- Complete urinalysis with qualitative analysis for protein (dipstick).Positive results (urine protein > 30 mg/dL by dipstick) will require quantitative analysis (assessment of urine protein to creatinine ratio) if not previously noted in medical history.
- Serum or Urine Pregnancy test for WCBP
- Serum quantitative immunoglobulin evaluation to include IgA, IgG, IgM, and where routinely performed, IgE, should be collected at visits as specified in Table 2.
- Immunophenotyping evaluation to include T lymphocytes, B lymphocytes, natural killer cells, cytotoxic T cells and helper T cells will be performed at visits as specified in Table 2.

Additional (unscheduled) assessments should be done as clinically indicated.

For Cycle 1, Day 1, routine hematology, liver function tests, blood chemistry, or coagulation evaluations and pregnancy test (if applicable) may be performed within 7 days prior to study treatment (Cycle 1, Day 1). If the Screening hematology, liver function tests, blood chemistry, or coagulation evaluations or pregnancy test are performed within 7 days of Cycle 1, Day 1, then these Screening results can be used in place of the Cycle 1, Day 1 hematology, liver function tests, blood chemistry, or coagulation results.

Clinically significant laboratory findings, including but not limited to those findings resulting in a drug interruption/reduction/discontinuation or medical requiring intervention should be reported as an AE (see protocol Section 8.1.1 for definition of an AE).

6.3.6 Study Drug Administration, Criteria for Treatment, and Drug Self-administration Diary

Beginning on Cycle 1, Day 1, IPI-145 will be administered daily in 28 day cycles BID.

Doses should be taken every 12 hours within ±2 hours of the scheduled dose. Missed doses outside this window or vomited doses should not be taken or repeated. IPI-145 doses will be dispensed at a minimum monthly through Cycle 8 and every two months thereafter to the subject so that the subject has enough IPI-145 doses until at least the next dispensation visit, taking into account the dispensation visit window. Additional details on study drug dosage and administration are described in Section 7.2.1 and 7.2.2, respectively.

The date, time, and quantity of each capsule strength taken will be recorded in a Drug Self-administration Diary for Cycles 1 through 3, per Study Manual. On Cycle 1, Day 15, the morning dose of study medication will be administered in the clinic to accommodate collection of PK samples. When doses are taken outside of the clinic, subjects should also record any deviation from taking the full daily dose (e.g., vomited doses, missed doses, doses reduced due to missing or lost capsules). An attempt should be made to enable each dose to be taken at approximately the same time of day. Missed doses outside the windows defined above or vomited doses should not be taken or repeated.

For dose modifications due to adverse events and laboratory abnormalities, see Section 4.2.

6.3.7 Adverse Events

Monitoring of AEs and SAEs will be performed from the signing of the informed consent form (after medical history is completed) for all subjects. All AEs will be collected from the signing of the ICF through 30 days after the last dose from all subjects (excluding screen failures). SAEs will be collected and immediately reported to the Sponsor or designee from the time of ICF (for all subjects including screen failures) through 30 days after the last dose of study drug for all subjects. See Section 8 for a full description of the collection and reporting of AEs during this study.

6.3.8 Concomitant Medication and Therapies

On Day 1 of each Cycle (as well as Day 15 for Cycles 1, 2, and 3) through Cycle 8, every second Cycle thereafter, and the EoT visit, assessment of prior and concomitant medications and procedures will occur.

Antimicrobial prophylaxis:

Based on clinical experience with IPI-145 and the higher risk for infections in this study population for infections due to the refractory nature of their disease, the following are guidelines for the use of antimicrobial prophylaxis during study treatment:

- Subjects are required to receive pneumocystis prophylaxis concomitant with treatment with IPI-145 per institutional guidelines. Subjects who are found to be intolerant of pneumocystis prophylaxis may continue with study treatment at the discretion of the Investigator.
- Subjects are required to receive prophylactic treatment for herpes simplex virus (HSV) and herpes zoster (VZV) concomitant with treatment with IPI-145 per institutional guidelines.
- For subjects with history of CMV infection that required treatment, prophylactic treatment per institutional guidelines is recommended. Subjects with history of CMV or EBV infection that required treatment, and/or who enter the study while receiving antiviral prophylaxis, should be monitored for reactivation via serology or viral load detection while on study treatment per institutional guidelines.
- Investigators should consider prophylactic treatment for thrombocytopenia with platelets as clinically indicated. Therapeutic treatments with platelets and /or other blood products to manage bleeding complications may be used at any time as clinically indicated.

6.3.8.1 Antiemetics and Antidiarrheals

Antiemetic and antidiarrheal treatments may be used at the discretion of the Investigator and in accordance with the American Society of Clinical Oncology (ASCO) guidelines. The choice of antiemetic or antidiarrheal treatment, if required, will be made at the discretion of the Investigator. Subjects on stable doses of antiemetics and/or antidiarrheals to treat baseline conditions may continue on these therapies at the baseline dose.

6.3.8.2 Hematopoietic Growth Factors

Hematopoietic growth factors may be used at the discretion of the Investigator and in accordance with the ASCO guidelines. Prophylactic use of growth factors such as granulocyte-colony

stimulating factor (G-CSF) and granulocyte macrophage-colony stimulating factor (GM-CSF) may be implemented if clinically indicated, in accordance with local guidelines and medical practice (e.g., if a subject has Grade 4 neutropenia for ≥7 days, Grade 4 febrile neutropenia, or according to the National Comprehensive Cancer Network [NCCN] practice guidelines for myeloid factors). Subjects on a stable dose of erythropoietin to treat baseline anemia may continue on this therapy at this dose.

6.3.8.3 Use with caution: Medications that are Substrates of CYP3A or CYP2C8

In vitro studies in human liver microsomes have demonstrated IPI-145 is an inhibitor of cytochrome P450 (CYP) enzyme CYP3A4. Coadministration of IPI-145 with midazolam, a probe CYP3A substrate, resulted in an approximate 4-fold increase in midazolam systemic exposure (AUC). Systemic exposure to other medications that are substrates for CYP3A4 may be increased in subjects receiving IPI-145. **Caution should be used if IPI-145 is used concomitantly with drugs or foods that are substrates of CYP3A4, particularly those with a narrow therapeutic index**. **Drugs that are substrates for CYP3A should be used only if medically necessary and therapeutic alternatives are not available.**

IPI-145 is an inhibitor of CYP2C8 in vitro. Physiologically based pharmacokinetic (PBPK) modelling indicates the inhibitory effect of IPI-145 on CYP2C8 substrates is not expected to be clinically meaningful at an IPI-145 dose of 25 mg BID. The predicted mean AUC ratio for rosiglitazone (a CYP2C8 substrate) with and without IPI-145 at 25 mg BID was 1.02. Inhibition of CYP2C8 metabolism appears to be negligible and only minor changes in the systemic exposure to CYP2C8 substrates are anticipated in the presence of IPI-145. **Medications that are metabolized via CYP2C8 may be used as medically indicated but with caution.**

Appendix 1 provides a list of medications known to be substrates of CYP3A or CYP2C8. Please note that Appendix 1 is not a comprehensive list of all medications which may be substrates of CYP3A or CYP2C8. The Sponsor should be contacted with any questions regarding concomitant use of medications that are CYP3A or CYP2C8 substrates.

6.3.8.4 Prohibited: Medications or Food that Inhibit or Induce CYP3A

In vitro data indicate that oxidative metabolism plays an important role in the elimination of IPI-145, with CYP3A4 identified as a primary contributor to drug metabolism. Data from a drug-drug interaction study with ketoconazole (a potent CYP3A inhibitor) indicate exposure to a single dose of IPI-145 increased approximately 4- fold in the presence of ketoconazole. Similarly, exposure to IPI-145 was reduced approximately 80% when co-administered with rifampin, a recognized CYP3A inducer. Based on these data, the concomitant use of drugs or foods that are strong inhibitors or inducers of CYP3A are not allowed during study treatment. Moderate or weak inhibitors or inducers may be used with caution.

Subjects should avoid eating grapefruits or grapefruit-containing products. In addition, subjects should avoid herbal supplements including, but not limited to, St. John's wort throughout the study as this is known to be a strong inducer of CYP3A.

Appendix 2 provides a list of medications known to be strong inhibitors or inducers of CYP3A. Please note that Appendix 2 is not a comprehensive list of all medications which may modulate CYP3A activity.

The Sponsor should be contacted with any questions regarding concomitant use of medications that are thought to modulate CYP3A activity.

6.3.8.5 Prohibited: Use of Vaccines

For all subjects, the use of live or live attenuated vaccines is prohibited during the treatment.

Note: The use of inactivated (or killed) vaccines is allowed during the study, however subjects and their physicians should be aware that the effectiveness of any vaccine administered concomitantly with IPI-145 may be diminished. The ability to generate an immune response to any vaccine following the administration of IPI-145 has not been studied.

6.3.8.6 Prohibited: Immunosuppressants

Subjects are not to receive ongoing treatment with chronic immunosuppressants (e.g., cyclosporine) or systemic steroids for > 1 week at doses > the equivalent of 20 mg prednisone once daily (QD).

Note: Acute treatment for underlying autoimmune disorders (e.g. reactive airway disease, rheumatoid arthritis etc) with corticosteroid doses > 20 mg prednisone or equivalent QD for ≤ 1 week is permitted during the study. Corticosteroid doses of ≤ 20 mg prednisone or equivalent QD are permitted during the study for physiological replacement or chronic treatment for underlying autoimmune disorders (e.g. reactive airway disease, rheumatoid arthritis etc.).

6.3.8.7 Prohibited: PI3K and BTK Inhibitors

Subjects are not to have any prior exposure to any PI3K inhibitor or BTK inhibitor and these medications are prohibited while on-study (excluding investigational agent IPI-145).

6.3.8.8 Prohibited: Other Anticancer Therapies or Investigational Agents

Subjects are not to receive any additional anticancer therapy or other investigational agents not outlined in the protocol, including chemotherapy, radiation, surgery or cancer immunotherapy, during the treatment period.

6.3.8.9 Use with caution: Medications that are Substrates or Inhibitors of P-glycoprotein (P-gp)

In vitro data indicate that IPI-145 is a substrate for P-glycoprotein (P-gp). Concomitant medications that inhibit P-gp may cause the steady state concentration of IPI-145 to be reached more quickly than usual. These medications may be used as medically indicated but with caution. Additionally, in vitro studies demonstrated that IPI-145 has the potential to inhibit the active transport of other P-gp substrates.

Appendix 3 provides a list of medications that are substrates or inhibitors of P-gp. Please note that Appendix 3 is not a comprehensive list of all medications which may be substrates of P-gp or may modulate P-gp activity. The Sponsor should be contacted with any questions regarding concomitant use of medications that are thought to modulate P-gp activity.

6.3.8.10 Photosafety

The effect of IPI-145 on the skin, especially when in direct sunlight or with artificial UV light (e.g. tanning booths) is not known. As a general precaution, subjects should be advised to use appropriate protective measures to minimize exposure to direct sunlight or UV light sources during the treatment period and for at least 30 days after the last dose of IPI-145.

6.3.8.11 Other Concomitant Therapies

Any other medication which is considered necessary for the subject's welfare, and which is not expected to interfere with the evaluation of IPI-145, or prohibited per protocol, may be given at the discretion of the Investigator.

6.3.9 Subject-reported Outcomes Assessment

Subject self-reported health related quality of life will be assessed at Screening, on Day 1 of Cycle 3, Cycle 5, Cycle 7, and Cycle 10, and Day 1 of every 4th Cycle thereafter while on treatment (i.e., Cycle 14, 18, etc.), and, when possible, upon treatment discontinuation for any reason. Subject-reported health-related quality of life will be assessed using the EQ-5D questionnaire. An English–language example of this instrument is shown in Appendix 6.

6.3.10 Pharmacokinetic Sampling

Peripheral blood will be collected in all study subjects to characterize the pharmacokinetics IPI-145 and, if applicable, its metabolite(s). PK samples will be collected pre-dose and approximately 1 and 4 hours after administration of the morning dose of study medication on Cycle 1, Day 15. The morning dose of study medication will be administered in the clinic on Cycle 1, Day 15. Additional samples will be collected on Day 1 of Cycle 2 and Cycle 3 at any time during the clinic visit. The exact date and time of the PK blood draws, along with the date and time of the previous 2 doses of study medication will be recorded. Additionally, collection of a spot PK sample is requested when feasible at the time of the start and end of a drug interruption/hold for an adverse event.

Subjects who have an unusual safety or efficacy event (i.e., an AE different in type or severity from that which is expected in the setting of IPI-145 use or an exceptional response to treatment) may be asked to have additional PK samples collected. These blood draws for pharmacokinetic analysis will only be performed after discussion between the Medical Monitor and the Principal Investigator.

6.3.11 Biomarker Assessments

Serum and plasma will be collected pre-dose on Cycle 1, Day 1 and Cycle 1, Day 15.On Day 1 of Cycle 2, Cycle 3, Cycle 5, Cycle 7, Cycle 10, and Cycle 14, and the EoT visit, samples will be collected at any time during the clinic visit. Pharmacodynamic biomarkers (e.g. signaling pathway markers, chemokines and cytokines) may be measured over time to explore changes that occur with IPI-145 treatment. The time points are selected to enable characterization of early changes (first 3 Cycles) as well as potential changes that could occur with long-term dosing (Cycle 5 and thereafter). Pre-treatment biomarker levels may also be correlated with clinical response to IPI-145 in order to identify biomarkers predictive of clinically responsive subject

populations and/or biomarkers predictive of safety. Serum and plasma will be collected at EoT to enable the study of biomarkers with respect to disease progression or safety on IPI-145. See the IPI-145-06 Laboratory Manual for predictive biomarker sample handling procedures.

Blood will be collected periodically (see Table 2 for time points) to monitor immunoglobulins and immunophenotyping (e.g. B- and T-cell subsets, NK cells). Additional studies may be performed to address B and T cell activation and function. Immunophenotyping studies will be performed at a central laboratory site. Immunophenotyping will also be performed if possible when subjects have drug held for toxicity and when drug is restarted after being held for toxicity. These results may be assessed for correlation to clinical response and/or safety as well as correlation to serum and plasma biomarkers (e.g. chemokines and cytokines). See the IPI-145-06 Laboratory Manual for handling procedures.

Archival tumor tissue will be collected at Screening for exploratory assessments of tumor characteristics that may predict clinical response to IPI-145. Archival tumor tissue may be utilized for assessment of PI3K pathway and/or disease-specific biomarkers (e.g. PTEN, PI3K isoforms) by immunohistochemistry and/or in situ hybridization. In addition, tumor genomic studies may be performed (e.g. DNA sequencing, DNA copy number analysis, RNA expression profiling) to explore whether specific genomic features correlate with response or resistance to IPI-145 in iNHL. Archival tumor tissue is not required for enrollment, but should be submitted from all subjects (along with corresponding pathology report if available), where possible. See the IPI-145-06 Laboratory Manual for archival tumor tissue sample handling procedures.

In addition to archival tissue, optional tumor biopsies (e.g. of easily accessible lymph nodes or whole blood from subjects with measurable disease in the blood may be performed before treatment (prior to Cycle 1, Day1), during treatment at Cycle 1, Day 15, and on the day of last dose in cases where subjects are going off study due to disease progression. Cycle 1, Day 1 biopsy is pre-IPI-145 therapy and may be collected at any time during the screening period. The Cycle 1 Day 15 on-treatment biopsy may be collected at any time during the clinic visit. Similarly, in cases where bone marrow biopsies and aspirates are a necessary part of the subject's clinical care, leftover blocks or unstained slides are requested for biomarker studies. Optional serial tumor biopsies and tissue from serial bone marrow biopsies will be utilized to study tumor pharmacodynamics (e.g. phospho-PRAS40, phospho-S6 and/or other markers of PI3K pathway activity). Comparisons will be made of pharmacodynamic biomarkers pre-dose, on-drug, and where available at the time of disease progression on drug with results ultimately being explored for correlation with pharmacokinetics and clinical outcome. Exploratory genomic studies may also be performed with a goal of characterizing changes in tumor DNA sequence, DNA copy number and/or RNA expression that occur with treatment and at disease progression. See the IPI-145-06 Laboratory Manual for handling procedures of optional tumor biopsies as well as tissue from on-study bone marrow biopsies and aspirates that are a part of the subject's clinical care.

6.3.12 Pharmacogenomic Sample Collection (Optional)

An optional whole blood sample for genetic research will be collected on a single occasion. It is recommended that the blood sample be taken on Cycle 1 Day 1 from subjects who signed the informed consent form for the genetic research. Subjects who do not wish to participate in the pharmacogenomic research may still participate in the clinical study.

DNA may be extracted from the pharmacogenomic samples and used to explore whether germline DNA sequence variations (e.g. in drug metabolizing enzymes, drug transporters, PI3K pathway members, and/or other signaling pathways involved in iNHL) correlate with pharmacokinetics, pharmacodynamics, safety and/or efficacy of IPI-145. In addition, DNA may be used as matched normal control to determine whether a DNA sequence variation detected in the tumor sample is a somatic mutation versus a germline polymorphism. See the IPI-145-06 Laboratory Manual for further instructions regarding the collection, handling, shipping, storage and destruction of pharmacogenomics samples.

6.3.13 Indolent NHL Response Assessments

All disease specific assessments are to be completed (see Table 8) and as outlined in Table 3. The modality chosen to evaluate each individual subject should be the same throughout the duration of the study. Copies of all scans will be sent for independent review of response assessment.

CT scans of the chest, abdomen and pelvis are required for all subjects at Screening. These assessments may be performed within 7 days of initiating the next cycle of therapy (Day -7 to Day 1) of Cycles 3, 5, 7, 10, 14 and every fourth Cycle thereafter (Cycle 18, 22, etc.) until disease progression or start of other anticancer therapy. Copies of all scans will be sent for independent review of response assessment. Other scans may be performed (e. g, neck/head CT) if clinically indicated or if the area is a site of known disease. MRI may be substituted if clinically indicated, but the modality chosen to evaluate each individual subject should be the same throughout the duration of the study. The frequency outlined is the minimum required for study participation.

Scans will be performed at the EoT if the subject is discontinued for reasons other than radiological disease progression and a previous assessment has not been performed within 30 days of the EoT visit. If the subject has discontinued treatment for reasons other than disease progression, scans should be performed until disease progression or start of additional anticancer therapy (see Table 3 for scan frequency).

Bone marrow biopsy and/or bone marrow aspirates are to be performed at Screening (where clinically indicated) and as required thereafter to confirm a complete response as per the revised IWG criteria.[1] If the screening samples are performed within 60 days of Cycle 1, Day 1 and frozen aspirate sample and unstained slides or blocks are available, these results can be used in place of the Screening assessment. If bone marrow aspirate and/or bone marrow biopsy is performed, the Screening and the post-Screening bone marrow biopsies and/or aspirate samples should be sent for biomarker analysis if available. See the IPI-145-06 Laboratory Manual for further instructions regarding the handling, shipping, and storage of the samples.

Table 8 shows the major criteria employed for disease response assessment.

Table 8: Disease Response Criteria

Response	Definition	Nodal Masses	Spleen Liver	Bone Marrow
CR	Disappearance of all evidence of disease	a) FDG-avid or PET positive prior to therapy: mass of any size permitted if PET negative b) Variable FDG-avid or PET negative prior to therapy: regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunochemistry should be negative
PR	Regression of measurable disease and no new sites	≥50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes a) FDG-avid or PET positive prior to therapy: one or more PET positive at previously involved site b) Variable FDG-avid or PET negative: regression on CT	≥50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver and spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	a) FDG-avid or PET positive prior to therapy: PET positive at prior sites of disease and no new sites on CT or PET b) Variable FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥50% of previously involved sites from nadir	Appearance of new lesion(s) >1.5 cm in any axis, ≥50% increase in SPD from nadir of more than one node, or ≥50% increase in longest diameter of a previously identified node >1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	>50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: CR, complete remission; FDG, [^{18}F] fluorodeoxyglucose; PET, positron emission tomography, CT; computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, Stable disease; PD progressive disease.

Adverse events, including SAEs, associated with any disease assessment must be collected per Section 8.2.1.

6.4 END OF TREATMENT VISIT

All subjects will have an end of treatment (EoT) visit within 7 days following the decision to permanently discontinue study treatment. Assessments to be performed at this visit are indicated in Table 1.

6.5 POST-TREATMENT PERIOD

6.5.1 Safety Follow up Visit (30 Days Post-Treatment)

A visit should occur for subjects approximately 30 days (+7 days) after discontinuation of IPI-145 administration. If possible, this visit should be conducted prior to initiation of any subsequent therapy. Assessments should include collection of AEs/SAEs and concomitant medication and procedures. This can be performed by telephone call as long as the study subject does not require laboratory and/or other procedures related to any new or ongoing AEs, in which case a clinical visit will be required

6.5.2 Long-term Follow-up

For subjects discontinuing treatment due to reasons other than radiologic disease progression, disease assessments should occur for 2 years after the first dose of IPI-145 (following the on-treatment response assessment schedule, Table 3) or until documented disease progression or other anticancer therapy is initiated, whichever occurs first. Disease response scans will be performed at the EoT, every 12 weeks within the first year of the start of dosing and then every 16 weeks after a year since the start of dosing of study drug.

All subjects who permanently discontinue treatment with IPI-145 for reasons other than withdrawal of consent from overall study participation will enter survival follow-up. Survival follow-up will occur every 6 months (±4 weeks) from permanently discontinuing IPI-145 treatment for up to 3 years after first dose of IPI-145 or until death. The assessments shown in Table 4 can be conducted by telephone interview. Information on initiation of other anticancer therapy will also be collected.

Please see Table 4 for more details on the long-term follow-up assessments.

6.6 MISSED VISITS

If a subject misses a scheduled visit, the subject will continue on the protocol and attend the next scheduled visit. If a subject misses 2 scheduled visits, then the subject's continued participation in the study must be re-evaluated (see Section 4.4).

7 INVESTIGATIONAL MEDICINAL PRODUCT

7.1 DESCRIPTION OF INVESTIGATIONAL MEDICINAL PRODUCT

IPI-145 drug substance is a white to off-white crystalline powder. The IPI-145 drug product is formulated with excipients (Diluent/glidant, disintegrant, and lubricant) that are listed in FDA's Inactive Ingredients Database for approved drug products and/or Generally Regarded as Safe (GRAS) in two different capsule strengths (5 mg and 25 mg) for oral delivery. IPI-145 drug product will be supplied in capsule form as size 2, white opaque hard gelatin capsules (25 mg) and size 2, orange opaque hard gelatin capsules (5 mg).

7.2 DOSAGE AND ADMINISTRATION

7.2.1 Dosage

IPI-145 will be administered daily in 28-day cycles. IPI-145 is administered orally as a capsule formulation and will be supplied by the Sponsor. IPI-145 will be administered as a fixed dose in mg/day and should be administered using the minimal number of capsules necessary. Dose levels are listed in Table 7.

For an individual subject, dose reductions and discontinuations may be based on the clinical judgment of the Investigator with notification to the Medical Monitor/Sponsor.

7.2.2 Administration

Beginning on Cycle 1, Day 1, IPI-145 will be taken daily for 28 days BID (every 12±2 hours) in 28-day cycles.

The date, time, and quantity of each capsule strength taken will be recorded in a Drug Self-administration Diary for Cycles 1 through 3, per Study Manual. On Cycle 1, Day 15, the morning dose of study medication will be administered in the clinic to accommodate PK sample collection. When doses are taken outside of the clinic, subjects should also record any deviation from taking the full daily dose (e.g., vomited doses, missed doses, doses reduced due to missing or lost capsules). An attempt should be made to enable each dose to be taken at approximately the same time of day. Missed doses outside the windows defined above or vomited doses should not be taken or repeated.

IPI-145 doses will be dispensed at a minimum monthly through Cycle 8 and every 2 months thereafter to the subject so that the subject has enough IPI-145 doses until at least the next dispensation visit, taking into account the dispensation visit window.

IPI-145 capsules should be swallowed whole with a glass of water (approximately 8 ounces or 240 mL) at approximately the same time(s) each day. Subjects must avoid grapefruit or grapefruit juice

IPI-145 may be administered without regard to meals.

7.3 PACKAGING AND LABELING

IPI-145 drug product capsules will be provided in opaque bottles with induction sealed, child resistant cap. IPI-145 will be supplied to the clinical trial site as open-label medication. The label attached to each bottle will include, at a minimum, a statement limiting its use for investigational study only.

7.4 STORAGE AND HANDLING

IPI-145 must be stored at room temperature (15 to 30°C).

Caution is required when handling IPI-145. Pharmacists should follow standard procedures for the handling of investigational drugs, including avoidance of eye or skin contact with the drug product. If there is exposure to the drug product, provide treatment as necessary for physical exposure (skin washing) or inhalation (move to fresh air) and seek medical advice as necessary.

When IPI-145 capsules are distributed for self-administration, they should only be handled by the study subject. After handling capsules, the subject should wash their hands thoroughly. If someone who is not enrolled in a clinical trial involving IPI-145 swallows a capsule or inhales drug powder from a broken capsule of IPI-145, they should contact the relevant Principal Investigator to determine whether safety monitoring is necessary. Capsules should always be stored in the container provided to the study subject. Refer to Section 8.2.3.2 for details on reporting any exposure.

7.5 INVESTIGATIONAL MEDICINAL PRODUCT ACCOUNTABILITY

The Investigator or designee is responsible for taking an inventory of each shipment of IPI-145 investigational supplies received, and comparing it with the accompanying drug accountability form.

All unused IPI-145 will be retained at the site. After full drug accountability and reconciliation, the Investigators will return all IPI-145 to the Sponsor, or its designee or, at the Sponsor's request, will dispose of the study drug at the clinical trial site, according to site procedures. If any study drug is lost or damaged, the disposition of the study drug should be documented.

Subjects should be instructed to bring all unused IPI-145 to each study visit. The study site should count all capsules that the subject returns, and should take account for taken doses, missed doses, doses reduced due to missing or lost capsules, etc., before dispensing new study drug to the subject. Any subject who does not take the prescribed dose should be requested to return the remaining drug to the clinical trial site for accountability.

7.6 ASSIGNMENT TO TREATMENT

Study IPI-145-06 is a Phase 2, open-label, safety and efficacy study. A distinct subject identifier will be assigned by the clinical site's IVRS system once the subject has met all entry criteria. If a subject discontinues from the study, the subject identifier will not be reused and the subject will not be allowed to re-enter the study.

7.7 ASSESSMENT OF COMPLIANCE

At each applicable visit, doses will be dispensed to the subject so that the subject will have enough doses until the next applicable visit, taking into account the window for that subsequent visit. Compliance for doses taken outside of the clinic will be assessed by a count of the capsules returned to the study trial site by the subject and will be reviewed with the subject by the Investigator/designee at each visit.

7.8 TREATMENT OF OVERDOSE

In the case of overdose, clinic staff should be notified immediately and supportive care is to be given as indicated. Subjects should be informed to contact their doctor immediately if they have taken an overdose and should stop taking IPI-145.

Overdoses will be collected as part of the investigational medicinal product dosing information and/or as a protocol violation, as required. AEs or SAEs associated with an IPI-145 overdose (intentional or unintentional) should be reported to the Sponsor or designee as outlined in Section 8.2.2.6 (Medication Errors).

8 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.1 DEFINITIONS

The definitions of AEs and SAEs are provided below.

8.1.1 Adverse Event

Adverse event (AE) is any untoward medical occurrence associated with the use of a drug or with study participation, regardless of the relationship of the occurrence to IPI-145 or study protocol. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the drug, whether or not considered related to the drug. An adverse event can arise from any use of the drug, and from any route of administration, formulation or dose, including an overdose.

Medical conditions present prior to the initiation of the study, as well as ongoing changes in laboratory values/conditions that are being treated at baseline, will be captured as an AE if the condition worsens.

8.1.2 Adverse Reactions and Suspected Adverse Reactions

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. Suspected adverse reactions are any adverse events for which there is a reasonable possibility that the drug caused the adverse event. Adverse reactions also include medication errors and uses outside of what is foreseen in the protocol, which may include misuse, abuse and overdose (intentional and unintentional) of the product.

8.1.3 Serious Adverse Event

An adverse event 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:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent form (as documented as medical history on the eCRF), or
    - Scheduled therapy for the target disease of the study, including admissions for transfusion support or convenience
- Results in persistent or significant disability / incapacity
- Results in congenital anomaly / birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered a serious adverse drug experience when, based upon

appropriate medical judgment, they may jeopardize the patient or subject and 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.

8.2 PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS

8.2.1 Eliciting and Recording Adverse Events

Subjects will be instructed to report all AEs and will be asked a general health status question at each study visit. All AEs will be recorded in the eCRF from the time of informed consent until 30 days after the last dose of study treatment for all subjects, excluding screen failures. All SAEs occurring from time of informed consent (for all subjects including screen failures) through 30 days after the last dose of study treatment will be processed as outlined in Section 8.2.3. An adverse event will be followed until it is either resolved, has returned to baseline, or is determined to be a stable or chronic condition.

At each required visit during the trial, all AEs that have occurred since the previous visit must be recorded. The Investigator or appropriate designee must determine if the adverse event is serious or non-serious.

8.2.1.1 Relationship to Study drug

The Investigator is required to provide an assessment of relationship of AEs and SAEs to IPI-145. A number of factors should be considered in making this assessment including: 1) the temporal relationship of the event to the administration of IPI-145; 2) whether an alternative etiology has been identified; and/or 3) biological plausibility. The following guidelines should be used by Investigators to assess the relationship of an AE to the administration of the study drug.

Relationship assessments that indicate the event is "Not Drug Related":

- None: The event is related to an etiology other than the study product administration (the alternative etiology must be documented in the study subject's medical record).
- Remote: The event is unlikely to be related to the study product and likely to be related to factors other than study product.

Relationship assessments that indicate the event is "Drug Related":

- Possible: There is an association between the event and the administration of IPI-145, and there is a plausible mechanism for the event to be related to the study product; but there may also be alternative etiology, such as characteristics of the subject's clinical status or underlying disease.
- Probable: There is an association between the event and the administration of IPI-145, there is a plausible mechanism for the event to be related to the study product, and the

event could not be reasonably explained by known characteristics of the subject's clinical status or an alternative etiology is not apparent.

- Definite: There is an association between the event and the administration of IPI-145, there is a plausible mechanism for the event to be related to the study product, and causes other than IPI-145 have been ruled out and/or the event re-appeared on re-exposure to IPI-145.

8.2.1.2 Adverse Event Severity

The Grade of the AE will be assessed according to the NCI-CTCAE Version 4.03. Toxicities that are not specified in NCI-CTCAE Version 4.03 will be defined as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

Note: it is important to distinguish between SAEs and severe AEs. Severity is a measure of intensity, whereas seriousness is classified by the criteria based on the regulatory definitions as described in Section 8.1.3 above.

8.2.2 Specific Instructions for Recording Adverse Events on the eCRF

8.2.2.1 Diagnosis versus Signs and Symptoms

If a diagnosis is known at the time of reporting, this should be recorded in the eCRF and the SAE Report Form, if applicable, rather than the individual signs and symptoms (e.g., record only hepatitis rather than elevated transaminases, bilirubin, jaundice). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an SAE or AE on the eCRF (and SAE Report Form, if applicable). If a diagnosis is subsequently established, it should be reported as follow-up on the eCRF (and follow-up SAE Report Form, if applicable) and should replace the individual signs and/or symptoms as the event term on the eCRF (and SAE report Form, if applicable).

8.2.2.2 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., clinical sequelae or a cascade of events) should be identified by their primary cause. For example, if severe vomiting is known to result in dehydration, it is sufficient to record only vomiting as the SAE or AE on the eCRF (and SAE Report Form, if applicable). However, medically significant AEs occurring secondary to an

initiating event that are separated in time should be recorded as independent events on the eCRF (and SAE Report Form, if applicable). For example, if severe vomiting leads to acute renal failure, both events (i.e. vomiting and acute renal failure) should be recorded on the eCRF (and SAE Report form if applicable).

8.2.2.3 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between subject evaluation time points. Such events should only be recorded once on the AE eCRF (and SAE Report Form, if applicable). If a persistent AE changes in grade, it should be recorded as a new AE on the eCRF.

A recurrent AE is one that occurs and resolves between subject evaluation time points and subsequently recurs. All recurrent AEs should be recorded on the eCRF (and SAE Report Form, if applicable).

8.2.2.4 Abnormal Laboratory Values

If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be reported as an AE or SAE and the associated laboratory value or vital sign should be considered additional information that is collected on the relevant eCRF.

Abnormal laboratory values should be reported as an AE if the laboratory result:

- requires an adjustment in the study drug or discontinuation of study treatment
- require additional testing or surgical intervention
- is associated with accompanying symptoms
- is considered to be an AE by the Investigator

Note: If the laboratory abnormality is a sign of a disease or syndrome, only the diagnosis needs to be recorded on the eCRF (and SAE Report Form, if applicable).

8.2.2.5 New Cancers

The development of a new primary cancer should be regarded as an AE and will generally meet at least one of the serious criteria (See Section 8.1.3). New primary cancers are those that are not the primary reason for the administration of the trial treatment and have developed after the inclusion of the subject into the study. They do not include metastases of the original cancer.

Progression of the disease under study (i.e. disease progression) is not considered an AE/SAE unless it is fatal.

8.2.2.6 Medication Errors, Misuse and Abuse of Study Drug

Overdose, medication error, misuse and abuse are defined as follows:

- *Overdose*: refers to the administration of a quantity of study drug given per administration or cumulative, which is above the maximum dose according to the protocol. Clinical judgment should always be applied.
- *Medication error:* refers to an unintentional error in dispensing or administration of the study drug not in accordance with the protocol.

- *Off-label use*: relates to situations where the study drug is intentionally used for medical purpose not in accordance with the protocol.
- *Misuse*: refers to situations where the study drug is intentionally and inappropriately used not in accordance with the protocol.
- *Abuse*: corresponds to the persistent or sporadic, intentional excessive use of the study drug , which is accompanied by harmful physical or psychological effects.
- *Occupational exposure*: refers to the exposure to the study drug as a result of one's professional or non-professional occupation.

Overdoses, medication errors, abuse or misuse will be collected as part of investigational medicinal product dosing information and/or as a protocol violation, as required.

Any AE associated with an overdose, medication error, misuse or abuse of study drug should be recorded on the AE eCRF with the diagnosis of the AE.

8.2.3 Reporting of Serious Adverse Events

8.2.3.1 Immediate Reporting of Serious Adverse Events by Investigator to Sponsor

All SAEs (including SAEs occurring in screen failures and treated subjects) from the time of informed consent will be reported to the Sponsor or designee within 24 hours of the Investigator's first knowledge of the event, even if the experience does not appear to be related to IPI-145.

Serious adverse events should be communicated on the Verastem SAE Report Form as follows:

- Email: [redacted]
- Fax: [redacted] (USA & Canada)
- Hotline (Phone): [redacted] (USA)
- For International numbers, please refer to the SAE Form and supporting documentation.

The initial SAE Report Form must be as complete as possible, including details of the current illness and (serious) AE, and an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an outcome and end date for the AE, relevant laboratory values received after the report, or final diagnosis) must be documented on a follow-up SAE Report form. All follow-up information must be reported in the same timelines as initial information (i.e. within 24 hours of the Investigator's first knowledge of information).

At any time after completion of the AE reporting period (i.e. 30 days post-treatment), if an Investigator becomes aware of an SAE that is suspected by the Investigator to be related to IPI-145, the event must be reported as described above.

8.2.3.2 Immediate Reporting of Medical Events of Interest

Reports or laboratory results of **AST or ALT >3x ULN in combination with bilirubin >2x ULN are medical events of interest,** and therefore immediately reportable events, even if the events do not meet serious adverse event criteria.

Clinical findings of **Grade 3 or higher rash are medical events of interest**, and therefore immediately reportable events, even if the events do not meet serious adverse event criteria. Pre-existing skin conditions that recur would not meet this definition unless the recurrence is of a greater severity/frequency than previously experienced.

All medical events of interest will be reported to the Sponsor or designee within 24 hours of the Investigator's first knowledge of the event, even if the experience does not appear to be related to IPI-145. Medical Events of Interest should be communicated on the Verastem SAE / MEOI report form as described above for SAEs.

Any occupational exposure or exposure of an individual not enrolled in the study to the investigational medicinal product must be reported to the Sponsor or designee within 24 hours of the Investigator's first knowledge of the event, even if the exposure does not result in an AE. Unintentional exposures should be communicated on the SAE/MEOI report form, as described above for SAEs.

8.2.3.3 Reporting of Serious Adverse Events to the Institutional Review Board (IRB)/ Ethics Committee (EC)

Verastem or designee shall notify the Investigator and/or the IRBs/ECs per institutional guidelines of potential serious risks from clinical trials or any other sources, including the following:

- Suspected adverse reaction that is both serious and unexpected.
- Any findings from other studies that suggest a significant risk in humans exposed to the drug.
- Any finding from animal or in vitro testing that suggest a significant risk to humans exposed to the drug, such as mutagenicity, teratogenicity, or carcinogenicity; or report of significant organ toxicity at or near the expected human exposure.

Verastem or designee shall notify the Central Ethics Committees (CEC) of new serious, related and unexpected AEs or significant risks to subjects, per local country requirements.

The Investigator will also notify the IRB/ Local Ethics Committee (LEC), of serious, related and unexpected AE(s) or significant risks to subjects per local country requirements.

The Investigator must keep copies of all AE information on file, including correspondence with Verastem and the IRB/LEC.

8.2.3.4 Reporting of Serious Adverse Events to Regulatory Authorities

Verastem or designee shall notify Regulatory Authorities of serious, unexpected adverse reactions for IPI-145, as well as other adverse events, per local requirements. Expectedness will be determined using the current IPI-145 Investigator Brochure.

8.2.4 Pregnancy and In Utero Drug Exposure

Since IPI-145 has not been evaluated in pregnant or nursing women, the administration of IPI-145 in pregnant women or women of childbearing potential who are not using effective contraception is contraindicated.

Pregnancies occurring in subjects or partners of male subjects during the study treatment period until 30 days after the subject's last dose of study treatment are considered immediately reportable events. If a pregnancy occurs in a subject, study treatment must be discontinued immediately. The pregnant woman should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

The pregnancy must be reported to Verastem or designee within 24 hours of the Investigator's knowledge of the pregnancy using the Pregnancy Notification Form as follows:

- Email: [redacted]
- Hotline (Phone): [redacted] (USA)
- Fax: [redacted] (USA & Canada)
- For International numbers, please refer to the Pregnancy Notification Form and supporting documentation.

The Investigator will follow the pregnant woman until completion of the pregnancy, and must notify Verastem of the outcome within 24 hours of the Investigator's knowledge of the pregnancy outcome. The Investigator will provide this information on the Pregnancy Outcome Report Form. This notification includes pregnancies resulting in live, "normal" births.

If the pregnant subject experiences an SAE during pregnancy, or the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting SAEs (i.e., report the event to Verastem within 24 hours of the Investigator's knowledge of the event).

All neonatal deaths and congenital anomalies that occur within 30 days of birth (regardless of causality) should be reported as SAEs to Verastem. In addition, any infant death or congenital anomaly occurring after 30 days that the Investigator suspects is related to the *in utero* exposure to the study drug should also be reported to Verastem.

9 STATISTICAL METHODS

Details of the statistical methods for this study will be documented in a Statistical Analysis Plan (SAP). The SAP may modify the statistical methods outlined in the protocol; however, any major modification will also be reflected in a protocol amendment.

9.1 SAMPLE SIZE DETERMINATION

This study will test the null hypothesis that the ORR is ≤30% against the alternative that ORR is ≥45%. Using a group sequential design with 1 interim analysis, 120 subjects will provide >90% power to achieve a one-sided overall significance level of 0.025. The interim analysis will occur approximately 4 months after at least 30 subjects (25% of the total) have initiated treatment with IPI-145. The cumulative Type II error to be spent at the interim and final analyses are 0.02 and 0.1, respectively. The interim analysis is intended for futility only and hence no Type I error will be spent.

Among the 120 subjects to be enrolled, approximately 80 will be diagnosed with FL.

9.2 RANDOMIZATION AND STRATIFICATION

Randomization and stratification are not applicable for this Phase 2, open-label single-arm study.

9.3 ANALYSIS SETS

The Full Analysis Set (FAS) will include all subjects who were treated with at least one dose of IPI-145. The FAS will be the primary analysis set for all efficacy and safety analyses.

The Evaluable Analysis Set (EAS) will include all subjects who had no major protocol violations and who remained in the treatment phase of the study for at least 8 weeks with an adequate baseline tumor assessment and at least 1 adequate post baseline tumor assessment. Subjects with documented disease progression before 8 weeks of treatment should be considered as "early progression" subjects and, therefore, should be considered evaluable. The EAS will be a secondary analysis set for selected efficacy analyses.

Major protocol violations include failure to satisfy key entry criteria, or taking other anticancer therapies or other prohibited medications during the treatment phase of the study that could seriously confound the effects of the study treatment.

For each of the above two analysis sets, subsets defined by disease subtypes will be identified so that efficacy analyses for disease subtypes can be performed.

9.4 EFFICACY ANALYSES

Assessment of response and progression status will be evaluated locally (i.e. Investigator's assessment) and by an independent, third party panel of radiologists and oncologists according to the revised IWG Response Criteria for Malignant Lymphoma[1]. The independent response assessment will be used for the primary analyses of response and progression-based efficacy endpoints (i.e. ORR, PFS, TTR and DOR). Data based on local assessment will also be presented for these endpoints.

The FAS will be the primary analysis set for all efficacy analyses. The evaluable analysis set will also be used for some efficacy analyses, with details specified in the SAP.

Analyses for primary and secondary efficacy endpoints will be performed for the overall study population (iNHL), the follicular lymphoma population and subsets defined by other disease subtypes.

Analyses of the exploratory efficacy endpoint will be specified in the SAP.

9.4.1 Analysis of Primary Endpoint

ORR will be tested against the null (≤30%) by 1-sided exact binomial test at 0.025 level. The estimated ORR along with the 2-sided 95% exact confidence interval will be provided. Missing data will be imputed by assuming that any subjects not exhibiting a response (CR or PR) are non-responders.

ORR will also be presented for the follicular lymphoma population, as well as the other disease subtypes, with 2-sided 95% exact confidence intervals.

9.4.2 Analyses of Secondary Endpoints

PFS will be presented using the Kaplan-Meier method. A 2-sided 95% confidence interval for median PFS will be provided. The details of PFS censoring will be specified in the SAP.

TTR will be presented using the Kaplan-Meier method. A 2-sided 95% confidence interval for median TTR will be provided. TTR will only be analysed for responders (CR or PR).

DOR will be presented using the Kaplan-Meier method. A 2-sided 95% confidence interval for median DOR will be provided. DOR will only be analysed for responders (CR or PR). DOR will be censored in the same way as PFS with details provided in the SAP.

OS will be presented using the Kaplan-Meier method. A 2-sided 95% confidence interval for median OS will be provided.

These analyses will also be performed similarly for the follicular lymphoma population, as well as the other disease subtypes.

9.5 SAFETY ANALYSES

The FAS will be the primary analysis set for safety evaluation. Safety will be assessed by AEs, ECG and laboratory test measurements.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 16.1 or higher and graded according to NCI-CTCAE Version 4.03. If the AE is not included in the NCI-CTCAE Version 4.03, the Investigator will assign a grade according to Section 8.2.1.

The focus of AE summaries will be on TEAEs. A TEAE is defined as any AE that emerges or worsens in the period from the first dose of study treatment to 30 days after the last dose of study treatment. AEs will be summarized by the frequency of subjects experiencing TEAEs by MedDRA system organ classes (SOC) and preferred terms (PT). Separate tabulations will also be

produced for drug-related AEs, SAEs, AEs that led to treatment discontinuation, and AEs of at least Grade 3 severity.

ECG measurements will be tabulated for changes over time on study.

Laboratory parameters will be summarized for changes over time by descriptive statistics, and laboratory values that are of Grade 3 severity or greater will be tabulated and listed on an individual subject basis.

9.6 PHARMACOKINETIC ANALYSES

Plasma samples will be analyzed for IPI-145 and potential metabolite concentrations using a validated high performance liquid chromatography-tandem mass spectrometry (LC/MS/MS) method.

The PK data collected will be analyzed by standard population PK methods, using appropriate software. The intent of this analysis is to obtain exposure data in subjects with indolent lymphoma, to characterize the parameters of PK disposition, and to identify relevant covariates affecting drug exposure. If there is only a limited amount of plasma concentration data from this study, the data may be pooled with the results of other studies to perform the population PK analysis.

Additional details on the pharmacokinetic methods and analysis will be provided in the SAP.

9.7 ANALYSIS OF OTHER ENDPOINTS

9.7.1 Biomarker Analyses

All biomarker analyses will be descriptive in nature. Summary tabulations may be produced if data from a sufficient number of subjects are collected. Additional details on the biomarker analysis methods will be provided in the SAP

9.7.2 Analyses of Health-Related QoL

Details on the analysis methods of health-related QoL endpoints will be provided in the SAP.

9.8 INTERIM AND FINAL ANALYSES

9.8.1 Interim Analysis

An interim futility analysis will be performed approximately 4 months after at least 30 subjects (25% of total) have initiated treatment with IPI-145. The futility boundary is non-binding, meaning that the Type I error will be properly controlled if the study continues after the futility boundary is crossed at the interim analysis. If the interim analysis occurs 4 months after exactly 30 subjects have initiated treatment, the one-sided p-value for futility is 0.6552. This is equivalent to a response rate of 26.4% or 7 responders or less out of the 30 subjects. Actual p-value boundary for futility will be calculated based on the number of subjects at the interim analysis by linear interpolation.

ORR based on the Investigator's assessment will be used for the interim analysis.

If the required total number of subjects are accrued for the interim analysis but follow-up is not sufficiently mature to reasonably assess the ORR, accrual may proceed while the data on interim analysis subjects are being collated.

An Independent Data Monitoring Committee (IDMC) will review ORR and other efficacy data at the planned interim analysis. Safety analyses will also be performed at this interim analysis. Further details will be contained in the IDMC charter.

9.8.2 Final Analysis

Final analyses will be conducted approximately 6 months after the final subject receives his / her first dose.

10 STUDY ADMINISTRATION

10.1 GOOD CLINICAL PRACTICE STATEMENT

This study is to be performed in accordance with the protocol, the Declaration of Helsinki, the ICH Harmonised Tripartite Guideline for GCP, and all applicable local regulatory requirements.

10.2 INFORMED CONSENT

Verastem will provide a sample subject Informed Consent Form (ICF) for modification, as appropriate, by the Investigator. The ICF must include all elements required by ICH, GCP, and must adhere to the IRB/IEC requirements and the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator or his/her staff will explain the nature of the study, its purpose and associated procedures, the expected duration, and the potential risks involved to the subject prior to enrollment. The Investigator or designee will obtain written, informed consent. The subject will have ample time and opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Following the discussion regarding the study, a subject will be asked if they are willing to sign and personally date a statement of informed consent. Only if the subject voluntarily agrees to sign the informed consent statement and has done so, may he/she enter the study. A copy of the signed and dated ICF will be provided to the subject. The signed ICF is to remain in the Investigator's file, per local requirements.

The ICF and any other written information provided to the subjects will be revised whenever important new information becomes available that may be relevant to the subject's consent, or if there is an amendment to the protocol which necessitates a change to the content of the subject's informed consent. The Investigator will inform the subject of changes in a timely manner and will ask the subject to confirm continuation of their participation in the study by their signature on the revised informed consent form (if applicable). Any written ICF and written information must receive the approval/favorable opinion of the IRB/IEC in advance of use. Any additional approvals from the initial informed consent form should be forwarded to the Sponsor.

10.3 SUBJECT CONFIDENTIALITY

The written ICF will explain that study data will be stored in a database, maintaining confidentiality in accordance with national data legislation. All data processed by Verastem or its representative(s) will be identified by subject number and study code.

The written ICF will also explain that for data verification purposes, authorized representatives of Verastem, a regulatory authority, and IRB/IEC may require direct access to parts of the hospital or clinic records relevant to the study that include the subject's medical history.

The Investigator must ensure that the subjects' anonymity is maintained. On the eCRFs or other documents submitted to the Sponsor, subjects should not be identified by their names, but by their assigned subject number and study code. Documents not for submission to the Sponsor, such as signed Informed Consent Forms, should be maintained in strict confidence by the Investigator.

10.4 INSTITUTIONAL REVIEW BOARD/ ETHICS COMMITTEE REQUIREMENTS

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB/IEC at each clinical trial site. The Principal Investigator must submit written approval to Verastem before he or she can enroll any subject into the study.

The Principal Investigator is responsible for informing the IRB/IEC of any amendment to the protocol. In addition, the IRB/IEC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB/IEC annually.

Progress reports and notifications of SAEs will be provided to the IRB/IEC according to regulations and guidelines.

10.5 CASE REPORT FORMS AND SOURCE DOCUMENTATION

Electronic CRFs will be provided for the recording of all data. The Principal Investigator / Sub-Investigator or designee will record data on all observations, tests, and assessments specified in the protocol on the eCRFs provided by Verastem .

10.6 SPONSOR MONITORING

Before the first subject is enrolled into the study, a representative of Verastem will visit the study site to:

- Determine the adequacy of the facilities.
- Discuss with the Investigator(s) (and other personnel involved with the study) their responsibilities with regard to the protocol, and the responsibilities of Verastem .

During the conduct of the study, a representative of Verastem, Inc. will have regular contact with the clinical trial site, and have regular visits to the clinical trial site to:

- Provide information and support the PI.
- Confirm that the facilities remain acceptable.
- Confirm that the study team is adhering to the protocol, data are being accurately recorded in the eCRFs, and the investigational product is being properly maintained and accountability records are current.
- Perform source data verification with access to all original clinical records for each subject.

10.7 INDEPENDENT DATA MONITORING COMMITTEE

An Independent Data Monitoring Committee (IDMC) will be assembled to periodically review all available safety information and recommend whether or not the trial should continue, or should continue with modifications, based on their review of this data. In addition, the IDMC will review preliminary efficacy data at the time of the interim analysis and make a recommendation on futility of the study. All final decisions regarding study conduct will reside with the Sponsor. Membership and responsibilities of the IDMC will be documented in a separate IDMC Charter.

10.8 QUALITY ASSURANCE

In compliance with GCP and regulatory requirements, the Sponsor, a third party on behalf of the Sponsor, regulatory agencies or IRB/IECs may conduct quality assurance audits at any time during or following a study. The Investigator must agree to allow auditors direct access to all study-related documents including source documents, and must agree to allocate his or her time and the time of his or her study staff to the auditors in order to discuss findings and issues.

10.9 STUDY OR CLINICAL SITE TERMINATION

Verastem, or designee, reserves the right to terminate the study or a clinical trial site at any time. Conditions that may warrant termination of the study include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to subjects enrolled in the study.
- The decision on the part of Verastem to suspend or discontinue testing or the treatment of the study drug.
- Failure of the Investigator to comply with GCP.
- Submission of knowingly false information from the clinical trial site to Verastem or regulatory authorities.
- Insufficient adherence to protocol requirements.

If terminating the study, Verastem and the Investigator(s) will assure that adequate consideration is given to the protection of the subjects' interests.

10.10 DURATION OF THE STUDY, EXPECTED DURATION OF SUBJECT PARTICIPATION, AND END OF STUDY

The study is estimated to complete enrollment within 30 months. Subjects will be followed for survival for up to 3 years after their first dose of IPI-145. The maximum number of months to complete the study is expected to be approximately 66 months.

10.11 RECORDS RETENTION

All correspondence related to this clinical study should be kept in appropriate study files. Records of subjects, source documents, eCRFs, drug inventory, IRB, and Sponsor correspondence pertaining to the study must be kept on file. All study documents must be kept secured for a period of 2 years after a marketing application is approved for IPI-145; or, until 2 years after shipment and delivery of the drug for investigational use is discontinued or as long as required by local regulations, whichever is longer. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted prior to removing study records for any reason.

10.12 PUBLICATIONS

Publication by the clinical trial site(s) of any data from this study must be carried out in accordance with the Clinical Trial Agreement.

11 REFERENCES

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APPENDICES

Appendix 1: Known CYP3A or CYP2C8 Substrates

Note: Drugs or foods that are substrates for CYP3A should be used only if medically necessary and therapeutic alternatives are not available. Medications that are metabolized via CYP2C8 may be used as medically indicated but with caution.

The following lists provide known sensitive CYP3A substrates, CYP3A substrates with a narrow therapeutic range, and CYP2C8 substrates.

Additional information can be found at
http://www.medicine.iupui.edu/clinpharm/ddis/ClinicalTable.asp and
http://www.pharmacytimes.com/issue/pharmacy/2008/2008-09/2008-09-8687.

Sensitive CYP3A Substrates	
budesonide buspirone eplerenone eletriptan felodipine fluticasone lovastatin	midazolam saquinavir sildenafil simvastatin triazolam vardenafil
CYP3A Substrates with a Narrow Therapeutic Range	
alfentanil astemizole cisapride cyclosporine diergotamine ergotamine	fentanyl pimozide quinidine sirolimus tacrolimus terfenadine
CYP2C8 Substrates	
paclitaxel torsemide amodiaquine	cervistatin repaglinide rosiglitazone pioglitazone

Appendix 2: Medications or Foods Known to Inhibit or Induce CYP3A

Note: Subjects receiving IPI-145 are prohibited from concomitant use of medications or foods that are known to be strong inhibitors or inducers of CYP3A.

The following list provides medications known to induce or inhibit CYP3A activity. Note that this is not a comprehensive list of all medications which may modulate CYP3A activity. Additional information can be found at

- http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

Classification of In Vivo Inhibitors of CYP3A

Strong Inhibitors[1]	Moderate inhibitors[2]	Weak inhibitors[3]
Boceprevir, clarithromycin, conivaptan, grapefruit juice,[5] indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, [6] nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, [5] imatinib, verapamil	Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo, [4] goldenseal,[4] isoniazid, nilotinib, oral contraceptives, ranitidine, ranolazine, tipranavir/ritonavir, zileuton

1. A strong inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a substrate for that CYP by equal or more than 5-fold or >80% decrease in CL.
2. A moderate inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 5-fold but equal to or more than 2-fold or 50-80% decrease in CL.
3. A weak inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 2-fold but equal to or more than 5-fold or 20-50% decrease in CL.
4. Herbal product.
5. The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low dose, single strength).
6. Withdrawn from the United States market because of safety reasons.

Classification of In Vivo Inducers of CYP3A

Strong Inducers ≥ 80% decrease in AUC	Moderate Inducers 50-80% decrease in AUC	Weak Inducers 20-50% decrease in AUC
Avasimibe,(1) carbamazepine, phenytoin, rifampin, St. John's wort(2)	Bosentan, efavirenz, etravirine, modafinil, nafcillin	Amprenavir, aprepitant, armodafinil, echinacea,(3) pioglitazone, prednisone, rufinamide

1. Not a marketed drug.
2. The effect of St. John's wort varies widely and is preparation-dependent.
3. Herbal product.

Appendix 3: P-gp Substrates and Medications that are Inhibitors of P-gp

Note: In subjects receiving IPI-145, caution should be used for the concomitant use of P-gp substrates or inhibitors

The following list provides medications that are substrates or inhibitors of P-gp. Note that this is not a comprehensive list of all medications which may be substrates of P-gp or may modulate P-gp activity.

P-gp Substrates	
Amitriptyline	Loperamide
Amiodarone	Losartan
Atorvastatin	Lovastatin
Cefoperazone	Methadone
Chlorpromazine	Methotrexate
Cimetidine	Methylprednisolone
Ciprofloxacin	Morphine
Clarithromycin	Nadolol
Colchicine	Norfloxacin
Cyclosporine	Nortriptyline
Dexamethasone	Ondansetron
Digoxin	Omeprazole
Diltiazem	Pantoprazole
Erythromycin	Phenytoin
Estradiol	Pravastatin
Fentanyl	Propranolol
Fexofenadine	Quinidine
Hydrocortisone	Ranitidine
Itraconazole	Sirolimus
Lansoprazole	Tacrolimus
Levofloxacin	Timolol
Lidocaine	Trimethoprim
	Verapamil

P-gp Inhibitors	
Amiodarone	Ketoconazole
Amitriptyline	Lovastatin
Carvedilol	Mefloquine
Chlorpromazine	Nicardipine
Clarithromycin	Nifedipine
Cortisol	Ofloxacin
Cyclosporine	Omeprazole
Desipramine	Pantoprazole
Diltiazem	Progesterone
Dipyridamole	Propafenone
Doxepin	Propranolol
Erythromycin	Quinidine
Felodipine	Rifampicin (Rifampin)
Fluphenazine	Saquinavir
Grapefruit juice	Simvastatin
Haloperidol	Sirolimus
Itraconazole	Tacrolimus
	Testosterone
	Verapamil

Source: Atkinson AJ et al. Principles of Clinical Pharmacology, 2nd ed. Academic Press, Massachusetts, 2007.

Appendix 4: ECOG Performance Status

Grade	ECOG
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 : Eastern Cooperative Oncology Group : http://www.ecog.org/general/perf_stat.html
As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982

Appendix 5: Examples of Suitable Prior Chemotherapy

1. Bendamustine
2. Cyclophosphamide
3. Ifosfamide
4. Chlorambucil
5. Melphalan
6. Busulfan
7. Nitrosoureas
8. Fludarabine

Please contact the Medical Monitor regarding the appropriateness of any prior chemotherapy not listed above prior to subject enrollment.

Appendix 6: QoL Instrument - EQ-5D Questionnaire

(English version for the US)

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility
I have no problems in walking about ☐
I have some problems in walking about ☐
I am confined to bed ☐

Self-Care
I have no problems with self-care ☐
I have some problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

Usual Activities (*eg., work, study, housework, family or leisure activities)*
I have no problems with performing my usual activities ☐
I have some problems with performing my usual activities ☐
I am unable to perform my usual activities ☐

Pain/Discomfort
I have no pain or discomfort ☐
I have moderate pain or discomfort ☐
I have extreme pain or discomfort ☐

Anxiety/Depression
I am not anxious or depressed ☐
I am moderately anxious or depressed ☐
I am extremely anxious or depressed ☐

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today.