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Protocol No. IPI-145-23

Title: A Long-term, Continued Treatment and Follow-up Study in Subjects with Hematologic Malignancies Treated with Duvelisib (IPI-145)

IND Number(s): 112,486

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Sponsor Approval:

[redacted] 12 Dec 2017

Date

Verastem, Inc.

APPROVAL

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):	

CONTACT INFORMATION

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PROTOCOL SYNOPSIS

Study Title:

A Long-term, Continued Treatment and Follow-up Study in Subjects with Hematologic Malignancies Treated with Duvelisib (IPI-145)

Protocol Number:

IPI-145-23

Phase: 2

Study Drug:

For subjects continuing on duvelisib (IPI-145) treatment, duvelisib will be administered orally twice daily (BID) (28 days = 1 cycle) as a capsule formulation. Subjects will continue on the same dose level they last received in their previous duvelisib study.

Dosage Modifications:

Up to 2 dose reductions are allowed, based on the subject's starting dose in this study:

Starting Dose	Dose Level -1	Dose Level -2
75 mg BID	50 mg BID	25 mg BID
50 mg BID	25 mg BID	15 mg BID
25 mg BID	15 mg BID	10 mg BID
15 mg BID	10 mg BID	NA

Abbreviations: BID = twice a day; NA = not applicable.

Note: No dosing below 10 mg BID is allowed.

Dose holds up to 42 days are permitted for management of treatment-related adverse events (AEs).

For subjects only being followed for overall survival (OS), no duvelisib will be administered.

Study Population:

The study population will consist of subjects who received treatment with duvelisib or participated in the survival follow-up phase in a previous duvelisib study.

The number of subjects will be based on the number of eligible subjects on previous duvelisib studies approved for this long-term continued treatment and follow-up study.

Study Duration:

Subjects who are continuing duvelisib will be treated until disease progression or unacceptable toxicity. The study will include a treatment period, a 30-day safety follow-up period, and a survival follow-up period. The length of survival follow-up is specified in the protocol of the subject's previous study.

For subjects only being followed for OS, the length of survival follow-up is specified in the protocol of the subject's previous study.

Study Centers:

Approved study sites participating in previous duvelisib studies will be eligible to participate.

Study Design:

This study is designed to allow for the collection of long-term safety, clinical activity, and OS data in subjects receiving duvelisib treatment and OS data in subjects who have discontinued duvelisib treatment but are in the survival follow-up period in a previous duvelisib study.

Subjects receiving duvelisib will continue treatment with duvelisib at the last dose level received in their previous study. Subjects being followed only for OS will not receive treatment with duvelisib.

While on duvelisib treatment, subjects will have study visits at regular intervals (approximately every 3 months [± 3-day window]) for the following assessments: review of adverse events (AEs) and concomitant medications, return of used drug supplies, and dispensing of duvelisib. Radiologic evaluations will be performed at least once a year.

At each study visit, the subject's disease status will be assessed, and information will be collected to determine response to treatment.

Subjects will be monitored continuously for safety while on duvelisib. Dose modifications should be made according to the guidelines set forth in this study protocol (Section 7.2.1). There should be no attempt to make up missed doses of duvelisib. Duvelisib may be withheld up to 42 days because of treatment-related AEs. Duvelisib treatment withheld for > 42 days because of treatment-related AEs will result in discontinuation from duvelisib. Any subject who requires dose reduction to below 10 mg BID will be discontinued from duvelisib.

Subjects being followed for OS will be contacted by the study site approximately every 6 months to collect survival status and data pertaining to any other alternative antineoplastic therapy. Subjects will be followed for OS for up to the length of time specified in the protocol of the subject's previous study.

Study Objectives:

Primary Objective:

- To capture long-term safety data in subjects with hematologic malignancies treated with duvelisib Secondary Objectives:
- To capture data on the long-term clinical activity of duvelisib in subjects with hematologic malignancies
- To capture data on OS of subjects with hematologic malignancies treated with duvelisib

Study Endpoints:

Primary Endpoints:

- AEs
- Safety laboratory test values

Secondary Endpoints:

There are no formal secondary endpoints planned for this long-term study. Data will be captured to support the clinical endpoints based on the disease response assessment and OS as defined in the subject's previous study.

Inclusion Criteria:

To be eligible to participate in the study, all subjects must:

1. Have participated in a previous study of duvelisib, and:
    a. Be actively receiving duvelisib monotherapy on the previous study (within 14 days of study entry) and demonstrating clinical benefit (complete response [CR]/ partial response [PR]/ stable disease [SD]) of continued use, *or*
    b. Be in the survival follow-up phase of a previous duvelisib study
2. Have completed the required components of the previous study and be appropriate for enrollment into this long-term continued treatment and follow-up study, as determined by the Sponsor
3. Understand and voluntarily sign the informed consent form (ICF) before the conduct of any study-related procedures/assessments

To be eligible to participate in the study, subjects actively receiving duvelisib must:

1. Have a negative serum or urine β human chorionic gonadotropin (β-hCG) pregnancy test if a woman of child-bearing potential (WCBP). WCBP are defined as sexually mature women who have not undergone surgical sterilization or who are not naturally postmenopausal for at least 24 consecutive months (women ≤ 55 years) or 12 consecutive months (women > 55 years)
2. Agree to use adequate methods of birth control throughout the study and for 30 days after the last dose of duvelisib for all WCBP, all sexually active male subjects, and all partners of subjects

Exclusion Criteria:

Any subject is to be excluded from the study if he or she:

1. Is unwilling or unable to comply with the requirements of the protocol

Subjects actively receiving duvelisib are to be excluded from this study if they:

1. Have any ongoing ≥ Grade 3 AE considered related to duvelisib treatment at screening
2. Are pregnant or nursing

Statistical Considerations:

Sample Size Determination

Not applicable.

Analysis Set

The All-Treated Analysis Set (ATS) will include all subjects who receive any amount of duvelisib on or after Cycle 1 Day 1 (C1D1) of this study. The ATS will be the primary analysis set for all safety endpoints.

Primary Analyses

Adverse events will be coded by using the Medical Dictionary for Regulatory Activities (MedDRA) version 16.1 or higher and will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 or higher.

Summaries of AEs will be focused on treatment-emergent AEs (TEAEs). In this long-term extension study, a TEAE is defined as any AE with an onset date on or after C1D1 and within 30 days after the last dose of duvelisib. Treatment-emergent AEs will be summarized by MedDRA system organ class and preferred term. Separate summaries for TEAEs related to duvelisib, TEAEs that led to treatment discontinuation, TEAEs that led to death, TEAEs by CTCAE grade, TEAEs of Grade 3 or higher, serious TEAEs, and serious TEAEs related to duvelisib will be provided.

Baseline laboratory values will be those collected at C1D1 in this long-term extension study or, if not available, the most recent values collected within 30 days before C1D1. Applicable laboratory values will be graded according to CTCAE criteria. Shifts from baseline to maximum postbaseline grades will be tabulated for hematology, blood chemistry, and liver function tests.

Secondary Analyses:

Analyses of efficacy endpoints may be performed, as appropriate, according to the statistical analysis plan of the subject's previous study. No analyses of efficacy endpoints are planned for this study.

Table 1: Schedule of Assessments for Subjects Continuing Duvelisib Treatment

Assessment	Treatment			Treatment Termination (TT)[b]	Safety Follow-up[c] 30 (+ 7) days after last dose	Survival Follow-up[d]
	Cycle 1 Day 1[a]	Every 3 cycles (Every 84 ±7 days)	Once a year			
Informed consent	X[e]					
Eligibility criteria	X					
Concomitant medications	X	X		X	X	
Physical examination[f]	X	X		X		
Disease-related symptoms assessment[g]	X	X		X		
Laboratory assessments[h]	X	X		X		
Serum or urine β-hCG pregnancy test	X[i]	X[j]				
Radiologic evaluations	X[a]		X[k]	X		
Investigator response assessment	X[a]		X[k]	X		
AE/SAE assessments[l]	X	X		X	X	
Dispense/return duvelisib	X	X		X		
Duvelisib administration	----------X----------					
Survival		X				X

Table footnotes appear on the following page.

Abbreviations: AE = adverse event; β-hCG = β human chorionic gonadotropin; C1D1 = Cycle 1 Day 1; CR = complete response; ICF = informed consent form; MR = minor response; PE = physical examination; PR = partial response; SAE = serious adverse event; SD = stable disease; TT = Treatment Termination; WCBP = women of childbearing potential.

[a] Procedures captured on the previous duvelisib study within 30 days of C1D1 do not need to be repeated, unless otherwise specified. Exception: Radiologic evaluations and response assessments performed on the previous duvelisib study within 60 days of C1D1 do not need to be repeated at the C1D1 visit.

[b] The TT Visit should be scheduled no more than 7 days after the decision to terminate duvelisib. Assessments performed within the previous 2 weeks, or previous 30 days for investigator response assessments, need not be repeated at the TT visit.

[c] All subjects will have a Safety Follow-up visit approximately 30 (+ 7) days after the last dose of duvelisib. At a minimum, this visit should include collection of AEs/SAEs and concomitant medications/procedures. This visit 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 clinic visit will be required.

[d] All subjects will be followed for overall survival after discontinuation of duvelisib for the duration of time outlined in their previous duvelisib study. Survival follow-up will occur every 6 months (± 4 weeks). Information on initiation of other anticancer therapy will also be collected and should include therapy name(s), start and stop date(s) of other subsequent therapies, as well as the best response on the subsequent therapies, as applicable. This assessment can be conducted by telephone interview. [e] Subjects must voluntarily sign the ICF before any study-specific procedures/assessments are conducted. Standard-of-care assessments that fulfill study eligibility requirements may be performed before the subject signs the ICF.

[f] The initial PE will include vital sign measurements (temperature, blood pressure [after the subject has been seated for at least 5 minutes], pulse, and respiratory rate), height, weight, and liver and spleen assessment (C1D1). Subsequent PEs will be focused and include liver and spleen assessments.

[g] Disease-related constitutional symptoms include symptoms of fever (ie, temperature > 38 C/100.4 F) without evidence of infection, weight loss, and drenching night sweats without evidence of infection.

[h] Laboratory assessments include hematology with 5-part differential, chemistry panel, and liver function tests.

[i] For all WCBP, the C1D1 Screening pregnancy test must be performed within 7 days before the first dose to confirm eligibility.

[j] While subjects are receiving duvelisib, serum or urine pregnancy tests will be repeated every 3 cycles.

[k] Radiologic evaluations and response assessments will be performed once a year, approximately 1 year from the most recent scan on the previous duvelisib study. Magnetic resonance imaging may be substituted if clinically indicated, but the modality chosen to evaluate each individual subject should be the same as the previous duvelisib study and maintained throughout the duration of this study.

[l] Any ongoing AEs from the previous duvelisib study must be ≤ Grade 3 at the time of entry into this study. Any new or worsening preexisting medical conditions arising after the subject signs the ICF but before the first dose of duvelisib on this study will be captured as the subject's medical history. All AEs should be monitored from the time the subject receives the first dose of duvelisib after signing the ICF (ie, C1D1) through 30 days after the last dose of duvelisib.

Table 2: Schedule of Assessments for Subjects Only Being Followed for Overall Survival

Assessment	Screening/Day 1	Survival Follow-up[a] (Every 6 months ± 4 weeks)
Informed consent	X[b]	
Survival status[c]	X	X

[a] Subjects will be followed for survival for the duration of time outlined in their previous duvelisib study.

[b] Subjects must voluntarily sign the informed consent form before any study related-procedures/assessments are conducted.

[c] Subjects will be contacted every 6 months (± 4 weeks) to assess survival status. Information on initiation of other anticancer therapy will also be collected and should include therapy name(s), start and stop date(s) of other subsequent therapies, as well as the best response on the subsequent therapies, as applicable. This assessment can be conducted by telephone interview. Additional survival follow-up calls may occur periodically.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
ADL	activities of daily living
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATS	All-treated Analysis Set
β-hCG	β human chorionic gonadotropin
BID	twice daily
C1D1	Cycle 1 Day 1
CEC	Central Ethics Committees
CR	complete response/remission
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
eCRF	electronic case report form
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
GI	gastrointestinal
ICF	informed consent form
ICH	International Council for Harmonisation
IRB	institutional review board
LEC	Local Ethics Committees
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
MEOI	medical events of interest
NCI	National Cancer Institute
OS	overall survival
P-gp	P-glycoprotein
PE	physical examination
PI3K	phosphoinositide-3-kinase
PR	partial response/remission
QD	once daily
QTcF	QT interval corrected with Fridericia's formula
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
TEAE	treatment-emergent adverse event
TT	Treatment Termination
ULN	upper limit of normal
UV	ultraviolet
WCBP	woman/women of child-bearing potential

1. BACKGROUND AND STUDY RATIONALE

1.1. Background

Duvelisib (IPI-145) is a dual inhibitor of phosphoinositide-3-kinase (PI3K)-δ and PI3K-γ being developed by Verastem, Inc. as an orally administered potential therapeutic in hematologic malignancies.

The PI3K-δ and PI3K-γ isoforms are necessary for adaptive and innate immunity. In addition to their role in normal immune cell types, PI3K-δ and PI3K-γ are expressed in hematopoietic malignancies, and pathways mediated by PI3K-δ and PI3K-γ are thought to contribute to survival, proliferation, and differentiation of hematopoietic tumor cells.[1,2,3,4,5]

Please see the Investigator Brochure for more information regarding completed and ongoing studies with duvelisib.

1.2. Study Rationale

This study will provide the opportunity for subjects with hematologic malignancies treated with duvelisib on a previous duvelisib clinical study to continue to receive duvelisib treatment for as long as they derive clinical benefit (complete response/remission [CR], partial response/remission [PR], minor response for subjects with Waldenström's macroglobulinemia, or stable disease [SD]). This study will also allow for the collection of long-term safety, clinical activity, and overall survival (OS) data in subjects receiving duvelisib treatment and OS data in subjects who have discontinued duvelisib treatment but are in the survival follow-up period in a previous duvelisib study.

2. OBJECTIVES

2.1. Primary Objective

The primary objective of this study is to capture long-term safety data in subjects with hematologic malignancies treated with duvelisib.

2.2. Secondary Objectives

The secondary objectives of this study are to capture data on:

- The long-term clinical activity of duvelisib in subjects with hematologic malignancies.
- OS of subjects with hematologic malignancies treated with duvelisib.

3. ENDPOINTS

3.1. Primary Endpoints

The primary endpoints in this study are adverse events (AEs) and safety laboratory test values.

3.2. Secondary Endpoints

There are no formal secondary endpoints planned for this long-term study. Data will be captured to support the clinical endpoints based on the disease response assessment and OS as defined in the subject's previous study.

4. STUDY DESIGN

This study is designed to allow for the collection of long-term safety, clinical activity, and OS data in subjects receiving duvelisib treatment and OS data in subjects who have discontinued duvelisib treatment but are in the survival follow-up period in a previous duvelisib study.

Subjects receiving duvelisib will continue treatment with duvelisib at the last dose level received in their previous study. Subjects being followed only for OS will not receive treatment with duvelisib.

While on duvelisib treatment, subjects will have study visits at regular intervals (approximately every 3 months [± 3-day window]) for the following assessments: review of AEs and concomitant medications, return of used drug supplies, and dispensing of duvelisib. Radiologic evaluations will be performed at least once a year.

At each study visit, the subject's disease status will be assessed, and information will be collected to determine response to treatment.

Subjects will be monitored continuously for safety while on duvelisib. Dose modifications should be made according to the guidelines set forth in this study protocol (Section 7.2.1). There should be no attempt to make up missed doses of duvelisib. Duvelisib may be withheld up to 42 days because of treatment-related AEs. Duvelisib treatment withheld for > 42 days because of treatment-related AEs will result in discontinuation from duvelisib. Any subject who requires dose reduction to below 10 mg twice daily (BID) will be discontinued from duvelisib.

Subjects being followed for OS will be contacted by the study site approximately every 6 months to collect survival status and data pertaining to any other alternative antineoplastic therapy. Subjects will be followed for OS for up to the length of time specified in the protocol for the subject's previous study.

4.1. Randomization and Stratification

Not applicable.

4.2. Schedule of Administration

For subjects continuing on duvelisib treatment, subjects will self-administer duvelisib orally BID (28 days = 1 cycle) as a capsule formulation. Subjects will continue on the same dose level they last received in their previous duvelisib study.

4.2.1. Dose Modifications

Up to 2 dose reductions are allowed, based on the subject's starting dose in this study:

Starting Dose	**Dose Level -1**	**Dose Level -2**
75 mg BID	50 mg BID	25 mg BID
50 mg BID	25 mg BID	15 mg BID
25 mg BID	15 mg BID	10 mg BID

15 mg BID	10 mg BID	NA

Abbreviations: BID = twice a day; NA = not applicable.

Note: No dosing below 10 mg BID is allowed.

Dose holds up to 42 days are permitted for management of treatment-related AEs. For subjects only being followed for OS, no duvelisib will be administered.

4.3. Treatment Discontinuation

Treatment discontinuation occurs when a subject is no longer receiving any duvelisib. A subject should be discontinued from duvelisib if, in the opinion of the Investigator, it is medically necessary, or if it is the wish of the subject.

Subjects will be discontinued from treatment in case of any of the following reasons:

- An AE or unacceptable toxicity that requires discontinuation of duvelisib
- Disease progression
- Subject death
- Noncompliance to protocol
- Investigator decision
- Subject becomes pregnant
- Subject lost to follow-up
- Termination of the study by the Sponsor
- Voluntary withdrawal from study treatment by subject

Adverse events leading to the discontinuation of a subject will be followed until the event resolves, resolves to baseline, or is considered stable or chronic.

If a subject discontinues duvelisib, then a Treatment Termination (TT) Visit should occur within 7 days after the last dose of duvelisib. Each TT assessment need not be performed if the subject has had all the same assessments within the previous 2 weeks.

All subjects receiving duvelisib will have a Safety Follow-up visit approximately 30 (+ 7) days after the last dose of duvelisib. If possible, this visit should occur before the initiation of any subsequent anticancer therapy. At a minimum, this visit should include collection of AEs/serious AEs (SAEs), and concomitant medications/procedures. This follow-up visit may 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 clinic visit will be required.

Subjects who discontinue duvelisib and have not withdrawn consent from overall study participation will enter the survival follow-up period described in Section 6.5.

4.4. Study Discontinuation/Withdrawal

Subjects may discontinue/withdraw from the study for any of the following reasons without prejudice:

- Subject death
- Subject lost to follow-up
- Completion of the follow-up period
- Termination of the study by the Sponsor
- Voluntary withdrawal from study by subject

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

5. STUDY POPULATION

The study population will consist of subjects who received treatment with duvelisib or participated in the survival follow-up phase in a previous duvelisib study.

The number of subjects will be based on the number of eligible subjects on previous duvelisib studies approved for this long-term continued treatment and follow-up study.

5.1. Inclusion Criteria

To be eligible to participate in the study, all subjects must:

1. Have participated in a previous study of duvelisib, and:
    a. Be actively receiving duvelisib monotherapy on the previous study (within 14 days of study entry) and demonstrating clinical benefit (CR/PR/SD) of continued use, *or*
    b. Be in the survival follow-up phase of a previous duvelisib study
2. Have completed the required components of the previous study and be appropriate for enrollment into this long-term continued treatment and follow-up study, as determined by the Sponsor
3. Understand and voluntarily sign the informed consent form (ICF) before the conduct of any study-related procedures/assessments

To be eligible to participate in the study, subjects actively receiving duvelisib must:

1. Have a negative serum or urine β human chorionic gonadotropin (β-hCG) pregnancy test if a woman of child-bearing potential (WCBP). WCBP are defined as sexually mature women who have not undergone surgical sterilization or who are not naturally postmenopausal for at least 24 consecutive months (women ≤ 55 years) or 12 consecutive months (women > 55 years)
2. Agree to use adequate methods of birth control throughout the study and for 30 days after the last dose of duvelisib for all WCBP, all sexually active male subjects, and all partners of subjects

5.2. Exclusion Criteria

Any subject is to be excluded from the study if he or she:

1. Is unwilling or unable to comply with the requirements of the protocol

Subjects actively receiving duvelisib are to be excluded from this study if they:

1. Have any ongoing ≥ Grade 3 AE considered related to duvelisib treatment at screening
2. Are pregnant or nursing

6. STUDY PROCEDURES AND ASSESSMENTS

Time points for assessments to be collected throughout the study can be found in Table 1 for subjects continuing duvelisib treatment and Table 2 for subjects being followed for OS. A brief description of each of these assessments can be found below.

6.1. Screening Assessments for All Subjects

Before starting screening assessments, the Investigator (or Investigator's designee) will discuss with the potential study subject the nature of the study and its risks, requirements, and restrictions, and will obtain written informed consent. During the screening period, a unique subject identification number will be assigned.

Screening assessments are described in Table 1 for subjects continuing duvelisib treatment and Table 2 for subjects being followed for OS. Procedures captured on the previous duvelisib study within 30 days of Cycle 1 Day 1 (C1D1) do not need to be repeated. However, for WCBP receiving duvelisib, the C1D1 pregnancy test must be performed within 7 days before the first dose to confirm eligibility.

6.1.1. Informed Consent

Subjects potentially eligible for participation must sign an ICF before initiating any study-specific procedures or assessments. Standard-of-care assessments that fulfill study eligibility requirements may be performed before the subject signs the ICF.

6.1.2. Inclusion and Exclusion Criteria

Inclusion and exclusion criteria (Section 5.1 and Section 5.2, respectively) will be reviewed for each potential subject and documented in the subject medical record and electronic case report form (eCRF).

6.2. Treatment Assessments for Subjects Receiving Duvelisib

Subjects receiving duvelisib treatment will have the following assessments performed according to Table 1. Subjects enrolled in the survival follow-up portion of the study will be assessed as described in Section 6.5.

6.2.1. Concomitant Medication and Therapies

Assessment of concomitant medications and procedures will be performed according to Table 1.

6.2.2. Initial (Cycle 1 Day 1) Physical Examination and Disease-related Symptom Assessment

The initial physical examination (PE) will be performed at C1D1 and will include vital sign measurements (temperature, blood pressure [after the subject has been seated for at least 5 minutes], pulse rate, and respiratory rate), height, and weight, and liver and spleen assessments. The initial PE will also include review of disease-related symptoms (symptoms of fever [ie, temperature > 38°C/100.4°F] without evidence of infection, weight loss, and drenching night sweats without evidence of infection).

6.2.3. Focused Physical Examination and Disease-related Symptom Assessment

Subsequent PEs will be focused and include liver and spleen assessments and review of disease-related symptoms (symptoms of fever [ie, temperature > 38°C/100.4°F] without evidence of infection, weight loss, and drenching night sweats without evidence of infection). Any new clinically significant abnormality from baseline should be recorded as an AE.

6.2.4. Clinical Laboratory Tests

Clinical laboratory tests include hematology with 5-part differential, chemistry panel, liver function tests (LFTs), and serum or urine β-hCG pregnancy tests. These laboratory tests will be performed throughout the study to monitor safety as presented in Table 1. In addition, monitoring of subjects receiving anticoagulation therapy should be done as clinically appropriate.

Laboratory assessments captured on the previous duvelisib study within 30 days of C1D1 do not need to be repeated at the C1D1 visit.

The following laboratory parameters will be measured and analyzed locally:

- Hematology laboratory parameters include red blood cell (RBC) count, hemoglobin, hematocrit, and white blood cell count with differential to include an absolute neutrophil count.
- Chemistry laboratory parameters include albumin, total protein, uric acid, sodium, potassium, calcium, phosphorous, chloride, bicarbonate (or CO_2), blood urea nitrogen or urea, creatinine, lipase, amylase, magnesium, and glucose.
- Liver function tests include lactate dehydrogenase, serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), total and direct bilirubin, and alkaline phosphatase.
- A serum or urine β-hCG pregnancy test should be performed within 7 days before the first dose to confirm eligibility. If negative test results are available from the subject's previous duvelisib study within this time, the test does not need to be repeated. While subjects are receiving duvelisib, serum or urine pregnancy tests will be repeated every 3 cycles.

Unscheduled assessments should be done as clinically indicated.

Clinically significant abnormal laboratory test results, including but not limited to those findings resulting in a drug hold/reduction/discontinuation or medical intervention, should be reported as an AE (see Section 8.1.1 for definition of an AE). In the presence of Grade 3 or higher cytopenias, more frequent monitoring per institutional guidelines is recommended.

6.2.5. Radiographic Assessment

Radiologic evaluations performed on the previous duvelisib study within 60 days of C1D1 do not need to be repeated at the C1D1 visit. Radiologic evaluations will be performed once a year, approximately 1 year from the most recent scan on the previous duvelisib study. Magnetic

resonance imaging may be substituted if clinically indicated, but the modality chosen to evaluate each individual subject should be the same as the previous duvelisib study and maintained throughout the duration of this study.

6.2.6. Investigator Response Assessment

Disease response assessments should be performed as needed or no later than every 12 months while the subject is receiving treatment.

All response assessments are to be completed as applicable to disease type. The modality chosen to evaluate each individual subject should be the same as in the previous duvelisib study and maintained throughout the duration of the study. The subject's entire duvelisib treatment course, including the previous duvelisib study, should be considered when determining response or progression. Baseline for evaluating response is the baseline of the previous study.

Given the diversity of the disease types being enrolled, it is beyond the scope of this protocol to list all of the response criteria that will be used to evaluate efficacy. Table 3 shows the major criteria employed for disease response assessment.

Table 3: Disease Response Criteria

Disease type	**Examples of tumor assessment include:**	**Efficacy criteria**
Lymphoma (except CTCL)	CT scan of chest, abdomen, and pelvis; FDG-PET where indicated	IWG criteria (Cheson et al, 2007)[6]
CTCL	Skin assessments	mSWAT (Olsen et al, 2011)[7]
CLL	CT scan of chest, abdomen, and pelvis; complete blood count	NCI-WG criteria (Hallek et al, 2008)[8]

Abbreviations: CLL = chronic lymphocytic leukemia; CT = computed tomography; CTCL = cutaneous T-cell lymphoma; FDG = [^{18}F]fluorodeoxyglucose; IWG = International Working Group; mSWAT = modified Skin
Weighted Assessment Tool; NCI-WG = National Cancer Institute-sponsored Working Group; PET = positron emission tomography.
Note: Tumor assessments shown are examples and not necessarily comprehensive of the requirements needed for associated disease-specific efficacy criteria.

In this long-term extension study, a blinded central review of response assessments will not be performed. In addition, the following items are not required for investigator response assessments:

- Bone marrow biopsies and bone marrow aspirates, and
- Blood samples to determine minimal residual disease.

Adverse events, including SAEs, associated with any disease assessment must be collected as described in Section 8.2.

6.2.7. Adverse Events

Any ongoing AEs from the previous duvelisib study must be ≤ Grade 3 at the time of entry into this study. Any new or worsening preexisting medical conditions arising after the subject signs the ICF but before the first dose of duvelisib on this study will be captured as the subject's medical history. For all subjects continuing duvelisib treatment, AEs should be monitored from the time the subject takes the first dose of duvelisib on this study (C1D1) through 30 days after the last dose of duvelisib.

All SAEs for all subjects will be reported from the time the subject signs the ICF until 30 days after the last dose of duvelisib. If an Investigator becomes aware of an SAE that he or she considers to be related to duvelisib at any time after completion of the AE reporting period (ie, 30 days after the last dose of duvelisib), the event must be reported.

See Section 8.2 for a full description of the collection and reporting of AEs during this study.

6.2.8. Study Drug Administration/Dispensing/Return

Detailed instructions on administration of duvelisib can be found in Section 7.

6.3. Treatment Termination Assessments for Subjects Receiving Duvelisib

Assessments to be performed at the TT Visit are presented in Table 1. The TT Visit should be scheduled no more than 7 days after the decision to terminate duvelisib. Assessments performed within the previous 2 weeks, or previous 30 days for investigator response assessments, need not be repeated at the TT Visit.

Subjects who discontinue duvelisib and have not withdrawn consent from overall study participation will enter the survival follow-up period as determined by the previous study.

If the subject withdraws consent from overall study participation and not just treatment with duvelisib, no further attempts should be made to collect additional data from these subjects.

6.4. Safety Follow-up Assessments for Subjects Receiving Duvelisib

All subjects will have a Safety Follow-up Visit approximately 30 (+ 7) days after the last dose of duvelisib. At a minimum, this visit should include collection of AEs/SAEs and concomitant medications and procedures. The Safety Follow-up Visit 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 clinic visit will be required.

6.5. Survival Follow-up Assessments for All Subjects

Subjects receiving duvelisib treatment will be followed for OS after discontinuation of duvelisib as indicated in Table 1. Subjects enrolled only in the survival follow-up portion of this study will be assessed according to Table 2.

All subjects will be followed for OS for the duration of time outlined in their previous duvelisib study. Survival follow-up will occur every 6 months (± 4 weeks). Information on initiation of

other anticancer therapy will also be collected and should include therapy name(s), start and stop date(s) of other subsequent therapies, as well as the best response on the subsequent therapies, as applicable. This assessment can be conducted by telephone interview.

6.6. Concomitant Medications for Subjects Receiving Duvelisib

The recommendations and restrictions in this section apply only to subjects receiving duvelisib.

6.6.1. Antimicrobial Prophylaxis

Antimicrobial prophylaxis should be continued as prescribed in the subject's previous duvelisib study.

6.6.2. Transfusion and Growth Factor Support (Prophylaxis or Supportive Care)

At any time during treatment, blood cell transfusion (packed RBCs or platelets) to maintain a subject's hemoglobin level ≥ 8.0 mg/dL or platelet count ≥ 10,000/μL is recommended. Transfusions may be used at any time as clinically indicated.

Hematopoietic growth factors may be used at the discretion of the Investigator and in accordance with standard cancer treatment guidelines. Prophylactic use of growth factors such as granulocyte-colony stimulating factor (G-CSF) or PEGylated G-CSF may be implemented if clinically indicated, in accordance with local guidelines and medical practice (eg, if a subject has Grade 4 neutropenia for ≥ 7 days, febrile neutropenia, or according to the National Comprehensive Cancer Network practice guidelines for myeloid factors). Subjects on a stable dosage of erythropoietin to treat baseline anemia may continue on this therapy at this dosage.

6.6.3. Prohibited: Use of Vaccines

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

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 duvelisib may be diminished. The ability to generate an immune response to any vaccine after the administration of duvelisib has not been studied.

6.6.4. Prohibited: Immunosuppressants

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

Note: Acute treatment for underlying autoimmune disorders (eg, reactive airway disease, rheumatoid arthritis) 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 (eg, reactive airway disease, rheumatoid arthritis).

6.6.5. Prohibited: Other Anticancer Therapy or Investigational Agents

Subjects receiving duvelisib are not to receive any additional anticancer therapy or other investigational agents not outlined in the protocol.

6.6.6. Prohibited: Medications or Food that Inhibit or Induce Cytochrome P450 3A4

In vitro data indicate cytochrome P450 (CYP) 3A4 plays an important role in the metabolism of duvelisib; therefore, the concomitant use of drugs or foods that are strong inhibitors or inducers of CYP3A are not allowed during study treatment with duvelisib.

Appendix 1 provides a list of medications known to be strong inhibitors or inducers of CYP3A. However, it should be noted that this is not a comprehensive list of all medications that may modulate CYP3A activity.

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.

The Sponsor should be contacted with any questions regarding concomitant use of medications that are thought to modulate CYP3A activity. The concomitant use of moderate or weak inhibitors may be allowed in selected circumstances after consultation with the Medical Monitor.

6.6.7. Use with Caution: Medications that are Substrates of CYP3A or CYP2C8

In vitro studies have demonstrated duvelisib is an inhibitor of CYP3A4. Coadministration of duvelisib with midazolam, a sensitive CYP3A substrate, resulted in an approximate 4-fold increase in the midazolam. Systemic exposure to other medications that are substrates for CYP3A may be increased in subjects receiving duvelisib. Caution should be used if duvelisib is administered concomitantly with drugs that are substrates for CYP3A, particularly those with a narrow therapeutic range. Drugs that are substrates for CYP3A should be used only if medically necessary and therapeutic alternatives are not available.

Duvelisib is an inhibitor of CYP2C8 in vitro. Physiologically based pharmacokinetic modeling indicates that the inhibitory effect of duvelisib on CYP2C8 substrates is not expected to be clinically meaningful at a duvelisib dosage of 25 mg BID. The predicted mean area under the concentration-time curve ratio for rosiglitazone (a CYP2C8 substrate) with and without duvelisib 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 duvelisib. Medications that are metabolized via CYP2C8 may be used as medically indicated but with caution.

Appendix 2 provides a list of medications known to be substrates of CYP3A or CYP2C8. It should be noted that this is not a comprehensive list of all medications that 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.

6.6.8. Use with Caution: Medications that are Substrates or Inhibitors of P-glycoprotein

In vitro data indicate duvelisib is a substrate for P-glycoprotein (P-gp) and may have the potential to inhibit the activity of P-gp. P-glycoprotein substrates or inhibitors may be used as medically indicated but with caution.

Appendix 3 provides a list of medications that are substrates or inhibitors of P-gp. It should be noted that this is not a comprehensive list of all medications that 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.

6.6.9. Other Concomitant Therapies

Any other medication that is considered necessary for the subject's welfare and that is not expected to interfere with the evaluation of duvelisib may be given at the discretion of the Investigator.

6.6.10. Photosafety

The effect of duvelisib on the skin, especially when in direct sunlight or with artificial ultraviolet (UV) light (eg, 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 while receiving duvelisib and for at least 30 days after the last dose.

6.6.11. Contraception and Pregnancy

The effects of duvelisib on conception, pregnancy, and lactation are unknown.

At screening, all male 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 duvelisib. Acceptable forms of contraception for females are nonhormonal and hormonal intrauterine devices, 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 diaphragms.

The use of birth control methods is not required if the male partner (of the female subject) has a documented history of a vasectomy or if the female partner (of the male subject) has a documented history of bilateral oophorectomy, hysterectomy, tubal ligation, or if she is > 55 years of age and postmenopausal for at least 1 year.

Male subjects should not donate sperm for 3 months after the last dose of duvelisib.

7. INVESTIGATIONAL MEDICINAL PRODUCT

7.1. Duvelisib

7.1.1. Description of Investigational Medicinal Product

Duvelisib drug substance is a white to off-white crystalline powder. The duvelisib drug product is formulated in 2 different capsule strengths (5 mg and 25 mg) for oral delivery with excipients (diluent, glidant, disintegrant, and lubricant) that are listed in the United States Food and Drug Administration Inactive Ingredients Database for approved drug products and/or Generally Regarded as Safe. Additional information is provided in the IPI-145-23 Pharmacy Manual.

7.1.2. Dosage

Duvelisib is administered as an oral capsule supplied by the Sponsor.

For subjects continuing on duvelisib treatment:

- Oral duvelisib BID over 28-day cycles at the dose level received in the previous study.

Dose holds up to 42 days are permitted for management of treatment-related AEs.

Dose reductions and discontinuations for individual subjects may be made based on the clinical judgment of the Investigator with notification to the Sponsor's Medical Monitor (see Section 7.2).

7.1.3. Administration

Duvelisib should be self-administered orally BID (every 12 ± 2 hours) in 28-day cycles. The morning dose will be administered in the clinic on C1D1. 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 retaken or repeated.

Duvelisib capsules should be swallowed whole with a glass of water (approximately 8 ounces or 240 mL). Duvelisib may be administered without regard to meals; however, subjects must avoid grapefruit and grapefruit juice while on duvelisib.

7.2. Dose Holds and Modifications

Subjects will be monitored continuously for toxicity while on duvelisib. Toxicity will be assessed using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03 or higher. If a subject has an AE at least possibly related to duvelisib, then dose holds with possible modifications as described in Table 4 may be implemented. Adjustments to these guidelines may occur based on the clinical judgment of the Investigator with notification to the Sponsor's Medical Monitor.

Table 4: Dose Holds for Treatment-related Adverse Events

Treatment-related Toxicity[a,b]	**Duvelisib[c]**
Hematologic	
≥ Grade 3 FN	Hold until afebrile and negative culture
≥ Grade 3 Thrombocytopenia with ≥ Grade 2 Hemorrhage	Hold until no evidence of hemorrhage and stabilization of platelet count
Other Grade 4 Hematologic Toxicity (excluding FN and Thrombocytopenia)	Continue
Nonhematologic	
≥ Grade 2 Pneumonitis/Pneumonia	Hold until completion of course of therapy and resolution of symptoms
≥ Grade 3 Nonhematologic Toxicity	Hold until ≤ Grade 1 or return to Baseline

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; FN = febrile neutropenia.

[a] Treatment-related AEs: possible, probable, or definite relationship to duvelisib.

[b] Toxicity grades are defined per CTCAE Version 4.03. Note if a parameter is not defined by CTCAE, then AE grading criteria (Section 8.2.1.2) should be utilized.

[c] Dosages of duvelisib may be reduced after subsequent occurrences of the same treatment-related AE. See Section 7.2.1 for more information on dosing modification and discontinuation.

7.2.1. Duvelisib Dosing Modifications and Discontinuation

As described in Table 4 and in Section 7.2.1.1 (treatment hold for hematologic toxicities) and Section 7.2.1.2 (treatment hold for nonhematologic toxicities), duvelisib should be held upon the first occurrence of certain toxicities. Upon resolution of the AE, duvelisib treatment should be reinitiated at the current dose level according to the guidelines in Table 4. On subsequent occurrences of the same event, duvelisib should be reinitiated at 1 dose level lower than current dose level (see Table 5). Duvelisib may be held up to 42 days because of treatment-related AEs. Doses held for > 42 days because of treatment-related AEs will result in permanent discontinuation from duvelisib. Any subject who requires a dose-level reduction to below 10 mg BID because of treatment-related AEs will be permanently discontinued from duvelisib treatment.

Subjects who discontinue duvelisib should return to the clinic for the TT Visit assessments and may continue to be followed for OS based on the length of survival follow-up defined in the subject's previous study.

Dose levels for duvelisib are shown in Table 5.

Table 5: Duvelisib Dose Levels

Starting Dose	Dose Level -1	Dose Level -2
75 mg BID	50 mg BID	25 mg BID
50 mg BID	25 mg BID	15 mg BID
25 mg BID	15 mg BID	10 mg BID
15 mg BID	10 mg BID	NA

Abbreviations: BID = twice a day; NA = not applicable.
Note: No dosing below 10 mg BID is allowed.

Subjects who have a dose reduction because of a toxicity may be eligible for a dose increase back to the dose level before the reduction (ie, the starting dose level or dose level of previous reduction if subject's dose was reduced more than 1 level) if the following criteria are met:

- Subject has tolerated the lower dose level for > 1 treatment cycle
- Subject has recovered to baseline levels from the toxicity that caused the dose reduction

7.2.1.1. Treatment Hold for Hematologic Toxicity

Treatment with duvelisib should be held 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 reevaluated at least weekly until the toxicity improves according to the guidelines in Table 4.

Subjects experiencing Grade 4 hematologic toxicities other than febrile neutropenia or thrombocytopenia with hemorrhage may continue on their current dosage of duvelisib at the discretion of the Investigator.

7.2.1.2. Treatment Hold for Nonhematologic Toxicity

Treatment with duvelisib should be held for Grade 2 or higher pneumonitis/pneumonia or Grade 3 or higher other nonhematologic toxicities:

- Grade 2 or higher pneumonitis/pneumonia, defined as symptomatic and requiring medical intervention, including oral antimicrobials and/or steroids:
  - New onset or worsening of cough, shortness of breath, hypoxia, or new radiographic findings should be evaluated for pneumonitis. If pneumonitis is suspected, duvelisib should be held, and administration of corticosteroids considered while the infectious etiology is being determined. Restarting treatment with duvelisib is allowed after completion of the course of therapy and complete resolution of symptoms.

- Grade 3 or higher other nonhematologic toxicities including the following:
  - Infections: Subjects who develop infections requiring intravenous treatment with antibiotics/antifungals/antivirals should have duvelisib held until the infection resolves (subject may restart duvelisib when completing a course of oral therapy). Prophylaxis to prevent recurrent/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 duvelisib held until the values return to baseline. Duvelisib should be reintroduced after laboratory values have remained at baseline levels for at least 1 week. Additional work-up to evaluate viral infection/reactivation, exposure to environmental toxins (eg, alcohol/concomitant medications), or other causes is recommended before restarting treatment with duvelisib.

    If ALT/AST elevations ≥ Grade 3 recur upon rechallenge with duvelisib, hold duvelisib, and administer corticosteroids. A reduced dose of duvelisib may be reintroduced after laboratory values have remained at baseline levels for at least 1 week.

    Any subject with new evidence of hepatitis B surface antigen seropositivity or other evidence of hepatitis B reactivation will be discontinued from duvelisib.
  - Gastrointestinal (GI) events: In the setting of new or worsening Grade 2 GI events, early intervention is recommended to ameliorate risk of worsening symptoms. Subjects who develop Grade 3 or higher nausea, vomiting, or diarrhea despite optimal treatment should have duvelisib held until resolution of symptoms. Evaluation of concomitant medications, GI infections, or inflammatory bowel (via endoscopy and biopsy) should be considered with persistent diarrhea or recurrence with restarting duvelisib. As diarrhea induced by treatment with PI3K inhibitors has limited response to antimotility agents,[9] early consideration of corticosteroid treatment is recommended.

    If diarrhea ≥ Grade 3 recurs upon rechallenge with duvelisib, hold duvelisib and administer oral corticosteroids. A reduced dose of duvelisib may be introduced after all symptoms resolve to baseline.
  - Skin rash: Subjects who develop Grade 3 or higher skin rashes should have duvelisib held until resolution of symptoms. In the setting of new Grade 1 or 2 skin rash, early intervention is recommended to ameliorate risk of worsening symptoms. Evaluation of concomitant medications (eg, pneumocystis prophylaxis), environmental exposure, infections, or other contributing factors is recommended.

If rash ≥ Grade 3 recurs upon rechallenge with duvelisib, hold duvelisib (also hold pneumocystis prophylaxis if not already done or other ongoing concomitant medications that may be contributing) and administer corticosteroids. A reduced dose of duvelisib may be reintroduced after all symptoms resolve.

- Cardiac: Subjects who develop new Grade 3 or higher cardiac events should have duvelisib held until resolution of symptoms. This includes new Grade 3 QT interval corrected with Fridericia's formula (QTcF) prolongation. A Grade 3 QTcF prolongation requires triplicate electrocardiograms with the average measurement used and the calculation of QTcF.

Where otherwise not specified, subjects requiring duvelisib treatment holds should be reevaluated at least weekly until the toxicity resolves according to the guidelines in Table 4. Duvelisib dosing will be restarted at doses described in Table 5.

7.3. Drug Accountability

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

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

Subjects should be instructed to bring all used and unused duvelisib packaging to each study visit. The study site should count and document all capsules that the subject returns and should account for taken doses, missed doses, doses reduced due to missing or lost capsules, etc, before dispensing new duvelisib to the subject.

7.4. Assignment to Treatment

All eligible subjects who are continuing treatment will receive duvelisib at the last dose level they were receiving in their previous study.

7.5. Assessment of Compliance

At each applicable visit, duvelisib will be dispensed to the subject so that the subject will have enough doses until the next 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 reviewed with the subject.

7.6. Treatment of Overdose

Adverse events or SAEs associated with overdosage (intentional or unintentional) of duvelisib should be reported to the Sponsor as outlined in Section 8.2.1.4.

In the case of overdose of duvelisib, 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 duvelisib until further instructed by the treating physician or Investigator (or designee).

8. SAFETY DATA COLLECTION, RECORDING AND REPORTING

8.1. Adverse Events

8.1.1. Definition of an Adverse Event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have to have a causal relationship to this treatment.

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

Adverse events include worsening of a preexisting medical condition as well as clinically significant changes from baseline laboratory values or conditions. Worsening of the preexisting medical condition (eg, diabetes, hypertension) means that it has increased in severity, frequency, and/or duration, and/or has an association with a significantly worse outcome. A preexisting condition that has not worsened during the study is not considered an AE.

8.1.2. Definition of Serious Adverse Event

An SAE is any untoward medical occurrence that at any dosage:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization.
  - Elective or preplanned treatment for a preexisting condition that is unrelated to the indication under study and has not worsened since signing the ICF (as documented as medical history on the eCRF) is not considered an SAE
  - Scheduled therapy for the target disease of the study, including admissions for transfusion support or convenience, is not considered an SAE
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect
- Is considered an important medical event
  - If an AE does not meet 1 of the serious criteria, but the Investigator or Sponsor considers an event to be clinically important, the event could be classified as a SAE under the criterion of “Important medical event.” Examples of such medical events may include allergic bronchospasm requiring intensive treatment in an emergency room or at home or blood dyscrasias or convulsions that do not result in inpatient hospitalization.

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 occurring in eligible subjects will be recorded in the eCRF from the time the subject takes the first dose of duvelisib on this study (C1D1) through 30 days after the last dose of duvelisib. An AE will be followed until it is either resolved, has returned to baseline, or is determined to be a stable or chronic condition. All SAEs occurring from the signing of the ICF through 30 days after the last dose of duvelisib will be processed as outlined in Section 8.2.2.

At each required visit during the trial, all AEs that have occurred since the previous visit must be reviewed by the Investigator or designee. The Investigator or designee must determine if the AE is serious or nonserious.

The Investigator must assign the following AE attributes:

- AE diagnosis or syndrome(s) if known
  - If not known at time of the report, record the signs and/or symptoms as AEs and provide an updated report with diagnosis when obtained
- Dates of onset and resolution
- Severity as defined in this protocol
- Assessment of relatedness to duvelisib, and
- Action taken with duvelisib as a result of the AE

In general, an AE that is the primary cause of subsequent events should be identified by the primary cause (eg, for dehydration due to diarrhea, the AE would be diarrhea). However, AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events (eg, sepsis secondary to pneumonia, both events should be recorded).

Progression of disease should not be reported as an AE/SAE but rather the signs and/or symptoms manifesting as the progression of disease should be reported (eg, for dyspnea due to progression of disease, the AE would be dyspnea). All fatal events must be reported as an SAE.

8.2.1.1. Relationship to Study Drug

The Investigator must assess whether the AE may be related to duvelisib or study-mandated procedure, when applicable. The relationship is indicated by a ‘yes’ or ‘no’ response to the question: Is there a reasonable possibility that the event may have been caused by duvelisib or study procedure. A number of factors should be considered in making this assessment including:

1. the temporal relationship of the event to the administration of duvelisib or study procedure;
2. whether an alternative etiology has been identified;

3. mechanism of action of duvelisib; and/or
4. biological plausibility

8.2.1.2. Adverse Event Severity

The Investigator will assess the grade of the AE according to the NCI CTCAE, Version 4.03 or higher.

Toxicities that are not specified in the NCI CTCAE, Version 4.03 or higher, 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 8.1.2.

8.2.1.3. Abnormal Laboratory Values

The Investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in a subject represents a clinically significant change from the subject's baseline value. In general, abnormal laboratory findings without clinical significance (based on the Investigator's judgment) should not be recorded as AEs. In general, abnormal laboratory test results should be reported as an AE if the laboratory result:

- requires an adjustment or discontinuation of duvelisib
- requires treatment or adjustment to current therapy
- is considered to be an AE by the Investigator

8.2.1.4. 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 dosage according to the protocol. Clinical judgment should always be applied

- Medication error: refers to an unintentional error in dispensing or administration of study drug not in accordance with the protocol
- Off-label use: relates to situations where the study drug is intentionally used for a 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 nonprofessional occupation
- Overdoses, medication errors, misuse, or abuse 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 duvelisib should be recorded on the AE eCRF with the diagnosis of the AE.

8.2.2. Reporting of Serious Adverse Events

A SAE Report Form will be completed and submitted 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 duvelisib, from the time the subject signs the ICF through 30 days after the last dose of duvelisib. Please refer to the SAE Report Form for where and how to submit the form.

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 relationship between the event and duvelisib. Additional information relating to a previously reported SAE must also be reported within 24 hours of the Investigator's first knowledge of information. The Investigator may also be asked, by the Sponsor, to provide clarifications or additional information. If the Investigator becomes aware of an SAE, considered related to duvelisib by the Investigator, occurring more than 30 days after the last dose of duvelisib, the SAE must be reported as described above.

8.2.2.1. Immediate Reporting of Medical Events of Interest

The following are medical events of interest (MEOIs) and, therefore, must be reported to the Sponsor or designee on a SAE/MEOI report form within 24 hours of the Investigator's knowledge of the MEOI, whether serious or not and regardless of relationship to duvelisib:

- Reports or laboratory results of AST or ALT > 3 × the upper limit of normal (ULN) in combination with bilirubin > 2 × ULN.
- Clinical findings of Grade 3 or higher rash. Preexisting skin conditions that recur would not meet this definition unless the recurrence is of a greater severity or frequency than previously experienced.

8.2.2.2. Reporting of Serious Adverse Events to Regulatory Authorities, Ethics Committees and Institutional Review Boards

The Sponsor will determine the expectedness of each reported SAE based on the appropriate reference safety information for the Verastem product, in accordance with local requirements. The Sponsor or designee shall notify regulatory authorities of serious, unexpected, and related AEs or other AEs, according to local requirements. Serious, unexpected, and related AEs reported for subjects receiving a non-Verastem study drug will be also submitted according to local requirements.

The Sponsor or designee shall notify the Investigator of serious, related, and unexpected AEs submitted to the regulatory agencies, according to local country requirements.

The Sponsor or designee shall notify the appropriate Central Ethics Committees (CEC), Institutional Review Boards (IRBs), and Local Ethics Committees (LECs) of serious, related, and unexpected AEs or significant risks to subjects, in accordance with local country requirements.

The Investigator must keep copies of all AE information on file, including correspondence with the Sponsor and CECs/IRBs, and LECs.

8.2.3. Pregnancy and In Utero Drug Exposure

Since duvelisib has not been evaluated in pregnant or nursing women, the treatment of pregnant women or WCBP who are not using effective contraception is contraindicated (see Section 6.6.11 and Section 6.2.4 for instructions on birth control and pregnancy testing, respectively).

Pregnancies occurring in female subjects or partners of male subjects are considered immediately reportable events if the pregnancy occurs during the study treatment through 30 days after the subject's last dose of duvelisib. If a pregnancy occurs in a subject, duvelisib 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 the Sponsor or designee within 24 hours of the Investigator's knowledge of the pregnancy using the Pregnancy Notification Form.

The Investigator will follow the pregnant subject until completion of the pregnancy and must notify the Sponsor of the pregnancy outcome within 24 hours of the Investigator's knowledge of the 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 any of the serious criteria (ie, 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 (ie, reporting the event to the Sponsor or designee 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 the Sponsor or designee. In addition, any infant death or congenital anomaly occurring after 30 days that the Investigator suspects is related to the in utero exposure to duvelisib should also be reported to the Sponsor or designee.

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

The study population will consist of subjects who received duvelisib or participated in the survival follow-up phase in a previous duvelisib study.

The number of subjects will be based on the number of eligible subjects in previous duvelisib studies approved for this long-term continued treatment and follow-up study.

9.2. Analysis Sets

One analysis set is defined in this section, with any additional analysis sets to be defined in the SAP.

9.2.1. All-Treated Analysis Set

The All-treated Analysis Set (ATS) will include all subjects who receive any amount of duvelisib on or after C1D1 of this study. The ATS will be the primary analysis set for all safety endpoints.

9.3. Efficacy Analyses

Analyses of efficacy endpoints may be performed, as appropriate, according to the SAP of the subject's previous study. No analyses of efficacy endpoints are planned for this study.

9.4. Safety Analyses

Adverse events will be coded by using the Medical Dictionary for Regulatory Activities (MedDRA) version 16.1 or higher and will be graded according to the CTCAE, version 4.03 or higher.

Summaries of AEs will be focused on treatment-emergent AEs (TEAEs). In this long-term extension study, a TEAE is defined as any AE with an onset date on or after C1D1 and within 30 days after the last dose of duvelisib. TEAEs will be summarized by MedDRA system organ class and preferred term. Separate summaries for TEAEs related to duvelisib, TEAEs that led to treatment discontinuation, TEAEs that led to death, TEAEs by CTCAE grade, TEAEs of Grade 3 or higher, serious TEAEs, and serious TEAEs related to duvelisib will be provided.

Baseline laboratory values will be those collected at C1D1 of this long-term extension study, or if not available, the most recent values collected within 30 days before C1D1. Applicable laboratory values will be graded according to CTCAE criteria. Shifts from baseline to maximum postbaseline grades will be tabulated for hematology, blood chemistry, and LFTs.

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 International Council for Harmonisation (ICH) Harmonised Tripartite Guideline for good clinical practice (GCP), and all applicable local regulatory requirements.

10.2. Informed Consent

The Sponsor or designee will provide a sample subject ICF for modification, as appropriate, by the Investigator. The ICF must include all elements required by ICH GCP and must adhere to the

IRB/LEC 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 before 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. After 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, according to 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 that 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 ICF (if applicable). Any written ICF and written information must receive the approval/favorable opinion of the IRB/LEC in advance of use. Any additional approvals from the initial ICF 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 the Sponsor 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 the Sponsor, a regulatory authority, and IRB/LEC 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 ICFs, 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/LEC at each clinical trial site. The Principal Investigator must submit written approval to the Sponsor before he or she can enroll any subject into the study.

The Principal Investigator is responsible for informing the IRB/LEC of any amendment to the protocol. In addition, the IRB/LEC must approve all advertising used to recruit subjects for the study. The protocol must be reapproved by the IRB/LEC annually or as applicable.

Progress reports and notifications of SAEs will be provided to the IRB/LEC 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 or

Sub-investigator (or designee) will record data from all observations, tests, and assessments specified in the protocol on the eCRFs provided by the Sponsor.

10.6. Sponsor Monitoring

Before the first subject is enrolled into the study, a representative of the Sponsor will visit the study site to discuss with the Investigator(s) (and other personnel involved with the study) their responsibilities with regard to this protocol, and the responsibilities of the Sponsor.

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

- Provide information and support the Principal Investigator
- Confirm that the facilities remain acceptable
- Confirm that the study team is adhering to the protocol, data are being accurately recorded in the eCRFs, 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 external data safety monitoring committee will not be used. The Sponsor will conduct periodic internal safety reviews.

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/LECs may conduct quality assurance audits at any time during or after 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

The Sponsor, 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 the Sponsor 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 the Sponsor or regulatory authorities
- Insufficient adherence to protocol requirements

If terminating the study, the Sponsor 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

Subjects from several clinical studies with duvelisib are expected to enroll in this study. The total number of subjects and the expected length of their participation in this study will be dependent on the specifics of their previous study and will likely be variable.

Subjects who are continuing duvelisib will be treated until disease progression or unacceptable toxicity. The study will include a treatment period, a 30-day safety follow-up period, and a survival follow-up period. The length of survival follow-up is specified in the protocol of the subject's previous study.

For subjects only being followed for OS, the length of survival follow-up is specified in the protocol of the subject's previous study.

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, and IRB/LEC 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 duvelisib 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 before 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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4. Billottet C, Grandage VL, Gale RE, Quattropani A, Rommel C, Vanhaesebroeck B, et al. A selective inhibitor of the p110delta isoform of PI 3-kinase inhibits AML cell proliferation and survival and increases the cytotoxic effects of VP16. Oncogene. 2006 Oct 26;25(50):6648-59.
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8. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Döhner H, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood. 2008 Jun 15;111(12):5446-56.
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12. APPENDICES

Appendix 1. Medications or Foods Known to Inhibit or Induce Cytochrome P450 3A

The following list provides medications known to induce or inhibit cytochrome P450 (CYP) 3A activity. Note that this is not a comprehensive list of all medications that may modulate CYP3A activity. Additional information can be found at:

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table3-2

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

Classification of In Vivo Inhibitors of CYP3A

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

Abbreviations: AUC = area under the curve; CL = clearance; CYP = cytochrome P450.

[a] A strong inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a substrate for that CYP by ≥ 5-fold or > 80% decrease in CL.

[b] A moderate inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by < 5-fold but ≥ 2-fold or 50%-80% decrease in CL.

[c] A weak inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by < 2-fold but ≥ 5-fold or 20%-50% decrease in CL.

[d] 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 (eg, high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (eg, low dose, single strength).

[e] Withdrawn from the United States market because of safety reasons. [f] Herbal product.

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,[a] carbamazepine, phenytoin, rifampin, St. John's wort[b]	Bosentan, efavirenz, etravirine, modafinil, nafcillin	Amprenavir, aprepitant, armodafinil, echinacea,[c] pioglitazone, prednisone, rufinamide

Abbreviations: AUC = area under the curve; CYP = cytochrome P450.

[a] Not a marketed drug.

[b] The effect of St. John's wort varies widely and is preparation-dependent.

[c] Herbal product.

Appendix 2. Cytochrome P450 3A or 2C8 Substrates

The following lists provide known sensitive cytochrome P450 (CYP) 3A substrates, CYP3A substrates with a narrow therapeutic range, and CYP2C8 substrates. Drugs or foods that are substrates of CYP3A should only be used if medically necessary and therapeutic alternatives do not exist. Medications that are metabolized via CYP2C8 may be used as medically indicated but with caution.

Additional information can be found at: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table3-2.

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	cerivastatin repaglinide rosiglitazone pioglitazone

Appendix 3. P-Glycoprotein Substrates and Medications that are Inhibitors of P-Glycoprotein

The following list provides medications that are substrates or inhibitors of P-glycoprotein (P-gp), which should be used with caution during treatment with duvelisib. Note that this is not a comprehensive list of all medications that may be substrates of P-gp or may modulate P-gp activity.

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

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

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