NCT#: NCT02711852

STATISTICAL ANALYSIS PLAN

Protocol IPI-145-23

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

Protocol Version:	**Amendment 1 (30 November 2017)**
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Author:	[redacted]

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

The undersigned has developed this statistical analysis plan (SAP):

Name/Title	Signature	Date
[redacted] [redacted] Acumen Medical Communications		

The undersigned have reviewed this SAP and approve it in its entirety:

Name/Title	Signature	Date
[redacted] [redacted] Verastem, Inc.		

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LIST OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse Event
AT	All-Treated
BID	Twice a day
BOR	Best Overall Response
CLL	Chronic Lymphocytic Leukemia
CR	Complete Response
CRi	Complete Response with Incomplete Marrow Recovery
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	Electronic Case Report Form
FL	Follicular Lymphoma
IPI-145	(S)-3-(1-(9H-purin-6-ylamino)ethyl)-8-chloro-2-phenylisoquinolin-1(2H)-one
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
OS	Overall Survival
PD	Progressive Disease
PR	Partial Response
PRwL	PR with Lymphocytosis
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SI	Standard International System of Units
SLL	Small Lymphocytic Lymphoma
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

1 INTRODUCTION

This is the statistical analysis plan (SAP) for study IPI-145-23, *A Long-term, Continued Treatment and Follow-up Study in Subjects with Hematologic Malignancies Treated with Duvelisib (IPI-145)*. This SAP is prepared according to Amendment 1 of the protocol, dated 30 November 2017.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this trial 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.
- Overall survival (OS) of subjects with hematologic malignancies treated with duvelisib.

3 STUDY DESIGN

3.1 Overview

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 the study protocol. 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.

3.2 Sample Size Consideration

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.

3.3 Randomization

Not applicable as this study is a rollover study and subjects will receive duvelisib at the dose they were on during their previous trial.

3.4 Blinding

Not applicable as this study is an open-label rollover study.

3.5 Planned Analyses

There are no formal inferential statistical analyses planned for this study.

4 ANALYSIS SETS

4.1 All-Treated Analysis Set

The all-treated set (ATS) includes all subjects who receive any amount of duvelisib on or after C1D1 of this study. The ATS will serve as the primary analysis set for all safety endpoints and demographics.

5 STUDY ENDPOINTS

5.1 Primary Endpoints

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

5.2 Secondary Endpoints

There are no formal secondary endpoints 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.

6 GENERAL STATISTICAL METHODS AND DATA HANDLING

6.1 General Methods

Summary statistics will be presented by treatment group, unless stated otherwise.

Unless otherwise specified, descriptive statistics for continuous data will include the number of subjects with data to be summarized (n), mean, standard deviation, 25% quartile, median, 75% quartile, and minimum and maximum. The same number of decimal places as in the raw data will be presented when reporting the minimum and maximum, one more decimal place than the raw data will be presented when reporting mean and median, and 2 more decimal places than the raw data will be presented when reporting standard deviation.

Descriptive statistics for categorical/qualitative data will include frequency counts and percentages. The total number of subjects in the treatment group will be used as the denominator for percent calculations, unless stated otherwise. All percentages will be presented with one decimal, unless otherwise specified. Percentages equal to 100 will be presented as 100, and percentages will not be presented for zero frequencies.

Listings will be provided for selected endpoints.

6.2 Handling of Missing Data

In general, values for missing data will not be imputed unless methods for handling missing data are specified.

6.2.1 Handling of Missing Dates/Months/Years for Adverse Events

Adverse events (AEs) with incomplete onset dates will be handled as follows for the sole purpose of determining treatment emergence (TEAE is defined in Section 7.3.1): If the start date is completely missing, an AE will be considered treatment-emergent. The original partial or missing date will be shown in listings of AEs.

6.3 Multiple Comparisons/Multiplicity Adjustment

Not applicable.

6.4 Adjustments for Covariates

Not applicable.

6.5 Subgroups

Not applicable.

6.6 Visit Windows

All data will be categorized based on the scheduled visit at which it was collected. These visit designators are predefined values that appear as part of the visit tab in the eCRF. There will be no additional analysis windowing done based on the assessment date.

6.7 Unscheduled Visits

Unscheduled visits will not be included in by-visit summary tables, unless otherwise specified. For laboratory tests, data from unscheduled visits will be included in listings and summaries of maximum changes from baseline, and the best or worst post-baseline values.

6.8 Baseline Values

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.

6.9 Computing and Coding Standards

Activities will be performed using the following tools:

Table, listing, and figure production	SAS Version 9.4 or higher
Coding	
Adverse Events	MedDRA Version 19
Medical Histories	MedDRA Version 19
Prior and Concomitant Medications	WHODrug WHO-DD Sep-15
Grading	
AEs	CTCAE Version 4.03 or higher

7 STATISTICAL ANALYSES

7.1 Study Subjects

7.1.1 Disposition of Subjects

An enrollment table will be provided and will include categories of continuing treatment or survival follow-up. Data will be summarized by previous study. An end-of-treatment disposition (still on treatment vs discontinued from treatment) will be provided. The primary reason for treatment discontinuation will be included in the table. An end-of-study disposition (still on study vs discontinued from study) will also be provided.

7.1.2 Demographic and Disease History

Demographic will be summarized. The variables will include age, age group (<65 versus >=65), sex, race, ethnicity, height and weight. Disease history will be summarized. Diagnoses include (Chronic Lymphocytic Leukemia (CLL), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), Waldenstrom macroglobulinemia (WM)).

7.1.3 Exposure to Study Drug

Extent of exposure will be summarized for the following variables:

- Duration (weeks): (date of last dose–date of first dose in this study+1) divided by 7
- Number of cycles started (continuous and categorical)
- Relative dose intensity, defined as 100% x (total dose received)/ (planned cumulative dose for the duration of treatment)
- Number and percentage of subjects with a dose reduction
- Number and percentage of subjects with a dose increase
- Number and percentage of subjects with a dose hold
- Number and percentage of subjects with study drug discontinued

7.2 Efficacy Analyses

A listings of investigator determined best overall response (BOR) obtained on this study will be provided. BOR is defined as the best time point response that a subject achieves during the course of the study, with the response ranked according to the following order (from best to worst): complete response (CR)>complete response with incomplete marrow recovery (CRi)>partial response (PR)>partial response with lymphocytosis (PRwL)>stable disease (SD)>progressive disease (PD) (CRi applies to CLL only).

7.3 Safety Analyses

7.3.1 Adverse Events

Adverse events will be coded using MedDRA Version 19. The Grade of the AE will be assessed according to the NCI-CTCAE Version 4.03. If an AE is not included in the NCI-CTCAE Version 4.03, the Grade of the AE will be assessed according to the protocol, Section ***8.2.1.2***.

The summary of AEs will be focused on treatment-emergent AEs. Since this is an extension study, a treatment-emergent AE (TEAE) is defined as any AE that is reported out to 30 days after the last dose of study treatment. The onset date of an AE will be compared to the last dose date plus 30 days to determine whether the AE is treatment-emergent or not.

TEAEs will be summarized for each treatment arm by MedDRA system organ class (SOC) and preferred term (PT), or PT only. For summary tables by SOC and PT, SOC will be sorted alphabetically and PT will be sorted by decreasing frequency in the duvelisib arm within each SOC. For summary tables by PT only, PT will be sorted by decreasing frequency in the duvelisib arm.

If multiple TEAEs of the same PT occur within a subject, only the maximum grade observed for this PT will be used in summary of TEAEs by grade, the subject will be counted only once in the number of subjects for this PT and only once for the number of subjects for the SOC to which this PT belongs.

An overview TEAE summary table will be provided, which will include the number of subjects with AEs in selected categories. In addition, TEAEs will be summarized for the following categories, and will be tabulated by SOC and PT, unless otherwise specified.

- Treatment-emergent AEs
- Treatment-emergent AEs related to duvelisib
- Treatment-emergent AEs leading to treatment discontinuation
- Treatment-emergent AEs by maximum grade
- Grade 3 or higher treatment-emergent AEs
- Treatment-emergent SAE
- Treatment-emergent SAE related to duvelisib

Adverse events of special interest (AESI) will be summarized overall and with grading specifications. The AESI categories and associated PT's are provided in Appendix A of this document.

7.3.2 Laboratory Data

Laboratory tests will be reported separately for hematology and blood chemistry.

For the purposes of presentation in listings, the following laboratory test results will be converted to the International System of Units (SI) before presentation: sodium, potassium, chloride, bicarbonate (or CO_2), albumin, total protein, creatinine, uric acid, calcium, phosphorus,

magnesium, glucose, total and direct bilirubin, and alkaline phosphatase, red blood cell (RBC) count, hemoglobin, hematocrit, platelets, white blood cell count with 5-part differential performed manually or by flow cytometry (lymphocytes, neutrophils, monocytes, basophils, and eosinophils), etc.

7.3.3 Overall Survival

A listing of each subject's last survival status will be provided, including total time on study. If the subject has died, cause of death will be provided.

8 CHANGES IN PLANNED ANALYSES

8.1 Changes in Planned Analyses from Protocol Amendment 1 to SAP V1.0

AESIs were not defined in Protocol Amendment 1. An analysis of AESIs is included in this SAP and the AESIs are defined in Appendix A.

9 REFERENCES

None.

10 APPENDICES

10.1 Appendix A

Adverse Events of Special Interest (AESI)

AESI	**MedDRA Version 16.1 Grouped Preferred Terms**
Diarrhoea/Colitis & Diarrhoea GE Grade 3/Colitis GE Grade 2	Colitis Colitis erosive Colitis microscopic Colitis ulcerative Enterocolitis Enterocolitis haemorrhagic Necrotising colitis Diarrhoea Diarrhoea haemorrhagic
Infection (including pneumonia) & Infection (including pneumonia) GE Grade 3	Each PT in the Infections and Infestations SOC

AESI	**MedDRA Version 16.1 Grouped Preferred Terms**
Neutropenia & Neutropenia GE Grade 4	Neutropenia Neutrophil count decreased
Pneumonitis & Pneumonitis GE Grade 2	Acute interstitial pneumonitis Interstitial lung disease Lung infiltration Pneumonitis
Severe Cutaneous Reactions (Rash) & Severe Cutaneous Reactions (Rash) GE Grade 3	Dermatitis Dermatitis bullous Dermatitis exfoliative Dermatitis exfoliative general Drug eruption Drug reaction with eosinophilia and systemic symptoms Erythema Erythema multiforme Exfoliative rash Generalised erythema Mucocutaneous rash Palmar erythema Perivascular dermatitis Plantar erythema Rash Rash erythematous Rash follicular Rash generalised Rash macular Rash maculo-papular Rash maculovesicular Rash papular Rash mapulosquamous Rash pruritic Rash pustular Rash vesicular

AESI	**MedDRA Version 16.1 Grouped Preferred Terms**
	Skin reaction Skin toxicity Stevens-Johnson syndrome Toxic epidermal necrolysis Toxic skin eruption
Transaminase elevation & Transaminase elevation GE Grade 3	Acute hepatic failure Alanine aminotransferase increased Aspartate aminotransferase increased Drug-induced liver injury Hepatic enzyme increased Hepatic failure Hepatocellular injury Hepatotoxicity Transaminases increased