CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211155Orig1s000
211155Orig2s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	Original NDA
Application Number(s)	211155
Priority or Standard	Priority
Submit Date(s)	February 5, 2018
Received Date(s)	February 5, 2018
PDUFA Goal Date	October 5, 2018
Division/Office	Division of Hematology Products / OHOP
Review Completion Date	September 18, 2018
Established Name	Duvelisib (IPI-145)
(Proposed) Trade Name	COPIKTRA
Pharmacologic Class	Kinase inhibitor
Code name	Phosphatidylinositol 3-kinase inhibitor
Applicant	Verastem, Inc.
Formulation(s)	Capsules (25 mg, 15 mg)
Dosing Regimen	25 mg orally twice daily (b) (4)
Applicant Proposed Indication(s)/Population(s)	Treatment of patients with: • Chronic lymphocytic leukemia (CLL) / small lymphocytic lymphoma (SLL), (b) (4) • Follicular B-cell non-Hodgkin lymphoma (FL) who have received at least two prior therapies
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Treatment of adult patients with: • Relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) after at least two prior therapies • Relapsed or refractory follicular lymphoma (FL) after at least two prior systemic therapies

Table of Contents

Table of Tables

Table of Figures

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OPQ=Office of Pharmaceutical Quality

OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE=Office of Surveillance and Epidemiology
DEPI=Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

ADME	absorption, distribution, metabolism, excretion
AESI	adverse event of special interest
ANC	absolute neutrophil count
AR	adverse reaction
BCR	B-cell receptor
BID	twice daily
CI	confidence interval
CLL	chronic lymphocytic leukemia
CR	complete response
CMC	chemistry, manufacturing, and controls
CRF	case report form
CSR	clinical study report
DOR	duration of response
EAS	evaluable analysis set
EFD	embryo-fetal development
ER	exposure-response
FAS	full analysis set
FL	follicular lymphoma
HR	hazard ratio
HV	healthy volunteer
IGHV	immunoglobulin heavy chain variable region
INV	investigator
IR	information request
IRC	independent review committee
ITT	intention-to-treat
IWCLL	international workshop on chronic lymphocytic leukemia
IWG	international working group
MedDRA	Medical Dictionary for Regulatory Activities
MZL	marginal zone lymphoma
NHL	non-Hodgkin lymphoma
ORR	overall response rate
OS	overall survival
PBPK	physiologically based pharmacokinetic
PD	progressive disease
PFS	progression-free survival
PI	prescribing information
PI3K	phosphatidylinositol 3-kinase
PMC	postmarketing commitment
PMR	postmarketing requirement

PR	partial response
PRwL	partial response with lymphocytosis
PT	preferred term
REMS	risk evaluation and mitigation strategy
RDI	relative dose intensity
SAE	serious adverse event
SCE	summary of clinical efficacy
SCS	summary of clinical safety
SD	stable disease, standard deviation
SLL	small lymphocytic lymphoma
SMQ	standardized MedDRA query
SOC	system organ class
TE	treatment-emergent
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
W and P	warnings and precautions

1 Executive Summary

1.1. Product Introduction

This review team recommends approval of duvelisib (COPIKTRA) for two indications:

- Regular approval for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) after at least two prior therapies
- Accelerated approval for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after at least two prior systemic therapies.

Duvelisib, a new molecular entity (NME), is a phosphatidylinositol 3-kinase (PI3K) inhibitor with dual activity against the PI3K-δ and PI3K-γ isoforms. The PI3K pathway is involved in diverse cellular processes (including growth, survival, proliferation, differentiation, migration, and metabolism) and is also involved in the development, maintenance, and progression of some hematologic malignancies. The recommended dose of duvelisib is 25 mg orally twice daily (BID), (b) (4) in 28-day cycles (b) (4) A communication Risk Evaluation and Mitigation Strategy (REMS) is recommended to mitigate the fatal and/or serious risks of infections, diarrhea or colitis, cutaneous reactions, and pneumonitis.

The recommended indications contrast with the Applicant's proposed indications for patients with CLL/SLL, (b) (4) and for patients with FL who have received at least two prior therapies.

1.2. Conclusions on the Substantial Evidence of Effectiveness

CLL/SLL
The application contains sufficient evidence of efficacy derived from a randomized clinical trial in patients with previously treated CLL/SLL. Efficacy is based on a multicenter, open-label, randomized, actively controlled phase 3 trial (Study IPI-145-07) in adult patients with CLL/SLL treated with at least one prior therapy. The trial randomized 319 patients in a 1:1 ratio to receive duvelisib 25 mg twice daily or ofatumumab. Progression-free survival (PFS) per independent review committee (IRC) was statistically significantly longer in the duvelisib arm (median 13.3 months; 95% CI: 12.1, 16.8) than the ofatumumab arm (median 9.9 months; 95% CI: 9.2, 11.3), with a hazard ratio (HR) of 0.52 (95% CI: 0.39, 0.70; 1-sided stratified log-rank test $p<0.0001$). The overall response rate (ORR) per IRC was statistically significantly higher with duvelisib (73%) than ofatumumab (45%), with an odds ratio of 3.37 (95% CI: 2.09, 5.43; $p<0.0001$).

The recommended indication is restricted to patients with at least 2 prior therapies (60% of the overall efficacy population), because the benefit/risk balance appeared greater in this more heavily pretreated population than in the overall trial population. Subgroup analysis of Study

IPI-145-07 revealed sufficient evidence of effectiveness to support this indication. Among patients having at least 2 prior therapies, recipients of duvelisib (N = 95) had a median PFS of 16.4 months (standard error [SE]: 2.1) compared to a median PFS of 9.1 months (SE: 0.5) in recipients of ofatumumab, with a HR of 0.4 (SE: 0.2). ORR per IRC was 78% and 39%, respectively, a difference of 39% (SE: 6.5) in favor of duvelisib.

FL

The application contains sufficient evidence of efficacy to support the recommended indication in FL. Efficacy is based on a single-arm, multicenter phase 2 trial (Study IPI-145-06) that included 83 patients with refractory FL treated with duvelisib 25 mg twice daily (median exposure, 5 months). All patients were required to have disease refractory to rituximab and to either chemotherapy or radioimmunotherapy. The ORR per IRC was 42% (95% CI: 31, 54). Due to early censoring, the estimated median duration of response (DOR) is not reliable. However, of the 35 patients that responded, 43% maintained a response at 6 months, and 17% maintained a response at 12 months. Thus, the data support the determination that duvelisib has clinically meaningful activity in patients with double-refractory FL.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The benefit-risk assessment supports regular approval of duvelisib for the treatment of adult patients with relapsed or refractory CLL or SLL after at least two prior therapies and accelerated approval of duvelisib for the treatment of adult patients with refractory FL after at least two prior systemic therapies.

Efficacy:
Efficacy in relapsed or refractory CLL/SLL is based on the results of a single, multicenter, open-label, randomized phase 3 trial (Study IPI-145-07) comparing duvelisib to ofatumumab in 319 adult patients with CLL/SLL after at least one prior therapy. In the analysis of the primary endpoint, PFS per IRC, patients in the duvelisib arm had a median PFS of 13.3 months (95% CI: 12.1, 16.8) whereas patients in the ofatumumab arm had a median PFS of 9.9 months (95% CI: 9.2, 11.3), with a HR of 0.52 (95% CI: 0.39, 0.70; 1-sided stratified log-rank test p<0.0001). ORR per IRC was statistically significantly higher for duvelisib (73%; 95% CI: 66, 80) than ofatumumab (45%; 95% CI: 38, 53), with an odds ratio of 3.4 (95% CI: 2.1, 5.4; 1-sided p<0.0001).

In this trial population, 60% of patients had 2 or more prior therapies (range: 1, 10). Because of the toxicity concerns with duvelisib and other agents in this class, the efficacy in patients with CLL/SLL with 2 or more prior therapies was evaluated. Patients receiving duvelisib (N = 95) had a median PFS per IRC of 16.4 months (SE: 2.1) versus 9.1 months (SE: 0.5) in patients receiving ofatumumab, with a hazard ratio of 0.4 (SE: 0.2). ORR per IRC of 78% with duvelisib and 39% with ofatumumab, a difference of 39% (SE: 6.5%).

Efficacy in refractory FL is based on a multicenter, open-label, single-arm phase 2 trial of duvelisib that included 83 patients with FL who were refractory to rituximab and to either chemotherapy or radioimmunotherapy (Study IPI-145-06). ORR per IRC was 42% (95% CI: 31, 54), with most responses being partial. Due to early censoring, the estimated median DOR was not reliable. However, of the 35 patients that achieved a response, 43% maintained a response at 6 months and 17% at 12 months.

Safety:
The evaluation of safety with duvelisib demonstrated a substantial risk for serious toxicity, including fatal events. The primary safety evaluation was based on 442 patients with hematologic malignancies that received duvelisib 25 mg twice daily. The median exposure duration was 9 months (range <1 month to 53 months), with 40% of patients having at least 12 months of exposure. The most common adverse reactions (ARs), occurring in ≥20%, were diarrhea or colitis, neutropenia, rash, fatigue, pyrexia, cough, nausea, upper respiratory infection, pneumonia,

musculoskeletal pain, and anemia. Fatal ARs occurred in 8% of patients treated with duvelisib, primarily due to infection. The incidence of serious adverse events for diarrhea or colitis, pneumonitis, and cutaneous reactions were numerically higher for patients with 2 or fewer prior therapies compared to 3 or more prior therapies. On exploratory analysis of Study IPI-145-07, the estimated cumulative incidence of non-relapse death in patients with relapsed or refractory CLL/SLL was 16% in the duvelisib arm and 9% in the ofatumumab arm.

The primary safety issues identified with duvelisib include serious, including fatal, infections, diarrhea or colitis, cutaneous reactions, and pneumonitis, along with serious hepatotoxicity and neutropenia. In patients with hematologic malignancies, 65% of patients experienced a serious adverse event and 84% of patients experienced a grade 3 or 4 toxicity. Additionally, 35% of patients discontinued duvelisib due to an adverse reaction. Due to the frequency and seriousness of duvelisib-associated infections, diarrhea or colitis, cutaneous reactions, and pneumonitis, a boxed warning is warranted along with a communication REMS.

Benefit-Risk:
The benefit/risk determination considered the totality of safety data on duvelisib, as well as information on same-in-class agents, including the 2016 termination of six idelalisib trials due to excess toxicity (largely infection-driven) and death.

Although Study IPI-145-07 required failure of at least one prior regimen, the review team felt that the severity of risks associated with duvelisib warrants restricting the CLL/SLL indication to a more pretreated patient population. Because patients who require third-line therapy or beyond have few or no available therapies, it is reasonable to assume more risk for the potential of clinical benefit. In the phase 3 trial in CLL/SLL, 60% of patients had 2 or more prior therapies. In this subset of patients, as in the overall efficacy population, PFS and ORR were clinically meaningful in favor of duvelisib. The benefit/risk assessment of duvelisib is favorable for the treatment of adult patients with relapsed or refractory CLL or SLL after at least two prior therapies.

In the single-arm phase 2 trial in FL, patients were refractory to rituximab and to either chemotherapy or radioimmunotherapy, thus representing a highly refractory patient population, with a median of 3 prior lines. The benefit/risk of duvelisib is favorable for patients with FL that is refractory to two or more prior systemic therapies. Study IPI-145-06 was specifically for refractory disease, and the efficacy of duvelisib is not defined for patients with chemosensitive relapse. However, given the meaningful clinical activity of duvelisib in the refractory setting and the unmet medical need, the clinical review team recommends expanding the indication to patients with either relapsed or refractory disease for third-line treatment or beyond. The benefit/risk assessment of duvelisib is deemed favorable for the treatment of adult patients with relapsed or refractory FL after at least two prior systemic therapies.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• CLL, SLL, and FL are considered largely incurable, and relapse is nearly universal. • With successive treatment regimens for relapsed or refractory disease, response rates and response duration tend to diminish. Patients with symptoms continue to receive treatment repeatedly until fatal resistant disease occurs.	CLL/SLL and FL are serious and life-threatening diseases.
Current Treatment Options	• Treatment options for relapsed or refractory CLL/SLL include chemotherapy, immunochemotherapy, anti-CD20 monoclonal antibodies, and other targeted therapies such as ibrutinib, idelalisib, and venetoclax. • Treatment options for FL include chemotherapy, immunochemotherapy, and anti-CD20 monoclonal antibodies. • Numerous patients with relapsed or refractory CLL/SLL or FL cannot tolerant intensive chemotherapy due to age or comorbidities.	New treatments are needed for patients with relapsed or refractory CLL/SLL or FL, including chemotherapy-free treatments.
Benefit	CLL/SLL • Study IPI-145-07 was a randomized, open-label, actively controlled phase 3 trial of duvelisib versus ofatumumab in patients with CLL/SS after at least 1 prior therapy. • The ITT analysis of 319 patients demonstrated statistically significantly prolonged PFS per IRC in patients receiving duvelisib compared to ofatumumab, with an estimated 48% reduction in the risk of progression or death. The ORR per IRC was statistically significantly higher with duvelisib (73%) versus ofatumumab (45%). • In the subset of 196 patients with CLL/SLL with 2 or more prior therapies, PFS per IRC demonstrated an estimated 60% reduction in the risk of progression or death in favor of duvelisib. The ORR per IRC showed a higher ORR for duvelisib at 78% compared to 39% with ofatumumab.	Based on PFS and ORR in a randomized, actively controlled trial and ORR in a single-arm trial, duvelisib has clinically meaningful activity in patients with CLL/SLL after at least 1 prior therapies and in patients with refractory FL after at least 2 prior systemic therapies.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	FL • Study IPI-145-06 was a single-arm, phase 2 trial with 83 patients with FL who were refractory to rituximab and to either chemotherapy or radioimmunotherapy. • ORR per IRC was 42% with 1 patient (1%) achieving a complete response and 34 patients (41%) achieving a partial response. • Due to early censoring, the estimated median duration of response was not reliable. Of the 35 patients that achieved a response, 43% maintained a response at 6 months and 17% at 12 months.	
Risk and Risk Management	• Of 442 patients with hematologic malignancies treated with duvelisib (25 mg twice daily): o 8% had fatal ARs. o 65% experienced a serious adverse event and 84% experienced a grade 3 or 4 toxicity, both of which were primarily driven by infection (including pneumonia and sepsis), diarrhea or colitis, cytopenias, cutaneous reactions, hepatotoxicity, and pneumonitis. o 35% discontinued duvelisib due to an AR. o The most common ARs (≥20% of patients) were diarrhea or colitis, neutropenia, rash, fatigue, pyrexia, cough, nausea, upper respiratory infection, pneumonia, musculoskeletal pain, and anemia. • On exploratory analysis of the phase 3 study IPI-145-07, recipients of duvelisib had an estimated 16% cumulative incidence of death versus 9% in recipients of ofatumumab.	• The safety profile of duvelisib is acceptable in the intended populations, but necessitates risk mitigation efforts. • Based on frequency and severity, a boxed warning is indicated for serious, including fatal, infections, diarrhea or colitis, cutaneous reactions and pneumonitis. • A REMS is warranted for toxicities included in the boxed warning to ensure safe use of the drug. • Additional warnings and precautions are indicated for hepatotoxicity and neutropenia. • Labeling should include comprehensive instructions for monitoring and dose modifications for infections, diarrhea or colitis, cutaneous reactions, pneumonitis, hepatotoxicity, neutropenia, and thrombocytopenia, as well as specific recommendations for PJP and CMV prophylaxis.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application

X	The patient experience data that was submitted as part of the application, include:				Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as			
			X	Patient reported outcome (PRO)	Health-related quality of life measurements (Section 8.3.6)
			□	Observer reported outcome (ObsRO)	
			□	Clinician reported outcome (ClinRO)	
			□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			
	□	Patient-focused drug development or other stakeholder meeting summary reports			
	□	Observational survey studies designed to capture patient experience data			
	□	Natural history studies			
	□	Patient preference studies (e.g., submitted studies or scientific publications)			
	□	Other: (Please specify)			
□	Patient experience data that was not submitted in the application, but was considered in this review.				

X

Primary Clinical Reviewer
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X

Cross-Disciplinary Team Leader
Yvette Kasamon, MD

2 Therapeutic Context

2.1. Analysis of Condition

CLL/SLL

CLL has an incidence in the United States of 5.1 per 100,000 and is the most common type of leukemia in Western countries, accounting for approximately 30% of all leukemias (Teras et al. 2016). Based on SEER data from 2011-2015, the incidence rate of CLL in men is nearly double the rate in women, and the incidence of CLL is 1.5 times higher in white patients than in black patients, and about 2 times higher in non-Hispanic patients than Hispanic patients. The median age of diagnosis is 70 years with >65% of patients being diagnosed at age 65 or later (Noone et al. 2018).

Patients with CLL can be asymptomatic or have symptoms that include weakness, fatigue, weight loss, fever, night sweats, or enlarged lymph nodes, liver, or spleen. Patients with CLL are classified as low, intermediate, or high risk by the Rai staging system or Binet classification, which helps to determine whether treatment should be initiated. Additionally, chromosomal abnormalities of 17p del, 11q del, and IGHV unmutated, β2-microglobulin >3.5 mg/L, lymphocyte doubling time <12 months, and age >60 years are poor prognostic markers and factor in to treatment decisions (Francis et al. 2006, Stilgenbauer 2015). Treatment can range from observation to immunochemotherapy to targeted therapies. Although, despite high response rates to initial treatment, relapse is common and relapsed or refractory disease is often characterized by resistance to chemotherapy. The slowly progressing nature of CLL allows patients to receive intermittent treatment with periods of remission or stable disease, but each successive treatment yields diminished response rates and shorter durations of response (Wierda et al. 2010). Treatments for patients with CLL have advanced, yet the disease remains incurable and new drugs and approaches are needed.

SLL is the same biological entity as CLL except with disease primarily in the lymph nodes for SLL compared to the bone marrow for CLL. SLL and CLL have similar treatment paradigms and expected clinical outcomes.

CLL/SLL is characterized by clonal proliferation and accumulation of malignant B lymphocytes in the blood and lymphoid tissues. The B-cell receptor (BCR) and PI3K play key roles in the proliferation and survival in CLL/SLL (Pongas and Cheson 2016), making them rationale therapeutic targets.

FL

FL is the second most common subtype of non-Hodgkin's lymphoma (NHL), with an estimated 13,960 new cases diagnosed in 2016 in the United States (Teras et al. 2016). The median age of diagnosis is 60 years old and incidence is highest among whites (80%) and lowest among blacks (4%) (Luminari et al. 2012; Nabhan et al. 2014). Patients with FL typically present with waxing and waning asymptomatic peripheral adenopathy. Bone marrow involvement occurs in 50% to

70% of patients (Freedman 2015; Luminari et al. 2012). FL is characterized by an indolent clinical course, but the majority of patients have advanced stage disease at diagnosis (Freedman 2015). The indolent nature of FL affords responses to initial therapy, but is followed by frequent relapses and shorter durations of response to subsequent treatments (Rivas-Delgado et al. 2017). Moreover, patients with refractory or relapsed FL within 2 years of first-line therapy have a 5-year overall survival of 50% (range 40% to 59%) (Byrtek et al. 2013).

Treatment for patients with advanced stage FL ranges from observation to hematopoietic stem cell transplantation (HSCT). Patients with asymptomatic, advanced stage FL do not require immediate treatment and can be observed. Patients with symptomatic nodal disease, extranodal disease, B symptoms, cytopenias, and end organ dysfunction require treatment. First-line therapy typically consists of rituximab monotherapy or combination chemotherapy plus rituximab (Colombat et al. 2001; Hiddemann et al. 2005; Martinelli et al. 2010; Rummel et al. 2013; Witzig et al. 2005). Treatment of patients with refractory or relapsed FL can consist of rituximab monotherapy, combination chemotherapy plus anti-CD20 therapy, radioimmunotherapy, and HSCT (Freedman 2015). Given that treatment for FL is usually not curative, new drugs and approaches are still needed.

FL arises from malignant germinal center B-cells, making B-cell kinases rationale therapeutic targets. As in CLL, the B-cell receptor (BCR) and PI3K play key roles in the proliferation and survival of indolent B-cell lymphomas, including FL (Pongas and Cheson 2016; Wiestner 2015).

2.2. Analysis of Current Treatment Options

CLL/SLL

There are currently 14 agents FDA-approved for the treatment of patients with CLL or SLL. This includes idelalisib, the first-in-class PI3K inhibitor. The indications relevant to the CLL/SLL application are listed in Table 1. Because SLL overlaps with CLL but is classifiable as NHL, the table includes indications relevant to NHL.

Table 1: FDA-Approved Drugs for Patients With CLL or SLL

Drug	Year of Initial Approval	Excerpted Relevant Indication(s)[a]
Chlorambucil	1957	Treatment of chronic (lymphocytic) leukemia, malignant lymphomas including lymphosarcoma, giant FL, and Hodgkin's disease
Cyclophosphamide	1959	Treatment of malignant lymphomas: Hodgkin's disease, lymphocytic lymphoma, mixed-cell type lymphoma, Burkitt's lymphoma, multiple myeloma, leukemias, mycosis fungoides
Vincristine	1963	Useful in combination with other oncolytic agents in NHLs
Doxorubicin	1974	Treatment of Hodgkin lymphoma, NHL

Drug	Year of Initial Approval	Excerpted Relevant Indication(s)[a]
Fludarabine	1991	Adult patients with B-cell CLL who have not responded to or whose disease has progressed during treatment with at least one standard alkylating-agent containing regimen.
Fludarabine, cyclophosphamide, rituximab (FCR)	1997	Previously untreated and previously treated CD20-positive CLL
Rituximab	1997	Treatment of patients with CLL, NHL
Alemtuzumab	2001	B-cell CLL
Bendamustine	2008	Treatment of patients with - CLL - Indolent B-cell NHL that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen
Ofatumumab	2009	Treatment of CLL: - In combination with chlorambucil, for the treatment of previously untreated patients with CLL for whom fludarabine-based therapy is considered inappropriate - In combination with fludarabine and cyclophosphamide for the treatment of patients with relapsed CLL - For extended treatment of patients who are in complete or partial response after at least two lines of therapy for recurrent or progressive CLL - Treatment of patients with CLL refractory to fludarabine and alemtuzumab
Obinutuzumab	2013	In combination with chlorambucil, for the treatment of patients with previously untreated CLL
Ibrutinib	2014	Adult patients with CLL/SLL
Idelalisib	2014	Treatment of patients with - Relapsed CLL, in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities (regular approval) - Relapsed SLL in patients who have received at least two prior systemic therapies (accelerated approval)
Venetoclax	2016	Treatment of patients with CLL or SLL, with or without 17p deletion, who have received at least one prior therapy
Rituximab and hyaluronidase	2017	Treatment of adult patients with previously untreated and previously treated CLL in combination with fludarabine and cyclophosphamide

Source: FDA table, created from review of drug labeling

[a] Regular approval except where noted

FL

There are currently nine agents with regular FDA approval and two agents with accelerated approval for the treatment of patients with FL or other low-grade non-Hodgkin lymphomas (NHLs). The two agents under accelerated approval include idelalisib, the first-in-class PI3K inhibitor, and copanlisib, the second-in-class PI3K inhibitor. Agents with accelerated approval are not considered to be available therapy because clinical benefit is yet to be confirmed. The indications relevant to the FL application are listed in Table 2.

Table 2: FDA-Approved Drugs for Patients With FL and Indolent Forms of NHL

Drug	Year of Initial Approval	Type of Approval	Excerpted Relevant Indication(s)
Chlorambucil	1957	Regular	Per Table 1
Cyclophosphamide	1959	Regular	Per Table 1
Vincristine	1963	Regular	Per Table 1
Doxorubicin	1974	Regular	Per Table 1
Rituximab	1997	Regular	Per Table 1
^{90}Y-ibritumomab tiuxetan	2002	Regular	Treatment of patients with relapsed or refractory, low-grade or follicular B-cell NHL, and previously untreated follicular NHL who achieve partial or complete response to first-line chemotherapy
Bendamustine	2008	Regular	Per Table 1
Obinutuzumab	2013	Regular	In combination with bendamustine followed by obinutuzumab monotherapy, for the treatment of patients with FL who relapsed after, or are refractory to, a rituximab-containing regimen
Idelalisib	2014	Accelerated Approval	Treatment of patients with relapsed follicular B-cell NHL in patients who have received at least two prior systemic therapies
Copanlisib	2017	Accelerated Approval	Treatment of adult patients with relapsed FL who have received at least two prior systemic therapies
Rituximab and hyaluronidase	2017	Regular	Treatment of adult patients with FL: - Relapsed or refractory FL as a single agent - Previously untreated FL in combination with chemotherapy and as single-agent maintenance therapy - Nonprogressing FL as a single-agent after first-line CVP chemotherapy

Source: FDA table, created from review of drug labeling

In clinical practice, common treatment regimens for relapsed or refractory CLL/SLL and FL include single agents or combination of the following agents listed in Table 3. Radiation therapy, radioimmunotherapy, HSCT, and observation are other considerations.

Table 3: Agents and Combinations for Treatment of Patients With CLL/SLL or FL

Drug or Regimen	CLL /SLL	FL
Acalabrutinib	X	
Alemtuzumab ± rituximab	X	
Bendamustine ± rituximab	X	X
Bendamustine + obinutuzumab		X
Bortezomib + dexamethasone		
Bortezomib + dexamethasone + rituximab		
Bortezomib ± rituximab		
Carfilzomib + rituximab + dexamethasone		
Chlorambucil ± rituximab	X	X
Chlorambucil + obinutuzumab	X	
Cladribine ± rituximab		
Copanlisib		X
Cyclophosphamide ± rituximab		X
Everolimus		
Fludarabine + cyclophosphamide + mitoxantrone + rituximab		X
Fludarabine + cyclophosphamide + rituximab	X	
Fludarabine + cyclophosphamide + ofatumumab	X	
Fludarabine ± rituximab	X	X
Ibritumomab tiuxetan		X
Ibrutinib	X	
Ibrutinib + bendamustine + rituximab	X	
Idelalisib ± rituximab	X	X
Idelalisib + bendamustine + rituximab	X	
Lenalidomide ± rituximab	X	X
Obinutuzumab	X	X
Obinutuzumab + cyclophosphamide + doxorubicin + vincristine + prednisone		X
Obinutuzumab + cyclophosphamide + vincristine + prednisone		X
Ofatumumab ± chlorambucil	X	
Oxaliplatin, fludarabine, cytarabine, rituximab	X	
Pentostatin + cyclophosphamide + rituximab	X	
Rituximab	X	X
Rituximab + cyclophosphamide + doxorubicin +		X

Drug or Regimen	CLL /SLL	FL
vincristine + prednisone		
Rituximab + cyclophosphamide + vincristine + prednisone		X
Rituximab + cyclophosphamide + prednisone		
Rituximab + fludarabine + mitoxantrone + dexamethasone		X
Thalidomide ± rituximab		
Venetoclax ± rituximab	X	

Source: NCCN CLL/SLL, NHL, and LPL Guidelines Versions 1.2019, 4.2018, and 1.2019, respectively

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Duvelisib is an NME and is not currently marketed in any country.

3.2. Summary of Presubmission/Submission Regulatory Activity

Date	Event Summary
18 August 2011	IND 112486 was activated and opened in the United States
15 April 2013	Orphan drug designation granted for treatment of CLL and SLL (13-3944)
08 July 2013	Type B, End-of-Phase 1 meeting to discuss design of phase 3 study (IPI-145-07) in patients with CLL/SLL
01 August 2013	Orphan drug designation granted for treatment of FL (13-3999)
18 December 2013	Type B, End-of-Phase 1 meeting to discuss proposed design of phase 3 study (IPI-145-08) of duvelisib plus rituximab in patients with CD20-positive NHL.
29 October 2014	Type B, End-of-Phase 2 meeting to discuss CMC plans for drug substance and drug product
02 March 2015	Type C meeting to discuss clinical pharmacology studies including analysis in special population, drug-drug interactions, and QT/QTC analysis
26 June 2015	Type B Pre-NDA meeting to discuss CMC content.
16 July 2015	Type B meeting to discuss design of Phase 3 studies in patients with relapsed or refractory, indolent forms of NHL.
01 December 2015	Type C meeting to discuss data content for planned NDA submission.
01 July 2016	Discussion of results of interim analysis of Study IPI-145-07 in patients with CLL/SLL. FDA recommended the study continue to its final analysis.

Date	Event Summary
30 August 2016	Type B, End-of-Phase 2 meeting to discuss results of phase 2 study (IPI-145-06) in patients with NHL, including FL. Discuss the design of a phase 2, randomized study of duvelisib + rituximab versus R-CHOP in patients with relapsed or refractory FL
17 October 2017	Pre-NDA meeting to discuss clinical components of NDA submission for patients with CLL/SLL or FL.
05 February 2018	NDA submission complete. The Applicant requested priority review, which the Agency granted.
February to September 2018	During the review, multiple regulatory issues were addressed and resolved through information requests (IRs) that included inadequate efficacy data for patients with FL in Study IPI-145-06, death narratives, characterization of primary safety issues identified and risk mitigation strategies, objection of the proposed design of a confirmatory trial in patients with FL, (b) (4).

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

OSI conducted inspections for Study IPI-145-07 and Study IPI-145-06 at two clinical sites: Site 001 (Dr. Ian Flinn, Nashville, TN) and Site 3 (Dr. Scott Lunin, Fort Myers, FL). These sites were selected based on highest patient accrual and slight differences in efficacy (PFS, response rates) and safety (deaths, serious adverse events, and protocol violations) compared to the overall study results. The regulatory classification for inspection for Site 001 and Site 3 is No Action Indicated. The Applicant Verastem, Inc. was also audited. The regulatory classification of the Applicant is No Action Indicated. The study data derived from the inspected clinical sites and the Applicant are considered reliable in support of the requested indications.

4.2. Product Quality

Major issues: The product quality of the 15-mg and 25-mg capsules was acceptable. (b) (4)

(b) (4)

(b) (4)

Novel excipients: No

Any impurity of concern: A modified Ames test was positive for the impurity (b) (4) (b) (4) (b) (4), it can be regarded as an unspecified impurity. The specification for any individual unspecified impurity was proposed at no more than (b) (4)% w/w, whereas the qualification threshold of this genotoxic impurity in this drug product would be no more than (b) (4)% w/w.

4.3. Clinical Microbiology

The microbial tests for product release and stability specifications were adequate.

4.4. Devices and Companion Diagnostic Issues

Not applicable

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Duvelisib (IPI-145) is an inhibitor of PI3K with predominant activity against the δ and γ kinase isoforms, which show a preferential expression in cells of the immune system. The Applicant hypothesizes that dual inhibition of PI3K-δ and PI3K-γ by duvelisib may synergize to suppress tumor growth by effecting intrinsic survival pathways and by blocking growth and survival of malignant B-cells that are activated by signals from the tumor microenvironment. The established pharmacological class for duvelisib is kinase inhibitor.

The primary pharmacology of duvelisib was characterized using an array of in vitro enzymatic and cellular studies conducted to assess binding affinity, inhibitory selectivity for PI3K isoforms, and mechanisms of anti-tumor activity. Binding affinity studies showed the K_D values for duvelisib at the Class I PI3K-δ, -γ, -β, and -α isoforms are 0.023, 0.24, 1.56 and 25.9nM, respectively. Selectivity studies showed that duvelisib has lower half-maximal inhibitory concentrations (IC_{50s}) for δ and γ isoforms in comparison to β and α. In anti-tumor studies,

duvelisib inhibited cellular proliferation of PI3K-δ and/or PI3K-γ-expressing tumor cell lines, in addition to inhibiting proliferation of primary B-cell lymphoma cells from patients with CLL. The major human metabolite of duvelisib is IPI-656, and IPI-656 is essentially inactive at PI3Ks, with IC_{50} values approximately 1000-times higher than duvelisib in comparative studies.

Neoplastic B-cells in some hematologic malignancies are thought to rely upon the support of non-neoplastic cells within their microenvironment for proliferation and survival. Duvelisib activity was tested in an assay designed to recapitulate tumor microenvironment-induced malignant B-cell proliferative responses utilizing a mixture of cytokines (CD40L/IL-2/IL-10). The proliferative signals were determined to be PI3K-δ dependent, using PI3K isoform-selective inhibitory compounds. Results from other experiments using PI3K isoform-selective inhibitory compounds suggest PI3K-γ plays relatively greater roles in chemokine-induced (e.g., CXCL12) recruitment of CD3+ T-cells, and other immune cells, to the tumor microenvironment. PI3K-isoform selective inhibitors were also employed in vivo. In a xenograft model of DoHH2 human transformed follicular B-cell lymphoma in CB17.SCID mice, the dual inhibition of PI3K-δ and PI3K-γ by duvelisib appeared synergistic when compared to the anti-tumor activity of either IPI-3063 (a PI3K-δ inhibitor) or IPI-549 (a PI3K-γ inhibitor) alone as single agents.

The binding specificity of duvelisib and IPI-656 was assessed against a panel of >400 non-mutant and mutant kinases, and in competitive binding assays against a panel of 80 receptors, ion channels, and transporters. Neither duvelisib or IPI-656 exhibited any toxicologically significant off-target binding. In vitro and in vivo safety pharmacology studies with duvelisib did not reveal any adverse effects on vital organ function (i.e., cardiovascular, respiratory, CNS and behavior).

Nonclinical in vitro and vivo pharmacokinetic (PK) studies characterized the absorption, distribution, metabolism, and excretion (ADME) of duvelisib. Absorption into systemic circulation as measured by time to maximal plasma concentration (T_{max}) ranged from 0.1-3 hours. Oral bioavailability (F) was 7%, 40%, 40-90%, and 57% in mice, monkeys, dogs, and rats, respectively. Increases in systemic exposures were generally proportional to increases in dose. Sex differences in exposures were noted in rats (females experienced higher exposures to duvelisib than males), but not in monkeys. Duvelisib appeared to accumulate in the plasma of rats and monkeys over the course of the 4-week repeated dose studies, however longer studies showed that blood levels eventually plateaued in animals. Duvelisib was highly bound to plasma proteins in all the species tested; human > dog > rat. IPI-656 also demonstrated high plasma protein binding in all tested species.

The average volume of distribution (Vss) across the nonclinical species was 1.14 L/kg (range 0.5 to 1.7 L/kg). In whole body autoradiography studies in pigmented Long-Evans and albino Sprague-Dawley rats, [^{14}C]duvelisib-derived radioactivity was widely distributed to all analyzed tissues except the brain and lens. The pattern of radioactivity distribution was consistent with uptake by tissues involved in the metabolism and excretion of duvelisib, i.e., the gastro-

intestinal and urinary tracts. Cytochrome P450 3A4 was identified as the primary enzyme involved in duvelisib phase 1 metabolism. Elimination half-lives ($t_{1/2}$) range from 0.2-5 hours in animals to approximately 7 hours in humans. The majority of duvelisib and its metabolites (including IPI-656) is excreted in feces via the hepatobiliary route.

Repeat-dose general toxicology studies of 4-weeks and 13-weeks in duration were conducted in rats and monkeys. Mortality and moribund euthanasia occurred in animals of higher dose groups in the 4-week studies, which was attributable to erythroid hypoplasia in rats, and inflammation and opportunistic intestinal infections in monkeys. The predominant toxicities were similar in both species; mainly exaggerated pharmacology from kinase inhibition manifesting as lymphoid depletion and secondary effects such as multi-organ inflammation, stress, and infections. The monkey is more sensitive to the toxicities of duvelisib than the rat. T-cell dependent antibody responses (TDAR) were decreased in monkeys exposed to duvelisib. Target organs of toxicity for duvelisib are mainly the lymphoid tissues, gastro-intestinal tract, liver, and male and female reproductive organs.

Increased serum glucose levels observed in the high dose animals in the 4-week studies were also considered a pharmacological effect of duvelisib. There were no concurrent changes in serum insulin levels in either species. Ocular changes (lens opacities) were noted in female rats and may be related to hyperglycemic effect of duvelisib. Although increased serum glucose levels were not noted in the 13-week studies, histopathological findings in pancreas (inflammation, islet cell hyperplasia, fibrosis, and acinar cell atrophy) in rats at the end of 13-week treatment may be associated with PI3K-δ inhibition. Pancreatic findings (inflammation, hemorrhage, and low-incidence of acinar degeneration and hyperplasia) have been noted in rats treated with a more selective PI3K-δ inhibitor.

Fertility studies with duvelisib were not conducted; however, adverse findings in male and female reproductive tissues were observed in the repeat dose toxicity studies in rats. These included testicular (seminiferous epithelial atrophy, decreased weight, soft testes) and epididymal (small size, oligo/aspermia) findings in males, and ovarian (decreased weight) and uterine (atrophy) in females. Thus, duvelisib may impact male and female fertility in humans.

In a GLP embryo-fetal development (EFD) study in rats, pregnant animals were administered duvelisib orally at doses of 0, 10, 50, 150 or 275 mg/kg (0, 60, 300, 900, or 1650 mg/m^2) from gestation day (GD) 6 to GD 17. At 300 mg/m^2, exposure to duvelisib resulted in reduced fetal weights and external abnormalities (in 2/8 litters: bent tail and fetal anasarca). Duvelisib at doses ≥900 mg/m^2 resulted in maternal toxicities (mortality and weight loss) that were accompanied by 100% resorption (no live fetuses) in surviving dams. In another EFD study in pregnant rats receiving oral doses of duvelisib up to 35 mg/kg (210 mg/m^2) from GD 6 to GD 17, no maternal or embryo-fetal effects were observed. The dose of 300 mg/m^2 in rats is approximately 10-times the recommended 25 mg twice daily dose (BID) for patients. The dose comparison was used because the animal AUCs were not available for the pilot study. The

female AUC value for the 300 mg/m^2 dose level in a 4-week repeat-dose toxicity study in rats approximates 4-times the AUC in patients taking the recommended 25 mg BID.

In an EFD study in rabbits, pregnant animals received daily oral doses of duvelisib of 0, 25, 100, and 200 mg/kg (0, 300, 1200 and 2400 mg/m^2) from GD 7 to GD 20. Doses ≥1200 mg/m^2 resulted in maternal toxicity (body weight losses or lower mean body weights and increased mortality) and adverse developmental outcomes (increased resorptions and postimplantation loss, abortion, and decreased numbers of viable fetuses). In another EFD study in pregnant rabbits receiving oral doses of duvelisib up to 75 mg/kg (900 mg/m^2), no maternal or embryo-fetal effects were observed. The dose of 1200 mg/m^2 in rabbits is approximately 39-times the recommended dose of 25 mg twice daily. AUC values for the 1200 mg/m^2 dose level were not found elsewhere in the rabbit toxicology database.

There are data available that suggest PI3 kinases play critical roles in embryo-fetal development. In mice, mutations of the gene coding for PI3K subunit p110 have been associated with placental development (Hu et al. 2016) and embryonic lethality/fetal mortality (Bi et al., 1999; Kieckbusch et al., 2015). In humans, a study employing multiplex targeted sequencing on genomic DNA isolated from pediatric cortical brain specimens reported that PI3K/AKT pathway mutations may cause brain malformations in children (Jansen et al. 2015).

Based on findings in animals and literature reports, duvelisib can cause fetal harm when administered to a pregnant woman. Female patients of reproductive potential will be advised to use highly effective contraception during treatment with duvelisib and for at least one month after the last dose. Male patients with female partners of reproductive potential will also be advised to use highly effective contraception during treatment with duvelisib and for at least one month after the last dose.

There are no data on the presence of duvelisib and/or its metabolites in animal or human milk. Because of the potential for serious ARs from duvelisib in a breastfed child, lactating women will be advised not to breastfeed while taking duvelisib and for at least 1 month after the last dose.

Duvelisib was not genotoxic in the in vitro bacterial reverse mutation assay or chromosome aberration test in human peripheral blood lymphocytes, and was not genotoxic in the in vivo rat bone marrow micronucleus test. No carcinogenicity studies were conducted or are required to support marketing of duvelisib for the current indication.

The nonclinical pharmacology and toxicology data submitted to this NDA are adequate to support the approval of duvelisib for the proposed indication.

5.1. Referenced NDAs, BLAs, DMFs

None

5.2. Pharmacology

5.2.1. Primary Pharmacology

PI3Ks are a family of enzymes involved in cellular functions such as cell growth, proliferation, differentiation, motility, survival and intracellular trafficking. PI3Ks are activated by G protein-coupled receptors and tyrosine kinase receptors and are in turn responsible for the production of phosphatidylinositols: 3-phosphate (PI(3)P), (3,4)-bisphosphate ($PI(3,4)P_2$), and (3,4, 5)-triphosphate ($PI(3,4,5)P_3$). Notable proteins involved in PI3K signaling include Ras and src family kinases and those in the AKT/mTOR pathway. The $PI(3,4,5)P_3$ phosphatase PTEN that antagonizes PI3K signaling is absent from many cancers. These factors suggest PI3K is involved in tumorigenesis and provides a rationale for the development of duvelisib as a potential treatment for hematological malignancies.

In Vitro Studies

Binding

Duvelisib binding affinity and kinetics were evaluated for the Class I PI3K isoforms, δ, γ, β and α.

Table 4: Duvelisib Binding Affinity and Kinetics

Duvelisib Binding Data	PI3K-δ	PI3K-γ	PI3K-β	PI3K-α
K_{off} (s^{-1})	0.000365	0.000832	0.00426	0.109
K_{on} (10^6 M^{-1} s^{-1})	15.6	3.43	2.73	4.20
$t_{1/2}$ (min)	31.6	13.8	2.7	0.10
K_d (nM)	0.023	0.24	1.56	25.9

Source: Applicant's table[1]

Inhibitory activity at selected δ PI3K targets

- Duvelisib and metabolite IPI-656

The inhibitory and selectivity properties of duvelisib and its major metabolite were measured as IC_{50} values for the Class I PI3K isoforms.

Table 5: Duvelisib and IPI-656 PI3K IC_{50} Values

Class I PI3K isoform	IC_{50} value (nM)[a]	
	Duvelisib	IPI-656
PI3K-δ	2.5	3827
PI3K-γ	27	19034
PI3K-β	85	26060
PI3K-α	1602	>100000

[1] Winkler et al., Chem Biol 21: 20(11): 1364-1374, 2013

Cell line	PI3K isoform	Stimulus[b]	IC_{50} value (nM)	
			Duvelisib[c]	IPI-656
RAJI (human lymphoma)	PI3K-δ	Anti-IgM	0.36±0.09	2608
RAW (murine macrophage-like)	PI3K-γ	C5a	19.5±9.1	>10000
786-O (human renal cancer)	PI3K-β	None	26.2±10.2	>8333
SKOV-3 (human ovarian cancer)	PI3K-α	None	1410±1090	>10000

[a] IC_{50} values were determined in an endpoint assay run in the presence of 3.0mM ATP (i.e., physiological levels)
[b] Serum starved murine RAW264.7 cells stimulated with C5a were used to assess inhibition of the PI3K-γ isoform, and serum starved human RAJI cells stimulated with antiimmunoglobulin M were used to assess inhibition of the PI3K-δ isoform.
[c] $IC_{50:}$ mean ±SD

Duvelisib activity in hematologic malignancies (cell lines and primary cells)
The anti-tumor activity of duvelisib was evaluated in a panel of hematologic malignancy cell lines, including: diffused large B-cell lymphoma (DLBCL, both Activated B-cell type [ABC] and Germinal B-cell type [GCB]), transformed FL, mantle cell lymphoma, multiple myeloma, and T-cell lymphoma. Cell viability was assessed by quantitation of ATP after a 72-hour treatment with varying concentrations of duvelisib and reported as growth inhibition (GI). Several cell lines were sensitive to duvelisib with GI_{50} values ranging from 0.5 to 200nM, while other cell lines were not (GI <50%) (Data not shown).

The effects of duvelisib on primary tumor cell viability were also assessed. Malignant B-cells isolated from the peripheral blood of 12 CLL patients were incubated with duvelisib (0.25 to 5 μM), which approximates the plasma concentrations in the patients at the recommended dose.[2] According to the authors, duvelisib antagonized BCR-crosslinking-activated prosurvival signals, and reduced the viability of normal T- and NK-cells, as well as the production of inflammatory and antiapoptotic cytokines from T-cells. Duvelisib-induced direct cytotoxicity was time- and concentration-dependent.

Whole blood activity of duvelisib
IC_{50} values were 96.1nM and 1028nM for PI3K-δ and PI3K-γ, respectively, in human whole blood using PI3K-δ- and PI3K-γ-specific degranulation of basophils as the endpoint. In comparison, the IC_{50} value was 4700nM for duvelisib on PI3K-β-mediated platelet activation, assessed by thrombin peptide-induced GPIIb/IIIa stimulation.

The effects on supportive microenvironment of malignant B-cells
Important contributors to the tumor microenvironment include cellular components, such as stromal cells, macrophages, T-cells, and essential proteins (cytokines, chemokines, and angiogenic factors). These factors exert oncogenic support via interactions with membrane receptors on the malignant cells that signal through PI3K.

[2] Dong et al., Blood, 124(24): 3583-3586, 2014

To see whether the anti-tumor activity of duvelisib could be mediated through direct cytotoxicity on malignant cells, as well as through effects on the microenvironment, a series of studies were conducted.

- Blockage of PI3K-BCR axis

Peripheral blood mononuclear cells were obtained from patients with CLL including samples with poor prognostic markers (unmutated IGHV and prior treatment), and stimulated with anti-IgM to activate the BCR or co-cultured with stromal cells.[3] Treatment of CLL cells with either anti-IgM or stromal co-culture results in enhanced tumor cell survival. Duvelisib-mediated reductions in CLL cell viability as measured by increased apoptosis are concentration- and time-dependent, with effects observed at a concentration as low as 500nM and at time point as early as 12 hours. Duvelisib also reduced activation of the BCR-PI3K signaling proteins AKT, ERK and S6.

- Duvelisib inhibited the CD40L/IL2/IL10 induced proliferation of CLL cells.

CLL cells in proliferation centers receive survival and proliferation signals from non-neoplastic stromal, T-cells, and/or myeloid/dendritic cells.[4] To recapitulate the effects of the microenvironment on CLL cells, cells were obtained from the peripheral blood of three patients with CLL and stimulated with a combination of tumor microenvironment-derived cytokines: sCD40L, IL-2 and IL-10. Cytokine stimulation led to time-dependent induction of phosphorylated AKT and proliferation as measured by Ki67. Duvelisib inhibited cytokine-induced CLL cell proliferation with a mean EC_{50} of 0.5nM.

- Duvelisib diminished BCR-induced secretion of chemokines CCL3 and CCL4

Stromal- and cancer cell-derived cytokines, growth factors, and chemokines (such as CXCL12, CXCL13, and CCL3/4) can recruit T-cells and myeloid cells that promote tumor cell survival and growth. Duvelisib at a concentration of 1 μM led to inhibition of anti-IgM stimulation-mediated increases of CCL3 and CCL4 in CLL cells.

- Duvelisib inhibited the chemotaxis toward CXCL12

The chemokine CXCL12 is a potent chemotactic signal for lymphocytes and mesenchymal stem cells, which when recruited can provide the basis for a tumor supporting microenvironment. Duvelisib as well as PI3K isoform-selective compounds were utilized in a study in peripheral blood mononuclear cells obtained from 3 patients with CLL. The isoform-selective compounds revealed that T-cell migration was a PI3K-γ-mediated process. Duvelisib was also shown to inhibit the migration of T-cells in response to CXCL12, with an average EC_{50} of 128nM (data not shown).

[3] Balakrishnan et al., Leukemia 29: 1811-1822, 2015
[4] Herrreros et al., Leukemia 24(4): 872-876, 2010

- Duvelisib inhibited survival signals produced by M2 macrophages

Tumor-associated macrophages (TAMs) of the "M2 phenotype" contribute to the immunosuppressive microenvironment by preventing the induction of T-cell mediated tumor immunity and promoting tumor growth.[5] TAMs also provide survival signals to tumor cells. Duvelisib inhibited the differentiation of bone marrow-derived myeloid cells to the tumor promoting M2 phenotype. Duvelisib also inhibited the macrophage colony-stimulating factor (MCSF1) and interleukin-4 (IL-4) driven M2 polarization of murine bone marrow-derived myeloid cells (BMDM), as measured by Arginase I (*Arg1*) expression, in a concentration-dependent manner. The data with PI3K isoform-selective compounds and as well as duvelisib suggest that inhibition of M2 macrophage polarization is primarily mediated through inhibition of PI3K-γ.

In Vivo Studies

Duvelisib, a dual inhibitor of PI3K-δ and PI3K-γ, is hypothesized to have enhanced anti-tumor activity in comparison to drugs that target either isoform alone. The anti-tumor activity of duvelisib was compared to that of IPI-3063 (a selective PI3K-δ inhibitor) and IPI-549 (a selective PI3K-γ inhibitor) in CB17.SCID mice, in a xenograft model of the DoHH2 cell line, which is derived from a human transformed follicular B-cell lymphoma. The dose and schedule for each compound was selected to achieve comparable inhibition of the PI3K targets.[6] The mice (n=15/group) were treated for a total of 25 consecutive days with either vehicle control (BID and QD), duvelisib (50 mg/kg BID), IPI-3063 (10 mg/kg QD), or IPI-549 (2 mg/kg QD).[7] Treatment with duvelisib resulted in significantly greater tumor growth inhibition than either of the isoform-selective inhibitors alone, as did the combination of IPI-3063 and IPI-549.

5.2.2. Secondary Pharmacology

Binding specificity

The binding specificity of duvelisib and IPI-656 were assessed against a panel of >400 nonmutant and mutant kinases (KINOMEscan™) and in competitive binding assays against a panel of 80 receptors, ion channels, and transporters (b) (4).

- KINOMEscan™

  Duvelisib was screened at a concentration of 1 μM and only selectively bound to PI3K-δ, PI3K-γ, and PI3K-β. IPI-656 was also screened a concentration of 1 μM and only displayed binding to PI3K-δ and anaplastic lymphoma kinase (ALK).

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[5] De Palma and Lewis, Cancer Cell 23(3): 277-86, 2013

[6] The ratio of $C_{max,free}$ and $C_{min,free}$ to the cellular IC_{50} for each isoform was used as a marker of target inhibition. Using existing pharmacokinetic data for each compound, the doses for IPI-3063 and IPI-549 were selected such that the ratios of $C_{max,free}/C_{min,free}$ to the cellular PI3K isoform IC_{50} were within 2-fold of the ratios for duvelisib.

[7] The dose was chosen to most closely match the PK profile of patients receiving the recommended dose of duvelisib at 25 mg BID.

- (b) (4) studies (Study# (b) (4)
  Duvelisib as well as IPI-656 were screened at 10 μM, and both compounds demonstrated little or no activity against any of the targets.

Hyperglycemic and hyperinsulinemic effects
Literature reports suggest a class-effect regarding pan PI3K inhibitor-induced blood glucose and insulin level elevation. Following a single-dose or 5-day repeat-dose administration of duvelisib at 30 or 100 mg/kg, male Sprague-Dawley rats were assessed for responses to oral glucose (OGTT) or intraperitoneal insulin (IITT) challenge. Duvelisib at doses at 100 mg/kg resulted in plasma concentrations expected to inhibit all PI3K isoforms (i.e., >25,000 ng/mL) and hyperglycemic and hyperisulinemic effects in the rats. However, no hyperglycemic or hyperinsulinemic effects were observed at 30 mg/kg, which resulted in plasma concentrations between 3,000 to 6,000 ng/mL and no PI3K-α inhibition. In humans at the recommended dose of 25 mg BID (Cycle 2, Day 1), the mean C_{max} value is 1511 ng/mL.

5.2.3. Safety Pharmacology

Table 6: Summary of Safety Pharmacology Studies

Type of Study	Test system	Concentrations/Doses	Salient results
hERG (#100709.JPH)	hERG assay (Duvelisib)	10, 30, 100 and 300 μM	The mean IC_{50} value for duvelisib inhibition of the hERG potassium current was 49.8 μM.[8]
hERG (#130124.JPH)	hERG assay (IPI-656)	10, 100 μM	The mean IC_{50} value for IPI-656 inhibition of the hERG potassium current was >100 μM.
CNS (FOB)* assessment (#693969)	Male rats (n=8/group)	Single oral doses: 0, 5, 50, and 350 mg/kg (10 mL/kg)	At 350 mg/kg, a statistically significant decrease in locomotor activity was observed in the figure 8 maze at 2 hr post-dose. A similar but not statistically significant trend was observed at 6- and 24-hr post-dose. Given the lack of other effects on locomotor activity or arousal in the FOB, a definitive effect could not be concluded.
Cardiovascular telemetry (#693971)	Male Cynomolgus monkeys (conscious non-naïve) (n=4/sex/group)	5, 30 and 150 mg/kg (10 mL/kg), (6x4 modified Latin square design; with 7-day washout period between doses). Telemetry data collected pre-dose to 24 hr** post-dose.	No remarkable treatment related effects were observed on blood pressure, ECG waveforms and duration/interval or cardiac rhythms.
Respiratory system (#693970)	Male rats (n=6/group)	Single oral doses: 0, 5, 50, and 350 mg/kg (10 mL/kg)	No remarkable treatment related effects were observed on respiratory rate, tidal volume, or minute volume.

*FOB (Function Observation Battery) including home-cage, handling, and open-field observations.

[8] The IC_{50} value of hERG inhibition is approximately 14 times of the C_{max} (1511 ng/mL, or 3.6 μM) in patients receiving the recommended dose of 25 mg BID.

**Tmax values range from 1-12 hours in the monkey general toxicology studies; time points were twice prior to each dose, then 1, 1.5, 2, 3, 2.5, 4, 6, 8, and 24 hours post-dose.

5.3. ADME/PK

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>Absorption</td><td></td></tr>
<tr><td>From Pharmacokinetic Written Summary</td><td>T_{max}: 0.1-3 hours in animals
Oral bioavailability: 7% (mice), 57% (rat), 40-90% (dog), and 40% (monkey)</td></tr>
<tr><td>Distribution</td><td></td></tr>
<tr><td>Duvelisib Blood to Plasma Ratio: In vivo data from Study #RPT02744 (rat), # (b) (4) 207007 (monkey) and Clinical Study Report IPI-145-05 (human)

In vitro blood to plasma partitioning and blood and plasma stability of IPI-145 and its metabolite IPI-656 in Sprague-Dawley Rats, cynomolgus monkeys and humans/INF-R4074</td><td>Blood to plasma (B/P) partitioning ratio
Duvelisib (in vivo data)
<table>
<tr><th colspan="2">Species</th><th>B/P ratio (Mean±SD)</th></tr>
<tr><td>Rat</td><td>Male</td><td>0.73±0.11</td></tr>
<tr><td></td><td>Females</td><td>0.79±0.13</td></tr>
<tr><td>Monkey</td><td>Male</td><td>0.78</td></tr>
<tr><td></td><td>Female</td><td>0.78</td></tr>
<tr><td>Human</td><td>Male</td><td>0.51±0.19</td></tr>
</table>
IPI-656 (in vitro data)
<table>
<tr><th></th><th colspan="3">B/P ratio (Mean±SD)</th></tr>
<tr><th></th><th>1 μM</th><th>10 μM</th><th>100 μM</th></tr>
<tr><td>Rat</td><td>0.54±0.10</td><td>0.77±0.02</td><td>0.82±0.11</td></tr>
<tr><td>Monkey</td><td>0.77±0.01</td><td>01±0.05</td><td>0.96 (n=2)</td></tr>
<tr><td>Human</td><td>0.79±0.02</td><td>0.581±0.1</td><td>0.66±0.1</td></tr>
</table>
Mean±SD</td></tr>
<tr><td>Determination of in vitro protein binding of [^{14}C]IPI-145 in CD-1 mouse, Sprague-Dawley Rat, New Zealand white rabbit, beagle dog, Cynomolgus monkey, and human plasma using equilibrium dialysis/#346N-1001</td><td>Duvelisib protein binding
<table>
<tr><th rowspan="2">Duvelisib</th><th colspan="6">Mean percent free fraction (protein binding %)</th></tr>
<tr><th>Mouse</th><th>Rat</th><th>Rabbit</th><th>Dog</th><th>Monkey</th><th>Human</th></tr>
<tr><td>1 μM</td><td>5.5
(94.5)</td><td>11.1
(88.9)</td><td>3.8
(96.2)</td><td>2.2
(97.8)</td><td>8
(92)</td><td>4.1
(95.9)</td></tr>
<tr><td>3 μM</td><td>5.2
(94.8)</td><td>10.9
(89.1)</td><td>6.7
(93.3)</td><td>2.4
(97.6)</td><td>8.8
(91.2)</td><td>4.6
(95.4)</td></tr>
<tr><td>10 μM</td><td>6
(94)</td><td>11.4
(88.6)</td><td>9.6
(90.4)</td><td>6.2
(93.8)</td><td>13.4
(86.6)</td><td>5.6
(94.4)</td></tr>
<tr><td>30 μM</td><td>6.5
(93.5)</td><td>12.9
(87.1)</td><td>10.4
(89.6)</td><td>13
(87)</td><td>18.7
(81.3)</td><td>9.2
(90.8)</td></tr>
<tr><td>100 μM</td><td>8.4
(91.6)</td><td>14.2
(85.8)</td><td>12.2
(87.8)</td><td>17.5
(82.5)</td><td>23.2
(76.8)</td><td>14.1
(85.9)</td></tr>
</table>
3 μM of duvelisib is considered a clinically relevant concentration based on a steady state C_{max} value of 1511 ng/mL (3.6 μM) at the recommended dose of 25 mg BID in humans.</td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>IPI-656 Cross -Species Plasma Protein Binding/#IPI-145-013</td><td>IPI-656 protein binding
<table>
<tr><th rowspan="2">Nominal Concentration (µM)</th><th colspan="5">Percent Free Fraction (Mean; n = 2)</th></tr>
<tr><th>Mouse</th><th>Rat</th><th>Rabbit</th><th>Monkey</th><th>Human</th></tr>
<tr><td>1</td><td>3.1</td><td>4.5</td><td>5.2</td><td>0.4</td><td>1.3</td></tr>
<tr><td>10</td><td>4.4</td><td>4.5</td><td>7.5</td><td>2.5</td><td>1.3</td></tr>
<tr><td>100</td><td>6.7</td><td>5.8</td><td>7.2</td><td>9.7</td><td>2.7</td></tr>
</table>
(Table from Applicant)</td></tr>
<tr><td>Human Dosimetry Prediction for Oral [^{14}C]IPI-145/#Report RPT02832 (b)(4) study #11708)</td><td>Tissue distribution
Peak [^{14}C]duvelisib-derived tissue radioactivity concentrations were observed at approximately 1 hour after dosing. The radioactivity was widely distributed to tissues, excluding the brain and eye lens, after a single oral (5 mg/kg) dose to Long-Evans and Sprague-Dawley rats. Tissues with the highest exposure were the liver and gastrointestinal (GI) tract.</td></tr>
<tr><td colspan="2">Metabolism</td></tr>
<tr><td>In vitro Metabolism Profile of IPI-145 in Mouse, Rat, Dog, Monkey, and Human Liver Microsomes and Human Hepatic S9 Fractions/#IPI-145-004</td><td>• Duvelisib was extensively metabolized by liver microsomes from mouse and monkey, to a lesser extent in human and dog, and minimally in rat.
• The primary metabolic pathway for all species was oxidation, primarily mono-oxidation (M+16), and subsequent glucuronidation.
• No human specific or disproportional human metabolites were identified in vitro.</td></tr>
<tr><td>In Vitro Metabolism and P450 Reaction Phenotyping of [^{14}C]IPI-145 in Human Liver Microsomes/ #RPT02584</td><td>• CYP3A4 was the primary enzyme involved in the phase 1 metabolism of duvelisib, including the formation of IPI-656.
• Other potential contributors to the phase 1 metabolism of duvelisib were CYP1A2 and CYP2B6.
• CYP2C8; CYP2C9, CYP2C19, CYP2D6, and CYP2E1 were not involved in the metabolism of duvelisib.</td></tr>
<tr><td>Statement from pharmacokinetic written summary, source: studies: #8000454, # (b)(4)-692038, #13-01-0 #8000455</td><td>The major human metabolite of duvelisib was confirmed as IPI-656 (M17 designation in metabolite studies). Following oral administration of duvelisib to rat, rabbit, and monkey, the exposure (AUC_{0-24}) ratio of IPI-656 to duvelisib was approximately 0.01, 0.71, and 1.43, respectively. Although the exposure to IPI-656 in the rat was low, the exposure to IPI-656 relative to duvelisib in monkeys and rabbits was similar to humans. This indicates IPI-656 was sufficiently qualified in the monkey general toxicology studies and reproductive toxicity was sufficiently qualified in the rabbit EFD studies.</td></tr>
<tr><td colspan="2">Excretion</td></tr>
<tr><td>Pharmacokinetic written summary; source: #PRT02754, #PRT02755, # (b)(4)-207007, #RPT02860</td><td>The primary clearance mechanism of duvelisib was CYP450-mediated metabolism. The major elimination pathway for duvelisib and duvelisib metabolites (including IPI-656) was the feces via the hepatobiliary route.

Duvelisib has an elimination half-life ($T_{1/2}$) of 0.2-5 hours in the animal species tested.</td></tr>
<tr><td colspan="2">TK data from general toxicology studies</td></tr>
<tr><td>A 13-week study of IPI-145 by oral gavage in the rat with a 4-week recovery period/Study# 805592</td><td>Peak duvelisib plasma concentrations (T_{max}) were observed at 1 to 2 hours through the dosing period. $T_{1/2}$ values ranged 1.2-4.8 hours (Day 1), 1.8-3.9 hours (Day 28), and 2.6-4.2 hours (Day 91). Exposures (C_{max} and $AUC_{0-24\ hr}$) were greater in females than males (female:male ratios on Day 1 ranging from 1.5 to 2.2 (C_{max}) or 1.8 to 3.2 ($AUC_{(0-24hr)}$). The female to male ratio was approximately 2-3 on Day 28 and 1-3 on Day 91.</td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td></td><td>Summary Mean Toxicokinetic Values in 4-Weeks Study in Rats
<table>
<tr><th>Day</th><th>Dose (mg/kg/day)</th><th>C_{max} (ng/mL)</th><th></th><th>$AUC_{(0\text{-}24hr)}$ (ng·hr/mL)</th><th></th></tr>
<tr><th></th><th></th><th>Males</th><th>Females</th><th>Males</th><th>Females</th></tr>
<tr><td>1</td><td>0.5</td><td>5.7</td><td>12.6</td><td>19.4</td><td>63.6</td></tr>
<tr><td></td><td>5</td><td>150</td><td>247</td><td>586</td><td>1270</td></tr>
<tr><td></td><td>25</td><td>1930</td><td>2910</td><td>8170</td><td>14700</td></tr>
<tr><td>28</td><td>0.5</td><td>9.4</td><td>25.4</td><td>32.6</td><td>77.1</td></tr>
<tr><td></td><td>5</td><td>162</td><td>472</td><td>803</td><td>2010</td></tr>
<tr><td></td><td>25</td><td>1890</td><td>3210</td><td>9590</td><td>13000</td></tr>
<tr><td>91</td><td>0.5</td><td>13.5</td><td>26.1</td><td>28</td><td>99.2</td></tr>
<tr><td></td><td>5</td><td>209</td><td>467</td><td>1190</td><td>2100</td></tr>
<tr><td></td><td>25</td><td>3300</td><td>3900</td><td>14300</td><td>14000</td></tr>
</table>
The increases in C_{max} and $AUC_{(0\text{-}24hr)}$ were greater than dose proportional.
Accumulation ratios for $AUC_{(0\text{-}24hr)}$ ranged from 0.883 to 2.04.</td></tr>
<tr><td>A 13-week oral gavage toxicity study of IPI-145 in the cynomolgus monkey with a 6-week recovery period/Study# 805593</td><td>Peak duvelisib plasma concentrations (T_{max}) were observed at 1 to 2 hours through the dosing period. $T_{1/2}$ values ranged 2.6-10 hours (Day 1), 3.7-9.4 hours (Day 28), and 3.8-8.6 hours (Day 91). There were no apparent sex differences in exposures as measured by C_{max} and $AUC_{(0\text{-}24hr)}$.
Summary Mean Toxicokinetic Values in 4-Weeks Study in Rats
<table>
<tr><th>Day</th><th>Dose (mg/kg/day)</th><th>C_{max} (ng/mL)</th><th></th><th>$AUC_{(0\text{-}24hr)}$ ng·hr/mL</th><th></th></tr>
<tr><th></th><th></th><th>Males</th><th>Females</th><th>Males</th><th>Females</th></tr>
<tr><td>1</td><td>0.2</td><td>5.8</td><td>6</td><td>16.9</td><td>14.1</td></tr>
<tr><td></td><td>1</td><td>37</td><td>20.3</td><td>119</td><td>70.4</td></tr>
<tr><td></td><td>5</td><td>152</td><td>103</td><td>555</td><td>412</td></tr>
<tr><td>28</td><td>0.2</td><td>5.1</td><td>8.3</td><td>17.9</td><td>26.7</td></tr>
<tr><td></td><td>1</td><td>38.2</td><td>31</td><td>182</td><td>142</td></tr>
<tr><td></td><td>5</td><td>720</td><td>476</td><td>4010</td><td>2120</td></tr>
<tr><td>91</td><td>0.2</td><td>5.1</td><td>5.6</td><td>16</td><td>19.4</td></tr>
<tr><td></td><td>1</td><td>44</td><td>43.1</td><td>158</td><td>156</td></tr>
<tr><td></td><td>5</td><td>786</td><td>471</td><td>3830</td><td>4200</td></tr>
</table>
The increases in C_{max} and AUC were greater than proportional fashion, especially on Days 28 and 91.
Accumulation ratios for $AUC_{(0\text{-}24hr)}$ ranged from 0.948 to 10.2.</td></tr>
<tr><td colspan="2">TK data from reproductive toxicology studies</td></tr>
<tr><td>An Oral (Gavage) Study of the Effects of IPI-145 on Embryo/Fetal Development in Rats/ (b) (4)-0692021</td><td>
<table>
<tr><th>Day</th><th>Dose (mg/kg)</th><th>C_{max} (ng/mL)</th><th>$AUC_{(0\text{-}24h)}$ (ng·hr/mL)</th><th>C_{max}/Dose (ng/mL)/(mg/kg)</th></tr>
<tr><td>6</td><td>5</td><td>463</td><td>3160</td><td>93</td></tr>
<tr><td></td><td>10</td><td>1110</td><td>7100</td><td>111</td></tr>
<tr><td></td><td>35</td><td>5240</td><td>44700</td><td>150</td></tr>
<tr><td>17</td><td>5</td><td>582</td><td>3600</td><td>116</td></tr>
<tr><td></td><td>10</td><td>1100</td><td>7810</td><td>110</td></tr>
<tr><td></td><td>35</td><td>5980</td><td>62200</td><td>171</td></tr>
</table>
Data shown are group means</td></tr>
</table>

Type of Study	Major Findings
An Oral (Gavage) Study of the Effects of IPI-145 on Embryo/Fetal Development in Rabbits/ (b) (4)0692023	

Day	Dose (mg/kg)	C_{max} (ng/mL)	$AUC_{(0\text{-}24h)}$ (ng·hr/mL)	GD20/GD7 $AUC_{(0\text{-}24h)}$
7	10	305	1350	NA
	25	919	3780	NA
	75	4830	17700	NA
20	10	2220	25100	18.7
	25	2550	28700	7.97
	75	8300	66200	3.95
Data shown are group means				

Table 7: Summary Mean PK Parameters in Different Species

Species (report number)	# animals/gender	Route	Dose (mg/kg)	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0\text{-}last}$ (ng*h/mL)	$AUC_{0\text{-}inf}$ (ng*h/mL)	$t_{½}$ (h)	CL (L/h/kg)	V_{ss} (L/kg)	F_{oral} (%)
Mouse (IPI-145-007)	24/M	IV[a]	10	5563	0.083	1900	1903	0.22	5.25	1.14	---
	24/M	PO[b]	10	390	0.083	136.8	NC	NC	---	---	7[c]
Rat (IPI-145-008)	3/M	IV[a]	2	1519	0.083	1153	1157	0.73	1.83	1.66	---
	3/M	PO[b]	10	785	1.2	2929	3298	2.4	---	---	57
Dog (ADME-11-008)	3/M	IV[d]	0.5	4413[e]	NC	11738[f]	11921	2.00	0.051	0.13	---
	3/M	PO[g]	5	9597	3.00	105068[f]	107062	3.90	---	---	97[c,h]
Dog (ADME-11-009 V1)	3/M	IV[d]	1	1804[e]	NC	5875[f]	6268	1.83	0.194	0.493	---
	3/M	PO[g]	5	2367	1.33	10942[f]	13805	3.15	---	---	40[c,i]
Monkey (IPI-145-009)	4/(2M, 2F)	IV[a]	1	1545	0.083	2357	2379	5.0	0.43	1.27	---
	4/(2M, 2F)	PO[b]	5	1327	1.5	4596	4685	5.4	---	---	40

Source: Applicant's table
--- = not applicable; NC = not calculated
[a] IV formulation (mouse, rat, monkey) =5% NMP, 10% Solutol® HS 15, 30% PEG 400, 55% sterile water for injection with 3% dextrose
[b] PO formulation (mouse, rat, monkey) =0.5% (w/v) low viscosity CMC and 0.05% (v/v) TWEEN® 80 in sterile water for injection
[c] F_{oral} was calculated using $AUC_{0\text{-}last}$
[d] IV formulation (dog) =5% 0.1N HCl, 5% PEG 400 in 10% (2-hydroxypropyl)–β-cyclodextrin or 2.5% 1N HCl, 20% PEG 400 in PBS
[e] Reported value is C0
[f] $AUC_{0\text{-}24}$
[g] PO formulation (dog) =5% NMP, 60% PEG 400 and 35% water solution (Report ADME-11-008) or 5% NMP and 95% water suspension (Report ADME-11-009 V1)

[h] F_{oral} was calculated using 0.5 mg/kg IV dose as reference
[i] F_{oral} was calculated using 1 mg/kg IV dose as reference

5.4. Toxicology

5.4.1. General Toxicology

Study title/number: A 13-week Oral Gavage Toxicity Study of IPI-145 in the Rat with a 4-week Recovery Period (#805592)

Key Study Findings

- Orally administered duvelisib was generally tolerated in this 13-week rat study.
- The target organs included lymphoid organs (thymus, spleen) and male reproductive organs (testes).
- The 13-week study did not identify additional toxicities compared to the 4-week study in rats.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 0.5, 5, and 25 mg/kg (as control, LD, MD and HD) once daily for 13 weeks; 4-week recovery period Dose selection was based on the STD10 (50 mg/kg) of the 4-week study.
Route of administration:	Oral gavage (10 mL/kg)
Formulation/Vehicle:	0.5% (w/v) Carboxymethylcellulose (low viscosity) and 0.05% (v/v) TWEEN® 80 in Ultra pure water
Species/Strain:	Rat/Sprague Dawley (Crl:CD(SD))
Number/Sex/Group:	Main Study: 15/sex/group Recovery: 10/sex/group
Age:	Approximately 6 weeks at receipt
Satellite groups/ unique design:	Toxicokinetics: 3/sex for 0 mg/kg/day group and 9/sex/day for duvelisib-treated groups
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	No treatment-related deaths
Clinical Signs	Not remarkable

Body Weights	Not remarkable
Food Consumption	Not remarkable
Ophthalmoscopy	Not remarkable
Hematology (For white cell counts: % decrease compared to control, based on absolute counts)	RDW ↑Week 6 (Females: 14% HD) ↑Week 13 (Males: 8% MD; 12% HD) (Females: 8% HD) Reticulocyte (absolute) ↑Week 13 (Males: 36% MD) White blood cell ↓Week 6 (Males: 16% LD; 35% HD) (Females: 18% LD; 36% HD) ↓Week 13 (Males: 24% HD) (Females: 18% LD; 36% HD) Lymphocyte ↓Week 6 (Males: 18% LD; 38% HD) (Females: 43% HD) ↓Week 13 (Males: 27% HD) (Females: 18% LD; 36% HD) LUC ↓Week 6 (Males: 32% HD) (Females: 36% HD) ↓Week 13 (Females: 37% LD; 43% HD) Platelet ↑Week 6: (Males: 11% HD) (Females: 11% MD, 16% HD) ↑Week 13: (Males: 22% MD; 19% HD) (Females: 13% LD, 16% HD) All findings resolved.
Bone marrow analysis	Myeloid:erythroid (M:E) ratios at all doses: comparable to the concurrent control and within the reported range (1.07-1.93:1.00)
Coagulation	HD (males) ↑Fibrinogen (11% from the control) Finding resolved.
Clinical Chemistry	HD (males) ↑Cholesterol during treatment period (24%-25% from the control). Finding resolved
Urinalysis	Not remarkable
Gross Pathology	HD (males) Pancreas (dark foci, 3/15 males); testes (small and soft, 8/15 males); epididymis (small, 2/15 males) At the end of recovery period, findings were comparable to the control.
Organ Weights	Summary of organ weight data were tabulated for Day 91 and Day 120 (recovery). See tables below.
Histopathology Adequate battery:	Yes; peer review: Yes • Summary of histopathological findings are tabulated below. • Findings in the thymus and testes resolved, while some evidence of recovery was observed in the spleen and pancreas. • Changes in pancreas were more prominent in males despite lower systemic exposure than females. Literature reports indicate islet hyperplasia is a spontaneous occurrence in aging rats, with no sex differences reported. The islet hyperplasia observed in this study is not considered adverse, as there was no indication of compromised vital function.

↑,↓: indicates increase or decrease in parameter compared to control.

Table 8 Summary of Day 91 (Top) and Day 120 (Bottom) Organ Weight Data in Rats

	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (mg/kg/day)	**0**	**0.5**	**5**	**25**	**0**	**0.5**	**5**	**25**
No. Animals per Group	**15**	**15**	**15**	**15**	**15**	**15**	**15**	**15**
Spleen [a]								
Absolute value	–	-5	**-23**	**-34**	–	-8	**-20**	**-35**
% of body weight	–	-4	**-21**	**-31**	–	-8	**-24**	**-33**
% of brain weight	–	-3	**-23**	**-34**	–	-8	**-19**	**-34**
Testes								
Absolute value	–	-5	**-16**	**-45**				
% of body weight	–	-5	**-14**	**-43**				
% of brain weight	–	-3	**-16**	**-45**				
Thymus								
Absolute value	–	4	-12	**-24**	–	-9	-10	**-31**
% of body weight	–	2	-10	**-21**	–	-8	-16	**-29**
% of brain weight	–	5	-12	**-24**	–	-9	-10	**-30**
Ovaries								
Absolute value					–	-6	**-14**	**-15**
% of body weight					–	-6	**-19**	-13
% of brain weight					–	-7	**-14**	**-14**

[a] All values expressed as percent difference of control group means.
Based upon statistical analysis of group means, values highlighted in **bold** were significantly different from those of the control group – $P \leq 0.05$; refer to data tables for actual significance levels and tests used.

	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (mg/kg/day)	**0**	**0.5**	**5**	**25**	**0**	**0.5**	**5**	**25**
No. Animals per Group	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Thymus [a]								
Absolute value	–	-17	-24	-23	–	7	-6	-9
% of body weight	–	-22	**-25**	-23	–	7	-4	-2
% of brain weight	–	-18	**-26**	**-24**	–	10	-8	-9
Testes								
Absolute value	–	1	-6	**-28**				
% of body weight	–	-4	-6	**-30**				
% of brain weight	–	1	-7	**-29**				

[a] All values expressed as percent difference of control group means.
Based upon statistical analysis of group means, values highlighted in bold are significantly different from control group - $P \leq 0.05$; refer to data tables for actual significance levels and tests used.

Source: Applicant's table

Table 9: Summary of Day 91 (Top) and Day 121 (Bottom) Histopathological Findings in Rats

	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (mg/kg/day)	**0**	**0.5**	**5**	**25**	**0**	**0.5**	**5**	**25**
No. Animals Examined	**15**	**15**	**15**	**15**	**15**	**15**	**15**	**15**
Pancreas								
Inflammation	(2)	(–)	(4)	(9)	(–)	(–)	(2)	(1)
Minimal	2	–	2	4	–	–	2	1
Slight	–	–	1	1	–	–	–	–
Moderate	–	–	1	4	–	–	–	–
Inflammation: granulomatous	(–)	(–)	(1)	(5)	(–)	(–)	(–)	(1)
Minimal	–	–	–	1	–	–	–	1
Slight	–	–	1	2	–	–	–	–
Moderate	–	–	–	2	–	–	–	–
Hyperplasia: islet cell	(5)	(4)	(5)	(9)	(–)	(–)	(–)	(1)
Minimal	2	2	2	2	–	–	–	1
Slight	3	2	2	5	–	–	–	–
Moderate	–	–	1	2	–	–	–	–
Fibrosis	(–)	(–)	(1)	(2)	(–)	(–)	(–)	(–)
Minimal	–	–	–	1	–	–	–	–
Slight	–	–	1	1	–	–	–	–
Atrophy: acinar cell	(-)	(-)	(1)	(3)	(-)	(-)	(1)	(2)
Minimal	-	-	1	1	-	-	1	1
Slight	-	-	-	2	-	-	-	1
Spleen								
Hyperplasia: lymphoid	(2)	(7)	(15)	(15)	(–)	(1)	(5)	(15)
Minimal	1	5	3	–	–	1	2	3
Slight	1	2	11	14	–	–	3	12
Moderate	–	–	1	1	–	–	–	–
Thymus								
Depletion: lymphoid	(–)	(2)	(2)	(6)	(–)	(–)	(2)	(7)
Minimal	–	2	2	6	–	–	2	5
Slight	–	–	–	–	–	–	–	2
Testes								
Degeneration/atrophy: seminiferous epithelium	(1)	(–)	(–)	(8)				
Minimal	1	–	–	8				

Numbers in parentheses represent the number of animals with the finding.

	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (mg/kg/day)	**0**	**0.5**	**5**	**25**	**0**	**0.5**	**5**	**25**
No. Animals Examined	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Pancreas								
Hyperplasia: islet cell	(3)	(2)	(3)	(6)	(–)	(–)	(–)	(1)
Minimal	3	2	2	2	–	–	–	1
Slight	–	–	1	2	–	–	–	–
Moderate	–	–	–	2	–	–	–	–
Fibrosis	(1)	(–)	(–)	(4)	(–)	(–)	(–)	(–)
Minimal	1	–	–	2	–	–	–	–
Slight	–	–	–	1	–	–	–	–
Moderate	–	–	–	1	–	–	–	–
Inflammation	(-)	(–)	(1)	(1)	(–)	(–)	(–)	(–)
Minimal	–	–	1	1	–	–	–	–
Spleen								
Hyperplasia: lymphoid	(–)	(4)	(7)	(5)	(1)	(–)	(–)	(4)
Minimal	–	4	4	3	1	–	–	3
Slight	–	–	3	2	–	–	–	1

Numbers in parentheses represent the number of animals with the finding.

Source: Applicant's table

Monkeys

Study title/number: A 13-week Oral Gavage Toxicity Study of IPI-145 in the Cynomolgus Monkey with a 6-week Recovery Period (#805593)

Key Study Findings

- Orally administered duvelisib was generally tolerated in this 13-week monkey study.
- Duvelisib treatment induced lymphoid depletion and compromised immune responses (i.e., decreased T-cell dependent antibody responses).
- The immunosuppressive effects led to opportunistic intestinal infections.
- Inflammatory changes were noted (in 2/10 MD animals and 9/14 HD animals).

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 0.2, 1, and 5 mg/kg (as control, LD, MD and HD) once daily for 13 weeks; 6-week recovery period Dose selection was based on the HNSTD (5 mg/kg) of the 4-weeek study.
Route of administration:	Oral gavage (5 mL/kg)
Formulation/Vehicle:	0.5% (w/v) Carboxymethylcellulose (low viscosity) and 0.05% (v/v) TWEEN® 80 in Ultra

	pure water
Species/Strain:	Cynomolgus monkey (Macaca fascicularis)
Number/Sex/Group:	Main Study: 4/sex/group (Control and HD), 3/sex/group (LD and MD) Recovery: 3/sex/group (Control and HD), 2/sex/group (LD and MD)
Age:	Approximately 2.5-3.5 years at receipt
Satellite groups/ unique design:	None. All animals were bled for toxicokinetics.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	No treatment-related deaths
Clinical signs	**≥0.2** mg/kg/day: **Dose (mg/kg/day): 0 0.2 1 5** **Sex: M F M F M F M F** Soft feces 29 (7) 41 (6) 2 (1) 65 (5) 120 (5) 58 (5) 204 (7) 215 (7) Liquid feces 5 (4) 11 (4) - 27(5) 56 (5) 14 (3) 258 (7) 269 (7) A dash (-) indicates absence of finding in group. Data are expressed as the total number of occurrences/group (number of animals affected). (Table from Applicant) Due to low degree fevers and positive responses to bacterial cultures of the feces, antidiarrhea drugs and/or antibiotics (for up to 10 days) were given to the HD group. In addition, reduced appetite and dehydration were noted at the MD (2/10) and HD (9/14), which were considered secondary to opportunistic intestinal infections associated with the immunosuppressive effects of duvelisib. During the recovery period, abnormal feces were observed, with reduced frequency.
Body Weights	Not remarkable
Food Consumption	Not remarkable
Ophthalmoscopy	Not remarkable
Electrocardiology	Not remarkable
Hematology (For total and differential white blood cell counts: data shown as % decrease compared to control, based on absolute counts)	Reticulocyte (absolute) (HD males only) ↑Days 23 (31%); ↑Days 52 (14%), restored on Day 91. White blood cell: HD ↑Days 23, 52 and 91 (22%-58%) Neutrophil: HD ↑ Days 23, 52 and 91 (99%-222%) Platelet ↑Days 23, 52 and 91: at ≥MD (males) and HD (females) ↑Day 91: statistically significant (males: 61% HD) (females: 39% HD) ↑Day 120: males at HD (42%) Findings resolved, except for changes in platelet counts.
Bone marrow analysis	M:E ratios: comparable to the concurrent control and within the reported range (0.67-1.85:1.00) Greater M:E ratios were noted at HD (2 males and 1 female) in monkeys with apparent signs of intestinal infection. Increased absolute neutrophil count was noted in one of the males. Corresponding histopathological findings in bone marrow included minimal to slight myeloid

	hypercellularity. Findings resolved.
Coagulation	HD (males) ↑Fibrinogen (Days 52 and 91; 66-76%) Finding resolved.
Clinical Chemistry	**≥MD** (Day 91) • Electrolyte changes in females (attributable to digestive losses based on evidence such as diarrhea, inflammation of large and small intestine and mucosal atrophy in small intestine), including: ↓Potassium: 14-15% (MD and HD); ↓ chloride: 2% (HD) • ↓Urea: 27% (M and F HD) Findings resolved.
Urinalysis	No significant changes in group means when compared to the control. Decreases in electrolyte concentrations were noted in individuals which were secondary to immunomodulatory effects of duvelisib. These included decreases in potassium (-53%, HD males), decreases in sodium (-43% to -75%, MD and HD females). Findings resolved.
Gross Pathology	HD (males) Thin (1/4) and small thymus (1/4) **≥LD** (females) Thickening colon (1/4 MD); thickening duodenum and colon (each: 1/4 MD); small spleen (1/4 HD); small thymus (1/4 HD). At the end of recovery period, dark foci or areas in various GI sections in one HD female monkey (#456). The macroscopic findings were correlated with moderate and slight hemorrhage histologically, with numerous surface and deep intracryptal ciliated protozoal organisms consistent with *Balantidium*. Other findings resolved.
Organ Weights	Summary of organ weight data were tabulated for Day 91. See tables below. Thymus weights remained reduced compared to control at the end of recovery period: -37% absolute and -36% both relative weight to body weight and to brain weight.
Histopathology Adequate battery:	Yes; peer review: Yes Lympho-hematopoietic system • Bone marrow: myeloid hypercellularity (minimal-slight): 2/4 HD Males, 3/4 HD females • Spleen: lymphoid depletion (slight): 1/4 HD female; neutrophilic cell infiltration (minimal-slight): 2/4 HD males, 1/3 LD female, 3/4 HD females • Thymus: lymphoid depletion (minimal-marked): 1/3 MD male, 1/4 HD male, 2 each in control, LD, MD and HD females • GALT: lymphoid depletion (minimal to marked): 1 each in LD and MD males, 3/4 HD males, 2 each in LD and MD females, 3/4 HD females • Lymph node, mandibular: lymphoid depletion (minimal-slight): 3/4 HD males, 3/4 HD females; histiocytosis (minimal-slight): 3/4 HD males and females. • Lymph node, mesenteric: lymphoid depletion (minimal-slight): 1/3 MD male, 2/4 HD males; 1/4 HD females; histiocytosis (minimal-slight): 4/4 HD males, 1/3 MD female, 3/4 HD females. GI tract and gallbladder • Duodenum: villous/mucosal atrophy (minimal): 2/4 HD males; smooth muscle hypertrophy (minimal-moderate): 1/3 LD male, one each LD, MD and HD females • Jejunum: goblet cell hyperplasia (minimal): 1/4 HD female; smooth muscle hypertrophy

	(minimal-slight): one each LD, MD and HD females • Ileum: villous/mucosal atrophy (slight), goblet cell hyperplasia (minimal): and smooth muscle hypertrophy (slight): 1/4 HD females • Cecum: inflammation (minimal-slight): 2/3 MD males, 3/4 HD males, 4/4 HD females • Colon: inflammation (minimal-slight): 1/3 MD males, 3/4 HD males, 4/4 HD females; smooth muscle hypertrophy (slight): 1/3 MD male, 1/3 MD female, 1/4 HD females • Gallbladder: inflammation (slight): 1/4 HD female Other findings • Femorotibial joint: fibrinosuppurative inflammation (moderate): 1/4 HD male • Brain: mixed cell infiltrates with a prominent eosinophilic component (slight): 1/4 HD male Findings were completely reversed or significantly reduced in severity and/or incidence. Slight smooth muscle hypertrophy was present in the colon at 1 mg/kg/day. At 5 mg/kg/day, weight changes and lymphoid depletion in thymus, and microscopic residual changes in large intestine were found only in few animals.
Lymphocyte immunopheno-typing	• Total lymphocyte (TLC): >+/-30% of the control in all treated monkeys (due to inter-animal variability) • ↓ Absolute and relative % B lymphocyte (CD45+/CD19+) (M and F HD) in Weeks 6 and 13 (up to -30% of the control and/or pre-treatment values). • ↑Relative % of total T lymphocytes (CD45+CD3+) and cytotoxic T lymphocytes (CD45+CD3+CD8+): males HD in Weeks 6-13. • Relative % of NK lymphocytes (CD45+CD3-CD16+): variability noted, i.e., >+/- 30% of the control. • Absolute and relative % of regulatory CD4+ T lymphocytes: variability noted, i.e., >+/- 30% of the control. • Findings resolved
T-cell dependent Antibody Response (TDAR)	Anti-IgM and IgG antibody Decreased anti-KLH antibody responses at ≥1 mg/kg/day. Findings resolved.
[Other evaluations]	Immunology analysis (ELISA assay) for serum IgE levels: Not remarkable

↑,↓: indicates increase or decrease in parameter compared to control.

Table 10: Summary of Organ Weight Data (Study #805593)

	Males			Females		
Group	**2**	**3**	**4**	**2**	**3**	**4**
Dose (mg/kg/day)	**0.2**	**1**	**5**	**0.2**	**1**	**5**
No. Animals per Group	**3**	**3**	**4**	**3**	**3**	**4**
Liver (No. Weighed)						
Absolute value	18	25	**39**	-1	3	4
% of body weight	1	2	25	-4	2	-1
% of brain weight	12	11	32	0	9	9
Thymus (No. Weighed)						
Absolute value	15	-56	-28	-25	-33	-36
% of body weight	0	-62	-43	-27	-35	-45
% of brain weight	11	-60	-31	-26	-30	-35

[a] All values expressed as percent difference of vehicle control group means.
Based upon statistical analysis of group means, values highlighted in bold are significantly different from vehicle control group - $P \leq 0.05$; refer to data tables for actual significance levels and tests used.

Source: Applicant's table

Additional toxicology studies

- Study title/number: A 28-day of IPI-145 by Oral Gavage in the Rat with a 14-day Recovery Period (#805097)

Rats were treated with duvelisib at 5, 50 and 350 mg/kg/day in the 4-week toxicology study. The toxicity profile was mainly attributable to exaggerated pharmacological effects of the drug. At 350 mg/kg (the high dose), where dosing was stopped after Day 6, increases in serum glucose and hemolymphoid changes were observed, including histopathologic changes of bone marrow and lymphoid tissues (erythroid hypoplasia, lymphoid hyperplasia and/or atrophy), in addition to signs of inflammatory and stress responses. Other target organs were GI tract (ulceration, inflammation and hemorrhage, and atrophy/necrosis of GALT), adrenal (degradation, necrosis), and male and female reproductive tracts (atrophy in testes and uterus, oligo/aspermia). The increased glucose levels were not associated with changes in serum insulin, thus the finding was not considered adverse. Mortalities occurred from Day 7 onwards. Erythroid hypoplasia (bone marrow) was also noted in 2/5 recovery females at 50 mg/kg. The females experienced higher exposures (AUC) and were more susceptible to duvelisib-related toxicities.

- Study title/number: A 28-day of IPI-145 by Oral Gavage in the Cynomolgus Monkey with a 14-day Recovery Period (#805098)

Monkeys were treated with duvelisib at 5, 30 and 150 mg/kg/day in the 4-week toxicology study. Similar to rats, the toxicities in monkeys were mainly exaggerated pharmacological effects of PI3K inhibition. Treatment-related mortality occurred at 150 mg/kg (moribund sacrifice in one each of both sexes). Clinical signs, decreased body weight and weight gains, loss of appetite, clinical pathology changes, and anatomical pathology findings were all associated with the hemo-lymphoid lesions (changes in bone marrow and lymphoid depletion in multiple lymphoid organs/tissues). The secondary effects included inflammation and opportunistic infections in multiple vital organs. Hyperglycemia was found in treated female monkeys at 150 mg/kg. There were no concurrent changes in serum insulin. The majority of the findings resolved or were improved at the end of recovery period.

The 4-week toxicology study in monkeys was used to determine the first in human (FIH) starting dose, enabling the clinical trial for duvelisib in advanced hematologic malignancies. The starting dose was based on 1/6 the highest non-severely toxic dose (HNSTD); HNSTD was between 5 and 30 mg/kg/day (human equivalent dose [HED] 1.6-10 mg/kg or 100-600 mg/day).

5.4.2. Genetic Toxicology

<u>In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)</u>
Study title/number: *Salmonella-E. coli*/Mammalian Microsome Reverse Mutation Assay (MBR 10-408)
Key Study Findings:

- Duvelisib did not increase in the number of revertant colonies in test strains TA98, TA100, TA1535, TA1537, and WP2 *uvrA* with or without metabolic activation. Therefore, duvelisib was negative for mutagenicity in the reverse mutation assay.

GLP compliance: Yes
Test system: *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537; *Escherichia coli* tester strain WP2 *uvrA*; tested at concentrations up to 5000 μg/plate; +/- S9 activation.
Study is valid: Yes

In Vitro Clastogenicity Assays in Mammalian Cells
Study title/number: In vitro Chromosome Aberration Test in Cultured Human Peripheral Blood Lymphocytes (#MBR10-409)
Key Study Findings:

- Duvelisib did not induce chromosome aberrations in human peripheral blood lymphocytes with or without metabolic activation. Therefore, duvelisib was negative for clastogenicity in the in vitro chromosome aberrations assay.

GLP compliance: Yes
Test system: Human peripheral blood lymphocytes; +/- S9 activation; exposure to duvelisib of 3 or 22 hours without S9 activation and 3 hours with S9 activation; 22 hours fixation time; for cytogenetic assays, concentrations of up to 100 μg/mL (without S9) and 125 μg/mL (with S9) for 3 hour exposure, and 100 μg/mL for 22 hour exposure.
Study is valid: Yes

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)
Study title/number: A GLP Rat Bone Marrow Micronucleus Assay (OECD 474) of Infinity Compound Number IPI-145 ([(b) (4)]-692013)
Key Study Findings:

- At the high dose (maximum tolerated dose [MTD], 350 mg/kg/day), the decrease in PCE:TE ratio was statistically significant in male and female rats, whereas the increase in % MN-PCEs was statistically significant only in male rats. These data were within the historical control range for the vehicle.
- The increased micronucleus formation in males at 350 mg/kg/day in the presence of bone marrow toxicity (i.e., reduced PCE ratio) indicated a positive result without biological relevance, since the change was slight (0.28% at 350 mg/kg versus 0.09% in vehicle control), and possibly was an indirect effect of duvelisib at the MTD via lesions in bone marrow.

GLP compliance: Yes
Test system: Sprague-Dawley rats; males and females; oral dose of 0, 5, 50, or 350 mg/kg/day duvelisib for 3 days; a single oral dose of 60 mg/kg cyclophosphamide (CPS) (Day 2); euthanized and bone marrow collection on Day 3.
Study is valid: Yes

Parameters
PCE: polychromatic erythrocytes; NCEs: normochromatic erythrocytes; MN-PCEs: micronucleated polychromatic erythrocytes

Table 11: Historical Control (n=25 per Sex), Years 2007-2008)

	Males		Females	
	Ratio of PCE/Total erythrocytes	MN PCEs (%)	Ratio of PCE/Total erythrocytes	MN PCEs (%)
Vehicle control	0.29-0.78	0-0.4	0.24-0.76	0-0.35
	0.55±0.1	0.12±0.11	0.55±0.12	0.12±0.09
Positive control*	0.18-0.71	0.65-8.4	0.19-0.66	0.4-2.7
	0.35±0.13	2.9±1.95	0.37±0.12	1.27±0.63

Compiled results from three studies conducted in (b) (4) (20007-2008), the numbers indicate the range of the data (lowest-highest), and mean ±SD; ratio of PCE/Total erythrocytes = PCE:TE ratio (PCE/PCE+NCE ratio)
*Cyclophosphamide, 60 mg/kg

Table 12: Micronucleus Assay Data (24 Hours After Dosing) (Study #(b) (4)692013)

	Males		Females	
	Ratio of PCE/Total erythrocytes	MN PCEs (%)	Ratio of PCE/Total erythrocytes	MN PCEs (%)
Vehicle control	0.6±0.06	0.08±0.07	0.63±0.05	0.08±0.04
IPI-145 5 mg/kg/d	0.56±0.08	0.07±0.06	0.60±0.06	0.06±0.07
IPI-145 50 mg/kg/d	0.45±0.06	0.19±0.10	0.53±0.13	0.13±0.13
IPI-145 350 mg/kg/d	0.45±0.14*	0.28±0.07*	0.31±0.13*	0.21±0.07
Cyclophosphamide	0.37±0.11*	2.23±0.57*	0.38±0.11*	0.96±0.3*

n=5/sex/group; Data were expressed as mean±standard deviation (M±SD); * statistically significant changes, p≤0.05

5.4.3. Carcinogenicity

Not conducted at this time per ICH S9.

5.4.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development
Neither submitted nor required

Embryo-Fetal Development
Rats:
Study title/number: An Oral (Gavage) Dose Range-Finding Study of the Effects of IPI-145 on Embryo/Fetal Development in Rats/ (b) (4)-0692020
Key Study Findings

- Duvelisib induced both maternal and embryofetal toxicities. Mortality, reduced food consumption, and total resorptions occurred in dams treated with duvelisib at doses ≥150 mg/kg/day. Body weight loss was observed ≥50 mg/kg. The embryofetal toxicities

included reduced mean fetal body weight and external malformations in fetus at ≥50 mg/kg.
- The NOAEL for maternal toxicity was 50 mg/kg/day.
- The NOAEL for developmental toxicity was 10 mg/kg/day.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing:	10, 50, 150 and 275 mg/kg/day (as LD, MD1, MD2 and HD); once daily dosing starting GD 6 through GD 17
Route of administration:	Oral garage (10 mL/kg)
Formulation/Vehicle:	Oral suspension in 0.5% (w/w) high viscosity CMC and 0.05% (w/w) TWEEN® 80 in deionized water
Species/Strain:	Rat/Crl:CD(SD)
Number/Sex/Group:	8 females/group
Satellite groups:	None
Study design:	Pregnant female rats (14 weeks of age) were administered duvelisib once daily on GD 6-17, scheduled necropsy/cesarean section conducted on GD 20. Due to excessive toxicity in 7/8 rats, and one found dead, the females at 275 mg/kg/day were terminated early on GDs 10-12. Uterine examinations and maternal necropsy were conducted, and all females had entirely resorbed litters. Laparohysterectomy data were not available for this group of females.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	150 mg/kg/day: one female found dead on GD13, 2 females were euthanized in extremis GDs 13-14. 275 mg/kg/day: one found dead on GD 11, 7 females were euthanized in extremis GDs 10-12.
Clinical Signs	150 mg/kg/day: similar to findings at 275 mg/kg/day, plus labored and decreased respiration, cool to touch; surviving

	females sporadically showed similar findings. 275 mg/kg/day: appearance (hunched posture, hypoactivity, half-closed eyelids), secretions (red or yellow material on the urogenital and anogenital areas, mouth, nose, forelimbs), GI signs (mucoid feces, decreased defecation)
Body Weights (dams)	50 mg/kg/day: Both net body weight and net body weight gain were not statistically different from the control. Significantly reduced mean body weight gain between GD 6-18 (↓17% of the control), and gravid uterine weight (↓19% of the control) was due to reduced mean fetal weights. 150 mg/kg/day: <u>Unscheduled deaths</u> Statistically significant reduction of mean body weight starting GD 8 (↓10% of the control), up to ↓27-25% of control on GD 13-14 <u>Surviving females:</u> during GD 13-14 to GD 20 Significant reduction of body weights: up to 34% reduction from control; weight gain: GD 12-18 (13 g vs 61 g of the control, ↓79%). Mean net body weight, net body weight gain, and gravid uterine weight in this group were significantly lower than the control (↓17%, 78% and 98% of the control, respectively). 275 mg/kg/day: Statistically significant reduction of mean body weight starting GD 7 (↓8% of the control), up to ↓29% of control on GD 11
Food Consumption (g/animal/day)	150 mg/kg/day: statistically significant reductions starting GD 6 (first day of treatment); mean reduction: ↓50% of the control (GD 6-9); ↓42% (GD6-18) 275 mg/kg/day: statistically significant reductions stating GD 6 (first day of treatment); mean reduction (GD 6-9): ↓77% of the control
Necropsy Findings Cesarean Section Data	150 mg/kg/day: unscheduled deaths Dark red contents of the stomach and vagina All dams at 150 mg/kg/day had entirely resorbed litters 275 mg/kg/day: in 7/8 dams: thymus (white discoloration); in 2-3/8 dams: adrenal gland (enlarged), mesenteric lymph nodes (red discoloration), stomach (dark red areas)

	All dams showed entirely resorbed litters
Necropsy Findings Offspring	50 mg/kg/day: ↓mean fetal weights (male, female and combined: 18.4%, 16.7% and 16.2% lower than control, respectively) External malformations in 4 fetuses (in 2 litters): bent tail in 3 fetuses and fetal anasarca in1 fetus.[9]**
Maternal NOAEL: 10 mg/kg/day Embryofetal NOAEL: 10 mg/kg/day	

**The Applicant claimed that the findings of external malformations were not duvelisib-related, based on the following: Anasarca and vertebral anomalies (e.g., bent tail) are common external malformations that were likely spontaneous. Anasarca was observed in an animal from a litter with 17 fetuses, and the fetus was the smallest animal in the litter; this finding was likely not related to duvelisib administration. The bent tail findings are likely secondary to the reduced fetal body weights in this dose group.

Table 13: External Malformation (Study (b) (4)-692020)

	FETUSES					LITTERS				
DOSE GROUP:	1	2	3	4	5	1	2	3	4	5
NUMBER EXAMINED EXTERNALLY	123	120	117	A	B	8	8	8	A	B
FETAL ANASARCA	0	0	1	NA	NA	0	0	1	NA	NA
BENT TAIL	0	0	3	NA	NA	0	0	2	NA	NA
TOTAL NUMBER WITH MALFORMATIONS										
EXTERNAL :	0	0	4	NA	NA	0	0	2	NA	NA

1- 0 MG/KG/DAY 2- 10 MG/KG/DAY 3- 50 MG/KG/DAY 4- 150 MG/KG/DAY 5- 275 MG/KG/DAY

A = NO VIABLE FETUSES WERE AVAILABLE FOR EXAMINATION
B = NO DAMS SURVIVED TO THE SCHEDULED NECROPSY
NA = NOT APPLICABLE

Source: Applicant's table

Table 14: Historical Control Data of Anasarca and Bent Tail (and Related External Malformations)

External malformations:

MALFORMATIONS (% Per Litter)	Mean	S.D.	SEM	Median	Min	Max	25th Quartile	75th Quartile
Fetal Anasarca	0.0	0.12	0.01	0.0	0.0	1.3	0.0	0.0
Spina Bifida	0.0	0.02	0.00	0.0	0.0	0.3	0.0	0.0
Tail- Short	0.0	0.04	0.00	0.0	0.0	0.3	0.0	0.0

Excerpted from (b) (4) (Version 3.10 [Crl:CD(SD) rats])"

Study title number: An Oral (Gavage) Study of the Effects of IPI-145 on Embryo/Fetal Development in Rats/ (b) (4)-0692021

Key Study Findings

- Daily doses up to 35 mg/kg/day in pregnant rats during GD 6-17 were tolerated and induced no embryo-fetal toxicities.
- The NOAEL for maternal and developmental toxicity was 35 mg/kg/day in rats.

[9] Fetal anasarca, defined by the presence of generalized subcutaneous edema, is a rare sonographic finding associated with end-stage hydrops fetalis and impeding fetal death. (Having and Bullock, Journal of Diagnostic Medical Sonography 27:19-25, 2011)

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing: 5, 10, and 35 mg/kg/day (as LD, MD and HD); once daily dosing starting GD 6 through GD 17
Route of administration: Oral garage (10 mL/kg)
Formulation/Vehicle: Oral suspension in 0.5% (w/w) high viscosity CMC and 0.05% (w/w) TWEEN® 80 in deionized water
Species/Strain: Rat/Crl:CD(SD)
Number/Sex/Group: 25 females/group
Satellite groups: Toxicokinetics; n=8/group dosing from GD 6 through GD 17. At the following time points on GD 6 and GD 17 blood samples were obtained: 0 (predose), 1, 2, 4, 8 and/or 24 hours post-dosing (n=4/timepoint).
Study design: Pregnant female rats (14 weeks of age) were administered duvelisib once daily on GD 6-17, scheduled necropsy/cesarean section conducted on GD 20.
Deviation from study protocol affecting interpretation of results: No

Observations and Results

Parameters	Major findings
Mortality	All rats survived
Clinical Signs	Not remarkable
Body Weights	Not remarkable (including: maternal weight changes, gravid uterine, net body weight changes)
Necropsy Findings Cesarean Section Data	Not remarkable
Necropsy Findings Offspring	35 mg/kg: ↓mean fetal weights (combined male and female data) (5% vs. control) which is within the range of historical control of (b) (4).

LD: low dose; MD: mid dose; HD: high dose

Rabbits

Study title/ number: An Oral (Gavage) Dose Range-Finding Study of the Effects of IPI-145 on Embryo/Fetal Development in Rabbits/ (b) (4) 0692022
Key Study Findings

- Duvelisib induced mortality, body weight loss, reduced food consumption and abortion in dams at ≥100 mg/kg/day, and reduced mean fetal body weight at 200 mg/kg/day. Increased early and/or total resorption, postimplantation loss and reduced viable fetuses occurred at doses ≥100 mg/kg/day.
- No external malformations or developmental variations were observed under the conditions of the study.
- The NOAEL for maternal and developmental toxicity was 25 mg/kg/day in rabbits.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing:	25, 100 and 200 mg/kg/day (as LD, MD, and HD); once daily dosing starting Gestation Day (GD) 7 through GD 20
Route of administration:	Oral garage (10 mL/kg)
Formulation/Vehicle:	Oral suspension in 0.5% (w/w) high viscosity CMC and 0.05% (w/w) TWEEN® 80 in deionized water
Species/Strain:	New Zealand white Rabbit/[Hra:(NZW)SPF]
Number/Sex/Group:	6 females/group
Satellite groups:	None, all females were used for toxicokinetics assessment (blood samples were collected from all surviving rabbits at 0 (pre-dose) and 2 hours after dosing on GD 20.
Study design:	Pregnant female rabbits (5.5 months of age) were administered duvelisib once daily on GD 7-20, scheduled necropsy/cesarean section conducted on GD 29.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	100 mg/kg/day: two females aborted, and were subsequently euthanized on GD 19. 200 mg/kg/day: two found dead on GD 14 and 23, 1 female was euthanized in extremis on GD 14.
Clinical Signs	100 mg/kg/day: prior to abortion and euthanasia: similar to findings at 200 mg/kg/day, secretion around eyes, disorientation, erratic movements repetitive movement (head and eyes) and shallow respiration.

<table>
<tr><td></td><td>The two unscheduled deaths aborted on GD 19, with 1 and 4 resorptions, respectively, upon necropsy examination.
200 mg/kg/day: prior to mortality/moribund euthanasia appearance (dehydration, closed eyelids, lethargic), secretions (red material on the urogenital area in the pan or at the base of the tail, indicating abortion), GI signs (small/soft feces, decreased defecation)

The unscheduled deaths all showed body weight loss and reduced food consumption.

Surviving females at ≥100 mg/kg/day: mainly excreta-related, fecal changes, noted as early as on GD 12.</td></tr>
<tr><td>Body Weights (dams)</td><td>100 mg/kg/day: mean body weights and weight gains were lower than the control. The reductions were not statistically significant.
<u>Including unscheduled deaths</u>
GD 7-10: -20 g vs 6 g (control); GD 10-13: 40 g vs 50 g (control);
<u>Surviving females only</u>
GD 7-21: 127 g vs 247 g (control).
200 mg/kg/day:
<u>Including unscheduled deaths</u>
Statistically significant reduction of mean body weight change:
Mean group body weight changes (g)
<table>
<tr><th></th><th>GD 11-12</th><th>GD 12-13</th><th>GD 7-10</th><th>GD 10-13</th></tr>
<tr><td>Control</td><td>13</td><td>35</td><td>6</td><td>50</td></tr>
<tr><td>HD</td><td>-31</td><td>-33</td><td>-27</td><td>-79</td></tr>
</table>
During GD 14-21: the treated rabbits weighed 5-13% lower than the controls (not statistically significant).

<u>Surviving females only:</u>
Statistically significant reduction of mean body weight change:
Mean group body weight changes (g)
<table>
<tr><th></th><th>GD 13-21</th><th>GD 7-21</th></tr>
<tr><td>Control</td><td>208</td><td>247</td></tr>
<tr><td>HD</td><td>-246</td><td>-322</td></tr>
</table>
The body weight remained 11.3% lower than the control on GD 29.

Mean gravid uterine weight in this group was lower than</td></tr>
</table>

<table>
<tr><td></td><td>the control (↓7%, not significant), may be due to increased postimplantation loss, decreased mean number of viable fetuses, and lower fetal weights.</td></tr>
<tr><td>Food Consumption (g/animal/day)</td><td>100 mg/kg/day: sporadically significant reductions were noted, up to ↓60% of the control; no remarkable reduction of overall food intake (GD 7-21)
200 mg/kg/day: statistically significant reductions of daily food intakes starting GD 11-12 (↓61% of the control), the reduction was up to ↓83%. Periodical reductions: ↓45% and ↓63% of the control (GD 10-13 and GD 13-21) and overall food intake: ↓43% of the control.</td></tr>
<tr><td>Necropsy Findings
Cesarean Section Data</td><td>25 mg/kg/day: nongravid: 1/6; no remarkable findings of fetal data
100 mg/kg/day: nongravid: 1/6, aborted (also euthanized): 2/6. The two deaths (also aborted): one with 1 early absorption, another with 4 early absorption.
200 mg/kg/day: nongravid: 1/6 (also found dead), entire resorption: 2/6 (one found dead and one euthanized, the latter had a mottled liver (all lobes).
Summary of fetal data at scheduled necropsy
<table>
<tr><th>Dose (mg/kg/day)</th><th>Control</th><th>100</th><th>200</th></tr>
<tr><td>Number of gravid females</td><td>5</td><td>3</td><td>3</td></tr>
<tr><td>Early resorption (%)</td><td>2.9</td><td>22.2</td><td>66.7</td></tr>
<tr><td>Total resorption (%)</td><td>6.2</td><td>25</td><td>66.7</td></tr>
<tr><td>Post implantation loss</td><td>0.6</td><td>2.7</td><td>3.7</td></tr>
<tr><td>Post implantation loss (%)*</td><td>6.2</td><td>25</td><td>66.7</td></tr>
<tr><td>Viable fetus per dam*</td><td>7.2</td><td>6.7</td><td>3.3</td></tr>
<tr><td>Viable fetuses per litter (%)*</td><td>93.8</td><td>75</td><td>33.3</td></tr>
<tr><td>Fetal weight (g) (% reduction from the control)*</td><td>46.1</td><td>42.2 (8%)</td><td>27.3 (41%)</td></tr>
<tr><td colspan="4">* (b) (4) historical control of postimplantation loss: 11.9% per litter. M number and litter proportion of viable fetuses: 7.5 per dam and 88.1% per litter, respectively. The minimum mean value in the (b) (4) historical control data of mean fetal weight was 36.4 g.</td></tr>
</table></td></tr>
<tr><td>Necropsy Findings
Offspring</td><td>Not remarkable</td></tr>
<tr><td colspan="2">Maternal NOAEL: 25 mg/kg/day
Embryofetal NOAEL: 25 mg/kg/day</td></tr>
</table>

Table 15: Plasma Concentrations of Duvelisib (Study # (b) (4) 92022)

	Gestation Day 20 Mean Plasma Concentration ± SD, ng/mL			
	Group 1 (0 mg/kg/day)	Group 2 (25 mg/kg/day)	Group 3 (100 mg/kg/day)	Group 4 (200 mg/kg/day)
Pre-dose	1.67 ± 0.48	707.50 ± 525.34	2569.75 ± 1860.63	6582.50 ± 4531.92
2 hr post-dose	5.08 ± 1.76	2796.67 ± 904.23	10080.00 ± 5707.59	16032.50 ± 11234.53

LLOQ = 0.500 ng/mL

Source: Applicant's table

Study title/number: An Oral (Gavage) Study of the Effects of IPI-145 on Embryo/Fetal Development in Rabbits/ (b) (4) 0692023
Key Study Findings

- Daily doses up to 75 mg/kg/day in pregnant rabbits during gestation days (GDs) 7-20 were tolerated and induced no embryo-fetal toxicities.
- At 75 mg/kg/day, the mean C_{max} and $AUC_{0\text{-}24hr}$ values were 8300 ng/mL and 66200 ng·h/mL, respectively, on GD 20.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Prenatal and Postnatal Development
Not conducted at this time per ICH S9.

5.4.5. Other Toxicology Studies

Genetic Toxicology Studies with Metabolite and Impurities

Table 16: Summary of Genotoxicity Studies of Metabolites and Impurities of Duvelisib

Study#	Metabolite or impurity tested	Assay	Strains/cells tested	Other test system details	Results
MBR13-109	IPI-656 (metabolite)	Bacterial reverse mutation assay	Salmonella- (TA98, TA100, TA 1535 and TA1537) and E. coli (WP2 *uvrA*)	+/- S9 activation; concentrations up to 5000 μg per plate	Negative
MBR13-110	IPI-656 (metabolite)	Chromosomal aberration	Human peripheral blood lymphocytes	+/- S9 activation; exposures of 3 and 22 hr (- S9) and 3 hr (+ S9); harvest at 22 hrs; Concentrations	Negative

Study#	Metabolite or impurity tested	Assay	Strains/cells tested	Other test system details	Results
				up to 275 μg /mL for 3 hr exposures and up to 110 μg /mL for 22 hr exposure	
MBR13-113	(b) (4)	Bacterial reverse mutation assay	Salmonella-(TA98, TA100, TA 1535 and TA1537) and E. coli (WP2 *uvrA*)	+/- S9 activation; concentrations up to 5000 μg per plate	Negative
MBR13-114		Bacterial reverse mutation assay	Salmonella-(TA98, TA100, TA 1535 and TA1537) and E. coli (WP2 *uvrA*)	+/- S9 activation; concentrations up to 5000 μg per plate	Negative
TX15-223		Modified 6-well Ames test	Salmonella-(TA98, TA100, TA 1535 and TA1537) and E. coli (WP2 *uvrA*)	+/- S9 activation; concentrations up to 1000 μg per well	(b) (4): Negative (b) (4): positive (see below)
(b) (4) 692058		Bacterial reverse mutation assay	Salmonella-(TA98, TA100, TA 1535 and TA1537) and E. coli (WP2 *uvrA*)	+/- S9 activation; concentrations up to 5000 μg per plate	Negative
(b) (4) 692065		Bacterial reverse mutation assay	Salmonella-(TA98, TA100, TA 1535 and TA1537) and E. coli (WP2 *uvrA*)	+/- S9 activation; concentrations up to 5000 μg per plate	Negative

Study title/number: 6-Well Bacterial Reverse Mutation Assay (b) (4) (b) (4))

Key Study Findings:

- The impurity (b) (4) induced dose-dependent increases of revertant colonies in the following bacterial strains and conditions: TA100 and TA1535 (with and without S9 activation) and E. coli WP2 uvrA (without S9).
- The impurity (b) (4) was not mutagenic under the study condition.

GLP compliance: Yes
Test system: *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537; *Escherichia coli* tester strain WP2 *uvrA*; modified 6-well assay; tested at concentrations up to 1000 μg/well; +/- S9 activation
Study is valid: Yes

X	X
Primary Reviewer Shwu-Luan Lee, PhD	Team Leader Christopher M. Sheth, PhD

6 Clinical Pharmacology

6.1. Executive Summary

Duvelisib, a dual inhibitor of PI3K-δ and PI3K-γ, is proposed for the treatment of patients with previously treated CLL/ SLL, and FL. The proposed dose of duvelisib is 25 mg orally twice daily (BID) without regard to food. The key review issues from a clinical pharmacology perspective are the appropriateness of the duvelisib dose in the proposed population, and recommendations for duvelisib starting dose adjustments in patient subgroups per intrinsic or extrinsic factors, such as hepatic or renal impairment, and drug-drug interaction (DDI).

The Office of Clinical Pharmacology has reviewed the information contained in NDA 211155. This NDA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations and comments are summarized:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The results from Study IPI-145-06 and Study IPI-145-07 provide pivotal evidence of effectiveness of duvelisib in patients with CLL/SLL or FL. Clinical pharmacology data and exposure-response (E-R) analysis for efficacy and safety provided supportive evidence.
General dosing instructions	The proposed dose of 25 mg once daily without regard to food is effective and appears to be safe. Food is not anticipated to affect efficacy or safety. Per the available data and E-R analysis, there is a lack of evidence to support an alternative dosing regimen to the proposed regimen.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No dose adjustments are recommended for age, body weight, sex, race, hepatic or renal impairment. Drug interactions are anticipated with the concomitant use of cytochrome P450 (CYP) modulators, as duvelisib is primarily metabolized by CYP 3A4. The following are recommended when duvelisib concomitantly used with: • Strong CYP3A4 inhibitors: Reduce the starting dose to 15 mg BID • Strong CYP3A4 inducers: Avoid concomitant use with strong CYP3A4 inducers; A postmarketing commitment (PMC) is requested to evaluate dosing with concomitant moderate CYP3A4 inducers. • Sensitive CYP3A4 substrates: Monitor toxicity and adjust the dose of sensitive CYP3A4 substrates per the labeling instruction.
Labeling	Labeling language and changes to the specific content and formatting from the review team are reflected in the final approved labeling.

Review Issue	Recommendations and Comments
Bridge between the to-be-marketed and clinical trial formulations	A bioequivalence (BE) study was conducted and comparative pharmacokinetic (PK) data was provided for bridging between the to-be-marketed formulation (DP-B) and the formulations used during early clinical development (DP-A).

Postmarketing Requirements and Commitments

Postmarketing Requirements (PMR): None.

Postmarketing Commitments (PMC):

1. Conduct a clinical pharmacokinetics trial to evaluate the effect of repeat doses of a moderate CYP3A inducer on the single dose pharmacokinetics of duvelisib and its active metabolites to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations. (b) (4)
(b) (4)

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Duvelisb is an orally bioavailable small molecule inhibitor that inhibits the enzyme activities of PI3K-δ and PI3K-γ. The following is a summary of the clinical pharmacokinetics of duvelisib:

Absorption: Duvelisib exposure increases dose proportionally across the dose range from 8 to 75 mg. The median duvelisib T_{max} ranged from 1-2 hours. Absolute bioavailability was approximately 42%. Food did not affect duvelisib exposure.

Distribution: The estimated volume of distribution was 46.9 L (CV% 78%) in patients at 25 mg BID single dose. High plasma protein binding was observed (98 %). Duvelisib is a substrate of P-gp and BCRP.

Metabolism: Duvelisib is metabolized primarily by CYP3A. Duvelisib and the major non-active metabolite IPI-656 inhibit the activity of CYP2C8 and CYP3A4.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The Applicant proposes an oral dosing regimen of 25 mg twice daily without regard to food. The phase 3 study IPI-145-07 and phase 2 study IPI-145-06 evaluated duvelisib at the proposed dose in patients with CLL/SLL and FL respectively. The proposed dose is effective and appears to have a manageable safety profile.

Therapeutic Individualization

Specific Populations

Patients with hepatic impairment: Duvelisib is primarily metabolized in the liver and excreted through the hepatobiliary pathway. A dedicated hepatic impairment trial in healthy subjects with normal hepatic function and non-cancer patients with mild, moderate and severe hepatic impairment was conducted. Hepatic impairment has no apparent effect on the duvelisib exposure. No dose adjustment is necessary for patients with hepatic impairment.

Drug-Drug Interactions

Strong or moderate CYP3A Inhibitors: In a dedicated drug-interaction trial in healthy subjects (N=16), concomitant ketoconazole (a strong CYP3A4 inhibitor and P-gp inhibitor) increased duvelisib C_{max} and AUC by 66% and 295% respectively. PBPK modeling and simulation estimated the increase in exposure to duvelisib (AUC) is estimated to be 70% at steady state and the DDI effects are expected to be the same in patients. It is recommended that the starting dose of duvelisib be reduced to 15 mg twice daily when co-administered with strong CYP3A4 inhibitors in the proposed indication. No dose adjustment is necessary for concomitant use with moderate CYP3A4 inhibitors.

Strong or moderate CYP3A Inducers: Based on a dedicated drug-interaction trial in healthy subjects (N=14), concomitant rifampin (a strong CYP3A4 inducer) decreased the C_{max} and AUC resulting from a single dose of duvelisib by 66% and 82%, respectively, when compared to duvelisib given alone. The concomitant use of strong CYP3A4 inducers should be avoided. A PMC study will be issued to evaluate the effects of a moderate CYP3A4 inducer on (b) (4) (b) (4) duvelisib (b) (4).

CYP3A4 Substrates: In a dedicated drug-interaction trial in healthy subjects, midazolam (a CYP3A4 substrate) single dose C_{max} and AUC were increased by 120% and 330% respectively, when co-administered with duvelisib (steady state dosing). The inhibition of CYP3A4 activity by duvelisib and subsequently increasing of midazolam exposure might be clinically relevant. Thus, safety should be monitored when duvelisib is concomitantly used with other sensitive CYP3A4 substrates with a narrow therapeutic window and the dose of the substrate should be adjusted according to toxicities per the labeling of the co-administered substrates.

Outstanding Issues

A PMC will be issued from Clinical Pharmacology: Conduct a clinical pharmacokinetic trial with repeat doses of a moderate CYP3A4 inducer and a single dose of duvelisib to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Pharmacology		
Mechanism of Action	PI3K inhibitor (PI3K-δ IC_{50} =2.5nM, PI3K-γ IC_{50} =27.4nM).	
Active Moieties	Duvelisib. Its major metabolite IPI-656 is not active.	
QT Prolongation	No clear duvelisib-QTc relationship from 8-75 mg BID	
General Information		
Bioanalysis	Duvelisib and IPI-656 were measured using validated LC/MS/MS methods. A summary of the bioanalysis reports is included as an appendix.	
Healthy vs. Patients	The exposure following a single dose is higher in patients compared to healthy subjects (120% higher, cross study-comparison).	
Drug Exposure at Steady State Following the Therapeutic Dosing Regimen	The $AUC_{0\text{-}12h}$ (CV%) was 7.9 mcg.h/mL (76.8%)and C_{max} (CV%) was 1.5 mcg/mL (63.6%) in patients at a dose of 25 mg BID.	
Maximally Tolerated Dose or Exposure	75 mg BID.	
Dose Proportionality	8 mg to 75 mg BID in patients.	
Accumulation	$AUC_{SS} \div AUC_{Single\ Dose}$ =1.9 in patients receiving 25 mg BID	
Absorption		
Bioavailability	42%	
T_{max} [oral]	1-2 hours in patients	
Food Effect (High-Fat)	$AUC_{0\text{-}\infty}$	C_{max}
Geometric Mean Ratio (90% CI)	0.94 (90% CI: 0.88, 1.0)	0.63 (90% CI: 0.55, 0.71)
Distribution		
Volume of Distribution (Vss/F)	46.9 L (CV% 78%) in patients at 25 mg BID single dose	
Plasma Protein Binding	98%	
Substrate of Transporters [in vitro]	Duvelisib is a substrate of P-gp and BCRP. Not a substrate of OCT1, OATP1B1, OATP1B3, or BSEP.	
Elimination		
Terminal Elimination Half-Life	6.8 (CV% 45.8%) hours in patients at 25 mg BID single dose	
Metabolism		
Primary Metabolic Pathway(s) [in vitro]	Primarily by CYP3A4	
Excretion		
Primary Excretion Pathways (% dose)	Feces: 79% (10.9% unchanged); Urine: 13.5% (<1 % unchanged). The renal route appears to be a minor elimination pathway.	

Interaction liability (Drug as perpetrator)	
Inhibition/Induction of Metabolism [in vitro]	Duvelisib and IPI-656 inhibit the activity of CYP2C8 and CYP3A4.
Inhibition/Induction of Transporter Systems [in vitro]	Duvelisib inhibits OCT1, OATP1B1, OATP1B3, MATE1, MATE2K, BSEP, BCRP, and P-gp, but not OAT1, OAT3, or OCT2. IPI-656 inhibited MATE1, MATE2, OATP1B1, OATP1B3, and BSEP, but not OAT3, OCT1, OCT2, BCRP, or P-gp.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. The clinical pharmacology program provided supportive evidence of effectiveness. The clinical pharmacology program is composed of the single administered dose (SAD) and multiple administered doses (MAD) studies in healthy subjects and patients with hematologic malignancies, mass balance, bioavailability and bioequivalence studies, food effect and drug-drug interaction (DDI) studies of concomitant use of duvelisib with a CYP3A4 inhibitor, a CYP3A4 inducer and a CYP3A4 substrate. PBPK, PopPK and E-R analyses were also conducted with the evaluable PK data collected from the early stage clinical trials and the pivotal trials (Study-IPI-145-07 and Study IPI-145-06) in the proposed indications of patients with CLL/SLL or FL. The pivotal evidence of effectiveness comes from the efficacy results in Study-IPI-145-07 and Study IPI-145-06.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The proposed dose of 25 mg BID is effective and appears to have a manageable safety profile based on the available data from the early stage clinical trials and pivotal trials for the patients with CLL/SLL or FL. The justification of the appropriateness of the proposed dose are summarized below:

- Maximum tolerated dose (MTD) is 75 mg BID, identified in the dose escalation phase of the dose finding trial, which is three times higher than the proposed dose.

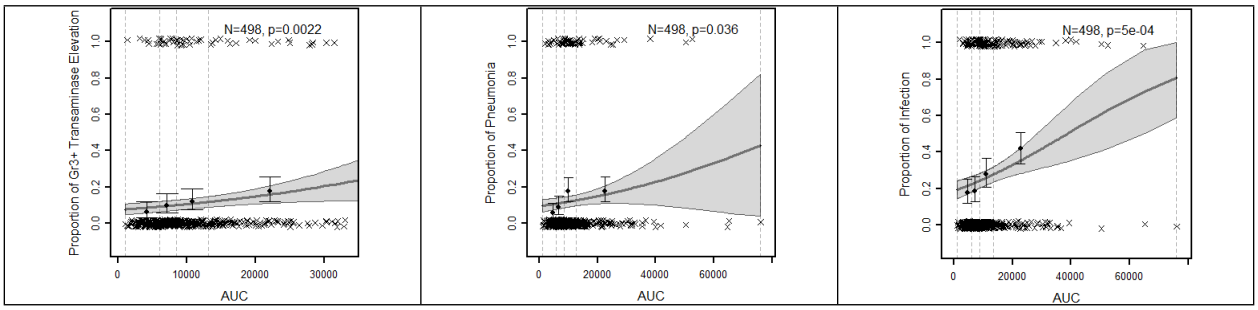
- At the proposed dose of 25 mg BID, the trough concentrations of duvelisib at steady state exceeded and maintained above the IC90 for PI3K-δ and IC50 for PI3K-γ inhibitions (determined with in vitro assays) in the efficacy trials.

- In the efficacy trial for the patients with CLL/SLL, the median duration of exposure was 45.3 weeks (17.6, 75.3). The median time to the first dose reduction or dose withhold due to any TEAEs was 119 days (7 – 631 days) after starting duvelisib administration, although there were 73.3% patients enrolled in the CLL/SLL trial had at least one dose reduction or dose interruption due to TEAEs from the starting dose.

- Exposure-Response (E-R) analysis suggests a flat relationship for efficacy; data are insufficient to conclude that a lower dose level or longer dose interval would result in benefit.

E-R analysis for efficacy is limited by the narrow dose/exposure range in the two registration studies (i.e. IPI-145-06 and IPI-145-07). Even though positive E-R relationships were not observed between duvelisib exposure and efficacy endpoints in the two registration studies, there is no adequate data to support equivalent efficacy at a lower dose level. E-R analysis for safety suggested a positive relationship between duvelisib exposure and the probability of grade 3 and above transaminase increase, infection, and pneumonia in the range of 8-mg to 75-mg doses (Figure 1). However, the probability of specific adverse events or the probability of any major grade 3 and above adverse events (i.e. transaminase increase, infection, pneumonia, neutropenia, rash, colitis, pneumonitis, or diarrhea) is not predicted to decrease substantially at lower dose levels. See Appendix 19.4.4 for details.

Figure 1: Exposure-Safety Relationship for Grade 3 and Above Transaminase Increase, Pneumonia and Infection



Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No. Age (18-90 years), sex, race, renal impairment (creatinine clearance 23 to 90 mL/ min), hepatic impairment (Child Pugh Class A, B, and C) and body weight (40 to 154 kg) had no clinically significant effect on the exposure of duvelisib based on population PK analysis. No dose adjustments are needed for hepatic or renal impairment, or other intrinsic factors such as age, sex, or race.

Hepatic Impairment

Duvelisib is primarily metabolized in the liver and excreted through hepatobiliary pathway. Single doses of 25 mg duvelisib were evaluated in non-cancer patients under fasted conditions with chronic hepatic impairment (n=6 each in Child Pugh Class A, B, and C) and in matched healthy subjects (n=6) with normal hepatic function. Duvelisib exposures in the patients with Child Pugh Class A (mild impairment), Child Pugh Class B (moderate impairment) and Child Pugh Class C (severe impairment) were similar to that in normal healthy subjects (Table 17). The plasma unbound fraction of duvelisib increased as hepatic impairment level increased to

moderate and severe, but not to a clinically meaningful extent. No dose adjustment is necessary for patients with hepatic impairment.

Table 17: Summary of PK Parameters and Geometric LSM Test for Duvelisib in Hepatic Impairments Study

Hepatic impairment levels	C_{max} (ng/mL)			AUC (ng*h/mL)		
	Mean (CV %)	GMR*	90% CI	Mean (CV %)	GMR*	90% CI
Healthy (Normal)	899 (41%)	-	-	4946 (29%)	-	-
Child-Pugh A (Mild)	1150 (35%)	1.28	0.72-2.29	4385 (45%)	0.89	0.47-1.66
Child-Pugh B (Moderate)	701 (51%)	0.78	0.44-1.39	4647 (46%)	0.94	0.50-1.76
Child-Pugh C (Severe)	553 (56%)	0.62	0.34-1.10	4008 (67%)	0.81	0.43-1.52

*GMR: Geometric mean ratio to healthy subjects.
Source: Data adapted from CSR of Study IPI-145-14.

Renal Impairment

Dedicated studies in patients with renal impairment have not been performed, as less than 1% of unchanged duvelisib was excreted through the kidneys in a radiolabeled mass balance study in healthy subjects. PopPK analysis indicated that renal function (creatinine clearance 23 to 80 mL/ min) is not a covariate for the PK of duvelisib. No dose adjustment is needed for renal impairment.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Food effect

The administration with food is unlikely to have a clinically meaningful effect on duvelisib exposure. The labeling recommends that duvelisib be taken with or without food.

The preliminary food effects were assessed with a standard FDA high fat breakfast using the initial Clinical Trial Formulation drug product A (DP-A) in healthy subjects after oral single administration of 25-mg (n=6 crossover). The high fat meal increased the exposure (AUC) by 9% as compared to the fasted conditions (Table 18).

In a dedicated food effect study in healthy subjects, the Market-Image formulation DP-B (commercial 25-mg capsule) was given at a dose of 25 mg under fasted conditions or within 30 minutes after consuming a high fat breakfast (fat accounted for approximately 50% of the total caloric content of the meal). The high fat meal decreased AUC_{inf} and C_{max} by 6% and 37%, respectively, when compared to fasted condition (Table 18). The reduction of duvelisib exposure by food is not expected to be clinically meaningful.

Table 18: Food Effect Under High Fat Breakfast

	Fed Conditions (Test)			Fasted Conditions (Reference)			LSGM Test/Reference	
Parameters	n	GeoMean	CV%	n	Geo Mean	CV%	Ratio	90% CI
Clinical Trial Formulation DP-A								
Cmax (ng/mL)	6	699	25	6	776	47	0.9	0.61-1.34
AUCinf(ng*h/mL)	6	3440	32	6	3158	44	1.09	0.88-1.34
Market-Image Formulation DP-B								
Cmax (ng/mL)	19	561.5	42	20	897.8	44	0.63	0.55-0.71
AUCinf (ng*h/mL)	18	2791	42	16	2965	38	0.94	0.88-1.01

Source: Adapted data from CSR Study IPI-145-01 & CSR Study IPI-145-15;

CYP3A Inhibitor

Duvelisib is primarily metabolized by CYP3A4 enzymes. Co-administration of drugs that inhibit CYP3A enzymes could have clinically meaningful effects on the steady state exposure of duvelisib. It is recommended to reduce the dose of duvelisib to 15 mg twice daily when co-administered with strong CYP3A4 inhibitors (e.g., ketoconazole).

A nonrandomized, open-label, single-sequence drug-drug interaction study (n=16) indicated that co-administration of the strong CYP3A inhibitor ketoconazole (at 200 mg twice daily for 5 days) with a single oral 10-mg dose of duvelisib in healthy adults (n=16) increased duvelisib Cmax by 66% and AUC by 295% (Table 19). Based on physiologically-based pharmacokinetic (PBPK) modeling and simulation, the increase in exposure to duvelisib is estimated to be 70% at steady state when concomitantly used with a strong CYP3A4 inhibitor such as ketoconazole. Similar DDI effects are expected in patients with hematological malignancies with concomitant use of duvelisib with strong CYP3A inhibitors. Thus, the starting dose of duvelisib should be reduced to 15 mg twice daily when co-administered with strong CYP3A4 inhibitors in the proposed indication.

PBPK modeling and simulation estimated 40% increase in duvelisib exposures when concomitantly used with a moderate CYP3A4 inhibitors, which is considered not clinically meaningful. See Appendix 19.4.5 for details.

Table 19: PK and Geometric LSM Test for Duvelisib in Subjects When Duvelisib Concomitantly Dosed With Ketoconazole

	Treatments		LSGM Test: Combo /alone	
Mean ±SD (CV %)	10 mg	10 mg+ Ketoconazole	Ratios	90% CI
Cmax (ng/mL)	517 ±201 (39)	838 ±243 (29)	1.66	1.47-1.87
AUC (ng*hr./mL)	1570 ±666 (42)	6147 ±2249 (37)	3.95	3.64-4.27

LSGM: least squares geometric mean
Source: CSR for study IPI-145-01; Table 14.2.7;

CYP3A Inducer

It is recommended to avoid the concomitant use of duvelisib with strong CYP3A4 inducers. A PMC study will be issued to evaluate the effects of moderate CYP3A4 inducer on (b) (4) (b) (4) duvelisib (b) (4).

A dedicated open-label, two-period, single-sequence drug-drug interaction study (n=14) indicated that co-administration of 600 mg once-daily rifampin, a strong CYP3A inducer, for 7 days with a single, oral 25-mg duvelisib dose in healthy adults decreased duvelisib Cmax by 66% and AUC by 82% (Table 20). Thus, the concomitant use of duvelisib with strong CYP3A inducers should be avoided.

The effect of moderate CYP3A4 induction has not been studied. Given duvelisib is predominantly metabolized by the CYP3A4 pathway and had a significant exposure change with strong CYP3A4 induction, the potential impact on duvelisib efficacy from concomitant use with moderate CYP3A4 inducers warrants consideration.

Table 20: Summary of PK and Geometric LSM Test When Duvelisib Concomitantly Used With Rifampin

	Treatments		LSGM Test: Combo /alone	
Mean ±SD (CV %)	25 mg	25 mg+ Rifampin	Ratios	90% CI
Cmax (ng/mL)	1017 ±364 (36)	386 ±154 (40)	0.34	0.30-0.39
AUC (ng*hr/mL)	3410 ±1277 (38)	604 ±172 (28)	0.18	0.16-0.21

Source: CSR for study IPI-145-11; Table 14.2.2.2 & Table 14.2.3.2;
LSGM: least squares geometric mean

CYP3A4 Substrates

In vitro studies show that duvelisib and its major metabolite IPI-656 inhibit CYP3A4 enzyme activity. It is recommended to consider reducing the dose of sensitive CYP3A4 substrates and monitor for signs of toxicities of the co-administered sensitive CYP3A substrate.
A single-sequence, two-period DDI study indicated that COPIKTRA 25 mg twice daily for 5 days with single oral 2 mg midazolam, a sensitive CYP3A4 substrate, in healthy adults (n =14), increased midazolam AUC by 330% and Cmax by120%.

Table 21: Summary of PK and Geometric LSM Test When Duvelisib Concomitantly Used With Midazolam

	Treatment		LSGM Test: Combo /alone	
Mean ±SD (CV %)	2 mg MDZ	25 mg BID + 2 mg MDZ	Ratios	90% CI
Cmax (ng/mL)	9.7 ±3.1 (32.5)	20.5 ±4.6 (23)	2.2	1.88-2.58
AUC (ng*hr./mL)	23.9 ±5.6 (24.5)	102.8±29.8 (28.9)	4.3	3.76-4.88

Source: data adapted from CSR of Study IPI-145-10.
MDZ: midazolam; LSGM: least squares geometric mean

CYP2C8 Substrates

In vitro data suggested that duvelisib (Ki =1.1 μM) and IPI-656 (Ki =5 μM) are direct inhibitors of CYP2C8. No clinical study was conducted due to the limited number of narrow therapeutic drugs predominantly metabolized by CYP2C8. PBPK modeling and simulations were used to assess the effect of duvelisib on two CYP2C8 substrates, repaglinide and rosiglitazone. The PBPK simulations suggested that duvelisib 25 mg BID would have negligible impact on either repaglinide or rosiglitazone exposures. Therefore, drugs that are predominately metabolized by CYP2C8 can be administered with duvelisib.

Acid-Reducing Agents (ARAs)

The solubility of duvelisib is pH dependent. Treatments that alter gastrointestinal pH such as PPIs, H_2-receptor antagonists, and antacids may lower the solubility of duvelisib, thus decrease exposure.

PBPK modeling and simulations were conducted and suggested that the effect of elevated stomach pH on duvelisib PK is dependent on particle size distribution. Simulation for the market-image formulation DP-B (batch 02140013) suggested that when stomach pH was increased to 5, AUC and Cmax were decreased by 17% and 63%, respectively. When the particle size distribution was altered to be close to the specification upper limit, simulation suggested duvelisib AUC and Cmax were decreased by 28% and 66%, respectively, when gastric pH was increased to 5. The effect is considered not clinically meaningful and duvelisib can be administered with acid reducing agents.

Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support the to-be-marketed formulation?

The proposed to-be-marketed formulation is the market-image formulation DP-B, which was used in the pivotal clinical Study IPI-145-07 in the population of CLL/SLL and other phase 1 and phase 2 clinical trials. Clinical-trial formulation DP-A was initially developed and used in the early stage trials including the phase 2 clinical Study IPI-145-06 in the proposed indication of FL. A bioequivalence (BE) study was conducted under fasted conditions to compare the formulations in healthy subjects (n=32) following a single oral administration of 25 mg duvelisib in a two-period, two-treatment, two-sequence crossover design. The BE study suggests that there is no clinically meaningful difference in exposure of duvelisib following administration of the DP-A and DP-B formulations (Table 22). These data support the pooling of all available data for these formulations to describe the PK and assess safety and efficacy. For additional details, see the CMC/Biopharm review.

Table 22: Bioequivalence of Duvelisib Following the Administration of Two Formulations at 25 mg (Strength of 25 mg)

	DP-B (Test)			DP-A (Reference)			LSGM Test/Reference	
Parameters	n	GeoMean	CV%	n	Geo Mean	CV%	Ratio	90% CI
Cmax (ng/mL)	32	1115	40	32	947	49	1.18	1.04-1.33
AUCinf (ng*h/mL)	28	3392	38	26	3310	33	1.01	0.97-1.05

Source: Adapted data from Summary of Biopharmaceutic Studies. Table 5 & Table 6;

X

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7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The Applicant submitted data from 17 clinical studies of duvelisib monotherapy or in combination with other agents. Of these 17 studies, 4 studies evaluating duvelisib monotherapy in patients with relapsed or refractory CLL/SLL, and NHL, including FL, were included to support efficacy and safety. To provide a comprehensive analysis of safety, the Applicant included data from completed studies of duvelisib in combination with other therapies, other NHL indications, healthy volunteers, and pharmacovigilance data for all ongoing studies. Table 23 lists the efficacy and safety studies emphasized in this review.

Table 23: Summary of Key Clinical Studies Supporting Efficacy or Safety

Study	Trial Design	Treatment Regimen	Study Population	Study Endpoints	No. of patients enrolled
Studies to support efficacy and safety					
IPI-145-07	Phase 3, randomized, open-label, actively controlled trial comparing duvelisib to ofatumumab	Duvelisib 25 mg BID; ofatumumab per USPI	Relapsed or refractory CLL/SLL after ≥1 prior therapy	PFS per IRC ORR per IRC OS	319
IPI-145-06	Phase 2, open-label, single-arm trial of duvelisib	Duvelisib 25 mg BID	Refractory NHL, including FL, SLL, and MZL	ORR per IRC	129
Studies to support safety					
IPI-145-02	Phase 1, open-label, dose-escalation trial of duvelisib	Duvelisib doses of 8 mg to 100 mg BID	Advanced hematologic malignancies	Safety	158
IPI-145-12	Crossover extension of IPI-145-07	Duvelisib 25 mg BID	Relapsed or refractory CLL/SLL after ≥1 prior therapy	Safety	89

7.2. Review Strategy

The key materials used for the review of efficacy and safety included:

- NDA datasets (raw and derived), clinical study reports, and responses to the review team's IRs.
- Relevant published literature
- Relevant information in the public domain

The clinical review of efficacy was primarily based on an analysis of Study IPI-145-07 and IPI-145-06 for patients with CLL/SLL and FL, respectively.

The review of safety is primarily based on the pooled data from the four studies in Table 23. The review emphasis was placed on the 25 mg BID dose administered in 28-day treatment cycles.

All major efficacy and safety analyses were reproduced or audited. Statistical analyses by the reviewers were performed using SAS/JMP 13.0 (SAS Institute, Inc., Cary, NC) and MedDRA-Based Adverse Event Diagnostics (MAED) 1.8 (Enterprise Performance and Lifecycle System Design).

8 Statistical and Clinical Evaluation

8.1. Chronic Lymphocytic Leukemia

8.1.1. Review of Relevant Individual Trials Used to Support Efficacy

Study IPI-145-07

Title: A Phase 3 Study of Duvelisib (IPI-145) vs Ofatumumab in Patients with Relapsed or Refractory CLL/SLL

ClinicalTrials.gov identifier: NCT02004522
First patient randomized: 21 January 2014
Completed enrollment: 09 December 2015
Clinical cut-off dates for this submission:

19 May 2017 (Efficacy)
19 July 2017 (Primary safety data)
01 March 2018 (120-day safety update)

Overview and Objective

Study IPI-145-07 was a randomized, open-label, actively controlled phase 3 trial to evaluate the efficacy and safety of duvelisib compared to ofatumumab in 319 patients with relapsed or refractory CLL or SLL. The primary endpoint was progression-free survival as determined by independent review committee.

Primary Objective

- PFS per IRC with duvelisib monotherapy versus ofatumumab monotherapy

Secondary Objectives

- ORR per IRC, overall survival (OS), lymph node response rate, duration of response (DOR), hematologic improvement rate
- Safety of duvelisib in patients with CLL or SLL
- PK of duvelisib and, if applicable, its metabolites

Exploratory Objectives

- Evaluate the health-related quality of life of patients, PD biomarkers of duvelisib, mechanisms of resistance, and genomic features of tumors predictive of response in patients treated with duvelisib or ofatumumab
-

Study Population (Key Eligibility Criteria)

- 18 years of age or greater, ECOG 0-2
- Diagnosis of CLL or SLL that meets at least one of the IWCLL 2008 criteria for requiring treatment (Binet Stage ≥B or Rai Stage ≥I)
    - Disease that has progressed during or relapsed after at least one previous CLL or SLL therapy
- Not appropriate for treatment with a purine-based analogue regimen (per NCCN or ESMO guidelines), including relapse ≤36 months from a purine-based chemoimmunotherapy regimen or relapse ≤24 months from a purine-based monotherapy regimen
- Measurable disease with a lymph node or tumor mass >1.5 cm in at least one dimension
- Organ and Marrow function:
    - Serum AST or ALT ≤3 x upper limit of normal (ULN)
    - Total bilirubin ≤1.5 x ULN
    - Serum creatinine ≤2.0 x ULN
    - Hemoglobin ≥8.0 g/dL with or without transfusion support
    - Platelet count ≥10,000/μL with or without transfusion support
- Exclude patients with Richter's transformation or prolymphocytic leukemia
- Exclude patients with autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura that is uncontrolled or requiring >20 mg once daily of prednisone
- Exclude patients refractory to ofatumumab
- Exclude prior allogeneic HSCT (autologous HSCT >6 months prior is permitted)
- Exclude CNS lymphoma or leukemia
- Exclude patients with prior exposure to a PI3K inhibitor or a Bruton's tyrosine kinase (BTK) inhibitor
- Exclude patients with administration of medications or foods that are strong inhibitors or inducers of CYP3A within 2 weeks of randomization

Study Design

Study IPI-145-07 was a randomized, open-label, actively controlled phase 3 study to evaluate the efficacy and safety of duvelisib compared to ofatumumab in patients with relapsed or refractory CLL or SLL. Patients were randomized 1:1 and were stratified by:

1. High-risk cytogenetics (presence or absence of deletion 17p)
2. Refractory or early relapse to purine analog based therapy (defined as progression <12 months after fludarabine/pentostatin)
3. Grade 4 cytopenias (presence or absence of neutropenia or thrombocytopenia at baseline)

Treatment
The first treatment cycle for each treatment arm will be 21 days and subsequent treatment cycles will be 28 days.

Arm 1 – Duvelisib
Patients will receive duvelisib 25 mg, orally, twice daily until disease progression or unacceptable toxicity.

Duvelisib dose levels for toxicity are shown in the table below.

Duvelisib Dose Level	Dose (mg)
1	25 twice daily
-1	15 twice daily
-2	10 twice daily
-3	5 twice daily

Any patient requiring a dose less than 5 mg twice daily was permanently discontinued from treatment. Concomitant use of a strong CYP3A4 inhibitor or inducer was prohibited.

Arm 2 – Ofatumumab
Patients will receive eight weekly IV infusion of ofatumumab, starting with an initial dose of 300 mg followed by 7 weekly doses of 2000 mg. Thereafter, patients will receive 2000 mg on Day 1 of a 28-day treatment cycle for four cycles or until disease progression or unacceptable toxicity. Ofatumumab is being administered per the prescribing information and will not exceed 12 doses.

Patients who have documentation of progressive disease confirmed centrally at any time during the study may be eligible to receive the opposite study medication as part of a separate extension protocol (Study IPI-145-12).

Patients will be followed for survival for up to 6 years from randomization or until death.

Statistical Analysis Plan

Efficacy Endpoints

Primary Endpoint

- PFS, defined as time from randomization to first documentation of progressive disease as determined by independent review or death due to any cause. The censoring method of PFS is shown in Table 24.

Table 24: PFS Censoring Method

Situation	Date of Event or Censoring	Outcome
No adequate baseline disease status assessment	Date of randomization	Censored
No adequate post-baseline disease status assessment unless death occurs prior to first post-baseline assessment	Date of randomization + 1 day	Censored
No documented progression or death before data cutoff	Date of last adequate disease status assessment	Censored
Documented progression with ≤1 missing scheduled disease status assessment before progression	Date of the earliest assessment that results in a finding of unequivocal progression	Event
Death before progression being documented with ≤1 missing scheduled disease status assessment before death	Date of death	Event
Documented progression or death following a long gap between adequate disease status assessments (e.g., 2 or more consecutive missed scheduled disease status assessments)	Date of last adequate disease status assessment before the gap	Censored
New anticancer treatment or procedure started before documented progression	Date of last adequate disease status assessment prior to new treatment	Censored

Source: Table on Page 39 in the Applicant's Statistical Analysis Plan.

Secondary Endpoints

- ORR, with overall response defined as the best response of complete response/remission (CR), CR with incomplete marrow recovery (CRi), partial response/remission (PR), or PR with lymphocytosis (PRwL), according to the International Workshop on CLL (IWCLL) or revised International Working Group (IWG) Response Criteria, with modification for treatment-related lymphocytosis.
- OS, defined as time from randomization to death.
- Lymph node response rate, defined as ≥50% decrease in the sum of the products of target lymph nodes.
- Hematologic improvement rate, defined as any of the following hematologic improvement sustained for at least 60 days without transfusion or exogenous growth factors:
    - Neutrophil count >1,500/μL or an increase ≥50% from baseline; or
    - Hemoglobin >11 g/dL or an increase ≥50% from baseline; or
    - Platelet count >100,000/μL or an increase ≥50% from baseline.
- DOR, defined as time from the first documentation of response to first documentation of PD or death due to any cause.

Statistical Review Comment: The Applicant defined overall response as the best response of CR, CRi, PR, or PRwL. However, FDA does not accept PRwL as part of the definition of overall response.

Sample Size

A total of 185 PFS events were determined to provide approximately 93% power to detect a hazard ratio (HR) of 0.6 using a one-sided log-rank test at a 2.5% overall significance level with one interim analysis planned at 50% information time for both efficacy and futility. The study design employed the Lan-DeMets spending function for O'Brien-Fleming boundary as the alpha spending function and the Hwang-Shih-DeCani gamma (-4) spending function as the beta spending function. The futility boundary of this study was non-binding.

Analysis Population

Intent-To-Treat (ITT)

The ITT population will be used for the primary analysis of all efficacy endpoints, which includes all patients who are randomized, with treatment
group designated according to randomization.

All-Treated (AT)

The AT population includes all patients who receive any amount of study drug (duvelisib or ofatumumab), with treatment group designated according to actual study treatment received.

Per-Protocol (PP)

The PP population includes all patients in the ITT population who do not violate

the terms of the protocol in a way that would significantly affect the study outcome, with treatment group designated according to randomization.

Analysis Methods for Primary Endpoint of PFS

Two analyses are planned for PFS, one interim analysis and one final analysis. The interim analysis will be performed after approximately 50% of the planned PFS events have been observed. If the study is not stopped at the interim analysis, the final analysis will be performed when approximately 185 PFS events have occurred.

The primary analysis of PFS will use a stratified log-rank test to compare PFS of the duvelisib arm against PFS of the ofatumumab arm based on IRC assessment with a one-sided overall significance level of 0.025 in the ITT population. The strata for the test will be those used for stratified randomization per interactive response technology (IRT), with potential pooling of strata. If the interim analysis and final analysis occur exactly at 93 and 185 PFS events, the *p*-value boundaries for efficacy at the two analyses are 0.0015 and 0.0245. The actual *p*-value boundary for efficacy at the interim analysis will be calculated based on the actual number of PFS events at the interim analysis and the planned number of PFS events for the final analysis; the actual *p*-value boundary for efficacy at the final analysis will be calculated based on the actual number of PFS events at the interim analysis and at the final analysis. The HR (duvelisib/ofatumumab) and its 95% confidence interval (CI) will be estimated using a stratified Cox proportional hazards model.

The following sensitivity analyses of PFS will be performed:

- *PFS based on investigator assessment*
  This endpoint will be analyzed using the same methods as the primary analyses described for PFS based on IRC assessment.
- *Worst-case sensitivity analysis*
  Patients who are alive and have not had documented progression by data cutoff and who are lost to follow-up (missing at least one disease assessment right before data cut-off) will be treated as censored at their last adequate disease assessment if they are on ofatumumab and treated as having a PFS event at the time of the next scheduled assessment following the last adequate disease assessment if they are on duvelisib. PFS based on IRC assessment with the above worst-case censoring/event rule will be analyzed using the same methods as the primary analysis for PFS.
- *Event-free survival*
  This is defined as time from randomization to the first documentation of PD as determined by IRC, start of new anticancer treatment or procedure, or death due to any cause. *Event-free survival (EFS)* will be analyzed using the same methods as the primary analyses for PFS.
- *Analysis in the PP population*
- *Analysis in the AT population*
- *Unstratified analyses*
  An unstratified log-rank test will be used to compare the two arms. An unstratified Cox

regression will be used to estimate the HR with its 95% CI.

- *Cox regression with baseline covariates*
  A stratified Cox regression will be used to test treatment effect on PFS based on IRC assessment, adjusting for demographic and other baseline characteristics. A stepwise variable selection will be performed to choose the variables in the Cox regression. Candidate variables are age, gender, race, disease diagnosis (CLL or SLL), years from initial diagnosis, months from most recent relapse/refractory diagnosis, stage at diagnosis, stage at baseline, and number of prior systemic therapies.

Subgroup analyses for PFS will be performed in the following subgroups:

- Stratification factors
  1. High-risk cytogenetics (presence vs absence of del[17p]; captured from central lab)
  2. Refractory/early relapse to purine analog-based therapy (defined as progression <12 months after fludarabine/pentostatin: yes vs no; captured on the eCRF)
  3. Grade 4 cytopenia(s) (presence vs absence of neutropenia or thrombocytopenia at baseline; captured on the eCRF)
- Diagnosis (CLL or SLL)
- Gender (Male or Female)
- Age group (<65 or ≥65)
- Race (White or Non-White)
- Previously treated with ofatumumab (yes vs no)
- Time from last dose of most recent prior anti-cancer therapy to randomization <12 months: yes vs no
- del[17p] or TP53 mutation (either or both present vs neither present; del[17p] will be as captured from central lab)

Analysis Methods for Key Secondary Endpoints

Of the secondary endpoints, ORR and OS are designated as key secondary efficacy endpoints.

Overall Response Rate (ORR)

The primary analyses of ORR will use the Cochran-Mantel-Haenszel test to compare the two treatment groups based on IRC assessment with a one-sided significance level of 0.025 in the ITT population. The strata for the test will be those used for stratified randomization per IRT, with potential pooling of strata.

The following sensitivity analyses will be performed for ORR:

- *ORR based on investigator assessment*
- *Overall confirmed response rate (OCRR)* based on IRC assessment
  Overall confirmed response is defined as best confirmed response (time between response and confirmation must be ≥8 weeks in duration) of CR, CRi, PR, or PRwL, according to the IWCLL or revised IWG Response Criteria, with modification for treatment-related lymphocytosis.

- *ORR without PRwL based on IRC assessment*
- *OCRR without PRwL based on IRC assessment*
- *ORR in subset of patients with baseline assessment other than Unknown (UNK) and no evidence of disease (NED)*
  This analysis will be performed if there are at least 5% patients with baseline assessment of UNK or NED.
- *ORR in subset of patients who are on treatment for 60 days or longer*
- *Analysis in the PP population*
- *Analysis in the AT population*

Subgroup analyses for ORR will be performed in the same subgroups specified for PFS.

Overall Survival (OS)
Two interim analyses and one final analysis are planned for OS. The first OS interim analysis will be performed at the time of the planned PFS interim analysis after 93 PFS events have occurred. The second interim analysis of OS will be performed at the planned PFS final analysis after 185 PFS events have occurred. The final analysis of OS will take place after the completion of follow-up for all patients.

The primary analysis of OS will use a stratified log-rank test to compare OS of the duvelisib arm against OS of the ofatumumab arm with a one-sided significance level of 0.025 in the ITT population. The strata will be those used for stratified randomization per IRT, with potential pooling of strata. The estimated number of OS events at the three analyses are 24, 58 and 161. The information fractions will be calculated at the two OS interim analyses and the OS final analysis. If the OS analyses occur at 24, 58, and 161 OS events, the *p*-value stopping boundaries for the three analyses will be 0.0001, 0.0249 and 0.0003, respectively. The actual *p*-value boundaries for efficacy at the interim analyses will be calculated based on the actual number of OS events at the preceding (if any) and current analyses, and the planned number of PFS events for future analysis/analyses; the actual *p*-value boundary for efficacy at the final analysis will be calculated based on the actual number of PFS events at the two interim analyses and at the final analysis. The HR (duvelisib/ofatumumab) and its 95% CI will be estimated using a stratified Cox proportional hazards model. OS follow-up time will be summarized using the reverse Kaplan-Meier method.

The following sensitivity analysis of PFS will be performed:

- *Primary analyses except additional censoring at the start date of subsequent* anti-cancer *therapy*

Subgroup analyses for OS will be performed in the same subgroups specified for PFS.

<u>Multiplicity Adjustment</u>
The primary endpoint PFS and key secondary endpoints ORR and OS will be tested at a one-sided overall significance level of 0.025 based on a gatekeeping approach. ORR will be tested at

the one-sided 0.025 level only if PFS is declared statistically significant. OS will be tested according to the planned *p*-value boundaries only if PFS and ORR are declared statistically significant. If any null hypothesis is not rejected in this sequence of tests, formal sequential testing will be stopped. The analyses of other secondary efficacy endpoints will claim no statistical significance.

Protocol Amendments
The study protocol was amended 3 times:

- Original protocol (21 August 2013)

- Amendment 1 (02 April 2014) added the secondary endpoint of lymph node response rate. The efficacy boundaries for evaluating PFS were changed from Pocock type to O'Brien-Fleming. Key secondary endpoints including overall survival, overall response rate, lymph node response rate, and hematologic improvement rate are under type I error protection and will be tested if and only if the primary endpoint is significant. The eligibility criteria were revised for previous purine-analogue therapy to specifically clarify the criteria for a patients not appropriate for treatment or retreatment with purine-analogue based therapy. Prior exposure to a BTK inhibitor was added to the exclusion criteria because of a lack of safety data in this population. Baseline QTcF exclusion criteria was changed from >480 ms to >500 ms based on safety data for QT prolongation. Dose reductions level were revised that include -1 =15 mg BID, -2 =10 mg BID, and -3 =5 mg BID

- Amendment 2 (02 March 2015) extended the length of survival follow-up from 3 to 6 years from randomization. It removed all urinalysis testing and the requirement for on-treatment monitoring of coagulation values because neither duvelisib nor ofatumumab have an identified risk of proteinuria or changes in coagulation or severe hemorrhage. The QTcF exclusion criteria was changed from QTcF >500 ms to >480 ms and the protocol was revised to interrupt treatment for all QTcF prolongation ≥grade 3 (≥500 ms).

- Amendment 3 (09 February 2017) revised the maximum number of duvelisib treatment cycles from 39 to allowing continuous duvelisib treatment until disease progression or unacceptable toxicity in patients experiencing clinical benefit. Additionally, text was added to confirm that centralized IRC review of response will be employed up to the time of the final analysis.

Study Results - ITT

Compliance with Good Clinical Practices
The protocol, protocol amendments, and patient informed consent forms for Study IPI-145-07 were reviewed and approved by the Institutional Review Boards or Independent Ethics Committees of the participating study centers.

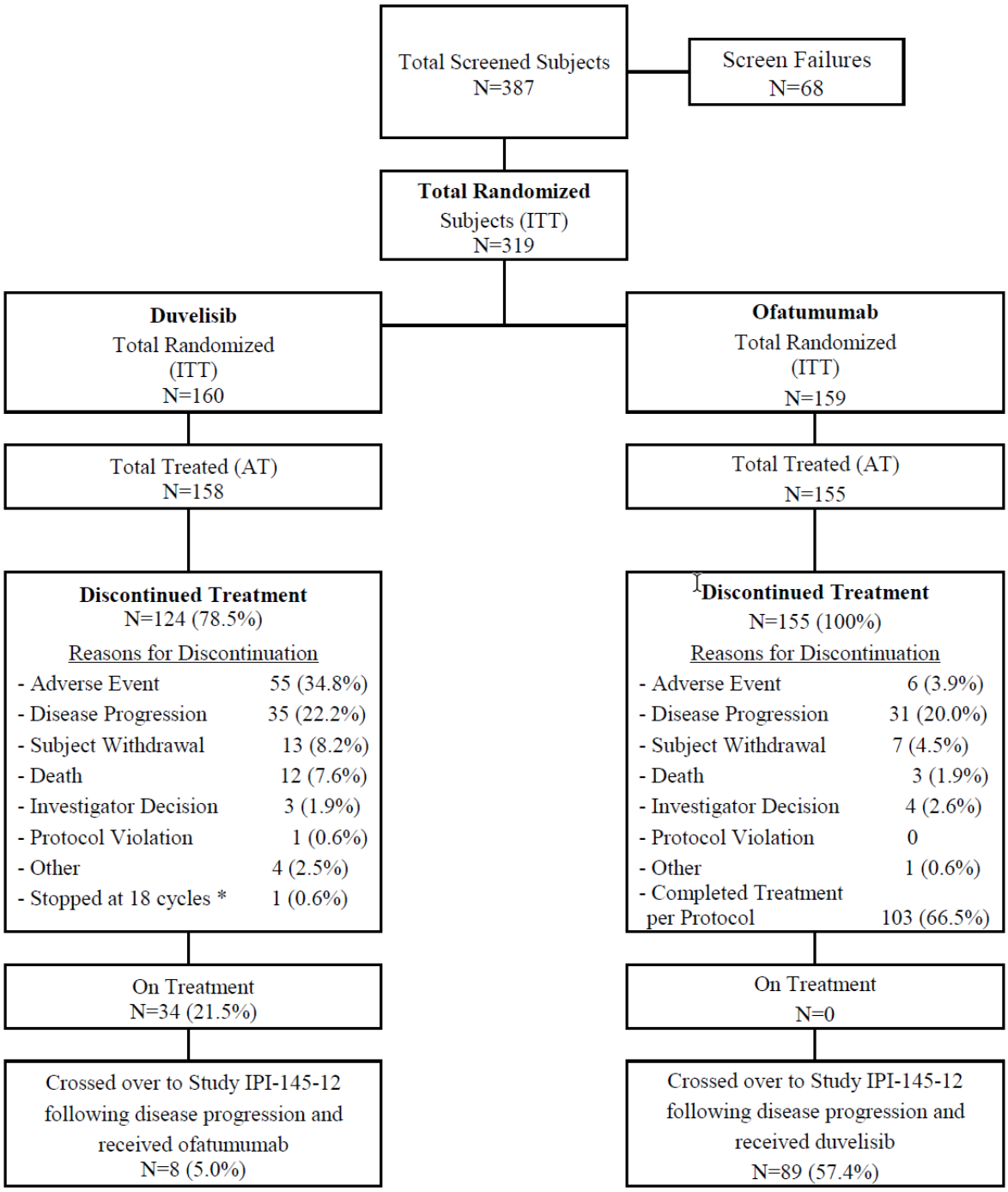
Study IPI-145-07 was conducted in accordance with the International Council for Harmonization guideline for Good Clinical Practice, the principles of the Declaration of Helsinki, and the U.S. Code of Federal Regulations, Title 21, Parts 50, 56, and 312 providing the protection of the rights and welfare of human patients participating in biomedical research. All patients or their legal representatives voluntarily consented prior to trial enrollment.

Financial Disclosure
The Applicant submitted financial disclosure information from 2,920 investigators from five studies indicating that none of the investigators had disclosable financial interests or arrangements. For details, refer to the Clinical Investigator Financial Disclosure Review Template in Section 19.2.

Data Quality and Integrity
The data quality is acceptable. In general, the reviewers were able to perform independent review and confirm the Applicant's analysis results using the submitted datasets.

Patient Disposition
A total of 387 patients were screened, of which 319 patients were randomized and included in the ITT population (160 subjects in the duvelisib arm and 159 patients in the ofatumumab arm). The patients disposition and discontinuation summary are shown in Figure 2. As of May 19, 2017, 34 patients remained on duvelisib treatment and no patients remained on ofatumumab treatment.

Figure 2: Disposition of Patients



Source: Figure 1 in the Applicant's Clinical Study Report on Page 88.

Protocol Violations/Deviations

There were 19 patients with protocol violations. In the duvelisib arm, one patient had a potential overdose while under the influence of alcohol, another had no reported measurable

disease and 8 patients did not receive PJP prophylaxis per protocol. In the ofatumumab arm, one patient was reported as refractory to ofatumumab and 8 patients did not receive PJP prophylaxis per protocol. The protocol violations do not appear to be a significant cause of bias influencing the study results.

Demographics and Baseline Characteristics

In the ITT population for Study IPI-145-07 (N=319), the median age was 69 years, 60% were male, and 92% were White. Demographic characteristics were balanced between treatment arms (Table 25).

Table 25: Demographics (ITT)

	Duvelisib N=160	Ofatumumab N=159	Total N=319
Age, years			
Median (Min, Max)	69 (39, 90)	69 (39, 89)	69 (39, 90)
≥65 years, n (%)	112 (70)	105 (66)	217 (68)
Sex, n (%)			
Male	96 (60)	95 (60)	191 (60)
Female	64 (40)	64 (40)	128 (40)
Race, n (%)			
White	150 (94)	142 (89)	292 (92)
Black	1 (<1))	1 (<1)	2 (<1)
Not Reported	6 (4)	9 (6)	15 (5)
Other or Unknown	3 (2)	7 (4)	10 (3)
Region, n (%)			
Europe	115 (72)	120 (75)	235 (74)
United States	30 (19)	21 (13)	51 (16)
Other	15 (9)	18 (11)	33 (10)
ECOG, n (%)			
0-1	149 (93)	142 (89)	291 (91)
2	11 (7)	17 (11)	28 (9)

Source: FDA reviewer's analyses.

Table 26 summarizes disease characteristics and prior therapies in the ITT efficacy population. The majority of patients had CLL (duvelisib: 155/160, 98%; ofatumumab: 157/159, 99%) and 33 patients (21%) and 44 patients (28%) had a 17p deletion in the duvelisib and ofatumumab arms, respectively. The median number of prior therapies was 2 (range 1 to 10), with 61% of patients have 2 or more prior therapies. Nineteen percent of patients were refractory/early relapse, defined as progression <12 months after fludarabine/pentostatin.

Table 26: Disease Characteristics (ITT)

Characteristic	Duvelisib N=160 n (%)	Ofatumumab N=159 n (%)	Total N=319 n (%)
Diagnosis			
CLL	155 (98)	157 (99)	312 (98)
SLL	5 (3)	2 (1)	7 (2)
Cytogenetics			
17p deletion	33 (21)	44 (28)	77 (24)
TP53 mutation	31 (19)	29 (18)	60 (19)
IGHV mutation	29 (18)	25 (16)	54 (17)
Tumor Burden			
ALC ≥25 x 10^9/L	91 (57)	84 (53)	175 (55)
Bulky disease	74 (46)	72 (45)	146 (46)
Number of Prior Therapies			
Median (Min, Max)	2 (1, 10)	2 (1, 8)	2 (1, 10)
1	64 (40)	58 (36)	122 (38)
2	45 (28)	46 (29)	91 (28)
≥3	50 (31)	55 (35)	105 (33)
Refractory/Early Relapse			
Yes	25 (16)	36 (23)	61 (19)
Prior Treatment			
Purine-based	96 (60)	113 (71)	209 (65)
Alkylator	148 (92)	151 (95)	299 (94)
Chlorambucil	62 (39)	51 (32)	113 (35)
Bendamustine	59 (37)	61 (38)	120 (38)
Cyclophosphamide	95 (59)	111 (70)	206 (65)
Anti-CD20	125 (78)	132 (83)	257 (81)
Rituximab	123 (74)	131 (83)	254 (80)
Ofatumumab	3 (2)	4 (2)	7 (2)
Obinutuzumab	1 (<1)	3 (2)	4 (1)

Source: FDA reviewer's analyses.

Exposure

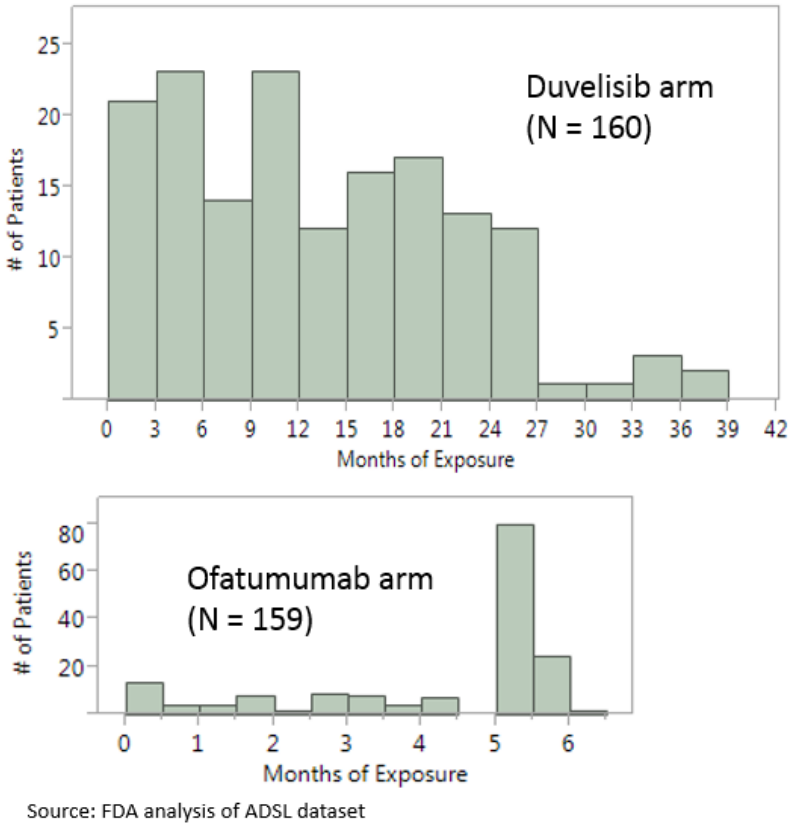
Exposure by treatment arm is summarized in Table 27 and Figure 3. The median exposure duration for patients on the duvelisib arm was 12 months compared to 5 months on the ofatumumab arm. Ofatumumab was given and completed by 6 months per the U.S. prescribing information.

Table 27: Exposure During Randomized Treatment (ITT)

Parameter		Duvelisib N=160	Ofatumumab N=159
Exposure duration, months	Median	12	5
	Range	0.2, 37	0, 6
	Q1, Q3	5, 19	4, 6
Cycles initiated[a]	Median	13	7
	Range	1, 43	1, 7
	Q1, Q3	5, 21	6, 7
Relative dose intensity	Mean (SD)	99.5 (1.7)	98.6 (11.3)
	≥90%	98%	96%
	≥80%	99%	96%
Patients on treatment by month	≥2 months	93%	81%
	≥3 months	87%	75%
	≥6 months	72%	65%
	≥12 months	48%	NA
	≥18 months	31%	NA
	≥24 months	12%	NA

Source: FDA analysis of ADSL dataset
[a] Cycle length is 28 days
NA: not applicable; SD: standard deviation

Figure 3: Duration of Randomized Treatment in ITT Efficacy Population



Source: FDA analysis of ADSL dataset

Treatment Compliance, Concomitant Medications, and Rescue Medication Use
Of concomitant medications taken by ≥20% of patients in either treatment arm, the use of specific types of medicine was comparable between arms. The most common was systemic antibacterial agents (duvelisib 94%, ofatumumab 89%), due to protocol required PJP prophylaxis, and antivirals (duvelisib 84%, ofatumumab 82%).

Based on a relative dose intensity of 99% in both treatment arms, noncompliance was not reported as a concern by the Applicant or found upon review of exposure.

Efficacy Results – Primary Endpoint

PFS
The final analysis of the primary endpoint PFS were performed based on the efficacy data cut on May 19, 2017.

Primary Analysis
The results of Study IPI-145-07 demonstrate that treatment with duvelisib was associated with a statistically significant improvement in PFS per IRC compared to ofatumumab with a HR of 0.52 (95% CI: 0.39, 0.69) with a one-sided *p*-value less than 0.0001 (stratified log-rank test).

Table 28 provides a summary of PFS per IRC. Of the 319 patients in the ITT population, 93 patients (58%) in the duvelisib arm and 110 patients (69%) in the ofatumumab arm experienced PFS events. The median PFS was 13.3 months for duvelisib and 9.9 months for ofatumumab. The Kaplan-Meier (KM) curves for PFS per IRC are shown in Figure 4.

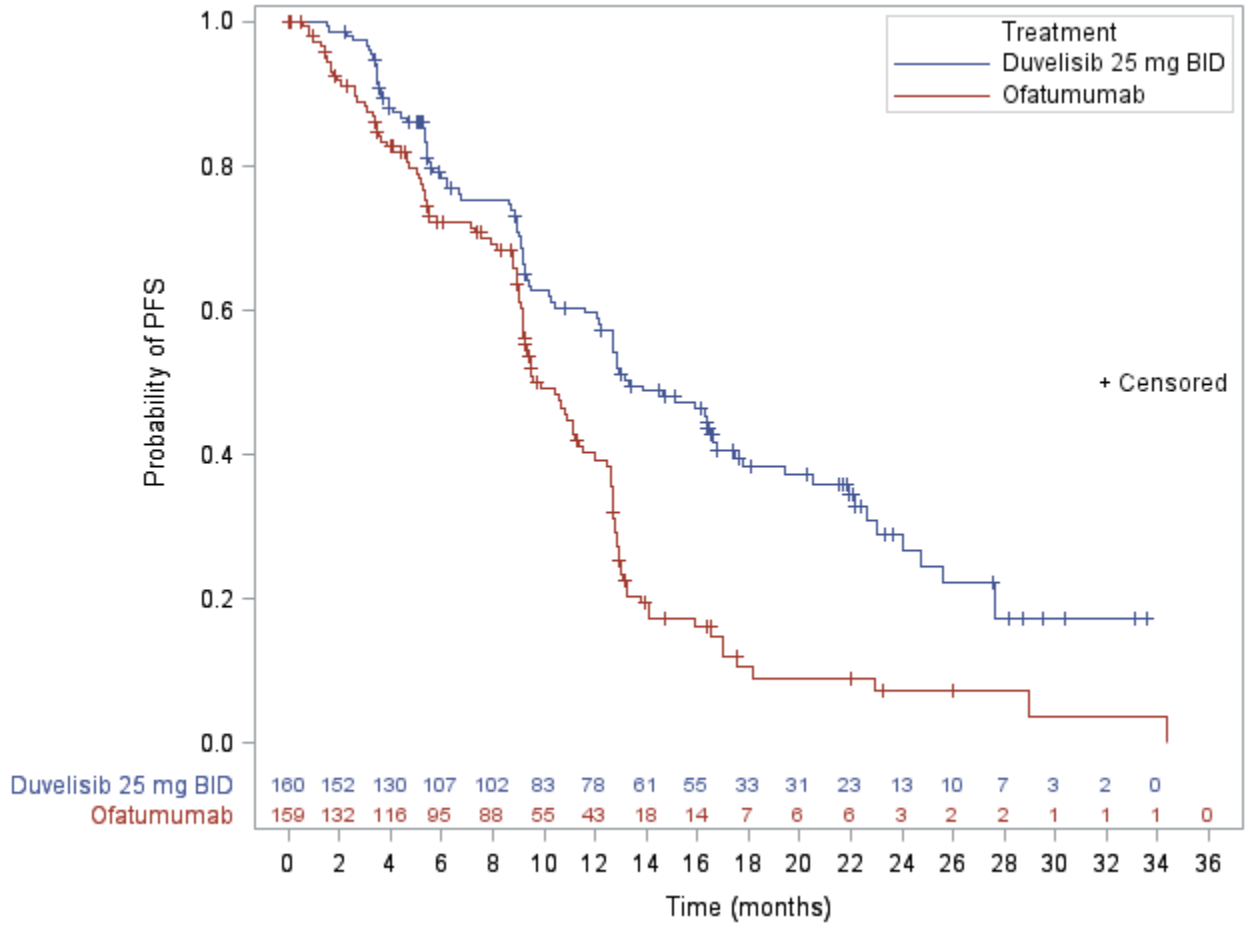
In the PFS per IRC analysis, it's noted that a higher proportion of patients on the duvelisib arm died before progression (12%) compared to the ofatumumab arm (6%), raising a concern for increased death due to toxicity with duvelisib.

Table 28: Primary Analysis Results of PFS per IRC (ITT)

	Duvelisib (N=160)	Ofatumumab (N=159)
Number of Patients with PFS Events	93 (58.0%)	110 (69.2%)
Progression	74 (46.3%)	101 (63.5%)
Death	19 (11.9%)	9 (5.7%)
Number of Patients Censored	67 (41.9%)	49 (30.8%)
KM Estimate, month		
Median PFS (95% CI)	13.3 (12.1, 16.8)	9.9 (9.2, 11.3)
Median follow-up (95% CI)	21.6 (16.6, 22.1)	16.5 (14.0, 23.2)
Hazard Ratio [1] (95% CI)	0.52 (0.39, 0.69)	
p-value [2]	<0.0001	

Source: FDA reviewer's analyses.
[1] Stratified Cox proportional hazards model.
[2] One-sided stratified log-rank test.

Figure 4: Kaplan-Meier Curves for PFS per IRC (ITT)

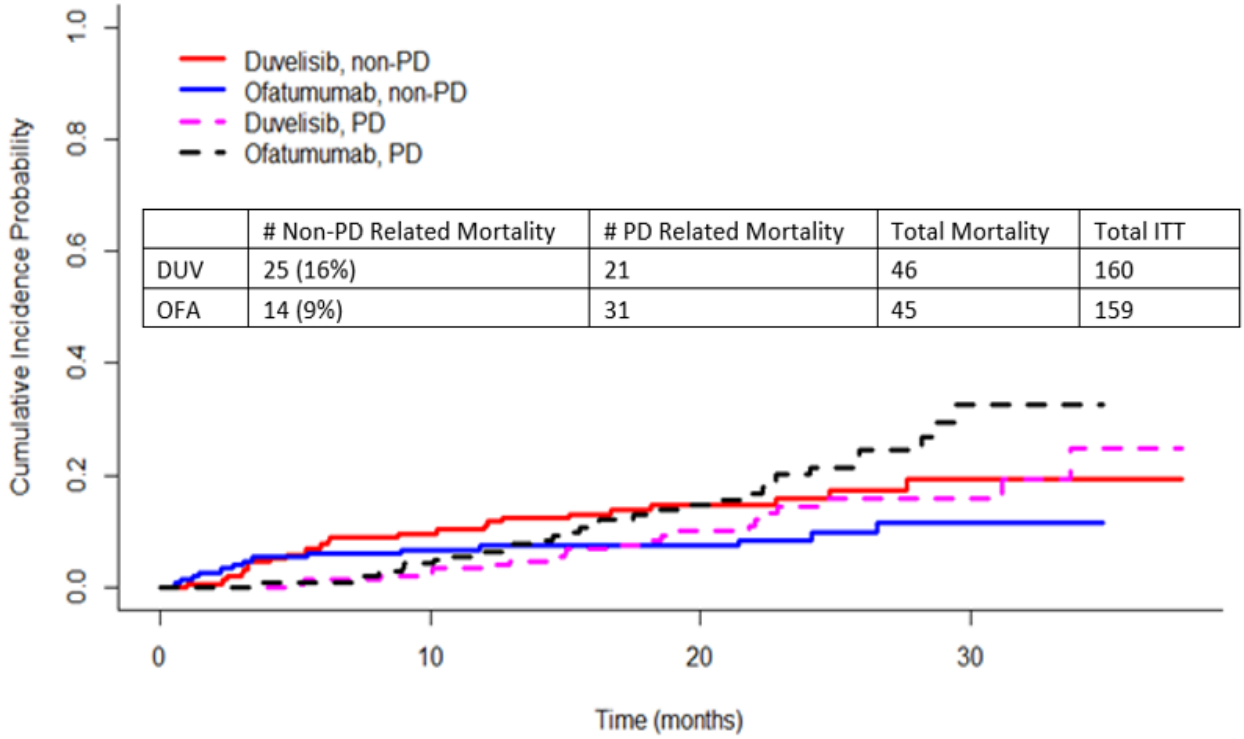


Source: FDA reviewer's analyses.

Clinical Reviewer Comment: Despite the statistically significant PFS in favor of duvelisib, the benefit of 3 months is modest for patients with CLL/SLL after one prior therapy. Additionally, the benefit may be offset by the risk of serious toxicity, as partly indicated by the 12% of patients with death before progression with duvelisib compared to 6% with ofatumumab.

Because of the risk of serious, including fatal, toxicity and the higher incidence of death before progression with duvelisib, death with or without progression was further explored. The FDA statistical reviewer conducted a competing risk analysis of death without progression (non-PD mortality) versus death with progression (PD mortality). Figure 5 displays the competing risk analysis, in which duvelisib has a numerically higher estimated cumulative incidence of death without progression (16%) compared to ofatumumab (9%).

Figure 5 Cumulative Incidence of Non-PD Mortality Versus PD Mortality Using Competing Risks (ITT)



	# Non-PD Related Mortality	# PD Related Mortality	Total Mortality	Total ITT
DUV	25 (16%)	21	46	160
OFA	14 (9%)	31	45	159

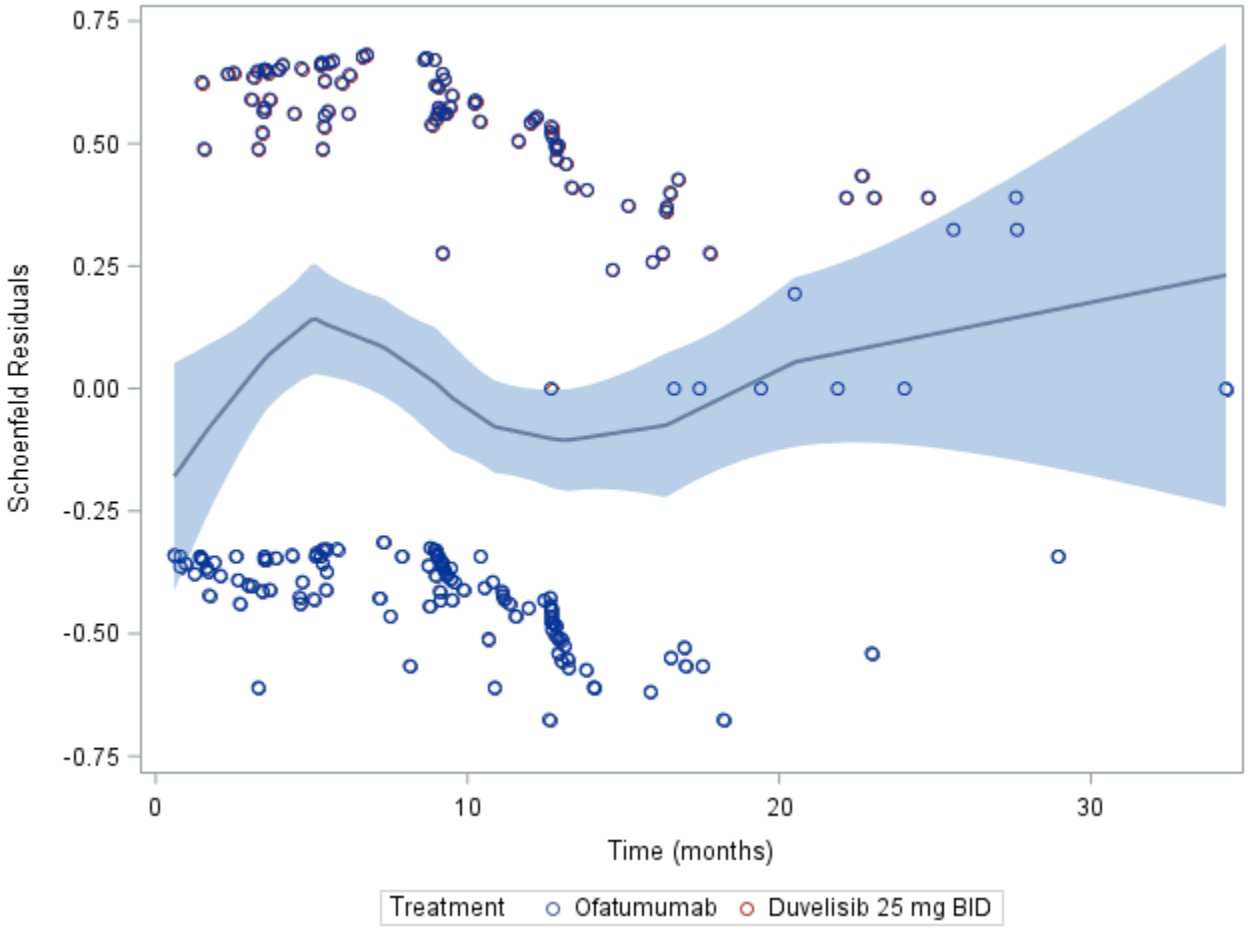
Source: FDA reviewer's analyses
PD: Progressive disease

Clinical Reviewer Comment: The PFS per IRC analysis and the competing risk analysis support that patients receiving duvelisib have a higher incidence of death without progression compared to ofatumumab. This is likely driven by serious, including fatal, toxicity with duvelisib.

Proportional Hazard Evaluation for PFS

The KM curves for PFS per IRC (Figure 4) show a slight separation starting around 2 months, followed by a larger separation around 10 months, which indicates a potential violation of the proportional hazards assumption. The FDA statistical reviewer further examined the proportional hazards assumption by checking Schoenfeld residuals for treatment (Figure 6). The non-zero slope indicates a potential violation of the proportional hazards assumption. Therefore, the HR estimate from the Cox proportional hazards model may not be a clear comparison between the two treatment arms.

Figure 6: Schoenfeld Residuals of PFS for Treatment (ITT)



Source: FDA reviewer's analyses.

Based on the Schoenfeld Residuals results, the FDA statistical reviewer conducted an alternative measurement using Restricted Mean Survival Time (RMST), which does not require a proportional hazards assumption. Table 29 displays the RMST results. The maximum difference between treatment arms in the RMST was 2.3 months at 29 months.

Table 29: Restricted Mean Survival Time at Different Truncated Times (ITT)

Truncated Time (months)	Duvelisib	Ofatumumab	Difference
1	0.96	0.94	0.03
2	1.93	1.85	0.07
3	2.88	2.75	0.13
4	3.83	3.64	0.18
5	4.75	4.50	0.24
6	5.63	5.35	0.28
7	6.48	6.16	0.31
8	7.32	6.97	0.35
9	8.17	7.76	0.41
10	9.00	8.49	0.51
11	9.83	9.19	0.64
12	10.64	9.88	0.76
13	11.45	10.57	0.89
14	12.24	11.19	1.05
15	13.01	11.77	1.25
16	13.76	12.32	1.44
17	14.42	12.82	1.59
18	14.97	13.27	1.70
19	15.50	13.69	1.80
20	16.02	14.11	1.91
21	16.53	14.53	2.00
22	17.01	14.95	2.06
23	17.35	15.30	2.05
24	17.65	15.58	2.07
25	17.93	15.85	2.09
26	18.22	16.10	2.11
27	18.50	16.28	2.22
28	18.77	16.45	2.31
29	18.95	16.63	2.32
30	19.08	16.80	2.27
31	19.17	16.98	2.19
32	19.24	17.15	2.08
33	19.31	17.33	1.98
33.6	19.34	17.43	1.90

Source: FDA reviewer's analyses.

Statistical Reviewer Comment: The RMST results support the overall results that duvelisib prolongs PFS compared to ofatumumab.

PFS Censoring

As shown in Table 30, the majority of censored observation for PFS were due to absence of progression or death before the data cutoff in the duvelisib arm, and to new anticancer treatment prior to progression in the ofatumumab arm.

Table 30: Reasons for Censoring of PFS

	Duvelisib (N=160)	Ofatumumab (N=159)
Number of Patients Censored	67 (42%)	49 (31%)
No adequate baseline disease assessment	2	4
No adequate post-baseline disease assessment	4	6
New anticancer treatment or procedure started before documented progression	10	27
No documented progression or death before data cutoff	51	12

Source: FDA reviewer's analyses.

Further evaluation of PFS censoring shows imbalanced censoring between the treatment arms, with patients receiving ofatumumab being censored earlier (Table 31 and Table 32). This raises concern for premature censoring and informative censoring. Despite this concern, the pre-specified sensitivity analyses support the efficacy findings with duvelisib.

Table 31: Censoring Time (in Months) in Analysis of PFS (ITT)

Treatment Arm (# Censored)	Mean (SD)	Median (Min, Max)
Duvelisib 25 mg BID (N=67)	14.40 (9.27)	16.39 (0.03, 33.61)
Ofatumumab (N=49)	7.19 (6.67)	5.82 (0.03, 25.95)

Table 32: Censoring Rate in Analysis of PFS According to Censoring Time (ITT)

Censoring Time, months	Duvelisib (N=160)	Ofatumumab (N=159)
≤10	24 (15.0%)	37 (23.3%)
10-20	22 (13.8%)	9 (5.7%)
20-30	18 (11.3%)	3 (1.9%)
>30	3 (1.9%)	0 (0.0%)
Total	67 (41.9%)	49 (30.8%)

Source: FDA reviewer's analyses.

Statistical Reviewer Comment: Concerning potential premature censoring and informative censoring, the PFS estimate including the median may not be reliable. Also, early censoring in the ofatumumab arm may potentially favor ofatumumab in the PFS comparison depending

on the censoring reasons, and therefore could potentially make the results conservative. Note that the imbalanced censoring may be one of the reasons causing the potential non-proportional hazard.

Sensitivity Analyses

The results of the Applicant's pre-specified sensitivity analyses are supportive to the primary efficacy results of PFS.

To further inform the PFS sensitivity analysis, the FDA statistical reviewer requested an additional sensitivity analysis using interval censoring to account for the impact of assessment frequency. Each patient's PFS duration was represented as an interval, derived from the observed assessment time as follows:

- For patients with disease progression, the time interval uses the date of the last disease assessment as the left end, which is prior to the event time, and the date of the assessment at which progression was observed as the right end.
- For patients without a progression or death event (administratively censored), the time interval uses the date of the event as reported in the database as the left end, and infinity as the right end.
- For patients with death in the absence of disease progression, the time interval uses the date of death for both left and right ends of the time interval.

Using this method, the Applicant's analysis demonstrated that treatment with duvelisib was associated with a statistically significant improvement in PFS with a HR of 0.49 (95% CI: 0.37, 0.65) with a one-sided *p*-value less than 0.0001 (stratified generalized log-rank test). The difference in median PFS was 3.6 months in favor of duvelisib. The results were supportive of the primary PFS analysis.

PFS Subgroup Analyses

Gender, Race, Age, and Geographic Region

Table 33 displays the FDA statistical reviewer's subgroup analysis results for PFS per IRC by age, sex, race, and region. Generally, the results are consistent with the primary analyses of PFS across subgroups. All subgroups had a larger median PFS with duvelisib compared to ofatumumab except for the subgroup "Non-White" where there were only 12 patients.

Table 33: Demographic Subgroup Analysis of PFS per IRC (ITT)

Subgroup	Total	Event/Total		Median		Hazard Ratio (SE) [1]
		DUV	OFA	DUV	OFA	
Age Category						
≥65 years	217	66/112	67/105	13.3	10.8	0.56 (0.18)
<65 years	102	27/48	43/54	12.9	9.1	0.47 (0.25)
Sex						
Male	191	59/96	64/95	13.8	10.9	0.61 (0.18)
Female	128	34/64	46/64	12.8	9.5	0.44 (0.24)
Race[2]						
White	292	88/150	99/142	13.3	9.5	0.52 (0.15)
Non-White	12	4/4	5/8	6.1	11.2	3.40 (0.73)
Region						
Europe	235	68/115	86/120	12.9	9.5	0.50 (0.17)
North America	51	15/30	14/21	17.8	10.7	0.32 (0.44)
Asia Pacific	33	10/15	10/18	12.7	9.6	1.11 (0.46)

Source: FDA reviewer's analyses.
[1] Unstratified Cox proportional hazards model.
[2] If the patient's race is not "White" or "Non-reported", then the race will be "Non-White"; if the patient's race is "Non-reported", then the race will be missing.

Other Special/Subgroup Populations

Table 34 displays the FDA statistical reviewer's subgroup analysis results for PFS per IRC by other baseline characteristics. Across these analyses, the direction of the treatment effect was consistent, with the results favoring duvelisib.

Table 34: Subgroup Analysis of PFS per IRC, by Other Baseline Characteristics (ITT)

Subgroup	Total	Event/Total		Median		Hazard Ratio (SE) [1]
		DUV	OFA	DUV	OFA	
17p Deletion						
Absent	213	61/111	67/102	16.3	11.3	0.55 (0.18)
Present	77	19/33	35/44	12.7	9.0	0.41 (0.30)
Refractory/early relapse						
Absent	258	77/135	83/123	15.1	10.8	0.53 (0.16)
Present	61	16/25	27/36	10.4	8.1	0.51 (0.32)
Time from Last Dose of Prior Anticancer Therapy						
≥12 months	203	60/107	69/96	13.8	12.0	0.59 (0.18)
<12 months	115	32/52	41/63	12.8	8.1	0.40 (0.26)
Number of Prior Therapies						
1	122	37/64	40/58	12.7	12.0	0.80 (0.23)
2	91	26/45	31/46	16.5	9.2	0.37 (0.31)
≥3	105	29/50	39/55	16.4	5.8	0.38 (0.25)

Source: FDA reviewer's analyses.
[1] Unstratified Cox proportional hazards model.

Statistical Review Comment: The interpretation of those subgroup results is difficult, since the sample size in each subgroup was not planned to power such analyses for detecting the same magnitude of the treatment effect. Therefore, the reviewer recommends that those subgroup analyses are only exploratory.

Efficacy Results – Secondary Endpoints

Overall Response Rate

Overall response rate per IRC was analyzed as a key secondary endpoint and included patients that achieved a CR, CRi, or PR. ORR was higher for duvelisib (73%; 95% CI: 66, 80) compared to ofatumumab (45%; 95% CI: 38, 53) and statistically significant with an odds ratio of 3.4 (95% CI: 2.09, 5.43) with a one-sided p-value less than 0.0001 (stratified Cochran-Mantel-Haenszel test). Based on IRC, the estimated median DOR was 11.1 months with duvelisib and 9.3 months with ofatumumab. Table 35 provides a summary of ORR per IRC.

Table 35: Primary Analysis of Overall Response Rate per IRC, Responders (ITT)

Response, n (%)	Duvelisib (N=160)	Ofatumumab (N=159)
CR	1 (0.6)	1 (0.6)
CRi	0 (0.0)	0 (0.0)
PR	116 (72.5)	71 (44.7)
SD	34 (21.3)	63 (39.6)
PD	2 (1.3)	10 (6.3)
Other	6 (3.8)	14 (8.8)
ORR (CR, CRi, or PR)		
n (%)	117 (73.1%)	72 (45.3%)
p-value [1]	<0.0001	
Odds ratio (95% CI)	3.4 (2.1, 5.4)	
Median DOR in responders, months (95% CI)	11.1 (9.2, 18.3)	9.3 (7.7, 11.0)

Source: FDA reviewer's analyses.
[1] Cochran-Mantel-Haenszel test controlling for pooled randomization strata.
Abbreviations: CR = complete response, CRi = CR with incomplete marrow recovery, PR = partial response, SD = stable disease, PD = progressive disease, Other includes Unknown and No Evidence of Disease.

Statistical Review Comments: The Applicant used PRwL in its definition of ORR, but PRwL was excluded in the FDA definition of ORR. All patients in the ITT population were included in the denominator for the calculation of ORR. Therefore, any missing data was considered as non-responders in the primary analyses.

Sensitivity Analyses

The results of the Applicant's pre-specified sensitivity analyses are supportive to the primary efficacy results of ORR.

Subgroup Analyses

Gender, Race, Age, and Geographic Region

Table 36 displays the FDA statistical reviewer's subgroup analysis for ORR per IRC by age, sex, race, and region. The results are consistent with the analysis of ORR per IRC. The ORR estimate for duvelisib was greater than the ORR estimate for ofatumumab in all subgroups.

Table 36: Demographic Subgroup Analyses for Overall Response Rate per IRC (ITT)

Subgroup	Total	Responder/Total		ORR		Odds Ratio
		DUV	OFA	DUV	OFA	
Age Category						
≥65 years	217	84/112	49/105	75.0%	46.7%	3.43
<65 years	102	33/48	23/54	68.8%	42.6%	2.97
Sex						
Male	191	67/96	42/95	69.8%	44.2%	2.92
Female	128	50/64	30/64	78.1%	46.9%	4.05
Race[1]						
White	292	110/150	65/142	73.3%	45.8%	3.26
Non-White	12	3/4	4/8	75.0%	50.0%	3.00
Region						
Europe	235	86/115	53/120	74.8%	44.2%	3.75
North America	51	20/30	10/21	66.7%	47.6%	2.20
Asia Pacific	33	11/15	9/18	73.3%	50.0%	2.75

Source: FDA reviewer's analyses.

[1] If the patient's race is not "White" or "Non-reported", then the race will be "Non-White"; if the patient's race is "Non-reported", then the race will be missing.

Other Special/Subgroup Populations

Table 37 displays the FDA statistical reviewer's subgroup analysis for ORR per IRC by other baseline characteristics. Across these analyses, the ORR estimate for duvelisib was greater than the ORR estimate for ofatumumab in all subgroups.

Table 37: Subgroup Analyses for Overall Response Rate per IRC, by Other Baseline Characteristics (ITT)

Subgroup	Total	Responder/Total		ORR		Odds Ratio
		DUV	OFA	DUV	OFA	
17p Deletion						
Absent	213	83/111	49/102	74.8%	48.0%	3.21
Present	77	23/33	19/44	69.7%	43.2%	3.03
Refractory/Early Relapse						
Absent	258	98/135	61/123	72.6%	49.6%	2.69
Present	61	19/25	11/36	76.0%	30.6%	7.20
Time from Last Dose of Prior Anticancer Therapy						
≥12 months	203	82/107	57/96	76.6%	59.4%	2.24
<12 months	115	34/52	15/63	65.4%	23.8%	6.04
Number of Prior Therapies						
1	122	42/64	33/58	65.6%	56.9%	1.45
2	91	37/45	24/46	82.2%	52.2%	4.24
≥3	105	38/50	15/55	76.0%	27.3%	8.44

Source: FDA reviewer's analyses.

Statistical Review Comment: The interpretation of the subgroup results is difficult, since the sample size in each subgroup was not planned to power such analyses for detecting the same magnitude of the treatment effect. Therefore, the reviewer recommends that those subgroup analyses be considered exploratory.

Overall Survival

The analysis of OS fails to demonstrate a significant difference in OS between patients treated with duvelisib compared to ofatumumab with a hazard ratio of 0.99 (95% CI: 0.65, 1.50) with a one-sided *p*-value 0.4807 (stratified log-rank test). Table 38 provides a summary of the OS results. Of the 319 patients in the ITT population, 46 patients (29%) in the duvelisib arm and 45 patients (28%) in the ofatumumab arm experienced the event of death. The median OS for both duvelisib and ofatumumab were not estimable, with a median follow-up of 24 months for both treatment arms. The KM curves of OS are shown in Figure 7.

Table 38: Primary Analyses of Overall Survival (ITT)

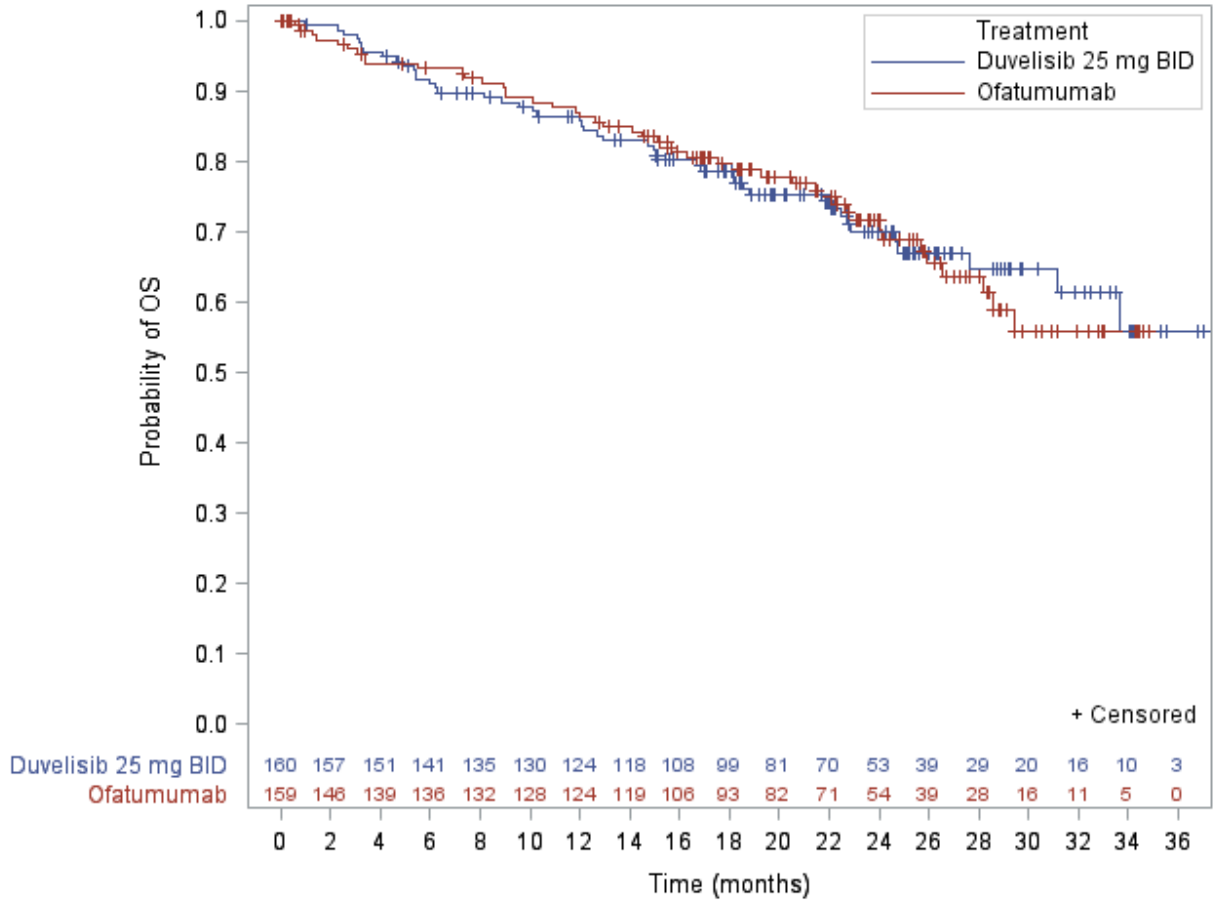
	Duvelisib (N=160)	Ofatumumab (N=159)
Number of patients died	46 (28.8%)	45 (28.3%)
Number of patients censored	114 (71.3%)	114 (71.7%)
KM estimate, month Median PFS (95% CI) Median follow-up (95% CI)	 NE (NE, NE) 23.8 (22.0, 25.2)	 NE (NE, NE) 23.7 (22.0, 25.4)
Hazard ratio[1] (95% CI)	0.99 (0.65, 1.50)	
p-value [2]	0.4807	

Source: FDA reviewer's analyses.

[1] Stratified Cox proportional hazards model.

[2] One-sided stratified log-rank test.

Figure 7: Kaplan-Meier Curves for Overall Survival (ITT)



Source: FDA reviewer's analyses.

Statistical Review Comment: The median OS was not estimable in either treatment arm, which indicates that the data may be premature to make reliable conclusion. The reviewer recommends the Applicant continue the OS follow-up and perform the final OS analysis after the planned 161 OS events occurs for OS evaluation.

Since the benefit demonstrated in PFS did not translate into an OS benefit, the FDA statistical reviewer issued an IR for the Applicant to explain possible reasons an OS benefit was not seen. In response (06 April 2018), the Applicant surmised that OS was affected by administration of subsequent anti-cancer therapy received following discontinuation of study treatment. Based on a review of subsequent anti-cancer therapy (Table 39) and comparison of the time of new anti-cancer therapy between treatment arms (Table 40), the death rates among patients who took subsequent cancer therapy in the two treatment arms were similar, and the ofatumumab arm showed slightly earlier average time to receiving new anti-cancer therapy than the duvelisib arm.

Table 39: Summary of Patients Who Took Subsequent Cancer Therapy

Event	Duvelisib (n=49)	Ofatumumab (n=106)
Death, n (%)	13 (26.5%)	28 (26.4%)
Death among patients who had progression, n (%)	*10 (25.6%)*	*23 (29.1%)*
Death among patients whose PFS was censored, n (%)	*3 (30.0%)*	*5 (18.5%)*

Source: FDA reviewer's analyses.

Table 40: Time to Receipt of New Anti-Cancer Therapy in Months

Treatment	N	Mean (SD)	Median (Min, Max)
Duvelisib 25 mg BID	49	13.6 (6.4)	11.7 (3.8, 27.3)
Ofatumumab	106	10.6 (5.9)	10.2 (0.8,30.9)

Source: FDA reviewer's analyses.

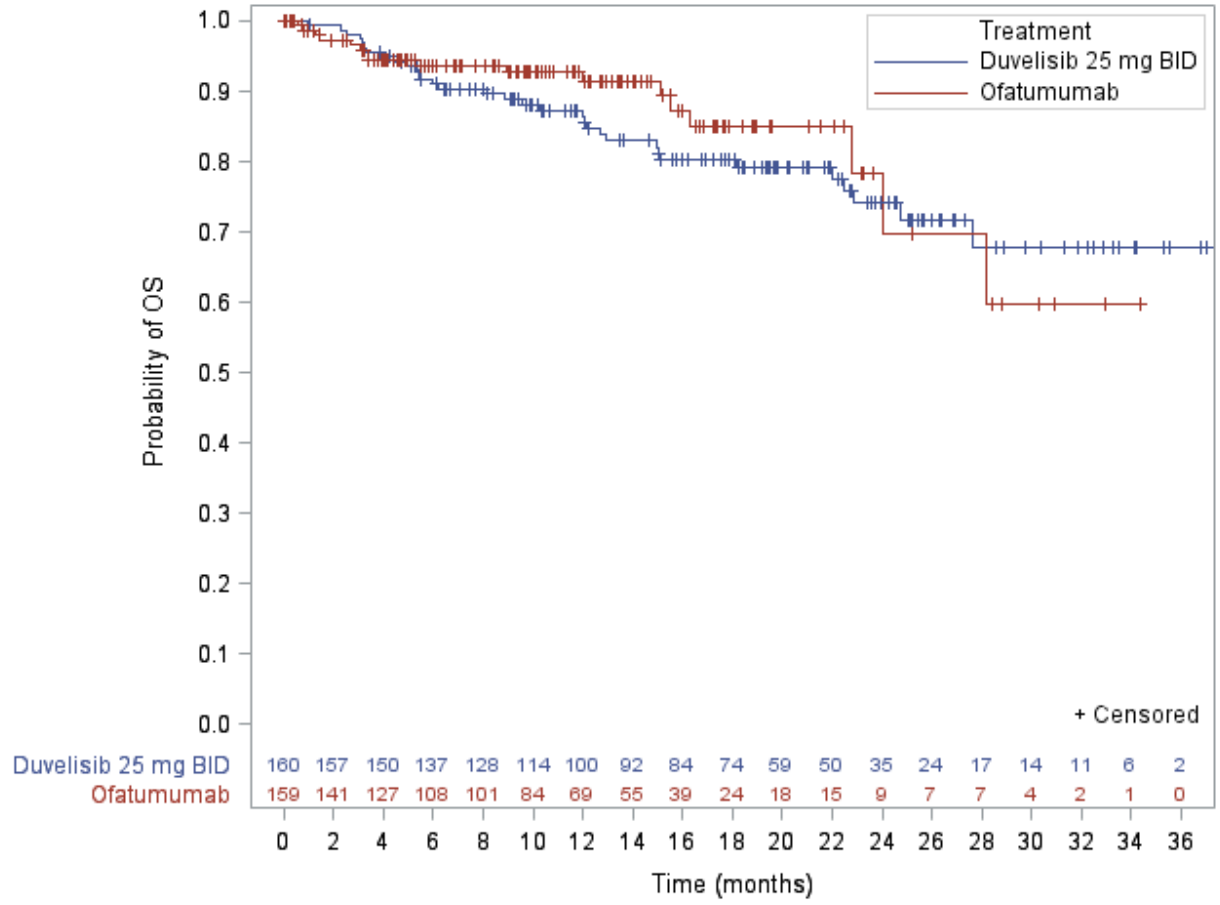
Further, the FDA statistical reviewer performed a sensitivity analysis where patients were censored at the time of receiving subsequent anti-cancer therapy (Table 41, Figure 8), which suggest that the administration of subsequent anti-cancer therapy may not explain why duvelisib did not demonstrate an OS benefit.

Table 41: Exploratory Analysis of Overall Survival Censored at Time of New Anti-Cancer Therapy (ITT)

	Duvelisib (N=160)	Ofatumumab (N=159)
Number of patients died	33 (20.6%)	17 (10.7%)
Number of patients censored	127 (49.3%)	142 (89.3%)
Hazard ratio [1] (95% CI)	1.29 (0.71, 2.34)	

Source: FDA reviewer's analyses.
[1] Stratified Cox proportional hazards model.

Figure 8: Kaplan-Meier Curves for Overall Survival Censored at Time of New Anti-Cancer Therapy (ITT)



Source: FDA reviewer's analyses.

Subgroup Analyses

Gender, Race, Age, and Geographic Region

Table 42 shows the reviewer's subgroup analysis results for OS by age, sex, race, and region. Generally, the results appear to be consistent with the primary OS analysis.

Table 42: Demographic Subgroup Analysis of Overall Survival (ITT)

Subgroup	Total	Event/Total		Median		Hazard Ratio (SE) [1]
		DUV	OFA	DUV	OFA	
Age Category						
≥65 years	217	31/112	28/105	NE	NE	0.95 (0.26)
<65 years	102	15/48	17/54	33.7	NE	1.05 (0.36)
Sex						
Male	191	32/96	24/95	33.7	NE	1.42 (0.27)
Female	128	14/64	21/64	NE	NE	0.57 (0.35)
Race[2]						
White	292	44/150	40/142	NE	NE	1.02 (0.22)
Non-White	12	1/4	2/8	31.1	28.6	0.00 (1.09e5)
Region						
Europe	235	33/115	34/120	NE	NE	0.99 (0.24)
North America	51	6/30	7/21	NE	28.2	0.60 (0.57)
Asia Pacific	33	7/15	4/18	31.1	NE	1.52 (0.65)

Source: FDA reviewer's analyses.
[1] Unstratified Cox proportional hazards model.
[2] If the patient's race is not "White" or "Non-reported", then the race will be "Non-White"; if the patient's race is "Non-reported", then the race will be missing.

Other Special/Subgroup Populations

Table 43 shows the reviewer's subgroup analysis results for OS by other baseline characteristics. Generally, the results appear to be consistent with the primary analysis of OS.

Table 43: Subgroup Analysis of Overall Survival by Other Baseline Characteristics (ITT)

Subgroup	Total	Event/Total		Median		Hazard Ratio (SE) [1]
		DUV	OFA	DUV	OFA	
17p Deletion						
Absent	213	30/111	26/102	NE	NE	1.00 (0.27)
Present	77	13/33	16/44	33.7	28.6	1.09 (0.38)
Refractory/early relapse						
Absent	258	35/135	26/123	NE	NE	1.20 (0.26)
Present	61	11/25	19/36	31.1	22.8	0.75 (0.38)
Time from Last Dose of Prior Anticancer Therapy						
≥12 months	203	27/107	20/96	NE	NE	1.26 (0.30)
<12 months	115	19/52	25/63	31.1	28.6	0.79 (0.31)
Number of Prior Therapies						
1	122	18/64	11/58	NE	NE	1.50 (0.38)
2	91	12/45	11/46	NE	NE	1.15 (0.42)
≥3	105	16/50	23/55	31.1	28.2	0.64 (0.33)

Source: FDA reviewer's analyses.
[1] Unstratified Cox proportional hazards model.

Statistical Review Comment: The interpretation of those subgroup results is difficult, since the sample size in each subgroup was not planned to power such analyses for detecting the same magnitude of the treatment effect. Therefore, the reviewer recommends that those subgroup analyses are only exploratory.

Lymph Node Response Rate

The Applicant conducted an evaluation of lymph node response rate, which was defined as ≥50% decrease in the sum of the product diameters of target lymph nodes. In patients randomized to duvelisib, 136 patients (85%, 95% CI: 79.5, 90.5) had a lymph node response per IRC compared to 25 patients (16%, 95% CI: 10.1, 21.4) randomized to ofatumumab.

Study Results – Two or More Prior Therapies

Despite the evidence of effectiveness in patients with relapsed or refractory CLL/SLL after one prior therapy, the risk of serious, including fatal, toxicity with duvelisib warranted further consideration of an appropriate CLL/SLL population. Study IPI-145-07 required at least one prior therapy in patients with CLL/SLL. In the trial population, the median number of prior therapies was 2 (range 1, 10) with 60% of patients having 2 or more prior therapies. Because of the severity of the safety profile with duvelisib, the efficacy in patients with CLL/SLL with 2 or more prior therapies was evaluated.

Demographics and Baseline Characteristics

In the subset population of patients with two or more prior therapies for Study IPI-145-07 (N=196), the median age was 69 years, 59% were male, and 88% had an ECOG performance status of 0 to 1. Demographic characteristics were relatively balanced between treatment arms (Table 44).

Table 44: Demographics (Patients With **≥2** Prior Therapies)

	Duvelisib N=95	Ofatumumab N=101
Age, years		
Median (Min, Max)	70 (40, 90)	68 (44, 89)
≥65 years, n (%)	68 (72)	69 (68)
Sex, n (%)		
Male	59 (62)	56 (55)
Female	36 (38)	45 (45)
Race, n (%)		
White	90 (95)	93 (92)
Black	0	1 (1)
Not Reported	3 (3)	3 (3)
Other or Unknown	2 (2)	4 (4)
Region, n (%)		
Europe	71 (75)	82 (81)
United States	18 (19)	9 (9)
Other	6 (6)	10 (10)
ECOG, n (%)		
0-1	87 (92)	90 (89)
2	8 (8)	11 (11)

Source: FDA review of ADSL dataset

Table 45 summarizes disease characteristics and prior therapies in the subset population of patients with two or more therapies. The majority of patients had CLL (duvelisib: 97%; ofatumumab: 98%) and 18 patients (19%) and 25 patients (25%) had a 17p deletion in the duvelisib and ofatumumab arms, respectively. The median number of prior therapies was 3 (range 2 to 10), with 75% of patients having 2 or 3 prior therapies. There were 29% to 36% of patients who were refractory/early relapse, defined as progression <12 months after fludarabine/pentostatin.

Table 45: Disease Characteristics (Patients With **≥2** Prior Therapies)

	Duvelisib N=95 n (%)	Ofatumumab N=101 n (%)
Diagnosis		
CLL	92 (97)	99 (98)
SLL	3 (3)	2 (2)
Cytogenetics		
17p deletion	18 (19)	25 (25)
TP53 mutation	17 (18)	16 (16)
IGHV mutation	17 (18)	15 (15)
Tumor Burden		
Bulky disease	49 (52)	53 (45)
Number of Prior Therapies		
Median (Min, Max)	3 (2, 10)	3 (2, 8)
2	45 (47)	46 (46)
3	28 (29)	28 (28)
≥4	22 (23)	27 (27)
Refractory/Early Relapse		
Yes	28 (29)	36 (36)

Source: FDA review of ADSL dataset

Exposure

Exposure by treatment arm is summarized in Table 46 and Figure 9. The median exposure duration for patients on the duvelisib arm was 13 months compared to 5 months on the ofatumumab arm. Ofatumumab was given and completed by 6 months per the U.S. prescribing information.

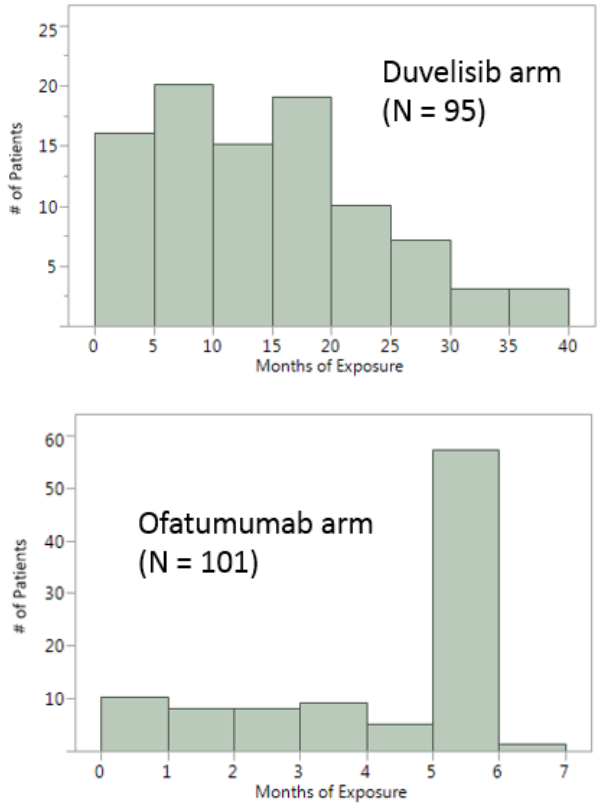
Table 46: Exposure During Randomized Treatment (Patients With **≥2** Prior Therapies)

Parameter		Duvelisib N=95	Ofatumumab N=101
Exposure duration, months	Median	13	5
	Range	0.2, 37	0, 6
	Q1, Q3	7, 20	3, 5
Cycles initiated[a]	Median	14	7
	Range	1, 41	1, 7
	Q1, Q3	8, 22	4, 7
Relative dose intensity	Mean (SD)	99.6 (1.7)	98.8 (10.2)
	≥90%	97%	96%

	≥80%	98%	96%
Patients on treatment by month	≥2 months	93%	79%
	≥3 months	89%	71%
	≥6 months	78%	54%
	≥12 months	49%	NA
	≥18 months	35%	NA
	≥24 months	14%	NA

Source: FDA analysis of ADSL dataset
[a] Cycle length is 28 days
NA: not applicable; SD: standard deviation

Figure 9: Duration of Randomized Treatment (Patients With **≥2** Prior Therapies)



Efficacy Results – Primary Endpoint

Progression Free Survival

The results of Study IPI-145-07 in patients with two or more therapies demonstrate that treatment with duvelisib was associated an improvement in PFS per IRC compared to ofatumumab with a HR of 0.40 (95% CI: 0.27, 0.59). In this subgroup, 55 patients (58%) in the

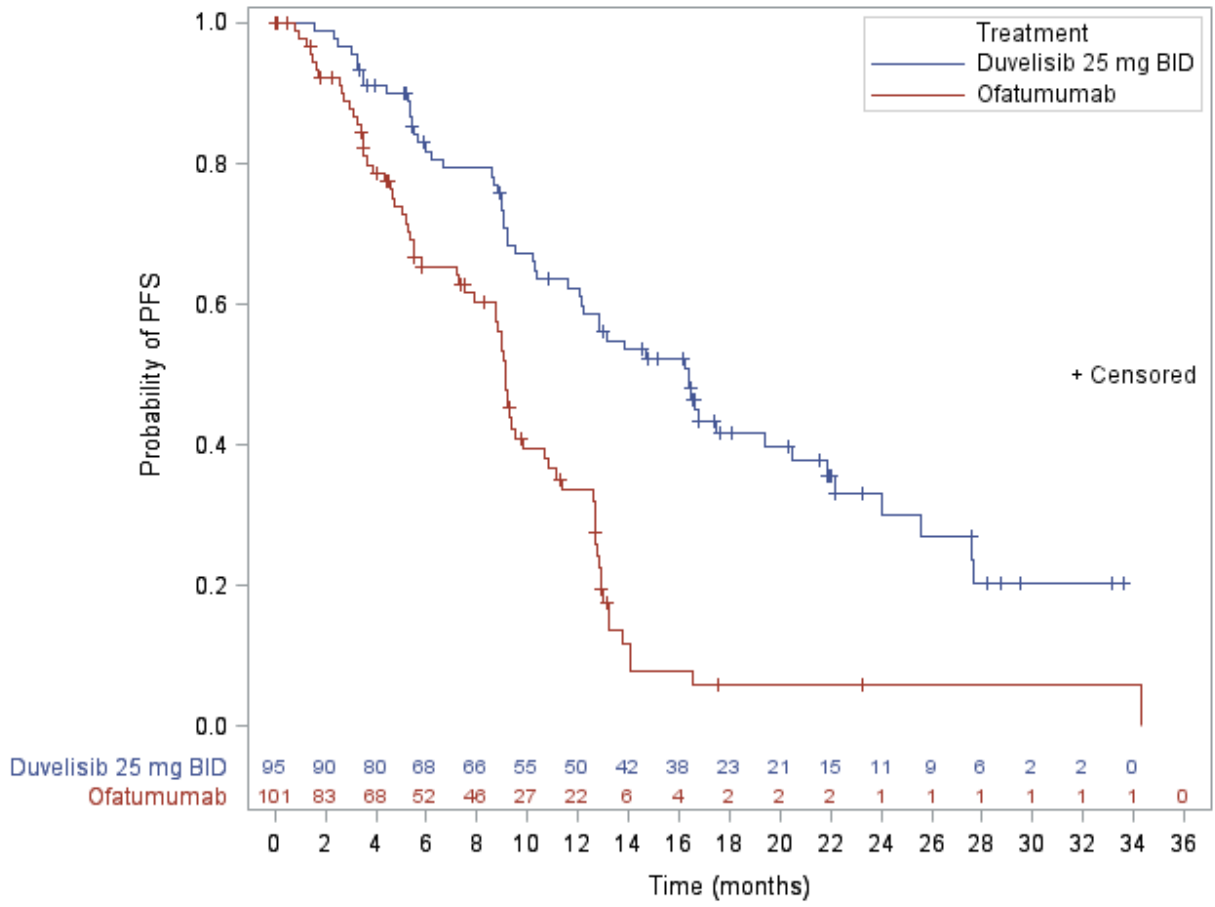
duvelisib arm and 70 patients (69%) in the ofatumumab arm experienced PFS events. The median PFS was 16.4 months for duvelisib and 9.1 months for ofatumumab. Table 47 and Figure 10 summarize PFS per IRC in patients with two or more prior therapies.

Table 47: Subgroup Analysis of PFS per IRC in Patients With **≥2** Prior Therapies

	Duvelisib (N=95)	Ofatumumab (N=101)
Number of patients with PFS events *Progression* *Death*	55 (57.9%) 44 (46.3%) 11 (11.6%)	70 (69.3%) 62 (61.4%) 8 (7.9%)
Number of patients censored	40 (42.1%)	31 (30.7%)
KM estimate, month Median PFS (95% CI)	 16.4 (12.0, 20.5)	 9.1 (7.9, 10.7)
Hazard ratio[1] (95% CI)	0.40 (0.27, 0.59)	

Source: FDA reviewer's analyses.
[1] Unstratified Cox proportional hazards model

Figure 10: Kaplan-Meier Curves for PFS per IRC in Patients With **≥2** Prior Therapies



Source: FDA reviewer's analyses.

Clinical Reviewer Comment: The efficacy of duvelisib in patients with CLL or SLL with two or more prior therapies is clinically meaningful based on an improvement in PFS, despite the risk of serious toxicity. The subset of patients with two or more prior therapies should be considered when evaluating the benefit-risk profile for duvelisib in patients with CLL or SLL.

Efficacy Results – Secondary Endpoints

Overall Response Rate

Overall response rate per IRC in patients with two or more therapies was higher for duvelisib (78%) compared to ofatumumab (39%). The median DOR in the responders was 11.3 months for duvelisib and 8.0 months for ofatumumab. Table 48 provides a summary of ORR per IRC in patients with two or more prior therapies.

Table 48: Subgroup Analysis of ORR per IRC in Patients With **≥2** Prior Therapies

Response, n (%)	Duvelisib (N=95)	Ofatumumab (N=101)
PR	74 (77.9)	39 (38.6)
SD	15 (15.8)	46 (45.5)
PD	1 (1.1)	5 (5.0)
Other	5 (5.3)	11 (10.9)
ORR (CR or PR)		
n (%)	74 (77.9)	39 (38.6)
Odds ratio (95% CI)	5.60 (2.99, 10.50)	
Median DOR in responders, month (95% CI)	11.3 (7.4, 18.8)	8.0 (7.4, 10.9)

Source: FDA reviewer's analyses.
Abbreviations: PR = partial response, SD = stable disease, PD = progressive disease, Other includes Unknown and No Evidence of Disease

Overall Survival

Overall survival in patients with two or more prior therapies demonstrated no difference in OS between treatment arms with a HR of 0.99 (95% CI: 0.65, 1.50). Of the 196 patients in the subgroup population, 28 patients (29%) in the duvelisib arm and 34 patients (34%) in the ofatumumab arm experienced the event of death. The median OS time for both duvelisib and ofatumumab were not estimable, with a median follow-up of 24 months. Table 49 provides a summary of OS for patients with two or more prior therapies.

Table 49: Subgroup Analysis of Overall Survival in Patients With **≥2** Prior Therapies

	Duvelisib (N=95)	Ofatumumab (N=101)
Number of patients died	28 (29.5%)	34 (33.7%)
Number of patients censored	67 (70.5%)	67 (66.3%)
KM estimate, month Median PFS (95% CI) Median follow-up (95% CI)	 NE (27.6, NE) 23.9 (21.7, 25.4)	 NE (24.1, NE) 23.7 (21.5, 26.2)
Hazard ratio [1] (95% CI)	0.82 (0.49, 1.37)	

Source: FDA reviewer's analyses.
[1] Stratified Cox proportional hazards model.

8.1.2. Integrated Assessment of Effectiveness

In adult patients with CLL or SLL after at least one prior therapy, Study IPI-145-07, a multicenter, open-label, randomized, actively controlled phase 3 trial demonstrated that duvelisib 25 mg twice daily resulted in a statistically significant improvement in PFS per IRC compared to ofatumumab.

A total of 319 patients were enrolled in the trial. The majority had CLL (98%), a 17p deletion (24%) and had received two or more prior therapies (61%). Nineteen percent of patients were refractory or had early relapse, defined as progression <12 months after fludarabine/pentostatin.

The analysis of PFS per independent review committee demonstrated a statistically significant improvement in PFS with duvelisib compared to ofatumumab with a hazard ratio of 0.52 (95% CI: 0.39, 0.70; one-sided stratified log-rank test p<0.0001). For patients in the duvelisib arm, the estimated median PFS was 13.3 months (95% CI: 12.1, 16.8) whereas patients in the ofatumumab arm had an estimated median PFS of 9.9 months (95% CI: 9.2, 11.3), with a median follow-up of 22 months and 17 months, respectively. In addition, the analysis of the key secondary endpoint overall response rate per IRC was higher for duvelisib (73%; 95% CI: 66, 80) compared to ofatumumab (45%; 95% CI: 38, 53), resulting in a statistically significant odds ratio of 3.4 (95% CI: 2.1, 5.4; p<0.0001 per one-sided stratified Cochran-Mantel-Haenszel test). Further, sensitivity analyses of PFS and ORR were supportive of the observed treatment effect with duvelisib.

Importantly, although the difference in PFS was statistically significant in favor of duvelisib, the difference in estimated median PFS was 3 months and is a modest improvement in patients with CLL or SLL after at least one prior therapy. Further, because of the risk of serious, including fatal, toxicity with duvelisib, additional CLL or SLL populations were evaluated. As noted, Study IPI-145-07 required at least one prior therapy. In the trial population, the median number of prior therapies was 2 (range 1, 10) with 60% of patients receiving duvelisib having 2 or more

prior therapies. Because of the severity of the safety profile with duvelisib, the efficacy in patients with CLL or SLL with 2 or more prior therapies was evaluated.

In the subset of patients with two or more prior therapies (N=196), 95 patients were randomized to the duvelisib arm and 101 to the ofatumumab arm. The majority of patients had CLL (97%), 22% had a 17p deletion, 46% received 2 prior lines of therapy, and 54% received three or more prior therapies.

In the analysis of PFS per IRC in patients with two or more prior therapies, patients receiving duvelisib had a median PFS of 16.4 months (SE: 2.1) compared to a median PFS of 9.1 months (SE: 0.5) in patients receiving ofatumumab, with a HR of 0.4 (SE: 0.2). The evaluation of ORR per IRC demonstrated an ORR of 78% with duvelisib and 39% with ofatumumab, a difference of 39% (SE: 6.5%) in favor of duvelisib.

The PFS and ORR results in patients with two or more prior therapies demonstrated improved PFS and ORR results compared to the ITT population in Study IPI-145-07. The subset population is a more heavily pretreated population, thus the efficacy findings are substantial and clinically meaningful.

The Applicant proposed an indication for patients with CLL or SLL based on the ITT population in Study IPI-145-07, (b) (4). Because of the severity of the toxicity profile with duvelisib and that 61% of the ITT population in Study IPI-145-07 received two or more prior therapies, the data support restricted use of duvelisib to patients with at least two prior therapies. Therefore, the clinical review team recommends to restrict the indication for duvelisib to adult patients with relapsed or refractory CLL or SLL after at least two prior therapies.

8.2. Follicular Lymphoma

8.2.1. Review of Relevant Individual Trials Used to Support Efficacy

Study IPI-145-06

Title: A Phase 2 Study of Duvelisib (IPI-145) in Subjects with Refractory Indolent NHL

ClinicalTrials.gov identifier: NCT01882803
First patient treated: 24 June 2013
Clinical cut-off dates for this submission:
07 April 2016 (Efficacy – Original)
18 May 2018 (Efficacy – Update; used for FDA analyses)
19 July 2017 (Primary safety data)
01 March 2018 (120-day safety update)

Overview and Objectives
Study IPI-145-06 was a single-arm, open-label, phase 2 study to evaluate the efficacy and safety of duvelisib in patients with FL, marginal zone lymphoma (MZL), or SLL refractory to rituximab and chemotherapy combined or radioimmunotherapy. The primary endpoint is overall response rate as determined by independent review committee.

Primary Objective
- Evaluate ORR per IRC per 2007 Revised Response Criteria for Malignant Lymphoma

Secondary Objectives
- DOR, PFS, OS
- Safety and tolerability of duvelisib, PK of duvelisib and, if applicable, its metabolites

Exploratory Objectives
- PD biomarkers of duvelisib, mechanisms of resistance, genomic features of tumors, and health-related quality of life of patients

Study Population (Key Eligibility Criteria)
- 18 years or greater, ECOG performance status 0-2
- Patients who have been diagnosed with indolent NHL [defined as FL, MZL (splenic, nodal, and extranodal), or SLL] that has progressed.
    - Patients must have exhibited no response or progression within 6 months after the last dose of a chemotherapy induction regimen (containing at least one alkylating or purine nucleoside antagonist chemotherapy) or radioimmunotherapy
    - Patients must have rituximab-refractory disease based on history of rituximab treatment with no objective response or documented progression within 6 months:

        - Previous treatment regimen of a full course of single-agent rituximab (≥4 doses of 375 mg/m^2, weekly)
        - Completion of rituximab maintenance therapy or progression before the next scheduled rituximab dose
        - Completion of a full course of rituximab in combination with chemotherapy
- Adequate organ function:
    - Serum AST or ALT ≤3 x upper limit of normal (ULN)
    - Total bilirubin ≤1.5 x ULN
    - Serum creatinine ≤1.5 x ULN
- Exclude the following:
    - Patients who are candidates for potentially curative therapies
    - Treatment with a PI3K inhibitor within previous 30 days
    - Prior allogeneic HSCT
    - Grade 3B FL or clinical evidence of transformation
    - Symptomatic central nervous system lymphoma
    - Receipt of medications or foods that are strong inhibitors or inducers of CYP3A within 2 weeks before first dose of study drug

Study Design
Study IPI-145-06 was a single-arm, open-label, phase 2 study to evaluate the efficacy and safety of duvelisib in patients with FL, MZL, or SLL refractory to rituximab and chemotherapy combined or radioimmunotherapy.

Treatment
All patients received duvelisib at a starting dose of 25 mg orally, twice daily in 28-day treatment cycles until disease progression or unacceptable toxicity. Duvelisib dose levels for toxicity are shown in the table below.

Table 50. Dose Levels for Toxicity

Duvelisib Dose Level	Dose (mg)
1	25 twice daily
-1	15 twice daily
-2	10 twice daily
-3	5 twice daily

Any patient requiring a dose less than 5 mg twice daily was permanently discontinued from treatment. Concomitant use of a strong CYP3A4 inhibitor or inducer was prohibited.

Patients were followed for survival for up to 3 years after first dose of duvelisib.

Statistical Analysis Plan

Efficacy Endpoints

Primary Endpoint

- Overall response rate, with overall response defined as the best response of complete response or partial response, according to the 2007 revised IWG Criteria.

Secondary Endpoints

- DOR defined as the time from the first documentation of response to the first documentation of PD or death due to any cause.
- PFS defined as the time from the first dose of study treatment to the first documentation of PD or death due to any cause.
- Overall survival defined as the time from the first dose of study treatment to the date of death.
- Time to response, defined as the time from the first dose of study treatment to the first documentation of response (complete or partial).

Table 51: PFS Censoring Method

Situation	Date of Event or Censoring	Outcome
No adequate baseline disease status assessment	Date of first dose	Censored
No adequate post-baseline disease status assessment unless death occurs prior to first post-baseline assessment	Date of first dose + 1	Censored
No documented progression or death before data cutoff	Date of last adequate disease status assessment	Censored
Documented progression with ≤1 missing scheduled disease status assessment before progression	Date of the earliest assessment that results in a finding of unequivocal progression	Event
Death before progression being documented with ≤1 missing scheduled disease status assessment before death	Date of death	Event
Documented progression or death following a long gap between adequate disease status assessments (e.g., 2 or more consecutive missed scheduled disease status assessments along with a gap of more than 6 months)	Date of last adequate disease status assessment before the gap	Censored
New anticancer treatment or procedure started before documented progression	Date of last adequate disease status assessment	Censored

Source: Table on Page 24 in the Applicant's Statistical Analysis Plan.

Note:
Partial/missing dates for NHL diagnosis date and last anticancer therapy completion date will be imputed as follows:

- If both date and month are missing and the year is prior to the year of screening, the

imputed date and month will be 01 July.
- If both date and month are missing and the year is the same as the year of screening, the imputed date will be the middle point between 01 Jan of the year and the screening date. If the middle point falls between two dates, the first of the two dates will be used.
- If date is missing and the month and year are prior to the month and year of screening, the imputed date will be 15th day of the month.
- If date is missing and the month and year are the same as the month and year of screening, the imputed date will be the middle point between the first date of the month and the screening date. If the middle point falls between two dates, the first of the two dates will be used.
- No imputation will be performed if the year is missing.

Exploratory Endpoint

- Lymph node response rate (LNR rate), with LNR defined as ≥50% reduction in the sum of the products of the perpendicular diameters of nodal target lesions

Sample Size

This study will test the null hypothesis that the ORR is ≤30% against the alternative that ORR is ≥45%. Using a group sequential design with one interim analysis, 120 patients will provide >90% power to achieve a one-sided overall significance level of 0.025. Among the 120 patients to be enrolled, approximately 80 will be FL.

Interim Analysis

One interim analysis was planned for only futility at approximately 4 months after at least 30 (25%) patients have initiated treatment. The cumulative Type II error to be spent at the interim and final analyses are 0.02 and 0.1, respectively. If the interim analysis occurs 4 months after exactly 30 patients have initiated treatment, the *p*-value boundary for futility is 0.6552. Actual *p*-value boundary for futility will be calculated based on the number of patients at the interim analysis by linear interpolation. The futility boundary is non-binding.

Analysis population

Full Analysis Set (FAS)

The Full Analysis Set (FAS) will be used for the primary analysis of all efficacy endpoints, which includes all patients who have been treated with at least one dose of duvelisib.

Evaluable Analysis Set (EAS)

The Evaluable Analysis Set (EAS) includes all patients who meet the following criteria:

- Remain in the treatment phase of the study for at least 8 weeks or have a documented disease progression per revised IWG criteria before 8 weeks of treatment
- Have an adequate baseline tumor assessment (at least one nodal target lesion ≥1.5 cm in the longest diameter)
- Have at least one adequate post baseline tumor assessment unless death due to disease progression

- No major protocol deviations that could have an impact on efficacy.

Analysis Methods for Primary Endpoint Overall Response Rate (ORR)
ORR will be tested against the null (≤30%) by one-sided exact binomial test at the significance level of 0.025 in FAS.

Subgroup analyses for ORR will be performed in the following subgroups:
- Number of prior therapies (<3 or ≥3)
- Number of prior therapies (1 or >1)
- Prior treatment with bendamustine (Yes or No)
- Refractory to bendamustine (Yes or No)
- Prior treatment with bendamustine-rituximab (Yes or No)
- Refractory to bendamustine-rituximab (Yes or No)
- FL patients received only 1 prior therapy of bendamustine-rituximab and is refractory
- Refractory to last therapy status (Yes or No)
- Last therapy contains bendamustine and is refractory (Yes or No)
- Bulky status (longest diameter of baseline lesion <5cm or ≥5cm)
- Gender (male of female)
- Age group (<65 or ≥65 years)
- Race (White or Non-White)
- Region (US or Non-US)

Protocol Amendments

The study protocol was amended three times:
- Original protocol (02 April 2013)

- Amendment 1 (08 April 2014) clarified that the primary objective and endpoint definition was ORR, with overall response defined as best response of CR or PR. Prior PI3K inhibitors or BTK inhibitors were prohibited.

- Amendment 2 (30 April 2015) revised the enrollment to 80 patients from 100 patients based on the accrual pattern of NHL subtypes. Patients were able to continue to receive duvelisib for an additional year after 13 cycles if they achieved a CR, PR, or SD. An independent DMC was assembled to review safety information and review efficacy data at the interim analysis.

- Amendment 3 (03 November 2015) allowed patients who display evidence of clinical benefit after 1 year of treatment to continue duvelisib until disease progression or unacceptable toxicity.

Study Results

Compliance with Good Clinical Practices
The protocol, protocol amendments, and patient informed consent forms for Study IPI-145-06

were reviewed and approved by the Institutional Review Boards or Independent Ethics Committees of the participating study centers.

Study IPI-145-06 was conducted in accordance with the International Council for Harmonization guideline for Good Clinical Practice, the principles of the Declaration of Helsinki, and the US Code of Regulations, Title 21, Parts 50, 56, and 312 providing the protection of the rights and welfare of human patients participating in biomedical research. All patients or their legal representatives voluntarily consented prior to trial enrollment.

Financial Disclosure
The Applicant submitted financial disclosure information from 2,920 investigators from 5 studies indicating that none of the investigators had disclosable financial interests or arrangements. For details, refer to the Clinical Investigator Financial Disclosure Review Template in Section 19.2.

Patient Disposition

A total of 129 patients were enrolled and treated in the study, among which 83 patients (64%) with FL, 28 patients (22%) with SLL, and 18 patients (14%) with MZL. Table 52 displays patient disposition at the data cutoff of May 18, 2018.

Table 52: Patient Disposition (FAS, May 18, 2018)

	FL (N=83)	Overall (N=129)
Patients on treatment	3 (3.6)	5 (3.9)
Patients off treatment, still in follow-up	24 (28.9)	33 (25.6)
Patients off study	56 (67.5)	91 (70.5)
Discontinued treatment	80 (96.4)	124 (96.1)
Adverse event	*17 (20.5)*	*31 (24.0)*
Disease progression	*46 (55.4)*	*66 (51.2)*
Death	*5 (6.0)*	*7 (5.4)*
Noncompliance to protocol	*1 (1.2)*	*1 (0.8)*
Investigator decision	*7 (8.4)*	*12 (9.3)*
Voluntary withdrawal by patient	*4 (4.8)*	*6 (4.7)*
Other	*0 (0.0)*	*1 (0.8)*
Discontinued Study	56 (67.5)	91 (70.5)
Death	*40 (48.2)*	*61 (47.3)*
Lost to follow-up	*1 (1.2)*	*3 (2.3)*
Voluntary withdrawal by patient	*6 (7.2)*	*9 (7.0)*
Follow-up completed	*7 (8.4)*	*15 (11.6)*
Other	*2 (2.4)*	*3 (2.3)*

Source: Table 4 on Page 9 in the Applicant's Clinical Information Amendment submitted on June 11, 2018. Data cutoff: May 18, 2018.

Protocol Violations/Deviations
Of the 129 patients assigned to treatment, 49 patients (38%) had at least 1 major protocol deviation. The most common major protocol deviation included prophylactic medication not administered per protocol (10%), disease not refractory to a chemotherapy induction regimen or radioimmunotherapy (7%), and viral screening tests not performed (6%).

Clinical Reviewer Comment: The major protocol deviations are not likely to bias the study in favor of duvelisib, and all patients were included in the FDA's analysis of the efficacy endpoint. The analysis of ORR using the evaluable analysis set demonstrated consistent results with the FAS population.

Demographics and Baseline Characteristics

Demographics are summarized in Table 53 below. Overall, in the FAS, the median age was 65 years (range 30 – 90 years), 68% were male, and 95% had an ECOG of 0 to 1.

In patients with FL, the median age was 64 years (range 30 – 82 years), 68% were male, and 93% had an ECOG of 0 to 1.

Table 53: Demographics (FAS)

	FL (N=83)	Total (N=129)
Age, years		
Median (Min, Max)	64 (30, 82)	65 (30, 90)
≥65 years, n %	40 (48)	65 (50)
Sex, n (%)		
Male	56 (68)	88 (68)
Female	27 (32)	41 (32)
Race, n (%)		
White	74 (89)	116 (90)
Black or African American	3 (4)	6 (5)
Asian	1 (1)	1 (<1)
American Indian or Alaska Native	1 (1)	1 (<1)
Other	4 (5)	5 (4)
Country, n (%)		
Non-US	58 (70)	83 (64)
US	25 (30)	46 (36)
ECOG, n (%)		
0	42 (51)	60 (47)
1	35 (42)	62 (48)
2	6 (7)	7 (5)

Source: FDA review of ADSL dataset

Disease characteristics are summarized in Table 54 below. Overall, in the FAS population, 39% had bulky disease, the median number of prior therapies was 1 (range 1 - 18) , with 96% being refractory to their last therapy and 77% being refractory to 2 or more prior lines of therapy.

In the FL population, 37% had bulky disease, the median number of prior therapies was 3 (range 1 – 10), with 94% being refractory to their last therapy and 81% being refractory to 2 or more prior lines of therapy.

Table 54: Disease Characteristics (Full Analysis Set)

	FL (N=83)	Total (N=129)
Bulky disease (baseline lesion ≥5cm)		
Yes	31 (37)	51 (39)
Number of prior therapies		
Median (min, max)	3 (1, 10)	3 (1, 18)
1	10 (12)	17 (13)
2	19 (22)	31 (24)
≥3	54 (65)	81 (63)
Refractory to bendamustine-rituximab		
Yes	36 (43)	55 (43)
Refractory to last therapy		
Yes	78 (94)	124 (96)
Refractory to 2 or more prior therapies		
Yes	67 (81)	99 (77)
Last therapy contains bendamustine and is refractory		
Yes	26 (31)	37 (29)
No	57 (69)	92 (71)

Source: FDA review of ADSL dataset

Exposure

Exposure with duvelisib in the FL population is summarized in Table 55 and Figure 11. The median exposure duration for patients with FL was 5 months (range 0.4 to 46 months), with 43% of patients receiving at least 6 months and 18% receiving at least 12 months.

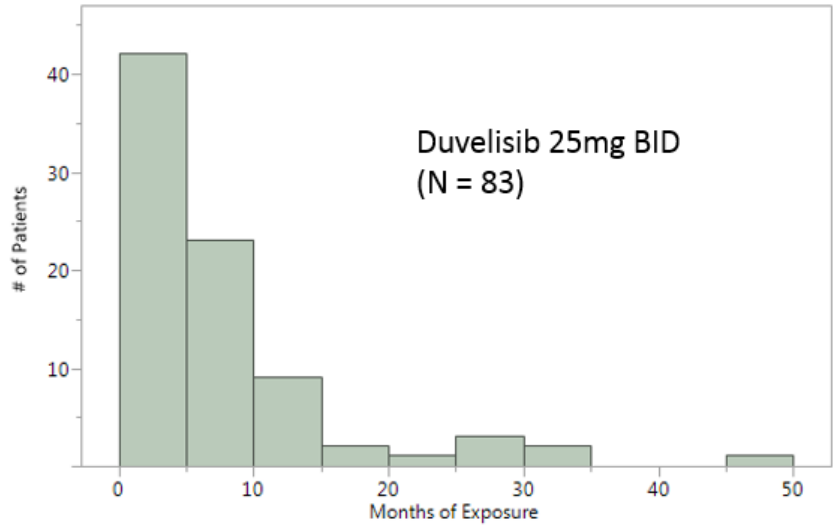
Table 55: Exposure in Patients with Follicular Lymphoma

Parameter		FL N=83
Exposure duration, months	Median	5
	Range	0.4, 46
	Q1, Q3	3, 9
Cycles initiated[a]	Median	6
	Range	1, 50
	Q1, Q3	3, 11
Relative dose	Mean (SD)	91.2 (13.6)

Parameter		FL N=83
intensity	≥90%	75%
	≥80%	82%
Patients on treatment by month	≥2 months	81%
	≥3 months	71%
	≥6 months	43%
	≥12 months	18%
	≥18 months	10%
	≥24 months	7%

Source: FDA analysis of ADSL dataset
[a] Cycle length is 28 days

Figure 11: Duration of Treatment in Patients with FL



Treatment Compliance, Concomitant Medications, and Rescue Medication Use
Of concomitant medications taken by ≥20% of patients with FL, the most common was systemic antibacterial agents (95%) due to protocol required PJP prophylaxis, and antivirals (92%).

Based a relative dose intensity of 91% in patients with FL, noncompliance was not reported as a concern by the Applicant or found upon review of exposure.

Efficacy Results – Primary Endpoint

Overall Response Rate (ORR)
The review of the efficacy endpoints is based on the FL study population (N=83) and the overall study population (N=129) because the indication the Applicant seeks is for patients with

follicular B-cell NHL who have received at least two prior therapies.

The data cutoff date in the original submission was April 7, 2016. In response to FDA's IR, the Applicant has submitted updated efficacy based on a data cutoff of March 01, 2017, July 19, 2017 and May 18, 2018. Table 56 shows the results for ORR per IRC based on the most updated data cut-off on May 18, 2018.

Among the patients with FL, 35 patients achieved an overall response, with an estimated ORR per IRC of 42.2% (95% CI: 31.4%, 53.5%). Of the 35 responders, 1 patient (1%, 1/83) achieved a CR and 34 patients (41%, 34/83) achieved a PR. The in the FAS, 61 patients achieved an overall response, including 59 PRs and 2 CRs. The estimated ORR per IRC was 47.3% with 95% CI (38.4%, 56.3%).

Table 56: Response per IRC (Full Analysis Set, May 18, 2018)

Response, n (%)	FL (N=83)	Overall (N=129)
CR	1 (1.2)	2 (1.6)
PR	34 (41.0)	59 (45.7)
SD	29 (34.9)	42 (32.6)
PD	14 (16.9)	18 (14.0)
UNK	5 (6.0)	7 (5.4)
NED	0 (0.0)	1 (0.8)
ORR		
n (%)	35 (42.2)	61 (47.3)
95% CI	(31.4, 53.5)	(38.4, 56.3)
Duration of response		
Median, months	10.0	10.0
95% CI	(4.5, 21.9)	(6.5, 10.5)
Median follow-up, months	10.2	16.5

Source: FDA reviewer's analyses.
Abbreviations: CR = complete response, FL = follicular lymphoma, PR = partial response, SD = stable disease, PD = progressive disease, UNK = unknown, NED = no evidence of disease.

Table 57 summarizes the results for ORR per IRC for previous data cutoffs.

Table 57: Response per IRC, and Duration of Response, by Data Cutoff Date, Full Analysis Set

Data Cutoff	April 07, 2016		March 01, 2017		July 19, 2017	
Response, n (%)	FL (N=83)	Overall (N=129)	FL (N=83)	Overall (N=129)	FL (N=83)	Overall (N=129)
CR	0 (0.0)	0 (0.0)	1 (1.2)	1 (0.8)	1 (1.2)	1 (1.2)
PR	34 (41.0)	59 (45.7)	35 (42.2)	60 (46.5)	34 (41.0)	59 (45.7)
SD	30 (36.1)	44 (34.1)	28 (33.7)	42 (32.6)	29 (34.9)	43 (33.3)
PD	14 (16.9)	18 (14.0)	14 (16.9)	18 (14.0)	14 (16.9)	18 (14.0)
UNK	5 (6.0)	7 (5.4)	5 (6.0)	7 (5.4)	5 (6.0)	7 (5.4)
NED	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.8)
ORR						
n (%)	34 (41.0)	59 (45.7)	36 (43.4)	61 (47.3)	35 (42.2)	60 (46.5)
95% CI	(30.3, 52.3)	(36.9, 54.7)	(32.5, 54.7)	(38.4, 56.3)	(31.4, 53.5)	(37.7, 55.5)
Median DOR, month (95% CI)	9.2 (4.1, NE)	9.9 (4.5, 10.3)	7.9 (4.1, 12.6)	9.9 (4.5, 10.3)	10.0 (4.5, 21.9)	10.0 (7.9, 12.5)

Source: FDA reviewer's analyses.
Abbreviations: CR = complete response, DOR = duration of response, PR = partial response, SD = stable disease, PD = progressive disease, UNK = unknown, NED = no evidence of disease.

Statistical Reviewer Comment: Due to the single-arm study design, the reviewer presents the analysis results for all the efficacy endpoints with descriptive statistics only without formal hypothesis testing.

Subgroup Analyses

Gender, Race, Age, and Geographic Region

Table 58 shows the reviewer's subgroup analysis results for ORR per IRC by age, sex, race, and region for the FL population and for the FAS.

Table 58: Demographic Subgroup Analysis of Overall Response Rate per IRC, Full Analysis Set, May 18, 2018

	Follicular Lymphoma			Overall		
Subgroup	Total	ORR, n (%)	SE	Total	ORR, n (%)	SE
Age Category						
≥65 years	40	14 (35.0)	0.08	65	28 (43.1)	0.06
<65 years	43	21 (48.8)	0.08	64	33 (51.6)	0.06
Sex						
Male	56	25 (44.6)	0.06	88	43 (48.9)	0.06
Female	27	10 (37.0)	0.10	116	54 (46.6)	0.08
Race						
White	74	29 (39.2)	0.06	116	54 (46.6)	0.04
Non-White	7	4 (57.1)	0.18	11	5 (45.5)	0.16
Region						
US	25	14 (56.0)	0.10	46	27 (58.7)	0.08
Non-US	58	21 (36.2)	0.06	83	34 (41.0)	0.06

Source: FDA reviewer's analyses.

Statistical Review Comment: The clinical significance may not be adequately interpreted in these subgroups. The reviewer recommends that those subgroup analyses are only exploratory.

Data Quality and Integrity

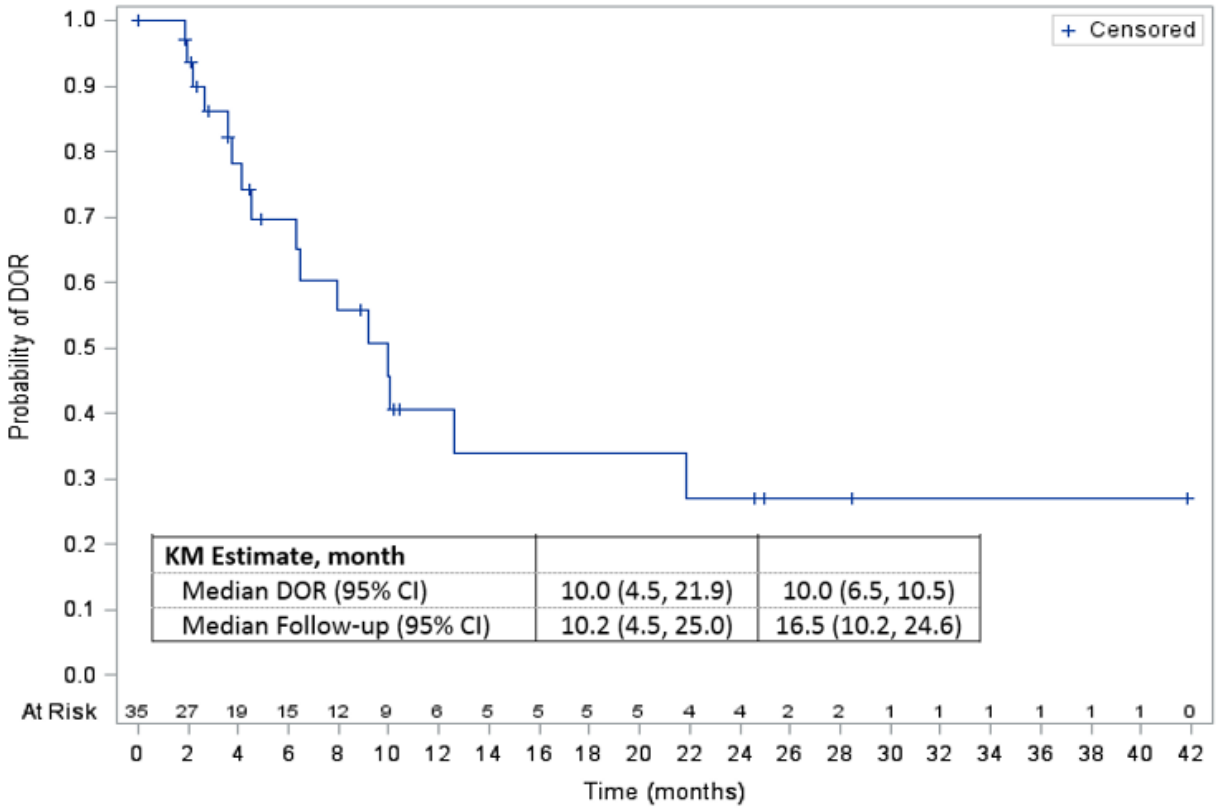
The data quality is acceptable. In general, the reviewer was able to perform independent review and confirm the Applicant's analysis results using the submitted datasets.

Efficacy Results – Secondary Endpoint

Duration of Response

The analysis results of DOR per IRC (data cut-off 18 May 2018) are summarized in Table 57 and Figure 12. In patients with FL, the estimated median DOR was 10.0 months, with a median follow-up of 10.2 months.

Figure 12: Kaplan-Meier Curve for Duration of Response per IRC in Patients With FL



Source: FDA reviewer's analyses

Notably, in patients with FL, 19 of the 35 responders (54%) were censored in the evaluation of DOR (Table 59). Of the 19 patients censored, 63% (12/19) were censored before 5 months and 79% (15/19) were censored before 12 months (Table 60). Therefore, the estimated DOR may not be reliable because of early censoring.

Table 59: Duration of Response in Patients With Overall Response per IRC, Full Analysis Set, May 18, 2018

	FL (N=35)	Overall (N=61)
Number of patients with PFS events	16 (45.7%)	35 (57.4%)
Progression	*15 (42.9%)*	*32 (52.5%)*
Death	*1 (2.9%)*	*3 (4.9%)*
Number of patients censored	19 (54.3%)	26 (42.6%)
New anticancer treatment or procedure started before documented progression	*10 (28.6%)*	*13 (21.3%)*
No documented progression or death	*9 (25.7%)*	*13 (21.3%)*
KM estimate, month		

	FL (N=35)	Overall (N=61)
Median DOR (95% CI)	10.0 (4.5, 21.9)	10.0 (6.5, 10.5)
Median follow-up (95% CI)	10.2 (4.5, 25.0)	16.5 (10.2, 24.6)

Source: FDA reviewer's analyses.

Table 60: Censoring Rate in Analysis of Duration of Response, by Censoring Time, in Patients With Overall Response per IRC

Censoring Time, months	FL (N=35)	Overall (N=61)
≤5	12 (34.3%)	12 (19.7%)
5-10	1 (2.9%)	3 (4.9%)
10-20	2 (5.7%)	7 (11.5%)
20-30	3 (8.6%)	3 (4.9%)
>30	1 (2.9%)	1 (1.6%)
Total	19 (54.3%)	26 (42.6%)

Source: FDA reviewer's analyses.

Clinical Reviewer Comment: The early censoring in the evaluation of DOR, especially since 63% were censored before 5 months and 79% were censored before 12 months, makes the estimate unreliable. Further, the most common reason for censoring was new anticancer treatment because patients were experiencing unacceptable toxicity with duvelisib. Further, the early censoring with DOR prolongs the median follow-up estimate per KM method. Using follow-up durations only, the median follow-up for responder was 4.5 months, which was confirmed by IRC assessment. Thus, the ability to interpret DOR beyond 5 months is uncertain.

Due to early censoring, an evaluation of DOR for each individual response was conducted and is shown in Table 61. In patients with FL, there were 15 patients (18%) achieving a response of at least 6 months in duration and 11 patients (13%) achieving a response of at least 9 months in duration.

Table 61: Duration of Response in Total Population

DOR, months	FL		Overall	
	N	% of FAS N=83	N	% of FAS N=129
≥3	22	27	42	33
≥6	15	18	31	24
≥9	11	13	26	20
≥12	6	7	12	9
≥24	4	5	4	3

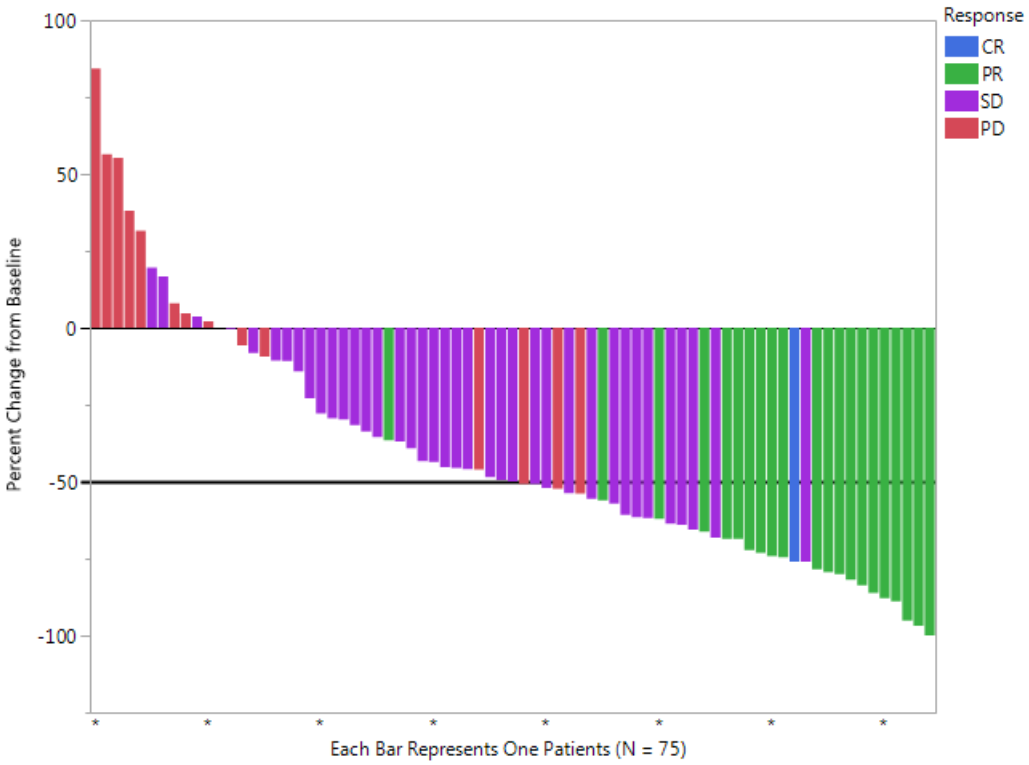
Source: FDA reviewer's analyses.

Statistical Reviewer Comment: Due to the single-arm study design, other secondary endpoints PFS, OS, TTR were not analyzed because the clinical significance cannot be adequately interpreted due to the confounding effects of an uncontrolled study and the natural history of the diseases.

Time to Response
Based on responders per the IRC, the median time to response was 1.9 months (range 1.6 to 12 months). Of the responders, 97% had a response in under 6 months.

Response – Change from Baseline
The maximum percent change from baseline is displayed in Figure 13. A total of 75 patients of 83 had available data to review response from baseline. Thirty-five patients (47%) experienced at least a 50% maximum reduction from baseline.

Figure 13 Percent Change from Baseline per IRC in Patients With FL



Source: FDA analysis of ADEF dataset (18 May 2018 data cutoff)
CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease

8.2.2. Integrated Assessment of Effectiveness

In adult patients with refractory FL, Study IPI-145-06, a multicenter, open-label, single-arm, phase 2 trial demonstrated that duvelisib 25 mg twice daily resulted in clinically meaningful, durable responses.

The trial enrolled 83 patients with refractory FL who were refractory to rituximab and to either chemotherapy or radioimmunotherapy. Refractory disease was defined as less than a partial response or relapse within 6 months after the last dose. The median number of prior therapies was 3, with 94% of patients being refractory to their last therapy and 81% being refractory to 2 or more prior therapies.

The analysis of ORR per IRC in the 83 patients with FL demonstrated an ORR of 42% (95% CI: 31, 54), with 1 patient (1%) achieving a complete response and 34 patients (41%) achieving a partial response. Due to early censoring, the estimated median DOR was not reliable. Although, of the 35 patients that achieved a response, 43% maintained a response at 6 months and 17% at 12 months.

In patients with refractory FL, who were refractory to rituximab and to either chemotherapy or radioimmunotherapy, the magnitude of responses and durability achieved with duvelisib can be clinically meaningful.

The Applicant proposed an indication (b) (4) (b) (4) (b) (4). Study IPI-145-06 specifically enrolled patients with refractory FL and the efficacy of duvelisib is not defined for patients with chemosensitive relapse. However, given the meaningful clinical activity of duvelisib in the refractory setting and the unmet medical need in patients with FL who require third-line therapy or beyond, the clinical review team recommends including patients with either relapsed or refractory disease. Therefore, the recommended indication for duvelisib is for the treatment of adult patients with relapsed or refractory FL after at least two prior systemic therapies.

8.3. Review of Safety

8.3.1. Safety Review Approach

The safety population is defined as all patients assigned to study treatment with at least one study drug administration.

The clinical review of safety for this NDA is based on all-causality treatment-emergent adverse events (TEAEs) in recipients of study drug on Studies IPI-145-02, IPI-145-06, IPI-145-07, and IPI-145-12. TEAEs were defined as adverse events that are new or worsened from baseline grade

or are unknown to have worsened from baseline. TEAEs were reported from the start of study drug to 30 days following the last dose of study drug. Adverse events indicating progressive disease were not included in the safety analysis.

The Applicant reported adverse events using single MedDRA preferred terms (PTs). For increased sensitivity, FDA used a combination of ungrouped and custom grouped PTs, as defined in Appendix 0. Additionally, adverse events that involve more than one body system were consolidated and reported under the most commonly involved or most appropriate body system. Unless noted, all presented analyses use the FDA grouped PTs.

8.3.2. Review of the Safety Database

The safety review was conducted using the integrated datasets provided by the Applicant from clinical studies listed in Table 23. A data pool primarily including patients with CLL/SLL, FL, and MZL was used to develop the safety profile in patients treated with duvelisib 25 mg BID. This data pool provided 442 patients with hematologic malignancies, which is an adequate number of patients exposed for a review of safety.

Exposure

Exposure by patient group is summarized in Table 62 and Figure 14. The median exposure duration for patients with hematologic malignancies was 9.0 months with a range of <1 months to 53 months. Sixty-eight percent of patients achieved a relative dose intensity (RDI) ≥90% and 78% had an RDI ≥80%. Of the 442 patients with hematologic malignancies treated with duvelisib 25 mg BID, 66 (15%) remain on treatment as of 19 July 2017.

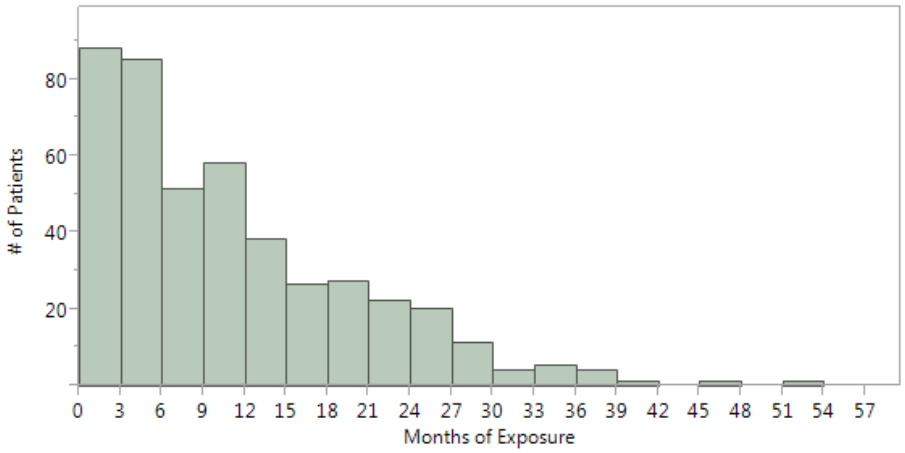
Table 62: Exposure to Duvelisib 25 mg BID

Parameter		FL N=96	CLL/SLL N=303	All Heme N=442
Exposure duration, months	Median	6	10	9
	Range	0.1, 39	0.2, 47	0.1, 53
	Q1, Q3	3, 10	4, 17	4, 16
Cycles initiated[a]	Median	7	12	10
	Range	1, 50	1, 51	1, 58
	Q1, Q3	3, 11	5, 19	4, 18
Relative dose intensity	Mean (SD)	88.2 (17.0)	88.7 (17.9)	88.3 (17.9)
	≥90%	69%	68%	68%
	≥80%	76%	79%	78%
Patients on treatment by month	≥2 months	80%	91%	88%
	≥3 months	71%	84%	81%
	≥6 months	46%	66%	61%

	≥12 months	20%	42%	37%
	≥18 months	9%	24%	22%
	≥24 months	7%	10%	11%

Source: FDA analysis of ADSL dataset
[a] Cycle length is 28 days
SD: Standard deviation

Figure 14: Duvelisib 25 mg BID Exposure (N=442)



Source: FDA analysis of ADSL dataset

Demographics and Baseline Characteristics

The patient characteristics for patients with hematologic malignancies is shown in Table 63. In the 442 patients with hematologic malignancies, the median age was 67 years, 65% were male, 92% were white, and 93% had an ECOG status of 0-1. The median number of prior therapies was 2, with a range of 0 to 18.

Table 63: Demographics and Baseline Characteristics in Patients with Hematologic Malignancies

Characteristic	FL N=96	CLL/SLL N=303	All Heme N=442
Age (years)			
Median	64	68	67
Min, Max	30, 82	39, 90	30, 90
Age group (n, %)			
≥65 years	46 (48%)	194 (64%)	270 (61%)
Sex (n, %)			
Male	66 (69%)	194 (64%)	289 (65%)
Female	30 (31%)	109 (36%)	153 (35%)
Race (n, %)			
White	86 (90%)	281 (93%)	407 (92%)
Black	4 (4%)	6 (2%)	12 (3%)
Other or Unknown	6 (6%)	16 (5%)	23 (5%)
BMI (kg/m2)			
Median	26.9	26.3	26.6
Min, Max	20.0, 48.8	17.3, 80.9	17.3, 80.9
Baseline ECOG status, n (%)			
0	49 (51%)	133 (44%)	200 (45%)
1	41 (43%)	146 (48%)	212 (48%)
2	6 (6%)	24 (8%)	30 (7%)
Number of prior systemic therapies			
Median	3	2	2
Min, Max	1, 10	1, 18	0, 18
eGFR (n, %)			
Normal	81 (84%)	214 (71%)	328 (74%)
Mild impairment	13 (14%)	66 (22%)	87 (20%)
Moderate impairment	2 (2%)	19 (6%)	23 (5%)
Hepatic impairment (n, %)			
Normal	83 (87%)	236 (78%)	358 (81%)
Mild impairment	12 (12%)	59 (19%)	74 (17%)
Moderate impairment	1 (1%)	2 (1%)	3 (1%)

Source: FDA analysis of ADSL dataset
BMI: Body mass index, ECOG: Eastern Cooperative Oncology Group, eGFR: Estimated glomerular filtration rate

Adequacy of the Safety Database

The safety database was adequate to provide a reasonable estimate of ARs that may be observed with duvelisib. The duration of exposure, with a median of 9 months, is moderate. Therefore, an estimate of ARs with long-term use of duvelisib remains uncertain. The safety database is representative of patients with relapsed or refractory B-cell hematologic

malignancies. However, Blacks and Hispanics are under-represented compared with the overall B-cell hematologic malignancy population in the United States.

8.3.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The data submitted to this NDA was of adequate quality to perform the safety review. Overall, there were no concerns regarding the integrity of the NDA submission.

Categorization of Adverse Events

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 16.1 and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.03. TEAEs were defined as any event arising or worsening after the start of study drug administration until 30 days after the last study drug administration.

The Applicant reported adverse events using single MedDRA preferred terms, whereas the FDA used a combination of ungrouped and custom grouped PTs, as defined in Appendix 19.4.

Routine Clinical Tests

The schedule of routine clinical testing was adequate for safety evaluation.

8.3.4. Safety Results

Deaths

Deaths with duvelisib were assessed during treatment and up to 30 days post treatment discontinuation. On FDA analysis, a total of 35 patients with hematologic malignancies (8%, 35/442) treated with duvelisib (25 mg twice daily) died in the absence of progressive disease. A root cause analysis demonstrated that infection, primarily including sepsis and pneumonia, was the most common cause of non-relapse death. Other causes included diarrhea or colitis, pneumonitis, sepsis in the setting of drug reaction with eosinophilia and systemic symptoms and toxic epidermal necrolysis, and respiratory failure (Table 64).

Table 64: Summary of Deaths in Recipients of Duvelisib

	FL N=96 n (%)	CLL/SLL N=303 n (%)	All Heme N=442 n (%)
All deaths	11 (11)	37 (12)	50 (11)
Progressive disease	7 (7)	6 (2)	15 (3)
Treatment-related Infection	3 (3) 3 (3)	12 (4) 9 (3)	18 (4) 13 (3)

	FL N=96 n (%)	CLL/SLL N=303 n (%)	All Heme N=442 n (%)
Sepsis[1]	3 (3)	3 (1)	6 (1)
Pneumonia	0	4 (2)	5 (1)
Viral infection	0	1 (<1)	1 (<1)
Pneumonitis	0	1 (<1)	1 (<1)
Respiratory failure[2]	0	1 (<1)	1 (<1)
Diarrhea or colitis	0	0	1 (<1)
General health deterioration	0	1 (<1)	1 (<1)
Hemorrhagic stroke[3]	0	1 (<1)	1 (<1)
Multiorgan failure[4]	0	1 (<1)	1 (<1)
Unknown	0	2 (<1)	2 (<1)
Other causes	1 (1)	17 (6)	15 (3)

Source: FDA analysis of ADAE dataset and narratives
[1] Includes one patient with sepsis in the setting of drug reaction with eosinophilia and systemic symptoms (DRESS) and another in the setting of toxic epidermal necrolysis (TEN)
[2] Includes a case of respiratory failure due to pleural effusion that progressed to pleural hemorrhage in the setting of neutropenia, bacterial pneumonia, and disease progression
[3] In setting of Grade 4 thrombocytopenia and sepsis
[4] Includes a case with a precipitating event of pneumonia, acute respiratory distress syndrome, and respiratory failure

Deaths during treatment and up to 30 days following treatment discontinuation in patients with CLL/SLL in Study IPI-145-07, the randomized actively controlled phase 3 trial comparing duvelisib to ofatumumab, and Study IPI-145-12, a single-arm extension study are detailed in Table 65. For Study IPI-145-12, 89 patients previously randomized to ofatumumab who developed disease progression received subsequent treatment with duvelisib whereas 4 patients previously randomized to duvelisib who developed disease progression received subsequent ofatumumab. The subset of patients below that received duvelisib 25 mg BID were included in the all heme population presented above.

Table 65: Summary of Deaths in Study IPI-145-07 and IPI-145-12

	Duvelisib N=247 n (%)	Ofatumumab N=163 n (%)
All deaths	29 (12)	7 (4)
Disease progression	2 (1)	3 (2)
Treatment-related	11 (5)	0
Infection	6 (2)	0
Pneumonitis	1 (<1)	0
Respiratory failure[1]	1 (<1)	0
General health deterioration	1 (<1)	0
Hemorrhagic stroke[2]	1 (<1)	0
Multiorgan failure[3]	1 (<1)	0
Unknown	2 (1)	0
Other causes	14 (6)	4 (2)
Sepsis	6 (2)	0
Respiratory failure[4]	3 (1)	0
Cardiac failure	3 (1)	0
Hemorrhagic stroke	1 (<1)	0
General health deterioration	1 (<1)	0
Second malignancy	0	2 (1)
Hepatic failure	0	1 (<1)
Fall	0	1 (<1)

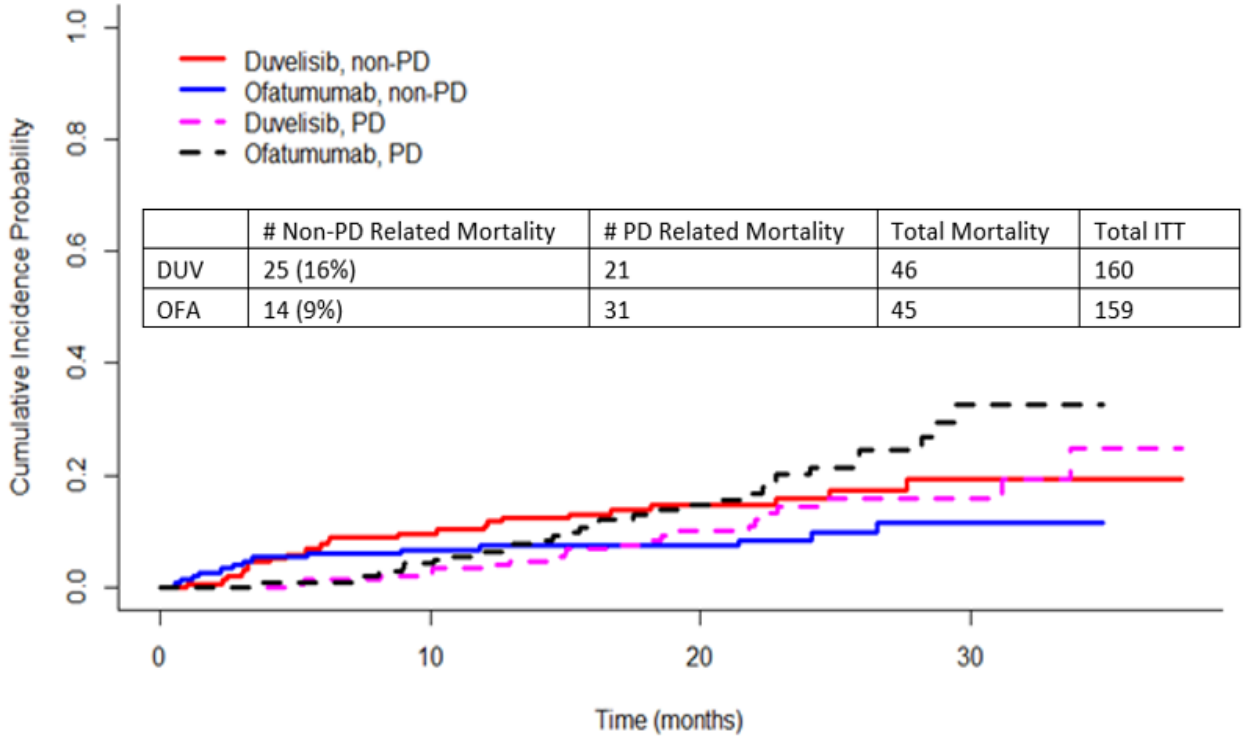
Source: FDA analysis
[1]Includes a case of respiratory failure due to pleural effusion that progressed to pleural hemorrhage in the setting of neutropenia, bacterial pneumonia, and disease progression
[2] In setting of Grade 4 thrombocytopenia and sepsis
[3] Includes a case with a precipitating event of pneumonia, acute respiratory distress syndrome, and respiratory failure
[4] Includes cases of respiratory failure due to COPD, acute bronchitis, and unknown cause, respectively

There were a total of 29 deaths in patients on duvelisib for Study IPI-145-07 and IPI-145-12. Following FDA adjudication, 11 patients receiving duvelisib had treatment-related death and no treatment-related deaths were identified in patients who received ofatumumab. Duvelisib-associated cases were reviewed for root cause, which were consistent with the all heme population above and primarily included infection, mostly due to pneumonia and sepsis.

Death Without Progression

Using data from Study IPI-145-07, FDA performed an exploratory competing-risk analysis to further evaluate the risk of death in patients with CLL/SLL who received duvelisib. In this analysis, death after progression/relapse was considered a competing risk for death without progression/relapse. The estimated cumulative incidence of non-relapse death was 16% in the duvelisib arm and 9% in the ofatumumab arm (Figure 15).

Figure 15: Cumulative Incidence of Death Without Progression Versus Death With Progression Using Competing Risks (Study IPI-145-07)



	# Non-PD Related Mortality	# PD Related Mortality	Total Mortality	Total ITT
DUV	25 (16%)	21	46	160
OFA	14 (9%)	31	45	159

Source: FDA reviewer analysis
PD: Progressive disease

Reviewer Comment:

- *The competing-risk analysis above has multiple limitations, including being unadjusted, exploratory, and restricted by small numbers of events. In addition, death in the absence of progression is not necessarily due to treatment-related toxicity. No formal comparisons are intended between treatment arms. Nevertheless, the results are from a randomized phase 3 trial and raise concern for an increased risk of treatment-related mortality in recipients of duvelisib compared to ofatumumab.*
- *A root cause analysis of duvelisib-associated toxic deaths identified infections, including pneumonia and sepsis, as the most common reason for death without progressive disease. In addition to infection, fatal ARs occurred in patients with diarrhea or colitis, cutaneous reactions, and pneumonitis. Labeling should reflect the potential for fatal ARs with duvelisib that include infections, diarrhea or colitis, cutaneous reactions, and pneumonitis. These risks, which are class effects, warrant a boxed warning.*

Serious Adverse Events

A serious adverse event (SAE) during treatment or within 30 days after end of treatment

occurred in 65% (289/442) of patients with hematologic malignancies. Of those, 91% (263/289) were grade 3 or higher events. The most common SAEs were diarrhea or colitis, pneumonia, sepsis, febrile neutropenia, rash, and pneumonitis. The distribution of SAEs by system organ class and preferred terms is shown in Table 66. Table 67 displays the most common SAEs by preferred term in patients with hematologic malignancies.

Table 66: Serious Adverse Events Occurring in **≥3%** of Patients

System Organ Class Preferred Term	FL N=96 n (%)	CLL/SLL N=303 n %	All Heme N=442 n %
Any SAE	56 (58)	206 (68)	289 (65)
Any Grade ≥3 SAE	52 (54)	186 (61)	263 (60)
Any Grade ≥4 SAE	27 (28)	71 (23)	104 (24)
Blood and lymphatic system disorders	11 (11)	35 (12)	47 (11)
Febrile neutropenia	6 (6)	19 (6)	25 (6)
Gastrointestinal disorders	18 (19)	74 (24)	102 (23)
Diarrhea or colitis	12 (13)	59 (19)	81 (18)
General disorders and administration site conditions	15 (16)	31 (10)	50 (11)
Pyrexia	4 (4)	12 (4)	16 (4)
Infections and infestations	20 (21)	106 (35)	137 (31)
Pneumonia	8 (8)	64 (21)	79 (18)
Sepsis	6 (6)	19 (6)	25 (6)
Lower respiratory tract infection	2 (2)	12 (4)	14 (3)
Renal and urinary disorders	7 (7)	13 (4)	19 (4)
Renal insufficiency	7 (7)	9 (3)	16 (4)
Respiratory, thoracic and mediastinal disorders	7 (7)	29 (10)	43 (10)
Pneumonitis	4 (4)	14 (5)	20 (4)
Skin and subcutaneous tissue disorders	7 (7)	18 (6)	26 (6)
Rash	6 (6)	14 (5)	23 (5)

Source: FDA analysis of ADAE dataset

Table 67: Most Common Serious Adverse Events by Preferred Term

SAE Preferred Term	All Heme N=442 n (%)
Diarrhea or colitis	81 (18)
Pneumonia	79 (18)

SAE Preferred Term	All Heme N=442 n (%)
Sepsis	25 (6)
Febrile neutropenia	25 (6)
Rash	21 (5)
Pneumonitis	20 (4)
Pyrexia	16 (4)
Renal insufficiency	16 (4)

Source: FDA analysis of ADAE dataset

Reviewer Comment: The pattern of serious adverse events is consistent with the identified safety signals associated with duvelisib that include diarrhea or colitis, infection, including pneumonia, neutropenia, rash, and pneumonitis. Labeling should contain appropriate warning and precautions for the identified safety signals associated with duvelisib.

Treatment Modifications

Dropouts and/or Discontinuations Due to Adverse Effects

Table 68 provides a summary of discontinuations, dose reduction, and dose interruption due to treatment-emergent adverse events (TEAEs) with duvelisib.

Table 68: Discontinuations, Dose Reductions, and Dose Interruption Due to TEAEs

Outcome	FL N=96 n(%)	CLL/SLL N=303 n(%)	All Heme N=442 n(%)
Discontinuation due to AE	28 (29)	115 (38)	156 (35)
Dose reduction due to AE	21 (22)	71 (23)	101 (23)
Dose interruption due to AE	56 (58)	195 (64)	282 (64)

Source: FDA analysis of ADAE dataset
AE: Adverse event

The most common TEAEs leading to permanent treatment discontinuation of duvelisib in patients with hematologic malignancies were diarrhea or colitis (10%), rash (4%), pneumonia, and pneumonitis (3% each). A summary of adverse events leading to discontinuation is shown below in Table 69.

Table 69: TEAEs Leading to Discontinuation in **≥1%** of Patients

Preferred Term	FL N=96 n (%)	CLL/SLL N=303 n (%)	All Heme N=442 n (%)
Any TEAE leading to discontinuation	28 (29)	115 (38)	156 (35)
Diarrhea or colitis	4 (4)	33 (11)	43 (10)
Rash	3 (3)	14 (5)	17 (4)

Preferred Term	FL N=96 n (%)	CLL/SLL N=303 n (%)	All Heme N=442 n (%)
Pneumonia	2 (2)	10 (3)	14 (3)
Pneumonitis	3 (3)	9 (3)	14 (3)
Transaminase elevation	2 (2)	3 (1)	6 (1)
Sepsis	0	5 (2)	5 (1)

Source: FDA analysis of ADAE dataset
TEAE: Treatment emergent adverse event

The most common TEAEs leading to dose reduction of duvelisib in patients with hematologic malignancies were diarrhea or colitis (6%), transaminase elevation (4%), neutropenia (3%), rash, and febrile neutropenia (2% each). A summary of adverse events leading to dose reduction is shown below in Table 70.

Table 70: TEAEs Leading to Dose Reduction in **≥1%** of Patients

Preferred Term	FL N=96 n (%)	CLL/SLL N=303 n (%)	All Heme N=442 n (%)
Any TEAE leading to dose reduction	21 (22)	71 (23)	101 (23)
Diarrhea or colitis	5 (5)	18 (6)	26 (6)
Transaminase elevation	7 (7)	10 (3)	18 (4)
Neutropenia	1 (1)	9 (3)	12 (3)
Rash	1 (1)	8 (3)	10 (2)
Febrile neutropenia	0	7 (2)	7 (2)
Lipase increased	3 (3)	3 (1)	6 (1)

Source: FDA analysis of ADAE dataset
ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, TEAE: Treatment emergent adverse event

The most common TEAEs leading to dose interruption of duvelisib in patients with hematologic malignancies were diarrhea or colitis (19%), pneumonia (10%), neutropenia and rash (8% each), and transaminase elevation (6%). A summary of adverse events leading to dose interruption is shown below in Table 71.

Table 71: TEAEs Leading to Dose Interruption in **≥3%** of Patients

Preferred Term	FL N=96 n (%)	CLL/SLL N=303 n (%)	All Heme N=442 n (%)
Any TEAE leading to dose interruption	56 (58)	195 (64)	282 (64)
Diarrhea or colitis	13 (13)	60 (20)	84 (19)
Pneumonia	3 (3)	38 (12)	45 (10)
Neutropenia	5 (5)	30 (10)	37 (8)
Rash	8 (8)	24 (8)	34 (8)

Preferred Term	FL N=96 n (%)	CLL/SLL N=303 n (%)	All Heme N=442 n (%)
Transaminase elevation	11 (11)	14 (5)	27 (6)
Pyrexia	1 (1)	16 (5)	20 (4)
Anemia	5 (5)	9 (3)	15 (3)
Febrile neutropenia	3 (3)	10 (3)	13 (3)
Lipase increased	5 (5)	8 (3)	13 (3)
Thrombocytopenia	5 (5)	6 (2)	13 (3)

TEAE: Treatment emergent adverse event
Source: FDA analysis of ADAE dataset

Reviewer Comment: The reasons for discontinuation of duvelisib for toxicity (diarrhea or colitis, rash, pneumonia, pneumonitis, transaminase elevation, and sepsis) are consistent with the SAEs and AEs of special interest with duvelisib. Although, 35% of patients discontinued duvelisib due to toxicity, which is concerning that the risk modification strategies of dose interruption or dose reduction are not sufficient or the risks cannot be mitigated for some patients to be able to continue treatment. Labeling will need to include monitoring, comprehensive dose modification guidelines, and prophylactic or treatment guidelines as appropriate, for ARs with duvelisib.

Dose Levels
The dose levels utilized in Studies IPI-145-07 and IPI-145-06 for dose reduction due to toxicity are shown below.

Duvelisib Dose Level	Dose (mg)
1	25 twice daily
-1	15 twice daily
-2	10 twice daily
-3	5 twice daily

Any patient requiring a dose less than 5 mg twice daily was permanently discontinued from treatment. Concomitant use of a strong CYP3A4 inhibitor or inducer was prohibited. There were no dose reductions recommended for concomitant CYP3A4 inhibitor or inducers or P-gp substrates in the study protocols (IPI-145-07 and IPI-145-06).

Reviewer Comment: (b) (4) *The dose levels in the label are limited to 25 mg twice daily and 15 mg twice daily because only a 25 mg and 15 mg strength capsule are available for approval. Further, in the pivotal trials, patients were prohibited from receiving a strong CYP3A4 inhibitor and no dose reduction recommendations were included in the study protocols. Based on PK data, the label for*

duvelisib recommends reducing the dose of duvelisib to 15 mg twice daily for a patient that requires concomitant administration of a strong CYP3A4 inhibitor. See Section 6.3.2 and Appendix 19.4.5 for further information on the recommendation for a reduced dose of 15 mg twice daily for patients requiring a strong CYP3A4 inhibitor, which differs from the pivotal study protocols.

Adverse Events of Special Interest

The Applicant identified adverse events of special interest (AESIs) including infection, diarrhea or colitis, pneumonia, neutropenia, pneumonitis, rash, and transaminase elevation. A summary of adverse events of special interest is shown below in Table 72.

Table 72: Adverse Events of Special Interest

AESI	FL N=96 n (%)		CLL/SLL N=303 n (%)		All Heme Malignancies N=442 n (%)		
	All Grades	Grade **≥3**	All Grades	Grade **≥3**	All Grades	Grade **≥3**	Grade 4
Infection	53 (55)	19 (20)	195 (64)	94 (31)	276 (62)	119 (27)	24 (5)
Pneumonia	9 (9)	7 (7)	75 (25)	58 (19)	92 (21)	66 (15)	7 (2)
Diarrhea/colitis	47 (49)	19 (20)	151 (50)	71 (23)	222 (50)	101 (23)	7 (2)
Neutropenia	27 (28)	23 (24)	108 (36)	97 (32)	151 (34)	132 (30)	78 (18)
Rash	30 (31)	10 (10)	90 (30)	28 (9)	136 (31)	42 (9)	2 (<1)
Transaminase elevation	21 (22)	12 (12)	39 (13)	18 (6)	69 (16)	35 (8)	6 (1)
Pneumonitis	5 (5)	4 (4)	20 (7)	11 (4)	29 (7)	17 (4)	7 (2)

Source: FDA analysis of ADAE dataset

Each adverse event of special interest is further reviewed in Section 8.3.5.

Treatment Emergent Adverse Events and Adverse Reactions

TEAEs were assessed from the start of study drug until 30 days after the last study drug administration. TEAEs were reported in 98% (435/442) of patients with hematologic malignancies with 84% (370/442) experiencing a grade 3 or 4 event. The number of patients with TEAEs (≥6% of patients) are displayed in Table 73 in decreasing order of incidence by system organ class and preferred term.

Table 73: TEAEs Occurring in **≥6%** of Patients

System Organ Class and Preferred Term	FL N=96 n (%)		CLL/SLL N=303 n (%)		All Heme Malignancies N=442 n (%)	
	All Grades	Grade 3-4	All Grades	Grade 3-4	All Grades	Grade 3-4
Any TEAE	95 (99)	79 (82)	297 (98)	257 (85)	435 (98)	370 (84)
Blood and lymphatic system disorders	49 (51)	34 (35)	155 (51)	128 (42)	225 (51)	179 (40)

System Organ Class and Preferred Term	FL N=96 n (%)		CLL/SLL N=303 n (%)		All Heme Malignancies N=442 n (%)	
	All Grades	Grade 3-4	All Grades	Grade 3-4	All Grades	Grade 3-4
Neutropenia	27 (28)	23 (24)	108 (36)	97 (32)	151 (34)	132 (30)
Anemia	25 (26)	13 (13)	55 (18)	33 (11)	90 (20)	48 (11)
Thrombocytopenia	20 (21)	13 (13)	47 (15)	29 (10)	74 (17)	46 (10)
Febrile neutropenia	8 (8)	8 (8)	21 (7)	21 (7)	29 (7)	29 (7)
Cardiac disorders	10 (10)	1 (1)	36 (12)	13 (4)	56 (13)	15 (3)
Arrhythmia	8 (8)	1 (1)	16 (5)	3 (1)	32 (7)	5 (1)
Gastrointestinal disorders	70 (73)	24 (25)	215 (71)	88 (29)	317 (72)	123 (28)
Diarrhea/colitis	47 (49)	19 (20)	151 (50)	71 (23)	222 (50)	101 (23)
Nausea	31 (32)	3 (3)	59 (19)	0	104 (23)	4 (1)
Abdominal pain	22 (23)	2 (2)	46 (15)	5 (2)	78 (18)	9 (2)
Vomiting	21 (22)	6 (6)	39 (13)	0	69 (16)	6 (1)
Mucositis	22 (23)	1 (1)	30 (10)	4 (1)	61 (14)	6 (1)
Constipation	12 (12)	0	40 (13)	1 (<1)	57 (13)	1 (<1)
General disorders and administration site conditions	62 (65)	11 (11)	153 (50)	26 (9)	247 (56)	41 (9)
Fatigue	33 (34)	8 (8)	76 (25)	11 (4)	126 (28)	22 (5)
Pyrexia	25 (26)	0	76 (25)	7 (2)	115 (26)	7 (2)
Edema	15 (16)	1 (1)	33 (11)	4 (1)	61 (14)	6 (1)
Infections and infestations	53 (55)	17 (18)	195 (64)	88 (29)	276 (62)	111 (25)
Pneumonia	9 (9)	7 (7)	75 (25)	51 (17)	95 (21)	61 (14)
URI	12 (12)	0	71 (23)	2 (<1)	94 (21)	2 (<1)
LRI	6 (6)	1 (1)	37 (12)	9 (3)	44 (10)	10 (2)
UTI	6 (6)	0	22 (7)	4 (1)	30 (7)	4 (1)
Candidiasis	9 (9)	1 (1)	15 (5)	0	29 (7)	1 (<1)
Sepsis	6 (6)	5 (5)	21 (7)	15 (5)	27 (6)	20 (4)
Investigations	45 (47)	25 (26)	116 (38)	55 (18)	184 (42)	90 (20)
Transaminase elevation	21 (22)	12 (12)	39 (13)	18 (6)	69 (16)	35 (8)
Weight decreased	8 (8)	0	25 (8)	0	38 (9)	0
Lipase increased	9 (9)	8 (8)	17 (6)	10 (3)	27 (6)	19 (4)
Metabolism and nutrition disorders	38 (40)	14 (15)	110 (36)	39 (13)	169 (38)	61 (13.8)
Decreased appetite	10 (10)	0	43 (14)	1 (<1)	63 (14)	2 (<1)
Hypokalemia	12 (12)	2 (2)	26 (9)	13 (4)	45 (10)	17 (4)
Dehydration	8 (8)	0	15 (5)	3 (1)	28 (6)	6 (1)
Musculoskeletal and connective tissue disorders	38 (40)	3 (3)	86 (28)	11 (4)	149 (34)	17 (4)
Musculoskeletal pain	28 (29)	2 (2)	48 (16)	4 (1)	86 (19)	6 (1)
Arthralgia	11 (11)	0	24 (8)	0	46 (10)	1 (<1)
Nervous system disorders	36 (37)	2 (2)	82 (27)	10 (3)	139 (31)	13 (3)
Headache	23 (24)	1 (1)	23 (8)	0	55 (12)	1 (<1)
Dizziness	7 (7)	0	20 (7)	1 (<1)	35 (8)	1 (<1)

System Organ Class and Preferred Term	FL N=96 n (%)		CLL/SLL N=303 n (%)		All Heme Malignancies N=442 n (%)	
	All Grades	Grade 3-4	All Grades	Grade 3-4	All Grades	Grade 3-4
Renal and Urinary disorders	13 (13)	6 (6)	45 (15)	15 (5)	64 (14)	21 (5)
Renal insufficiency	11 (11)	7 (7)	31 (10)	11 (4)	43 (10)	18 (4)
Respiratory, thoracic and mediastinal disorders	45 (47)	6 (6)	127 (42)	29 (10)	201 (45)	41 (9)
Cough	26 (27)	0	65 (21)	2 (<1)	111 (25)	2 (<1)
Dyspnea	13 (13)	1 (1)	32 (11)	5 (2)	52 (12)	8 (2)
Pneumonitis	5 (5)	4 (4)	20 (7)	11 (4)	29 (7)	17 (4)
Skin and subcutaneous tissue disorders	48 (50)	10 (10)	136 (45)	33 (11)	207 (47)	47 (11)
Rash	30 (31)	10 (10)	90 (30)	28 (9)	136 (31)	41 (9)
Dry skin	14 (15)	1 (1)	18 (6)	0	40 (9)	0
Pruritus	10 (10)	0	22 (7)	3 (1)	36 (8)	3 (1)

Source: FDA analysis of ADAE dataset
LRI: Lower respiratory tract infection, URI: Upper respiratory tract infection, UTI: Urinary tract infection

The most frequently reported TEAEs in patients with hematologic malignancies are shown below in Table 74. The adverse events reported for at least 20% of patients with hematologic malignancies were diarrhea or colitis, neutropenia, rash, fatigue, pyrexia, cough, nausea, pneumonia, upper respiratory infection, and anemia.

Table 74: Most Common TEAEs **(≥10%** of Patients) by Preferred Term

Preferred Term	All Heme Malignancies N=442 n (%)	
	All Grades	Grade 3-4
Any TEAE	435 (98)	370 (84)
Diarrhea/colitis	222 (50)	100 (23)
Neutropenia	151 (34)	132 (30)
Rash	136 (31)	41 (9)
Fatigue	126 (28)	22 (5)
Pyrexia	115 (26)	7 (2)
Cough	111 (25)	2 (<1)
Nausea	104 (23)	4 (1)
Pneumonia	95 (21)	61 (14)
URI	94 (21)	2 (<1)
Anemia	90 (20)	48 (11)
Musculoskeletal pain	86 (19)	6 (1)
Abdominal pain	78 (18)	9 (2)

Preferred Term	All Heme Malignancies N=442 n (%)	
	All Grades	Grade 3-4
Thrombocytopenia	74 (17)	46 (10)
Transaminase elevation	69 (16)	35 (8)
Vomiting	69 (16)	6 (1)
Decreased appetite	63 (14)	2 (<1)
Mucositis	61 (14)	6 (1)
Edema	61 (14)	6 (1)
Constipation	57 (13)	1 (<1)
Headache	55 (12)	1 (<1)
Dyspnea	52 (12)	8 (2)
Arthralgia	46 (10)	1 (<1)
LRI	44 (10)	10 (2)
Renal insufficiency	43 (10)	18 (4)

Source: FDA analysis of ADAE dataset

Reviewer Comment: The FDA utilized grouped MedDRA preferred terms, which were accepted by the Applicant, to more accurately describe the safety profile of duvelisib. Given that duvelisib is a new molecular entity, all-cause TEAEs were considered as ARs to allow for a comprehensive description of safety for labeling. The most common ARs ***(≥20%)*** *are* diarrhea or colitis, neutropenia, rash, fatigue, pyrexia, cough, nausea, pneumonia, upper respiratory infection, and anemia.

Laboratory Abnormalities

Table 75 below summarizes common (≥10% of patients) treatment emergent hematologic laboratory abnormalities in patients with hematologic malignancies treated with duvelisib 25 mg BID.

Table 75: Treatment Emergent Hematology Laboratory Abnormalities **(≥10%** of Patients)

Hematology Laboratory Abnormality[a]	All Heme N=442		
	All Grades n (%)	Grade 3-4 n (%)	Grade 4 n (%)
Neutropenia	284 (64)	192 (43)	111 (25)
Anemia	216 (49)	73 (17)	0
Thrombocytopenia	186 (42)	73 (17)	35 (8)
Lymphocytosis	132 (30)	92 (21)	0
Leukopenia	129 (29)	34 (8)	7 (2)
Lymphopenia	90 (21)	39 (9)	13 (3)

Source: FDA analysis of ADLB dataset
[a] Represents new or worsening abnormalities, or worsening from baseline unknown

Cytopenias were common during treatment with duvelisib and 43% of patients experienced grade 3-4 neutropenia. The evaluation of laboratory data demonstrated the frequency of all grade neutropenia and grade 3-4 neutropenia was higher than that reported as a TEAE (64% versus 34% and 43% versus 30%). The same occurred with anemia (all grade: 49% vs 20%, grade 3-4: 17% vs 11%) and thrombocytopenia (all grade: 42% vs 17%, Grade 3-4: 17% vs 10%). Alternatively, 21% (91/442) patients experience grade 3-4 lymphocytosis, but all cases were asymptomatic and without development of tumor lysis syndrome.

Reviewer Comment: Hematologic lab abnormalities were common during treatment with duvelisib. Grade 3-4 neutropenia occurred in 43% of patients. Neutropenia with duvelisib is further discussed in Section 8.3.5. Interestingly, 21% of patients experienced grade 3-4 lymphocytosis, which may be due to a similar etiology as ibrutinib-associated lymphocytosis in patients with CLL where downstream signaling beyond the B-cell receptor and PI3K may allow for survival of lymphocytes in the peripheral blood despite appropriate inhibition via drug (Rossi and Gaidano 2014).

Table 76 below summarizes common (≥10% of patients) treatment emergent biochemical laboratory abnormalities in patients with hematologic malignancies treated with duvelisib 25 mg BID.

Table 76: Treatment-Emergent Biochemical Laboratory Abnormalities

Biochemical Laboratory Abnormality[a]	All Heme Malignancies N=442		
	All Grades n (%)	Grade 3-4 n (%)	Grade 4 n (%)
ALT increase	188 (43)	35 (8)	6 (1)
AST increase	173 (39)	24 (5)	3 (<1)
Hypophosphatemia	150 (34)	27 (6)	3 (<1)
Lipase increase	141 (32)	62 (14)	14 (3)
ALP increase	138 (31)	7 (2)	0 (0)
Hypoalbuminemia	126 (29)	9 (2)	0 (0)
Hyponatremia	125 (28)	34 (8)	0 (0)
Hyperkalemia	122 (28)	15 (3)	5 (1)
Hypocalcemia	117 (26)	14 (3)	3 (<1)
Creatinine increase	116 (26)	7 (2)	1 (<1)
Amylase increase	102 (23)	16 (4)	1 (<1)
Hypokalemia	91 (21)	33 (7)	7 (2)
Hyperbilirubinemia	76 (17)	7 (2)	2 (<1)
Hypomagnesemia	76 (17)	3 (<1)	1 (<1)
Hypernatremia	63 (14)	1 (<1)	0 (0)
Hypermagnesemia	61 (14)	4 (<1)	0 (0)
Hypoglycemia	49 (11)	2 (<1)	1 (<1)

Source: FDA analysis of ADLB dataset
[a] Represents new or worsening abnormalities, or worsening from baseline unknown
ALP: Alkaline phosphatase, ALT: alanine aminotransferase, AST: aspartate aminotransferase

The most common biochemical abnormalities were increased ALT and AST, with 5% to 8% being grade 3-4 elevations. Additionally, increased lipase occurred in 32% of patients, with 14% of patients experiencing a grade 3-4 elevation. However, no patients had clinical pancreatitis.

Reviewer Comment: Overall, the biochemical profile is composed of mild elevations (Grade 1 or 2) of transaminases, lipase, and electrolytes. It is important to note that hepatotoxicity is associated with the PI3K drug class administered in an oral formulation and is further discussed in Section 8.3.5.

Vital Signs

The Applicant provided a record of the vital signs and a description of the changes in vital signs during treatment with duvelisib. A review of weight, heart rate, blood pressure, and temperature did not reveal any identified safety signals

Electrocardiograms (ECGs)

For Study IPI-145-02, ECGs were performed at baseline and day 1 of cycle 1 and 2. ECGs were performed pre-dose and 1, 2, 4, 6, and 8 hours post-dose. For Study IPI-145-06, ECGs were

performed a baseline, day 1 of cycle 1, and day 15 of cycle 1. On day 15, cycle 1, ECGs were performed pre-dose, 1 hour post-dose and 4 hours post-dose. ECGs were collected at baseline and then as clinically indicated in Study IPI-145-07. TEAEs related to ECG changes were reviewed along with all cardiac events.

In patients with hematologic malignancies treated with duvelisib 25 mg BID (N=442), there was one patient with an ECG-related TEAE in the system organ class investigations. The patient experienced grade 1 prolonged QT on day 1 following the first dose of duvelisib. The investigator assessed the event as unrelated. ECG-related TEAEs in the SOC cardiac disorders included atrial fibrillation (3%), tachycardia (2%), and bradycardia (<1%).

QT interval
The evaluation of electrocardiogram QTc interval prolongation was based on Fridericia's correction (QTcF). In patients with hematologic malignancies, less than 1% of patients had a QTcF >500 ms or a QTcF increase ≥60 ms.

The FDA Interdisciplinary Review Team (IRT) for QT studies reviewed the QT study report. The following summary statements were taken from the QT-IRT review:

> No large QTc prolongation effect (i.e., >20 ms) of duvelisib (25 and 75 mg BID) was detected in the QT study.
>
> The effect of duvelisib was evaluated in a phase 1, open-label, dose escalation, maximum tolerated dose finding study in patients with advanced hematologic malignancies, which included two dose expansion cohorts (25 and 75 mg BID). A total of 210 patients received duvelisib (8 mg to 100 mg) in dose scalation and dose expansion phases of the study. Most of the data came from two expansion phase cohorts – duvelisib 25 mg BID and duvelisib 75 mg BID (the maximum tolerated dose). The data from both the escalation and expansion phases were pooled and analyzed using ER analysis, which suggest that duvelisib is not associated with large mean increases in the QTc interval and an absence of dose-response for QTc. The findings of this analysis are further supported by available preclinical results (hERG assay and monkey cardiovascular safety study) and by-time analysis of the 25 mg and 75 mg BID dose groups.
>
> The highest dose studies (75 mg BID) produce mean C_{max} values ~2-fold higher than the mean C_{max} for the therapeutic dose (25 mg BID). These concentrations are above those for the predicted worst case scenario (drug interaction with ketoconazole). It is expected from drug interaction studies that co-administration of duvelisib with ketoconazole can elevate duvelisib's mean C_{max} as much as 1.7-fold higher than the Cmax of the 25 mg BID dose.

Immunogenicity
There were no studies of anti-drug antibodies performed.

8.3.5. Analysis of Submission-Specific Safety Issues

Diarrhea or Colitis

Diarrhea or colitis is an important identified risk for patients who receive treatment with duvelisib. The Applicant identified events of diarrhea or colitis based on selected MedDRA preferred terms for diarrhea or colitis. Because the clinical presentation of diarrhea or colitis overlaps, FDA used a grouped MedDRA PT (Appendix 19.4) to evaluate the incidence and pattern of duvelisib-associated diarrhea or colitis. Table 77 summarizes the treatment-emergent adverse event of diarrhea or colitis.

Table 77: Summary of Diarrhea or Colitis TEAEs

Diarrhea or Colitis	All Heme N=442
All grade adverse events, n (%)	222 (50)
Grade ≥3 events, n (%)	101 (23)
Grade 4 events, n (%)	7 (2)
Serious adverse events, n (%)	81 (18)
Median onset All grade Grade ≥3	 4.2 months 5.6 months
Median duration All grade Grade ≥3	 17 days 17 days
Diarrhea or colitis leading to: Dose interruption, n (%) Dose reduction, n (%) Discontinuation, n (%)	 84 (19) 26 (6) 43 (10)

Source: FDA analysis of ADAE dataset

Diarrhea or colitis occurred in 50% of patients with hematologic malignancies, with just under half of those patients experiencing grade 3 or greater toxicity (45%, 101/222). Eighteen percent of patients experienced serious adverse events. Diarrhea or colitis led to dose interruption in 19%, dose reduction in 6%, and treatment discontinuation in 10% of patients. A total of 35 patients underwent biopsies to evaluate for colitis and 89% (31/35) had biopsy confirmed colitis. Further, one patient experienced a fatal event of colitis.

For all grade diarrhea or colitis, the median time to onset was 4.2 months (range 2 days to 33 months) with a median duration of 17 days (range 1 days to 29 months). For patients with grade ≥3 diarrhea or colitis, the median time to onset was 5.6 months (range 19 days to 35

months) with a median duration of 17 days (range 1 day to 4 months).

Around 50% (113/222) of patients with diarrhea or colitis received treatment that included systemic steroids, anti-diarrheal (loperamide), anti-inflammatory agents, antibiotics, and anti-fungals. The most common treatment was loperamide and budesonide. For the 113 patients that did receive treatment, 87% had an outcome of resolved or recovered. Forty-four percent of patients were able to continue duvelisib without modification, 31% percent had a dose interruption, 12% had a dose reduction, and 12% discontinued treatment. For patients that were rechallenged following an event of diarrhea or colitis, around 4% experienced recurrence of the diarrhea or colitis.

Reviewer Comment: Duvelisib caused diarrhea and colitis, including life-threatening and one fatal case of colitis. Numerous patients were treated with anti-diarrheal agents or systemic steroids, with the most common treatments including loperamide and budesonide. Based on the data, there is no established standard of treatment for duvelisib-associated diarrhea or colitis, but loperamide and budesonide may be considered. Labeling will need to include a warning for diarrhea or colitis and dose modifications to ensure safe use of the drug. Patients should be aware that duvelisib should be discontinued in the event of severe diarrhea or colitis.

Neutropenia

Neutropenia was a common laboratory abnormality during treatment with duvelisib. Based on laboratory data, 64% (284/442) of patients with hematologic malignancies treated with duvelisib 25 mg BID experienced any-grade neutropenia. Of the 284 patients with neutropenia, 68% (192/284) experienced grade 3 or greater events and 39% (111/284) had Grade 4 neutropenia. For all-grade neutropenia, the median time to onset was 27 days (range 2 days to 31 months) with a median duration of 15 days (range 1 day to 24 months). For grade ≥3 events, the median time to onset was 50 days (range 3 days to 31 months) with median duration of 14 days (range 1 day to 11 months).
Adverse events of neutropenia led to dose interruption in 10% of patients, dose reduction in 4% of patients, and treatment discontinuation in 1% of patients. Around 13% of patients received treatment with granulocyte colony stimulating factor for an event of neutropenia. Table 78 displays a summary of neutropenia events in patients treated with duvelisib.

Table 78: Summary of Neutropenia TEAEs

Neutropenia	All Heme N=442
All grade*, n (%)	284 (64)
Grade ≥3 events*, n (%)	192 (43)
Grade 4 events*, n (%)	111 (25)
Serious adverse events, n (%)	28 (6)
Median onset* All grade	27 days

Neutropenia	All Heme N=442
Grade ≥3	50 days
Median duration All grade Grade ≥3	 15 days 14 days
Neutropenia leading to: Dose interruption, n (%) Dose reduction, n (%) Discontinuation, n (%)	 44 (10) 18 (4) 4 (1)

Source: FDA analysis of ADAE and ADLB dataset
*Based on laboratory data

Additionally, the Applicant performed a risk assessment, based on laboratory data, that determined that patients with grade 1-2 neutropenia exhibit a 13% risk of infection within 1 week of the neutropenia and patients with grade 3-4 neutropenia exhibit a 26% risk of infection within 1 week.

Reviewer Comment: Treatment with duvelisib is associated with grade 3-4 neutropenia and is associated with a 26% risk of infection within 1 week of the neutropenia. Labeling will need to include a warning for neutropenia and appropriate treatment modifications to attempt to mitigate risk for infection.

Infection

Infection was one of the most common adverse events experienced by patients with hematologic malignancies receiving duvelisib 25 mg BID, with 62% (276/442) reporting any-grade infection. Of the 276 patients reporting an infection, 43% (119/276) experienced a grade 3 or greater infection and 6% (18/276) had a fatal infection. For all-grade infections the median time to onset was 3 months (range 1 day to 32 months) with a median duration of 14 days (range 1 day to 23 months).
For grade ≥3 infections the median time to onset was 5 months (range 2 days to 27 months) with a median duration of 11 days (range 1 day to 5 months). Duvelisib was held for any infection requiring antimicrobial treatment. Thus, adverse events of infection led to dose interruption in 20% of patients, dose reduction in 2% of patients, and 5% of patients discontinued treatment. Table 79 displays a summary of infection events in patients treated with duvelisib.

Table 79: Summary of Infection TEAEs

Infection	All Heme N=442
All grade, n (%)	276 (62)
Grade ≥3 events, n (%)	119 (27)

Infection	All Heme N=442
Grade 4 events, n (%)	24 (5)
Grade 5 events, n (%)	18 (4)
Serious adverse events, n (%)	137 (31)
Median onset	
All grade	3 months
Grade ≥3	5 months
Median duration	
All grade	14 days
Grade ≥3	11 days
Infection leading to:	
Dose interruption, n (%)	87 (20)
Dose reduction, n (%)	8 (2)
Discontinuation, n (%)	24 (5)

Source: FDA analysis of ADAE dataset

The most common infections reported included pneumonia, upper respiratory tract infections and lower respiratory infections (Table 80). The most common grade ≥3 infections were pneumonia and sepsis (Table 80), which were also the most common cause of fatal infections.

Table 80: Summary of Common Infections

Infections and Infestations	All Heme N=442 n (%)
Common all-grade infections	
Pneumonia	95 (21)
URI	94 (21)
LRTI	44 (10)
UTI	30 (7)
Candidiasis	29 (7)
Sepsis	27 (6)
HSV infection	22 (5)
Respiratory tract infection	21 (5)
Skin infection	19 (4)
Common grade **≥3** infections	
Pneumonia	68 (15)
Sepsis	26 (6)
LRTI	11 (2)
Gastroenteritis	5 (1)
Skin infection	5 (1)
UTI	4 (1)

Source: FDA analysis of ADAE dataset
HSV: Herpes simplex virus, LRTI: Lower respiratory tract infection, URI: Upper respiratory tract infection, UTI: Urinary tract infection

Pneumonia was the most common infection reported by patients treated with duvelisib 25 mg BID. A total of 95 patients (21%) experienced an event of pneumonia with 72% of cases (68/95) being grade 3 or greater events. For all-grade pneumonia, the median time to onset was 5 months (range 7 days to 27 months) with a median duration of 13 days (range 1 day to 4 months). For grade ≥3 pneumonia, the median time to onset was 5 months (range 13 days to 27 months) with a median duration of 12 days (range 1 day to 2 months). Pneumonia was one of the leading causes of death (2%) in patients treated with duvelisib. Table 81 summarizes pneumonia events in patients treated with duvelisib.

Table 81: Summary of Pneumonia TEAEs

Pneumonia	All Heme N=442
All grade, n (%)	95 (21)
Grade ≥3 events, n (%)	68 (15)
Grade 4 events, n (%)	7 (2)
Grade 5 events, n (%)	8 (2)
Serious adverse events, n (%)	79 (18)
Median onset All grade Grade ≥3	 5 months 5 months
Median duration All grade Grade ≥3	 13 days 12 days
Pneumonia leading to: Dose interruption, n (%) Dose reduction, n (%) Discontinuation, n (%)	 45 (10) 2 (<1) 14 (3)

Source: FDA analysis of ADAE dataset

Reviewer Comment: Life-threatening and fatal infections, including pneumonia, were the most common adverse events reported in patients treated with duvelisib. Treatment with duvelisib is associated with an increased risk of serious and fatal infections, which may be further increased in the setting of duvelisib-associated neutropenia. Labeling will need to include a warning for fatal and/or serious infections, including pneumonia.

Rash

To evaluate dermatologic toxicity, FDA used a grouped preferred term to characterize the incidence and pattern of duvelisib-associated rash (Appendix 19.4).

In patients with hematologic malignancies, 30% (136/442) of patients reported an event of rash, with 31% (42/136) of those being grade 3 or greater events. In general, the rash was described as a regional, pruritic, erythematous, and maculopapular rash. For all-grade events of rash, the median time to onset was 3 months (range 1 days to 29 months) with a median duration of 25 days (range 1 day to 37 months). For grade ≥3 rash, the median time to onset was 4 months (range 10 days to 18 months) with a median duration of 19 days (range 2 day to 8 months). Common treatment for rash included corticosteroids and antihistamines. There was one case each of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, and drug reaction with eosinophilia and systemic symptoms (DRESS). The cases of TEN and DRESS were fatal events. Table 82 displays a summary of rash in patients with hematologic malignancies treated with duvelisib.

Table 82: Summary of Rash TEAEs

Rash	All Heme N=442
All grade, n (%)	136 (30)
Grade ≥3 events, n (%)	42 (9)
Grade 4 events, n (%)	2 (<1)
Serious adverse events, n (%)	23 (5)
Median onset All grade Grade ≥3	 3 months 4 months
Median duration All grade Grade ≥3	 25 days 19 days
Rash leading to: Dose interruption, n (%) Dose reduction, n (%) Discontinuation, n (%)	 34 (8) 10 (2) 18 (4)

Source: FDA analysis of ADAE dataset

Reviewer Comment: Duvelisib is associated with rash, which can be severe and possibly fatal. Labeling needs to include a warning for serious, including fatal, cutaneous reactions, which includes discontinuation of duvelisib in the setting of severe or life-threatening cutaneous reactions.

Hepatotoxicity

Based on laboratory data, 51% of patients with hematologic malignancies receiving duvelisib 25 mg BID experienced any grade elevation in either AST or ALT. Grade 3 to 4 ALT or AST elevation occurred in 10% of patients with a median onset of 2 months (range of 15 days to 19 months) and a median duration of 15 days (range 3 to 60 days). For patients receiving duvelisib 25 mg twice daily, transaminase elevation led to dose interruption in 6%, dose reduction in 4%, and discontinuation in 1%. The Applicant reported no cases of liver failure in patients with

hematologic malignancies.

Hy's Law

The Applicant performed an analysis for Hy's law cases and used a definition of AST or ALT values >3 times the upper limit of normal in combination with total bilirubin value >2 times the upper limit of normal within 7 days of the transaminase elevation. The FDA clinical reviewer corroborated the Applicant's analysis and identified eight cases that met the laboratory criteria for Hy's law. Table 83 displays the liver-related laboratory parameters greater than the specified upper limit of normal and the laboratory definition of Hy's law.

Table 83: Liver Laboratory Abnormalities

Liver Laboratory Parameter	FL N=96		CLL/SLL N=303		All Heme N=442	
	Events/ Patients[a] (No.)	% of Patients	Events/ Patients (No.)	% of Patients	Events/ Patients (No.)	% of Patients
AST or ALT						
AST or ALT >3x ULN	17/95	18	53/302	18	77/440	18
AST or ALT >5x ULN	10/95	11	26/302	9	41/440	9
AST or ALT >20x ULN	2/95	2	6/302	2	8/440	2
Total bilirubin						
TB >1.5x ULN	9/95	9	20/302	7	34/440	8
TB >2x ULN	5/95	5	8/302	3	18/440	4
Combination						
AST or ALT >3x ULN and TB >2x ULN within 7 days	4/95	4	3/302	1	8/440	2

Source: FDA analysis of ADLB dataset
[a] Denominator represents the number of patients with available laboratory data
ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, TB: Total bilirubin, ULN: Upper limit of normal

Of the eight patients meeting laboratory criteria for Hy's law, 7 patients had concomitant elevation of alkaline phosphatase. A description of the remaining patient is provided:

Subject (b) (6) was a 55-year-old female with SLL treated with duvelisib 25 mg BID. The patient developed AST grade 3, ALT grade 4, total bilirubin grade 2 on Day 65 of treatment. Alkaline phosphatase was within normal limits. Duvelisib 25 mg BID was continued and AST and ALT recovered to grade 1 and bilirubin remained grade 2, but trending down, by Day 81. On Day 86, AST and ALT returned to grade 3 and bilirubin was normal. Alkaline phosphatase remained less than two times the upper limit of normal throughout this time. Duvelisib was interrupted on Day 87 and AST and ALT were normal by Day 108 and bilirubin by Day 115. Duvelisib was resumed at 15 mg BID on Day 120 and able to be escalated back to 25 mg BID on Day 171. The patient experienced intermittent grade 1 or 2 elevations of AST, ALT and/or bilirubin for the remainder of treatment and continued duvelisib until Day 473. Duvelisib was discontinued due

to investigator's decision. The patient did not experience drug-induced liver injury and was able to tolerate duvelisib with close monitoring, treatment interruption, and dose reduction.

Reviewer Comment: Duvelisib caused hepatotoxicity as indicated by grade 3 to 4 transaminase elevation. The incidence of any grade elevation of AST or ALT is high at 51% and grade 3-4 elevations at 10%. The cases of potential Hy's law were not consistent with drug-induced liver injury, however life-threatening and fatal cases may have been prevented by treatment modifications in response to close monitoring as part of the clinical trial. Therefore, labeling will need to include hepatotoxicity as a Warning and Precaution to ensure safe use of duvelisib. The pattern of duvelisib-associated hepatotoxicity, specific monitoring procedures, and dose modifications will need to be included in labeling to inform healthcare providers and patients.

Pneumonitis

The Applicant identified suspected non-infections pneumonitis events using MedDRA PTs that included acute interstitial pneumonitis, interstitial lung disease, lung infiltration and pneumonitis. The FDA included acute respiratory distress syndrome in the MedDRA PTs for pneumonitis. In patients with hematologic malignancies treated with duvelisib 25 mg BID, 29 patients (7%) experienced an event of pneumonitis. Of the 29 patients, 17 patients (59%) had grade ≥3 events with 1 patient experiencing a fatal event of pneumonitis. Twenty patients (4%) had a serious adverse event of pneumonitis. Pneumonitis was one of the most common reasons for treatment discontinuation (3%). Of the 29 patients with pneumonitis, 14 (47%) received treatment. The most common treatment was systemic corticosteroids. Table 84 displays a summary of non-infectious pneumonitis events in patients treated with duvelisib.

Table 84: Summary of Pneumonitis TEAEs

Pneumonitis	All Heme N=442
All grade adverse events, n (%)	29 (7)
Grade ≥3 events, n (%)	17 (4)
Grade 4 events, n (%)	7 (2)
Serious adverse events, n (%)	20 (4)
Median onset All grade Grade ≥3	 4.3 months 3.9 months
Median duration All grade Grade ≥3	 41 days 27 days
Pneumonitis leading to: Dose interruption, n (%) Dose reduction, n (%) Discontinuation, n (%)	 84 (19) 26 (6) 43 (10)

Source: FDA analysis of ADAE dataset

For all grade pneumonitis, the median time to onset was 4.3 months (range 9 days to 27 months) with a median duration of 41 days (range 7 days to 7 months). For patients with grade ≥3 pneumonitis, the median time to onset was 3.9 months (range 36 days to 27 months) with a median duration of 27 days (range 11 days to 4 months).

Reviewer Comment: The evidence suggests that duvelisib may contribute to direct lung toxicity. The overall incidence of pneumonitis remains unclear since it is a diagnosis of exclusion, however 59% of patients with pneumonitis experienced grade 3 or greater pneumonitis and one patient experienced a fatal event. Despite 14 of 29 patients receiving treatment with systemic corticosteroids, the optimal treatment strategy for duvelisib-associated pneumonitis is not established. Labeling will need to include a warning for pneumonitis with appropriate dose modifications to ensure safe use.

AESIs by Prior Therapy

The FDA evaluated adverse events of special interest with duvelisib that included diarrhea or colitis, hepatotoxicity, pneumonitis, rash, and infection by prior therapy. The analysis is based upon the hypothesis that as the median number of prior therapies increases, the risk of immune-mediated toxicity decreases because of lasting-effects of prior treatment and the effect of disease itself on the immune system along with accruing immune senescence with age (Lampson and Kasar et al. 2016). Since the collection of immune-mediated adverse events was not a pre-specified component of duvelisib safety data collection, the Agency performed the analysis on the identified adverse events of special interest. In patients with hematologic malignancies (N=442), the median number of prior therapies was 2 (range 0 to 18). Thus, the analysis was conducted using patients with 2 or less prior therapies versus 3 or more. Table 85 provides a summary of the adverse events of special interest by prior therapy in patients with hematologic malignancies.

Table 85: Adverse Events of Special Interest by Prior Therapy

Adverse events of special interest	All Heme N=442				Risk Difference
	# prior therapies				
	≤2 N=222		**≥3** N=220		
	n	%	n	%	
Diarrhea/colitis					
All-grade events	116	52	106	48	4
Grade ≥3	56	25	45	20	5
Serious adverse events	48	22	33	15	7
Hepatotoxicity					
All-grade events*	110	49	115	52	-3
Grade ≥3*	21	9	16	7	2
Serious adverse events	6	3	1	<1	3

Adverse events of special interest	All Heme N=442				Risk Difference
	# prior therapies				
	≤2 N=222		**≥3** N=220		
	n	%	n	%	
Pneumonitis					
All-grade events	17	8	12	5	3
Grade ≥3	9	4	8	4	0
Serious adverse events	12	5	8	4	1
Rash					
All-grade events	73	33	63	29	4
Grade ≥3	28	13	14	6	7
Serious adverse events	15	7	8	4	3
Infection					
All-grade events	132	59	144	65	-6
Grade ≥3	54	24	65	29	-5
Serious adverse events	60	27	77	35	-8

Source: FDA analysis of ADAE and ADLB dataset
*Based on laboratory data

Based on the incidence of serious adverse events, patients with 2 prior therapies or less had a higher incidence of diarrhea or colitis, hepatotoxicity, and rash. Patients with 3 or more prior therapies had an 8% higher incidence of serious adverse events of infection. The risk difference for all-grade AEs, Grade ≥3 AEs and SAEs between the groups are marginal and do not substantially alter the safety profile of duvelisib when evaluating one group versus the other.

CLL/SLL

The adverse events of special interest were evaluated in the CLL/SLL population because the initial report of an increased risk of immune-mediated AEs was in patients with untreated CLL ((Lampson and Kasar et.al. 2016). The median number of prior therapies in patients with CLL was 2 (range 1 to 18) and the analysis was conducted using patients with 2 or less prior therapies versus 3 or more. Table 86 provides a summary of AESIs in patients with CLL by prior therapy.

Table 86: Adverse Events of Special Interest by Prior Therapy in Patients With CLL/SLL

Immune-related adverse events	CLL/SLL N=303				Risk Difference
	# prior therapies				
	≤2 N=156		**≥3** N=147		
	n	%	n	%	

Immune-related adverse events	CLL/SLL N=303				Risk Difference
	# prior therapies				
	≤2 N=156		**≥3** N=147		
	n	%	n	%	
Diarrhea/colitis					
All-grade events	82	53	69	47	6
Grade ≥3	42	27	29	20	7
Serious adverse events	37	24	22	15	9
Hepatotoxicity					
All-grade events*	73	47	73	50	-3
Grade ≥3*	14	9	10	7	2
Serious adverse events	2	1	0	0	1
Pneumonitis					
All-grade events	13	8	7	5	3
Grade ≥3	7	4	4	3	1
Serious adverse events	10	6	4	3	3
Rash					
All-grade events	54	35	36	24	11
Grade ≥3	21	13	8	5	8
Serious adverse events	13	8	2	1	7
Infection					
All-grade events	94	60	101	69	-9
Grade ≥3	44	28	50	34	-6
Serious adverse events	47	30	59	40	-10

Source: FDA analysis of ADAE dataset
*Based upon laboratory data

Based on the incidence of serious adverse events, patients with CLL/SLL with 2 prior therapies or less had a higher incidence of diarrhea or colitis, pneumonitis, and rash. Patients with 3 or more prior therapies had a 10% higher incidence of serious adverse events of infection. The risk difference for all-grade AEs, Grade ≥3 AEs and SAEs displayed a trend for increased risk of diarrhea or colitis, pneumonitis, and rash for patients with 2 or less prior therapies compared to those with 3 or more. The risk of all-grade, Grade ≥3, or SAEs of infection remains higher in patients with 3 or more prior therapies.

Reviewer Comment: The toxicities diarrhea or colitis, hepatotoxicity, pneumonitis, and rash may have an immune-mediated component. The data above have potential to support the hypothesis that patients with less prior therapy have a more robust immune system and are at higher risk of immune-mediated toxicity, but further investigation and evaluation is required. Patients with hematologic malignancies, including the subset with CLL/SLL, that had

3 or more prior therapies did show an increased risk of infection, including serious cases, which is consistent with the fact that more heavily pretreated patients are at higher risk of infection. Nevertheless, the trends noted above are worth consideration given supportive literature that patients with a more intact immune system are at higher risk of immune-mediated toxicity from a PI3K inhibitor and patients with a high burden of comorbidities are at increased risk of toxicity, including fatal events.

8.3.6. Clinical Outcome Assessment Analyses Informing Safety/Tolerability

In Study IPI-145-07, two quality of life instruments were used, the EuroQol-5D health related QoL assessment (EQ-5D) and the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F). The EQ-5D contain 5 dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression. The FACIT-F contains 5 subscales: Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, Functional Well-Being, and Fatigue. Each scale used a Likert scale for item responses.

In Study IPI-145-07, there were no discernable differences in any of the domains in the EQ-5D or FACIT-F between treatment arms.

In Study IPI-145-06, the EQ-5D was used to measure health-related quality of life. There were minor improvements from baseline in mobility, usual activities, pain/discomfort, and anxiety/depression. However, by the end of treatment, scores in all domains tended to return towards baseline values.

Reviewer Comment: Study IPI-145-06 and -06 were open-label trials and the -06 trial was a single-arm trial, which confounds the results of patient-reported outcomes. The analyses revealed no difference between treatment arms in Study IPI-145-07 and no substantial improvements in any domain in Study IPI-145-06. The patient reported outcome data will not be included in the prescribing information.

8.3.7. Safety Analyses by Demographic Subgroups

Age
There were no relevant differences in TEAEs when assessed by age in patients with hematologic malignancies. Patients 65 years and older had a 5% and 9% increase in Grade ≥3 adverse events and SAEs, respectively, compared to patients younger than 65 years. Patients 65 years and older had slightly more diarrhea or colitis, anemia, fatigue, pneumonia, and hepatotoxicity compared to patients younger than 65 years. Table 87 lists the adverse events by age group in decreasing order of the difference in incidence between patient ≥65 years of age versus <65 years of age.

Table 87: TEAEs by Age

	≥65 Years N=270		<65 Years N=172		Risk Difference
	n	%	n	%	
Any TEAE	267	99	168	98	1
Grade ≥3 TEAE	237	88	142	83	5
SAE	186	69	103	60	9
Preferred Term					
Diarrhea/Colitis	141	52	81	47	5
Anemia	60	22	30	17	5
Fatigue	81	30	45	26	4
Pneumonia	62	23	33	19	4
Hepatotoxicity	46	17	23	13	4
Neutropenia	91	34	60	35	-1
MSK pain	51	19	35	20	-1
Cough	66	24	45	26	-2
Rash	78	29	60	35	-6
Pyrexia	64	24	51	30	-6
Nausea	58	21	46	27	-6
URI	51	19	43	25	-6

Source: FDA analysis of ADAE dataset

Gender

There were some differences in TEAEs when assessed by gender in patients with hematologic malignancies. Female patients experienced a 3% and 7% increase in grade ≥3 adverse events and SAEs, respectively, compared to male patients. Male patients experience a 12% and 7% higher incidence of pneumonia and rash compared to female patients. Whereas female patients experienced higher rates of vomiting (11%), nausea (13%) and diarrhea or colitis (16%) compared to male patients. Despite the difference in adverse events by gender, the overall safety profile with duvelisib remains consistent with the profile in patients with hematologic malignancies. Table 88 list the adverse events by gender in decreasing order of the difference in incidence between male and female patients.

Table 88: TEAEs by Gender

	Male N=289		Female N=153		Risk Difference
	n	%	n	%	
Any TEAE	283	98	152	99	-1
Grade ≥3 TEAE	245	85	134	88	-3
SAE	182	63	107	70	-7
Preferred Term					
Pneumonia	74	26	21	14	12

	Male N=289		Female N=153		Risk Difference
	n	%	n	%	
Rash	98	34	41	27	7
Cough	73	25	38	25	0
Anemia	59	20	31	20	0
URI	62	21	32	21	0
Pyrexia	75	26	40	26	0
Fatigue	76	26	50	33	-7
Neutropenia	91	31	60	39	-8
MSK pain	48	17	38	25	-8
Vomiting	34	12	35	23	-11
Nausea	55	19	49	32	-13
Diarrhea/colitis	129	45	93	61	-16

Source: FDA analysis of ADAE dataset

A further analysis of TEAEs by race, ethnicity, and body mass index did not reveal clinically meaningful differences. When separated by race or ethnicity, the number of patients were unequal with the majority of patients being Caucasian (407/442, 92%). Similar incidence of TEAEs were reported among three BMI categories 1) BMI <25, 2) BMI ≥25 to <30, and 3) BMI ≥30.

Reviewer Comment: There were difference in TEAEs by gender, however the overall safety profile remained consistent with the overall population of patients with hematologic malignancies. There were no clinically meaningful differences in safety when assessed by age, race, and body mass index.

8.3.8. Specific Safety Studies/Clinical Trials

A total of 273 healthy subjects were exposed to duvelisib, including single dose and multiple dose cohorts, through several clinical pharmacology and clinical studies/trials (Table 89). In the 273 healthy subjects, there were no SAEs, AEs leading to discontinuation, or deaths reported.

Table 89: Clinical Studies in Healthy Subjects

Study Number	Title	Number of Healthy Subjects Receiving Duvelisib
IPI-145-01	A Randomized, Double-Blind, Placebo-Controlled, Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics (PK), Pharmacodynamics (PD) and the Effect of Food and Ketoconazole on the PK of IPI-145 when Administered to Healthy	106

Study Number	Title	Number of Healthy Subjects Receiving Duvelisib
	Subjects	
IPI-145-05	A Phase 1, Open-Label Study of the Absorption, Distribution, Metabolism and Excretion of ^{14}C-Labeled IPI-145 and the Absolute Bioavailability of IPI-145 in Health Subjects	6
IPI-145-10	A Phase 1, Open-Label, Single-Sequence, 2-Period Study to Evaluate the Effect of IPI-145 on Single-Dose PK of Midazolam in Healthy Subjects	14
IPI-145-11	A Phase 1, Open-Label, Single-Sequence, 2-Period Study to Evaluate the Effect of Rifampin on the PK of IPI-145 in Healthy Subjects	14
IPI-145-15	A Phase 1, Open-Label, 2-Part Study to Evaluate the Bioequivalence of the IPI-145 Market-Image Formulation to the IPI-145 Clinical-Trial Formulation and to Assess the Effect of Food on the PK of IPI-145 in Healthy Adult Subjects	103
M15-412	A Blinded, Randomized, Placebo-Controlled Single Ascending Dose Study and Open-Label Multiple Dose Study to Evaluate the Safety, Tolerability and PK of Duvelisib in Japanese Healthy Adult Male Subjects	27
M15-789	A Phase 1, Open-Label Study to Assess the PK of Duvelisib in Chinese Healthy Adult Subjects	3

Source: Summary of Clinical Safety Section 1.1; Table 2
Total Number of Health Subjects =273

8.3.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

[There were no analyses for second cancers submitted by the Applicant. FDA reviewed the adverse event dataset for patients that developed neoplasms (identified using the Neoplasms, Benign, Malignant, and Unspecified SOC).

Human Reproduction and Pregnancy

Duvelisib has not been administered to pregnant or lactating women.

Pediatrics and Assessment of Effects on Growth

There were no children enrolled in any of the studies submitted with this application. The safety of duvelisib in pediatric patients has not been established.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There was one experience of a potential overdose in the clinical studies of duvelisib. A patient may have taken more than the prescribed dose, amount unknown, while under the influence of alcohol. The patient had reports of grade 3 diarrhea, grade 1 flushing, grade 3 rash, and Grade 1 nausea around the time of the potential overdose. The patient was withdrawn from subsequent duvelisib treatment due to the protocol violation. Nevertheless, duvelisib is prescribed by specialists in hematology and oncology and there is no evidence that duvelisib produces physical or psychological dependence in patients with hematologic malignancies.

8.3.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Duvelisib is not marketed in any country. There is no postmarketing safety data available.

Expectations on Safety in the Postmarket Setting

Safety in the postmarket setting is expected to be similar to that observed on the clinical trials reviewed in this application.

8.3.11. Integrated Assessment of Safety

The evaluation of safety with duvelisib demonstrated a substantial risk for serious toxicity, including fatal events.

The safety evaluation was based on two single-arm, open-label clinical trials, one open-label extension clinical trial, and one randomized, open-label, actively controlled clinical trial totaling 442 patients with hematologic malignancies primarily including CLL/SLL (69%) and FL (22%). Patients received duvelisib 25 mg twice daily until unacceptable toxicity or progressive disease. The median exposure duration for patients with hematologic malignancies was 9 months (range <1 month to 53 months), with 40% of patients having at least 12 months of exposure.

For the 442 patients, the median age was 67 years (range 30 to 90 years), 65% were male, 92% were White, and 93% had an ECOG performance status of 0 to 1. Patients had a median of 2 prior therapies (range 0 to 18). The trials from which the safety population was derived required hepatic transaminases at least ≤3 times ULN, total bilirubin ≤1.5 times ULN, and serum creatinine ≤1.5 times ULN. Patients were excluded for prior exposure to a PI3K inhibitor within 4 weeks.

Analysis of the 442 patients with hematologic malignancies revealed:

- Thirty-six patients (8%) died in the absence of progressive disease within 30 days of the last dose of duvelisib. Fatal ARs were primarily due to infection. Other fatal ARs included diarrhea or colitis, cutaneous reactions, and pneumonitis.

- In the randomized, actively controlled, phase 3 trial in patients with relapsed or refractory CLL/SLL, an exploratory competing risk analysis of mortality without progressive disease versus mortality with progressive disease demonstrated that patients in the duvelisib arm had a 16% cumulative incidence of mortality without progressive disease compared to 9% in the ofatumumab arm, suggesting an increased risk of death from toxicity with duvelisib compared to ofatumumab.
- Serious adverse events were reported for 65% of patients. The most common SAEs were diarrhea or colitis, pneumonia, sepsis, febrile neutropenia, rash, and pneumonitis.
- Grade 3 or greater ARs occurred in 84% of patients, most often due to infection, including pneumonia and sepsis, diarrhea or colitis, cytopenias, cutaneous reactions, hepatotoxicity, and pneumonitis.
- The most common ARs (≥20%) in patients with hematologic malignancies were diarrhea or colitis, neutropenia, rash, fatigue, pyrexia, cough, nausea, upper respiratory infection, pneumonia, musculoskeletal pain, and anemia.
- Grade 3 or greater laboratory abnormalities in ≥5% of patients included neutropenia, lymphocytosis, lipase increased, anemia, thrombocytopenia, lymphopenia, leukopenia, ALT increased, hyponatremia, AST increased, and hypophosphatemia.
- A total of 35% of patients discontinued duvelisib due to an adverse reaction, most often due to diarrhea or colitis, infection, and rash. Duvelisib was dose reduced in 23% of patients due to an adverse reaction, most often due to diarrhea or colitis, and hepatotoxicity. The median time to first dose modification or discontinuation was 4 months (range 0.1 to 21 months), with 75% of patients having their first dose modification or discontinuation within 7 months.

In summary, the primary safety issues identified with duvelisib include serious, including fatal, infections, diarrhea or colitis, cutaneous reactions, and pneumonitis, along with serious hepatotoxicity and neutropenia. Further, an exploratory competing risk analysis of mortality without progressive disease in a randomized clinical trial suggests that patients in the duvelisib arm had an increased risk of death from toxicity with duvelisib (16%) compared to ofatumumab (9%). Additional notable findings include a 65% incidence of SAEs, an 84% incidence of grade 3 or greater ARs, and a total of 35% of patients that discontinued duvelisib due to an AR. The substantial risk with duvelisib is primarily driven by infections, diarrhea or colitis, cutaneous reactions, pneumonitis, hepatotoxicity, and neutropenia. Therefore, due to the frequency and seriousness of duvelisib-associated toxicity, a boxed warning in the U.S. prescribing information is warranted for infections, diarrhea or colitis, cutaneous reactions, and pneumonitis in combination with a REMS to help ensure safe use of the drug. The toxicities to be included in the boxed warning included fatal events, and each contain an SAE incidence that is consistent with or higher than other in-class PI3K agents. Additional Warning and Precautions are recommended for hepatotoxicity and neutropenia.

For the consideration of safety, information on same-in-class agents from the literature and postmarketing experience warrant consideration. Idelalisib, the first-in-class PI3K inhibitor, received regular approval in July 2014 for patients with relapsed CLL in combination with

rituximab and accelerated approval as monotherapy for patients with relapsed FL and SLL. In March 2016, three ongoing phase 3 trials evaluating the addition of idelalisib to standard therapies in front-line CLL and relapsed indolent forms of NHL (Trials: GS-US-312-0123, GS-US-313-0124, and GS-US-313-0125) demonstrated increased rates of serious adverse events and decreased overall survival on the idelalisib arms. Deaths on the idelalisib arm were primarily due to infections, including fatal PJP and CMV infections, and respiratory disorders (Ward 2016). The rates of serious infections, diarrhea or colitis, cutaneous reactions, pneumonitis, and hepatotoxicity were consistently higher in the idelalisib arms (Ward 2016). Therefore, the three phase 3 trials along with three other trials with idelalisib were terminated due to increased toxicity and decreased overall survival.

Additional evaluation with idelalisib has revealed that serious adverse events are more common in less heavily pretreated patients and in younger patients (Lampson and Kasar et al. 2016; Ward 2016; Greenwell et al. 2017). The more common SAEs included diarrhea or colitis, hepatotoxicity, pneumonitis, and cutaneous reactions (Ward 2016). A study of patients with CLL receiving idelalisib as upfront therapy demonstrated a high rate of serious hepatoxicity and identified risk factors included less prior therapy, younger age, mutated IGHV, and decreased regulatory T cells. An autoimmune mechanism for the hepatotoxicity was identified with activated T-cell infiltrate on liver biopsy and increased cytokine levels of CCL-3 and CCL-4, which are known mediators of human immune-mediated hepatitis (Lampson and Kasar et al. 2016). Additionally, several studies, non-clinical and clinical, have demonstrated that PI3K-δ inhibition can induce an autoimmune colitis with histopathology showing intraepithelial lymphocytosis (Okkenhaug et al. 2002; Louie et al. 2015; Weidner et al. 2015). Further, PI3K-δ inhibition causes inhibition of regulatory T cells, which in clinical and non-clinical studies, disruption of regulatory T cells leads to autoimmune syndromes with hepatitis, enteritis, and pneumonitis (Patton et al. 2006; Torgerson and Ochs, 2007; Ramsdell and Ziegler, 2014; Lampson and Kasar et al. 2016). Collectively, the evidence supports the hypothesis that patients with less prior therapy and younger age have a more robust immune system and may be at increased risk for immune-mediated toxicity with PI3K inhibitors. In patients with hematologic malignancies receiving duvelisib, the incidence of serious adverse events for diarrhea or colitis, pneumonitis, and cutaneous reactions were numerically higher for patients with 2 or less prior therapies compared to 3 or more prior therapies, but further investigation is warranted. Nevertheless, the potential risks for immune-mediated toxicity, increased rates of serious adverse events, and potential for fatal toxicities is important when considering an appropriate patient population to receive duvelisib.

SUMMARY AND CONCLUSIONS – Statistical and Clinical

8.4. Statistical Issues

Study IPI-145-07 demonstrated a statistically significant improvement in PFS and ORR with duvelisib compared to ofatumumab, but failed to demonstrate any significant difference in OS.

Since the median OS time was not reached in either arm at the time of data cut-off, the OS follow-up should be continued.

Study IPI-145-06 was a single-arm study with ORR as the primary endpoint. Therefore, no statistical inference was performed and only descriptive statistics such as estimate and 95% CI were presented. Also, time-to-event endpoints such as PFS and OS were not analyzed because their clinical significance cannot be adequately interpreted in single-arm studies. In addition, due to high early censoring rate, the follow-up time was not sufficient and the DOR estimate may not be reliable.

8.5. Conclusions and Recommendations

The benefit-risk assessment supports regular approval of duvelisib for the treatment of adult patients with relapsed or refractory CLL or SLL after at least two prior therapies and accelerated approval of duvelisib for the treatment of adult patients with refractory FL after at least two prior systemic therapies.

Efficacy:
Efficacy in patients with relapsed or refractory CLL/SLL is based on the results of a single, multicenter, open-label, randomized, actively controlled phase 3 trial comparing duvelisib to ofatumumab in 319 adult patients with CLL/SLL after at least one prior therapy. In the analysis of the primary endpoint, PFS per IRC, patients in the duvelisib arm had a median PFS of 13.3 months (95% CI: 12.1, 16.8) whereas patients in the ofatumumab arm had a median PFS of 9.9 months (95% CI: 9.2, 11.3), with a hazard ratio of 0.52 (95% CI: 0.39, 0.70; 1-sided stratified log-rank test p<0.0001). In addition, the key secondary endpoint of overall response rate per IRC was higher for duvelisib (73%; 95% CI: 66, 80) compared to ofatumumab (45%; 95% CI: 38, 53), resulting in a statistically significant odds ratio of 3.4 (95% CI: 2.1, 5.4; p<0.0001 per 1-sided stratified Cochran-Mantel-Haenszel test). Further, sensitivity analyses of PFS and ORR were supportive of the observed treatment effect with duvelisib. Therefore, the statistically significant improvement in PFS and ORR with duvelisib demonstrate substantial evidence of effectiveness in patients with CLL or SLL after at least one prior therapy.

Despite the substantial evidence of effectiveness in patients with relapsed or refractory CLL/SLL after one prior therapy, the severity of the toxicity profile of duvelisib in patients with hematologic malignancies warranted further consideration of the most appropriate CLL/SLL population for the duvelisib indication statement . The randomized, actively controlled phase 3 trial supporting efficacy in patients with CLL/SLL required at least one prior therapy. In the trial population, the median number of prior therapies was 2 (range 1, 10) with 61% of patients having 2 or more prior therapies. Because of the toxicity concerns with duvelisib, the efficacy in patients with CLL/SLL with 2 or more prior therapies was evaluated. In this subset, 95 patients were randomized to the duvelisib arm and 101 to the ofatumumab arm. In the analysis of PFS per IRC, patients receiving duvelisib had a median PFS of 16.4 months (SE: 2.1) compared to a median PFS of 9.1 months (SE: 0.5) in patients receiving ofatumumab, with a hazard ratio of 0.4

(SE: 0.2). The evaluation of ORR per IRC demonstrated an ORR of 78% with duvelisib and 39% with ofatumumab, a difference of 39% (SE: 6.5%).

The PFS and ORR results in patients with CLL/SLL with 2 or more prior therapies demonstrated improved PFS and ORR results compared to the ITT population in Study IPI-145-07. The subset population is a more heavily pretreated population, thus the efficacy findings are substantial and clinically meaningful.

Efficacy in patients with refractory FL is based on a multicenter, open-label, single-arm, phase 2 trial in adult patients with FL who were refractory to rituximab and to either chemotherapy or radioimmunotherapy. In the primary analysis of ORR per IRC in 83 patients with refractory FL, duvelisib demonstrated an ORR of 42% (95% CI: 31, 54) with 1 patient (1%) achieving a complete response and 34 patients (41%) achieving a partial response. Due to early censoring, the estimated median DOR was not reliable. However, of the 35 patients that achieved a response, 43% maintained a response at 6 months and 17% at 12 months.

In patients with refractory FL, who were refractory to rituximab and to either chemotherapy or radioimmunotherapy, the magnitude of responses and durability achieved with duvelisib can be clinically meaningful.

Safety:
The evaluation of safety with duvelisib demonstrated a substantial risk for serious toxicity, including fatal events. The safety evaluation was based on 442 patients with hematologic malignancies who received duvelisib 25 mg twice daily until progressive disease or unacceptable toxicity. The median exposure duration for patients with hematologic malignancies was 9 months (range <1 month to 53 months), with 40% of patients having at least 12 months of exposure. The most common ARs (≥20%) in patients with hematologic malignancies were diarrhea or colitis, neutropenia, rash, fatigue, pyrexia, cough, nausea, upper respiratory infection, pneumonia, musculoskeletal pain, and anemia. Deaths in the absence of progressive disease occurred in 8% of patients treated with duvelisib, primarily due to infection. Further, in the randomized, actively controlled, phase 3 trial in patients with relapsed or refractory CLL/SLL, an exploratory competing-risk analysis suggested that patients in the duvelisib arm had a 16% cumulative incidence of mortality without progressive disease compared to 9% in the ofatumumab arm, raising concern for an increased risk of fatal toxicities with duvelisib compared to ofatumumab.

The primary safety issues identified with duvelisib include serious, including fatal, infections, diarrhea or colitis, cutaneous reactions, and pneumonitis, along with serious hepatotoxicity and neutropenia. In patients with hematologic malignancies, 65% of patients experienced a serious adverse event and 84% of patients experienced a grade 3 or 4 toxicity, both of which were primarily driven by infection (including pneumonia and sepsis), diarrhea or colitis, cutaneous reactions, pneumonitis, cytopenias, and hepatotoxicity. Additionally, 35% of patients discontinued duvelisib due to an AR. Due to the frequency and seriousness of duvelisib-

associated infections, diarrhea or colitis, cutaneous reactions, and pneumonitis, a boxed warning in the U.S. prescribing information is warranted for those toxicities along with a risk evaluation and mitigation strategy (REMS) to ensure safe use of the drug.

In the consideration of safety and benefit/risk, information on same-in-class agents from the literature and postmarketing experience was considered. Idelalisib, the first-in-class PI3K inhibitor, received regular approval in July 2014 for patients with relapsed CLL in combination with rituximab and accelerated approval as monotherapy for patients with relapsed FL and SLL. In March 2016, three ongoing phase 3 trials evaluating the addition of idelalisib to standard therapies in front-line CLL and relapsed indolent forms of NHL (Trials: GS-US-312-0123, GS-US-313-0124, and GS-US-313-0125) demonstrated increased rates of serious adverse events and decreased overall survival on the idelalisib arms. Deaths on the idelalisib arm were primarily due to infections, including fatal PJP and CMV infections, and respiratory disorders (Ward 2016). The rates of serious infections, diarrhea or colitis, cutaneous reactions, pneumonitis, and hepatotoxicity were consistently higher in the idelalisib arms (Ward 2016). Therefore, the three phase 3 trials along with three other trials with idelalisib were terminated due to increased toxicity and decreased overall survival.

Additional studies with idelalisib have demonstrated that serious adverse events, including diarrhea or colitis, hepatotoxicity, pneumonitis, and cutaneous reactions, are more common in less heavily pretreated patients and in younger patients (Lampson and Kasar et al. 2016; Ward 2016; Greenwell et al. 2017). Autoimmune mechanisms have been identified for colitis, hepatotoxicity, and pneumonitis with PI3K inhibition (Okkenhaug et al. 2002; Patton et al. 2006; Torgerson and Ochs, 2007; Ramsdell and Ziegler, 2014; Louie et al. 2015; Weidner et al. 2015; Lampson and Kasar et al. 2016; Greenwell et al. 2017). Collectively, the evidence supports the hypothesis that patients with less prior therapy and younger age have a more robust immune system and may be at increased risk for immune-mediated toxicity with PI3K inhibitors. In patients with hematologic malignancies receiving duvelisib, the incidence of serious adverse events for diarrhea or colitis, pneumonitis, and cutaneous reactions were numerically higher for patients with 2 or less prior therapies compared to 3 or more prior therapies, but further investigation is warranted. Nevertheless, the potential risks for immune-mediated toxicity, increased rates of serious adverse events, and fatal toxicities is important when considering an appropriate patient population to receive treatment with duvelisib.

Accordingly, to achieve a more favorable benefit/risk, the review team recommends that the CLL/SLL indication for duvelisib be restricted to a more pretreated patient population. There is a substantial risk for toxicity, including fatal events, and the need to mitigate risk, including a boxed warning and a REMS. Further, a same-in-class agent demonstrated increased rates of serious adverse events and decreased overall survival, along with potential increased risk of serious immune-mediated toxicity in patients with less prior therapy and younger age.

Benefit-Risk:

The toxicity concerns associated with duvelisib warrant restricting use to the later line setting. In the randomized, actively controlled, phase 3 trial in patients with CLL/SLL, 61% of patients had 2 or more prior therapies. Efficacy, based on PFS and ORR, in this subset is clinically meaningful in favor of duvelisib. Patients with CLL/SLL after 2 or more prior therapies have limited treatment options and are able to assume a greater level of risk than patients having 1 prior therapy. Therefore, to achieve a more favorable benefit/risk, the review team recommends that approval be based on the subset of patients with at least 2 prior therapies. The recommended indication is thus for the treatment of adult patients with relapsed or refractory CLL or SLL after at least 2 prior therapies. The benefit/risk of duvelisib is deemed favorable in this setting.

In the single-arm phase 2 trial in patients with FL, patients must have been refractory to rituximab and to either chemotherapy or radioimmunotherapy, and thus represent a highly refractory patient population. Patients with refractory FL having at least 2 prior systemic therapies have no approved available therapy. Study IPI-145-06 was specifically for refractory disease, and the efficacy of duvelisib is not defined for patients with chemosensitive relapse. However, given the meaningful clinical activity of duvelisib in the refractory setting and the unmet medical need for patients with either relapsed or refractory disease, the clinical review team recommends extending the FL indication to patients with either relapsed or refractory disease for third-line treatment or beyond. Thus, for FL, the recommended indication is for the treatment of adult patients with relapsed or refractory disease after at least 2 prior systemic therapies. The benefit/risk of duvelisib is deemed favorable for this intended population.

X	X
Primary Statistical Reviewer Mengdie Yuan, Ph.D.	Statistical Team Leader Jingjing Ye, Ph.D.
X	X
Primary Clinical Reviewer Nicholas Richardson, DO, MPH	Clinical Team Leader Yvette Kasamon, MD

9 Advisory Committee Meeting and Other External Consultations

This application was not presented to the Oncologic Drug Advisory Committee or other external consultants because duvelisib is not first-in-class, and the application did not raise new efficacy or safety issues for the recommended indications.

10 Pediatrics

Patients less than 18 years of age were excluded from Applicant-sponsored clinical studies of duvelisib. The efficacy and safety of duvelisib in pediatric patients has not been studied.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

The following are recommendations for the duvelisib (COPIKTRA) PI based on this review. Refer to the approved PI for final language.

Table 90: Summary of Significant Labeling Changes

Section	Originally Proposed Labeling	Recommended Labeling
Indication	Treatment of patients with: • Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), (b) (4) • Follicular B-cell non-Hodgkin lymphoma (FL) who have received at least two prior therapies	Treatment of adult patients with: • Relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) after at least two prior therapies • Relapsed or refractory follicular lymphoma (FL) after at least two prior systemic therapies
Safety	(b) (4)	• Boxed warning for the following fatal and serious toxicities, with accompanying communication REMS: infections, diarrhea or colitis, cutaneous reactions, and pneumonitis
Warnings and Precautions	(b) (4)	• Add W and P for hepatotoxicity • Combine warnings for diarrhea and

Table 90: Summary of Significant Labeling Changes

Section	Originally Proposed Labeling	Recommended Labeling
	colitis	colitis, given overlapping presentations
Dosage Forms and Strengths; Dosage and Administration	• Capsule: 25 mg, 15 mg (b) (4) (b) (4)	(b) (4) • For patients who do not tolerate 15 mg BID, discontinue duvelisib
Dosage and Administration	(b) (4)	• Add dedicated section on recommended prophylaxis (Section 2.2) • "Provide prophylaxis for PJP during treatment with COPIKTRA. Following completion of COPIKTRA treatment, continue PJP prophylaxis until the absolute CD4+ T cell count is greater than 200 cells/ µL"
Adverse Reactions	(b) (4)	• Present ARs using grouped PTs for more sensitive and informative labeling. Organize the ARs by body system. • Present treatment-emergent laboratory abnormalities using dedicated lab datasets for more sensitive labeling
Adverse Reactions	(b) (4)	• Add pooled safety analysis of 442 patients with hematologic malignancies treated with duvelisib 25 mg twice daily. Use this as the primary safety population and basis for the W and P.
Clinical Studies	(b) (4)	• To match the revised indication, limit efficacy reporting to the CLL/SLL population having 2 or more prior therapies

W and P=warning and precaution

12 Risk Evaluation and Mitigation Strategies (REMS)

The clinical review team and Division of Risk Management (DRISK) agree that a communication REMS is necessary for the safe use of duvelisib. The Applicant did not originally propose a REMS but agreed to its implementation. The goal of the COPIKTRA REMS is to mitigate the following fatal and/or serious risks: infections, diarrhea or colitis, cutaneous reactions, and pneumonitis. Refer to the DRISK review for details of the REMS program.

13 Postmarketing Requirements and Commitments

Clinical
The clinical review team recommends three PMRs and a PMC.

1. PMR: Conduct a randomized phase 3 clinical trial in patients with relapsed or refractory follicular lymphoma that verifies and isolates the clinical benefit of duvelisib. The primary endpoint would be progression-free survival as determined by an independent review committee.
   Rationale: A randomized trial is required as a condition of accelerated approval in FL in order to confirm clinical benefit.
   Milestone dates:

Final Protocol Submission:	12/2018
Interim Report Submission:	11/2019
Final Report Submission:	11/2020

2. PMR: Characterize the safety of long-term use of duvelisib monotherapy in patients with hematologic malignancies treated with a planned dose of 25 mg twice daily on Trials IPI-145-02, IPI-145-06, IPI-145-07, and IPI-145-12 combined. Submit a complete study report and datasets characterizing safety and exposure after patients have been followed for an additional 2 years on treatment. Include evaluations, supplemented by narratives, of deaths in the absence of treated progressive disease, serious ARs, and ARs of special interest.
   Rationale: In the overall safety population, the median duration of duvelisib exposure was 9 months, which is not sufficient to evaluate longer-term safety of a medication that carries significant risks and is intended for prolonged use.
   Milestone dates:

Final Protocol Submission:	12/2018
Interim Report Submission:	11/2019
Final Report Submission:	11/2020

3. PMR: Submit reports and datasets for overall survival from trial IPI-145-07 with 5 years of follow-up, with an interim report after 3 years of follow-up, measured from the last

patient's randomization date. Include causes of death and narratives for death in the absence of treated disease progression.
Rationale: In Study IPI-145-07, an estimated 16% of patients treated with duvelisib died without progression, as compared to 9% of patients treated with ofatumumab, with a median follow-up of 22 months and 17 months, respectively. For safety, the long-term survival outcomes for patients treated with duvelisib should be characterized.
Milestone dates:

Interim Report Submission:	6/2019
Final Report Submission:	6/2021

4. PMC: To allow dose reduction of duvelisib in patients who do not tolerate 15 mg twice daily, develop and test the product characteristics of a lower strength (5 mg or 10 mg) duvelisib formulation. Include Include results of process validation in the final report.

(b) (4)

Milestone date:

Final Report Submission:	12/2019

Clinical pharmacology
The clinical pharmacology review team recommends the following PMC:

PMC: Conduct a clinical pharmacokinetics trial to evaluate the effect of repeat doses of a moderate CYP3A inducer on the single dose pharmacokinetics of duvelisib (b) (4)

Final Protocol Submission:	02/2019
Draft Report Submission:	10/2019
Final Report Submission:	01/2020

14 Division Director (DHOT)

X

John Leighton, PhD

15 Division Director (OCP)

X

NAM Atiqur Rahman, PhD

16 Division Director (OB)

X

Rajeshwari Sridhara, PhD

17 Division Director (Clinical)

Duvelisib is a phosphatidylinositol 3-kinase (PI3K) inhibitor with dual activity against the PI3K-δ and PI3K-γ isoforms. This product is the third PIK3K inhibitor application submitted to the division for treatment of a hematologic malignancy. Both idelalisib (PI3K-δ inhibitor) approved in 2014 and copanlisib (dual PIK3K inhibitor) approved in 2017 are currently marketed. The Applicant submitted single arm and randomized controlled trial data in support of approval. The Applicant sought approval for relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) based on a randomized controlled trial and for follicular lymphoma accelerated approval based on a single arm trial in a population where the disease is thought to be refractory to approved therapies. Based on a review of the data, the risk-benefit is favorable for approval. The toxicities seen in the duvelisib application are consistent with what was seen with the two prior applications therefore the products will carry similar warnings. The recommended duvelisib dose is 25 mg orally twice daily (BID), administered continuously in 28-day cycles (b) (4). A communication Risk Evaluation and Mitigation Strategy (REMS) is recommended to mitigate the fatal and/or serious risks of infections, diarrhea or colitis, cutaneous reactions, and pneumonitis.

I concur with the review team regarding the approval of COPIKTRA (duvelisib) for following two indications:

- Regular approval for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) after at least two prior therapies
- Accelerated approval for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after at least two prior systemic therapies.

X

Ann T. Farrell, MD

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

Richard Pazdur, MD

19 Appendices

19.1. References

Byrtek, M., K. L. Dawson, X. Zhou, C. Farber, C. R. Flowers, J. D. Hainsworth, B. K. Link, A. D. Zelenetz and J. W. Friedberg (2013). "Early Relapse Of Follicular Lymphoma After R-CHOP Uniquely Defines Patients At High Risk For Death: An Analysis From The National Lymphocare Study." Blood 122(21): 510.

Colombat, P., G. Salles, N. Brousse, P. Eftekhari, P. Soubeyran, V. Delwail, E. Deconinck, C. Haioun, C. Foussard, C. Sebban, A. Stamatoullas, N. Milpied, F. Boue, B. Taillan, P. Lederlin, A. Najman, C. Thieblemont, F. Montestruc, A. Mathieu-Boue, A. Benzohra and P. Solal-Celigny (2001). "Rituximab (anti-CD20 monoclonal antibody) as single first-line therapy for patients with follicular lymphoma with a low tumor burden: clinical and molecular evaluation." Blood 97(1): 101-106.

Francis, S., M. Karanth, G. Pratt, J. Starczynski, L. Hooper, C. Fegan, C. Pepper, D. Valcarcel, D. W. Milligan and J. Delgado (2006). "The effect of immunoglobulin VH gene mutation status and other prognostic factors on the incidence of major infections in patients with chronic lymphocytic leukemia." Cancer 107(5): 1023-1033.

Freedman, A. (2015). "Follicular lymphoma: 2015 update on diagnosis and management." American Journal of Hematology 90(12): 1171-1178.

Greenwell, I. B., A. Ip and J. B. Cohen (2017). "PI3K Inhibitors: Understanding Toxicity Mechanisms and Management." Oncology (Williston Park) 31(11): 821-828.

Hiddemann, W., M. Kneba, M. Dreyling, N. Schmitz, E. Lengfelder, R. Schmits, M. Reiser, B. Metzner, H. Harder, S. Hegewisch-Becker, T. Fischer, M. Kropff, H. E. Reis, M. Freund, B. Wormann, R. Fuchs, M. Planker, J. Schimke, H. Eimermacher, L. Trumper, A. Aldaoud, R. Parwaresch and M. Unterhalt (2005). "Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group." Blood 106(12): 3725-3732.

Lampson, B. L., S. N. Kasar, T. R. Matos, E. A. Morgan, L. Rassenti, M. S. Davids, D. C. Fisher, A. S. Freedman, C. A. Jacobson, P. Armand, J. S. Abramson, J. E. Arnason, T. J. Kipps, J. Fein, S. Fernandes, J. Hanna, J. Ritz, H. T. Kim and J. R. Brown (2016). "Idelalisib given front-line for treatment of chronic lymphocytic leukemia causes frequent immune-mediated hepatotoxicity." Blood 128(2): 195.

Louie, C. Y., M. A. DiMaio, K. E. Matsukuma, S. E. Coutre, G. J. Berry and T. A. Longacre (2015). "Idelalisib-associated Enterocolitis: Clinicopathologic Features and Distinction From Other Enterocolitides." Am J Surg Pathol 39(12): 1653-1660.

Luminari, S., M. Bellei, I. Biasoli and M. Federico (2012). "Follicular lymphoma - treatment and prognostic factors." Revista Brasileira de Hematologia e Hemoterapia 34(1): 54-59.

Martinelli, G., S. F. Schmitz, U. Utiger, T. Cerny, U. Hess, S. Bassi, E. Okkinga, R. Stupp, R. Stahel, M. Heizmann, D. Vorobiof, A. Lohri, P. Y. Dietrich, E. Zucca and M. Ghielmini (2010). "Long-term follow-up of patients with follicular lymphoma receiving single-agent rituximab at two different schedules in trial SAKK 35/98." J Clin Oncol 28(29): 4480-4484.

Nabhan, C., B. Aschebrook-Kilfoy, B. C. Chiu, K. Kruczek, S. M. Smith and A. M. Evens (2014). "The impact of race, age, and sex in follicular lymphoma: A comprehensive SEER analysis across consecutive treatment eras." Am J Hematol 89(6): 633-638.

Noone AM, H.N., Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds), *SEER Cancer Statistics Review, 1975-2015, National Cancer Institute. Bethesda, MD,* https://seer.cancer.gov/csr/1975_2015/, *based on November 2017 SEER data submission, poster to SEER web site, April 2018.*

Okkenhaug, K., A. Bilancio, G. Farjot, H. Priddle, S. Sancho, E. Peskett, W. Pearce, S. E. Meek, A. Salpekar, M. D. Waterfield, A. J. Smith and B. Vanhaesebroeck (2002). "Impaired B and T cell antigen receptor signaling in p110delta PI 3-kinase mutant mice." Science 297(5583): 1031-1034.

Patton, D. T., O. A. Garden, W. P. Pearce, L. E. Clough, C. R. Monk, E. Leung, W. C. Rowan, S. Sancho, L. S. Walker, B. Vanhaesebroeck and K. Okkenhaug (2006). "Cutting edge: the phosphoinositide 3-kinase p110 delta is critical for the function of CD4+CD25+Foxp3+ regulatory T cells." J Immunol 177(10): 6598-6602.

Pongas, G. and B. D. Cheson (2016). "PI3K signaling pathway in normal B cells and indolent B-cell malignancies." Semin Oncol 43(6): 647-654.

Ramsdell, F. and S. F. Ziegler (2014). "FOXP3 and scurfy: how it all began." Nat Rev Immunol 14(5): 343-349.

Rivas-Delgado, A., L. Magnano, M. Moreno-Velazquez, O. Garcia, P. Mozas, I. Dlouhy, T. Baumann, J. Rovira, B. Gonzalez, A. Martinez, O. Balague, J. Delgado, N. Villamor, E. Campo, E. Gine, J. M. Sancho and A. Lopez-Guillermo (2017). "Progression-free survival shortens after each relapse in patients with follicular lymphoma treated in the rituximab era." Hematological Oncology 35: 360-361.

Rossi, D. and G. Gaidano (2014). "Lymphocytosis and ibrutinib treatment of CLL." Blood 123(12): 1772.

Rummel, M. J., N. Niederle, G. Maschmeyer, G. A. Banat, U. von Grunhagen, C. Losem, D. Kofahl-Krause, G. Heil, M. Welslau, C. Balser, U. Kaiser, E. Weidmann, H. Durk, H. Ballo, M. Stauch, F. Roller, J. Barth, D. Hoelzer, A. Hinke and W. Brugger (2013). "Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial." Lancet 381(9873): 1203-1210.

Stilgenbauer, S. (2015). "Prognostic markers and standard management of chronic lymphocytic leukemia." Hematology Am Soc Hematol Educ Program 2015: 368-377.

Teras, L. R., C. E. DeSantis, J. R. Cerhan, L. M. Morton, A. Jemal and C. R. Flowers (2016). "2016 US lymphoid malignancy statistics by World Health Organization subtypes." CA Cancer J Clin.

Torgerson, T. R. and H. D. Ochs (2007). "Immune dysregulation, polyendocrinopathy, enteropathy, X-linked: forkhead box protein 3 mutations and lack of regulatory T cells." J Allergy Clin Immunol 120(4): 744-750.

Weidner, A. S., N. C. Panarelli, J. T. Geyer, E. B. Bhavsar, R. R. Furman, J. P. Leonard, J. Jessurun and R. K. Yantiss (2015). "Idelalisib-associated Colitis: Histologic Findings in 14 Patients." Am J Surg Pathol 39(12): 1661-1667.

Wierda, W. G., T. J. Kipps, J. Mayer, S. Stilgenbauer, C. D. Williams, A. Hellmann, T. Robak, R. R. Furman, P. Hillmen, M. Trneny, M. J. Dyer, S. Padmanabhan, M. Piotrowska, T. Kozak, G. Chan, R. Davis, N. Losic, J. Wilms, C. A. Russell and A. Osterborg (2010). "Ofatumumab as single-agent CD20 immunotherapy in fludarabine-refractory chronic lymphocytic leukemia." J Clin Oncol 28(10): 1749-1755.

Wiestner, A. (2015). "The role of B-cell receptor inhibitors in the treatment of patients with chronic lymphocytic leukemia." Haematologica 100(12): 1495-1507.

Witzig, T. E., A. M. Vukov, T. M. Habermann, S. Geyer, P. J. Kurtin, W. R. Friedenberg, W. L. White, H. I. Chalchal, P. J. Flynn, T. R. Fitch and D. A. Welker (2005). "Rituximab therapy for patients with newly diagnosed, advanced-stage, follicular grade I non-Hodgkin's lymphoma: a phase II trial in the North Central Cancer Treatment Group." J Clin Oncol 23(6): 1103-1108.

19.2. Financial Disclosure

Covered Clinical Study: IPI-145-07

Was a list of clinical investigators provided:	Yes ☒	No ☐
Total number of investigators identified: 846		
Number of investigators who are Sponsor employees (both full-time and part-time): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 7		
Is an attachment provided with the reason:	Yes ☒	No ☐

Covered Clinical Study: IPI-145-06

Was a list of clinical investigators provided:	Yes ☒	No ☐
Total number of investigators identified: 1,196		
Number of investigators who are Sponsor employees (both full-time and part-time): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 22		
Is an attachment provided with the reason:	Yes ☒	No ☐

Covered Clinical Study: IPI-145-12, IPI-145-02, IPI-145-15

Study ID	Number of Investigators	Number with Disclosable Financial Interests/Arrangements	Number with Certification of Due Diligence
IPI-145-12	753	0	19
IPI-145-02	165	0	3
IPI-145-15	11	0	0
Source: Response to IR, Table 1, on 29 August 2018			

19.3. OCP Appendices (Technical documents supporting OCP recommendations)

19.3.1. Summary of Bioanalytical Method Validation and Bioanalysis Reports

A listing of the bioanalytical methods used in each of the studies is provided in Table 91. Analytical Methods and Validation Reports for duvelisib used in the registration Study IPI-145-06 and Study IPI-145-07 are summarized in Table 92.

Table 91: Analytical Methods and Assay Validation Reports of Duvelisib in Clinical Studies

Validation Report No. / Method No.	Analytes	LLOQ (ng/mL)	Applied to Studies	Matrix
(b) (4)	Duvelisib	0.3	IPI-145-01 (b) (4)	Plasma
	Duvelisib and IPI-656	0.1	IPI-145-03 IPI-145-04 IPI-145-05	Plasma
	Duvelisib	0.5	IPI-145-01 IPI-145-05	Urine
	Duvelisib	1	IPI-145-02	Plasma
	Duvelisib and IPI-656	1	IPI-145-02 IPI-145-06 IPI-145-07 IPI-145-10 IPI-145-11 IPI-145-14 IPI-145-15	Plasma
	Duvelisib and IPI-656	3	IPI-145-06 IPI-145-07 IPI-145-19	Plasma
	Midazolam and 1'-hydroxymidazolam	0.1	IPI-145-10	Plasma

Table 92: Summary of Analytical Methods of Duvelisib in Plasma for Study IPI-145-106 and Study IPI-145-107

Validation Report No. (b) (4)	Method (b) (4)
Analyte	Duvelisib and IPI-656
Range	1.00 to 1000 ng/mL
QC	3, 50 and 500 ng/mL
Accuracy	Ranged from -4.4% to 2.2% for duvelisib Ranged from -2.0% to 3.7% for IPI-656
Precision	Ranged from 1.9% to 4.7% for duvelisib Ranged from 1.7% to 5.4% for IPI-656

Dilution	10-fold dilution and quantification up to 8000 ng/mL is valid
Extraction recovery	Ranged from 67.1% to 72.0% for duvelisib Ranged from 51.1% to 53.4% for IPI-656 71.3% for IPI-145-d5 53.4% for IPI-656-d5
Stock stability (IPI-656 only)	24 hours at ambient temperature (range 12°C to 33°C), 85 days at -20°C
Autosampler stability	169 hours at 10°C in processed sample for duvelisib 169 hours at 10°C in processed sample for IPI-656
Re-injection reproducibility (original calibration curve)	142 hours at 10°C in processed sample for duvelisib 125 hours at 10°C in processed sample for IPI-656
Re-injection reproducibility (re-injected calibration curve)	142 hours at 10°C in processed sample for duvelisib 125 hours at 10°C in processed sample for IPI-656
Bench-top stability	24 hours in plasma at ambient temperature for duvelisib and IPI-656
Freeze/thaw stability	5 cycles at -20°C and at -70°C for duvelisib and IPI-656
Long-term stability	1048 days at -20°C and at -70°C for duvelisib and IPI-656
Stability in whole blood	2 hours at 0°C and at ambient temperature for duvelisib and IPI-656

Validation Report No. (b) (4) **/ Method** (b) (4)	
Analyte	Duvelisib and IPI-656
Range	3.00 to 3000 ng/mL
QC	9, 150 and 2400 ng/mL
Accuracy	Within run bias: Ranged from -8.7% to 0.2% for duvelisib Ranged from -6.7% to 3.5% for IPI-656 Overall bias: Ranged from -7.9% to -0.7% for duvelisib Ranged from -3.6% to -0.5% for IPI-656
Precision	Ranged from 2.7% to 4.3% for duvelisib Ranged from 2.5% to 7.1% for IPI-656
Dilution	10-fold dilution up to 8,000 ng/mL
Extraction Recovery	Ranged from 77.1% to 79.3% for duvelisib Ranged from 74.2% to 80.1% for IPI-656 81.0% for IPI-145-d5 76.1% for IPI-656-d5

Autosampler Stability	97 hours at 10°C in processed sample
Re-injection Reproducibility (Original Calibration Curve)	105 hours at 10°C in processed sample
Re-injection Reproducibility (Re-injected Calibration Curve)	105 hours at 10°C in processed sample

19.3.2. Clinical PK/PD Assessments

PK in healthy subjects:
The PK of duvelisib in healthy subjects was assessed in Study IPI-145-01 including single ascending doses (SAD) and multiple ascending doses (MAD) parts. Single doses of duvelisib 1, 2, 5, 10, 20, and 30 mg were administered under fasting conditions in the SAD part (n=4 per cohort). Mean PK parameters are listed in Table 93.

Table 93: Summary of Mean Pharmacokinetic Parameters of Duvelisib Following Single Ascending Oral Doses of Duvelisib to Healthy Subjects Under Fasted Conditions

Duvelisib Dose (n = 4/group)	**C_{max} (ng/mL)**	**t_{max} (h)[a]**	**$AUC_{0\text{-}last}$ (ng•h/mL)**	**$AUC_{0\text{-}\infty}$ (ng•h/mL)**	**CL/F (L/h)**	**V_z/F (L)**	**$t_{½}$ (h)**
1 mg	43.4 (31)	1.00 (1.00-1.00)	148 (68)	151 (68)	8.39 (42)	38.8 (28)	3.52 (29)
2 mg	78.8 (16)	1.00 (0.50-2.00)	291 (45)	296 (44)	7.69 (37)	57.9 (38)	5.43 (25)
5 mg	246 (16)	1.00 (0.50-1.50)	733(5)	743 (5)	6.74 (5)	53.0 (15)	5.43 (10)
10 mg	454 (40)	0.50 (0.50-1.50)	905 (15)	914 (14)	11.1 (15)	147 (29)	9.47 (38)
20 mg	997 (32)	1.00 (1.00-1.00)	2243 (16)	2250 (16)	9.09 (18)	99.1 (46)	7.79 (51)
30 mg	1140 (38)	1.00 (0.50-1.00)	3384 (38)	3395 (38)	9.73 (33)	113 (31)	8.12 (18)

AUC = area under the concentration vs time curve; CL/F = apparent plasma clearance; C_{max} = maximum observed plasma concentration; CV% = variability; SAD = single ascending dose; t_{max} = time of maximum observed plasma concentration; V_z/F = apparent volume of distribution
[a] Median (range)

Two dosing schedules were evaluated in the MAD part (n=9 per cohort). For the BID schedule, subjects received a single dose of duvelisib 1, 2, or 5 mg on Days 1 and 14, and BID doses on Days 2 through 13. For the QD schedule, subjects received duvelisib 10 mg on Days 1 through 14. Mean PK parameters are listed in Table 94.

Table 94: Summary of Mean Pharmacokinetic Parameters of Duvelisib Following Multiple Ascending Oral Doses of Duvelisib to Healthy Subjects Under Fasted Conditions

Duvelisib Dose (n = 9/group)	Day	C_{trough}	C_{max} (ng/mL)	t_{max} (h)[a]	AUC_{0-tau} (ng•h/mL)	$AUC_{0-\infty}$ (ng•h/mL)	$t_{½}$ (h)	Rac
1 mg q12h[b]	1	< LLOQ	49.1 (26)	0.52 (0.50-1.00)	124 (40)	132 (43)	3.46 (39)	--
	14	5.56 (58)	66.8 (36)	1.00 (0.50-1.50)	199 (39)	--	6.46 (20)	1.65 (19)
2 mg q12h[b]	1	< LLOQ	101 (31)	1.00 (0.50-2.00)	290 (49)	323 (55)	6.34 (35)	--
	14	19.5 (79)	140 (36)	1.00 (0.50-2.00)	524 (47)	--	9.75 (37)	1.83 (22)
5 mg q12h[b]	1	< LLOQ	257 (38)	1.00 (0.50-1.50)	774 (41)	848 (44)	5.76 (11)	--
	14	45.2 (68)	355 (37)	1.00 (0.50-2.02)	1291 (38)	--	8.32 (35)	1.71 (15)
10 mg q24h[c]	1	< LLOQ	553 (27)	0.52 (0.50-1.52)	1527 (37)	1555 (38)	6.00 (13)	--
	14	8.11 (52)	605 (16)	1.00 (0.50-1.55)	2232 (25)	--	11.7 (82)	1.54 (18)

AUC_{0-tau} = area under the concentration vs time curve from 0 to time constant; $AUC_{0-\infty}$ = area under the concentration vs time curve from 0 to infinity ; C_{max} = maximum observed plasma concentration; C_{trough} = plasma concentration observed at the end of the dosing interval; CV% = variability; LLOQ = lower limit of quantification; MAD = multiple ascending dose; q12h = every 12 hours; q24h = every 24 hours; Rac = accumulation ratio; $t_{1/2}$ = half-life

[a] Median (range)

[b] Once in the morning of Days 1 and 14 and twice daily on Days 2 through 13

[c] Once daily in the morning of Days 1 through 14

PK in patients:

Single-dose and multiple-dose PK studies were assessed in patients with advanced hematologic malignancies (Study IPI-145-02). The dose escalation phase consisted of an accelerated phase testing 8 and 15 mg BID, followed by the standard phase testing 25, 35, 50, 50, 75 (maximum tolerated dose), and 100 mg BID. The expansion phase tested 25 mg BID (n=59) and 75 mg BID (n=118) dose levels. Mean PK parameters after the first dose and at steady state on cycle 2 day 1 are listed in Table 95 and Table 96.

Table 95: Summary of Pharmacokinetic Parameters of Duvelisib after Single Ascending Oral Doses of Duvelisib to Patients With Cancer on Cycle 1 Day 1

Plasma PK Parameters[a]	Duvelisib Dose Cohort[d]							
	8 mg BID	15 mg BID	25 mg BID	35 mg BID	50 mg BID	60 mg BID	75 mg BID	100 mg BID
n	1	6	65	3	3	4	122	3
AUC_{0-12} (ng•h/mL)	1371.1 (NC)	3282.5 (23.7)	4783.8 (70.9)	6271.7 (78.4)	11457.2 (50.7)	11829.5 (74.7)	12313.3 (64.5)	8979.8 (59.2)
AUC_{0-last} (ng•h/mL)	1519.7 (NC)	4005.7 (29.2)	6090.2 (77.4)	8106.7 (74.0)	15362.2 (62.8)	15779.6 (66.1)	16234.9 (70.6)	12313.8 (57.7)
$AUC_{0-\infty}$ (ng•h/mL)	1562.1 (NC)	4320.9 (33.5)	7098.4 (103.8)[c]	9631.1 (64.2)	21546.6 (89.2)	21634.9 (64.9)	19153.3 (81.4)[c]	13541.6 (NC)[c]
C_{max} (ng/mL)	534.0 (NC)	842.2 (57.0)	1062 (69.9)	1162 (68.6)	2487 (46.4)	3242 (71.9)	2630 (60.3)	1573 (46.0)
t_{max}[b] (h)	1.00 (1.00, 1.00)	1.08 (0.52, 4.02)	1.95 (0.50, 6.03)	2.00 (1.00, 2.03)	1.12 (0.50, 2.00)	1.00 (0.50, 4.00)	1.16 (0.50, 24.85)	2.02 (1.00, 2.17)
$t_{½}$ (h)	5.180 (NC)	5.694 (36.4)	6.821 (45.8)[c]	9.227 (63.8)	10.885 (74.0)	9.570 (75.7)	7.693 (44.7)[c]	6.570 (NC)[c]
CL/F (L/h)	5.121 (NC)	3.842 (36.0)	5.599 (70.1)[c]	5.356 (80.0)	3.608 (61.1)	4.102 (67.9)	6.840 (85.8)[c]	11.18 (NC)[c]
Vss/F (L)	27.98 (NC)	26.48 (34.3)	46.93 (78.0)[c]	54.62 (59.5)	36.32 (26.0)	46.45 (52.0)	63.84 (104.0)[c]	101.8 (NC)[c]

AUC_{0-12} = area under the concentration vs time curve from 0 to 12 hours; AUC_{0-last} = area under the concentration vs time curve from 0 to last observed concentration; $AUC_{0-\infty}$ = area under the concentration vs time curve from 0 to infinity; BID = twice daily; CL/F = apparent plasma clearance; C_{max} = maximum observed plasma concentration; NC = not calculated; PK = pharmacokinetic; $t_{1/2}$ = half-life; t_{max} = time of maximum observed plasma concentration; Vss/F = apparent volume of distribution

[a] Arithmetic Mean (CV%) presented, unless otherwise indicated

[b] Median (Minimum, Maximum)

[c] n = 61 for 25 mg BID, n = 111 for 75 mg BID, and n = 2 for 100 mg BID. The concentration-time profile did not exhibit a terminal log-linear phase. The PK parameters $AUC_{0-\infty}$, $t_{½}$, CL/F, and Vss/F were not calculated for some subjects.

[d] The Cycle 1, Day 1 dose was administered once daily. BID dose administration began the next day on Cycle 1, Day 2 following collection of the 24-hour sample.

Table 96: Summary of Pharmacokinetic Parameters of Duvelisib After Multiple Ascending Oral Doses of Duvelisib to Patients With Cancer on Cycle 2 Day 1

	Duvelisib Dose — Cycle 2, Day 1							
PK Parameters[a]	**8 mg BID**	**15 mg BID**	**25 mg BID**	**35 mg BID**	**50 mg BID**	**60 mg BID**	**75 mg BID**	**100 mg BID**
n	1	5	57	2	3	3	90	1
AUC_{0-12} (ng•h/mL)	2000.6 (NC)	5111.4 (19.5)	7887.9 (76.8)[c]	11665.7 (NA)[c]	15779.5 (29.9)	8113.0 (79.7)[c]	19059.4 (59.2)[c]	NC (NC)
AUC_{0-last} (ng•h/mL)	1788.2 (NC)	4358.5 (21.2)	7178.5 (78.4)	13162.9 (45.2)	13062.2 (29.5)	6812.5 (58.3)	15820.5 (54.8)	16684.5 (NC)
C_{max} (ng/mL)	471.0 (NC)	1107 (37.7)	1511 (63.6)	1960 (43.3)	2760 (38.4)	1478 (69.9)	3294 (50.8)	2320 (NC)
t_{max}[b] (h)	2.00 (2.00, 2.00)	1.10 (0.92, 2.00)	1.42 (0.50, 5.92)	2.52 (1.03, 4.00)	1.15 (1.00, 2.37)	1.00 (0.00, 2.00)	1.08 (0.00, 8.00)	3.05 (3.05, 3.05)
$t_{1/2}$ (h)	2.735 (NC)	4.216 (34.7)	4.677 (56.9)[c]	7.502 (NC)[c]	5.090 (32.2)	4.080 (33.9)[c]	6.550 (201.6)[c]	NC (NC)
CL_{ss}/F (L/h)	3.999 (NC)	3.029 (20.1)	4.219 (55.5)[c]	3.000 (NA)[c]	3.339 (25.5)	10.83 (79.7)[c]	5.255 (61.1)[c]	NC (NC)
V_{ss}/F (L)	18.827 (NA)	19.524 (48.2)	28.513 (61.5)[c]	34.189 (NA)[c]	24.620 (12.0)	81.763 (101.3)[c]	40.633 (70.5)[c]	NC (NC)
RA	1.459 (NC)	1.670 (20.9)	1.941[d] (50.8)	2.946[d] (NC)	2.216[d] (54.2)	0.948[d] (120.3)	2.037[d] (67.9)	NC (NC)
LI	1.281 (NC)	1.287 (32.9)	1.402[e] (45.4)	1.205[e] (NC)	1.698[e] (49.3)	0.831[e] (123.1)	1.334[e] (53.3)	NC (NC)

AUC_{0-12} = area under the concentration vs time curve from 0 to 12 hours; AUC_{0-last} = area under the concentration vs time curve from 0 to the last observed plasma concentration; BID = twice daily; CL_{ss}/F = apparent plasma clearance at steady-state; LI = linearity index; NC = not calculated; PK = pharmacokinetic; RA = accumulation ratio; $t_{1/2}$ = half-life; t_{max} = time of maximum observed plasma concentration; V_{ss}/F = apparent volume of distribution at steady-state

Notes: RA was calculated as $AUC_{0-12,\ Cycle\ 2}/AUC_{0-12,\ Cycle\ 1}$.

LI or time invariance was calculated as $AUC_{0-12,\ Cycle\ 2}/AUC_{0-\infty,\ Cycle\ 1}$.

[a] Mean (CV%) presented, unless otherwise indicated

[b] Median (Minimum, Maximum)

[c] n = 49 for 25 mg BID, n = 1 for 35 mg BID, n = 2 for 60 mg BID, n = 81 for 75 mg BID. The concentration-time profile did not exhibit a terminal log-linear phase. The PK parameters $t_{½}$, CL_{SS}/F, and Vss/F were not calculated for some subjects.

[d] n = 47 for 25 mg BID, n = 1 for 35 mg BID, n = 2 for 50 mg BID, n = 2 for 60 mg BID, n = 80 for 75 mg BID

[e] n = 45 for 25 mg BID, n = 1 for 35 mg BID, n = 2 for 50 mg BID, n = 2 for 60 mg BID, n = 72 for 75 mg BID

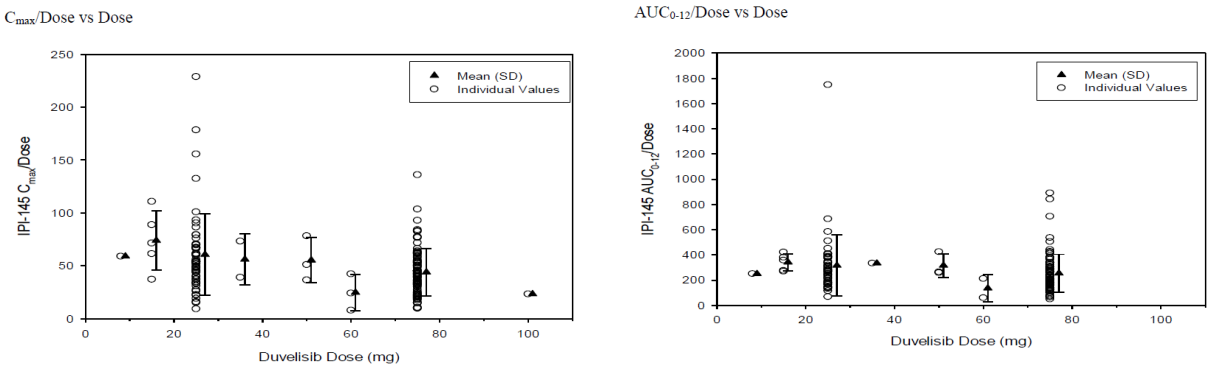
Note: The last PK sample was taken 8 hours postdose.

Source: Report (b) (4) Table 7

Dose proportionality:

In the dose escalation and expansion Study IPI-145-02, duvelisib exposures (Cmax and AUC_{0-12}) appear to be dose-proportional from 8 to 75 mg and 100 mg (n=3) had lower than expected exposures. Statistical analysis using a power model for ln-transformed AUC_{0-12} and C_{max} after the first dose in patients confirmed dose proportionality within this dose range (95% CI of the slope estimate included the value of 1). Individual and mean dose-normalized duvelisib exposures (C_{max} and AUC_{0-12}) at steady state on cycle 2 day 1 were plotted against the duvelisib doses in Figure 16 below.

Figure 16: Cmax and AUCs Versus Dose After Multiple Ascending Daily Oral Doses of Duvelisib to Patients With Cancer on Cycle 2 Day 1



19.3.3. Applicant's Population Pharmacokinetics Analysis

Objectives

To develop a PPK to describe concentration time data for duvelisib and to identify and characterize intrinsic and extrinsic factors which influence duvelisib PK.

Data, Software, Methods

The PPK analysis utilized pooled PK data collected from 13 studies including healthy subjects, patients with advanced hematologic malignancies, and patients with relapsed or refractory leukemia or lymphoma (Table 97). Missing covariates were replaced by Last Observation Carried Forward, Next Observation Carried Backward, or population median.

Table 97: Summary of Clinical Studies Used in the Population Pharmacokinetic Analysis and Duvelisib PK Assessment Schedule

Study	Study Population	Study Design	Dosage / Regimens	Study Size	Nominal PK Assessments (hour)
IPI-145-01	Healthy	Phase 1, single ascending, multiple ascending, food effect and DDI	1-30 mg SD 1-10 mg MD	82	Pre-dose, 3, 12, 24, 48, 72, 96, 120, 144, 168, 192, 264, 336, 504, 672, 840, 1008, and 1680 hours post-dose
IPI-145-02	Patients	Phase 1, in patients with advanced hematologic malignancies	8 - 100 mg QD or BID	208	Cycle 1: pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 24 hours on Day 1 and pre-dose on Day 8, 15, 22; Cycle 2: pre-dose, 0.5, 1, 2, 3, 4, 6, hrs. on Day 1; Cycle 3, 4, 5: pre-dose on Day 1
IPI-145-05	Healthy	Phase 1, ADME and absolute bioavailability	2.8 ug IV SD 25 mg PO SD	6	Pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24 and 48 hours post-dose
IPI-145-06	Patients	Phase 2, in subjects with refractory indolent NHL	25 mg BID	123	Pre-dose, 1, 4 hours post-dose on Cycle 1 Day 15, Cycle 2 Day 1, Cycle 3 Day 1
IPI-145-07	Patients	Phase 3, in patients with relapsed or refractory CLL/SLL	25 mg BID	152	Pre-dose, 0.5-2 hours, 3-5 hours on Cycle 2 Day 1, Cycle 3 Day 1, Cycle 7 Day 1
IPI-145-10	Healthy	Phase 1, DDI on midazolam	25 mg BID	14	Pre-dose samples on Days 4-6
IPI-145-11	Healthy	Phase 1, DDI by rifampin	25 mg BID	14	Pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 8, 12, 24, 36 and 48 hours post-dose
IPI-145-14	Healthy	Hepatic study	25 mg SD	24	Pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 8, 12, 24, 36, 48 and 72 hours post-dose
IPI-145-15	Healthy	Bioequivalence and food effect	5 or 25 mg SD	103	Pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16 and 24 hours post-dose
IPI-145-19	Patients	Phase 1/2, with rituzimab or obinutuzumab	12/25 mg BID	43	Pre-dose, 1, 4 hours post-dose on Cycle 1 Day 1, pre-dose on Cycle 2 Day 1, Cycle 3 & 4 Day 1
M14-412	Healthy	PK in Japanese adult male	5/20/30 mg SD; 10 mg QD	27	Pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 16 hours post-dose on Day 1 and at 24, 36 and 48 hours post-dose on Day 14, pre-dose on Day 2, 11, 12, 13, 14.
M15-460	Patients	Safety and PK in Japanese patients with relapsed or refractory lymphoma	25 mg BID	7	Cycle 1: pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 24 hours on Day 1 and pre-dose on Day 8, 15, 22; Cycle 2: pre-dose, 0.5, 1, 2, 3, 4, 6, 8 hours on Day 1 Cycle 3, 5: pre-dose on Day 1
M15-789	Healthy	Phase 1, PK in Chinese adults	25 mg BID	3	Pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 16, 24, 36, 48 and 72 hours post-dose

Source: Population PK report, Table 1

A Base model was developed without consideration of covariate effects. Covariates were tested in single covariate models if they showed a trend in post-hoc analysis of the base model or were expected to influence duvelisib PK based on prior knowledge. The single covariate models were developed using a power model for continuous covariates or a linear model for categorical covariates. Covariates were included in the Full model if they were tested significant ($p<0.01$) in the single covariate models, resulted in parameter estimates with <35% standard error, and resulted in >20% change in the parameter over the range of covariate values (5^{th} – 95^{th} range in the dataset). The Final model was developed based on the Full model using backwards elimination ($p<0.001$). Successful minimization and covariance steps were required in each step of model development. Standard goodness-of-fit plots and model stability were considered in model evaluation.

Table 98: Covariates Included in the PPK Analysis

Parameter	Covariates
CL/F	Age, ALB, ALT, ALP, AST, TBL, CRCL, NCI, Weight, FFM, BSA, BMI, Sex, Race, Dose, Food, Formulation, INH3A, COMED, POP
Vc/F	Age, WT, BMI, FFM, BSA, Sex, Race, POP
Ka	Dose, Food, Formulation, PPI, INH3A, POP
F	Dose, Food, Formulation, PPI, INH3A, POP

Source: Population PK report, Table 1
ALB = Albumin, ALP = Alkaline phosphatase, ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, BMI = Body mass index, BSA = Body surface area, COMED = Co-medication, CRCL = Creatinine clearance, FFM = Fat Free Mass, INH3A = CYP3A4 inhibitor co-administration, NCI = Hepatic impairment grade, POP = Study population, PPI = Proton pump inhibitor co-administration, TBL = Total bilirubin, WT = Weight, Ka = Absorption rate constant, F = Bioavailability

PPK models were developed with the NONMEM software (version 7 level 3). FOCE was used to fit log transformed PK data with an additive residual error model.

Results
For the PPK analysis, 216 records (1.0 %) from simultaneous oral and micro-iv dosing (in Study IPI-145-05) were excluded from the analysis. 2283 records (11% of total records) were excluded due to data records errors, insufficient time information, duplicates, or other data quality issues. 1447 concentration records (7.0 %) were excluded as below the limit of quantification (BLQ). The final PK database contained 806 subjects with 16737 concentration records including parent drug and the major metabolite. Key demographic information in the final PK dataset was summarized in Table 99 and Table 100.

Table 99: Summary of Baseline Demographic Information (Continuous) in the PPK Dataset

Covariate	Unite	All (N=806)		Healthy Volunteer (N=255)		Patient (N=551)	
AGE	Years	54.6 ± 18.4	[18.0, 90.0]	33.5 ± 11.0	[18.0, 61.0]	64.4 ± 11.6	[25.0, 90.0]
ALB	g/L	42.0 ± 4.89	[24.0, 55.0]	44.5 ± 3.48	[36.6, 55.0]	40.8 ± 5.00	[24.0, 51.8]
ALP	U/L	101 ± 74.4	[25.2, 888]	86.8 ± 51.1	[33.0, 357]	108 ± 82.2	[25.2, 888]
ALT	U/L	25.1 ± 16.7	[3.00, 150]	23.4 ± 10.1	[8.00, 67.0]	25.9 ± 18.9	[3.00, 150]
AST	U/L	26.1 ± 13.2	[5.00, 115]	22.1 ± 7.16	[8.00, 50.0]	27.9 ± 14.9	[5.00, 115]
BMI	kg/m^2	26.5 ± 4.92	[15.5, 50.1]	24.8 ± 3.42	[18.3, 31.9]	27.3 ± 5.31	[15.5, 50.1]
BSA	m^2	1.93 ± 0.237	[1.29, 2.85]	1.94 ± 0.184	[1.49, 2.46]	1.92 ± 0.259	[1.29, 2.85]
CRCL	mL/min	101 ± 38.9	[23.4, 328]	129 ± 25.4	[79.1, 293]	88.3 ± 37.5	[23.4, 328]
N by CRCL severity (%)	<30	3	(0.4)	0	(0.0)	3	(0.5)
	30-60	118	(14.6)	0	(0.0)	118	(21.4)
	60-90	207	(25.7)	6	(2.4)	201	(36.5)
	>90	478	(59.3)	249	(97.6)	229	(41.6)
DOSE	Mg	29.9 ± 21.2	[1.00, 100]	14.9 ±0 9.98	[1.00, 30.0]	36.9 ± 21.4	[8.00, 100]
FFM	Kg	55.3 ± 11.3	[28.2, 90.2]	57.9 ± 8.61	[36.3, 79.5]	54.1 ± 12.1	[28.2, 90.2]
TBL	Umol/L	10.8 ± 6.99	[1.60, 120]	10.9 ± 4.70	[3.42, 34.0]	10.7 ± 7.83	[1.60, 120]
WT	Kg	78.4 ± 16.6	[39.7, 154]	77.2 ± 12.1	[50.1, 112]	78.9 ± 18.3	[39.7, 154]

Source: Population PK report, Table 5
TBL: Bilirubin; CRCL: Creatinine Clearance; FFM: Fat Free Mass; “heathy volunteer” includes only heathy subjects (POP=1), “patient population” includes lymphoma and leukemia patients as well as hepatic impaired subjects (N=18).

Table 100: Summary of Baseline Demographic Information (Categorical, count [%]) in the PPK Dataset

covariate	category	All (N=806)	Healthy Volunteer (N=255)	Patient Population (N=551)
POP	Healthy	255 (31.6)	255 (100)	0 (0.0)
	Lymphoma	178 (22.1)	0 (0.0)	178 (32.3)
	Leukemia	355 (44)	0 (0.0)	355 (64.4)
	Hepatic Impaired	18 (2.2)	0 (0.0)	18 (3.3)
SEX	Male : Female	564 (70) : 242 (30)	220 (86.3) : 35 (13.7)	344 (62.4) : 207 (37.6)
RACE	White : Black : Asian : Others	631 (78.3) : 99 (12.3) : 44 (5.5) : 32 (4)	138 (54.1) : 74 (29) : 34 (13.3) : 9 (3.5)	493 (89.5) : 25 (4.5) : 10 (1.8) : 23 (4.2)
NCI	None	593 (73.6)	255 (100)	338 (61.3)
	Mild	6 (0.7)	0 (0.0)	6 (1.1)
	Moderate	6 (0.7)	0 (0.0)	6 (1.1)
	Severe	6 (0.7)	0 (0.0)	6 (1.1)
	unknown	195 (24.2)	0 (0.0)	195 (35.4)
FOOD	Fasted : Fed : unknown	467 (55.3) : 169 (20) : 209 (24.7)	241 (82) : 39 (13.3) : 14 (4.8)	226 (41) : 130 (23.6) : 195 (35.4)
FORM	Trial : Marketed : unknown	516 (58.1) : 369 (41.6) : 3 (0.3)	185 (54.9) : 149 (44.2) : 3 (0.9)	331 (60.1) : 220 (39.9) : 0 (0.0)
CYP3A4 Inhibitor	None : Weak : Moderate : Strong	802 (95.4) : 8 (1) : 10 (1.2) : 21 (2.5)	255 (94.1) : 0 (0.0) : 0 (0.0) : 16 (5.9)	547 (96) : 8 (1.4) : 10 (1.8) : 5 (0.9)
CYP3A4 Substrate	No : Yes	791 (97.1) : 24 (2.9)	241 (94.5) : 14 (5.5)	550 (98.2) : 10 (1.8)
Co-medication	None : Rituximab : Obinutuzumab	763 (94.7) : 21 (2.6) : 22 (2.7)	255 (100) : 0 (0.0) : 0 (0.0)	508 (92.2) : 21 (3.8) : 22 (4)
PPI	No : Yes	692 (84) : 132 (16)	255 (100) : 0 (0.0)	437 (76.8) : 132 (23.2)

Source: Population PK report, Table 6

The Base model was a 2-compartment model with first-order absorption followed by first order elimination. The Base model was stable and reasonably described the observed data.
After the Final model was developed after covariate search, the model structure was revised to evaluate the potential time-varying clearance of duvelisib given the fact that duvelisib is primarily metabolized by CYP3A4 and it is a moderate inhibitor of CYP3A4. The clearance of duvelisib was modeled as CLi = TVCL1*exp(η_i) + TVCL2*epx(-KIN*DAY)*exp(η_i*X), where TVCL1 was the population estimate of steady state clearance, TVCL2 was the difference between initial clearance and steady state clearance, KIN was the time-dependent rate constant, DAY was the study day relative to first dose, and X was the shared variability between two clearance terms. Covariate-parameter relationships identified with the time-independent clearance were re-estimated and refined in the Revised Final model. Revised Final model parameters are summarized in Table 101.

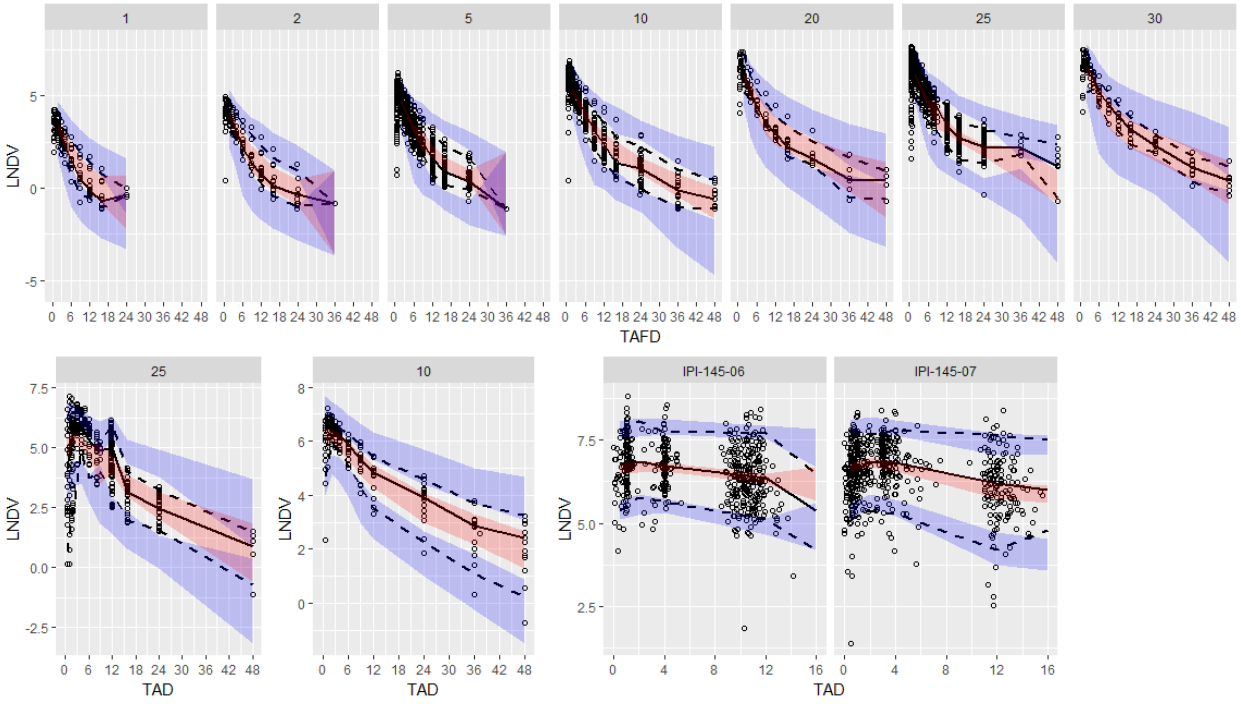
Table 101: Duvelisib Refined Revised Final PPK Model Parameters

Parameter (Units)	Refined revised final model	
	estimate	RSE (%)
Ka (/hr)	2.26	9.67
Vc (L)	22.5	3.39
TVCL1 (L/hr)	6.76	5.41
TVCL2 (L/hr)	1.57	15.2
time-dependency KIN (/day)	0.157	26.0
Q (L/hr)	1.60	4.49
Vp (L)	17.0	6.12
shared IIV on CL	0.799	31.3
Residual Error	0.556	2.79
IIV Ka (%CV)	1.06	103
IIV Vc (%CV)	0.064	25.3
IIV CL (%CV)	0.226	47.5
IIV Vp (%CV)	0.133	36.4
Covariate effects		
AGE on CL	-0.232	37.0
ALP on CL	-0.196	28.3
3A4I (mild-mod) on CL	0.824	8.35
3A4I (strong) on CL	0.451	9.07
CRCL on CL	0.146	56.7
Age on time-dependent CL	1.63	66.9
FOOD on CL	0.814	6.56
POP=2 on CL	0.418	8.38
POP=3 on CL	0.530	7.40
AGE on Vc	-0.267	23.5
WT on Vc	0.668	16.9
RACE=3 on Vc	0.782	6.84
PPI on Ka	0.504	15.4
3A4I (strong) on Ka	0.753	9.29
POP=3 on Ka	0.367	13.8
FOOD on Ka	0.191	23.9
3A4I (strong) on F	2.193	5.22
FOOD on F	0.726	8.18
DOSE on F	-0.135	14.6

Source: Table 3 in Response to Agency – Pharmacometrics IR, submitted on March 30, 2018
3A4I – CYP3A4 inhibitor, POP=2 (Lymphoma), POP=3 (Leukemia).

The parameters were generally well estimated with the majority of standard error less than 30%. However, the residual error was high. Shrinkage was low on clearance (ETA shrinkage=9.3% and EBV shrinkage=8.3%). The condition number, calculated as the ratio of largest and smallest eigenvalue, is 133.9, suggesting low collinearity and reasonable conditioning. Diagnostic plots showed reasonable fit and no substantial deviation from normality assumption. Visual predictive check plots showed good agreement in the observed and simulated median data although upper and lower simulated values were wider than observed range in healthy subjects.

Figure 17: Prediction Corrected Visual Predictive Check in Healthy Subjects Without Food and Ketoconazole use (Upper Panel, Separated by Dose Levels), Healthy Subjects With Food (Lower Panel, Left), Healthy Subjects with Ketoconazole (Lower Panel, Middle), and in Two Patient Studies (Lower Panel, Right).



Source: Reviewer's analysis based on Applicant's Revised Final Model

Reviewer's Comments:

1. *Only the parent drug model was reviewed as the major active metabolite is not pharmacologically active and the relative abundance to parent drug is not high. The total number of observations used in PPK analysis is 9650.*
2. *1627 records including 100 observations of parent drug concentration in Study IPI-145-02 were removed in Applicant's analysis as they were collected beyond 30 days after first dose. Reviewer's sensitivity analysis suggested a lack of effect on parameters estimates by including these records.*
3. *Even though dose was included in the final model as significant covariate on bioavailability, the effect on dose proportionality is not significant. Reviewer simulated dose escalation studies using a parallel study design. There is a high chance of concluding dose proportionality in the range of 8-75 mg with a sample size of 12 in each treatment arm.*

4. *PPK analysis suggests a lack of clinically significant effect on the exposure of duvelisib by age (18-90 years), sex, race, renal impairment (creatinine clearance 23 to 90 mL/ min), body weight (40 to 154 kg.*
5. *The effect of acid reducing agent (ARA) on duvelisib PK could not be evaluated with PPK analysis due to limited information on ARA dosing record in majority of study subjects.*
6. *There is no adequate data to evaluate the effect of strong CYP3A4 inhibitor on steady state duvisilib PK in patients. Of the 21 patients who took strong CYP3A4 inhibitor during the course of study, 16 were from the dedicated DDI study in healthy patients. Among the 5 patients who took strong CYP3A4 inhibitor, only 2 provided evaluable concentration data after taking the inhibitor.*
7. *Applicant's model was found acceptable to simulate exposure metrics in exposure-response analyses.*

19.3.4. Applicant's Exposure-Response Analysis

Objectives
To conduct graphical and statistical exposure-response (ER) evaluations for duvelisib efficacy and safety using logistic regression or time-to-event analysis depending on data type and quality.

Data, Software, and Methods
ER analysis for efficacy used data from Study IPI-145-06 and IPI-145-07. The efficacy endpoints were based on independent review committee (IRC) grading if available, or investigator assessment if not: objective response rate (ORR), progression-free survival (PFS), duration of response (DOR), and overall survival (OS).

ER analysis for safety used pooled data in Study IPI-145-02, IPI-145-06, IPI-145-07, IPI-145-19, and Study M15-460. The safety endpoints were grade 3 and above pneumonia, pneumonitis, rash, diarrhea, colitis, infection, rash, and transaminase elevation. Covariates tested in analysis were average daily dose, age, sex, race, disease type, CYP3A4 inhibitor, and Eastern Cooperative Oncology Group Score (ECOG).

Exposure metrics in ER analyses were the average daily exposure up to the time of event calculated as the average daily dose divided by the post hoc estimate of average CL during the course of treatment.

Graphical explorations were conducted for each of the safety and efficacy endpoints to evaluate potential trends with duvelisib exposure. PFS, OS, DOR, and time to safety events were analyzed using Cox-proportional hazards model. ORR and safety endpoints were analyzed using logistic regression model. Covariate selections were guided by stepwise model building process using Akaike Information criteria (AIC) or the chi-squared test ($p<0.01$), if a exposure metric was identified as a potential covariate in univariate analysis.

Results
In Study IPI-145-06, a total of 83 patients provided PFS and OS data, 79 patients provided ORR, and 44 patients provided DOR data. AUC was not found significant in ER analysis for PFS, OS, ORR or DOR, based on univariate statistical analysis.

In Study IPI-145-07, a total of 154 patients provided PFS and OS data, 153 patients provided ORR, and 125 patients provided DOR data. AUC was not found significant in ER analysis for PFS, ORR or DOR,

based on univariate statistical analysis. AUC was significant (p<0.01) in univariate Cox-proportional hazards model.

Table 102 summarizes the number of AE events (Yes/No) with ≥ grade 3 in the ER-safety dataset. In univariate analysis, duvelisib exposure was a potential predictor for transaminase elevation, infection, and pneumonia from both logistic regression and Cox-proportional hazards model. Duvelisib exposure was significant with rash in the Cox-proportional hazards model. Significant ER relationships remain after multivariate analysis considering potential covariate effect.

Table 102: Grade 3 and Above Adverse Events

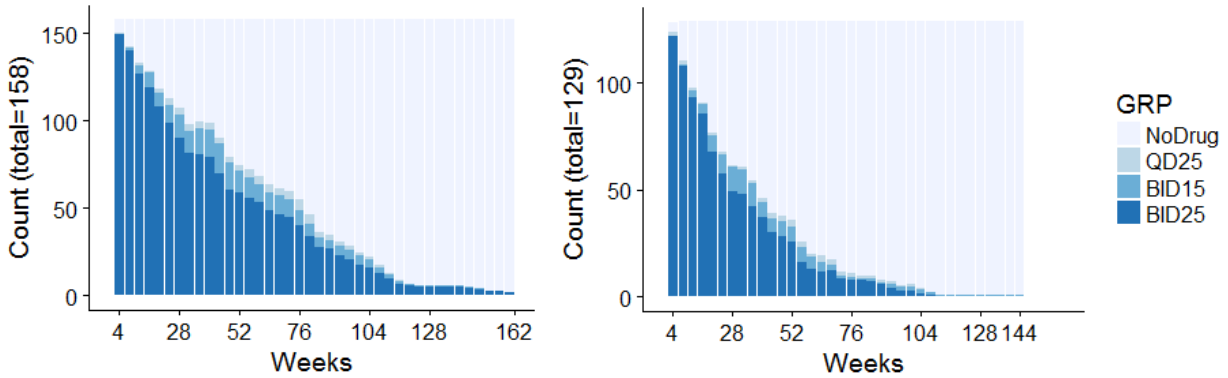
Adverse event	All	CLL/SLL	FL	Other
	N=552	N=258	N=167	N=127
AST or ALT ELEVATION (%)	57 (10.3)	18 (7.0)	15 (9.0)	24 (18.9)
COLITIS (%)	37 (6.7)	28 (10.9)	4 (2.4)	5 (3.9)
DIARRHEA (%)	56 (10.1)	30 (11.6)	17 (10.2)	9 (7.1)
INFECTION (%)	132 (23.9)	80 (31.0)	20 (12.0)	32 (25.2)
NEUTROPENIA (%)	138 (25.0)	81 (31.4)	32 (19.2)	25 (19.7)
PNEUMONIA (%)	62 (11.2)	42 (16.3)	8 (4.8)	12 (9.4)
PNEUMONITIS (%)	12 (2.2)	7 (2.7)	4 (2.4)	1 (0.8)
RASH (%)	33 (6.0)	13 (5.0)	10 (6.0)	10 (7.9)

Source: Table 1 in Response to Agency – Pharmacometrics IRs, submitted on April 9 and May 29, 2018

Reviewer's Comments:

1. *Applicant's ER analyses for PFS or OS were wrong because censored events were mistakenly treated as events. Reviewer re-analyzed the dataset and concluded negative ER relationships between the average daily exposure and ORR, PFS, and OS, in either Study IPI-145-06 or Study IPI-145-07.*
2. *Reviewer conducted additional ER analyses for efficacy and confirmed a lack of ER relationship between ORR, PFS, and OS vs steady state exposure per assigned dose or early exposure metrics (i.e. AUC, Cmax, and Cmin after the first dose).*
3. *ER analysis for efficacy is difficult because of the limited range of study dose levels. In both Study IPI-145-06 and Study IPI-145-07, at any time during the course of treatment, majority of patients on treatment receive the 25 mg BID dose (Figure 18). Prediction of efficacy outcome at a lower or higher dose level should be taken with caution.*

Figure 18: Number of Patients on Different Dose Levels in Study 007 (Left) and Study 006 (Right)

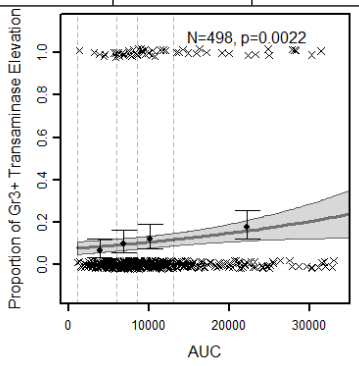


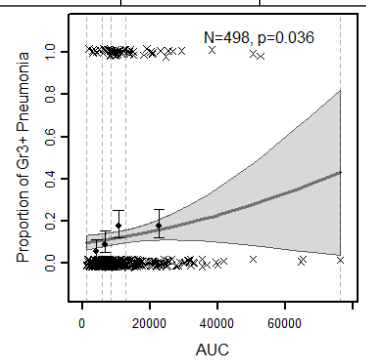
Source: Reviewer's analysis

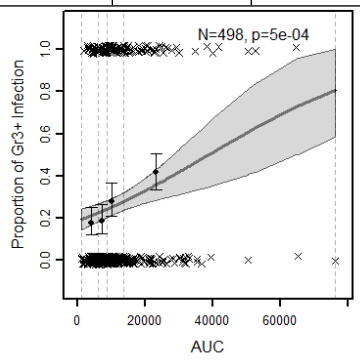
4. *Reviewer repeated Applicant's ER analysis for safety using pooled data from studies IPI-145-02, IPI-145-06, IPI-145-07, and Study M15-460; Study IPI-145-19 was excluded because patients were on combination treatment. Reviewer confirmed positive ER relationships between duvesilib exposure vs the incidence of grade 3 and above transaminase increase, infection, and pneumonia. However, the predicted probability of these AE events was not substantially different at lower dose levels, even with univariate model prediction. In addition, duvesilib exposure did not positively correlate with the probability or time to grade 3 and above AE of any kind.*

Table 103: Predicted Probability of Grade 3 and Above Transaminase Increase, Pneumonia, and Infection at 25 mg BID, 20 mg BID, and 15 mg BID Dose Levels

Transaminase Increase			Pneumonia			Infection		
25 BID	20 BID	15 BID	25 BID	20 BID	15 BID	25 BID	20 BID	15 BID
14%	12%	11%	14%	13%	12%	31%	28%	26%







Source: Reviewer's analysis

19.3.5. Applicant's Physiologically based Pharmacokinetic Modeling Analysis

Application Number	211155
Drug Name	Duvelisib
Proposed Indication	Chronic lymphocytic leukemia/small lymphocytic lymphoma, and Follicular B-cell non-Hodgkin lymphoma
Clinical Division	DCP5
PBPK Consult request	Xianhua (Walt), Cao, Ph.D.
Primary PBPK Reviewer	Yuching Yang, Ph.D.
Secondary PBPK Reviewer	Xinyuan Zhang, Ph.D.
Applicant	Verastem, Inc.
Review Questions	There are five PBPK analyses reports submitted in the current submission. The PBPK review evaluates the PBPK analyses and addresses three review questions. 1) Whether the enzyme-mediated DDI simulations are appropriate and adequate for dosing recommendation. 2) Whether the PBPK simulations are appropriate for dosing recommendation in patients with

	hepatic impairment. 3) Whether the PBPK simulations are appropriate to evaluate the acid reducing agents (ARAs) effects on the PK of duvelisib.

ENZYME-MEDIATED DDI AND DOSING RECOMMENDATION

Objective
The objectives of this review are to evaluate the adequacy of the physiologically based pharmacokinetic (PBPK) modeling submitted by the Applicant to 1) predict the effect of CYP3A inhibitors/ inducers on the exposure of duvelisib; 2) predict the DDI potential of duvelisib as a perpetrator on CYP3A and CYP2C8 - mediated pathways; and 3) provide dosing recommendations based on the predicted DDI potential. The following PBPK reports were submitted for these purposes:

- PBPK report -Part A: Quantitative prediction of the systemic exposure of IPI-145 and its primary metabolite IPI-656 using prior in vitro and in vivo data: potential for drug-drug interactions as a victim drug in healthy volunteers and oncology patients
- PBPK report -Part B: Quantitative prediction of the potential for IPI-145 as a perpetrator to cause drug-drug interactions with midazolam, repaglinide and rosiglitazone in healthy volunteers and oncology patients
- PBPK report -Part C: Quantitative prediction of the systemic exposure of IPI-145 and its primary metabolite IPI-656 using prior in vitro and in vivo data: recommended dose adjustments in the presence of CYP3A4 inhibitors

Executive Summary
Duvelisib (IPI-145) is a kinase inhibitor developed for the treatment of patients with previously treated chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), and follicular lymphoma (FL). The recommended dose is 25 mg twice daily (BID), administered with or without food. Duvelisib and IPI-145 are used interchangeably in this review.

Duvelisib is metabolized by cytochrome P450 (CYP) 3A4 to form its major metabolite, IPI-656, by CYP3A4, and to a lesser extent by CYP1A2, 2B6, and 2C8. The Applicant reported that IPI-656 is pharmacologically inactive at clinically relevant exposures. Duvelisib and IPI-656 exhibit time-dependent inhibition (TDI) of CYP3A.

The Applicant used the PBPK simulation results to support the proposed prescription information (USPI) in section 12.3 Pharmacokinetics/ Drug Interactions.

(b) (4)

This review concluded that the Applicant's PBPK model is adequate to predict the duvelisib PK with concomitant use with a strong or moderate CYP3A inhibitor. When co-administrated with a strong (such

as ketoconazole) or moderate (such as fluconazole) CYP3A inhibitor, the model predicted a 66% or 40% increase in the AUC of duvelisib, respectively. Simulation results suggested that the effect of duvelisib on a CYP2C8 substrate is minimal.

Table 104 summarizes the ratios of observed and predicted ratio of area under curve (AUCR) of test substrates with and without co-administration with a perpetrator compound in these studies.

Table 104: Summary of Clinical and Simulated DDI Studies

Drug name	Description	Observed* Parent AUCR (single dose)	Simulated Parent AUCR (steady-state)	Analysis
IPI-145 autoinhibition after multiple dose administration (10 mg BID for 14 days)				
IPI-145	IPI-145 and IPI-656 are TDI of CYP3A	NA	1.6 [1]	Pred.-vs-Obs.
IPI-145 as Victim for CYP3A modulator				
Ketoconazole	Strong CYP3A4 Inhibitor	3.95 (10 mg)	1.66/1.59[2]	Pred.-vs-Obs.
Itraconazole	Strong CYP3A4 Inhibitor		1.65/1.56 [2]	Pred. only
fluconazole	Moderate CYP3A4 Inhibitor		1.40/1.34[2]	Pred. only
Rifampicin	Strong CYP3A4 and moderate 2C8 inducer	0.18		Obs.
IPI-145 and IPI-656 as Perpetrators for CYP enzyme				
Midazolam	CYP3A substrate	4.29		Pred.-vs-Obs.
Repaglinide	Dual CYP3A4 and 2C8 substrate		1.54 (single dose)	Pred. only

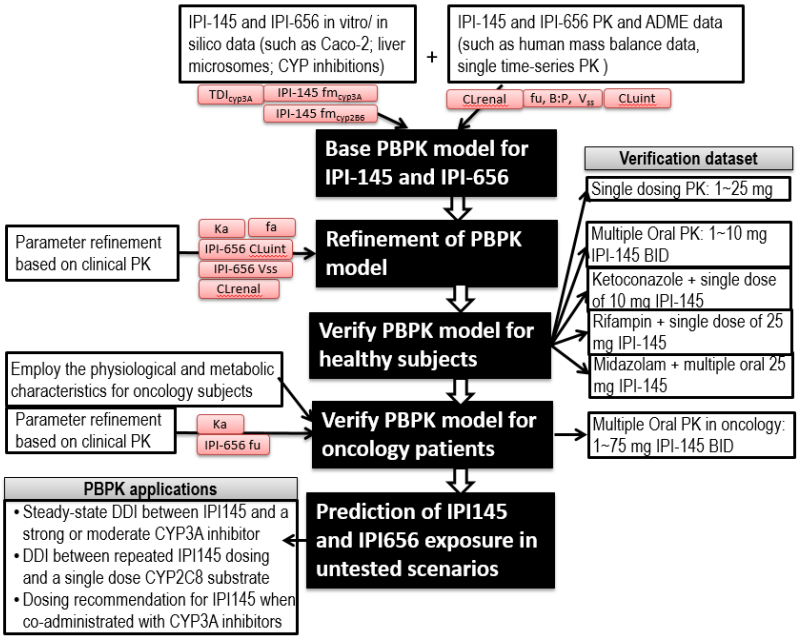
[1] AUC_{D14}/AUC_{D1}; [2] HV/Oncology Patients (IPI-145 25 mg BID)

Methods

PBPK development for duvelisib

The Applicant developed minimal PBPK models for duvelisib and IPI-656 using SimCYP (a Certara company, Sheffield, UK, version 13) based on available physicochemical properties, in vitro experiments and clinical study data. Figure 19 shows a workflow of the development, verification and application of PBPK model for duvelisib.

Figure 19: Workflow of Development, Verification and Application of Duvelisib PBPK Model

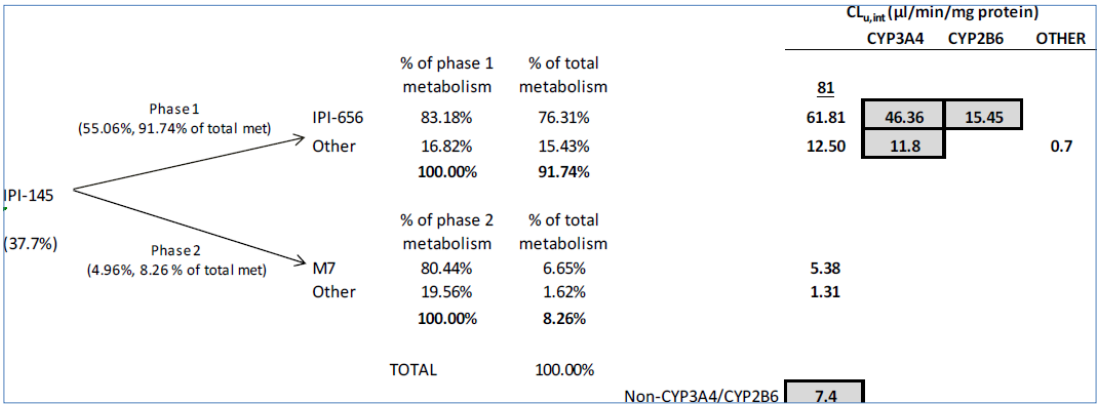


Duvelisib PBPK model for healthy subjects

In vitro data, human PK data and mass balance studies were used to construct a base duvelisib model in healthy subjects. The in-vitro intrinsic metabolic clearance (CLu_{int}) of 30.3 µL/min per mg protein was scaled to a hepatic clearance of 1.65 L/hr (CL_H). A value of 0.07 L/hr was assigned to the renal clearance (CL_R) of duvelisib based on observed values following a single oral dose of 30 mg and multiple doses (5 mg BID) (Study IPI-145-01). Thus, the systemic clearance was estimated to be 1.72 L/hr. This value was later adjusted to 4.6 L/hr (where CL_H =4.6-0.07 L/hr) based on the observed in-vivo clearance in a human mass balance/ADME study (Study IPI-145-05). Duvelisib is mainly metabolized to IPI-656 (75%) via phase I enzymes. The Applicant assigned the fractional metabolism by CYP3A4 ($fmCYP_{3A4}$) and 2B6 ($fmCYP_{2B6}$) of IPI-145 to be 0.75 and 0.25 respectively based on cytochrome P450 inhibition assay.

Figure 20 presents the schematic diagram of the metabolism of duvelisib and formation of IPI-656.

Figure 20: Contributions of CYP3A4 and CYP2B6 to the Metabolism of IPI-145 and Formation IPI-656



Reference Figure 3, PBPK report part A

The Applicant estimated the duvelisib fraction absorbed (fa) based on the clinical duvelisib PK study following a single dose of duvelisib ranging 1- 25 mg. Combined with in-vitro permeability data, and pH-dependent solubility data, the Applicant used Simcyp's ADAM module to estimate the values of fa over the dose range of 1 to 100 mg (Table 106). Values were predicted to be 0.98 over the dose range of 1 to 5 mg, 0.96 at 10 mg, and 0.72 at 25 mg. The Applicant noted that the data were consistent with the findings that while dose-normalized Cmax values of duvelisib were similar over the dose range of 1 to 10 mg, at 25 mg, the dose normalized Cmax value was approximately 20% lower than that at 10 mg. The value of ka, first order absorption rate constant, was set to 5.0 hr^{-1} to recover the Tmax values of 0.72/1.2 hour reported following single or multiple oral doses of duvelisib. A list of PBPK parameters and their sources are summarized in Table 105.

The developed duvelisib PBPK model for healthy subjects was verified by comparing the simulated plasma PK results for duvelisib and IPI-656 with those observed in the clinical PK and DDI studies conducted in healthy subjects.

Table 105: Input Parameters for Duvelisib PBPK Model

	IPI-145	IPI-656	Reference
MW	416.86	432.86	Provided (b) (4)
log P	2.9	2.6	Provided
Compound type	Neutral	Neutral	
B:P	0.55	0.55	Clinical Study - IPI-145-05
fu (healthy subjects)	0.014	0.013	Provided (b) (4)
fu (oncology patients)	0.014	0.008	
fa (1 to 10 mg)	0.98	n/a	
fa (25 mg)	0.72	n/a	Predicted from Caco-2 data,
fa (75 mg)	0.36	n/a	solubility data and ADAM
ka (h^{-1})	5	n/a	Derived from *in vivo* data
			Clinical Study - IPI-145-01
Q_{gut}	6.6	n/a	Predicted from Caco-2 data
Caco-2 data (10^{-6} cm/s)	2.55	n/a	(b) (4) Report Number 301068103
Metoprolol calibrator	17	n/a	(b) (4) Report Number 301068103
V_{ss} (L/kg)	0.155		Clinical Study - IPI-145-05
V_{ss}(m) (L/kg)		0.31	Predicted
CL_R (L/h)	0.07		Clinical Study - IPI-145-05
CLu_{int} (µl/min per mg protein)	81.0		
Formation of IPI-656 - CYP3A4	46.36		Clinical Study - IPI-145-05
Formation of IPI-656 - CYP2B6	16.64		Report Number (b) (4) 10722-RPT02548
Other metabolic routes - CYP3A4	11.8		
Non-CYP3A4/CYP2B6	7.4		
CLu_{int} (µl/min per mg protein)			
CYP3A4		12	Fitted using *in vivo* data from
Undefined route		48	Clinical Study - IPI-145-05
Ku_I (µM)	3.87	0.31	Report Number (b) (4) 115074 (IPI-145) Report Number 135032 (IPI-656)
k_{inact} (h^{-1})	0.9	1.02	

Reference: Table 1 of PBPK report-Part A

Reviewer's comments: Although the decrease of fa is plausible at higher dose given the low solubility of duvelisib, the PK of duvelisib following a single dose of duvelisib was not available in dose levels greater than 30 mg. Therefore, the estimated fa value cannot be verified in ranges higher than 30 mg in healthy volunteers. At 25 mg dose level, the simulated results using fa values of 0.72 or 0.98 would be both in agreement with the observed data. The Applicant's model development and validation process seems appropriate for developing the duvelisib PBPK model.

Duvelisib PBPK model for oncology population
The Applicant developed a duvelisib PBPK model for the oncology population by updating the age distribution of virtual healthy population to match the age distributions of oncology patients. The Applicant noted the higher median age in oncology patients relative to that in healthy subjects propagates into changes in physiology parameters such as cardiac blood flow and whole liver CYP3A4 abundance (relative values of 0.85 and 0.78, respectively) that may cause PK differences. Other key physiological differences between oncology population and healthy population include reduced albumin levels and increased α1-acid glycoprotein (AAG) levels.

The mean plasma unbound fraction (fu) value of IPI-145 in oncology patients was reported to be similar to that in healthy subjects (0.013 vs 0.014), while the fu values of IPI-656 were significantly lower in patients than in healthy subjects. As there was high variability observed in the free fraction of IPI-656 (ranges 0.08 to 0.48%), fu values of IPI-656 in oncology patients were scaled by the plasma AAG levels. The scaled fu values of IPI-656 are 0.013 and 0.007 for healthy and oncology subjects, respectively.

Perpetrator models
CYP3A TDI parameters, inactivation rate constant (k_{inact}) and mechanism-based inhibition constant (K_I), for duvelisib and IPI-656 were derived from two independent in-vitro experiments, and directly used as PBPK model parameters. Duvelisib, but not IPI-656, was shown to inhibit CYP2C8 in vitro with the Ki is 0.84 μM. The PBPK models of CYP inhibitors (such as ketoconazole) or CYP substrates (such as repaglinide) included in the PBPK analysis were the default models within Simcyp V13 without any modification.

Reviewer's comments: The reviewer noted the data for treatment-naïve cancer patients is often limited, and the physiology factors affecting PK properties may vary with different cancer types. Thus, the duvelisib PK profiles in target patients might be impacted by patient's intrinsic (such as transporter activity) or extrinsic factors (such as previous cancer treatments) which were not included in the Applicant's virtual cancer population. Although only a limited number of parameters were evaluated, it is still valuable to understand the potential effects of these general features of cancer patients on the PK of duvelisib, and the implication on the DDI.

Model application

DDI simulations

The Applicant used the PBPK model to predict DDI between strong and moderate CYP3A inhibitors on the PK of duvelisib at steady state in healthy and oncology subjects. The Applicant also applied duvelisib PBPK models to predict the effects of duvelisib on CYP2C8 substrates.

The Applicant used the duvelisib PBPK model to simulate three unknown DDI scenarios.

- *First*, the model was used to predict the DDI effects of ketoconazole (a strong CYP3A inhibitor) or fluconazole (a moderate CYP3A inhibitor) on the PKs of duvelisib at steady state with concomitant administration of multiple-dose of ketoconazole or fluconazole (both administrated with 200 mg BID, day 10-19) and multiple-dose of duvelisib (25 mg BID, day 1-19).

- *Second*, the model was used to predict the effects of duvelisib (as a CYP2C8 inhibitor) on the PKs of repaglinide or rosiglitazone with concomitant use of multiple-dose of duvelisib (25 mg BID, day 1-6) and a single dose of 0.25 mg repaglinide or 4 mg rosiglitazone on day 5.
- *Third*, the model was used to support the proposed DDI dosing regimen of 15 mg BID when duvelisib is co-administrated with a strong CYP3A4 inhibitor, and the proposed no dosing modification when co-administrated with moderate CYP3A inhibitors.

In response to an IR, the Applicant confirmed that there are negligible differences in the results of the PBPK analysis when the models were executed in either SimCYP version 13 or 17.

Results
Q1: Can the Applicant's PBPK model adequately describe the PK profiles of duvelisib following single or repeat doses of duvelisib in healthy volunteers (HVs) and patients?

Yes. The Applicant's PBPK model can predict the PK of duvelisib following single or multiple doses of duvelisib in HVs and cancer patients.

The duvelisib PBPK model was verified with the observed duvelisib PK following single and repeat doses of duvelisib in healthy subjects and cancer patients.

For healthy subjects, the simulated median values for Cmax and AUC of duvelisib agreed with those observed following single or repeat doses of duvelisib at various dose levels ranging from 1 mg to 25 mg twice daily (BID). Table 106 shows the comparison of the simulated and observed PK parameters for duvelisib and IPI-656 following single or repeat doses of duvelisib. The reviewer noted that the duvelisib AUC observed in HVs (Study IPI-145-01) is approximately 1.5-fold higher than those observed in subjects with mild asthma (Study IPI-145-03) following 5 mg BID for 14 days.

Table 106: Predicted and Observed Cmax and AUC Values for Duvelisib Following a Single or Repeating Dosing of Duvelisib at Different Dose Levels

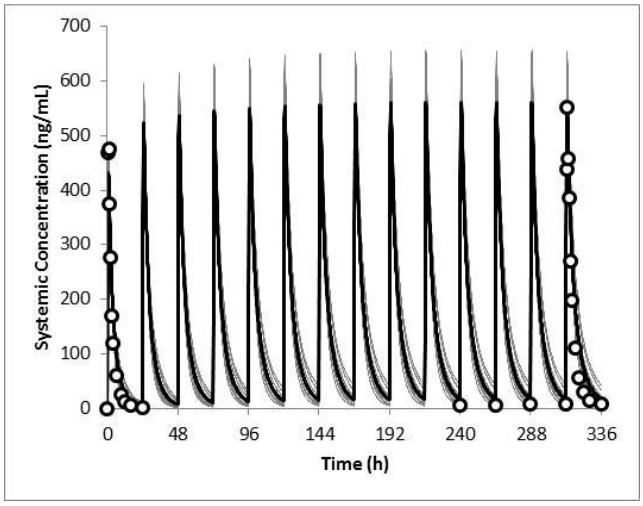
Dose (mg)	Study	Predictions Geomean		Observations Geomean	
		Cmax (ng/mL)	AUC (ng*hr/mL)	Cmax (ng/mL)	AUC (ng*hr/mL)
		duvelisib			
5 mg BID (Day 14)	IPI-145-03	322	1437	232	761
		IPI 656			
5 mg BID (Day 14)	IPI-145-03	119	1183	101	845
		duvelisib			
1 mg BID (Day 1)	IPI-145-01	40	157	49	121
1 mg BID (Day 14)	IPI-145-01	52	206	64	187
5 mg BID (Day 1)	IPI-145-01	212	840	242	757
5 mg BID (Day 14)	IPI-145-01	317	1475	331	1205
10 mg BID (Day 1)	IPI-145-01	421	1683	532	1429
10 mg BID (Day 14)	IPI-145-01	542	2748	598	2162
25 mg once daily (qd) (Day 1)	IPI-145-11	902	3538	938	3170

25 mg qd (Day 14)	Simulated*	1417	7840		

*Simulated by FDA reviewer
Reference: Table 4, 5, 7 ,8 and 10 of Applicant's PBPK-PartA report;

Figure 21 presents the comparison of simulated and observed plasma concentration-time profiles of IPI-145 after a single oral dose of 10 mg on day 1 followed by 10 mg twice daily on days 2 through 13 and then 10 mg on day 14.

Figure 21: Observed and Simulated PK of Duvelisib After Repeated Dosing of 10 mg Duvelisib in Healthy Volunteers



Simulated (lines) and observed (circles) plasma concentration-time profiles of duvelisib and IPI 656 during once daily dosing of 10 mg for 14 days.
Reference: Figure 12a of Applicant's PBPK-Part A report

Upon verification of the PBPK model for HVs, the Applicant updated the duvelisib PBPK model for cancer patients by incorporating the physiology difference observed in the oncology population (see the Method section).

The predicted total clearance for the virtual healthy and oncology subjects were 8.37 and 5.71 L/hr, respectively, following a single dose of 25 mg duvelisib. Reduced clearances are in agreement with those observed in healthy and oncology subjects (Table 107).

Table 107: Observed and Predicted Duvelisib PK in Healthy Subjects and Patients Following a Single Dose of 25 Mg Duvelisib

	Observed (Geo Mean)		Simulated (Geo Mean)		Pred/Obs ratio	
	AUCinf (CV%) (ng*h/mL)	Cmax (CV%) (ng/mL)	AUCinf (90% CI) (ng*h/mL)	Cmax (90% CI) (ng/mL)	AUC	Cmax
Healthy Subjects	3170 (38%)	937.7 (36%)	3538 (3002.0-3968.7)	902 (754.9-916.3)	1.11	0.96
Patients	5481.2 (103.8%)	1062 (70%)	5288.07* (4931-5670)	812.6* (776.0-851.0)	0.96	0.77

*simulated by Reviewer; Ref: Table 10 of Applicant's PBPK- Part A report (HV) and Study report infi-pcs-108

The Applicant evaluated the performance of the PBPK model for cancer patients by comparing the simulated and observed duvelisib PK following various dose levels ranging from 15 mg BID to 75 BID mg for 14 days as shown in Table 108. Although the model over-estimated the AUC of duvelisib by 2-fold following 25 mg duvelisib BID, the model largely captured the plasma-time profiles of duvelisib in patients (Figure 22).

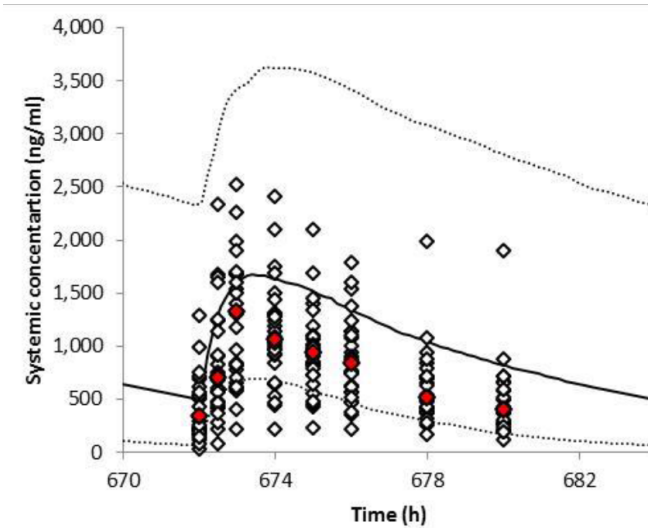
Table 108: Observed and Simulated Steady State PK of Duvelisib and IPI-656 Following Repeat Dosing of Duvelisib in Cancer Patients

Dose (mg)	Study	Predictions Geomean		Observations Geomean		Pred/Obs ratio	
		Cmax (ng/mL)	AUC (ng*hr/mL)	Cmax (ng/mL)	AUC (ng*hr/mL)	Cmax	AUC
		Duvelisib					
15 mg BID (Day 14)	IPI-145-02	1157.3*	8655.7*	1107	4358.5	1.05	1.99
25 mg BID (Day 14)	IPI-145-02	1666	13424	1308	6918	1.27	1.94
75 mg BID (Day 14)	IPI-145-02	2746	21684	2895	17183	0.95	1.26
		IPI 656					
25 mg BID (Day 14)	IPI-145-02	1109	12658	857	7445	1.29	1.70
75 mg BID (Day 14)	IPI-145-02	1705	19628	2113	20068	0.81	0.98

*Simulated by FDA reviewer
Reference: Table 5 of Applicant's Clinical Pharmacology Summary; Table 11 and 12 of Applicant's PBPK-Part A report

Figure 22: Observed and Simulated PK of Duvelisib After Repeated Dosing of 25 Mg Duvelisib in Cancer Patients

Simulated (lines) and observed (diamonds; Clinical Study IPI-145-02) plasma concentration-time profiles of IPI-145 following 25 mg IPI-145 BID for 29 days. The dotted lines represent the 5th and 95th percentiles for the simulated population.
Ref: Fig 15(a), PBPK report-Part A

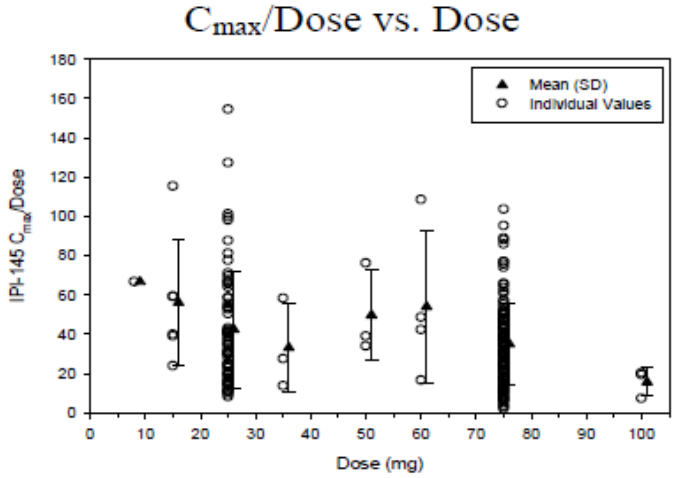


The Applicant predicted fa values of 0.98, 0.72 and 0.36 for 15, 25, and 75 mg BID respectively based on Caco-2 permeability data, and in-vitro solubility data. By applying a fa value of 0.36, the simulated

duvelisib PK parameters were in good agreement of the observed data following 75 mg BID in cancer patients. However, the Applicant's PBPK model over-predicted duvelisib AUC following 15 and 25 mg BID by approximately 2-fold in cancer patients. *Reviewer* noted that the predicted fa, 0.72, can predict a decreased dose-normalized Cmax following a single 25-mg dose of duvelisib, compared to those observed in lower dose levels (1 mg to 10 mg) in patients with advanced hematologic malignancies (Figure 22). However, as shown in Figure 23 the magnitude of decrease in dose-normalized Cmax at 75 mg level is less significant when compared to those observed at 25-mg dose level in patients. Thus, the predicted Cmax, following a single dose of 75 mg (1795 ng/mL), is lower than the observed Cmax of 2630 (ng/mL) following the first dose of a 75 mg BID dosing regimen.

Figure 23: Dose-normalized Cmax of Duvelisib Following a Single Dose of Duvelisib in Cancer Patients

Individual and mean dose-normalized Cmax of duvelisib following a single dose of duvelisib in patients with advanced hematologic malignancies



Reference: Figure 6, Clinical Pharmacology Summary

Simulation results showed that the predicted total clearance for the virtual healthy and oncology subjects were 3.9 and 2.5 L/hr, respectively following 25 mg BID. The decrease in the drug clearance can be explained by the difference in the age-distribution in the oncology population. Decrease of hepatic microsomal protein level and renal function has been reported in the elderly population.
Table 109 presents the geometric mean of the selected physiological parameters calculated in simulated healthy and oncology populations.

Table 109: Comparison of the Selected Physiological Parameters in Simulated Healthy and Oncology Subjects

	CL (L/hr) (AUC/Dose)	Age (yr)	BW (Kg)	Liver Wt (g)	GFR (mL/min)	MPPGL (mg/gram liver)
Healthy Subject (n=160)	3.9	28.6	78.6	1702.7	127.5	37.4
Oncology Subject (n=300)	2.5	62.8	74.9	1484.1	84.5	29.1

*GFR: Glomerular filtration rate; MPPGL: Microsomal protein per gram of liver
Reference. Simulation output files submitted by the Applicant (2_IPI-145_10.xls and 3_IPI-145_25mgBID.xls)

PBPK modeling approach can be used to evaluate potential effects of physiological and metabolic differences in special populations (such as cancer patients) on the drug PK profiles. At the same time, as

only a limited number of parameters were used to differentiate oncology patients from HVs, along with the possibility of unaccounted physiological/metabolic parameters (such as transporter and etiology-specific physiology parameters), the adequacy of the virtual population to describe the PK of the investigational drug for an intended population should be evaluated case-by-case. For the current submission, one limitation of the duvelisib PBPK model for oncology population is that the model predicted AUC following a single dose, while over predicted AUC by 2-fold at steady state, and consequently, over-estimated the duvelisib AUC accumulation ratio (AR). The observed and predicted AUC accumulation ratio for patients following 25 mg BID is 1.6 (reference: Applicant's clinical pharmacology summary Table 6 and 7) and 2.5, respectively. It raises concerns on whether the model captures the TDI well in patients. An IR was sent to gather the Applicant's input on the plausibility of using the same TDI parameters in healthy and cancer population. Applicant stated that the TDI potential was verified using in-vitro data, multiple PK data and midazolam DDI in healthy subjects. Reviewer noted that one possible reason of overprediction is that the CYP enzyme in patients has already been inhibited by the prior cancer treatments. Given that the model was able to capture the distribution of the individual's plasma-time profiles following the 25 mg BID (Figure 22), and the magnitude of TDI reduction observed in cancer patients (1.6) is similar to that observed in HVs following 5 mg BID (1.7)(reference: Applicant's clinical pharmacology summary Table 3), the model is adequate to describe the PK of duvelisib at steady state following 25 mg BID in cancer patients.

Q2: Can the Applicant's PBPK model adequately predict the effects of CYP3A modulators on the PK of duvelisib?
Yes, the Applicant's duvelisib PBPK model is adequate to predict the effects of various CYP3A4 modulators on the steady state pharmacokinetics of duvelisib in HVs. As shown in Table 110, the model reasonably described the observed DDI effects of ketoconazole and rifampin on PK of duvelisib and IPI-656 following co-administration of multiple doses of ketoconazole and rifampin and a single dose (sd) of duvelisib in healthy subjects.

Table 110: Predicted and Observed Cmax and AUC Values and Corresponding Ratios for Duvelisib With/Without Co-Administration With Strong CYP3A Modulators

	Cmax	AUC	Cmax	AUC	Cmax	AUC
	ng/ml	ng*hr/mL	ng/ml	ng*hr/mL		
	Control (10 mg duvelisib sd)		10 mg duvelisib sd + ketoconazole		Ratio	
Predicted GeoMean	429	1677	658	6127	1.43	3.45
Observed GeoMean	484	1443	803	5696	1.66	3.95
Pred/Obs	0.89	1.16	0.82	1.08	0.86	0.87
	Control (25 mg duvelisib sd)		25 mg duvelisib sd + rifampin		Ratio	
Predicted GeoMean	902	3538	503	1045	0.55	0.29
Observed GeoMean	938	3170	319	565	0.34	0.18
Pred/Obs	0.96	1.12	1.58	1.85	1.62	1.61

Given that duvelisib is a time-dependent CYP3A inhibitor which inhibits its own clearance pathway, increasing the dose and giving multiple dose of IPI-145 would lead to a decrease in CYP3A4 activity in the liver and gut, and consequently lead to a decrease in fmcyp3A4. As shown in Table 111, predictions

of DDI with CYP3A inhibitors (ketoconazole and fluconazole) are dose-dependent and the effects are smaller at steady states compared to those predicted after a single dose administration.

Table 111: Predicted Dose-Dependent DDI Effects of Duvelisib at Steady State When Co-Administrated With Ketoconazole or Fluconazole

	Ratios of duvelisib plasma PK with/without ketoconazole (200 mg BID)			
	1 mg BID	5 mg BID	25 mg BID	25 mg BID -oncology
CmaxR at steady state	1.6	1.44	1.27	1.36
AUCR at steady state	2.92	2.27	1.66	1.59
	Ratios of duvelisib plasma PK with/without fluconazole (200 mg BID)			
	1 mg BID	5 mg BID	25 mg BID	25 mg BID -oncology
CmaxR at steady state	1.33	1.25	1.17	1.20
AUCR at steady state	1.91	1.69	1.40	1.34

Reference: Table 13-14, 18-20, 22, 26 of the PBPK report part A

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DDI dosing recommendation for oncology patient

The Applicant used the duvelisib PBPK model for oncology patients to determine the dose of IPI-145 in the presence of strong CYP3A4 inhibitors that would provide similar exposure to IPI-145 25 mg BID administered alone. As shown in the Error! Reference source not found., predictions of steady state IPI-145 exposures following the administration of ketoconazole and 15 mg duvelisib BID were similar to those simulated following 25 mg BID in oncology patients. Reviewer repeated the Applicant's analysis by using the duvelisib PBPK for HVs. Similar results were obtained when the duvelisib PBPK model for healthy subjects was used to conduct the simulation (Error! Reference source not found.).

Table 112. Predicted Duvelisib Steady Stage PK Following 25 Mg BID Alone, and Following 15 Mg With Co-Administration With Ketoconazole

	PBPK Prediction (Geomean)		Ratio between 15 mg-BID with ketoconazole and 25 mg BID alone	
Dose (mg)	Cmax (ng/mL)	AUC (ng/mL-hr)	Cmax ratio	AUC ratio
	PBPK model for healthy subjects			
25 mg BID (Day 14) alone	1417.7	7840.2		
Co-administrated 15 mg BID with ketoconazole (Day 14)*	1356.3	9129.8	1.0	1.2
	PBPK model for cancer patients			
25 mg BID (Day 14) alone	1109.0	12658.0		
Co-administrated 15 mg BID with ketoconazole (Day 14)	1609.4	14292.5	1.5	1.1

*Simulated by Reviewer using the Applicant's duvelisib PBPK model for healthy subjects
Reference: Table 2 of the Applicant PBPK report Part C

As there is no difference in fmcyp3A values between HVs and cancer subjects in the current analysis, one can expect comparable DDI effects simulated using two models.

The Applicant's PBPK model predicted a 40% increase in AUC of duvelisib at steady state (Table 111) when co-administration with a moderate CYP3A inhibitor (such as fluconazole) in HVs.

Q3: Can the Applicant's PBPK model adequately predict the effect of duvelisib on CYP3A or CYP2C8 substrate?
Yes, the Applicant's duvelisib PBPK model is adequate to predict the inhibitory effects of steady-state duvelisib on the PK of CYP3A4 and/or CYP2C8 substrates.

DDI effects on the CYP3A substrate
The inhibitory effect of duvelisib as a CYP3A inhibitor was verified by comparing the predicted and observed PK of midazolam with/ without co-administration of 25 mg duvelisib BID. As shown in Table 113, the predicted geometric Cmax and AUC ratios of midazolam were in good agreement with the observed values in healthy subjects (Study IPI-145-10). Given that the Applicant's PBPK model can simultaneously simulate the PK of duvelisib after multiple doses and the DDI effects with midazolam, the Reviewer concluded that the Applicant's PBPK model was adequate to predict the DDI effects of duvelisib as a time-dependent CYP3A inhibitor.

Table 113: Predicted Cmax and AUC Values and Corresponding Ratios For Midazolam (2 mg) With/Without Co-Administration With Duvelisib (25 mg BID)

	Midazolam 2 mg alone		Ratio with/without 25 mg duvelisib BID	
	Cmax (ng/ml)	AUC (ng*hr/mL)	Cmax	AUC
Predicted G.M.	5.89	22.5	2.4	4.85
Observed G.M.	9.10	23.2	2.2	4.29

Reference: Table 2 and 5 PBPK report-Part B

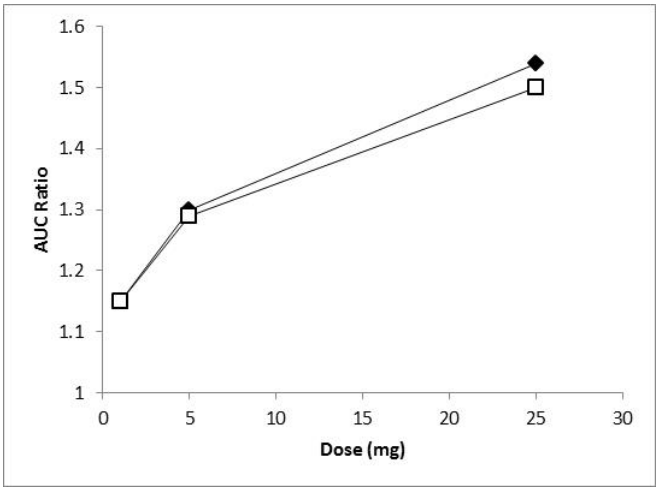
DDI effects with CYP2C8 substrate
The PBPK models for repaglinide (a substrate for CYP3A4 and 2C8) and rosiglitazone (CYP2C8 substrate) from Simcyp library were directly used by the Applicant. The ability of these models to be used as a substrate model for a target CYP-mediated pathway was verified by comparing the predicted DDI effects with observed data. For example, repaglinide as a substrate for CYP3A4 and 2C8 pathway was verified using the results of clinical DDI studies where repaglinide was co-administrated with clarithromycin (a CYP3A inhibitor), itraconazole (a CYP3A inhibitor), trimethoprim (a CYP2C8 inhibitor), and gemfibrozil (a CYP2C8 inhibitor). The values of fmcyp3A and fmcyp2C8 of repaglinide are 0.6 and 0.4, respectively. The fmcyp2C8 value for rosiglitazone is 0.5.

The Applicant's PBPK model predicted a 54% increase of repaglinide AUC following a single oral dose of 0.25 mg repaglinide on day 5 of 6 days dosing of 25 mg duvelisib BID in healthy subjects. The Applicant evaluated the inhibitory potential of duvelisib as a CYP2C8 inhibitor by conducting DDI simulations with and without considering the CYP2C8 inhibition in the duvelisib PBPK model (by setting the CYP2C8 Ki as zero). As shown in Figure 24, the simulated repaglinide AUC ratios were similar regardless of the CYP2C8-mediated inhibition.

Figure 24: Simulated Effect of Duvelisib on the AUC Ratio of Repaglinide With/Without Considering CYP2C8 Inhibition

The effect of duvelisib dose (1 to 25 mg BID) on the AUC ratio of repaglinide following a single oral dose of 0.25 mg repaglinide.
The solid diamonds and open squares represent the scenarios where CYP2C8-mediated inhibition is included and then excluded, respectively.

Reference: Figure 8 of PBPK report -Part B



Additionally, the Applicant's PBPK model predicted a minimal effect of duvelisib on the PK of rosiglitazone using the in-vitro reported CYP2C8 Ki (0.84 μM), and a less than 20% increase in rosiglitazone AUC when setting the CYP2C8 Ki values at 1/10 of the in-vitro value.
Reviewer concluded the effect of duvelisib on a CYP2C8 substrate is minimal.

Conclusions
The submiited duvelisib PBPK models are adequate to predict the PK of duvelisib and its metabolite IPI-656 under various DDI dosing scenarios in HV and patients. The simulation results predicted 1.66- and 1.4- fold increases in the steady-state duvelisib exposure in the presence of a strong CYP3A inhibitor (i.e. ketoconazole) or a moderate CYP3A inhibitor (i.e. fluconazole), respectively, in healthy subjects. For the effects of duvelisib on the CYP3A and/or 2C8 substrate, the models predicted a less than 20% increase in the PK of CYP2C8 substrates (such as repaglinide and rosiglitazone) when a single dose of CYP2C8 substrate is co-administered with 25 mg duvelisib twice daily for 5 days. For the DDI dosing recommendation, the simulation results indicated that the steady state IPI-145 exposures at 15 mg BID in the presence of a strong CYP3A inhibitor were similar to those simulated at 25 mg BID alone in healthy subjects. These analyses are determined to be adequate to support Applicant's proposed DDI dosing recommendation in USPI.

DOSING RECOMMENDATION FOR PATIENTS WITH HEPATIC IMPAIRMENT

Objective
The objective of this section of PBPK review was to evaluate the adequacy of the PBPK modeling submitted by the Applicant to predict the systemic exposure of IPI-145 and IPI-656 following oral administration of IPI-145 25 mg BID in subjects with mild, moderate and severe hepatic impairment (HI). The Applicant submitted a PBPK report for HI subjects title "Quantitative prediction of the systemic exposure of IPI-145 and its primary metabolite IPI-656 using prior in vitro and in vivo data: impact of hepatic impairment".

Executive Summary

The Applicant has conducted a clinical study to investigate the effects of hepatic impartment on the PK of duvelisib. Increases of 12%, 25%, and 51% of unbound duvelisib exposure were observed in patients with mild, moderate, and severe hepatic impairment, respectively. Geometric mean values of fu for IPI-145 in subjects with mild, moderate and severe HI were higher than those reported in healthy age matched subjects.

The Applicant developed a PBPK modeling to predict the PK of IPI-145 and IPI-656 during multiple oral dose administration of IPI-145 25 mg BID in subjects with mild, moderate and severe HI. The model predicted increases of 20%, 25%, and 45% of unbound duvelisib exposure in patients with mild, moderate, and severe hepatic impairment, respectively. The Applicant proposed no dose adjustment is necessary for patients with hepatic impairment (Child-Pugh Class A, B, and C) in their proposed prescription information (USPI).

This review concluded that the Applicant's PBPK model is adequate to estimate the steady-state duvelisib exposures in the healthy subjects with mild, moderate, and severe hepatic impairment.

Model Development
The Applicant developed three cirrhosis population models for subjects with mild, moderate, or severe HI. Some of the key changes in these models include liver volume, enzyme abundance levels and plasma protein levels. Input parameters for duvelisib were the same as duvelisib PBPK model for healthy population which has been verified with observed clinical PK and DDI data collected under various dosing scenarios. Fraction absorbed (fa) values were adjusted to fit the duvelisib Cmax observed in clinical HI study. Table 114presents the observed duvelisib PK in healthy subjects and subjects with mild, moderate, or severe hepatic Impairment. Child-Pugh (CP) score was used to define disease severity.

Table 114: Observed Total and Unbound Duvelisib PK in Healthy Subjects and Subjects With Mild, Moderate, or Severe Hepatic Impairment Following a Single Dose of 25 Mg Duvelisib

	Obs. fu	Observed Cmax			Observed AUC0-∞		
	G.M.	G.M. (ng/mL)	Ratio	Ratio (unbound)	G.M. (ng*h/mL)	Ratio	Ratio (unbound)
Healthy	1.0	899.2	1.0	1.0	4945.8	1.0	1.0
Mild	1.3	1149.5	1.3	1.6	4384.7	0.9	1.1
Moderate	1.3	700.8	0.8	1.0	4646.5	0.9	1.3
Severe	1.9	553.2	0.6	1.1	4008.0	0.8	1.5

Ratio = HI/HV, Reference-Table 10 of Applicant's ClinicalPharmSummary

Fa values in moderate and severe HI were reduced to 0.5 and 0.44 to match the observed Cmax values. The reduced fa could be partially explained by prolonged gastric emptying time in HI subjects (Table 115). The Applicant noted that although the Cmax did not change in the mild HI group in the clinical study, fa was reduced from 0.72 to 0.6 to capture the observed data. Table 115 lists some of the key changes in physiological and metabolic parameters included in the revised PBPK model to describe the characteristics of HI subjects.

In response to an IR, the Applicant re-run all simulation included in the PBPK analysis for hepatic impairment. There is negligible difference (<15%) between V13 and V17 results.

Table 115: Comparison of Key Physiological/Metabolic Parameters in HVs and Subjects With Hepatic Impairment

	Healthy	Mild	Moderate	Severe	Reference
liver volume (ratio)	1	0.89	0.71	0.63	Literature
CYP3A enzyme abundance (pmol P450/mg protein)*	137	108	56	31	expression/activity data reported in literature
CYP3A enzyme abundance (pmol P450/mg protein) (used revised model)	137	108	100	70	Modified to fit the clinical HI studies for duvelisib
CYP2B6 enzyme abundance (pmol P450/mg protein)*	17	17	15.3	13.6	expression/activity data reported in literature
gastric emptying time (hr)	0.3	0.48	0.55	0.6	Literature
fu of duvelisib	0.014	0.018	0.019	0.026	Reported values from clinical HI studies for duvelisib
fu of IPI-656	0.013	0.012	0.025	0.035	Modified to fit the clinical HI studies for duvelisib
fa	0.72	0.60	0.5	0.44	Modified to fit the clinical HI studies for duvelisib

*Simcyp V13/14 values

Model performance and application

Model performance when using the default HI population

Simulations using the original duvelisib PBPK model reasonably described the total and unbound exposure of IPI-656 following a single oral dose of 25 mg duvelisib (Table 116). For duvelisib, the model reasonably described the total and unbound exposure of duvelisib in mild HI subjects, but over-estimated those observed in moderate and severe HI subjects by approximately 2-fold (Table 116).

Table 116: Comparison Of Observed and Predicted Total and Unbound PK of Duvelisib and IPI-656 in HI Subjects Following a Single 25 Mg Duvelisib Using the Default HI Populations

	IPI-145				IPI-656			
	Observed		Predicted		Observed		Predicted	
	Ratio (total)	Ratio (unbound)	Ratio (total)	Ratio (unbound)	Ratio (total)	Ratio (unbound)	Ratio (total)	Ratio (unbound)
Healthy	1.0	1.0	1.0	1.0	1.0	NA	1.0	1.0
Mild	0.9	1.1	0.98	1.3	0.91	NA	1.05	0.99
Moderate	0.9	1.3	1.51	2.1	0.75	NA	0.66	1.05
Severe	0.8	1.5	1.56	3.0	0.48	NA	0.38	1.06

*fu observed for IPI-145 were 0.014,0.018,0.019, and 0.026 in HVs, mild, moderate and severe HI subjects, respectively

*fu for IPI-656 was adjusted by the Applicant to be 0.013,0.012,0.025, and 0.035 for HV, mild, moderate and severe HI subjects, respectively

Ratio = HI/HV, Reference: Table 6-7, PBPK report for HI subjects

Model performance when using the revised CYP3A abundance values in virtual HI populations
As the default HI models over predicted duvelisib PK in moderate and severe HI subjects, the Applicant increased the enzyme abundance values in those populations to match the observed PK data. The enzyme abundance values were adjusted from 56 to 100 and 31 to 70 pmol P450/mg protein for moderate and severe HI subjects, respectively, in the final duvelisib PBPK model. Simulations using the revised duvelisib PBPK model agreed with the observed total and unbound PKs of duvelisib and IPI-656 in moderate and severe HI subjects (Table 117).

Table 117: Comparison of Observed And Predicted Total And Unbound PK of Duvelisib and IPI-656 In HI Subjects Following a Single 25 Mg Duvelisib Using the Revised Duvelisib PBPK

	IPI-145				IPI-656			
	Observed		Predicted		Observed		Predicted	
	Ratio (total)	Ratio (unbound)	Ratio (total)	Ratio (unbound)	Ratio (total)	Ratio (unbound)	Ratio (total)	Ratio (unbound)
Healthy	1.0	1.0	1.0	1.0	1.0	NA	1.0	1.0
Mild	0.9	1.1	0.98	1.1	0.91	NA	1.1	1.1
Moderate	0.9	1.3	1.1	1.5	0.75	NA	0.7	1.1
Severe	0.8	1.5	1.0	2.0	0.48	NA	0.4	1.1

*fu observed for IPI-145 were 0.014,0.018,0.019, and 0.026 in HV, mild, moderate and severe HI subjects, respectively.
*fu for IPI-656 was adjusted by the Applicant to be 0.013,0.012,0.025, and 0.035 for HV, mild, moderate and severe HI subjects, respectively.
Ratio = HI/HV, Reference: Table 10-11, PBPK report for HI subjects

Model Application: Predict duvelisib PKs at steady state for mild, moderate and severe subjects.
Applicant then used the revised duvelisib PBPK model to predict duvelisib PK at steady state for mild, moderate and severe subjects. The model predicted steady state AUC ratios of 0.9, 0.9 and 0.8 for total duvelisib and 1.2, 1.25, and 1.45 for unbound duvelisib in patients with mild, moderate, and severe hepatic impairment compared to HVs, respectively (Table 118). The magnitudes of changes in duvelisib exposure in HI subjects at steady-state were predicted to be similar to those observed after a single dose of 25 mg duvelisib.

Table 118: Prediction of Total and Unbound Exposure of Duvelisib PK at Steady-State in Healthy Subjects and Subjects With Mild, Moderate, or Severe Hepatic Impairment Using Revised Model for HI Subjects

	fu	Cmax (steady state)			AUC0-∞ (steady state)		
	G.M.	G.M. (ng/mL)	ratio	Ratio (unbound)	G.M. (ng*h/mL)	ratio	Ratio (unbound)
Healthy	1.0	1648			10681		
Mild	0.9	1371	0.8	1.1	9540	0.9	1.2
Moderate	1.3	1258	0.8	1.0	9743	0.9	1.25
Severe	1.9	984	0.6	1.1	8104	0.8	1.45

*simulated by reviewer. Reference: Table 12, PBPK report for HI subjects

Reviewer's comments
PBPK modeling can be used as an in-silico testing tool to evaluate the impact of known physiological difference on the PK of an investigational drug for an intended population. The following limitations were noted in the Applicant's PBPK analysis:

- It is well-recognized that there is a decreased fraction of functional liver tissue and enzyme activity in HI subjects. In the current submission, reviewer considered that the original duvelisib PBPK models for HI subjects also reasonably predicted the duvelisib PKs in moderate and severe HI subjects (less than 2-fold of the observed data) (Table 116), considering only six subjects per HI groups were enrolled in clinical HI studies. In addition, the values of the revised CYP3A enzyme abundance for moderate and severe HI subjects were not much different than those reported for the mild HI subjects. Thus, the Applicant might over-fit the values of CYP3A enzyme abundance.
- The Applicant's virtual population for HI was built primarily using data collected from cirrhosis subjects, and have not been fully verified.
- Applicant assigned the same values of TDI parameters in PBPK model for HVs and HI subjects. Reviewer noted that effects of HI on the auto-inhibition potential is unknown. However, given the mechanism of enzyme inhibition is largely governed by the binding affinity of the drug, it is acceptable to use the same set of TDI parameters for HVs and HI subjects.

Reviewer noted that the observed duvelisib AUC in severe HI subjects was similar to that for HVs following a single dose of 25 mg duvelisib. Thus, the increase of unbound duvelisib AUC is largely driven by the higher fu observed in severe HI subjects (Table 114). The accuracy of the fu reported for a highly bound (fu <2%) compound such as duvelisib has been discussed within the multi-disciplinary review team. Given there are concerns on the validity of the measured fu values for duvelisib, the total duvelisib exposure is chosen as the matric for dosing recommendation in subjects with hepatic impairment. The revised PBPK model predicted less than 20% difference in total duvelisib exposures at steady-state in the subjects with mild, moderate, and severe hepatic impairment in comparison with that in normal healthy subjects (Table 118).

Reviewer used the Applicant's original duvelisib PBPK model to simulate the duvelisib PK at steady state for moderate and severe subjects. This analysis evaluates the changes in duvelisib PKs when lower clearances were assigned to subjects with moderate and severe HI. Table 119 presented the simulated total exposure of duvelisib PK at steady-state in healthy subjects and subjects with mild, moderate, or severe hepatic impairment using the Applicant's original and revised PBPK model. The original model predicted steady state AUC ratios of 0.9, 1.2 and 1.1 for total duvelisib in the subjects with mild, moderate, and severe hepatic impairment compared to that in normal healthy subjects. However, the unbound duvelisib exposure would likely to be higher in HI subjects.

Table 119: Comparison of Predicted Total Exposure of Duvelisib PK at Steady-State in Healthy Subjects and Subjects With Mild, Moderate, or Severe Hepatic Impairment Using the Applicant's Original and Updated PBPK Model

	AUC0-∞ (original CYP abundance)		AUC0-∞ (revised CYP abundance)	
	G.M. (ng/mL)	ratio	G.M. (ng*h/mL)	ratio
Healthy	10681		10681	

Mild	9540	0.9	9540	0.9
Moderate	12858*	1.2	9743	0.9
Severe	11507*	1.1	8104	0.8

*simulated by reviewer. Reference: Table 12, PBPK report for HI subjects

Conclusions
Applicant's PBPK model is adequate to estimate the steady-state duvelisib exposures in healthy subjects with mild, moderate, and severe hepatic impairment. The Applicant's final model predicted steady state AUC ratios of 0.9, 0.9 and 0.8 for total duvelisib in patients with mild, moderate, and severe hepatic impairment compared to those in HVs, respectively.

ACID REDUCING AGENTS (ARAS) EFFECTS ON THE PK OF DUVELISIB

Executive Summary
The Applicant submitted the simulation report QCL1177717 for duvelisib (IPI-145) to evaluate the impact of changes in particle size of active pharmaceutical ingredient (API), dose, and gastric pH on the exposure of duvelisib. The OCP review team and the Division of Biopharmaceutics (DB) review team worked jointly to evaluate the adequacy of the model to describe the impact of changes to particle size and gastric pH on exposure of IPI-145. This review only focuses on evaluating the adequacy of Applicant's model to assess the impact of gastric pH on the exposure of duvelisib. Refer to the review of biopharmaceutics for the evaluation of the Applicant's model to assess the impact of changes in particle size of API on the exposure of duvelisib.

This review concludes that the Applicant's absorption model was acceptable for assessing the impact of gastric pH on duvelisib PK. Simulation for the market-image formulation DP-B (batch 02140013) suggested that when stomach pH was increased to 5, AUC and Cmax were decreased by 17% and 63%, respectively. When the particle size distribution was altered to be close to the specification upper limit, simulation suggested duvelisib AUC and Cmax were decreased by 28% and 66%, respectively, when gastric pH was increased to 5.

Methods
The Applicant's modeling and simulation process consists of modeling development, model verification against clinical PK data, parameter sensitivity analysis, and simulations. The absorption model was built using the simulation software package GastroPlus (Simulations Plus, Inc., Lancaster, CA, USA). Measured in vitro values, ADMET Predictor™ predicted values, and modeling input values for key parameters are summarized in Table 120. Clinical PK studies that were used in model development, training, and verification are summarized in Table 121. Among the 15 sets of data, 9 were used in the training set and 6 used in the verification set. The verification set included a spread of doses (1 to 25 mg) and included a unique particle size distribution (PSD) (the induction DDI study) that had not been used in the building of the model. The studies used drug product prepared with different batches of IPI-145 drug substance covering a range of particle sizes (D10 (6.2-22 μm), D50 (32-258 μm), D90 (135-747 μm)).

After the model development and verification, the Applicant conducted parameter sensitivity analysis to assess the effect of particle size distribution, dose, and gastric pH on duvelisib PK.

Table 120: PBPK Input Parameters for Oral Absorption Model

Parameter	Measured Value	ADMET Predictor™ Value	Model input value
MW (g/mol)	416.9	416.9	416.9
pKa	3.65 (UV- metric)	3.35	3.9, fitted using solubility vs. pH data
Solubility (mg/mL)	Buffer: 5.94 at pH 1.2 0.38 at pH 2.0 0.17 at pH 3.0 0.05 at pH 4.0 0.03 at pH 4.5 0.02 at pH 5.5 0.02 at pH 6.5 0.02 at pH 7.4 Biorelevant 4.65 in SGF 0.02 in FaSSIF	Buffer: 0.06 at pH 6.77 Biorelevant 0.0634 in SGF 0.00876 in FaSSIF	Measure buffer solubility
Caco2 Papp (cm/s x 10^{-6})	2.5	NA	14, fitted using observed PK data
Estimated human Peff (cm/s x 10^{-4})	3.71	2.53	2.71
LogP	2.57	3.5	2.57
Unbound human plasma protein binding (%)	1.3	2.47	1.3
Blood to plasma ratio	1	0.72	1
Mean precipitation time (sec)	NA	900 (default)	5000, fitted using observed PK data
Particle size distribution	Tables 3, 4, 13, and 14 in report QCL117717	NA	Tables 3, 4, 13, and 14 in report QCL117717
Particle density (g/mL)	1.37	1.21 (default)	1.37
PK parameters	Calculated or fitted	NA	Calculated or fitted against IV PK data, see table 6 in report QCL117717

SGF: simulated gastric fluid, FaSSIF: fasted state simulated intestinal fluid. (source: modified from tables 1, 5, and 6 of simulation report QCL1177717)

Table 121: Formulations and Studies Used in Absorption Model Development and Verification

Study#/type	Batch	D10, D50, D90 (µm)	Formulation	Dose (mg)	N	Use in modeling
IPI-145-01 / SAD	6825-B-R0-01-43-01	6.2, 32, 135	DP-A	1, 2, 5, 10, 20, 30	4	Training
IPI-145-01 / MAD				1, 2, 5, 10	9	Verification
IPI-145-01 / FE				25	6	Verification
IPI-145-01 / DDI				10	16	Training
IPI-145-05 / ADME	7920-B-R0-01-50-01	22, 258, 747	DP-A/IV	0.0028 (IV)	6	Training

Study#/type	Batch	D10, D50, D90 (µm)	Formulation	Dose (mg)	N	Use in modeling
IPI-145-05 / ADME				25	6	
IPI-145-11 / Induction	8342-B-R0-01-50-01	6.5, 51, 462	DP-B	25	14	Verification
IPI-145-15 / BE	6825-B-R1-01-50-01	14, 57, 460	DP-A	5 mg reference	26	Predicted
IPI-145-15 / BE	8590-B-R1-02-48-01	18, 196, 637	DP-A	25 mg reference	16	Predicted
IPI-145-15 / BE	02140013	6, 48, 503	DP-B	5 mg and 25 mg test	26/16	Predicted

SAD: single ascending dose, MAD: multiple ascending dose, FE: food effect, DDI: drug-drug interaction, ADME: absorption, distribution, metabolism, and excretion, BE: bioequivalence, IV: intravenous, (source: modified from tables 2, 17, and a1 of simulation report QCL1177717)

Reviewer's comments:

1. Papp value of $14X10^{-6}$ cm/sec was optimized against clinical data, which was much higher than the measured Papp of $2.5X10^{-6}$ cm/sec at 10µM. The rationale provided by the Applicant was that the measured Papp of $11X10^{-6}$ cm/sec in the presence of a P-gp inhibitor represented a closer estimate of the intrinsic permeability. The measured Papp (A to B) was about $6X10^{-6}$ cm/sec at 100µM. Simulation suggested that GI luminal concentration of duvelisib at the main absorption site (duodenum and proximal jejunum) can be higher than 100µM after a single dose of 25 mg duvelisib. The proposed rationale is reasonable.
2. P-gp was not built in the absorption model as PK linearity was observed up to 30 mg.
3. The precipitation time was fitted to be 5000 secs (83 mins) based on the PK profiles of the training set. The selection was supported by the observation that duvelisib remained in solution at 0.1 and 0.3 mg/mL (supersaturation status) for up to 24 hours after dilution with FaSSIF (pH 6.5) and FeSSIF (fed state simulated intestinal fluid, pH 5.0).
4. Overall, the Applicant's absorption model development and verification process seems appropriate for assessing the effect of elevated gastric pH on duvelisib PK.

Results
Model performance assessment was assessed by comparing the predicted PK with observed geometric mean Cmax and AUCinf for individual clinical data sets. The prediction errors (%PE) are summarized in Table 122.

Table 122: Prediction Errors (% PE) for the Training and Verification Data Sets

	Cmax	AUCinf
Training (N=9)	-22% - 23%	-42% - 13%
Verification (N=6)	-19% - 16%	-8% - 13%

N: number of clinical data sets (also see Table 121)

Reviewer's comments:

1. The clinical PK studies were conducted using products manufactured by a range of wide range of particle sizes (D10 (6.2-22 µm), D50 (32-258 µm), D90 (135-747 µm)) which was beyond the

agreed particle size distribution specification (D10≥1 μm, D50=20-115 μm, and D90≤450 μm). The prediction errors were within 50%, and the model performance is acceptable.

2. The agreed particle size distribution specification (D10≥1 μm, D50=20-115 μm, and D90 ≤450 μm) was different from the proposed particle size distribution specification which had D90 ≤550 μm. The revised particle size distribution specification was based on virtual bioequivalence simulations conducted by DB reviewers.
3. The model was constructed for dose less than 30 mg where PK linearity was generally held. The proposed dose is 25 mg twice daily.

Evaluation of the effect of elevated gastric pH on duvelisib PK was conducted by the Applicant for batches 6825, 7920, 8342 (table 12 of report QCL117717, and table 16 of report QCL117717) following a single oral dose of 25 mg duvelisib. In response to an IR, the Applicant further evaluated the effect of elevated gastric pH on duvelisib PK at steady state. It should be noted that there were several limits in the steady state simulations. Auto-inhibition mechanism was not incorporated in the absorption. However, it is not expected to have an impact on the PK ratios in subjects with elevated stomach pH compared to subjects with normal stomach pH as the clearance is expected the same in those populations. Due to the limitation in the software, particle size is kept constant within each bin for steady state simulation. The impact of keeping particle size constant over time is a lower predicted Cmax by 2-10%. Nevertheless, steady state simulation suggested that the magnitude of changes in PK parameters was less at steady state compared to single dose. It was also noted that the simulated trough concentrations were increased in subjects with elevated stomach pH. For the limitations, simulations were conducted under single dose condition.

The reviewer verified the Applicant's simulation and conducted additional simulations to evaluate the effect of elevated gastric pH on duvelisib PK for the batches that were not evaluated by the Applicant. The results are summarized in Table 123. The reviewer's simulations results (see Table 123) are close to the Applicant's simulation results (see tables 12 and 16 in report QCL117717). Batch '2130075 it 843 um' can be considered a case close to the upper limit of particle size distribution specification where duvelisib AUC decreased about 28% and Cmax decreased about 66% when gastric pH was increased to 5.

Table 123: Changes in Duvelisib Cmax, AUCinf, and Fraction Absorbed (Fabs%) after Gastric pH is Elevated to pH 5 Following a Single Oral Dose of 25 Mg Duvelisib

					pH1.3			pH5			Ratios			decreased %		
Batch	G+RcdNo.	D10 (um)	D50 (um)	D90 (um)	Cmax(ng/mL)	AUCinf(ng*hr/mL)	Fabs(%)	Cmax(ng/mL)	AUCinf(ng*hr/mL)	Fabs(%)	Cmax(ng/mL)	AUCinf(ng*hr/mL)	Fabs(%)	Cmax(ng/mL)	AUCinf(ng*hr/mL)	Fabs(%)
02150035R lt 63 um	22	2.4	23	53	934.9	3267.2	99.9	482.4	3155.3	96.6	0.52	0.97	0.97	48.40	3.42	3.30
2140043	19	5.3	35	63	925.4	3267.1	99.9	393.7	3102.1	94.9	0.43	0.95	0.95	57.46	5.05	5.01
2150078	38	2	25	140	912.9	3228.0	98.8	495.6	3004.0	91.9	0.54	0.93	0.93	45.71	6.94	6.98
2150077	37	13	35	107	910.2	3230.7	98.9	429.9	2992.2	91.6	0.47	0.93	0.93	52.77	7.38	7.38
6825	27	6.2	32	135	888.3	3178.9	97.3	398.6	2854.2	87.3	0.45	0.90	0.90	55.13	10.21	10.28
02150035R lt 150 um	24	2.9	44	135	882.4	3214.6	98.4	355.7	2757.5	84.4	0.40	0.86	0.86	59.69	14.22	14.23
8342	29	6.5	51	462	823.4	3006.3	91.9	273.5	2489.6	76.1	0.33	0.83	0.83	66.78	17.19	17.19
2140013	18	6.3	48	503	811.4	2951.5	90.3	300.8	2441.1	74.5	0.37	0.83	0.83	62.93	17.29	17.46
2150037	39	3.6	49	288	841.1	3084.9	94.4	353.4	2526.8	77.2	0.42	0.82	0.82	57.98	18.09	18.22
6825-B-R1 (5mg)	33	14	57	460	170.6	589.5	89.5	58.8	480.4	71.9	0.34	0.81	0.80	65.53	18.51	19.66
02150035R	20	3	66	279	833.7	3081.0	94.3	335.1	2465.0	75.4	0.40	0.80	0.80	59.81	19.99	20.04
02140081R	21	3.8	78	285	817.7	3050.0	93.3	284.1	2357.8	72.2	0.35	0.77	0.77	65.26	22.70	22.62
02150035R gt 63 um	23	3.3	116	302	791.2	3004.3	91.9	259.7	2181.5	66.6	0.33	0.73	0.72	67.18	27.39	27.53
2130075 lt 843 um	26	3	150	580	739.6	2780.5	85.0	253.4	2012.0	61.3	0.34	0.72	0.72	65.74	27.64	27.88
2130075	17	4.4	158	595	711.1	2671.5	81.7	239.7	1908.2	58.1	0.34	0.71	0.71	66.29	28.57	28.89
8590-B-R1	32	18	196	637	717.5	2729.1	81.9	183.7	1921.1	55.1	0.26	0.70	0.67	74.39	29.61	32.72
02150035R gt 150 um	25	3.2	204	341	738.4	2830.4	86.6	277.7	1909.2	58.2	0.38	0.67	0.67	62.39	32.55	32.79
7920	28	22	258	747	672.4	2579.0	78.8	152.7	1705.9	51.8	0.23	0.66	0.66	77.29	33.85	34.26

Reviewer's comments:

- The reviewer's simulation confirmed the Applicant's simulation results.
- In general, the effect of elevated gastric pH on duvelisib PK increases with the increasing API particle size distribution, and dose.
- Duvelisib Cmax and AUC decreased when gastric pH is elevated to pH 5. The percentage decrease in Cmax was higher than the percentage decrease in AUC when gastric pH is elevated. The percentage decrease in Cmax and AUCtau was slighter lower at steady state than after a single dose. Cmin at steady state was increased when gastric pH is elevated to pH 5.

Conclusions

- The Applicant's absorption model is appropriate for evaluating the effect of elevated gastric pH on duvelisib PK.
- PBPK modeling and simulations suggested the effect of elevated stomach pH on duvelisib PK is dependent on particle size distribution. Simulation for the market-image formulation DP-B (batch 02140013) suggested that when stomach pH was increased to 5, AUC and Cmax were decreased by 17% and 63%, respectively. When the particle size distribution was close to the specification upper limit, simulation suggested duvelisib AUC and Cmax were decreased by 28% and 66%, respectively, when gastric pH was increased to 5.

19.4. FDA Grouped Preferred Terms

FDA Grouped PT	Included	Excluded
Abdominal pain	Abdominal pain, Abdominal pain lower, Abdominal pain upper, Gastrointestinal pain, Abdominal discomfort, Epigastric discomfort	Abdominal distension, Abdominal rigidity
Abscess	Abscess, specific types of abscess (e.g., limb/tooth/subcutaneous/Staphylococcal/perirectal/joint)	
Anemia	Anemia, Anemia macrocytic, Hemorrhagic anemia, Hemoglobin decreased, Hematocrit decreased, RBC count decreased	Pancytopenia
Arrhythmia	Arrhythmia, Arrhythmia supraventricular, Atrial fibrillation, Atrial flutter, Bradyarrhythmia, Bradycardia, Sinus bradycardia, Atrial tachycardia, Paroxysmal arrhythmia, Sinus arrhythmia, Sinus tachycardia, Supraventricular extrasystoles, Supraventricular tachycardia, Tachycardia, Ventricular arrhythmia, Ventricular extrasystoles, Ventricular fibrillation, Ventricular tachycardia, [Cardiac flutter], Extrasystoles, [Heart rate irregular]	Palpitations
Bronchospasm	Bronchospasm, Wheezing, Asthma	
Cardiac failure	Cardiac failure, Congestive cardiomyopathy, [Left ventricular failure, Cor pulmonale, Cardiac failure congestive, Cardiac failure chronic]	[Cardiac arrest, Cardiac hypertrophy, Ejection fraction decreased, Left ventricular dysfunction, Diastolic dysfunction, Ventricular dysfunction, Ventricular hypokinesia]
Candidiasis	Candidiasis, Candida infection, Oropharyngeal candidiasis, Oral candidiasis, Intertrigo candida, Genital candidiasis, Vulvovaginal candidiasis	Candiduria, Vulvovaginal mycotic infection
Chest pain	Chest discomfort, Chest pain, Noncardiac chest pain, Angina pectoris	Musculoskeletal chest pain
Colitis	Colitis, colitis erosive, enterocolitis, enterocolitis hemorrhagic colitis microscopic, colitis ulcerative	Colitis ischemic, enterocolitis infectious, CMV colitis, pseudomembranous colitis
Conjunctivitis	Conjunctivitis, Conjunctivitis allergic/bacterial/infective/viral	
Cough	Cough, Productive cough, Upper airway cough syndrome	
Depression	Depression, Depressed mood, [Depressive symptom], [major	

FDA Grouped PT	Included	Excluded
	depression]	
Diarrhea	Diarrhea, Diarrhea hemorrhagic, Defecation urgency	Colitis, Ileitis, Clostridium difficile colitis, gastroenteritis
Dizziness	Dizziness, [Dizziness exertional, Dizziness postural], Vertigo, Vertigo positional	
Dyspnea	Dyspnea, Dyspnea exertional, Dyspnea paroxysmal nocturnal	[Acute respiratory failure, Respiratory failure, Tachypnea, Respiratory rate increased, Wheezing, Bronchospasm]
Edema	Generalized edema, Face edema, Edema peripheral, Fluid overload, Fluid retention, Pulmonary edema	Localized edema, Joint swelling, Eyelid edema, Lip edema, Periorbital edema, Mouth edema, Edema genital, Lymphedema, Lymphatic edema, Catheter site edema, Scrotal edema
Fatigue	Asthenia, Fatigue, Lethargy, ECOG performance status worsened	Malaise
Gastroenteritis	Gastroenteritis, Gastroenteritis viral, Campylobacter gastroenteritis	
Gastrointestinal hemorrhage	Gastric hemorrhage, Large intestinal ulcer hemorrhage, Hematochezia, [Hematemesis], Intestinal hemorrhage, Upper gastrointestinal hemorrhage, Gastrointestinal hemorrhage, Intestinal hemorrhage, Melena, Rectal hemorrhage, Small intestinal hemorrhage	Hemorrhoidal hemorrhage
Headache	Headache, tension headache, sinus headache	
Hemorrhage intracranial	Hemorrhage intracranial, subdural hematoma, subdural hemorrhage, [Cerebral hemorrhage, Hemorrhagic stroke, Subarachnoid hemorrhage]	
Hepatitis	Hepatitis, Hepatitis acute, Hepatitis cholestatic, Hepatocellular injury, Hepatotoxicity	Hepatic failure, Hepatic encephalopathy
Herpes virus infection	Herpes simplex, Herpes simplex pneumonia, Herpes virus infection, Herpes zoster, Herpes dermatitis, Herpes ophthalmic, Oral herpes, [Genital herpes], Herpes zoster ophthalmic, [Varicella, Varicella zoster virus infection]	
Hyperbilirubinemia	Blood bilirubin increased, Hyperbilirubinemia, Jaundice	

FDA Grouped PT	Included	Excluded
Hyperglycemia	Hyperglycemia, Blood glucose increased	
Hypersensitivity	Drug hypersensitivity, Hypersensitivity, Urticaria, Angioedema, [Anaphylactic reaction, Anaphylactic shock]	Infusion related reaction, Skin reaction, Swollen tongue, Erythema multiforme
Hypertension	Hypertension, Essential Hypertension, Blood pressure increased, Blood pressure systolic increased	
Hypokalemia [a]	Hypokalemia, blood potassium decreased	
Hypoesthesia	Hypoesthesia, Hypoesthesia oral	
Hypotension	hypotension, Diastolic hypotension, Orthostatic hypotension	
Influenza	Influenza, H1N1 influenza	
Injection site reaction	Injection site erythema, Injection site extravasation, injection site reaction	
Leukopenia	Leukopenia, White blood cell count decrease	
Lower respiratory tract infection	Bronchitis, specific types of bronchitis (Bronchitis bacterial/viral), Bronchiolitis, Lower respiratory tract infection viral, Lung infection	
Lymphopenia	Lymphopenia, lymphocyte count decreased	
Mucositis	Stomatitis, Aphthous stomatitis, Mucosal inflammation, Mouth ulceration, Tongue ulceration, Oral pain, Oral discomfort, Oral mucosal blistering, Oral mucosal erythema, Oropharyngeal pain or discomfort	Proctalgia, Proctitis, Radiation mucositis, Vaginal inflammation, Gingival pain, Gingival swelling, Gingivitis, Gingival erythema, Glossitis, Mucosal hemorrhage, Esophagitis, Erosive esophagitis, Gastrointestinal tract irritation
Muscle spasms	Muscle spasms, Muscle contracture, Muscle contractions involuntary, [Muscle spasticity]	
Musculoskeletal pain	Back pain, Bone pain, Musculoskeletal chest pain, Musculoskeletal pain, Musculoskeletal discomfort, Myofascial pain syndrome, Neck pain, Pain in extremity, Myalgia, [Spinal pain]	Arthralgia, Flank pain, Noncardiac chest pain

FDA Grouped PT	Included	Excluded
Myocardial ischemia or infarction	Acute myocardial infarction, Myocardial ischemia, Angina unstable, Troponin increased, Acute coronary syndrome, Myocardial infarction, Coronary artery stenosis or occlusion	Cardiac arrest
Nausea	Nausea, Retching	
Neuropathy peripheral	Neuropathy peripheral, Peripheral sensory neuropathy, [Peripheral sensorimotor / motor neuropathy], Neuralgia	Hypoesthesia, Paresthesia, Sensory loss, Peripheral nerve palsy, [Polyneuropathy]
Neutropenia	Neutropenia, Neutrophil count decreased	Pancytopenia
Nonmelanoma skin cancer	Squamous cell carcinoma of skin, Basal cell carcinoma, Bowen's disease, Basosquamous carcinoma	Squamous cell carcinoma
Otitis	Otitis media, otitis media acute, otitis externa	
Paresthesia	Paresthesia, Paresthesia oral	
Pneumonia	Pneumonia, specific types of pneumonia (e.g. pneumonia bacterial/herpes simplex/influenzal/legionella/pneumococcal/mycoplasmal/pneumocystis jirovecii/atypical/pseudomonas/staphyloccal), Bronchopneumonia, Bronchopulmonary aspergillosis, Lung infection	Pneumonia aspiration
Pneumonitis	Pneumonitis, Acute respiratory distress syndrome, Interstitial lung disease, lung infiltration	
Pruritus	Excoriation, Pruritus, Pruritus generalized, Pruritus allergic, Prurigo	Eye pruritus
Pulmonary edema	Pulmonary edema, [Pulmonary congestion]	
Pulmonary hemorrhage	[Pulmonary hemorrhage, Pulmonary alveolar hemorrhage]	
Rash	Dermatitis, Dermatitis allergic/atopic/bullous/exfoliative/psoriasiform, Drug eruption, Drug reaction with eosinophilia and systemic symptoms, Erythema, Erythema multiforme, Generalized erythema, Exfoliative rash, Rash, Rash generalized, Rash erythematous/macular/maculopapular/papular/pruritic/pustular, Toxic skin eruption, Palmar erythema, Palmoplantar keratoderma, Palmar-plantar erythrodysesthesia syndrome, Perivascular dermatitis, Skin reaction, skin toxicity, Stevens-Johnson syndrome, Toxic epidermal necrolysis	Dermatitis acneiform, Dermatitis contact, Dermatitis infected Herpes dermatitis, Skin exfoliation, Eczema, Rosacea, Seborrheic Dermatitis, Seborrheic keratosis, Actinic keratosis, Acrodermatitis, Acne, Rosacea, Pityriasis rosea, Poikiloderma, Chronic actinic dermatitis, Macule,

FDA Grouped PT	Included	Excluded
		Psoriasis
Renal insufficiency	[Acute kidney injury], Blood creatinine increase, Creatinine renal clearance decreased, Glomerular filtration rate decreased, Renal failure, Renal failure acute/chronic, Renal impairment, Nephropathy, Nephropathy toxic, Hypercreatinemia	Renal disorder
Respiratory tract infection	Respiratory tract infection + specific types (e.g. respiratory tract infection viral, respiratory syncytial virus infection)	Upper / lower respiratory tract infection
Sepsis	Bacteremia, Sepsis, Septic shock, Sepsis syndrome, specific types of sepsis or bacteremia (e.g. Staphylococcal), Septic embolus, Neutropenic sepsis, Urosepsis	Candida sepsis, Device related infection
Skin infection	Skin infection, Skin bacterial infection, Staphylococcal skin infection, Erysipelas, Impetigo, specific types of impetigo (e.g. Staphylococcal impetigo), Periorbital cellulitis, Cellulitis, Dermatitis infected, Infected skin ulcer	Intertrigo candida, Skin candida, other references to candida infection
Thrombocytopenia	Thrombocytopenia, Platelet count decreased	Pancytopenia
Thrombosis or thromboembolism	Deep vein thrombosis, Embolism, Peripheral embolism, Pulmonary embolism, Thrombosis, Thrombosis in device, specific sites of thrombosis (e.g., jugular vein, aortic, intracranial venous sinus thrombosis)	Air embolism, Embolism, Septic embolism, Thrombophlebitis superficial
Transaminase elevation	Alanine aminotransferase increased, aspartate aminotransferase increased, transaminase increased, hepatitis acute, hepatitis, hypertransaminasemia, hepatic enzyme increased, acute hepatic failure, drug-induced liver injury, hepatic failure, hepatocellular injury, hepatotoxicity	Hepatic encephalopathy
Upper respiratory tract infection	[Acute sinusitis], Chronic sinusitis, Laryngitis, Laryngitis viral, Nasopharyngitis, Pharyngitis, specific types of pharyngitis (e.g. Viral pharyngitis, Pharyngitis streptococcal), Rhinitis, Viral rhinitis, Sinusitis, [Tonsillitis], Upper respiratory tract infection, [Upper respiratory tract infection bacterial], Viral upper respiratory tract infection, Rhinovirus infection, Tracheitis, Bacterial tracheitis, Tracheobronchitis	Respiratory tract infection, Rhinitis allergic, Rhinorrhea, Sinus congestion
Urinary tract infection	Cystitis, Urinary tract infection + specific types (e.g. Escherichia UTI), [Pyelonephritis, Kidney infection]	Bacteriuria, Candiduria, Dysuria, Urine leukocyte esterase positive

FDA Grouped PT	Included	Excluded
Visual impairment	Altered visual depth perception, Vision blurred, Visual acuity reduced, Visual impairment, [Vision decreased, Visual field defect, Blindness, Diplopia]	
Wound infection	Wound infection, specific types of wound infection (e.g. Wound infection staphylococcal)	
Xerosis	Dry skin, Dry eye, Dry mouth, Xerosis	

[a] Grouping for other lab-related AEs was similar.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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09/23/2018

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CHRISTOPHER M SHETH
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NAM ATIQUR RAHMAN
09/24/2018
I agree with the recommendation.

MENGDIE YUAN
09/24/2018

MENGDIE YUAN
09/24/2018

JINGJING YE
09/24/2018

THOMAS E GWISE on behalf of RAJESHWARI SRIDHARA
09/24/2018
This application was reviewed by Thomas Gwise, not Dr. Sridhara.

YVETTE L KASAMON
09/24/2018

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