

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205858Orig1s000**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

Application Type	NDA
Application Number(s)	205858
Priority or Standard	Standard
Submit Date(s)	September 11, 2013
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Division / Office	DHP/OHOP
Reviewer Name(s)	Barry W. Miller, MS, CRNP Donna Przepiorka, MD, PhD
Team Leader	R. Angelo de Claro, MD
Review Completion Date	May 9, 2014
Established Name	Idelalisib
(Proposed) Trade Name	Zydelig
Therapeutic Class	Kinase inhibitor
Applicant	Gilead Sciences, Inc.
Formulation(s)	100 mg, 150 mg tablets
Dosing Regimen	150 mg orally, twice daily
Indication(s)	<ul style="list-style-type: none"><li>• For the treatment of patients with relapsed follicular B-cell non-Hodgkin lymphoma (FL) who have received at least two prior systemic therapies</li><li>• For the treatment of patients with relapsed small lymphocytic lymphoma (SLL) who have received at least two prior systemic therapies</li></ul>
Intended Population	≥18 years of age

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# 1 Recommendations/Risk Benefit Assessment

## 1.1 Recommendation on Regulatory Action

This review team recommends approval of idelalisib under Subpart H (21 CFR 314.510) for treatment of patients with relapsed follicular B-cell non-Hodgkin lymphoma (FL) after two or more prior systemic therapies, and for treatment of patients with relapsed small lymphocytic lymphoma (SLL) after two or more prior systemic therapies. Accelerated approval is based on the finding of durable complete or partial responses. Confirmation of clinical benefit is required.

Approval for these indications is supported by the results of Protocol 101-09, a single-arm trial of idelalisib 150 mg BID in patients with indolent lymphomas. The applicant proposed that idelalisib (b) (4)

It remains to be confirmed in post-marketing studies that idelalisib is efficacious, safe, and tolerable in patients with FL and SLL when taken for an extended duration, i.e., 12 months or longer. The optimal idelalisib dosing regimen for chronic administration is unknown.

## 1.2 Risk Benefit Assessment

Table 1 Risk benefit assessment

<i>Decision Factor</i>	<i>Evidence and Uncertainties</i>	<i>Conclusions and Reasons</i>
<i>Analysis of Condition</i>	Approximately 20,500 patients will be newly diagnosed with FL or SLL in the US this year. Three-year progression free survival is estimated to range from 51 to 91% with a 3 year survival rate of 84 to 91%.	Many patients live years with FL or SLL.
<i>Unmet Medical Need</i>	No curative treatments exist for relapsed FL and SLL. The standard of care for patients with symptoms is to administer cytoreductive chemotherapy repeatedly until fatal resistant disease occurs.	Relapsed FL and SLL are serious and life-threatening lymphomas. Novel agents are needed to manage these cancers.
<i>Clinical Benefit</i>	Protocol 101-09 was a single-arm trial of idelalisib 150 mg PO BID for patients with indolent lymphoma that failed at least 2 prior therapies. For the 72 subjects with FL: <ul style="list-style-type: none"> <li>39 (54%) subjects had an objective response, including 6 CR and 33 PR.</li> <li>Median duration of response was not reached with a median follow-up of 8 months for responders.</li> </ul> For the 26 subjects with SLL: <ul style="list-style-type: none"> <li>15 (58%) subjects had an objective response, all of which were PR.</li> </ul>	Idelalisib is active in treating patients with relapsed FL and SLL. An optimal duration of treatment was not established.

<b>Decision Factor</b>	<b>Evidence and Uncertainties</b>	<b>Conclusions and Reasons</b>
	<ul style="list-style-type: none"> <li>Median duration of response was 12 months. Less than 12% of patients with response remained on treatment longer than 12 months.</li> </ul>	
<i>Risks</i>	<p>Safety was studied in 354 subjects with hematological malignancies at various doses of idelalisib monotherapy and in 146 subjects with indolent lymphoma treated with idelalisib 150 mg BID. Protocol-specified monitoring and dose modifications were used to control the risks.</p> <p>In the monotherapy population:</p> <ul style="list-style-type: none"> <li>2% had a fatal suspected AE, including neutropenia, sudden death, tumor lysis syndrome, respiratory failure, and enteropathy</li> <li>There were 3 potential Hy's law cases, but all had confounding features</li> </ul> <p>In the 146 subjects with indolent lymphoma:</p> <ul style="list-style-type: none"> <li>55% interrupted or stopped idelalisib for an adverse event.</li> <li>Frequent AEs (<math>\geq 20\%</math>) included diarrhea, fatigue, cough, nausea, pyrexia, neutropenia, elevated transaminases, pneumonia, rash, and abdominal pain.</li> <li>Grade <math>\geq 3</math> AEs included neutropenia, elevated transaminases, pneumonia and diarrhea.</li> <li>Grade <math>\geq 3</math> laboratory abnormalities included neutropenia, elevated transaminases and thrombocytopenia</li> <li>The actual incidence of drug-induced pneumonia is not clear, since there was a high background of infectious pneumonia.</li> </ul>	<p>The overall safety profile for idelalisib is potentially acceptable for patients with FL and SLL who have no other effective therapies. A safe duration of treatment is not known. In addition, since dosing had to be modified for more than half of the subjects, the optimal safe starting dose is not clear.</p>
<i>Risk Management</i>	<p>The protocol included monitoring for risks clinically and with laboratory testing. With this monitoring in place, dosing was modified for more than half of the subjects. The proposed labeling includes warnings, precautions including recommended monitoring, and dose modifications, but safe use will require that both the patients and healthcare providers are aware of these instructions.</p>	<p>A patient medication guide is required to inform and educate patients of treatments risks. A REMS communication plan is required for explicit iteration to healthcare providers of significant risks that may be outside of the usual scope of healthcare provider.</p>

Abbreviations: AE, adverse event; CR, complete response; FL, follicular lymphoma; PR, partial response; REMS, risk evaluation and mitigation strategy; SLL, small lymphocytic lymphoma

Although there are several active combinations of cytotoxic chemotherapeutics or radioimmunotherapeutics that can be used for treatment of relapsed FL or SLL, efficacy is variable, and the durations of response are limited. Moreover, repeat administration of intravenous combination chemotherapy with its attendant myelosuppression poses additional challenge. The results of Protocol 101-09 demonstrated that idelalisib, an oral agent, has activity in patients with FL or SLL who have failed a median of 4 prior regimens, and the incidence of grade  $\geq 3$  neutropenia is less than expected with many

combination chemotherapy regimens. The safety review, however, revealed substantial non-hematological risks, including fatal events. The risks were moderated in part by close monitoring and dose interruption and/or reduction for toxicities, a strategy that would be needed for safe use of the drug in practice. It is not clear that this can be accomplished with an oral medication without explicit instructions to the patients and education of the healthcare providers. With such controls of risk in place, the current measure of clinical benefit outweighs the expected risks for patients with FL or SLL who have no other effective therapy available.

### **1.3 Recommendations for Labeling**

The following are recommendations for idelalisib labeling based on this review:

- Limit use to patients who have no more effective therapy available
- Include Warning and Precautions that address hepatotoxicity, colitis, toxic epidermal necrolysis, and pneumonitis.
- Include instructions for dose interruption and modification for patients who develop elevated transaminases, diarrhea, rash, and drug-induced pneumonia.
- Include instructions for monitoring for elevated transaminases and neutropenia.
- Indicate that concurrent use of idelalisib with other drugs that cause liver damage or diarrhea should be avoided.
- Display the incidence of laboratory abnormalities rather than reported adverse events for transaminases, neutrophils and platelets.
- Include a Medication Guide for distribution to patients.

### **1.4 Recommendations for Post-market Risk Evaluation and Mitigation Strategies**

The applicant will develop a communication plan to inform healthcare professionals about the risk of hepatotoxicity, diarrhea and colitis, rash, and pneumonitis in patients taking idelalisib.

### **1.5 Recommendations for Post-market Requirements and Commitments**

1. Submit the complete study report and data showing clinical efficacy and safety from study GS-US-313-0124, a Phase 3, 2-arm, randomized, double-blind, placebo-controlled, parallel-group study of idelalisib in combination with rituximab in subjects with previously treated iNHL.
2. Submit the complete study report and data showing clinical efficacy and safety from study GS-US-313-0125, a Phase 3, 2-arm, randomized, double-blind,

placebo controlled, parallel-group study of idelalisib in combination with BR in subjects with previously treated iNHL.

3. Submit the complete study report and data showing long-term safety with 5 years of follow-up from study GS-US-313-0124, a Phase 3, 2-arm, randomized, double-blind, placebo-controlled, parallel-group study of idelalisib in combination with rituximab in subjects with previously treated iNHL.
4. Submit the complete study report and data showing long-term safety with 5 years of follow-up from study GS-US-313-0125, a Phase 3, 2-arm, randomized, double-blind, placebo controlled, parallel-group study of idelalisib in combination with BR in subjects with previously treated iNHL.
5. Submit the complete study report and data showing long-term safety with 5 years of follow-up from study 101-99, an extension study of safety and durability of idelalisib monotherapy in hematological malignancies.
6. Conduct a study to characterize the incidence, diagnosis and effective treatment of idelalisib-related pneumonitis
7. Conduct a clinical trial to determine the optimal dosing regimen for idelalisib for chronic administration (treatment duration of at least 12 months).

## 2 Introduction and Regulatory Background

The applicant includes the following B-cell malignancies in their definition of indolent NHL: follicular lymphoma (FL), small lymphocytic lymphoma (SLL), marginal zone lymphoma (MZL), and lymphoplasmacytic lymphoma (LPL) with or without Waldenström's macroglobulinemia (WM). In 2008, the WHO Classification of hematologic malignancies removed indolent NHL as a diagnosis in favor of using specific tumor type (Swerdlow, Campo, et al. 2008). Treatments of various indolent lymphomas are similar but there are some differences which are highlighted in Section 2.2.

The National Cancer Institute estimates that 70,800 newly diagnosed cases of non-Hodgkin lymphoma and 18,990 deaths will occur in 2014 (Siegel, Ma, et al. 2014). Based on the Non-Hodgkin Lymphoma Classification Project, follicular lymphoma is the most common indolent subtype of NHL accounting for 22% of cases of non-Hodgkin lymphomas (The Non-Hodgkin's Lymphoma Classification Project 1997). From this Project, extranodal marginal zone (MALT) accounted for 8% of NHL, SLL for 7%, nodal marginal zone for 2%, LPL for 1%, and splenic marginal zone for <1%. From the time of diagnosis, patients with FL have shown a 3 year progression free survival of 51-91% (based on Prognostic Index) with a 3 year survival rate of 84-91% (Federico, Bellei, et al. 2009).

Idelalisib is a selective inhibitor of the delta isoform of the Class 1 phosphatidylinositol 3-kinase (PI3K) which is involved in several cellular processes necessary for cancer progression. In B-cells, PI3K is part of signaling pathways that modulate cellular functions of motility, proliferation, survival and recruitment of additional intracellular signaling enzymes. Inhibition of B-cell receptor (BCR) signaling can be lethal to malignant B-cells.

## 2.1 Product Information

Established Names: Idelalisib, GS-1101, CAL-101, IC489666  
Trade Name: Zydelig  
Applicant: Gilead Sciences, Inc.  
Drug Class: Phosphatidylinositol 3-kinase (PI3K) delta inhibitor

Applicant's Proposed Indication: For the treatment of patients with refractory indolent non-Hodgkin lymphoma

Applicant's Proposed Dosage and Administration: 150 mg orally, twice daily

## 2.2 Tables of Currently Available Treatments for Proposed Indications

There are no approved PI3K inhibitors. There are five currently available agents approved for the treatment of patients with follicular lymphoma, low-grade non-Hodgkin lymphoma, or indolent NHL. These include chlorambucil, cyclophosphamide, rituximab, <sup>90</sup>Y-ibritumomab tiuxetan, and bendamustine. The indications relevant to this application are listed in Table 2.

**Table 2 FDA-approved drugs for FL or indolent NHL**

Approval	Drug	Oncologic Indication
1957	Chlorambucil	In the treatment of chronic lymphatic (lymphocytic) leukemia, malignant lymphomas including lymphosarcoma, giant follicular lymphoma, and Hodgkin's disease
1959	Cyclophosphamide	For treatment of malignant lymphomas: Hodgkin's disease, lymphocytic lymphoma, mixed-cell type lymphoma, histiocytic lymphoma, Burkitt's lymphoma; multiple myeloma, leukemias, mycosis fungoides, neuroblastoma, adenocarcinoma of ovary, retinoblastoma, breast carcinoma
1997	Rituximab	For the treatment of patients with: Non-Hodgkin's Lymphoma, (b) (4)
2002	<sup>90</sup> Y-ibritumomab tiuxetan	For the treatment of patients with: relapsed or refractory, low-grade or follicular B-cell non-Hodgkin's lymphoma, and previously untreated follicular NHL who achieve a partial or complete response to first-line chemotherapy
2008	Bendamustine	For treatment of patients with: Chronic lymphocytic leukemia and indolent B-cell non-Hodgkin lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen

In clinical practice, treatment regimens for relapsed follicular lymphoma, small lymphocytic lymphoma, marginal zone lymphoma, or lymphoplasmacytic lymphoma include single agent or combinations of the following agents listed in Table 3. Involved-site radiation therapy, radioimmunotherapy, stem cell transplant, and observation are other appropriate treatments.

**Table 3 Agents and combinations used in patients with non-Hodgkin lymphomas**

Drug or Regimen	FL	SLL	MZL	LPL
Alemtuzumab		X		X
Bendamustine ± rituximab	X	X	X	X
Bortezomib + dexamethasone				X
Bortezomib + dexamethasone + rituximab				X
Bortezomib ± rituximab				X
Chlorambucil ± rituximab	X	X	X	X
Cladribine ± rituximab		X		X
Cyclophosphamide ± rituximab	X		X	
Dexamethasone		X		
Everolimus				X
Fludarabine + cyclophosphamide + mitoxantrone + rituximab	X		X	
Fludarabine + cyclophosphamide + rituximab		X		X
Fludarabine ± rituximab	X	X	X	X
Lenalidomide ± dexamethasone	X	X	X	
Ofatumumab		X		X
Pentostatin + cyclophosphamide + rituximab		X		
Rituximab	X	X	X	X
Rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone	X	X	X	X
Rituximab + cyclophosphamide + vincristine + prednisone	X		X	
Rituximab + fludarabine + mitoxantrone + dexamethasone	X		X	
Thalidomide ± rituximab				X

### 2.3 Availability of Proposed Active Ingredient in the United States

Idelalisib is a new molecular entity and is not currently marketed in any country.

### 2.4 Important Safety Issues with Consideration to Related Drugs

Idelalisib is a first-in-class selective inhibitor of PI3K $\delta$ . There are no other approved PI3K $\delta$  inhibitors on which to base class-specific safety concerns.

GS-563117, the major metabolite of idelalisib, is a selective inhibitor of serine/threonine protein kinase 10 (STK10/LOK) and STE20-like kinase (SLK). Although not the primary targets, STK10 and SLK bind to and/or are inhibited by dasatinib, erlotinib, gefitinib and sunitinib (Federov, Marsden, et al. 2007; Karaman, Herrgard, et al. 2008). Preclinical data published by Yamamoto et al (2011) suggests that the cutaneous toxicity of erlotinib results from off-target inhibition of STK10 by enhancement of the immune response. There are otherwise no established toxicities resulting from inhibition of STK10 or SLK by approved drugs.

## 2.5 Summary of Pre-submission Regulatory Activity Related to Submission

**Table 4 Regulatory History**

Date	Event summary
21Feb2008	Pre-IND meeting was granted and advice provided on the first in human trials in healthy volunteers and in patients with CLL.
30May2008	IND 101254 was submitted and deemed safe to proceed with modifications
8Jul2010	Type B, End-of-phase 1 meeting was held to discuss trials in healthy volunteers and in patients with iNHL or CLL. Provided suggestions for defining an appropriate iNHL population and discouraged submission of single arm phase 2 as pivotal NDA trial.
26Apr2011	Notification of change in sponsorship from Calistoga Pharmaceuticals to Gilead Sciences, Inc.
8Jun2011	Type B, End-of-Phase 1 meeting to discuss overall development plan, primarily pertaining to randomized trials in the CLL population
30Jan2012	Fast Track designation of GS-1101 for the treatment of chronic lymphocytic leukemia
7Mar2012	Type C, Advice on the clinical pharmacology development plan
1Jul2013	Type B, Pre-NDA primarily advising on technical aspects of submission of the application
5Sep2013	Type B, End-of-phase 2 for CLL indication with advice on phase 3 trials in untreated CLL and consideration of appropriate comparator arms
11Sep2013	Submission of NDA 205858
7Oct2013	Type A, Advice provided regarding the CLL phase 3 randomized trial 312-0116 DMC recommendations for early termination. Acknowledged that submission of this trial data and study report will strengthen the current application.
8Nov2013	Breakthrough Therapy designation of idelalisib for the treatment of patients with relapsed chronic lymphocytic leukemia
10Nov2013	Filing of NDA 205858 complete

## 2.6 Other Relevant Background Information

Idelalisib has FDA Orphan Designation for several indications (Table 5) and is therefore exempt from the Pediatric Research Equity Act pediatric study requirements.

**Table 5 Idelalisib Orphan Drug indications**

Designation date	Indication
25Aug2011	Chronic lymphocytic leukemia
26Sep2013	Follicular lymphoma
26Sep2013	Lymphoplasmacytic lymphoma with or without Waldenström's macroglobulinemia
15Oct2013	Splenic marginal zone lymphoma
15Oct2013	Nodal marginal zone lymphoma
15Oct2013	Extra-nodal marginal zone lymphoma
15Oct2013	Chronic lymphocytic leukemia and small lymphocytic lymphoma

## 3 Ethics and Good Clinical Practices

### 3.1 Submission Quality and Integrity

The application was provided in accordance with the International Conference on Harmonization (ICH) Electronic Common Technical Document (eCTD). Data was provided using CDISC standard ADaM and SDTM datasets which facilitated review.

### 3.2 Compliance with Good Clinical Practices

The protocol, protocol amendments, and patient informed consent forms for trial 101-09 were reviewed and approved by the Institutional Review Boards (IRBs) or Independent Ethics Committees (IECs) of the participating trial centers.

The trial was conducted in accordance with the ICH 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 for 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.

#### Data Integrity

Of 125 patients enrolled on Trial 101-09, the applicant reported at least one protocol violation in 107 (86%) patients. There were 633 minor protocol deviations or waivers in 106 patients; most were unlikely to affect the analysis of benefit or risk. There were 77 instances of idelalisib tablet count discrepancies in 30 patients (24%) when vials were returned; most were cases where a higher than expected number of tablets was returned. Implications for idelalisib exposure will be explored more in Section 7.2.

There were six protocol violations that were considered major due to reporting delays or other timing; one patient did not meet the protocol definition for refractory to an alkylating agent. Analysis of frequency and rate of deviations or violations by investigator site did not reveal patterns for concern.

FDA identified two treated patients who did not meet trial inclusion criteria #1: "Small lymphocytic lymphoma (SLL) with absolute lymphocyte count  $<5 \times 10^9/L$ ". Patients 128-09073 and 149-09072 had absolute lymphocyte counts of 7.05 and  $15.24 \times 10^9/L$  respectively. These two patients were not included in this review of efficacy and safety.

#### Clinical Site Inspections

The following sites were inspected by the FDA Office of Scientific Investigations (OSI) as part of the NDA review. Their conclusions are provided by site:

1. University of Washington, Fred Hutchinson Cancer Research Center (PI: Ajay Gopal, M.D.)

While the FDA inspection revealed regulatory deficiencies of clinical investigator obligations in the conduct of the study, overall data derived from this site appear acceptable, as the findings were not considered pervasive and/or the nature of the findings is unlikely to impact data reliability.

2. Weill Cornell – New York Presbyterian Hospital (PI: Peter Martin, M.D.)  
Data submitted by this clinical site appear acceptable for this specific indication.
3. Gilead Sciences, Inc.  
While the FDA inspection revealed regulatory deficiencies of the sponsor obligations in the conduct of the study, data submitted by this sponsor appear acceptable in support of the respective indication

### **3.3 Financial Disclosures**

The applicant submitted financial disclosure information from 2,459 investigators from 13 trials applicant 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 9.4. None of the disclosures submitted revealed a potential conflict of interest.

## **4 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

### **4.1 Chemistry Manufacturing and Controls**

At the time of completion of this review, there were no clinical safety issues raised regarding drug substance, drug product, or microbiology. Three dosage forms and two formulations of the tablets were used in the clinical development program. Dissolution rates were similar between these dosage forms. How comparability between dosage forms affects conclusions from pooled safety analyses is discussed in Section 7.1.3.

### **4.2 Clinical Microbiology**

Review by Product Quality Microbiology found the microbial limits specification for the 100 mg and 150 mg coated drug tablets for oral administration acceptable. The microbiological quality of the drug product is controlled via a suitable testing protocol.

### **4.3 Preclinical Pharmacology/Toxicology**

#### **4.3.1 Toxicology In Vivo**

In tissue distribution studies in rats, idelalisib localized to most tissues but was relatively excluded from bone, brain, spinal cord and lens. Higher amounts were found in uvea

and in pigmented rather than non-pigmented skin, suggesting an association with melanin.

There were six pivotal toxicology studies in rats and dogs of repeat oral dosing of idelalisib (one pertaining to impurity qualification) reviewed by the Agency. The studies ranged over 4-39 weeks. Inflammation was observed in several tissues (e.g. in the GI tract, pancreas, lungs, heart, and liver). The preclinical reviewers noted additional toxicities in the following organ systems:

- Hematopoietic/lymphoid system (lymphoid depletion, reduced weight of spleen and thymus, thymic hemorrhage and necrosis, myeloid and granulopoietic hyperplasia)
- Liver (increased liver enzymes, increased liver weight, inflammation, hepatocellular necrosis)
- Gastrointestinal (GI) tract including the tongue (infiltration, hemorrhage, ulceration)
- Heart; seen in rats only (myocardium infiltrate, fibrosis, increased heart weight)
- Male reproductive systems (testicular seminiferous tubule degeneration, reduced testicular weight)
- Skin (erythema, dryness, swelling, and redness)

Idelalisib was genotoxic in males in the rat micronucleus study at the high dose of 2000 mg/kg. Carcinogenicity studies were not conducted.

The preclinical reviewers also considered the potential toxicity of (b) (4) a novel excipient, and several impurities, including two genotoxic impurities ( (b) (4) and (b) (4) ). Based on ICH guidance, publicly-available information and special toxicology studies submitted by the applicant, the preclinical reviewers found the specifications for these substances to be acceptable.

### **4.3.2 Reproductive and Developmental Toxicology**

In studies in rats, idelalisib had no effect on male fertility but did increase pre-implantation and post-implantation loss in treated females. Idelalisib was also teratogenic (skeletal variations, vertebral agenesis with anury, short tail, microphthalmia, anophthalmia and hydrocephaly). The preclinical reviewers recommended Pregnancy Category D for labeling.

## **4.4 Clinical Pharmacology**

### **4.4.1 Mechanism of Action**

Idelalisib is a lipid kinase inhibitor with selective activity for PI3K $\delta$ . The activity is mediated by competitive inhibition of the ATP binding site of the p110 $\delta$  subunit. PI3K $\delta$  transduces signals from a number of leukocyte membrane receptors, including the B

cell receptor, IL-6, C40, and several chemokines and integrins. In malignant B cells studied in vitro, idelalisib inhibited functions of the PI3K $\delta$  pathway (including secretion of chemokines, chemotaxis, and kinase phosphorylation via receptor signaling) and resulted in reduced cell viability and induction of apoptosis.

#### **4.4.2 Pharmacokinetics**

In clinical pharmacokinetics studies, the T<sub>max</sub> was achieved about 1.5 hours after oral administration of idelalisib in the fasted state. With a high-fat meal, the AUC increased about 1.4-fold. The terminal elimination half-life was 8.2 hours. In a population pharmacokinetics analysis, age, gender, race and weight had no effect on exposure. No exposure-response relationships were identified for primary endpoints or selected safety endpoints in the NHL and CLL registration trials, except for grade 3 diarrhea in Protocol 101-09. The geometric mean AUC increased 1.4-1.7-fold with ALT, AST or total bilirubin was greater than the upper limit of normal. In studies of volunteers with renal impairment, there was no substantial change in exposure when the creatinine clearance was > 15 mL/min.

Idelalisib is metabolized by aldehyde oxidase and CYP3A4. The major metabolite is GS-563117, which is inactive against PI3K $\delta$ . In clinical studies in healthy volunteers, rifampin (a strong CYP3A inducer) decreased the geometric mean idelalisib AUC by 75% and geometric mean C<sub>max</sub> by 58%, and ketoconazole (a strong CYP3A inhibitor) increased geometric mean idelalisib AUC by 1.8-fold. Idelalisib is also a substrate of UGT1A4. Both idelalisib and GS-563117 are substrates of BCRP and P-glycoprotein. For the assessment of potential drug-drug interactions, idelalisib was evaluated in vitro as an inhibitor or an inducer of key drug metabolism enzymes and transporters. In vitro, idelalisib inhibited CYP2C8, CYP2C19, CYP3A, UGT1A1, P-glycoprotein, OATP1B1 and OATP1B3. GS-563117 inhibited CYP2C8, CYP2C9, CYP2C19, CYP3A and UGT1A1. Idelalisib did not affect the exposure of P-glycoprotein or OATP1B1/OATP1B3 substrate in healthy volunteers. Idelalisib induced CYP2B6 and CYP3A4.

The flat dose of 150 mg was considered by the clinical pharmacology reviewer as acceptable for marketing. It was also recommended that patients be monitored closely for toxicity when idelalisib is used with CYP3A4 inhibitor or in patients with baseline hepatic impairment, and that co-administration with a strong CYP3A inducer or with a CYP3A substrate be avoided.

#### **4.5 Interdisciplinary Review Team (IRT)**

The IRT review included preclinical and clinical testing for cardiac safety. Idelalisib was tested in an hERG assay; the IC<sub>50</sub> of idelalisib was high at >50  $\mu$ M. A randomized, partially-blinded, placebo-and positive-controlled, 4-period cross-over study in 48 healthy subjects served as a thorough QT study. The IRT reviewer noted no significant prolongation of QT<sub>c</sub> in this study using clinically-relevant doses of idelalisib.

## 5 Sources of Clinical Data

### 5.1 Tables of Studies/Clinical Trials

The applicant submitted data from 24 clinical trials of idelalisib alone or in combination with other agents. Of these 24 trials, 6 were studies of idelalisib monotherapy for treatment of lymphoid malignancies, 7 were studies of combination treatments of lymphoid malignancies, and 11 were studies in healthy volunteers or other subjects without malignancy. One monotherapy study, 312-0117 has accrued only 11 subjects and remains blinded, so very limited information was available. Table 6 lists the other 5 monotherapy trials and 11 volunteers studies emphasized in this review.

**Table 6 Clinical Trials**

Trials / Status	Design	Population	Primary Endpoint
<b>Efficacy and Safety of Monotherapy in Patients with Lymphoma</b>			
<b>101-09</b> (On-going)	Phase 2, open-label, single-arm, 2-stage study · Idelalisib 150 mg BID until toxicity or progression	FL, SLL, LPL +/- WM, or MZL refractory to rituximab and an alkylating agent · 125 subjects enrolled	ORR
<b>Safety of Monotherapy in Patients with Lymphoid Malignancies</b>			
<b>101-02</b> (Complete)	Phase 1, dose-escalation · Idelalisib 150-300 mg qD or 50-350 mg BID x 28 days, or 150 mg BID for 21/28 days	Relapsed or refractory CLL, NHL, AML, and MM · 191 subjects enrolled	MTD
<b>101-10</b> (On-going)	Open-label, single-arm study · Idelalisib 150 mg BID x 28 days, up to 12 cycles	Low-grade B-cell NHL and at least 1 prior therapy · 11 subjects enrolled	Safety, ORR
<b>101-11</b> (On-going)	Phase 2, open-label, single-arm, 2-stage study · Idelalisib 150 mg BID until toxicity or progression	Relapsed or refractory HL after prior autologous SCT or after ≥ 2 prior regimen · 25 subjects enrolled	ORR
<b>101-99</b> (On-going)	Extension study · Idelalisib up to 300 mg BID until toxicity or progression	Subjects who completed a prior study with response · 171 subjects assessed	Safety
<b>Safety in Healthy Volunteers</b>			
<b>101-01</b> (Complete)	Phase 1, randomized, double-blind, placebo-controlled, study · Idelalisib 17-400 mg once vs placebo · Idelalisib 50-200 mg BID x 7 days vs placebo	Healthy male volunteers · 64 subjects randomized 3:1 at each dose schedule	Safety and PK
<b>101-04</b> (Complete)	Phase 1, randomized, double-blind, placebo-controlled, 2-period crossover study	Subjects with allergic rhinitis · 41 subjects randomized 1:2	Safety, prevention of nasal symptoms

Trials / Status	Design	Population	Primary Endpoint
	· Idelalisib 100 mg BID x 7 days vs placebo	by sequence	
<b>101-05</b> (Complete)	Three-period crossover single-dose study fasting, fed or with ketoconazole · Idelalisib 400 mg	Healthy male volunteers · 12 subjects enrolled	PK
<b>101-06</b> (Complete)	Three-period crossover single-dose study of 3 formulations · Idelalisib 100 mg	Healthy male volunteers · 15 subjects enrolled	PK
<b>313-0111</b> (Complete)	Single-dose PK study · Idelalisib 150 mg	Healthy male volunteers · 8 subjects enrolled	Mass balance
<b>313-0112</b> (Complete)	Phase 1, parallel-group, adaptive, single-dose study · Idelalisib 150 mg	Healthy volunteers or those with hepatic impairment · 32 subjects enrolled	PK
<b>313-0117</b> (Complete)	Randomized, single-blinded, cross-over study · Idelalisib 150 mg vs Idelalisib 400 mg vs Placebo vs Moxifloxacin	Healthy volunteers · 48 subjects randomized 1:1 by sequence	QTc
<b>313-0118</b> (Complete)	Phase 1, parallel-group, adaptive, single-dose study · Idelalisib 150 mg	Healthy volunteers or those with renal impairment · 12 subjects enrolled	PK
<b>313-0126</b> (Complete)	Single-dose PK study · Idelalisib 150 mg	Healthy Japanese and Caucasian volunteers · 20 subjects enrolled	PK
<b>313-0130</b> (Complete)	Multiple-period, multiple-cohort crossover study · Reference drug with or without Idelalisib 150 mg once or BID	Healthy volunteers · 24 subjects enrolled	Drug-drug interactions
<b>339-0101</b> (Complete)	Three-period crossover single-dose study · Idelalisib 100 -150 mg with or without GS-9973	Healthy female volunteers · 24 subjects enrolled	Safety, PK

## 5.2 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 information requests
- Relevant published literature
- Relevant information in the public domain

Mr. Miller reviewed the NDA submission for efficacy, Dr. Przepiorka reviewed the submission for safety, and both provided the benefit-risk assessment. The clinical review of efficacy was primarily based on an analysis of Trial 101-09. Analyses of

efficacy for the four lymphoma types were performed in addition to efficacy for indolent non-Hodgkin lymphoma. A limited analysis of Trial 101-02 was performed for selected subgroups of patients on relevant dose levels.

The results from the 16 trials listed in Table 6 were used in the analysis of safety. Since the subjects with lymphoid malignancies and the healthy volunteers were clearly not interchangeable, the safety profiles were developed separately for these two groups. Data from Protocol 101-99, the extension protocol, was concatenated with that from the primary protocol to allow for an analysis of changes in toxicity over a greater period of time. The review emphasis was placed on the 150 mg BID dosing schedule proposed for marketing.

Protocols 101-02, 101-09, 101-10, 101-11, and 101-99 were on-going at the time of submission of the NDA, and it is acknowledged that the safety dataset used was therefore incomplete. The new information submitted in the 120-day update was used only for the analyses presented in Section 7.7.3 as an addendum to the main review.

Analyses by the clinical reviewers were performed largely using JMP 9.0 (SAS Institute, Inc., Cary, NC). MedDRA Adverse Events Diagnostic (MAED) 1.0 (Clinical Trials & Surveys Corporation, Owings Mills, MD) was used to assess for safety signals, and cases of serious drug-related liver injury were sought with A Graphic Tool for Evaluation of Drug-Induced Serious Hepatotoxicity in Clinical Studies (eDISH) (U.S. Department of Health and Human Services, Silver Spring, MD).

## **5.3 Discussion of Individual Studies/Clinical Trials**

### **5.3.1 Trial 101-09**

**Protocol 101-09** - A Phase 2 Study to Assess the Efficacy and Safety of Idelalisib in Subjects with Indolent B-Cell Non-Hodgkin Lymphomas Refractory to Rituximab and Alkylating Agents

#### **Trial Design**

Protocol 101-09 is an open-label, multi-center, phase 2 trial of idelalisib at a starting dose of 150mg BID in patients with relapsed FL, SLL, MZL, or LPL±WM.

#### **Trial Population**

##### *Inclusion Criteria*

Patients must have met all of the following conditions to be eligible for enrollment into the study:

1. Histologically confirmed diagnosis of B-cell iNHL, with histological type limited to the following based on criteria established by the World Health Organization (WHO) 2008 classification of tumors of hematopoietic and lymphoid tissues:
  - Follicular lymphoma (FL) of any grade (Grade 1, 2, or 3)

- Small lymphocytic lymphoma (SLL) with absolute lymphocyte count  $<5 \times 10^9/L$
  - Lymphoplasmacytic lymphoma (LPL)
  - Marginal zone lymphoma (MZL) (splenic, nodal, or extra-nodal)
2. Histological materials documenting diagnosis of lymphoma available for review by a central pathology
  3. Measureable nodal disease, defined as the presence of  $\geq 1$  nodal lesion that measures  $\geq 2$  cm in a single dimension as assessed by CT or MRI
  4. Prior treatment with  $\geq 2$  prior chemotherapy- or immunotherapy-based regimens for iNHL
  5. Prior treatment with rituximab and with an alkylating agent (e.g., bendamustine, cyclophosphamide, ifosfamide, chlorambucil, melphalan, busulfan, nitrosoureas) for iNHL
  6. Lymphoma that is refractory to rituximab and to an alkylating agent. Refractoriness is defined as:
    - Rituximab (without chemotherapy)
      - Lack of a complete response (CR) or partial response (PR) during rituximab therapy comprising  $\geq 4$  doses of  $\geq 375$  mg/m<sup>2</sup> given weekly, or
      - Occurrence of progressive disease (PD) within 6 months of the completion of a regimen of rituximab therapy comprising  $\geq 4$  doses of  $\geq 375$  mg/m<sup>2</sup> given weekly, or
      - Occurrence of PD during rituximab maintenance therapy or within 6 months of completion of rituximab maintenance therapy
    - Rituximab (with chemotherapy)
      - Lack of a CR or PR during rituximab-containing therapy comprising  $\geq 2$  doses of  $\geq 375$  mg/m<sup>2</sup>, or
      - Occurrence of PD within 6 months of the completion of a regimen of rituximab-containing therapy comprising  $\geq 2$  doses of  $\geq 375$  mg/m<sup>2</sup>, or
      - Occurrence of PD during rituximab maintenance therapy or within 6 months of completion of rituximab maintenance therapy
    - Alkylating agent (administered with or without rituximab)
      - Lack of a CR or PR during alkylating-agent-containing therapy comprising  $\geq 2$  cycles of treatment, or
      - Occurrence of PD within 6 months of the completion of a regimen of alkylating agent-containing chemotherapy comprising  $\geq 2$  cycles of treatment
  7. Age  $\geq 18$  years by initiation of study treatment (Visit 2)
  8. Karnofsky performance score of  $\geq 60$  (Eastern Cooperative Oncology Group [ECOG] performance score of 0, 1, or 2)
  9. Discontinuation of all other therapies (including radiotherapy or chemotherapy) for the treatment of iNHL  $\geq 3$  weeks before initiation of study treatment (Visit 2)
  10. All acute toxic effects (excluding alopecia, neurotoxicity, or anemia) of any prior antitumor therapy resolved to Grade  $\leq 2$  before initiation of study treatment (Visit 2)
  11. Required baseline laboratory data (within 2 weeks prior to start of study drug administration) as follows:

- Bone marrow
    - ANC  $\geq 1.0 \times 10^9/L$
    - Platelets  $\geq 50 \times 10^9/L$
    - Hemoglobin  $\geq 80$  g/L (8.0 g/dL or 4.9 mmol/L)
  - Hepatic
    - Serum total bilirubin  $\leq 1.5 \times$  ULN (unless elevated due to Gilbert's syndrome)
    - Serum ALT  $\leq 2.5 \times$  ULN
    - Serum AST  $\leq 2.5 \times$  ULN
  - Renal
    - Serum creatinine  $< 1.5 \times$  ULN
  - Pregnancy
    - Negative serum  $\beta$ -HCG (for females of childbearing potential)
  - Infection
    - Negative HIV antibody
    - HBV: Negative HBsAg (if serology positive for infection)
    - HCV: Negative viral RNA (if serology positive for infection)
12. For men and women of childbearing potential (i.e., patients who are not postmenopausal or surgically sterile), willingness to abstain from sexual intercourse or employ an effective method of contraception during the study drug administration and follow-up periods.
13. Willingness and ability to provide written informed consent and to comply with scheduled visits, drug administration plan, imaging studies and contrast dye administration, laboratory tests, other study procedures, and study restrictions.
14. Evidence of a personally signed informed consent indicating that the patient is aware of the neoplastic nature of the disease and has been informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential benefits, possible side effects, potential risks and discomforts, and other pertinent aspects of study participation.
15. In the judgment of the investigator, participation in the protocol offers acceptable benefit:risk when considering current iNHL disease status, medical condition, and the potential benefits and risks of alternative treatments for iNHL.

#### *Exclusion Criteria*

The presence of any of the following conditions will exclude a patient from study enrollment:

1. Central nervous system or leptomeningeal lymphoma
2. Known histological transformation from iNHL to diffuse large B-cell lymphoma
3. History of a non-lymphoma malignancy except for the following: adequately treated local basal cell or squamous cell carcinoma of the skin, cervical carcinoma in situ, superficial bladder cancer, localized prostate cancer, other adequately treated Stage 1 or 2 cancer currently in complete remission, or any other cancer that has been in complete remission for  $\geq 5$  years.

4. Evidence of ongoing systemic bacterial, fungal, or viral infection (excluding viral upper respiratory tract infections) at the time of initiation of study treatment (Visit 2)
5. Pregnancy or breastfeeding
6. Ongoing alcohol or drug addiction
7. Known history of drug-induced liver injury, chronic active HCV, chronic active HBV, alcoholic liver disease, non-alcoholic steatohepatitis, primary biliary cirrhosis, ongoing extrahepatic obstruction caused by stones, cirrhosis of the liver or portal hypertension.
8. History of prior allogeneic bone marrow progenitor cell or solid organ transplantation
9. Ongoing immunosuppressive therapy, including systemic corticosteroids
10. Prior therapy with CAL-101
11. Exposure to another investigational drug within 3 weeks prior to start of study treatment
12. Concurrent participation in another therapeutic treatment trial
13. Prior or ongoing clinically significant illness, medical condition, surgical history, physical finding, ECG finding, or laboratory abnormality that, in the investigator's opinion, could affect the safety of the patient; alter the absorption, distribution, metabolism or excretion of the study drug; or impair the assessment of study results

#### Trial Treatment

All patients were started on 150 mg twice daily oral administration of idelalisib.

Idelalisib self-administration was assumed as patients did not record medication use in any way, i.e. medication diary. Idelalisib use was inferred from clinical site accountability of drug tablets dispensed to patient and drug returned at the end of the dosing interval: 4-week intervals for the first 24 weeks and 12-week intervals thereafter.

#### *Dose Delay and Modification*

The protocol included two dose level reductions (Table 7) for adverse events (AEs) graded according to NCI CTCAE 3.0.

**Table 7 Idelalisib dose levels**

Dose level	Dose
Starting	150 mg BID
-1	100 mg BID
-2	75 mg BID

Instructions to withhold drug and reduce dose were iterated for Grade 3 and 4 non-hematologic AE and for Grade 4 hematologic events in Table 8. Doses were not increased after any reduction. Treatment with idelalisib could continue indefinitely until disease progression or until intolerable toxicity at the lowest dose level.

**Table 8 Dose Modification for Adverse Event or Laboratory Abnormality**

CTCAE Grade	Grade 1	Grade 2	Grade 3	Grade 4
<b>Non-Hepatic and Non-Hematological Idelalisib-Related Event</b>				
Dosing Recommendation	Maintain dose level	Maintain dose level	Withhold drug until toxicity is Grade $\leq 1$ . May resume drug at next lower dose level.	
<b>Hepatic Idelalisib-Related Event (Elevation in ALT, AST, or Bilirubin)</b>				
ALT/AST	>ULN-3 x ULN	>3-5 x ULN	>5-20 ULN	>20 x ULN
Bilirubin	>ULN-1.5 x ULN	>1.5-3 x ULN	>3-10 x ULN	>10 x ULN
Dosing Recommendation	Maintain dose level	Maintain dose level. Monitor ALT, AST, ALP, and bilirubin at least 1x per week until all are Grade $\leq 1$ .	Withhold drug and confirm abnormalities within 3 days. Monitor ALT, AST, ALP, and bilirubin at least 1x per week until all abnormalities are Grade $\leq 1$ . May resume drug at next lower dose level.	
<b>Hematological Idelalisib-Related Event</b>				
Neutropenia (ANC x $10^9/\mu\text{L}$ )	<LLN-1.5	<1.5-1.0	<1.0-0.5	<0.5
Thrombocytopenia (platelets x $10^9/\mu\text{L}$ )	<LLN-75	<75-50	<50-25	<25
Dosing Recommendation	Maintain dose level	Maintain dose level	Maintain dose level	Monitor at least 1x per week. If Grade 4 for $\geq 3$ days, withhold drug until all abnormalities are Grade $\leq 3$ . May resume drug at next lower dose level.

### *Concomitant Treatment*

All concomitant drugs taken by a patient during the course of the trial and reason for use was to be recorded on the case report forms (CRFs). All routine and appropriate supportive care, including granulocyte colony-stimulating factors and erythropoietin, could be given if clinically indicated and in accordance with standard of care practices. Systemic corticosteroids were to be avoided if possible, but could be given for severe or life-threatening conditions without discontinuing the trial.

### *Prohibited Treatment*

Anticancer therapies of any kind were not permitted while the patient was on trial. Patients were to be discouraged from using herbal remedies, self-prescribed drugs, illicit drugs, tobacco, and excessive alcohol. Patients on CYP3A4 inhibitors were to be monitored for additional AEs, though their use was not prohibited.

### Schedule of Events

Patients were assessed for safety every 2 weeks for 3 months, then every 4 weeks for 3 months, then every 6 weeks for 6 months, and then every 12 weeks. Efficacy was routinely assessed at months 2, 4, 6, 9, 12, and then every 3 months. Long-term follow-

up will be conducted for all patients at 6 to 12 month intervals until 5 years. An overview of the schedule of events is included in Table 9.

**Table 9 Schedule of Events Overview**

Period	Screen																Treatment																Follow-up	
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16+	End	Post-																
Week	-4	0	2	4	6	8	10	12	16	20	24	30	36	42	48	of	treatment																	
Study Day	≤28																Q12	Wks	treat-	& long-														
Visit Window	Days	1	15	29	43	57	71	85	113	141	169	211	253	295	337	±7	ment	term																
		±2	±2	±2	±2	±2	±2	±2	±3	±3	±3	±3	±3	±3	±7	±7	±7																	
Informed consent	X																																	
Medical history	X																																	
Histopathology review	X																																	
Serum virology	X																																	
Coagulation	X																																	
Urinalysis	X																																	
β-HCG	X																																	
Genotyping		X																																
HRQL – FACT-Lym		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X																		
Study drug return/accounting			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X																	
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X																
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X																
Performance status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X																
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X																
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X																
Serum chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X																
Pharmacodynamics		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X																
Drug dispensing		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X																
Physical examination	X								X									X																
12-lead ECG	X								X									X																
Immunophenotyping		X			X			X		X			X		X	X	X	X																
Serum immunoglobulin		X			X			X		X			X		X	X	X	X																
Radiology assessments (CT/MRI)	X				X			X		X			X		X	X	X	X																
Bone marrow biopsy/aspirate <sup>a</sup>	X				X <sup>a</sup>			X <sup>a</sup>		X <sup>a</sup>			X <sup>a</sup>		X <sup>a</sup>	X <sup>a</sup>	X <sup>a</sup>	X <sup>a</sup>																
CAL-101 dosing in clinic		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X																
Limited pharmacokinetics		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X																
Pharmacokinetic sub-study		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X																

<sup>a</sup> Required at screening. If disease present at baseline, to be performed post-baseline to confirm response category in patients with potential CR by radiological assessments. If the baseline bone marrow biopsy/aspirate does not show lymphoma involvement, it is not necessary to obtain a follow-up bone marrow biopsy/aspirate to establish CR.

The determination of disease response and progression was based on the revised response criteria for malignant lymphoma resulting from the International Harmonization Project (Cheson, Pfister, et al. 2007) and included in Table 10. An independent review committee (IRC) was established to provide blinded review of radiographic and

pertinent clinical data. Consistent with the guidelines, repeat measures for best responses were not required.

Imaging based evaluation of disease included measurable nodal lesions >1.5 cm by >1 cm and extranodal lesions >1 cm by >1 cm. All non-measurable lesions, e.g., bone lesions, effusions, lymphangitis of the skin or lung, were to be recorded. Up to 6 measurable lesions could be identified as target lesions to be measured and recorded at each specified interval.

**Table 10 Definitions of Tumor Response**

Definition	Criteria
Complete Response (all criteria must be met)	<ul style="list-style-type: none"> <li>No evidence of new disease</li> <li>Disappearance of all detectable clinical evidence of disease (measurable and non-measurable) and disease-related symptoms (if present before therapy)</li> <li>Regression of all target nodal masses to normal size (<math>\leq 1.5</math> cm in their greatest transverse diameter for nodes that were <math>&gt; 1.5</math> cm before therapy and <math>\leq 1.0</math> cm in their greatest transverse diameter for nodes that were 1.1 to 1.5 cm in their diameters before therapy)</li> <li>Normal spleen and liver size by imaging studies, no hepatic or splenic lymphoma nodules, and no new organ enlargements</li> <li>Morphologically negative bone marrow based on an adequate unilateral core biopsy (<math>&gt; 20</math> mm unilateral core); if the sample is indeterminate by morphology, it should be negative by immunohistochemistry</li> <li>If PET performed (not required), no evidence of residual disease</li> </ul>
Partial Response (all criteria must be met)	<ul style="list-style-type: none"> <li>No evidence of new disease</li> <li>A <math>\geq 50\%</math> decrease in the SPD of the target nodal and extranodal lesions (e.g., splenic or hepatic nodules), taking as a reference the baseline SPD</li> <li>No increase in the size of non-target nodes or non-measurable disease</li> <li>No increase in the size of the liver or spleen and no new organ enlargements.</li> <li>Persistence of bone marrow involvement in a patient who meets other criteria for CR based on the disappearance of disease-related symptoms and all nodal and extranodal masses</li> <li>If PET performed (not required), no evidence of residual disease (if fluorodeoxyglucose [FDG]-avid at baseline or FDG-avid disease is present in <math>\geq 1</math> site)</li> </ul>
Stable Disease	<ul style="list-style-type: none"> <li>SD is defined as neither sufficient tumor shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as a reference the baseline SPD; no new evidence of new disease can be present</li> </ul>

Definition	Criteria
Progressive Disease (any criterion)	<ul style="list-style-type: none"> <li>• Evidence of any new disease that was not present as baseline:               <ul style="list-style-type: none"> <li>○ A new node that measures &gt;1.5 cm in any axis</li> <li>○ A new extranodal site that measures &gt;1.0 cm in any axis</li> <li>○ Disease of any size unequivocally attributable to lymphoma (usually requires PET, biopsy, cytology, or other non-radiologic confirmation to confirm disease attributable to lymphoma). Note: Isolated new effusions, ascites, or bone lesions are not sufficient evidence alone of PD unless histologically confirmed. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are usually benign. Thus, a declaration of PD should not be made if this is the only manifestation of an apparently new lesion.</li> </ul> </li> <li>• Evidence of worsening of measured lymph nodes or nodal masses:               <ul style="list-style-type: none"> <li>○ Increase from the nadir by <math>\geq 50\%</math> in the product of the perpendicular diameters for any individual node if the node has a longest diameter of &gt;1.5 cm and there is an absolute change of <math>\geq 0.5</math> cm in the longest or shortest diameter</li> <li>○ Increase from the nadir by <math>\geq 50\%</math> in the longest diameter for any individual node if the node has a longest diameter of &gt;1.5 cm and there is an absolute change of <math>\geq 0.5</math> cm in the longest diameter</li> <li>○ Increase from the nadir by <math>\geq 50\%</math> in the shortest diameter for any individual node if the site has a shortest diameter of &gt;1.5 cm and there is an absolute change of <math>\geq 0.5</math> cm in the shortest diameter</li> </ul> </li> <li>• Evidence of worsening of disease at measured extranodal sites:               <ul style="list-style-type: none"> <li>○ Increase from the nadir by <math>\geq 50\%</math> in the product of the perpendicular diameters for any individual extranodal site if the site has a longest diameter of &gt;1.0 cm and there is an absolute change of <math>\geq 0.5</math> cm in the longest or shortest diameter</li> <li>○ Increase from the nadir by <math>\geq 50\%</math> in the longest diameter for any individual extranodal site if the site has a longest diameter of &gt;1.0 cm and there is an absolute change of <math>\geq 0.5</math> cm in the longest diameter</li> <li>○ Increase from the nadir by <math>\geq 50\%</math> in the shortest diameter for any individual extranodal site if the site has a shortest diameter of &gt;1.0 cm and there is an absolute change of <math>\geq 0.5</math> cm in the shortest diameter</li> </ul> </li> <li>• Unequivocal increase in the size of non-target nodes or non-measurable disease (e.g., pleural effusions or bone lesions)</li> <li>• As visually estimated, an unequivocal increase in the size of the liver or spleen or an unequivocal new enlargement of another organ</li> <li>• If PET performed (not required):               <ul style="list-style-type: none"> <li>○ The appearance of any new lesion compatible with lymphoma with confirmation by other radiographic or histological modalities.</li> <li>○ The reappearance of any activity in a pre-existent lesion that meets size criteria for a new lesion on CT</li> </ul> </li> <li>• Note: If there is uncertainty regarding whether there is true progression, the patient may continue study treatment and remain under close observation (e.g., evaluated at 4-week intervals). If subsequent evaluations suggest that the patient is experiencing progression, then the date of progression should be the time point at which progression was first identified.</li> </ul>

## **Statistics**

### **Sample Size**

The applicant assumes an ORR of 20% to any available treatment in patients with iNHL that has refractory to both rituximab and alkylating agents. The trial intended to test the null hypothesis that the IRC-reviewed ORR is  $\leq 20\%$  against the alternative hypothesis response of  $\geq 40\%$ . With a sample size of 100 patients, an ORR of 32% would achieve a 1-sided 99.5% lower bound of 20.6%. A single formal interim analysis was planned using Simon's optimal 2-stage procedure for futility. After 31 patients were enrolled, the analysis showed that more than 9 had a response to treatment. The final analysis was planned after 69 additional patients were enrolled.

The Intent to treat (ITT) population consists of all patients who received at least one dose of idelalisib. The responding population will include all CRs and PRs. The per-protocol population includes all patients in the ITT and responding population who have a confirmed diagnosis of lymphoma, who have documented refractory disease, who have measurable nodal disease, and who can be evaluated for tumor response with both a baseline and  $\geq 1$  on-study tumor evaluations.

### **Efficacy Endpoints**

#### *Primary Endpoints*

The primary endpoint was overall response rate, defined as the proportion of patients who achieve a conformed complete response or partial response during protocol treatment.

#### *Secondary Endpoints*

- Duration of response (DOR), defined as the interval from the first documentation of PR or CR to the earlier of the first documentation of disease progression or death from any cause
- Change from baseline in the sum of the product of the greatest perpendicular diameters (SPD) of target lymph nodes as documented radiographically
- Time to response (TTR), defined as the interval from the start of CAL-101 treatment to the first documentation of CR or PR
- Progression free survival (PFS), defined as the interval from the start of CAL-101 treatment to the earlier of the first documentation of disease progression or death from any cause
- Time to treatment failure (TTF), defined as the interval from the start of CAL-101 treatment to the earlier of the first documentation of disease progression, the permanent cessation of CAL-101 therapy for any reason, or death from any cause
- Changes in health related quality of life (HRQL) as reported by patients using the FACT-Lym

- Changes in performance status as documented using the Karnofsky performance criteria
- Changes in the plasma concentrations of disease-associated chemokines and cytokines
- Overall safety profile of CAL-101 characterized by the type, frequency, severity, timing, and relationship to study therapy of any adverse events or abnormalities of physical findings, laboratory tests, or ECGs; drug discontinuations due to adverse events; or serious adverse events
- Study drug administration as assessed by prescribing records and compliance as assessed by quantification of used and unused drug
- CAL-101 trough and peak plasma concentrations assessed pre-dose and 1.5 hours post-dose
- Pharmacokinetic parameters (e.g.,  $T_{max}$ ,  $C_{max}$ , trough concentration [ $C_{trough}$ ], AUC) (for patients in pharmacokinetic sub-study)

### **Trial Landmarks and Protocol Amendments**

**Table 11 Protocol 101-09 Landmarks and key amendments**

Date	Landmark
11Nov2010	Original Protocol
22Dec2010	0 patients enrolled Amendment 1 <ul style="list-style-type: none"> <li>• Clarified the inclusion of Grades 1-3a Follicular lymphoma only</li> <li>• Update to schedule of events tables</li> <li>• Clarification to the PR definition if PET scans were obtained</li> </ul>
24Jan2011	0 patients enrolled Amendment 2 <ul style="list-style-type: none"> <li>• Change to shipping temperature of drug product</li> </ul>
23Apr2012	67 patients enrolled Amendment 3 <ul style="list-style-type: none"> <li>• Updated the toxicology section to include findings from 13-week GLP toxicology studies</li> <li>• Included a new section to provide new reproductive toxicity findings received from a definitive embryo-fetal development toxicity study</li> <li>• Provided clarification regarding the inclusion of patients with small lymphocytic lymphoma (SLL) to state that the absolute lymphocyte count (ALC) must be <math>\leq 5 \times 10^9/L</math> at the time of diagnosis and at the time of study entry. This clarification is made to ensure that patients with chronic lymphocytic leukemia (CLL) were excluded.</li> <li>• Clarified the inclusion criteria regarding presence of radiographically measurable lymphadenopathy description and included a requirement for the length of the longest perpendicular diameter.</li> <li>• Revised inclusion criteria to ensure resolution of all acute toxicities to Grade <math>\leq 1</math> before the initiation of study treatment (with the exception of alopecia, neurotoxicity and bone marrow parameters with resolution to Grade <math>\leq 2</math>).</li> <li>• Removed the treatment stratification enrollment limit for patients that have received prior bendamustine.</li> <li>• Further defined the criteria for lesion selection and tumor response. This aligns the protocol with the central imaging methods.</li> </ul>

Date	Landmark
	<ul style="list-style-type: none"> <li>• Provided a time window surrounding the collection of PK samples to minimize deviations.</li> <li>• Added the requirement for collection and consideration for overall response of IgM serum monoclonal protein levels assessed by serum protein electrophoresis (SPEP) for patients with lymphoplasmacytic lymphoma (LPL). The consideration of IgM is a component of the published response criteria for patients with LPL.</li> <li>• Included the provision “as allowed by local law” in the event of the potential transition of patients from study treatment to commercial supply, should study drug become approved in the country in which the patient lives.</li> <li>• Changed the Stage 1 ORR analysis to be based on investigator response assessment instead of IRC assessment.</li> </ul>
17Oct2012	Last patient enrolled (total 125)
22May2013	Amendment 4 <ul style="list-style-type: none"> <li>• Updated the non-clinical toxicology and clinical pharmacology sections.</li> <li>• Updated data based on the Phase 1 monotherapy study (101-02) in subjects with hematological malignancies.</li> <li>• Established storage of biological samples (with subject’s informed consent) for future studies.</li> <li>• Updated the statistical analysis section to align with the final analysis plan.</li> <li>• Clarified that the timing of the final efficacy analysis will be <math>\geq 24</math> weeks after the last subject was enrolled.</li> <li>• Aligned the clinical response section with the criteria for the IRC.</li> <li>• Updated recommendations for the management of toxicities.</li> <li>• Removed stratification analysis.</li> <li>• Revised dose modifications so that 100mg BID will be the lowest dose used. This was passed on PK data and exposure-response analysis for safety and efficacy.</li> <li>• Updated the pregnancy risk language based on new nonclinical toxicology data.</li> <li>• Updated AE reporting to include special situations reporting.</li> </ul>
25Jun2013	Last subject observation prior to submission of the NDA
9Sept2013	120 day safety update

### 5.3.2 Other Monotherapy Studies in Lymphoid Malignancies

#### 5.3.2.1 Protocol 101-02 - A Phase 1 Sequential Dose Escalation Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of CAL-101 (GS-1101 [Idelalisib]) in Patients with Selected, Relapsed or Refractory Hematologic Malignancies

Protocol 101-02 was an open-label study of idelalisib monotherapy conducted in 2 phases: dose escalation and single-arm cohort expansion. The primary objectives were to determine the MTD and PK of idelalisib. Eligible subjects were adults with relapsed or refractory CLL, NHL, AML, or MM. Cycle length was 28 days. Dose-schedules of idelalisib tested included 50 mg BID, 150 mg qD, 100 mg BID, 150 mg BID x 21 days only, 300 mg qD, 150 mg BID, 200 mg BID, and 350 mg BID. Up to 12 cycles were allowed on protocol, and subjects could continue treatment thereafter on Protocol 101-99. Intra-patient dose escalation was allowed after 6 cycles if a CR was not attained. The dose escalation phase followed the 3+3 rule with DLT defined as grade 4 hematologic AE persisting for  $\geq 7$  days or any  $\geq$  Grade 3 non-hematologic toxicity at

least possibly related to study drug and occurring by day 28. Up to 25% DLT was allowed in the expansion phase. Subject evaluations were weekly during cycle 1, biweekly during cycle 2, and every 28 days cycles 3-6, and every 56 days thereafter. Response was assessed at the end of cycles 1 and 2 and every 2 cycles thereafter. A total of 191 subjects were enrolled.

#### **5.3.2.2 Protocol 101-10 - Single-agent GS-1101 (CAL-101) for Previously Untreated Low-grade Lymphoma: A Phase 1/2 Study of Safety, Efficacy, and Flow-cytometric Assessment of Tumor-cell Signaling Events**

Protocol 101-10 was an open-label, single-arm study of idelalisib monotherapy in adults with low-grade B-cell NHL as defined by the WHO lymphoma classification. Enrollment was initially open to untreated patients, but due to toxicity in the first two subjects, the protocol was amended to include only those who had at least one prior systemic therapy. The primary endpoints were adverse event rates and overall response rate. Treatment consisted of up to twelve 28-day cycles of idelalisib 150 mg BID, and subjects could continue treatment thereafter on Protocol 101-99. The dose could be increased up to 300 mg BID in those with progressive disease on therapy. Subject evaluations were biweekly during cycle 1 and once every cycle thereafter, except that laboratory evaluations were performed every 14 days through the first 6 cycles. Response was assessed at the end of cycles 3 and every 3 cycles thereafter. A total of 11 of the planned 15 subjects were enrolled, and the study is on-going.

#### **5.3.3.3 Protocol 101-11 - A Phase 2 Study to Assess the Efficacy and Safety of GS-1101 (CAL-101) in Patients with Relapsed or Refractory Hodgkin Lymphoma**

Protocol 101-11 was an open-label, single-arm, 2-stage study of idelalisib monotherapy in patients with classic HL. Eligible patients were  $\geq 12$  years old and had HL relapsed or refractory after autologous HSCT or after at least 2 prior regimens. The primary endpoint was overall response rate. Treatment consisted of idelalisib 150 mg BID until toxicity or progression. The dose could be increased up to 300 mg BID in those with lack of response after 8 weeks. Subject evaluations were biweekly through the first 12 weeks of treatment, at 4-week intervals from weeks 12 to 24, at 6-week intervals from weeks 24 to 48, and at 12-week intervals thereafter. Tumor response was evaluated at 8, 16, and 24 weeks of therapy and every 12 weeks thereafter. The accrual target was 21 evaluable subjects, and 25 subjects have been enrolled. The study is on-going.

#### **5.3.3.4 Protocol 101-99 - An Extension Study to Investigate the Safety and Durability of Clinical Activity of Idelalisib in Subjects with Hematologic Malignancies**

Protocol 101-99 is an extension of treatment for subjects who have completed protocols 101-02, 101-07, 101-08 or 101-10 and had a "clinical benefit." The primary objectives were to determine the incidence of grade 3-5 adverse events and duration of response with long-term treatment. Subjects were treated at the dose level they were receiving at completion of the prior trial, and treatment continued until toxicity or progression of

disease. Doses could be increased up to 150 mg BID if disease worsened. On study assessments included grade 3-5 adverse events, SAEs and concomitant medications every 2-3 months. Response was evaluated according to the standard of care and at least every 12 months. There were 171 subjects enrolled, and the study is on-going.

### **5.3.3 Healthy Volunteer Studies**

#### **5.3.3.1 Protocol 101-01 - A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Sequential Dose Escalation Study to Investigate the Safety, Pharmacokinetics, and Pharmacodynamics of CAL-101 in Healthy Male Subjects**

Protocol 101-01 was a randomized, placebo-controlled, dose-escalation study in healthy adult male volunteers. Subjects were randomized 6:2 to receive idelalisib or placebo in eight dose cohorts. Dose-schedules tested included single doses of 17 – 400 mg and 7-day courses of 50-200 mg BID. The primary objectives were to determine safety and PK of each dose-schedule. Frequent ECGs were performed with the first dose in each cohort. Subjects were assessed daily through 4 days after the last dose, and laboratory testing was performed at last every other day. The protocol was amended to allow rechallenge in subject who develop treatment-emergent rash. All 8 dose-cohorts completed enrollment (total 64 subjects).

#### **5.3.3.2 Protocol 101-04 - A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Two-Period Crossover Study to Investigate the Safety of CAL-101 in Allergic Rhinitis Subjects and Effects on the Response to Environmental Chamber Allergen Challenge**

Protocol 101-04 was a randomized, placebo-controlled, cross-over study in adults with sensitivity to grass pollen by skin prick testing. Subjects were randomized 1:1 to receive idelalisib 100 mg BID x 7 days or placebo in the first of two treatment phases, and crossed over to the alternate treatment in the second phase. The primary objectives were to determine safety and effect on total nasal symptom scores after environmental challenge. Subjects were assessed on days 1 and 7 of each treatment period and 7 days after the last dose. Of the 41 subjects randomized, 39 completed both phases.

#### **5.3.3.3 Protocol 101-05 - A Phase 1, Three-Period Crossover Study to Investigate the Effects of Food and Ketoconazole on Pharmacokinetics of CAL-101 and Evaluate Absorption, Metabolism and Excretion of a Microdose of <sup>14</sup>C-labeled CAL-101 in Healthy Male Subjects**

Protocol 101-05 was a three-period cross-over study in adult males. The primary objectives were to evaluate the pharmacokinetics of CAL-101 administered in a) a fasting state, b) a fed state, or c) when preceded by a 4-day administration of ketoconazole. Idelalisib 400 mg was given once in each of the three periods. A subset of subjects also received a microdose of <sup>14</sup>C-labeled CAL-101. Subjects were assessed daily through day 5 of the first 2 treatment periods and through day 6 of the last

treatment period. Laboratory testing was performed prior to each treatment period and at the end of study. Of the 12 subjects enrolled, 11 completed all three phases.

**5.3.3.4 Protocol 101-06** - A Phase 1 Study to Compare the Pharmacokinetics of CAL-101 (b) (4) to Tablets in Healthy Male Subjects

Protocol 101-06 was a randomized, open-label, three-period cross-over study in adult males. The primary objective was to compare the pharmacokinetics of three different formulations of CAL-101. The order of administration was randomized for each subject. Idelalisib 100 mg was given during each treatment period. Subjects were assessed daily, and laboratory testing was performed prior to study and at the end of study. Fifteen subjects were enrolled and completed all three phases.

**5.3.3.5 Protocol 313-0111** - A Phase 1 Study to Evaluate the Pharmacokinetics, Metabolism, and Excretion of GS-1101

Protocol 313-0111 was an open-label, single-dose study in adult males. Subjects received idelalisib 150 mg of which 0.5% was radiolabelled. The primary objective was to determine the mass balance of idelalisib following administration of a single oral dose. Subjects were assessed pretreatment and on days 1-7, 12, 16 and 22. Laboratory testing was performed pretreatment and on days 2, 4, 8, 12, 16 and 22. Eight subjects were enrolled and completed the study.

**5.3.3.6 Protocol 313-0112** - A Phase 1 Open-Label Study to Evaluate the Pharmacokinetics of Idelalisib (GS-1101) in Subjects with Impaired Hepatic Function

Protocol 313-0112 was an open-label, single-dose, parallel-group study. Eligible subjects included healthy adults and those with chronic, stable hepatic impairment. Those with malignancies were excluded. The subjects were to be entered into one of four cohorts (mild, moderate or severe hepatic impairment, or healthy control). The primary objective was to evaluate the PK of idelalisib and its metabolite GS-563117 in subjects with impaired hepatic function relative to matched healthy controls. Treatment consisted of idelalisib 150 mg once. Subjects were assessed pretreatment, daily through day 6, and on day 22. Laboratory testing was performed pretreatment and on days 6 and 22. ECGs were performed frequently around dosing and in follow-up. The safety and PK results from the moderate and severe hepatic impairment cohorts (CPT classes B and C) supported not studying subjects with mild impairment, so only three of the four cohorts were enrolled. All 32 enrolled subjects completed the study.

**5.3.3.7 Protocol 313-0117** - A Phase 1, Partially-Blinded, Randomized, Placebo- and Positive-Controlled Study to Evaluate the Effect of Idelalisib (GS-1101) on the QT/QTc Interval in Healthy Subjects

Protocol 313-0117 was a randomized, controlled, four-period, cross-over study in adults. The primary objective was to evaluate the effects of idelalisib and the metabolite

GS-563117 on QTcF. Subjects were randomized 1:1 to 1 of 2 Williams squares, and then to 1 of 4 possible treatment sequence. The four planned treatments included placebo, idelalisib 150 mg, idelalisib 400 mg, and a positive control (moxifloxacin), and treatments were given 10 days apart. Subjects were assessed daily through day 31 and within 7 days after completion of study. ECGs were collected frequently, and there was 24-hour Holter monitoring on the day of each dose. Laboratory testing was performed prior to each dose and at the end of study. Of the 48 subjects randomized, 46 completed all four treatment phases.

#### **5.3.3.8 Protocol 313-0118** - A Phase 1 Open-Label Study to Evaluate the Pharmacokinetics of GS-1101 in Subjects with Impaired Renal Function

Protocol 313-0118 was an open-label, single-dose, parallel-group study. Eligible subjects included healthy adults and those with chronic, stable renal impairment. Those with active malignancy were excluded. The subjects were to be entered into one of four cohorts (mild, moderate or severe renal impairment, or healthy control). The primary objective was to evaluate the PK of idelalisib and its metabolite GS-563117 in subjects with impaired renal function relative to matched healthy controls. Treatment consisted of idelalisib 150 mg once. Subjects were assessed pretreatment, daily through day 6, and on day 15. Laboratory testing was performed pretreatment and on days 6 and 15. ECGs were performed frequently around dosing and in follow-up. The safety and PK results from the severe renal impairment cohort (CLCr <30 mL/min) supported not studying subjects with mild or moderate impairment, so only two of the four cohorts were enrolled. All 12 enrolled subjects completed the study.

#### **5.3.3.9 Protocol 313-0126** - A Phase 1, Single-Dose Study to Investigate the Pharmacokinetics, Safety, and Tolerability of Idelalisib (GS-1101) in Healthy Japanese and Caucasian Subjects

Protocol 313-0126 was an open-label, single-dose, parallel group study. Eligible subjects included healthy adults of Japanese or Caucasian descent. The primary objectives were to evaluate the PK, safety and tolerability of idelalisib. The study drug idelalisib 150 mg was administered once. Subjects were assessed pretreatment and on days 1-3 and 8. Laboratory testing was performed pretreatment and on days 2, 3 and 8. Twenty subjects were enrolled and completed the study.

#### **5.3.3.10 Protocol 313-0130** - A Phase 1 Study to Evaluate the Effect of Idelalisib on Probe Substrates of Cytochrome P450 3A (CYP3A) Enzymes or Drug Transporters P-glycoprotein (Pgp), Organic Anion Transporting Polypeptide (OATP) 1B1 and 1B3, and the Effect of Rifampin on Idelalisib Pharmacokinetics

Protocol 313-0139 was a multiple-dose study in adults. Eligible subjects were entered alternately into one of two cohorts. In the first cohort, subjects received idelalisib 150 mg BID on days 5-14; single doses of digoxin were given on days 1 and 14, and single doses of midazolam were given on days 3 and 12. In the second cohort, subjects

received idelalisib 150 mg BID on days 3-9 and as a single dose on day 18; single doses of rosuvastatin were given on days 1 and 9, and rifampin was given once daily on days 11-18. The primary objectives were to evaluate the effect of idelalisib on CYP3A (midazolam) and the drug transporters Pgp (digoxin), OATP1B1, and OATP1B3 (rosuvastatin), and to evaluate the effect of rifampin on the PK of idelalisib. Subjects were assessed daily through the end of the treatment period and 7 days after the last dose. Of the 24 subjects enrolled, 22 completed the study.

### **5.3.3.11 Protocol 339-0101 - A Phase 1 Open-Label, Multiple Dose-Escalation Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamic of GS-9973 and GS-1101 Each Administered Alone or in Combination**

Protocol 339-0101 was a multiple-dose, dose-escalation three-period cross-over study in adult females. The primary objectives were to evaluate the PK, safety and tolerability of multiple doses of GS-9973 and idelalisib. Treatment consisted of GS-9973 days 1-4, idelalisib days 15-18, and both drugs on days 29-32. Idelalisib 100 mg BID was used in the first two cohorts and 150 mg BID in the third cohort. Subjects were assessed daily during the treatment period and on days 35 and 43. Laboratory testing was performed pretreatment and on days 2-4, 7 and 35. Of the 24 subjects enrolled, 22 completed the study.

## **6 Review of Efficacy**

### **Efficacy Summary**

The efficacy of Zydelig was evaluated in 123 patients with previously treated indolent non-Hodgkin lymphomas in the single arm Phase 2 Trial 101-09. All patients were started on continuous oral dosing of 150mg twice daily. The primary endpoint was overall response rate (ORR) as determined by an independent review committee (IRC). A key secondary endpoint was duration of response (DOR).

For all patients on trial, the ORR was 55% (95% CI: 46, 64) with a median DOR of 12.5 months. By lymphoma type, a summary of key efficacy results follow:

- In patients with follicular lymphoma, the ORR was 54% (39 of 72 patients). The median DOR was not evaluable. Median follow-up was 8.1 months.
- In patients with small lymphocytic lymphoma, the ORR was 58% (15 of 26 patients) with a median DOR of 11.9 months.

There were inadequate numbers of patients with marginal zone lymphoma (15 patients) and lymphoplasmacytic lymphoma (10 patients) (b) (4)

For the FL and SLL populations, limitations of the efficacy data include a relatively short exposure to idelalisib and a short duration of response.

- Only 33 patients (24 FL, 9 SLL) remained on idelalisib longer than six months.

- Only 10 patients (5 FL, 5 SLL) were treated for more than 12 months.
- 9 patients (6 FL, 3 SLL) had duration of response of less than two months which represented 17% of the patients with responses.
- 89% of patients with response had a DOR shorter than 12 months.
- 54% of patients with responses had a DOR shorter than 6 months.

Confirmation of efficacy is needed and would be better described by an analysis of the results of the ongoing randomized controlled trials in indolent lymphomas.

## **6.1 Indication**

The applicant's proposed indication is for the treatment of patients with refractory indolent B-cell non-Hodgkin lymphoma.

### **6.1.1 Methods**

The efficacy review for idelalisib included the review of the following items submitted by the applicant:

- Clinical study report for Trial 101-09
- Protocol and statistical analysis plan for Trial 101-09
- Raw and derived datasets for Trial 101-09
- Case report forms for Trial 101-09
- Patient narratives for Trial 101-09
- Responses to information requests
- Proposed labeling for Zydelig

The data cutoff date for the efficacy analysis was 25 June 2013.

### **6.1.2 Demographics**

Trial 101-09 enrolled 125 patients from 40 sites in 6 countries: France, Germany, Italy, Poland, the United Kingdom, and the United States. Patients from the U.S. accounted for 66% of the total enrollment, with the remainder distributed over the 5 European countries. As mentioned in Section 3.2, two patients did not meet eligibility criteria, so 123 patients were included in the primary efficacy analysis.

Patients with relapsed follicular lymphoma represented 59% of the subjects enrolled and 21% of patients had relapsed small lymphocytic lymphoma. Caucasian patients represented 89% of the total enrollment. Detailed demographic features are presented in Table 12.

**Table 12 Demographics of patients on Trial 101-09**

	iNHL n=123	FL n=72	SLL n=26	MZL n=15	LPL n=10
<b>Age, years</b>					
Median	64	62	65	72	60
Mean (SD)	62 (11)	61 (12)	65 (9)	68 (3)	59 (2)
Range	33-87	33-84	50-87	50-87	49-73
<b>Groups</b>					
<40	3	3	0	0	0
40-64	65	43	10	6	6
≥65	55	26	16	9	4
<b>Sex</b>					
Male	78 (63%)	39 (54%)	19 (73%)	12 (80%)	8 (80%)
Female	45 (37%)	33 (46%)	7 (27%)	3 (20%)	2 (20%)
<b>Race</b>					
White or Caucasian	108 (89%)	64 (90%)	21 (81%)	14 (93%)	9 (90%)
Asian	3 (2%)	3 (4%)	0	0	0
Black or African American	2 (2%)	0	2 (8%)	0	0
Other	9 (7%)	4 (6%)	3 (11%)	1 (7%)	1 (10%)
<b>Ethnicity</b>					
Hispanic or Latino	6 (5%)	6 (8%)	0	0	0
<b>BMI, kg/m<sup>2</sup></b>					
Median	25.8	26.8	25.3	25.5	24.85
Mean (SD)	26.9 (5.6)	27.1 (5.4)	27.2 (7.0)	26.9 (5.2)	25.1 (2.4)
Range	17.2-51.1	17.2-42.6	19.6-51.1	20.3-40.0	21.7-28.2
<b>U.S. patients</b>					
	81 (66%)	44 (61%)	20 (77%)	11 (73%)	6 (60%)

The median time from initial diagnosis to treatment on trial was 5.2 years and ranged from 0.4 to 18.4 years. The median number of prior regimens was 4. As mandated for trial inclusion, all patients received at least 2 regimens and all received rituximab and an alkylating agent as part of their prior regimens. The most common prior combination regimens were BR<sup>1</sup> (47%), R-CHOP<sup>2</sup> (46%), and R-CVP<sup>3</sup> (28%). Of the patients with follicular lymphoma, 51% received R-CHOP, 49% BR, and 28% R-CVP. Of the patients with small lymphocytic lymphoma, 69% received BR, 46% FCR<sup>4</sup>, and 35% R-CHOP. Table 13 provides details on treatment history.

<sup>1</sup> Bendamustine, Rituximab

<sup>2</sup> Rituximab, Cyclophosphamide, doxorubicin, vincristine, Prednisone

<sup>3</sup> Rituximab, Cyclophosphamide, Vincristine, Prednisone

<sup>4</sup> Fludarabine, Cyclophosphamide, Rituximab

**Table 13 Treatment history of patients on Trial 101-09**

	iNHL n=123	FL n=72	SLL n=26	MZL n=15	LPL n=10
<b>Time from initial diagnosis, yrs</b>					
Median	5.2	4.7	6.7	4.4	2.9
Mean (SD)	5.8 (4.0)	5.9 (4.2)	6.8 (3.2)	5.4 (4.6)	3.7 (2.7)
Range	0.4-18.4	0.8-18.4	1.1-13.4	0.4-15.9	0.9-8.5
<b>Number of prior therapies</b>					
Median	4	4	4	2	3.5
Mean (SD)	4.2 (2.1)	4.2 (2.2)	4.8 (2.0)	3.3 (2.0)	3.6 (1.5)
Range	2-12	2-12	2-9	2-9	2-6
<b>Prior therapies</b>					
Stem cell transplant	12 (10%)	11 (15%)	1 (4%)	0	0
Radiation	36 (29%)	27 (38%)	3 (12%)	6 (40%)	0

Table 14 iterates clinical manifestations of disease in patients on trial. These results were derived from datasets of investigator clinical assessment, laboratory measures and IRC assessment of lymphadenopathy and extranodal disease. In determining baseline sum of product diameters (SPD) of target lesions, the smaller SPD result was selected from the interpretations of the two readers when adjudication was not needed. Target lesions measured to calculate SPD were nodal and extranodal sites of disease.

The majority of patients enrolled on trial had bulky lymphadenopathy and otherwise appeared representative of patients requiring treatment. Clinically relevant cut-off points were chosen for laboratory results: hemoglobin and platelet measures in the table are most frequently categorized as CTCAE Grade 1 (laboratory differences in the lower limits of normal vary) and neutrophil and lymphocyte measures are most frequently categorized as CTCAE Grade 2.

**Table 14 Baseline disease of patients on Trial 101-09**

	iNHL n=123	FL n=72	SLL n=26	MZL n=15	LPL n=10
<b>Target lesions</b>					
<b>Count</b>					
Median	5	5	6	3	5
Mean (SD)	4 (2)	4 (2)	6 (1)	3 (2)	5 (1)
Range	1-6	1-6	3-6	1-6	2-6
<b>SPD, cm<sup>2</sup></b>					
Median	26.9	22.7	55.7	8.1	23.7
Mean (SD)	40.7 (41.2)	34.0 (33.8)	71.7 (52.3)	23.6 (31.0)	30.4 (30.6)
Range	1.9-224.3	3.2-199.5	13.4-224.3	1.9-94.2	4.7-111.8

	iNHL n=123	FL n=72	SLL n=26	MZL n=15	LPL n=10
<b>Lymphadenopathy</b>					
Diameter of largest node, cm					
Median	4.1	3.9	5.4	3.7	4.0
Mean (SD)	4.7 (2.4)	4.5 (3.4)	5.7 (2.4)	4.4 (2.6)	3.9 (1.6)
Range	1.6-17.4	2-17.2	2.4-12.6	1.6-9.4	2.0-7.4
<b>Extranodal involvement</b>					
Liver nodules	43 (35%)	24 (33%)	7 (27%)	8 (53%)	4 (40%)
Liver nodules	2 (2%)	1 (1%)	0	0	1 (10%)
Spleen nodules	19 (15%)	11 (15%)	4 (15%)	2 (13%)	2 (20%)
Other <sup>1</sup>	24 (20%)	12 (16.7%)	3 (12%)	6 (40%)	3 (30%)
<b>Bone marrow</b>					
Infiltrate present	55 (45%)	19 (26%)	22 (85%)	4 (27%)	10 (100%)
Biopsy or aspirate collected	118 (96%)	71 (99%)	25 (96%)	12 (80%)	10 (100%)
<b>Cytopenias</b>					
Hemoglobin <125 g/L	90 (73%)	54 (75%)	18 (69%)	11 (73%)	7 (70%)
Hemoglobin <125 g/L	61 (50%)	28 (39%)	17 (65%)	10 (67%)	6 (60%)
Platelets <100 x10 <sup>9</sup> /L	22 (18%)	12 (17%)	5 (19%)	4 (27%)	1 (10%)
Neutrophils <1.5 x10 <sup>9</sup> /L	13 (11%)	9 (13%)	4 (15%)	0	0
Lymphocytes <0.8 x10 <sup>9</sup> /L	50 (41%)	36 (50%)	7 (27%)	4 (27%)	3 (30%)
<b>LDH</b>					
>ULN (234 U/L)	39 (32%)	21 (29%)	13 (50%)	4 (27%)	1 (10%)
<b>Disease-related symptoms</b>					
Disease-related symptoms	24 (20%)	13 (18%)	5 (19%)	3 (20%)	3 (30%)
B-symptoms <sup>2</sup>	21 (17%)	11 (15%)	5 (19%)	3 (20%)	2 (20%)
Other <sup>3</sup>	3 (2%)	2 (3%)	0	0	1 (10%)
<b>ECOG Performance Score</b>					
0-1	115 (93%)	66 (92%)	25 (96%)	15 (100%)	9 (90%)
2	8 (7%)	6 (8%)	1 (4%)	0	1 (10%)

<sup>1</sup> Partial list: soft tissue, peritoneum, lung, skin, muscle, kidney

<sup>2</sup> B-symptoms: fevers, weight loss, night sweats

<sup>3</sup> Included skin lesions, pruritus, unknown

### 6.1.3 Subject Disposition

At the time of the data cutoff date, 32% of patients enrolled on Trial 101-09 were continuing to receive idelalisib. A similar proportion (36%) had already stopped treatment for progressive disease or lack of efficacy. Refer to Table 15 for a breakdown by lymphoma type.

**Table 15 Disposition of patients on Trial 101-09**

	iNHL n=123	FL n=72	SLL n=26	MZL n=15	LPL n=10
Treatment ongoing	39 (32%)	21 (29%)	7 (27%)	4 (27%)	7 (70%)
<b>Discontinued</b>	<b>84 (68%)</b>	<b>51 (71%)</b>	<b>19 (73%)</b>	<b>11 (73%)</b>	<b>3 (30%)</b>
Progressive disease or lack of efficacy	44 (36%)	28 (39%)	9 (35%)	6 (40%)	1 (10%)
Adverse event	26 (21%)	14 (19%)	8 (31%)	2 (13%)	2 (20%)
Death	8 (7%)	4 (6%)	1 (4%)	3 (20%)	0
Withdrawal by subject	3 (2%)	3 (4%)	0	0	0
Planned SCT	3 (2%)	2 (3%)	1 (4%)	0	0

In 21% of patients on trial, adverse events were listed as the reason for discontinuing treatment. The most frequent AE's identified were diarrhea or colitis (in 7 patients), pneumonia or pneumonitis (in 6) and hepatic dysfunctions (in 5).

In the review of disposition, all instances of 'Investigator Request' were re-coded; sufficient investigator reported information was provided to more clearly code the reason. Refer to Table 16 for examples of FDA adjudication.

**Table 16 FDA adjudication of Investigator-reported disposition on Trial 101-09**

Investigator Reported Term	Applicant Standardized Term	FDA change
LACK OF RESPONSE	INVESTIGATOR REQUEST	Lack of efficacy
NEED FOR MORE AGGRESSIVE THERAPY	INVESTIGATOR REQUEST	Lack of efficacy
REFERRING PATIENT TO TRANSPLANT	INVESTIGATOR REQUEST	Planned SCT
INVESTIGATOR DECISION FOR TRANSPLANT	INVESTIGATOR REQUEST	Planned SCT
INVESTIGATOR DECIDED PATIENT'S ALLOGRAFT	INVESTIGATOR REQUEST	Planned SCT
STABLE DISEASE AFTER CYCLE 4 AND POOR QUALITY OF LIFE	INVESTIGATOR REQUEST	Adverse event
LACK OF EFFICACY	INVESTIGATOR REQUEST	Lack of efficacy

#### 6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint was overall response rate, defined as the proportion of patients who achieved a complete response or partial response while on idelalisib. FDA analyses produced results similar to the applicant's results.

**Table 17 Overall Response Rate (ORR) in patients on Trial 101-09**

	iNHL n=123	FL n=72	SLL n=26	MZL n=15	LPL n=10
ORR	68 (55%)	39 (54%)	15 (58%)	7 (47%)	7 (70%)
95% CI	46, 64	42, 66	37, 77	21, 73	35, 93
CR	7 (6%)	6 (8%)	0	1 (7%)	0
PR	61 (50%)	33 (46%)	15 (58%)	6 (40%)	7 (70%)

CI = confidence interval; CR = complete response; PR = partial response

Analysis for confirmed responses, defined here as at least two consecutive assessments of PR or CR with greater than two month duration of response, was performed to assess durability of best response. Most of the patients who achieved a response, sustained the response over more than one assessment period. There were 12 patients who achieved a partial response at only a single evaluation time point (6 with FL, 3 with SLL, 2 with LPL, 1 with MZL).

**Table 18 Overall Response Rate (ORR) at ≥2 consecutive assessments and >2 months in patients on Trial 101-09**

	iNHL n=123	FL n=72	SLL n=26	MZL n=15	LPL n=10
ORR	56 (46%)	33 (46%)	12 (46%)	6 (40%)	5 (50%)
95% CI	37, 55	34, 58	27, 67	16, 68	19, 81
CR	6 (5%)	5 (7%)	0	1 (7%)	0
PR	50 (41%)	28 (39%)	12 (45%)	5 (33%)	5 (50%)

CR = complete response; PR = partial response

Most patients who achieved a complete response sustained the response over multiple time points. Table 19 provides details on the patients that achieved a complete response. Three of the six patients that had complete response had to stop treatment with idelalisib due to gastrointestinal adverse events. Long term use and tolerability will be further addressed in Section 7.

**Table 19 Characteristics of patients with CR on Trial 101-09**

Patient	Disease	SPD, cm <sup>2</sup>	Marrow results	CR achieved	Subsequent staging
111-09031	FL	13.1	Not done (negative for baseline disease)	Week 16	PD at week 24
111-09032	FL	9.1	Not done (negative for baseline disease)	Week 16	CR continued to week 72 (last evaluation)
117-09023	FL	3.2	Not done (negative for baseline disease)	Week 8	CR continued to week 72 (last evaluation)
121-09123	MZL	2.6	Not done (negative for baseline disease)	Week 8	CR continued to week 48 (last evaluation)
133-09086	FL	28.1	No tumor infiltrates; no transformation of disease	Week 24	CR continued to week 36 (last evaluation). Stopped tx for AE: AUTOIMMUNE COLITIS
145-09074	FL	7.1	Not done (negative for baseline disease)	Week 60	CR continued to week 72 (last evaluation). Stopped tx for AE: ILEOCOLITIS
152-09102	FL	3.6	Not done (negative for baseline disease)	Week 16	CR continued to week 36 (last evaluation). Stopped tx for AE: DIARRHEA

### 6.1.5 Analysis of Secondary Endpoint(s)

The first secondary endpoint was duration of response, defined as the interval from the first documentation of PR or CR to the first documentation of progression of disease or death. Results of duration were not robust due to the large proportion of censored

patients to patients with responses. Ranges are provided in Table 20 as median DOR was not evaluable for the entire trial population and for some of the lymphoma types.

**Table 20 Duration of Response (DOR) in patients on Trial 101-09**

	iNHL n=123	FL n=72	SLL n=26	MZL n=15	LPL n=10
Median DOR, months	12.5	NE	11.9	NE	NE
95% CI	6.5, NE	4.5, NE	3.7, 14.7	3.6, NE	
Range	0.03-14.8+	0.03-14.8+	0.03-14.7	0.03-9.2	1.7-14.8+

NE = not evaluable; CI = confidence interval; + Includes censored

Analysis for duration of response for confirmed responses only, again defined as at least two consecutive assessments of PR or CR with greater than two month duration of response, was performed.

**Table 21 Duration of Response (DOR) in patients with ≥2 consecutive assessments of PR or CR on Trial 101-09**

	iNHL n=123	FL n=72	SLL n=26	MZL n=15	LPL n=10
Median DOR, months	14.7	NE	11.9	NE	NE
95% CI	7.4, NE	6.2, NE	3.7, 14.7	3.6, NE	
Range	2.1-14.8+	2.1-14.8+	2.3-14.7	3.6-9.2+	6.5-14.8+

NE = not evaluable; CI = confidence interval; + Includes censored

Review of the duration of response for individual response demonstrates a limitation of using Kaplan-Meier estimation of median duration of response. The following two tables list patients with a response of PR or CR and the duration of their response; note that less than 12% of responders had duration of response longer than 12 months. Median follow-up was 8.1 months.

**Table 22 Duration of Response by patient with FL on Trial 101-09**

Patient	Baseline SPD (cm <sup>2</sup> )	# of target lesions	Best response	Confirmed response <sup>1</sup>	DOR (months)	Censor	Reason
155-09095	24.0	6	PR	0	0.03	1	Withdrew from study
502-09154	89.3	6	PR	0	0.79	0	Death
703-09112	48.0	5	PR	0	1.18	0	Death
117-09139	11.9	4	PR	0	1.38	1	Discontinued due to AE
306-09107	69.6	3	PR	0	1.61	0	PD
117-09164	26.9	4	PR	0	1.87	1	Data Cut-off
602-09157	20.8	5	PR	0	1.87	1	Data Cut-off
131-09053	10.2	1	PR	1	2.07	1	Withdrew for SCT
703-09091	28.5	3	PR	1	2.79	0	PD
133-09119	15.7	3	PR	0	3.61	0	PD
127-09158	52.0	6	PR	1	3.68	0	PD
111-09031	13.1	4	CR	1	3.71	0	PD
154-09045	21.1	4	PR	1	3.84	0	PD
603-09097	42.7	5	PR	1	3.88	0	PD
304-09135	21.3	6	PR	1	3.91	1	Discontinued due to AE
401-09133	17.4	2	PR	1	4.17	0	PD

Patient	Baseline SPD (cm <sup>2</sup> )	# of target lesions	Best response	Confirmed response <sup>1</sup>	DOR (months)	Censor	Reason
502-09129	19.7	5	PR	1	4.47	0	PD
401-09151	52.2	5	PR	1	4.63	1	Data Cut-off
133-09125	17.1	6	PR	1	5.03	1	Discontinued due to AE
133-09127	17.5	2	PR	1	5.29	1	Data Cut-off
306-09150	4.8	3	PR	1	6.01	1	Data Cut-off
102-09051	72.9	3	PR	1	6.05	0	PD
133-09161	34.0	6	PR	1	6.14	1	Data Cut-off
121-09012	27.4	6	PR	1	6.21	0	PD
111-09006	24.4	3	PR	1	6.37	0	Death
119-09142	52.2	3	PR	1	6.47	0	PD
152-09102	3.6	1	CR	1	6.77	1	Discontinued due to AE
109-09117	32.4	5	PR	1	7.62	1	Data Cut-off
133-09120	16.4	4	PR	1	8.08	1	Data Cut-off
703-09090	14.3	4	PR	1	8.08	1	Data Cut-off
145-09074	7.1	2	CR	0	8.71	1	Discontinued due to AE
133-09086	28.1	5	CR	1	8.97	1	Discontinued due to AE
603-09109	12.2	5	PR	1	9.07	1	Data Cut-off
305-09124	75.9	5	PR	1	9.46	1	Discontinued due to AE
601-09076	40.9	6	PR	1	10.22	1	Data Cut-off
401-09030	103.4	6	PR	1	10.94	1	Data Cut-off
305-09039	43.0	6	PR	1	14.55	1	Data Cut-off
117-09023	3.2	1	CR	1	14.72	1	Data Cut-off
111-09032	9.1	2	CR	1	14.75	1	Data Cut-off

<sup>1</sup> ORR maintained ≥ 2 consecutive assessments >2 months apart

**Table 23 Duration of Response by patient with SLL on Trial 101-09**

Patient	Baseline SPD (cm <sup>2</sup> )	# of target lesions	Best response	Confirmed response <sup>1</sup>	DOR (months)	Censor	Reason
131-09048	74.7	6	PR	0	0.03	1	Discontinued due to AE
131-09111	50.3	6	PR	0	0.03	1	Withdrew for SCT
109-09020	45.9	5	PR	0	1.87	1	Discontinued due to AE
149-09108	21.3	4	PR	0	1.91	0	PD
147-09016	13.4	4	PR	1	2.27	1	Discontinued due to AE
111-09029	40.3	6	PR	1	3.71	0	PD
111-09049	65.5	6	PR	1	3.71	1	Discontinued due to AE
111-09038	76.2	6	PR	1	4.47	0	PD
405-09088	31.5	5	PR	1	7.33	1	Data Cut-off
119-09093	72.5	6	PR	1	7.39	0	PD
111-09018	102.6	6	PR	1	8.08	1	Data Cut-off
102-09013	120.3	6	PR	1	11.93	0	PD
128-09056	89.1	6	PR	1	12.45	0	PD
119-09034	136.7	6	PR	1	14.19	1	Data Cut-off
152-09059	31.5	6	PR	1	14.69	0	PD

<sup>1</sup> ORR maintained ≥ 2 consecutive assessments >2 months apart

SCT = stem cell transplant

Various other secondary endpoints were not analyzed since clinical significance is not known, i.e., change in the size of lymph nodes, or cannot be adequately evaluated in a single arm trial, i.e. progression-free survival.

### 6.1.6 Other Endpoints

No other endpoints were specified.

### 6.1.7 Subpopulations

The small size of the efficacy population limits the ability to perform useful subpopulation analyses of the various lymphoma types. For labeling purposes, an analysis of patients with FL or SLL who were 65 years of age and older was performed (Table 24). No major differences in efficacy could be identified when compared to patients younger than 65 years.

**Table 24 Overall Response Rate (ORR) for older patients on Trial 101-09**

	n	N (%)	ORR 95% CI
FL	72	39 (54%)	42.0, 66.0
Age			
<65	46	23 (50%)	34.9, 65.1
≥65	26	16 (62%)	40.6, 79.8
SLL	26	15 (58%)	36.9, 76.7
Age			
<65	10	6 (60%)	26.2, 87.8
≥65	16	9 (40%)	29.9, 80.3

CI = confidence interval; CR = complete response;  
PR = partial response

### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

An efficacy analysis of the small number of patients with indolent lymphomas on the dose escalation trial 101-02 does not provide sufficient evidence to alter initial dosing. Results based on investigator determined best responses are provided in Table 25 for both 100 mg BID and 150 mg BID dosing regimens over 21 or 28 days of 28 day cycles. Partial responses were seen in all three cohorts; there were no CRs.

**Table 25 Overall response rate (ORR) from Phase 1 dose-escalation Trial 101-02**

Dose	iNHL	FL	SLL	MZL	LPL
150 BID x 28d PR	n=10 2 (20%)	n=7 2	n=2 0	n=0 0	n=1 0
150 BID x 21d PR	n=12 2 (17%)	n=7 1	n=2 1	n=3 0	n=0 0
100 BID x 28d PR	n=7 5 (71%)	n=5 4	n=1 0	n=0 0	n=1 1

As conveyed in Section 4.4 from the review of clinical pharmacology, the drug exposure concentrations of 100mg BID and 150mg BID overlap. Subgroup analysis of the 40 patients that were dose reduced to 100mg BID is not feasible given such small numbers. Of the patients with follicular lymphoma, 19 were dose reduced; of the patients with small lymphocytic lymphoma, 9 were dose reduced.

### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The trial population size and design limits analysis of persistence of efficacy. Table 26 shows the time in months that patients in Trial 101-09 were on idelalisib, having discontinued treatment for any reason. Limited long-term use is available from this trial to make any claims of long-term efficacy.

**Table 26 Time on idelalisib and percentage of patients remaining on idelalisib for all lymphoma types on Trial 101-09**

Months on idelalisib	iNHL n=123		FL n=72		SLL n=26		MZL n=15		LPL n=10	
<1	7	100%	6	100%	1	100%	0	100%	0	100%
1-2	10	94%	5	92%	3	96%	1	100%	1	100%
2-3	8	86%	4	85%	3	85%	1	93%	0	90%
3-6	57	80%	33	79%	10	73%	9	87%	5	90%
6-9	20	34%	11	33%	4	35%	4	27%	1	40%
9-12	9	18%	8	18%	0	19%	0	0	1	30%
12-15	5	11%	3	7%	2	19%	0	0	0	20%
15-18	5	7%	1	3%	3	12%	0	0	2	20%
18-21	2	3%	1	1%	0	0	0	0	0	0
>21	0	0	0	0	0	0	0	0	0	0

### 6.1.10 Additional Efficacy Issues/Analyses

The heterogeneity of the patient population in Trial 101-09 has been an issue in evaluating idelalisib for the indication of indolent non-Hodgkin lymphoma. The enrolled population also varied within lymphoma type.

While the prognostic significance of the histologic grade of recurrent follicular lymphoma has not been established, they are presented here in Table 27 as supplemental information.

**Table 27 Histologic grade of patients with FL on Trial 101-09**

Histologic grade	n=72
1	21 (29%)
2	39 (54%)
3a	12 (17%)

The greatest dissimilarity was seen in the histologic types of marginal zone lymphomas where 9 of the 15 patients had extranodal MZL, a disease most commonly associated with chronic antigenic stimulation and occurring in non-lymphoid tissues. Prior treatments for marginal zone lymphomas vary greatly. Responses by histologic type are included in Table 28.

**Table 28 Histologic types patients with MZL on Trial 101-09**

Histologic type	n=15	ORR
Extranodal marginal zone (MALT lymphoma)	9 (60%)	5 (1 CR, 4 PR)
Nodal marginal zone	5 (33%)	1 (PR)
Splenic marginal zone	1 (7%)	1 (PR)

Assessment of monoclonal IgM by SPEP or total serum IgM, of patients with LPL was added by protocol amendment. Baseline screening of monoclonal IgM results ranged from 1.5 to 9.3 g/dL. No conclusions can be drawn from the review of the small numbers of patients with MZL or with LPL±WM.

## 7 Review of Safety

### Safety Summary

The final safety dataset included 354 adults with hematological malignancies treated with idelalisib as monotherapy in Phase 1 or Phase 2 trials. The original submission of the NDA included data for only 352 subjects, and it was this original dataset that was used for the initial assessment in the full monotherapy safety population. Of these 354 subjects, 146 were treated with idelalisib 150 mg BID for INHL (INHL 150 mg BID subgroup). Median time on study for the INHL 150 mg BID subgroup was 6.1 months (range, 0.3-26.4 months). The safety dataset also included information for 300 volunteers without hematological malignancies (18 of whom received only placebo) for studies of pharmacokinetics and drug-drug interactions. The study population was monitored for deaths, serious adverse events, adverse events of interest, common adverse events and common laboratory tests. A thorough QT study was conducted. There are no safety data in children.

Analysis of the full monotherapy safety population showed:

- Sixty-one deaths were reported. The root causes of death were progressive disease for 36 (59%) subjects, infection for 17 (28%) subjects, and other adverse event for 8 (13%) subjects.
- Seven deaths were considered at least possibly related to idelalisib. The fatal events included infection with neutropenia, sudden death, respiratory failure, tumor lysis syndrome, and enteropathy.
- Increases in transaminases, neutropenia and nausea appeared to be dose-related with the highest incidences in subjects treated with idelalisib 350 mg BID.
- There were three cases with transaminase and bilirubin elevations consistent with Hy's law, but concomitant use of other hepatotoxic drugs confounded the analysis.

Significant findings from analysis of the INHL 150 mg BID subgroup included:

- An SAE was reported for 74 (51%) subjects. The most common SAEs were pneumonia (16%), diarrhea (11%), and pyrexia (10%). The SAEs were considered related for 44 (30%) subjects.
- Adverse events of special interest considered related to use of idelalisib by history, rechallenge and/or biopsy included transaminase elevation, diarrhea/colitis, rash, and pneumonitis. The actual rate of drug-induced pneumonitis was difficult to discern due to the high background rates of infections in this population.
- An AE resulted in drug interruption or permanent withdrawal for 80 (55%) subjects.
- A TEAE was reported for 99% of the subjects. The TEAEs reported most frequently (>20%) were diarrhea (47%), fatigue (34%), cough (30%), nausea (29%), pyrexia (29%), neutropenia (27%), elevated transaminases (26%), pneumonia (25%), rash (23%), and abdominal pain (23%).
- The incidence of TEAEs was not affected by gender, age or race. There was also no consistent difference by the type of lymphoma. There was a trend for an increase in diarrhea, nausea, neutropenia, anemia and asthenia in subjects <55 kg in weight. There was also a trend for an increase in diarrhea when idelalisib was used concurrently with a proton pump inhibitor, although pharmacokinetics studies demonstrated this did not result from a drug-drug interaction.

- A grade  $\geq 3$  TEAE was reported for 64%. The grade  $\geq 3$  TEAEs reported most frequently ( $>10\%$ ) were neutropenia (21%), elevated transaminases (17%), pneumonia (16%) and diarrhea (14%).
- The most common grade  $\geq 3$  laboratory abnormalities were neutropenia (27%), ALT increased (18%), AST increased (12%) and thrombocytopenia (9%). Hypogammaglobulinemia occurred in a small percentage of subjects in whom it was not pre-existing due to the underlying disease or prior treatment.

The safety profile was similar in the volunteer studies, confirming that the toxicities seen were related to idelalisib.

Overall, the safety profile of idelalisib 150 mg BID was marked by substantial toxicity. Although much of the toxicity was self-limited when the drug was discontinued, safe use of idelalisib will require detailed labeling with adequate warnings, instructions for monitoring, and instructions for dose modifications. Given that follow-up for the majority of the study subjects was relatively short, the data were not sufficient to confirm safety of long-term use. Additional characterization of idelalisib-related pneumonitis is needed.

## 7.1 Methods

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The clinical review of safety for this NDA was based on the safety data from the sixteen studies listed in Table 6 in Section 5.1.

### 7.1.2 Categorization of Adverse Events

Treatment-emergent adverse events (TEAE) excluded events that started and ended before start of study drug. Adverse events were reported down to the verbatim term. The adverse event terms were coded using MedDRA version 15.1. Where indicated in the tables or text, some adverse events are presented as grouped terms as defined in Appendix 9.2.

### 7.1.3 Pooling of Data

The analyses were conducted using the integrated datasets provided by the applicant rather than the datasets from the individual studies. Data for subjects in Protocols 101-02, 101-09, 101-10, 101-11 and 101-99 were used to develop the safety profile in patients with hematological malignancies. The term "INHL 150 mg BID subgroup" used in the text refers to subjects with FL, SLL, LPL or MZL treated with idelalisib 150 mg BID continuously in 28-day cycles.

Data for the volunteer subjects without malignancies in Protocols 101-01, 101-04, 101-05, 101-06, 313-0111, 313-0112, 313-0117, 313-0118, 313-0126, 313-0130 and 339-0101 were used to provide supporting safety information. The results of Protocol 101-06, a comparison of the pharmacokinetics of different formulations of idelalisib, showed that the (b) (4) provided a slightly higher exposure than the other formulations used. As this was a single-dose cross-over study that included only 5% of the volunteer population, all available data was used in the analyses.

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Safety Population

Safety data were available for 352 subjects treated with various doses and schedules of idelalisib for malignancy, and for 281 subjects without malignancy treated with single or multiple doses of idelalisib in volunteer studies. The demographics of subjects in the volunteer studies are described in Section 7.7.2.

The results of the analyses of safety shown in Sections 7.3, 7.4, 7.5 and 7.6 refer specifically to the 352 subjects with malignancies treated on Protocols 101-02, 101-09, 101-10, 101-11 and the Extension Study (101-99). The demographics of these 352 subjects are shown in Table 29. The proposed dose-schedule of idelalisib is 150 mg BID for 28 days of a 28-day cycle. Demographics are shown in Table 29 for the subgroup of 206 subjects treated with the proposed dose-schedule, and for the subset of 146 subjects specifically with FL, SLL, MZL or LPL (INHL) treated with the proposed dose-schedule (the INHL 150 mg BID subgroup).

**Table 29 Demographics of Safety Population**

	All Subjects n=352 <sup>a</sup>		Subjects Treated with 150 mg BID n=206		INHL <sup>b</sup> Subjects Treated with 150 mg BID n=146	
	N	%	N	%	N	%
Median Age (Range)	64 yrs (21-91 yrs)		62 yrs (21-87 yrs)		63 yrs (31-87 yrs)	
<b>Age Group</b>						
<65 yrs	185	51	121	59	83	57
≥65 yrs	167	46	85	41	63	43
<b>Gender</b>						
Male	235	65	128	62	92	63
Female	117	32	78	38	54	37
<b>Race</b>						
White	299	83	175	85	127	87
Other	13	4	11	5	8	5
Black	12	3	8	4	4	3
Asian	5	1	5	2	3	2

	All Subjects n=352 <sup>a</sup>		Subjects Treated with 150 mg BID n=206		INHL <sup>b</sup> Subjects Treated with 150 mg BID n=146		
	N	%	N	%	N	%	
Not Reported	22	6	6	3	3	2	
Native American	1	0	1	0	1	1	
<b>Ethnicity</b>							
Not Hispanic/Latino	149	41	149	72	127	87	
Hispanic Or Latino	12	3	10	5	7	5	
Not Reported	189	52	45	22	10	7	
<b>Diagnosis</b>							
FL	119	33	88	43	88	60	
SLL	40	11	31	15	31	21	
MZL	22	6	16	8	16	11	
LPL	19	5	11	5	11	8	
CLL	54	15	11	5	0	0	
MCL	40	11	6	3	0	0	
HL	25	7	25	12	0	0	
AML	12	3	2	1	0	0	
MM	12	3	12	6	0	0	
DLBCL	9	2	4	2	0	0	
<b>ECOG or WHO</b>							
Performance Status	0	139	38	85	41	66	45
	1	168	46	87	42	56	38
	2	20	6	12	6	6	4
<b>Weight Groups</b>							
<55 kg	31	9	20	10	11	8	
55-100 kg	267	74	160	78	116	79	
>100 kg	52	14	26	13	19	13	
Missing	2	1	0	0	0	0	

<sup>a</sup>Subjects with malignancy treated with any of 8 dose-schedules in Protocols 101-02, 101-09, 101-10, 101-11 and Extension Study

<sup>b</sup>Subjects with FL, SLL, LPL, MZL

**Review Comment: The INHL subset treated at the proposed dose for marketing includes only 146 subjects, a relatively small number considering the prevalence of these diseases. The INHL subset includes a slightly higher proportion of males and fewer subjects >65 years of age than expected from SEER statistics (Dores, Anderson, et al. 2007; Morton, Wang, et al. 2006; Shiels, Engels, et al. 2013), but all expected subgroups are represented in the demographic characteristics.**

## 7.2.2 Explorations for Dose Toxicity Relationship

Eight dose-schedules of idelalisib were tested in subjects with malignancies and eight dose levels in the volunteer studies. Exposure of subjects in the volunteer studies is described in section 7.7.2.

Table 30 shows the numbers of subjects with malignancies starting therapy at each of the eight dose-schedules. Results of a formal dose-escalation trial are discussed in section 7.5.1.

**Table 30 Idelalisib Starting Dose-Schedules**

	N	%
50 mg BID x 28 days	17	5
150 mg QD x 28 days	16	5
100 mg BID x 28 days	25	7
150 mg BID x 21 days	17	5
150 mg BID x 28 days	206	59
300 mg QD x 28 days	19	5
200 mg BID x 28 days	35	10
350 mg BID x 28 days	17	5
All	352	

The ADSL dataset provided dates of start and end of therapy (through follow-up on 99 if applicable); when therapy end dates were missing, these were imputed as the cut-off date provided in the data set. The duration on therapy for the safety population is shown in Table 31.

**Table 31 Time on Study**

Months	All Subjects n=352 <sup>a</sup>			Subjects Treated with 150 mg BID n=206			INHL <sup>b</sup> Subjects Treated with 150 mg BID n=146		
	N	%	Cum <sup>c</sup>	N	%	Cum <sup>c</sup>	N	%	Cum <sup>c</sup>
<1	37	11	100	18	9	100	10	7	100
1-<2	60	17	89	32	16	91	15	10	93
2-<3	28	8	72	16	8	75	10	7	83
3-<4	41	12	64	25	12	67	16	11	76
4-<5	20	6	52	12	6	55	7	5	65
5-<6	15	4	46	13	6	49	13	9	60
6-<9	44	13	42	27	13	43	23	16	51
9-<12	30	9	29	26	13	30	21	1	35
12-<18	35	10	20	21	10	17	19	13	21
18-<24	20	5	10	13	6	7	12	8	8
>=24	22	5	5	3	1	1	0	0	0

<sup>a</sup>Subjects with malignancy treated with any of 8 starting dose-schedules in Protocols 101-02, 101-09, 101-10, 101-11 and Extension Study

<sup>b</sup>Subjects with FL, SLL, LPL, MZL

<sup>c</sup>Cumulative percentage treated for at least the minimum duration

The protocols stipulated that the actual doses could be reduced or interrupted for toxicity, or increased for lack of efficacy. Treatment compliance was assessed by pill

count in all five studies, and by interrogation for dose modifications/interruptions in Protocols 101-09 and 101-10. The applicant submitted the dataset ADEX (M 1.11.13 Efficacy Information Amendment received 1/31/2014) with actual doses over time based on pill count, the retrospective interrogation for dosing compliance, and imputation. For imputed treatment compliance, duration of treatment was calculated as [(number of pills dispensed x strength of pills) – (number of pills returned x strength of pills)] / daily dose level prescribed by the investigator, If duration of treatment as calculated was negative, the duration was set to zero. Duration of treatment for a given interval was imputed for 39 (11%) of the subjects. Table 32 shows a summary of durations of treatment by the actual dose of idelalisib for all 352 subjects in the safety population. The majority of subjects were treated with idelalisib doses of 150 mg BID (69%), 100 mg BID (25%), or 200 mg BID (12%).

**Table 32 Duration of Treatment with Idelalisib by Actual Dose**

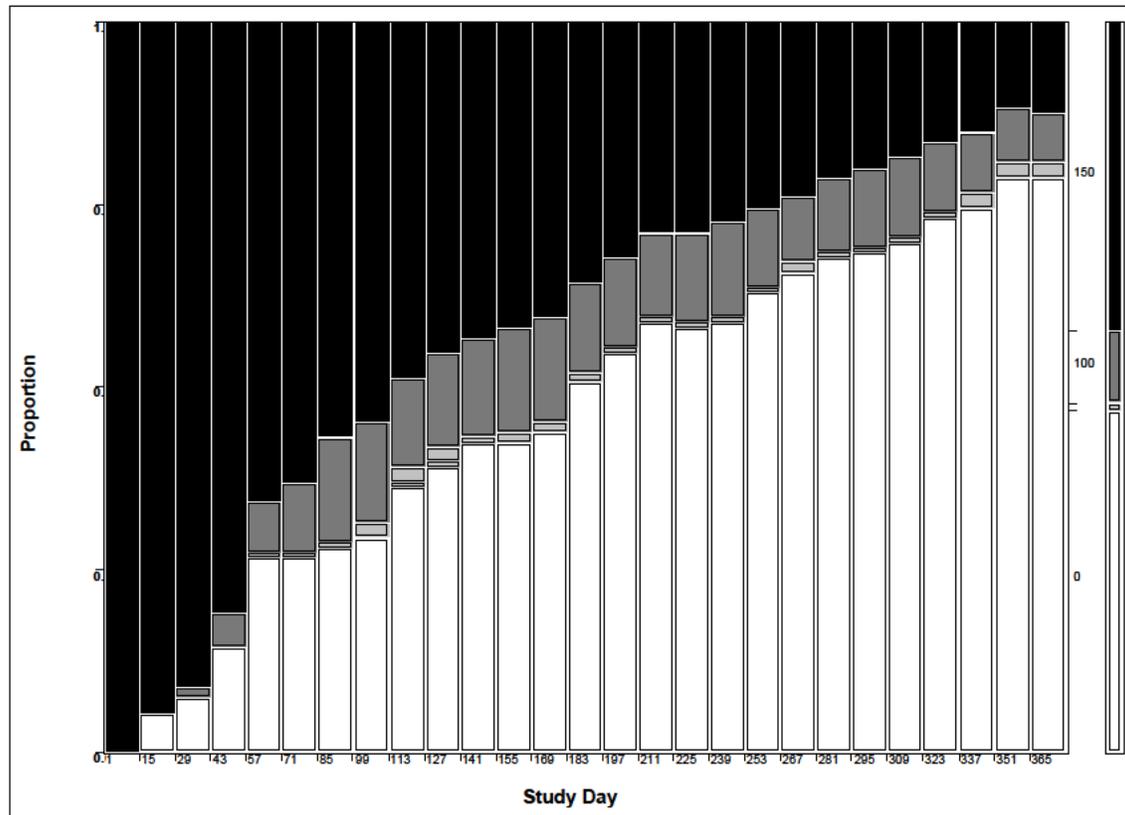
Duration (Months)	Numbers of Subjects Treated Anytime at the Dose (mg) and Schedule Indicated:											
	50 QD (n=2)	100 QD (n=6)	150 QD (n=21)	200 QD (n=4)	300 QD (n=19)	50 BID (n=22)	75 BID (n=19)	100 BID (n=88)	150 BID (n=243)	200 BID (n=43)	300 BID (n=7)	350 BID (n=18)
<1	2	2	3	2	3	5	8	13	34	13	2	4
1-<2	0	1	7	0	6	5	2	20	61	9	4	5
2-<3	0	0	0	0	1	2	5	8	29	4	1	2
3-<4	0	0	1	0	1	3	0	9	23	2	0	0
4-<5	0	0	2	0	1	3	0	9	12	1	0	2
5-<6	0	0	1	0	0	2	1	4	13	1	0	1
6-<9	0	1	1	0	0	1	2	7	29	4	0	2
9-<12	0	1	4	1	0	0	1	7	17	2	0	2
12-<18	0	0	1	1	3	0	0	7	14	2	0	0
18-<24	0	1	0	0	1	0	0	2	5	2	0	0
>=24	0	0	1	0	3	1	0	2	6	3	0	0

**Review Comment:** *There may be sufficient subjects treated with 100 mg BID, 150 mg BID and 200 mg BID to allow for a dose-toxicity assessment, but cohorts at doses higher or lower than those may need to be pooled to allow for detection of a signal.*

Figure 1 shows the change in dose over one year for the 146 INHL subjects who initiated treatment with idelalisib at 150 mg BID. Over 50% of the subjects were on a reduced dose or discontinued treatment at study day 113. Approximately half of the subjects were off treatment completely at study day 183.

**Figure 1 Daily Dosing: INHL Subjects Starting with Idelalisib 150 mg BID**

The legend bar at the right shows the color scheme for the BID doses shown. The proportions of subjects on 50 mg BID or 75 mg BID (light grey) are small.



### 7.2.3 Special Animal and/or In Vitro Testing

Results of the preclinical studies relevant to safety were summarized in Section 4.2. There were no issues raised by the preclinical reviewers of the in vivo preclinical testing that warranted clinical monitoring beyond that used routinely in development of oncolytic therapies. Additional preclinical studies not included in Section 4.2 are described below.

In study PC-312-3001, female dogs were treated with idelalisib at 15 mg/kg daily for 4-8 weeks. The applicant reported that transaminases rose and peaked days 13-27 of administration but normalized thereafter even with continued dosing. Inter-individual variation was noted. There were no test article-related changes in transferrin, inflammatory cytokines, or Kupffer cell function by MRI. At necropsy, affected animals

showed necrosis of centrilobular hepatocytes with occasional mononuclear aggregates. The applicant concluded there was hepatocellular damage due to idelalisib with secondary inflammation. Assessment of hepatic toxicities was included in routine adverse event monitoring in the clinical trials. An analysis of genetic risk for idelalisib-related liver injury was also conducted as a substudy of Protocol 101-02, and the results are discussed in Section 7.4.5.

In an in vitro phototoxicity study using the 3T3 cell line (Study 9152-100254), the applicant reported that results were inconclusive regarding the effect of idelalisib, since the drug was toxic even in the absence of UVA exposure, but GS-563117, the primary metabolite, induced photosensitivity. Assessment of cutaneous toxicities was included in routine adverse event monitoring in the clinical trials.

In vitro study DR-4001 showed that idelalisib inhibited anti-IgM-mediated B cell proliferation (EC<sub>50</sub> 6 nM), fMLP-mediated neutrophil degranulation (EC<sub>50</sub> 119 nM), and anti-CD3-induced T cell proliferation (EC<sub>50</sub> 973 nM) in a dose-dependent manner. Inhibition of the B cell proliferative response and of neutrophil degranulation occurred at concentrations within the range sustained in the subjects treated with idelalisib 150 mg BID.

In vitro study DR-4024 showed that idelalisib inhibited BFU-E, CFU-GM and CFU-MK in a dose-dependent manner. The range of concentrations of idelalisib tested in this study included clinically-relevant levels.

Section 7.2.6 describes the additional analyses performed to assess for the clinical relevance of inhibition of the B cell proliferative response, neutrophil degranulation and hematopoietic colony growth that was observed in these in vitro studies.

#### **7.2.4 Routine Clinical Testing**

The schedule of safety evaluations for each protocol was described in Section 5.3. The frequency of monitoring was considered adequate within the context of the study. Adequacy of the duration of follow-up is discussed in Section 7.2.2 above.

#### **7.2.5 Metabolic, Clearance, and Interaction Workup**

Results of the studies of human pharmacokinetics and pharmacodynamics relevant to safety were summarized in Section 4.3. Issues raised included dosing in patients with organ dysfunction and potential drug-drug interaction involving CYP3A and CYP2C19. Since the eligibility criteria in the protocols for treatment of malignancy excluded individuals with organ dysfunction, no assessment of the impact of baseline organ dysfunction on safety in the subjects with malignancy was possible. Subgroup analyses based on concomitant medications are summarized in Section 7.5.5.

Data were available from volunteer studies to assess safety of idelalisib in subjects with renal or hepatic impairment, and when used in combination with reporter drugs in assessment for drug-drug interactions. Reviews of the safety data from these volunteer studies is provided in section 7.7.2.

## 7.2.6 Adverse Events of Special interest

Since idelalisib is a first-in-class agent, there were no class effects identified for review. There were four adverse events of special interest (AESI) pre-specified by the applicant in the ISS statistical analysis plan. Since blocking B cell receptor function is an on-target effect of idelalisib, FDA also chose to assess hypogammaglobulinemia. Pneumonia and hypersensitivity were also evaluated.

**Table 33 Search Strategy for Adverse Events of Special Interest**

Adverse Event of Special Interest	Search Level	Terms Used By Applicant	Terms Used By FDA
Transaminase elevation	PT	Laboratory tests only	Alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, hepatocellular injury, hepatotoxicity, transaminases increased
Diarrhea	PT	Diarrhea	Colitis, diarrhoea, diarrhoea haemorrhagic, enterocolitis (colitis coded as infection was not included)
Rash	PT	Dermatitis exfoliative, drug eruption, exfoliative rash, rash, rash erythematous, rash generalised, rash maculo-papular, rash macular, rash morbilliform, rash papular, and rash pruritic	Dermatitis, dermatitis exfoliative, dermatitis psoriasiform, drug eruption, eczema, erythema, exfoliative rash, rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, rash vesicular, skin exfoliation
Infections	SOC	Infections and infestations	Infections and infestations
Pneumonia	PT	Not done	Bronchopneumonia, interstitial lung disease, lower respiratory tract infection, lower respiratory tract infection bacterial, lung infection, lung infection pseudomonal, lung infiltration, organising pneumonia, pneumocystis jiroveci pneumonia, pneumonia, pneumonia aspiration, pneumonia bacterial, pneumonia cytomegaloviral, pneumonia fungal, pneumonia necrotising, pneumonia pneumococcal, pneumonia staphylococcal, pneumonia streptococcal, pneumonia viral, pneumonitis, respiratory syncytial virus infection, respiratory tract infection
Hypogamma globulinemia	PT	Not done	Hypogammaglobulinaemia, hypoglobulinaemia,

Adverse Event of Special Interest	Search Level	Terms Used By Applicant	Terms Used By FDA
Hypersensitivity	PT	Not done	Anaphylactic reaction, anaphylactic shock, contrast media allergy, drug hypersensitivity, hypersensitivity, iodine allergy, urticaria

Abbreviations: PT, preferred term

## 7.3 Major Safety Results

### 7.3.1 Deaths

The applicant reported that 57 subjects died on study, including 9 due to adverse events at least possibly related to idelalisib. FDA reviewed all 57 cases for root cause. The root causes of death were progressive disease for 33 (58%) subjects, infection for 16 (28%) subjects, and other adverse event for 8 (14%) subjects. For the purpose of determining relatedness, infections were considered related only when associated with drug-related neutropenia. There were seven fatal adverse events for which FDA could not exclude a possible relation to idelalisib:

- Case 1: Subject 119-09061 was an 87 year old man treated with idelalisib 150 mg BID for MZL. His dose was interrupted after 3 months on therapy and subsequently reduced to 100 mg BID when he had grade 3 fatigue and dyspnea. At about day 194, the subject was admitted with fever, hypotension, tachycardia, atrial fibrillation, and confusion. Chest X-ray showed pneumonia. A CBC showed an ANC of 0.4 Gi/L, hemoglobin 72 g/L, and platelets 196 Gi/L. He was diagnosed as having sepsis and started on broad spectrum antibiotics. He expired the same day.
- Case 2: Subject 2512-101604 was a 55 year old man treated with idelalisib 200 mg BID for CLL. His course was complicated by intermittent grade 3 neutropenia. After 3 months of therapy, he developed nausea, vomiting, fever, bone aches and “breathing hard with a cough.” He was discovered pulseless after a fall in the bathroom. No autopsy was performed. The investigator suspected an infection unrelated to idelalisib was the cause of death, and the sponsor agreed with that assessment.
- Case 3: Subject 119-09106 was a 52 year old man treated with idelalisib 150 mg BID for FL. His treatment was complicated by mild elevations in transaminases starting week 12. At day 375, a chest CT was performed to follow-up treatment of viral pneumonia. Results were reported as “worrisome,” and idelalisib was discontinued. The pulmonary process progressed to diffuse infiltrates, and he required respiratory support. A wedge biopsy of the right lower lobe showed “mixed interstitial inflammatory infiltrate, including eosinophils with edema, reactive pneumocytes, and rare foci of organizing pneumonitis...compatible with drug-induced pneumonitis.” Evaluations for infection were negative. The subject was

treated with high-dose corticosteroids starting day 383, but he continued to require respiratory support. Following development of pneumomediastinum and a pneumothorax, the subject expired on day 398.

- Case 4: Subject 149-09104 was a 75 year old woman treated with idelalisib 150 mg BID for FL. On day 253 the subject was admitted to hospital with fever, dry cough and shortness of breath that worsened despite use of oseltamivir and azithromycin. Imaging showed bilateral infiltrates with peripheral air bronchograms and no masses. Idelalisib was discontinued. A thrombus was found in the right basilica, subclavian and axillary veins. Evaluation found no infectious etiology. The respiratory insufficiency failed to improve on medical therapy, and she expired day 277.
- Case 5: Subject 2514-103806 was 65 year old man treated with idelalisib 100 mg BID for CLL. The subject was admitted to hospital day 2 of therapy with fever and neutropenia. He was found to have a pneumonia, acute renal failure, elevated uric acid and elevated phosphate. A diagnosis of tumor lysis syndrome was made. He was intubated for respiratory failure and started on broad spectrum antibiotics. Evaluation, including bronchoscopy, revealed no infectious etiology. Idelalisib was discontinued on day 5. On the following day, he developed hypotension, asymmetric pupils, and worsening hypoxemia. Head CT showed no hemorrhage. The subject expired acutely. The sponsor agreed with the investigator's assessment that the febrile neutropenia and pneumonia were possibly related to idelalisib.
- Case 6: Subject 502-09154 was a 66 year old man treated with idelalisib 150 mg BID for FL. His treatment was complicated by a "massive stroke" on day 126. Grade 1 diarrhea had started on day 102, and this worsened to grade 4. Evaluation of the diarrhea was negative for any infectious etiology, and it did not abate with any symptomatic therapies. He developed an ileus. On day 133, CT scan showed acute splenic infarct and abdominal adenopathy. There was no colonic mucosal thickening. An ischemic bowel event was suspected. His condition deteriorated, and the patient expired on day 135. Idelalisib had been continued until expiration. The applicant concluded that the subject expired from progressive disease. FDA found no documentation of progressive disease.
- Case 7: Subject 2539-111802 was a 74 year old man treated with idelalisib 75 mg BID for SLL. The dose was reduced to 50 mg BID after 18 months of therapy and subsequently re-escalated to 75 mg BID after an additional 8 months. After approximately 26 months of therapy, the subject was admitted with acute renal failure (creatinine 3.5 mg/dL), hyperkalemia and partial small bowel obstruction. Urinalysis showed >100 RBC and 5-10 WBC per high power field with hyaline casts. Renal ultrasound showed bilateral cortical thinning and no hydronephrosis. He was treated with broad spectrum antibiotics and medical interventions, but the creatinine increased to 4.4 mg/dL and lactic acid to 4.1 mmol/L. It was stated that he "probably

had a bowel rupture causing sepsis, acute renal failure and multiorgan system failure.” The subject expired the following day.

**Review Comment: Cases 1, 3 and 5 are consistent with fatal neutropenic infection, pneumonitis and tumor lysis syndrome, respectively, associated with idelalisib use. Cases 2 and 4 are supportive in that no other cause of death was found. Cases 6 and 7 appear to be infections with an intestinal event as an etiology; histologic evidence is lacking, but no cause other than idelalisib was found. Labeling should reflect the potentially fatal drug-related adverse reactions.**

**It is also noted that three of the fatal suspected events occurred after more than 6 months of treatment with idelalisib. It is not possible to derive a good estimate of the risk, since there are so few subjects treated for more than 6 months.**

### 7.3.2 Serious Adverse Events

An SAE occurred in 177 (50%) of treated subjects, 101 (49%) of subjects treated with idelalisib 150 mg BID, and 73 (50%) of subjects with INHL treated with idelalisib 150 mg BID. The distribution of SAEs by SOC is shown in Table 34.

**Table 34 Serious Adverse Events by SOC**

System Organ Class	All Subjects n=352 <sup>a</sup>		Subjects Treated with 150 mg BID n=206		INHL <sup>b</sup> Subjects Treated with 150 mg BID n=146	
	N	%	N	%	N	%
Infections And Infestations	95	27	49	24	31	21
Gastrointestinal Disorders	45	13	26	13	23	16
General Disorders And Administration Site Conditions	28	8	25	12	21	14
Respiratory, Thoracic And Mediastinal Disorders	34	10	19	9	17	12
Blood And Lymphatic System Disorders	30	9	16	8	12	8
Metabolism And Nutrition Disorders	13	4	10	5	10	7
Cardiac Disorders	10	3	6	3	6	4
Renal And Urinary Disorders	18	5	8	4	6	4
Neoplasms Benign, Malignant And Unspecified	10	3	4	2	4	3
Injury, Poisoning And Procedural Complications	8	2	3	1	3	2
Nervous System Disorders	5	1	3	1	3	2
Vascular Disorders	6	2	4	2	3	2
Immune System Disorders	2	1	2	1	2	1
Psychiatric Disorders	2	1	2	1	2	1
Skin And Subcutaneous Tissue Disorders	6	2	5	2	2	1
Hepatobiliary Disorders	2	1	1	0	1	1
Investigations	6	2	3	1	1	1
Musculoskeletal And Connective Tissue Disorders	4	1	1	0	1	1

<sup>a</sup>Subjects with malignancy treated with any of 8 dose-schedules in Protocols 101-02, 101-09, 101-10, 101-11 and Extension Study

<sup>b</sup>Subjects with FL, SLL, LPL, MZL

The SAE was reported by the applicant as at least possibly related to study therapy in 86 (24%) of treated subjects, 52 (25%) of subjects treated with idelalisib 150 mg BID, and 44 (30%) of subjects with INHL treated with idelalisib 150 mg BID. The most common SAEs ( $\geq 2\%$ ) in subjects with INHL treated with idelalisib 150 mg BID were pneumonia (10%), diarrhea (10%), pyrexia (5%), dehydration (2%), febrile neutropenia (2%) and neutropenia (2%).

### 7.3.3 Dropouts and/or Discontinuations

Overall, 202 (57%) of treated subjects had a dose interruption, reduction or discontinuation due to an adverse event. Treatment modification was at most a dose interruption or reduction for 132 (38%) of treated subjects, 81 (39%) of subjects treated with idelalisib 150 mg BID, and 60 (41%) of subjects with INHL treated with idelalisib 150 mg BID. Treatment was permanently discontinued in the setting of an adverse event for 70 (20%) of treated subjects, 40 (19%) of subjects treated with idelalisib 150 mg BID, and 34 (23%) of subjects with INHL treated with idelalisib 150 mg BID. The adverse events associated with withdrawal in INHL treated with idelalisib 150 mg BID are summarized in Table 35. The majority of the adverse events resulting in withdrawal were considered at least possibly related to idelalisib.

**Table 35 Adverse Events Resulting in Withdrawal**

Description	INHL <sup>a</sup> Subjects Treated with 150 mg BID n=146			
	n	%	Related	
			Yes (n)	No (n)
Pneumonia	9	6	7	2
Transaminases Increased	7	5	6	1
Diarrhea/Colitis	5	3	5	0
Autoimmune Disorder	2	1	1	1
Septic Shock	2	1	1	1
Cardiac Failure	1	<1	0	1
Failure To Thrive	1	<1	1	0
Febrile Neutropenia	1	<1	1	0
Herpes Zoster	1	<1	1	0
Mucosal Inflammation	1	<1	1	0
Myelodysplastic Syndrome	1	<1	0	1
Neutropenia	1	<1	1	0
Rash	1	<1	0	1
Toxoplasmosis	1	<1	0	1
Urinary Tract Infection	1	<1	1	0

<sup>a</sup>Subjects with FL, SLL, LPL, MZL

### 7.3.4 Significant Adverse Events

Adverse events of special interest (AESI) as described in Section 7.2.6 were assessed in the subjects with INHL treated with idelalisib 150 mg BID. A summary of the

incidences are shown in Table 36. Small differences between the results reported by the applicant and the FDA may be due to difference in search strategies (Section 7.2.6).

**Table 36 INHL 150 mg BID Cohort – Adverse Events of Special Interest**

Adverse Event	INHL <sup>a</sup> Subjects Treated with Idelalisib 150 mg BID (n=146)			
	Applicant		FDA	
	Gr $\geq$ 1	Gr $\geq$ 3	Gr $\geq$ 1	%Gr $\geq$ 3
Transaminase Elevation (MeDDRA Term)	-	-	37 (25%)	24 (16%)
Transaminase Elevation (Laboratory Results)	77 (53%)	26 (18%)	85 (59%)	26 (18%)
Diarrhea	62 (43%)	17 (12%)	65 (45%)	21 (14%)
Rash	23 (18%) <sup>b</sup>	4 (3%) <sup>b</sup>	34 (23%)	6 (4%)
Infection	-	33 (23%)	84 (58%)	33 (23%)
Pneumonia	-	11 (8%)	36 (25%)	24 (16%)
Hypogammaglobulinemia (MeDDRA Term)	-	-	5 (3%)	-
Hypogammaglobulinemia (Laboratory Results)	-	-	59 (44%)	-
Hypersensitivity	-	-	5 (3%)	2 (<1%)

See Section 7.2.6 for a description of the search strategies used

<sup>a</sup>Subjects with FL, SLL, LPL, MZL

<sup>b</sup>The applicant's analysis was limited to subjects in Protocol 101-09

***Transaminase Elevation*** - The applicant identified 77 (53%) subjects in the INHL 150 mg BID subgroup as having elevated transaminases, and 26 (18%) were grade  $\geq$ 3 (M 2.7.4 Summary of Clinical Safety, Appendix 8.1, Table 8.7.1). The median time to onset of elevated transaminases was 6 weeks (range, 1-48 weeks). The applicant reported that grade 1-2 elevations resolved without interruption of treatment with idelalisib, and that grade 3-4 elevation resolved at a median of 3 weeks (range, 1-8 weeks) after interruption of therapy.

FDA assessed the transaminase levels for 145 subjects in the INHL 150 mg BID subgroup with laboratory data available. An elevation in either AST or ALT was considered a positive finding. A grade  $\geq$ 1 elevation occurred in 59%, with median time to onset being day 41 (range, days 7-301). Median duration was 24 days (range, 7-140 days) where end dates were available. A grade  $\geq$ 3 elevation occurred in 18%, with median time to onset at day 43 (range, 14-204), and the median time to resolution to grade 0 was 40 days (range, 9-140 days). The action taken with the study drug in response to a toxicity was available only in the adverse event dataset ADAE. Based on the information for the 37 subjects in the INHL 150 mg BID subgroup with an adverse event in ADAE dataset using the grouped term elevated transaminases, 7 subjects had drug withdrawn, 6 interrupted use, and 9 had a dose reduction.

The applicant reported no cases of liver failure in the full safety population. Two cases that fulfilled the laboratory criteria for Hy's law were identified, but the applicant cited other potential etiologies for liver dysfunction and concluded that neither was a true Hy's law case. Descriptions of the two cases are provided:

**Case 1:** Subject 2514-103601 was a 62 year old woman treated with idelalisib 350 mg BID for MZL. The subject underwent endoscopic retrograde cholangiopancreatography 1 and 3 months prior to study in order to remove stones and manage a stent. Grade 1 transaminase elevation was first identified on study day 15. Persistent grade 3 neutropenia was noted on study day 28, and the subject was treated with pegfilgrastim. Tylenol was administered starting study day 37. Idelalisib was discontinued on study day 43 when the transaminases rose to grade 3. Other adverse events reported at that time included diarrhea, thrombocytopenia and rash. The narrative also described mild nausea, low grade fever and malaise. The neutrophil count had risen to 2.75 Gi/L at that time. ALT peaked at 22.7x ULN, AST at 13.6x ULN, and total bilirubin at 2.6x ULN. Alkaline phosphatase remained within normal limits. Tests for viral hepatitis were negative. Ultrasound showed no biliary obstruction, but a 4 mm gallstone or sludge was present. On study day 65, an MRI showed hepatosplenomegaly, common bile duct stones, adenomyomatosis of the gallbladder fundus and progression of lymphoma. The transaminases and total bilirubin normalized by study day 78. The subject was not rechallenged and withdrew from the study.

**Case 2:** Subject 5840-0003 was a 31 year old woman treated with idelalisib 150 mg BID for FL. On study day 12, idelalisib was held due to a grade 2 rash, and prednisone was administered. Hydrocodone and ibuprofen were given for pain. Elevated transaminases were first found on study day 18 (AST 3.5x ULN and ALT 1.6x ULN). Other adverse events reported included malaise, nausea and vomiting. The rash resolved by study day 22, and idelalisib was restarted at 100 mg BID, but treatment lasted only one day, since the transaminases continued to rise. ALT peaked at 114.2x ULN, AST at 136.4x ULN, and total bilirubin at 2.8x ULN. Alkaline phosphatase remained within normal limits. The transaminases and total bilirubin nearly normalized by study day 47, and the subject was withdrawn from the study.

**Review Comment:** *Idelalisib caused hepatotoxicity. Although there were no fatal cases in the INHL 150 mg BID subgroup, and this reviewer agrees that the potential Hy's law cases have confounding factors, the incidence of any elevation of transaminases is high (59%), and life-threatening or fatal cases may have been prevented by dose modification in response to close monitoring as part of the clinical trial procedures. Labeling will need to include a warning regarding the specific monitoring procedures and dose modifications to ensure safe use of the drug. Patients should also be aware that monitoring is needed for safe use. Since the true incidence is not reflected by the adverse event reporting, labeling should use the incidence by laboratory results instead.*

**Diarrhea** - The applicant identified 62 (43%) subjects in the INHL 150 mg BID subgroup as having diarrhea, and 17 (12%) were grade  $\geq 3$  (M 2.7.4 Summary of Clinical Safety, Table 57); 6 subjects had colitis and 3 had diarrhea and colitis, but it was not clear in the report if these were overlapping with those identified as having diarrhea. The median time to onset of diarrhea was 3.1 months (range, 0-14.7 months). The median time to resolution was 0.6 months.

A fatality in a subject with idelalisib-related diarrhea is described in Section 7.3.1. The applicant identified in their global database 44 (7%) subjects with an SAE of diarrhea for which there was no etiology found other than idelalisib use and/or associated with recurrence on rechallenge. The applicant reported that these subjects “generally presented...with a history of several weeks of watery diarrhea that responded poorly to antidiarrheals or to empiric treatment with antimicrobials” (M 2.7.4 Summary of Clinical Safety, Section 2.3.5.2.3). Time to onset of severe diarrhea was 7 months. Use of idelalisib was interrupted in nearly all cases. Treatment of diarrhea included budesonide for about half of the subjects, and nine received systemic steroids. Median time to resolution was approximately one month. Thirteen subjects were rechallenged, and 9 had recurrent diarrhea. About half were able to resume idelalisib at a reduced dose or with concurrent use of an enteric steroid.

In the INHL 150 BID subgroup, FDA found that 45% of the subjects had diarrhea using the grouped term, and the diarrhea was grade  $\geq 3$  for 14%. The diarrhea was categorized as related for 48 (33%) of the subjects. Median time to onset of any diarrhea was 96 days (range, 1-448 days), and the median time to onset of grade  $\geq 3$  diarrhea was 183 days (range, 26-400 days). The median duration of any diarrhea was 16 days (range, 1-337 days), and the median duration of grade  $\geq 3$  diarrhea was 20 days (range 2-250 days) where an end date was provided in the dataset. The action taken with the drug when the diarrhea occurred was withdrawal for 5 subjects, interruption for 13 subjects and reduction in dose for 7 subjects. In addition, 8 subjects were treated with enteric steroids, 4 subjects with octreotide, and 3 subjects with systemic steroids.

The applicant also submitted lower GI biopsy reports for eleven subjects with diarrhea from the full safety population. Two biopsies showed no abnormalities. The most frequent findings in the other nine biopsies were cryptitis, crypt abscesses, crypt loss and apoptotic cells with or without crypt distortion. Eosinophils in the infiltrate were identified in only one report. There were also three biopsies from the duodenum; one was normal and the other two described active inflammatory changes that were the same as in the lower GI biopsies performed concurrently.

***Review Comment: Idelalisib caused diarrhea, including life-threatening and fatal cases. Labeling will need to include a warning regarding the dose modifications to ensure safe use of the drug. Patients should also be aware that use of idelalisib should be discontinued in the event of severe diarrhea. There is insufficient information to conclude that idelalisib can be used safely with enteric steroids as a means of controlling diarrhea.***

***Rash*** – The applicant reported an incidence on rash by grouped term of 18% at any grade in Protocol 101-09 (subjects with INHL on idelalisib 150 mg BID); grade 3 rash occurred in 3%, and none had a grade 4 rash (M 2.7.4 Summary of Clinical Safety, Section 2.3.5.3.1). They described a typical grade 3 rash as a “maculopapular rash on the trunk and extremities that was occasionally associated with fever and/or pruritus and

that responded to treatment with diphenhydramine and/or topical or oral steroids” (M 2.7.4 Summary of Clinical Safety, Section 2.3.5.3). Four subjects with rash were rechallenged after resolution, and only one had recurrence of the rash.

In the INHL 150 BID subgroup, FDA found that 23% of the subjects had a rash using the grouped term, and the rash was grade 3 for 4%. The rash was categorized as related for 21 (14%) of the subjects. Median time to onset of rash was 66 days (range, 11-346 days). The action taken with the drug when the rash occurred was withdrawal for 1 subject, interruption for 3 subjects and reduction in dose for 2 subjects. In addition, 11 (8%) subjects received systemic steroids for treatment of rash.

The applicant also submitted skin biopsy reports for four subjects with rash from the full safety population. One biopsy showed no abnormalities. Three biopsies showed a perivascular and interstitial dermal infiltrate of lymphocytes and eosinophils with or without epidermal spongiosis.

***Review Comment: Idelalisib caused rash. which could be severe. Labeling will need to include dose modifications to ensure safe use of the drug. Patients should also be aware that use of idelalisib should be discontinued in the event of severe rash.***

***Infection*** – The applicant identified 33 (23%) subjects in the INHL 150 mg BID subgroup as having a grade  $\geq 3$  infection (M 2.7.4 Summary of Clinical Safety, Table 63). They reported that the incidence of infection decreased over time, but the analysis provided showed essentially no change in the incidence of grade  $\geq 3$  infection over time (M 2.7.4 Summary of Clinical Safety, Figure 6).

FDA found that 58% of the subjects in the INHL 150 mg BID subgroup developed an infection, and confirmed that 23% had a grade  $\geq 3$  infection. The most common infection was pneumonia. There were six fatal infections (3 pneumonia and 3 sepsis). Fourteen (10%) of the subjects had an opportunistic infection, including aspergillosis, candidiasis, cytomegalovirus disease, Herpes zoster, Pneumocystis pneumonia, and toxoplasmosis.

***Review Comment: The occurrence of opportunistic infections is relatively low and may reflect prior use of cytotoxic drugs in this heavily pretreated patient population. The occurrence of life-threatening and fatal infections related to neutropenia remains a concern.***

***Pneumonia*** – The applicant identified 11 (8%) subjects in the INHL 150 mg BID subgroup as having a grade  $\geq 3$  pneumonia (M 2.7.4 Summary of Clinical Safety, Table 63). They reported that the incidence of pneumonia did not change over time. The applicant also assessed pneumonitis as an SAE. They identified 7 SAEs of pneumonitis on idelalisib monotherapy (M 2.7.4 Summary of Clinical Safety, Section 2.3.5.5). In 5 of these cases, there was no infectious etiology found. Time to onset ranged from 3 weeks to 1 year on idelalisib. The pneumonitis resolved after treatment

with steroids. Three subjects were rechallenged with idelalisib without recurrence of the pneumonitis. The applicant also calculated that the incidence rate of pneumonia overall was 0.16 per person-year (grade 3 pneumonia incidence rate 0.08 per person-year).

FDA identified 36 (25%) subjects in the INHL 150 mg BID subgroup with the grouped term “Pneumonia” according to Table 33. With regard to specific preferred terms, there were 16 Pneumonia, 4 Pneumonitis, 3 Interstitial Lung Disease, 3 Pneumonia Aspiration, 3 Respiratory Tract Infection, 2 Bronchopneumonia, 2 Lower Respiratory Tract Infection, 2 Lung Infection, 2 Lung Infiltration, and one each for Lung Infection Pseudomonal, Pneumocystis Jiroveci Pneumonia, Pneumonia Cytomegaloviral, Pneumonia Necrotising, Pneumonia Staphylococcal, Pneumonia Streptococcal, Respiratory Syncytial Virus Infection. There were 8 (5%) subjects who did not have a Preferred Term listed as infection. For these 8 subjects, median time to onset of the event was 151 days (range, 93-378). Six were considered related to idelalisib. Five had treatment with corticosteroids. Four had idelalisib withdrawn, while treatment was unchanged or interrupted only temporarily for the other four without recurrence after resolution. One fatal case is described in Section 7.3.1 above.

The applicant also submitted lung biopsy reports for five subjects from the full safety population with pneumonitis and no infectious etiology. Organizing pneumonia was seen in all five cases. In addition, one reported acute inflammation, one had a mononuclear infiltrate with scattered eosinophils and poorly formed granulomata, and one had a mixed interstitial infiltrate with eosinophils and reactive pneumocytes.

***Review Comment: The available evidence suggests that idelalisib may be a direct cause of lung toxicity, including life-threatening and fatal cases. The incidence is unclear, as the diagnostic criteria have not been established. Although five subjects with pneumonitis presumed to be drug-induced were treated with steroids, the optimal approach to therapy has not been established. Labeling will need to include a warning regarding the dose modifications to ensure safe use of the drug. Patients should also be aware that use of idelalisib should be discontinued in the event of symptoms of pneumonia. Additional studies are warranted to better characterize the incidence, diagnosis and treatment of idelalisib-related pneumonitis.***

***Hypogammaglobulinemia*** – There were 135 subjects in the INHL 150 mg BID subgroup with IgG levels measured after start of therapy. Of these, 59 (44%) had an IgG level below 4 g/L, but the low IgG level was not pre-existing for only 19 (14%) subjects. Replacement therapy with intravenous immunoglobulin was listed as a concomitant medication for only 8 subjects. Five (3%) subjects were identified by FDA as having an adverse event under the term “hypogammaglobulinaemia.”

With regard to B cell subset number, the applicant noted in the Clinical Study Report for Protocol 101-09 (Section 11.7.2) that there was no change over time in the number of B cells by flow cytometry in the study subjects treated with idelalisib. Since no integrated

dataset was submitted to the NDA, FDA could not determine the incidence of abnormalities in B cell number in the INHL 150 mg BID subgroup.

The applicant did provide an analysis of the correlation of low IgG with pneumonia in the safety population. The incidence of pneumonia did not differ by whether the worst postbaseline IgG level was normal vs abnormal (11% vs 14%, M1.11.3 Efficacy Information Amendment dated 2/17/2014, Table 9). They also used a Cox proportional hazards model of time to first pneumonia with IgG level as a time-dependent variable to test for an association between pneumonia and degree of severity of hypogammaglobulinemia. There was a numerical trend for increasing risk of pneumonia with decreasing IgG level (HR 1.06, 95% CI 0.49-2.26 for IgG 2 to <4 g/L; HR 1.99, 95% CI 0.78-5.11 for IgG <2 g/L), but the results were not statistically significant (M1.11.3 Efficacy Information Amendment dated 2/17/2014, Table 11).

***Review Comment: The available evidence suggests that idelalisib may cause hypogammaglobulinemia in a small proportion of subjects. However, the subjects in the majority of subjects in these studies were treated for a relatively short period of time, and the incidence of hypogammaglobulinemia may be higher with prolonged therapy. Additional studies are warranted to better characterize the risk of hypogammaglobulinemia during prolonged treatment with idelalisib.***

***Hypersensitivity*** – Five subjects had a hypersensitivity AESI (2 anaphylactic reactions, 1 contrast media allergy, 1 drug hypersensitivity, and 1 hypersensitivity), and all were considered related to concomitant medications. Idelalisib was interrupted temporarily for one subject with an anaphylactic reaction to ampicillin, and the remainder continued idelalisib without change in dose.

***Review Comment: There are no confirmed cases of hypersensitivity to idelalisib.***

## **7.4 Supportive Safety Results**

### **7.4.1 Common Adverse Events**

A TEAE was reported by 99% of the subjects with malignancy treated with idelalisib on Protocols 101-02, 101-09, 101-10, 101-11 and the Extension Study. The numbers of subjects with adverse events by SOC are shown in Table 37 in decreasing order of incidence in the INHL 150 mg BID subgroup.

**Table 37 Treatment-Emergent Adverse Events by SOC**

System Organ Class	All Subjects n=352 <sup>a</sup>		Subjects Treated with Idelalisib 150 mg BID n=206		INHL <sup>b</sup> Subjects Treated with Idelalisib 150 mg BID n=146	
	n	%	n	%	n	%
Gastrointestinal Disorders	233	66	139	67	105	72
General Disorders And Administration Site Conditions	235	67	134	65	97	66
Infections And Infestations	198	56	110	53	84	58
Respiratory, Thoracic And Mediastinal Disorders	171	49	100	49	74	51
Skin And Subcutaneous Tissue Disorders	159	45	95	46	69	47
Investigations	165	47	94	46	67	46
Blood And Lymphatic System Disorders	155	44	88	43	61	42
Metabolism And Nutrition Disorders	128	36	80	39	55	38
Nervous System Disorders	122	35	72	35	55	38
Musculoskeletal And Connective Tissue Disorders	123	35	70	34	49	34
Vascular Disorders	57	16	37	18	30	21
Psychiatric Disorders	60	17	33	16	28	19
Renal And Urinary Disorders	49	14	26	13	19	13
Cardiac Disorders	30	9	19	9	14	10
Eye Disorders	28	8	17	8	14	10
Injury, Poisoning And Procedural Complications	35	10	17	8	12	8
Immune System Disorders	14	4	12	6	10	7
Reproductive System And Breast Disorders	14	4	10	5	9	6
Hepatobiliary Disorders	18	5	12	6	7	5
Neoplasms Benign, Malignant And Unspecified	16	5	7	3	7	5
Ear And Labyrinth Disorders	14	4	7	3	4	3
Surgical And Medical Procedures	2	1	1	0	1	1
Congenital, Familial And Genetic Disorders	1	0	0	0	0	0

<sup>a</sup>Subjects with malignancy treated with any of 8 dose-schedules in Protocols 101-02, 101-09, 101-10, 101-11 and Extension Study

<sup>b</sup>Subjects with FL, SLL, LPL, MZL

The numbers of subjects with common TEAEs ( $\geq 10\%$ ) by PT are shown in Table 38 in decreasing order of incidence in the INHL 150 mg BID subgroup. Using grouped terms (see Section 7.1.2), the TEAEs reported for at least 20% of the INHL 150 mg BID subgroup were diarrhea (45%), fatigue (32%), cough (30%), nausea (28%), pyrexia (27%), neutropenia (27%), elevated transaminases (25%), pneumonia (25%), rash (23%), and abdominal pain (21%).

**Table 38 Common Treatment-Emergent Adverse Events**

Preferred Term	All Subjects n=352 <sup>a</sup>		Subjects Treated with Idelalisib 150 mg BID n=206		INHL <sup>b</sup> Subjects Treated with Idelalisib 150 mg BID n=146	
	n	%	n	%	n	%
<b>Any Event</b>	348	99	203	99	146	100
Diarrhea	125	36	77	37	62	42
Fatigue	115	33	62	30	47	32
Cough	82	23	60	29	44	30

Preferred Term	All Subjects n=352 <sup>a</sup>		Subjects Treated with Idelalisib 150 mg BID n=206		INHL <sup>b</sup> Subjects Treated with Idelalisib 150 mg BID n=146	
	n	%	n	%	n	%
Nausea	90	26	56	27	41	28
Pyrexia	94	27	59	29	40	27
Neutropenia	76	22	49	24	37	25
Thrombocytopenia	62	18	39	19	27	18
Alanine Aminotransferase Increased	64	18	35	17	26	18
Dyspnea	46	13	33	16	26	18
Decreased Appetite	48	14	32	16	25	17
Abdominal Pain	39	11	31	15	23	16
Aspartate Aminotransferase Increased	65	18	35	17	23	16
Rash	62	18	32	16	22	15
Vomiting	51	14	28	14	20	14
Weight Decreased	29	8	21	10	19	13
Asthenia	35	10	23	11	18	12
Upper Respiratory Tract Infection	51	14	23	11	18	12
Anemia	57	16	28	14	16	11
Back Pain	40	11	22	11	16	11
Headache	40	11	21	10	16	11
Pneumonia	46	13	22	11	16	11
Insomnia	33	9	19	9	15	10
Night Sweats	41	12	22	11	15	10
Edema Peripheral	37	11	21	10	15	10

<sup>a</sup>Subjects with malignancy treated with any of 8 dose-schedules in Protocols 101-02, 101-09, 101-10, 101-11 and Extension Study

<sup>b</sup>Subjects with FL, SLL, LPL, MZL

The numbers of subjects with severe (grades 3-5) TEAEs ( $\geq 2\%$ ) by PT are shown in Table 39 in decreasing order of incidence in the INHL 150 mg BID subgroup. Using grouped terms (see Section 7.1.2), the severe TEAEs reported for at least 5% of subjects in the INHL 150 mg BID subgroup were neutropenia (21%), elevated transaminases (16%), pneumonia (16%), diarrhea (14%) and thrombocytopenia (6%).

**Table 39 Severe Treatment-Emergent Adverse Events**

Preferred Term	All Subjects n=352 <sup>a</sup>		Subjects Treated with Idelalisib 150 mg BID n=206		INHL <sup>b</sup> Subjects Treated with Idelalisib 150 mg BID n=146	
	n	%	n	%	n	%
<b>Any Severe Event</b>	256	73	138	67	103	71
Neutropenia	56	16	37	18	28	19
Alanine Aminotransferase Increased	40	11	21	10	17	12
Diarrhea	33	9	18	9	17	12
Aspartate Aminotransferase Increased	28	8	13	6	12	8
Pneumonia	39	11	17	8	11	8
Thrombocytopenia	31	9	16	8	9	6
Anemia	28	8	13	6	6	4

Preferred Term	All Subjects n=352 <sup>a</sup>		Subjects Treated with Idelalisib 150 mg BID n=206		INHL <sup>b</sup> Subjects Treated with Idelalisib 150 mg BID n=146	
	n	%	n	%	n	%
Dehydration	10	3	7	3	6	4
Febrile Neutropenia	18	5	8	4	6	4
Hypokalemia	7	2	7	3	6	4
Colitis	11	3	5	2	5	3
Dyspnea	6	2	6	3	5	3
Pneumonitis	5	1	4	2	4	3
Abdominal Pain	4	1	4	2	3	2
Asthenia	5	1	3	1	3	2
Fatigue	7	2	3	1	3	2
Hepatic Enzyme Increased	4	1	3	1	3	2
Hypercalcemia	6	2	5	2	3	2
Hypotension	5	1	3	1	3	2
Hypoxia	5	1	5	2	3	2
Edema Peripheral	5	1	3	1	3	2
Pleural Effusion	4	1	3	1	3	2
Pulmonary Embolism	8	2	3	1	3	2
Vomiting	5	1	4	2	3	2

<sup>a</sup>Subjects with malignancy treated with any of 8 dose-schedules in Protocols 101-02, 101-09, 101-10, 101-11 and Extension Study

<sup>b</sup>Subjects with FL, SLL, LPL, MZL

The numbers of subjects with suspected (related at least possibly) TEAEs ( $\geq 5\%$ ) by PT are shown in Table 40 in decreasing order of incidence in the INHL 150 mg BID subgroup. Using grouped terms (see Section 7.1.2), the suspected TEAEs reported for at least 20% of subjects in the INHL 150 mg BID subgroup were diarrhea (33%), elevated transaminases (24%), and neutropenia (23%).

**Table 40 Suspected Treatment-Emergent Adverse Events**

Preferred Term	All Subjects n=352 <sup>a</sup>		Subjects Treated with Idelalisib 150 mg BID n=206		INHL <sup>b</sup> Subjects Treated with Idelalisib 150 mg BID n=146	
	n	%	n	%	n	%
<b>Any Suspected Event</b>	264	75	157	76	119	82
Diarrhea	74	21	50	24	45	31
Neutropenia	50	14	34	17	33	23
Alanine Aminotransferase Increased	62	18	34	17	25	17
Fatigue	49	14	31	15	25	17
Nausea	53	15	32	16	25	17
Aspartate Aminotransferase Increased	59	17	32	16	22	15
Pyrexia	28	8	22	11	20	14
Thrombocytopenia	30	9	23	11	19	13
Vomiting	32	9	20	10	15	10
Decreased Appetite	24	7	16	8	13	9
Rash	38	11	17	8	13	9

Preferred Term	All Subjects n=352 <sup>a</sup>		Subjects Treated with Idelalisib 150 mg BID n=206		INHL <sup>b</sup> Subjects Treated with Idelalisib 150 mg BID n=146	
	n	%	n	%	n	%
Cough	15	4	13	6	12	8
Asthenia	17	5	13	6	11	8
Weight Decreased	15	4	12	6	10	7
Pneumonia	17	5	10	5	9	6
Upper Respiratory Tract Infection	14	4	9	4	9	6
Abdominal Pain	10	3	10	5	8	5
Dyspnea	11	3	10	5	8	5
Headache	15	4	9	4	8	5
Leukopenia	11	3	10	5	8	5
Chills	16	5	11	5	7	5
Dehydration	11	3	7	3	7	5
Stomatitis	13	4	8	4	7	5

<sup>a</sup>Subjects with malignancy treated with any of 8 dose-schedules in Protocols 101-02, 101-09, 101-10, 101-11 and Extension Study

<sup>b</sup>Subjects with FL, SLL, LPL, MZL

#### 7.4.2 Vital Signs

The applicant provided no integrated analysis of vital signs. The integrated dataset included only systolic and diastolic blood pressures. A diastolic blood pressure greater than or equal to 100 mm Hg was recorded for 4% of the 352 subjects treated with idelalisib monotherapy; there was no relationship between the rate of elevated diastolic blood pressure and starting dose of idelalisib. For the subgroup of subjects with INHL treated with idelalisib 150 mg BID, 3% had a treatment-emergent elevated diastolic blood pressure recorded.

### 7.4.3 Laboratory Findings

Table 41 shows the incidence of worst post baseline abnormality in common laboratory tests in the INHL 150 mg BID subgroup as assessed by FDA.

**Table 41 INHL 150 mg BID Cohort - Maximal Laboratory Abnormalities**

Laboratory Abnormality	Evaluable <sup>a</sup>	Any Grade <sup>b</sup>		Grade 3 or Higher <sup>d</sup>	
		n	%	n	%
Anemia	145	91	63	2	1
Neutropenia	145	87	60	40	28
Lymphopenia	145	81	56	45	31
Alanine aminotransferase increased	145	76	52	26	18
Thrombocytopenia	145	69	48	12	8
Aspartate aminotransferase increased	145	67	46	17	12
Gamma glutamyl transferase increased	145	57	39	9	6
Elevated alkaline phosphatase	145	49	34	2	1
Hypoalbuminemia	144	43	30	2	1
Hypertriglyceridemia	140	41	29	3	2
Creatinine elevated	145	38	26	0	0
Hyponatremia	144	33	23	4	3
Hyperglycemia <sup>c</sup>	145	32	22	7	5
Hypokalemia	144	21	15	5	3
Hyperbilirubinemia	145	17	12	1	1
Hypercholesterolemia	140	17	12	0	0
Hypoglycemia	145	16	11	0	0
Hypernatremia	144	15	10	0	0
Hypercalcemia	144	14	10	3	2
Hypophosphatemia	141	11	8	3	2
Hypocalcemia	144	6	4	0	0
Hyperkalemia	144	2	1	0	0
Anemia	145	91	63	2	1

<sup>a</sup>Includes only subjects with INHL (FL, SLL, LPL, MZL) treated with idelalisib 150 mg BID

<sup>b</sup>Graded according to CTCAE version 4

<sup>c</sup>Any grade hyperglycemia includes only grades 2 or higher.

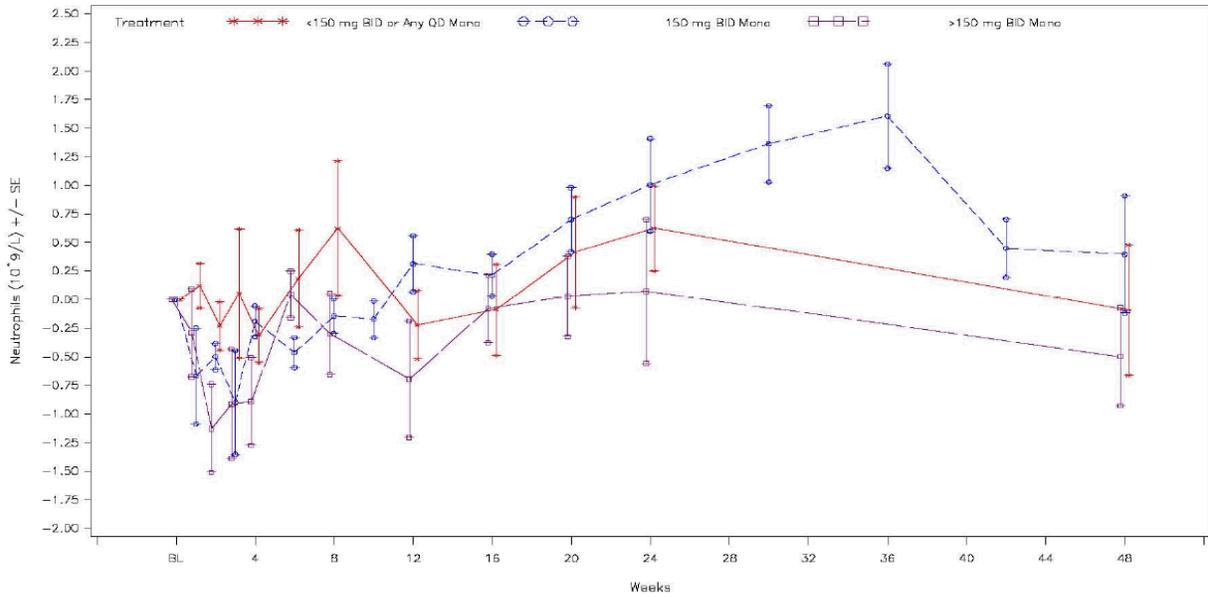
The applicant identified elevated transaminases as the major abnormality in chemistry parameters, and their results were discussed in Section 7.3.4. They also identified grade 1-2 abnormalities in albumin, cholesterol, phosphate and triglycerides for a substantial proportion of subjects in the full monotherapy safety population (M 2.7.4 Summary of Clinical Safety, Section 3.2). Most of the cases of hypertriglyceridemia were within the normal range for the laboratory, but 53 (15%) subject had grade 2 hypertriglyceridemia that was outside the normal range.

**Review Comment: It is unclear whether the low level of hypertriglyceridemia represents a safety issue, since the cases may have been pre-existing or postprandial. The adverse event dataset includes only a single report of hypertriglyceridemia that was possibly related to idelalisib; the event occurred at grade 2 and the dose was not modified. Additional information from studies with longer use of idelalisib would be helpful.**

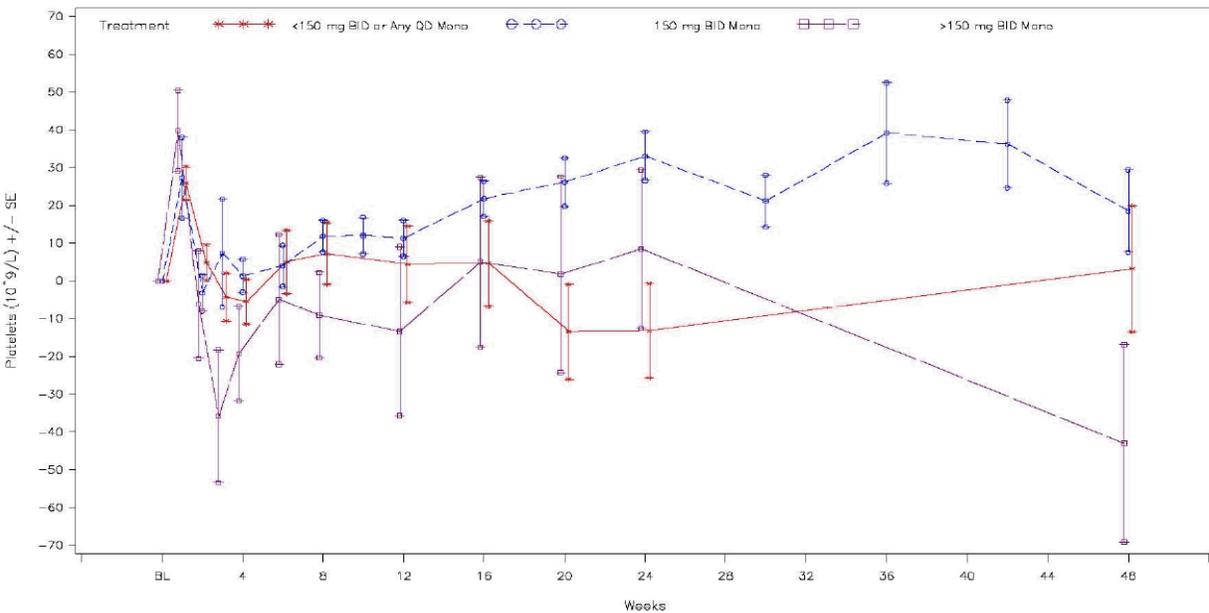
The applicant observed “clinically favorable changes” in hematological parameters with continuous administration of idelalisib in the INHL 150 mg BID subgroup ((M 2.7.4 Summary of Clinical Safety, Section 3.1.1 and Figures 11B, 15B and 19B). Graphical depictions are shown in Figure 2.

**Figure 2 Changes in Hematological Parameters for INHL Subjects by Dose Group**

**A. Change in Neutrophils (From M 2.7.4 Summary of Clinical Safety, Figure 11B)**



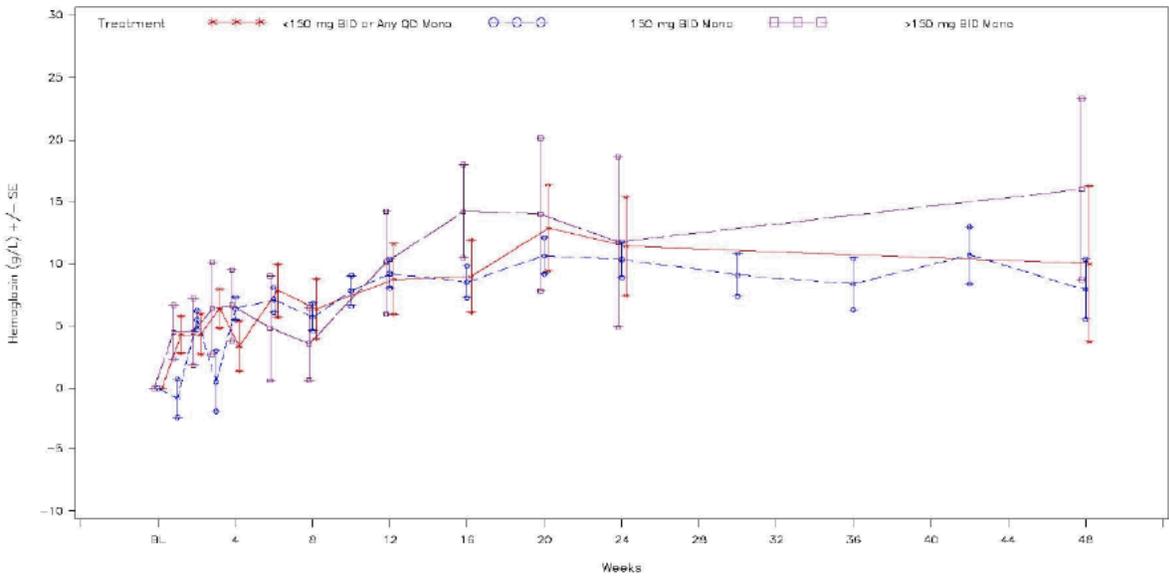
**B. Change in Platelets (From M 2.7.4 Summary of Clinical Safety, Figure 15B)**



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**C. Change in Hemoglobin (From M 2.7.4 Summary of Clinical Safety, Figure 19B)**



Shift tables were constructed by FDA for the hematological parameters from the INHL 150 mg BID subgroup (Tables Table 42, Table 43, Table 44 ). Grade 3-4 neutropenia occurred in 25 (20%) of 125 subjects with no or mild neutropenia at baseline, and grade 3-4 thrombocytopenia occurred in 8 (6%) of 133 subjects with no or mild thrombocytopenia at baseline. A new grade 3 anemia was rare (<1%) without pre-existing anemia, and an erythropoietin stimulating agent was used by only 7 subjects.

**Table 42 Shift Table - Neutropenia**

Baseline Grade	Maximum Grade After Start of Idelalisib <sup>a</sup>									
	Grade 0		Grade 1		Grade 2		Grade 3		Grade 4	
	n	%	n	%	n	%	n	%	n	%
Grade 0	74	80	14	15	1	1	1	1	3	3
Grade 1	1	3	24	60	11	28	3	8	1	3
Grade 2	0	0	6	86	1	14	0	0	0	0
Grade 3	0	0	0	0	0	0	2	67	1	33
Grade 4	0	0	0	0	0	0	0	0	1	100

<sup>a</sup> Graded according to CTCAE version 4. The analysis includes only subjects with INHL (FL, SLL, LPL, MZL) treated with idelalisib 150 mg BID. Subjects with missing baseline or posttreatment data are excluded.

**Table 43 Shift Table - Thrombocytopenia**

Baseline Grade	Maximum Grade After Start of Idelalisib <sup>a</sup>									
	Grade 0		Grade 1		Grade 2		Grade 3		Grade 4	
	n	%	n	%	n	%	n	%	n	%
Grade 0	74	80	14	15	1	1	1	1	3	3
Grade 1	1	3	24	60	11	28	3	8	1	3
Grade 2	0	0	6	86	1	14	0	0	0	0
Grade 3	0	0	0	0	0	0	2	67	1	33
Grade 4	0	0	0	0	0	0	0	0	1	100

<sup>a</sup> Graded according to CTCAE version 4. The analysis includes only subjects with INHL (FL, SLL, LPL, MZL) treated with idelalisib 150 mg BID. Subjects with missing baseline or posttreatment data are excluded.

**Table 44 Shift Table - Anemia**

Baseline Grade	Maximum Grade After Start of Idelalisib <sup>a</sup>							
	Grade 0		Grade 1		Grade 2		Grade 3	
	n	%	n	%	n	%	n	%
Grade 0	49	69	19	27	3	4	0	0
Grade 1	5	9	30	56	17	32	1	2
Grade 2	0	0	8	42	10	53	1	5
Grade 3	0	0	0	0	1	100	0	0

<sup>a</sup> Graded according to CTCAE version 4. The analysis includes only subjects with INHL (FL, SLL, LPL, MZL) treated with idelalisib 150 mg BID. Subjects with missing baseline or posttreatment data are excluded.

**Review Comment:** *The shift tables demonstrate that idelalisib is associated with severe or life-threatening neutropenia and thrombocytopenia. Even though the incidences are low, the severity warrants labeling with a warning regarding monitoring and dose modifications to ensure safe use of the drug. Patients should also be aware that monitoring is needed for safe use. Since the true incidence is not reflected by the adverse event reporting, labeling should use the incidence by laboratory results instead.*

#### 7.4.4 Electrocardiograms (ECGs)

For the 146 subjects with INHL treated with idelalisib 150 mg BID, there were no ECG-related TEAE in the SOC Investigations. ECG-related TEAE in the SOC Cardiac disorders included atrial fibrillation (3%), tachycardia (3%), sinus tachycardia (1%), supraventricular tachycardia (1%), and atrioventricular block (1%).

ECGs were performed at baseline and on cycle 1, days 1 and 28 in Protocol 101-02, and at baseline, on study day 113 and at end of therapy for Protocol 101-09. The applicant identified “no clinically concerning, treatment-emergent prolongation of the QT interval or ECG abnormalities” in these studies (Module 2.7.4 Summary of Clinical Safety Section 4).

This reviewer evaluated the results available for 97 subjects with INHL treated with idelalisib 150 mg BID who had post-treatment ECG results. In this subgroup, ECG

results were available at a median of 113 days (range 1-560 days) after start of therapy, 58% of which were performed between study days 100 and 148. None of the 97 subjects was reported to have a clinically significant ECG abnormality after start of treatment. The median (range) absolute change from baseline was 0 (-86 to +200) msec for the PR interval, 0 (-44 to +40) msec for the QRS interval, -1 (-45 to +92) msec for QTcB and 0 (-44 to +67) msec for QTcF. In the outlier analysis, no subject had a QTcF >500 msec, 1 subject had a new QTcF >480 msec, and 2 subjects had an increase in QTcF >60 msec from baseline.

A thorough QT study was performed in healthy subjects. The results are described in Section 4.4. The IRT reviewer concluded that idelalisib had no meaningful effects on QT, PR or QRS intervals.

***Review comment: There were no consistent effects of idelalisib on ECGs in the study population. This result is consistent with the thorough QT study.***

#### **7.4.5 Special Safety Studies**

The applicant conducted a genome-wide association study to determine if there were common genetic variants or rare functional genetic variants that correlated with drug-induced liver toxicity. Samples for genetic testing were available from the 191 subjects in Protocol 101-02. Subjects were classified as having or not having drug-induced liver injury by an independent panel of hepatologists on the basis of review of “subject records.” Subjects were excluded if they were lost to follow-up during within 8 weeks from initiation of therapy, were not of European ancestry, or had samples that could not be genotyped or sequenced. The analysis included 144 subjects with successful genotyping and 138 subjects with successful exome sequencing. The applicant reported that after correction for multiple testing, there was no significant association between any specific genetic variant and drug-induced liver injury, or between any rare functional variant and drug-induced liver injury.

***Review comment: The report does not identify which subjects were dropped from the initial population, so whether the selected subgroup is representative of the whole population is not clear. Further, the analysis did not appear to take dose into account. This reviewer concludes that the results of the analysis may not be interpretable due to these deficiencies.***

#### **7.4.6 Immunogenicity**

There were no studies of anti-drug antibodies performed.

## 7.5 Other Safety Explorations

### 7.5.1 Dose Dependency for Adverse Events

The applicant conducted a formal dose escalation study of idelalisib monotherapy (Protocol 101-02 described in Section 5.3.2.1). The dose escalation phase followed the 3+3 rule with DLT defined as grade 4 hematologic AE persisting for  $\geq 7$  days or any Grade  $\geq 3$  nonhematologic toxicity at least possibly related to study drug and occurring by day 28. Up to 25% DLT was allowed in the expansion phase as a stopping rule.

There were 191 subjects with advanced hematological malignancies accrued to Protocol 101-02. The applicant reported that “No DLTs were observed during the initial dose escalation phase. During cohort expansion, elevated ALT/AST was observed in a subject dosed at <sup>(b) (4)</sup> 350 mg BID and met the definition of DLT. Enrollment at that dose level was stopped. Lower doses were tested and elevated ALT/AST values that met the definition of DLT occurred in the 200 mg BID, 300 QD, and 150 mg BID dose cohorts. Seven subjects had DLTs for a total of 12 DLTs. Because the rate of DLT at any dose level tested was always less than the pre-specified 25%, no MTD was defined” (Protocol 101-02 Clinical Study Report, 6/18/2013, page 8). “Given that the exposure was not dose-proportional between 200 mg BID and 350 mg BID, and the PK data at the 100 mg BID dose showed exposures were substantially lower than the 200 mg BID dose, an intermediate level of 150 mg BID was selected” (Protocol 101-02 Clinical Study Report, 6/18/2013, page 191).

The incidences of adverse events at any grade in at least 10 subjects overall in Protocol 101-02 are listed in Table 45 in decreasing frequency in the highest dose cohort.

**Table 45 Protocol 101-02: TEAE by Dose Cohort**

Preferred Term	50 mg BID (n=17)	150 mg qD (n=16)	100 mg BID (n=25)	150 mg BID x 21 (n=17)	300 mg qD (n=19)	150 mg BID (n=45)	200 mg BID (n=35)	350 mg BID (n=17)
AST Increased	12%	6%	28%	6%	16%	16%	20%	53%
ALT Increased	12%	6%	28%	6%	26%	13%	17%	41%
Nausea	29%	13%	24%	24%	11%	24%	26%	35%
Neutropenia	24%	0	4%	18%	21%	13%	20%	35%
Diarrhea	41%	38%	24%	47%	21%	36%	26%	29%
Fatigue	35%	25%	36%	41%	42%	20%	40%	29%
Edema Peripheral	18%	6%	4%	0	0	16%	11%	29%
Pyrexia	24%	19%	20%	12%	21%	38%	29%	24%
Rash	12%	13%	16%	29%	37%	22%	23%	24%
Constipation	18%	6%	4%	6%	5%	18%	11%	24%
Thrombocytopenia	12%	6%	12%	12%	5%	16%	11%	24%
Anemia	18%	19%	20%	12%	0	13%	20%	24%
Pain In Extremity	6%	0	4%	0	5%	9%	6%	24%
Productive Cough	0	6%	16%	0	0	2%	3%	24%
Chills	30%	13%	16%	6%	16%	16%	20%	18%
Decreased Appetite	12%	6%	20%	6%	5%	13%	9%	18%
Abdominal Pain	12%	0	4%	0	11%	11%	0	18%

Preferred Term	50 mg BID (n=17)	150 mg qD (n=16)	100 mg BID (n=25)	150 mg BID x 21 (n=17)	300 mg qD (n=19)	150 mg BID (n=45)	200 mg BID (n=35)	350 mg BID (n=17)
Pneumonia	6%	6%	16%	24%	5%	11%	14%	18%
Creatinine Increased	6%	0	0	0	5%	11%	3%	18%
Dyspnea	18%	6%	8%	0	5%	11%	6%	18%
Night Sweats	35%	0	12%	0	5%	9%	17%	18%
Hyponatremia	12%	0	16%	0	0	9%	9%	18%
Vomiting	24%	0	12%	12%	16%	4%	17%	18%
URI	18%	19%	16%	29%	37%	9%	11%	12%
Headache	0	13%	16%	6%	16%	9%	17%	12%
Alkaline Phos Increased	0	0	16%	0	1%	7%	3%	12%
Hypophosphatemia	6%	0	4%	6%	5%	7%	9%	12%
Insomnia	12%	13%	8%	12%	5%	7%	9%	12%
Dehydration	12%	0	12%	0	0	4%	3%	12%
Cough	12%	6%	20%	6%	11%	33%	26%	6%
Back Pain	24%	0	12%	12%	11%	13%	11%	6%
Asthenia	12%	6%	16%	6%	5%	11%	6%	6%
Dizziness	0	6%	8%	12%	11%	9%	9%	6%
Hypocalcaemia	6%	0	8%	0	5%	7%	6%	6%
Arthralgia	18%	0	4%	0	0	7%	9%	6%
Stomatitis	0	0	16%	18%	0	4%	3%	6%
Febrile Neutropenia	12%	6%	4%	6%	5%	9%	6%	0
Hyperglycemia	12%	0	8%	0	5%	9%	6%	0
Weight Decreased	6%	0	12%	0	0	7%	9%	0

Data from Protocol 101-02 Clinical Study Report 6/18/2013 Table 11-7

A dose-toxicity relationship appears to exist for increases in transaminases. However, Protocol 101-02 allowed for dose modifications for toxicity and for intra-patient dose escalation after 6 cycles if a CR was not attained, so adverse events in any given dose cohort in Table 44 may have occurred at a modified dose. FDA therefore conducted an assessment of the incidence of adverse events by the actual dose at the time of the event for subjects in the full monotherapy safety population. Table 46 shows the incidence of adverse events by actual dose. The analysis included only those subjects on BID dosing; results are not shown for 300 mg BID, since the number of subjects was small (n=7).

**Table 46 TEAE by Actual Dose in the Safety Population**

Preferred Term <sup>a</sup>	<100 mg BID (n=41)	100 mg BID (n=88)	150 mg BID (n=243)	200 mg BID (n=43)	350 mg BID (n=18)
Diarrhea	22%	16%	31%	23%	17%
Fatigue	15%	10%	21%	28%	17%
Nausea	10%	11%	20%	14%	33%
Neutropenia	15%	11%	20%	21%	39%
Pyrexia	5%	14%	19%	21%	11%
Cough	2%	15%	19%	14%	6%
Hypertransaminasemia	7%	18%	17%	16%	50%
Rash	2%	10%	15%	23%	17%
Pneumonia	10%	17%	14%	12%	17%
Thrombocytopenia	5%	7%	12%	9%	11%
Abdominal Pain	2%	9%	10%	2%	11%

Preferred Term <sup>a</sup>	<100 mg BID (n=41)	100 mg BID (n=88)	150 mg BID (n=243)	200 mg BID (n=43)	350 mg BID (n=18)
Decreased Appetite	2%	8%	10%	5%	17%

<sup>a</sup> Includes any subject treated with the dose indicated on Protocols 101-02, 101-09, 101-10, 101-11 and the Extension Study.

<sup>b</sup> Using grouped terms as defined in Section 7.1.2.

**Review Comment:** *The analysis of the dose-toxicity relationship using actual dose at the time of the event (Table 46) appears to confirm the trend in the Phase 1 study for increasing incidence of elevated transaminases with dose. There is also a suggestion of a dose-toxicity relationship for neutropenia. The conclusions that can be drawn from this analysis are limited by the potential lack of accuracy of the actual dose due to the imputation used to identify the dose as discussed in Section 7.2.2.*

### 7.5.2 Time Dependency for Adverse Events

An assessment of the time to onset of adverse events of special interest is provided in Section 7.3.4. Since relatively few subjects with INHL were treated with idelalisib for more than 6 months, a meaningful analysis of late onset events could not be performed.

### 7.5.3 Drug-Demographic Interactions

The applicant indicated that there were no meaningful differences in adverse events when assessed by race, ethnicity or gender (Module 2.7.4 Summary of Clinical Safety Sections 5.1.1.2 and 5.1.1.3). The applicant also indicated that for subjects with INHL, in comparison to younger subjects, those >65 years of age had a higher overall incidence of AEs (100% vs 97%), higher incidence of grades 3-5 AEs (80% vs 66%), higher incidence of discontinuation due to an AE (27% vs 19%), higher incidence of SAEs (63% vs 36%) and higher incidence of death (11% vs 5%) (Module 2.7.4 Summary of Clinical Safety Sections 5.1.1.1).

FDA evaluated drug-demographic interactions in the 146 subjects with INHL 150 mg BID subgroup. All subjects in this cohort had at least one TEAE.

Table 47 lists the TEAE by gender in decreasing order of the difference in incidence between genders. Only adverse events with a difference in incidence of at least 5% are shown. Females had a substantially higher incidence of nausea, vomiting and diarrhea, while males had a substantially higher incidence of thrombocytopenia, pneumonia and cough. Differences were not significant when corrected for multiplicity.

**Table 47 INHL 150 mg BID Cohort - TEAE By Gender**

Preferred Term <sup>b</sup>	Females (n=54) <sup>a</sup>		Males (n=92) <sup>a</sup>		Risk Difference
	n	%	n	%	
Nausea	23	43	18	20	23
Vomiting	12	22	8	9	14
Diarrhea	28	52	37	40	12
Neutropenia	17	31	22	24	8
Alopecia	4	7	0	0	7
Rash	15	28	19	21	7
Constipation	7	13	6	7	6
Hot flush	4	7	1	1	6
Hypertension	4	7	1	1	6
Headache	8	15	8	9	6
Venous thrombosis	5	9	3	3	6
Leukopenia	6	11	5	5	6
Abdominal pain	13	24	17	18	6
Flatulence	3	6	0	0	6
Decreased appetite	7	13	18	20	-7
Anemia	4	7	13	14	-7
Thrombocytopenia	7	13	21	23	-10
Pneumonia	9	17	27	29	-13
Cough	11	20	33	36	-16

<sup>a</sup>Includes only subjects with INHL (FL, SLL, LPL, MZL) treated with idelalisib 150 mg BID

<sup>b</sup>Using grouped terms as defined in Section 7.1.2.

Table 48 lists the adverse events by race in decreasing order of the difference in incidence between whites and others. There were too few subjects of other races for meaningful comparison by specific race or ethnicity. Only adverse events with a difference in incidence of at least 10% are shown. Pneumonia and back pain occurred more frequently in nonwhites, while pyrexia and thrombocytopenia were more frequent in whites. Differences were not significant when corrected for multiplicity.

**Table 48 INHL 150 mg BID Cohort - TEAE By Race**

Preferred Term <sup>b</sup>	Other (n=19) <sup>a</sup>		White (n=127) <sup>a</sup>		Risk Difference
	n	%	n	%	
Pneumonia	7	37	29	23	14
Back pain	4	21	12	9	12
Dehydration	0	0	13	10	-10
Cough	4	21	40	32	-10
Dyspnea	1	5	25	20	-14
Pyrexia	2	11	38	30	-19
Thrombocytopenia	0	0	28	22	-22

<sup>a</sup>Includes only subjects with INHL (FL, SLL, LPL, MZL) treated with idelalisib 150 mg BID

<sup>b</sup>Using grouped terms as defined in Section 7.1.2.

Table 49 lists the adverse events by age group in decreasing order of the difference in incidence between those less than 65 years of age vs older subjects. Only adverse events with a difference in incidence of at least 10% are shown. Fatigue and decreased

appetite were more common in the elderly, while rash was more frequent in the younger subjects. Differences were not significant when corrected for multiplicity.

**Table 49 INHL 150 mg BID Cohort - TEAE By Age**

Preferred Term <sup>b</sup>	≥65 Years Old (n=63) <sup>a</sup>		<65 Years Old (n=83) <sup>a</sup>		Risk Difference
	n	%	n	%	
Fatigue	28	44	19	23	22
Decreased appetite	18	29	7	8	20
Dyspnea	16	25	10	12	13
Pyrexia	21	33	19	23	10
Neutropenia	13	21	26	31	-11
Rash	8	13	26	31	-19

<sup>a</sup>Includes only subjects with INHL (FL, SLL, LPL, MZL) treated with idelalisib 150 mg BID

<sup>b</sup>Using grouped terms as defined in Section 7.1.2.

Table 50 lists the adverse events by weight below 55 kg, 55-100 kg or above 100 kg. Events with an incidence of at least 10% in the 55-100 kg group are listed in decreasing order of incidence. The incidence of fatigue increased with increasing weight, and diarrhea, nausea, neutropenia, anemia and asthenia occurred more frequently in the lower weight subgroup. The trend across weight groups was not significant when corrected for multiplicity.

**Table 50 INHL 150 mg BID Cohort - TEAE by Weight Group**

Preferred Term <sup>b</sup>	<55 kg n=11 <sup>a</sup>		55-100 kg n=116 <sup>a</sup>		>100 kg n=19 <sup>a</sup>	
	n	%	n	%	n	%
Diarrhea	7	64	51	44	7	37
Fatigue	2	18	38	33	7	37
Cough	3	27	34	29	7	37
Nausea	5	45	34	29	2	11
Neutropenia	4	36	33	28	2	11
Pneumonia	1	9	31	27	4	21
Pyrexia	4	36	29	25	7	37
Hypertransaminasemia	3	27	28	24	6	32
Rash	3	27	27	23	4	21
Thrombocytopenia	0	0	26	22	2	11
Abdominal pain	3	27	24	21	3	16
Decreased appetite	2	18	22	19	1	5
Dyspnea	2	18	22	19	2	11
Vomiting	1	9	17	15	2	11
Weight decreased	1	9	16	14	2	11
Anemia	2	18	14	12	1	5
Asthenia	3	27	14	12	1	5
Back pain	1	9	14	12	1	5
Renal failure	0	0	14	12	2	11
Insomnia	0	0	13	11	2	11
Night sweats	1	9	13	11	1	5
Edema peripheral	1	9	12	10	2	11

<sup>a</sup>Includes only subjects with INHL (FL, SLL, LPL, MZL) treated with idelalisib 150 mg BID

<sup>b</sup>Using grouped terms as defined in Section 7.1.2.

## 7.5.4 Drug-Disease Interactions

The applicant provided no assessment of drug-disease interactions. FDA evaluated drug-disease interactions in the 146 subjects in the INHL 150 mg BID subgroup.

Table 51 lists the adverse events by lymphoma diagnosis. Events with an incidence of at least 10% in the FL subgroup are listed in decreasing order of incidence. Of note, the PT Decreased immunoglobulins occurred only in subjects with SLL (16%) (not shown in table). There were no significant differences across diagnoses when corrected for multiplicity.

**Table 51 INHL 150 mg BID Cohort - TEAE by Diagnosis**

Preferred Term <sup>b</sup>	LPL n = 11 <sup>a</sup>		MZL n = 16 <sup>a</sup>		SLL n = 31 <sup>a</sup>		FL n = 88 <sup>a</sup>	
	n	%	n	%	n	%	n	%
Diarrhea	6	55	5	31	12	39	42	48
Cough	5	45	3	19	9	29	27	31
Rash	2	18	3	19	2	6	27	31
Pyrexia	2	18	1	6	13	42	24	27
Nausea	4	36	4	25	9	29	24	27
Hypertransaminasemia	2	18	5	31	6	19	24	27
Fatigue	5	45	6	38	13	42	23	26
Neutropenia	3	27	6	38	10	32	20	23
Pneumonia	3	27	3	19	12	39	18	20
Abdominal pain	4	36	3	19	7	23	16	18
Dyspnea	2	18	3	19	5	16	16	18
Decreased appetite	2	18	4	25	4	13	15	17
Thrombocytopenia	2	18	3	19	10	32	13	15
Vomiting	1	9	2	13	5	16	12	14
Renal failure	0	0	1	6	3	10	12	14
Weight decreased	4	36	1	6	2	6	12	14
Asthenia	3	27	1	6	3	10	11	13
Upper respiratory tract infection	2	18	2	13	3	10	11	13
Constipation	0	0	1	6	1	3	11	13
Back pain	1	9	1	6	4	13	10	11
Headache	2	18	1	6	3	10	10	11
Insomnia	1	9	1	6	3	10	10	11
Anemia	1	9	2	13	5	16	9	10
Night sweats	1	9	1	6	4	13	9	10
Chills	0	0	0	0	3	10	9	10
Edema peripheral	2	18	2	13	2	6	9	10

<sup>a</sup>Includes only subjects treated with idelalisib 150 mg BID

<sup>b</sup>Using grouped terms as defined in Section 7.1.2.

Since marrow biopsies were not available for all subjects at baseline, thrombocytopenia was used as a surrogate for potential impaired hematopoiesis. Table 52 lists the adverse events by platelet count above (normal) or below (thrombocytopenia) 150 Gi/L at baseline. Events with a risk difference of at least 10% are shown. The only event that differed in incidence significantly was thrombocytopenia ( $p < 0.00001$ , uncorrected for

multiplicity). Other than hyponatremia, there were no nonhematological AEs that differed substantially by baseline platelet count.

**Table 52 INHL 150 mg BID Cohort - TEAE By Baseline Platelet Count**

Preferred Term <sup>b</sup>	Platelets <150 Gi/L (n = 59) <sup>a</sup>		Platelets ≥150 Gi/L (n = 86) <sup>a</sup>		Risk Difference
	n	%	n	%	
Thrombocytopenia	23	39	5	6	33
Neutropenia	26	44	13	15	29
Hyponatremia	6	10	0	0	10

<sup>a</sup>Includes only subjects with INHL (FL, SLL, LPL, MZL) treated with idelalisib 150 mg BID

<sup>b</sup>Using grouped terms as defined in Section 7.1.2.

### 7.5.5 Drug-Drug Interactions

The pH-dependent solubility of idelalisib raised concern over changes in exposure with changes in pH of the gastrointestinal tract (see Section 4.3). The applicant performed a limited analysis of Grades 3-5 adverse events by whether subjects were taking gastric acid reducers (histamine 2 receptor antagonists, proton pump inhibitors and antacids). The applicant concluded that “acid reducers did not impact the safety profile” of idelalisib (Module 1.11.3 Efficacy Information Amendment dated 1/17/2014). The applicant also evaluated population pharmacokinetics data from Protocol 101-09 to determine whether the use of proton pump inhibitors altered the exposure of idelalisib when used as monotherapy. They reported no significant differences in  $C_{max}$ ,  $C_{trough}$  or AUC, and they concluded that proton pump inhibitors did not alter the exposure of idelalisib (Module 1.11.3 Efficacy Information Amendment dated 1/17/2014).

FDA evaluated the effect of drugs that raise gastric pH in the INHL 150 mg BID subgroup. Subjects were categorized as whether they did or did not take an acid reducer (histamine 2 receptor antagonist, proton pump inhibitor and/or antacids). Table 53 lists the adverse events at any grade by use of an acid reducer. Events with a risk difference of at least 10% are shown. There were no significant differences between groups for any of the adverse events when corrected for multiplicity.

**Table 53 INHL 150 mg BID Cohort - TEAE by Use of Acid Reducer**

Preferred Term <sup>b</sup>	Use of Acid Reducer				Risk Difference
	Yes (n=65) <sup>a</sup>		No (n=81) <sup>a</sup>		
	n	%	n	%	
Pneumonia	25	38	11	14	25
Cough	27	42	17	21	21
Pyrexia	25	38	15	19	20
Diarrhea	36	55	29	36	20
Anemia	13	20	4	5	15
Dyspnea	17	26	9	11	15
Nausea	23	35	18	22	13
Abdominal pain	18	28	12	15	13

Preferred Term <sup>b</sup>	Use of Acid Reducer				Risk Difference
	Yes (n=65) <sup>a</sup>		No (n=81) <sup>a</sup>		
	n	%	n	%	
Night sweats	11	17	4	5	12
Hypotension	8	12	1	1	11
Back pain	11	17	5	6	11
Decreased appetite	15	23	10	12	11
Hypokalemia	9	14	3	4	10

<sup>a</sup>Includes only subjects with INHL (FL, SLL, LPL, MZL) treated with idelalisib 150 mg BID

<sup>b</sup>Using grouped terms as defined in Section 7.1.2.

Proton pump inhibitors are known to be associated with a risk of diarrhea. When the grouped PT Diarrhea was assessed by use of proton pump inhibitors only, the incidence of diarrhea was higher in users than in nonusers (58% vs 36%, p=0.01).

***Review Comment: Since there was no effect of proton pump inhibitors on idelalisib pharmacokinetics, the increase in diarrhea in subjects using both drugs is likely due to the overlap in the toxicity profile. Labeling should reflect the potential increase in diarrhea with concurrent use of other drugs that may cause diarrhea.***

The applicant acknowledged that there was potential for drug-drug interactions based on the role of CYP3A on the metabolism of idelalisib, but no assessment on safety during use of such combinations was performed (Module 2.7.4 Summary of Clinical Safety Section 5.3).

FDA evaluated the effect of drugs that alter CYP3A4 in the INHL 150 mg BID subgroup. Subjects were categorized subjects as whether they did or did not take a CYP3A4 inhibitor. Categorization was performed using the list of CP3A4 modulators at <http://medicine.iupui.edu/clinpharm/ddis/main-table/>. Two subjects who used a CYP3A inducer and two subjects who used both a CYP3A inducer and inhibitor were not included in the analysis. Table 54 lists the adverse events by use of a CYP3A inhibitor. The actual CYP3A inhibitors used included amiodarone, buprenorphine, ciprofloxacin, clarithromycin, diltiazem, fluconazole, itraconazole, ketoconazole, verapamil and voriconazole. Events with a risk difference of at least 20% are shown. The incidence of pneumonia was substantially higher in users than in nonusers (45% vs 12%, p=0.000018, uncorrected for multiplicity).

**Table 54 INHL 150 mg BID Cohort - TEAE By Use of CYP3A4 inhibitor**

Preferred Term <sup>b</sup>	CYP3A4 inhibitor				Risk Difference
	Yes (n=53) <sup>a</sup>		No (n=89) <sup>a</sup>		
	n	%	n	%	
Pneumonia	24	45	11	12	33
Abdominal pain	19	36	11	12	23
Vomiting	15	28	5	6	23
Diarrhea	30	57	32	36	21

<sup>a</sup>Includes only subjects with INHL (FL, SLL, LPL, MZL) treated with idelalisib 150 mg BID. Four subjects using CYP3A4 inducers were not included in the analysis.

<sup>b</sup>Using grouped terms as defined in Section 7.1.2.

**Review Comment:** *Although the difference in risk of pneumonia is striking, the analysis does not support a causal relationship. Since most of the CYP3A4 inhibitors used were antibiotics, the difference in incidence of pneumonia might result from therapeutic use for treatment of infection rather than an adverse effect of the combination.*

## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

No additional analyses for second cancers in general were submitted by the sponsor. FDA search the adverse event data file for the SOC Neoplasms benign, malignant and unspecified. Nine cases were identified in the safety population, including 3 cutaneous squamous cell carcinoma, 2 myelodysplastic syndrome, and 1 each of gastric cancer, adenocarcinoma of the lung, adenocarcinoma of the rectum and melanoma.

The applicant calculated that the incidence rate of squamous cell carcinoma was 0.011/person year (95% CI, 0.002-0.032). They concluded there was no increased risk of squamous cell carcinoma, since the incidence rate was not significantly greater than that reported in other studies of patients with malignant lymphoma (0.002-0.004/person-year) (Cheson, Friedberg, et al. 2010; Dong, Hemminki, 2001). They also concluded that there was no increased risk of myelodysplastic syndrome, since the calculated incidence rate in the safety population (0.009/person-year; 95%CI, 0.001-0.031) was not significantly greater than reported in studies of other therapeutics for treatment of lymphoma (0.002-0.012/person-year) (Cheson, Friedberg, et al. 2010; Czuczman MS, Emmanouilides C, et al. 2007; Sacchi S, Marcheselli L, et al. 2008; Tam CS, Seymour JF, et al. 2006).

### 7.6.2 Human Reproduction and Pregnancy Data

Use of highly effective contraception was required during conduct of the idelalisib trials. No pregnancies were reported.

### 7.6.3 Pediatrics and Assessment of Effects on Growth

There were no children enrolled in any of the studies submitted in this application.

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no experience with accidental overdose of idelalisib. The highest dose used in the clinical trial population was 350 mg BID.

## 7.7 Additional Submissions / Safety Issues

### 7.7.1 Literature Review

No additional safety information was found on PubMed searches for "idelalisib AND adverse event," "idelalisib AND toxicity," or "idelalisib AND safety."

### 7.7.2 Safety in Healthy Volunteer Studies

There were 300 individuals without malignancy in the 11 volunteer studies. The median age was 34 years (range, 18-68 years). There were 219 (73%) males and 81 (27%) females. In the group, 224 (75%) were white, 45 (15%) black, 19 (6%) Asian, and 12 (4%) other race. Six (2%) had renal impairment, 20 (7%) had hepatic impairment, and 274 (91%) had no organ impairment. Eighteen (6%) received only placebo, 120 (40%) received a single dose of idelalisib, 114 (38%) received multiple doses of idelalisib, and 48 (16%) were in studies of idelalisib in combination with other drugs. Single or multiple doses of idelalisib at 17 mg - 400 mg were administered, the dose schedules for each protocol were described in Section 5.3.3. The applicant provided no integrated summary of the safety information from the volunteer studies.

There were no deaths reported in the volunteer studies. There were two subjects with SAEs in Protocol GS-US-313-0130. Both experienced grade 3 fever and grade 3 drug-induced liver injury. Brief summaries of the subjects with SAEs are provided:

- Subject 2687-1001 was admitted study day 15, one day after completion of a 10-day course of idelalisib 150 mg BID and a single dose of digoxin 0.5 mg, with pyrexia, elevated transaminases, vomiting, malaise, anorexia and rash. The symptoms improved clinically, and the subject was discharged study day 19. ALT peaked at 9.0x ULN, AST at 6.7x ULN, and GGT at 3.7x ULN at approximately study day 24. Total bilirubin remained within normal limits, and the alkaline phosphatase peaked at 1.6x ULN. The subject was treated with corticosteroids study days 25-30. All events were essentially resolved by study day 37.

- **Subject 2687-1005** was admitted study day 15, one day after completion of a 10-day course of idelalisib 150 mg BID and a single dose of digoxin 0.5 mg, with pyrexia, elevated transaminases, vomiting, malaise, anorexia and headache. ALT peaked at 24.0x ULN, AST at 15.3x ULN, and GGT at 3.0x ULN. Total bilirubin remained within normal limits, and the alkaline phosphatase peaked at 1.3x ULN. A liver biopsy on study day 19 showed “a granulomatous-type hepatitis with portal mixed-cellular infiltrates (predominantly histiocytic) with fewer lymphocytes, plasma cells, and frequent granulocytes.” The subject was treated with corticosteroids starting study days 19. All events were essentially resolved by study day 62.

Adverse events are shown in Table 55 by treatment subgroup (i.e., a single dose of idelalisib, multiple doses, or treatment in combination with another drug). Only events that occurred in at least 5% of any treatment subgroup are shown, and the events are listed in decreasing order in the combination treatment subgroup. The most common AEs with a single dose were headache (14%) and diarrhea (6%). The most common AEs with multiple doses were headache (15%) and rash (9%). The highest rate of AEs occurred in the combination trials. It should be noted that subjects in the combination trials had the longest duration of treatment with idelalisib.

**Table 55 Adverse Events Reported in Volunteer Studies**

Preferred Term <sup>a</sup>	Placebo (n=18)		Single Dose (n=120)		Multiple Doses (n=114)		Combinations (n=48)	
	n	%	n	%	n	%	n	%
Headache	2	11	17	14	17	15	16	33
Nausea	0	0	4	3	4	4	7	15
Rash	0	0	2	2	10	9	7	15
Somnolence	0	0	0	0	2	2	7	15
Abdominal pain	0	0	4	3	1	1	5	10
Constipation	0	0	0	0	3	3	5	10
Decreased appetite	0	0	1	1	1	1	5	10
Hypertransaminasemia	1	6	0	0	1	1	5	10
Local Reaction	0	0	1	1	4	4	5	10
Pyrexia	0	0	0	0	0	0	4	8
Malaise	0	0	0	0	0	0	3	6
Pain in extremity	0	0	1	1	2	2	3	6
Vomiting	0	0	1	1	1	1	3	6
Diarrhea	0	0	7	6	5	4	1	2

<sup>a</sup>Using grouped terms as defined in Section 7.1.2.

Four subjects had grade 3 AEs (4 elevated transaminases, 2 pyrexia, 1 rash and 1 malaise). All were in the combination study Protocol GS-US-313-0130. The most common AEs considered at least possibly related were headache (9%), somnolence (3%), abdominal pain (2%), elevated transaminases (2%), nausea (2%) and diarrhea (2%). There were no cases that fulfilled Hy’s law. Two of the subjects with drug-related rash were rechallenged after resolution. One had no recurrence on idelalisib 100 mg BID x 7 days, and the other had recurrent rash after five days at 200 mg BID.

Table 56 shows the incidence of grade 1 or higher treatment-emergent laboratory abnormalities in the subjects without baseline renal or hepatic impairment in the volunteer studies. Grade 3 increases in ALT (5 (10%) subjects) and in AST (4 (8%) subjects) were seen in the combination studies. Grade 3 neutropenia occurred in one subject in the multiple-dose subgroup and one subject in the combination studies.

**Table 56 Laboratory Abnormalities in Healthy Volunteers<sup>a</sup>**

Laboratory Abnormality	Placebo (n=18)		Single Dose (n=94)		Multiple Doses (n=114)		Combinations (n=48)	
	n	%	n	%	n	%	n	%
Anemia	1	6	2	2	26	23	14	29
Neutropenia	0	0	7	7	12	11	13	27
Alanine aminotransferase increased	1	6	5	5	7	6	10	21
Aspartate aminotransferase increased	1	6	2	2	7	6	10	21
Gamma glutamyl transferase increased	0	0	2	2	0	0	7	15
Thrombocytopenia	0	0	2	2	0	0	1	2

<sup>a</sup>Subjects with baseline organ impairment were excluded from the analysis. Numbers reported include those with grade 1 or higher abnormality according to CTCAE version 4.

The applicant clarified that in Protocol GS-US-313-0130, there was no impact of idelalisib on digoxin or rosuvastatin exposure, nor did digoxin, midazolam or rosuvastatin increase idelalisib exposure. They did note that the majority of AEs occurred in subjects who had received idelalisib for at least 18 doses of 150 mg BID. They concluded, therefore, that the adverse events were related to the duration of idelalisib dosing and not a drug-drug interaction (M 1.11.3 Efficacy Amendment 2/18/2014).

***Review Comment: The common adverse events and laboratory abnormalities in the volunteer studies are consistent with those reported in the INHL population, supporting the contention that they are drug-related and not due to the underlying malignancy. The pharmacokinetics data also appear to support a direct toxicity of idelalisib rather than a drug-drug interaction.***

### 7.7.3 Safety Update

The applicant submitted a safety update 12/11/2013. The information in this section and any analyses by FDA represent an addendum to the review above.

The cut-off date for the updated integrated safety dataset was 9/9/2013. The update included two newly enrolled subjects in the INHL150 mg BID subgroup. The applicant concluded that the “data presented in this safety update are consistent with the data submitted in the original NDA, and no new safety signals have been observed” (M 5.3.5.3 Safety Update dated 11/29/2013, Section 1.1).

The applicant also noted that “the original NDA contained a minor error that resulted in 42 subjects from Study 101-09 having missing values for creatinine increased in the serum chemistry tables. That error has been corrected in this safety update (Appendix 8.1, Table 8.3.1 and Table 8.3.2). However, in this safety update, creatinine records for 9 subjects from Study 101-10 and 4 subjects from Study 101-11 were inadvertently not graded for the integrated dataset, among whom 3 subjects from Study 101-10 had treatment-emergent Grade 1 creatinine increased. Therefore, 19 subjects with iNHL treated with 150 mg BID (b) (4) monotherapy had treatment-emergent Grade 1 creatinine increased (instead of 16 subjects as shown in (Appendix 8.1, Table 8.3.1) and 26 subjects altogether treated with 150 mg BID (b) (4) monotherapy had treatment-emergent Grade 1 creatinine” (M 5.3.5.3 Safety Update dated 11/29/2013, Section 3.3).

In addition, the applicant identified a third potential Hy’s law case, but due to concurrent use of hepatotoxic drugs, it was concluded that the criteria were not fulfilled. The case is described below:

Case 3: Subject 6478-0042 was a 56 year old man treated with idelalisib 150 mg BID for MZL. He was first noted to have elevated transaminases on study day 22 when the ALT was 7.1x ULN. The transaminases continued to rise, and idelalisib was discontinued on study day 27. At that time, the subject also complained of nausea and fatigue. On study day 30, the ALT peaked at 82.3x ULN, AST at 41.3x ULN and total bilirubin at 3.0x ULN. Concurrent medication included niacin and oxycodone with acetaminophen. All medications were discontinued, and the transaminases normalized by study day 62. He was rechallenged with idelalisib 100 mg BID starting study day 68, but the transaminases had started to rise within 4 days, so idelalisib was discontinued permanently, and the subject was withdrawn from the study.

***Review Comment: This reviewer agrees that concurrent use of niacin confounds the analysis. It is noteworthy, however, that the transaminases fell when idelalisib was discontinued and rose again on rechallenge, independent of niacin ingestion. An interaction between niacin and idelalisib cannot be excluded.***

During the conduct of the initial review, the efficacy reviewer identified two subjects in Protocol 101-09 with CLL who were enrolled as SLL. For the FDA evaluation of the INHL 150 mg BID subgroup in the safety update, these two subjects with CLL were removed, leaving a total of 146 subjects for review. The subgroup included 91 (62%) males and 55 (38%) females of median age 63 years (range, 31-87 years). By race, 125 (86%) were white, 5 (3%) black, 3 (2%) Asian, and 12 (9%) other or not reported. There were 88 (60%) subjects with FL, 30 (21%) with SLL, 17 (11%) with MZL, and 11 (8%) with LPL.

At the time of data cut-off, 39 (27%) of the subjects were continuing on idelalisib. The reasons for withdrawal of the other subjects included progressive disease (38%), adverse event (21%), death (5%), physician decision (5%), withdrawal by the subject (3%), and other (1%).

Median time on study was 6.1 months (range, 0.3-26.4 months). The duration on study was less than 3 months for 33 (23%) subjects, 3 to less than 6 months for 40 (27%), 6 to less than 12 months for 34 (23%), and one year or longer for 39 (27%).

There were four additional deaths reported, three due to progressive disease and one to infection. None were considered related to idelalisib.

An assessment of cumulative major safety events was performed. Eleven subjects had adverse events with a fatal outcome. An SAE was reported for 74 (51%) subjects. The most common SAEs were pneumonia (16%), diarrhea (11%), and pyrexia (10%). SAEs were considered related for 44 (30%) subjects. An AE resulted in drug interruption or permanent withdrawal for 80 (55%) subjects.

A TEAE was reported for 145 (99%) of the INHL 150 mg BID subgroup, and a grade  $\geq 3$  TEAE for 93 (64%). TEAEs reported most frequently ( $\geq 10\%$ ) are shown in Table 57.

**Table 57 Safety Update – Treatment-Emergent Adverse Events**

Preferred Term <sup>b</sup>	INHL Subjects Treated with Idelalisib 150 mg BID <sup>a</sup> (n=146)			
	Any Grade		Grade 3 or Higher	
	n	%	n	%
Diarrhea	68	47	20	14
Fatigue	49	34	3	2
Cough	44	30	1	1
Nausea	42	29	2	1
Pyrexia	42	29	3	2
Neutropenia	39	27	30	21
Elevated transaminases	38	26	25	17
Pneumonia	37	25	23	16
Rash	34	23	6	4
Abdominal pain	33	23	3	2
Thrombocytopenia	28	19	9	6
Dyspnea	26	18	6	4
Decreased appetite	25	17	1	1
Vomiting	22	15	2	1
Weight decreased	21	14	0	0
Anemia	19	13	7	5
Asthenia	19	13	3	2
Night sweats	18	12	0	0
Upper respiratory tract infection	18	12	0	0
Insomnia	17	12	0	0
Renal failure	16	11	5	3
Back pain	16	11	2	1
Headache	16	11	1	1
Dehydration	14	10	6	4
Edema peripheral	15	10	3	2
Constipation	14	10	0	0

<sup>a</sup>Includes only subjects with INHL (FL, SLL, LPL, MZL) treated with idelalisib 150 mg BID

<sup>b</sup>Using grouped terms as defined in Section 7.1.2.

Table 58 shows the incidence of worst post baseline abnormality in common laboratory tests in the INHL 150 mg BID subgroup as assessed by FDA.

**Table 58 Safety Update - Maximal Laboratory Abnormalities**

Laboratory Abnormality	Evaluable <sup>a</sup>	INHL Subjects Treated with Idelalisib 150 mg BID <sup>a</sup> (n=146)			
		Any Grade <sup>b</sup>		Grade 3 or Higher <sup>b</sup>	
		n	%	n	%
Anemia	146	91	62	3	2
Neutropenia	146	90	62	40	27
Alanine aminotransferase increased	146	76	52	27	18
Thrombocytopenia	146	71	49	13	9
Aspartate aminotransferase increased	146	70	48	18	12
Creatinine elevated	146	37	25	0	0

<sup>a</sup>Includes only subjects with INHL (FL, SLL, LPL, MZL) treated with idelalisib 150 mg BID

<sup>b</sup>Graded according to CTCAE version 4

<sup>c</sup>Any grade hyperglycemia includes only grades 2 or higher.

**Reviewer Comment:** *The review of the safety update confirmed the previous findings in the INHL150 mg BID population. There remains concern about the potential for serious hepatotoxicity, diarrhea, neutropenia and pneumonia, and additional safety issues with long-term use that cannot be determined with short follow-up.*

#### 7.7.4 Safety Addendum

An additional related SAE was submitted to IND 101254 after the Safety Update. The narrative describes a 48 year old woman being treated with idelalisib 150 mg BID in addition to bendamustine and rituximab in Protocol GS-313-0125. On study day 11, the subject was admitted with neutropenic fever, severe mucositis, rash and corneal inflammation. She was treated with antibiotics, intravenous immunoglobulin and filgrastim. Idelalisib was discontinued. Esophagogastroduodenoscopy showed diffuse esophagitis with exudates and desquamation. The rash progressed to generalized erythroderma with foci of blistering, consistent with toxic epidermal necrolysis. A skin biopsy is pending. Surgical debridement was performed with placement of grafts on study day 31. Some improvement in the cutaneous lesions was seen after cyclosporine and corticosteroids were started. On study day 39, the subject developed respiratory distress. A pleural effusion was drained, and imaging showed right lower lobe atelectasis. There was no evidence of infection or progression of the primary malignancy. The subject expired two weeks later. The investigator considered the event related to related to study drugs. The applicant indicated this is the only case of toxic epidermal necrolysis in the safety experience and could not exclude causation by bendamustine or rituximab.

**Reviewer Comment:** *This reviewer agrees that toxic epidermal necrolysis is known to occur in subjects who have received bendamustine in combination with*

***other agents. However, given the established incidence of rash with idelalisib monotherapy, including grade  $\geq 3$  events in 4%, causation by idelalisib cannot be excluded. Labeling should reflect the risk of such serious skin toxicity.***

## 8 Post-market Experience

Idelalisib is not marketed in any country. There are no post-market safety data

## 9 Appendices

### 9.1 Literature Review/References

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## 9.2 Advisory Committee Meeting

This application was not discussed by the Oncologic Drug Advisory Committee.

### 9.3 Grouped Terms Used in the Safety Review

Grouped Term	Preferred Term
Abdominal pain	Abdominal pain, Abdominal pain lower, Abdominal pain upper
Anemia	Anaemia, Anaemia Macrocytic, Haematocrit Decreased, Haemoglobin Decreased
Autoimmune disorder	Anaemia haemolytic autoimmune, Autoimmune disorder, Autoimmune neuropathy, Autoimmune neutropenia
Depression	Depressed Mood, Depression, Depressive Symptom
Diarrhea	Colitis, Diarrhoea, Diarrhoea Haemorrhagic, Enterocolitis
Hypersensitivity	Anaphylactic Reaction, Anaphylactic Shock, Contrast Media Allergy, Drug Hypersensitivity, Hypersensitivity, Iodine Allergy, Urticaria
Elevated Transaminases	Alanine Aminotransferase Increased, Aspartate Aminotransferase Increased, Hepatic Enzyme Increased, Hepatocellular Injury, Hepatotoxicity, Transaminases Increased
Immunoglobulins decreased	Hypogammaglobulinaemia, Hypoglobulinaemia
Neutropenia	Neutropenia, Neutrophil Count Decreased
Pneumonia	Atypical pneumonia, Bronchopneumonia, Interstitial Lung Disease, Lower Respiratory Tract Infection, Lower Respiratory Tract Infection Bacterial, Lung Infection, Lung Infection Pseudomonal, Lung Infiltration Organising Pneumonia, Pneumocystis Jiroveci Pneumonia, Pneumonia, Pneumonia Aspiration, Pneumonia Bacterial, Pneumonia Cytomegaloviral, Pneumonia Fungal, Pneumonia Necrotising, Pneumonia Pneumococcal, Pneumonia Staphylococcal, Pneumonia Streptococcal, Pneumonia Viral, Pneumonitis, Respiratory Syncytial Virus Infection, Respiratory Tract Infection
Pruritus	Pruritus, Pruritus Generalised
Rash	Dermatitis, Dermatitis Exfoliative, Dermatitis Psoriasiform, Drug Eruption, Eczema, Erythema Exfoliative Rash, Erythema Multiforme, Rash, Rash Erythematous, Rash Generalised, Rash Macular, Rash Maculo-Papular, Rash Papular, Rash Pruritic, Rash Vesicular, Skin Exfoliation
Renal failure	Blood creatinine increased, Glomerular filtration rate decreased, Renal failure, Renal failure acute
Thrombocytopenia	Platelet Count Decreased, Thrombocytopenia
Venous thrombosis	Deep vein thrombosis, Jugular vein thrombosis, Pulmonary embolism, Subclavian vein thrombosis, Venous thrombosis limb

## 9.4 Clinical Investigator Financial Disclosure Review Template

Application Number: 205858  
 Submission Date: 9/11/2013  
 Applicant: Gilead Sciences, Inc.  
 Product: Idelalisib  
 Reviewer: Barry W. Miller  
 Date of Review: 11/26/2013

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>
Total number of investigators identified:		
	Principal Investigators (n)	Sub-Investigators (n)
Trial		
101-02	10	150
101-07	11	107
101-08	5	74
101-09	54	435
101-10	2	8
101-11	4	50
101-99	18	204
GS-US-312-0115	24	234
GS-US-312-0116	57	646
GS-US-312-0117	9	91
GS-US-312-0119	17	188
GS-US-313-0124	1	23
GS-US-313-0125	2	35
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
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: <u>N/A</u> Significant payments of other sorts: <u>N/A</u> Proprietary interest in the product tested held by investigator: <u>N/A</u> Significant equity interest held by investigator in sponsor of covered study: <u>N/A</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/> <u>N/A</u>	No <input type="checkbox"/>
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/> <u>N/A</u>	No <input type="checkbox"/>
Number of investigators with certification of due diligence (Form FDA 3454, box 3): <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/> <u>N/A</u>	No <input type="checkbox"/>

## 9.5 Abbreviations

AE	adverse event	LDH	lactate dehydrogenase
AESI	adverse event of special interest	LLN	lower limit of normal
Akt	protein kinase B	LPL	lymphoplasmacytic lymphoma
ALP	alkaline phosphatase	MAED	MedDRA Adverse Events Diagnostic
ALT	alanine aminotransferase	MedDRA	Medical Dictionary for Regulatory Activities
AML	acute myelogenous leukemia	MM	multiple myeloma
ANC	absolute neutrophil count	MRI	magnetic resonance imaging
AST	aspartate aminotransferase	MTD	maximum tolerated dose
AUC	area under the curve	mTOR	mammalian target of rapamycin
BID	<i>bis in die</i> or twice daily	MZL	marginal zone lymphoma
BMI	body mass index	NCI	National Cancer Institute
CBC	complete blood count	NHL	non-Hodgkin lymphoma
CLCr	creatinine clearance	OATP	organic anion transporting polypeptide
CLL	chronic lymphocytic leukemia	ORR	Overall response rate
C <sub>max</sub>	maximum concentration	OS	overall survival
CR	complete response	PD	progressive disease
CRF	case report form	PFS	progression free survival
CT	computed tomography	Pgp	P-glycoprotein
CTCAE	Common Terminology Criteria for Adverse Events	PI	Principal Investigator
C <sub>trough</sub>	trough concentration	PI3Kδ	phosphatidylinositol 3-kinase delta
CYP	cytochrome P450	PK	pharmacokinetics
DLT	dose limiting toxicity	PO	<i>per os</i> or by mouth
DOR	duration of response	PR	partial response
EC <sub>50</sub>	half maximal effective concentration	PT	preferred term
ECG	electrocardiogram	qD or QD	<i>quaque die</i> or daily
ECOG	Eastern Cooperative Oncology Group	QTcB	Bazett's corrected QT interval
eCTD	Electronic Common Technical Document	QTcF	Fridericia's corrected QT interval
eDISH	Evaluation of Drug-Induced Serious Hepatotoxicity	RBC	red blood cell
FACT-Lym	Functional Assessment of Cancer Therapy- Lymphoma	REMS	Risk Evaluation and Mitigation Strategy
FL	follicular lymphoma	SAE	serious adverse event
HL	Hodgkin lymphoma	SD	standard deviation
HR	hazard ratio	SLL	small lymphocytic lymphoma
HRQL	health-related quality of life	SOC	system organ class
HSCT	hematopoietic stem cell transplant	SPD	sum of product diameters
ICH	International Conference on Harmonization	SPEP	serum protein electrophoresis
IEC	Independent Ethics Committee	TEAE	treatment-emergent adverse event
IgM	immunoglobulin M	TLS	tumor lysis syndrome
IND	Investigational New Drug	TTF	time to treatment failure
iNHL	indolent non-Hodgkin lymphoma	TTR	time to response
IRB	Institutional Review Board	ULN	upper limit of normal
IRC	Independent Review Committee	WBC	white blood cell
IRT	Interdisciplinary review team	WHO	World Health Organization
ITT	intent to treat	WM	Waldenström's macroglobulinemia

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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BARRY W MILLER  
05/09/2014

DONNA PRZEPIORKA  
05/09/2014

ROMEO A DE CLARO  
05/09/2014

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA Number:** 205858

**Applicant:** Gilead Sciences

**Stamp Date:** 9/11/2013

**NDA Type:** Original

**Drug Name:** Zydelig (idelalisib)

**Applicant's proposed indication:** Treatment of patients with refractory indolent non-Hodgkin lymphoma

	Content Parameter	Yes	No	NA	Comment
<b>FORMAT/ORGANIZATION/LEGIBILITY</b>					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
<b>LABELING</b>					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
<b>SUMMARIES</b>					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			Text M2.7.4 Datasets M5.3.5.3
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			2.73
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			X	505(b)(1)
<b>DOSE</b>					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: 101.02 Study Title: A Phase 1 Sequential Dose Escalation Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of CAL-101 in Patients with Selected, Relapsed or Refractory Hematologic Malignancies Sample Size: 191 Location in submission: 5.3.3.2 Arms: Doses 50-350 bid, 150 or 300 qd, 150 bid x 21 d/7d off	X			
<b>EFFICACY</b>					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? <u>Study #1</u> 101.09: 125 pts refractory to both rituximab and an alkylating agent. 72 FL, 28 SLL, 15 MZL, 10 LPL±WM <u>Study #2:</u> 101.02: PK trial subset of pts on 150 bid: 31 iNHL (19 FL, 5 SLL, 3 MZL, 4 LPL/WM)	X			One uncontrolled trial for analysis. Confirmation to come from 2 ongoing RCT trials (R ± idelalisib, BR ± idelalisib)

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	No agreement was made [EOP1 mtg 7/8/10, preNDA mtg 7/1/13]
<b>SAFETY</b>					
17.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
18.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X			M5.3.4.1
19.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			M2.7.4
20.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dose (or dose range) believed to be efficacious?			X	
21.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
22.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?	X			MedDRA 15.1
23.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	
24.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
<b>OTHER STUDIES</b>					
25.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			[pre-NDA 7/1/13]
26.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
<b>PEDIATRIC USE</b>					
27.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Full waiver request
<b>ABUSE LIABILITY</b>					
28.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	

<sup>1</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

<sup>2</sup> The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

<b>FOREIGN STUDIES</b>					
29.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			83 patients (67%) from US sites. Non-US sites were Germany, France, Italy, Poland, and the UK.
30.	Has the applicant submitted the required documentation to demonstrate that the foreign studies not conducted under a US IND conformed to Good Clinical Practice?	X			
<b>DATASETS</b>					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
<b>CASE REPORT FORMS</b>					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
<b>FINANCIAL DISCLOSURE</b>					
38.	Has the applicant submitted the required Financial Disclosure information?	X			1.3.4
<b>GOOD CLINICAL PRACTICE</b>					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

### REVIEW COMMENTS:

Agreement with the Division was not reached for the indication of indolent non-Hodgkin lymphoma. See separate filing review for the indication of chronic lymphocytic leukemia.

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE?** Yes

**Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.**

None

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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BARRY W MILLER  
10/21/2013

DONNA PRZEPIORKA  
11/04/2013

ROMEO A DE CLARO  
11/05/2013