CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	See stamp date
From	R. Angelo de Claro, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 206545
Applicant	Gilead Sciences, Inc.
Date of Submission	6 December 2013
PDUFA Goal Date	6 August 2014
Proprietary Name / Established (USAN) names	Zydelig
Dosage forms / Strength	Tablets, 100 mg and 150 mg
Proposed Indication(s)	Treatment of patients with relapsed chronic lymphocytic leukemia (CLL), in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities
Recommended:	*Approval*

Material Reviewed/Consulted	Reviewer
Clinical Review	Nicole Gormley, M.D.
Statistical Review	Sirisha Mushti, Ph.D. / Yuan-Li Shen, Ph.D.
Pharmacology Toxicology Review	Natalie Simpson, Ph.D., Ramadevi Gudi, Ph.D. / Haleh Saber, Ph.D. / John Leighton, Ph.D.
ONDQA-CMC and Biopharmaceutics Reviews	CMC: Debasis Ghosh, Ph.D., M.Pharm (Drug substance)/ Li Shan Hsieh, Ph.D. (Drug product)/Ali Al-Hakim, Ph.D. Biopharm: Sandra Suarez Sharp, Ph.D. /Angelica Dorantes, Ph.D. Microbiology: Jessica Cole, Ph.D. / Bryan Riley, Ph.D. ONDQA: Ramesh Sood, Ph.D. (Tertiary Review)
Clinical Pharmacology Review	DCP V: Stacy Shord, Pharm.D., Julie Bullock, Pharm.D. Pharmacogenomics: Rosane Charlab Orbach, Ph.D. Pharmacometrics: Dhananjay Marathe, Ph.D., Nitin Mehrotra, Ph.D.
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Patient Labeling Team (DMPP)	Nathan Caulk, MS, BSN, RN / Barbara Fuller RN, MSN, CWOCN

1. Introduction

On December 6, 2013, Gilead Sciences, Inc. (Applicant) submitted a New Drug Application (NDA) for Zydelig. The Applicant proposed the following indication: Treatment of patients with relapsed chronic lymphocytic leukemia (CLL).

Zydelig (idelalisib) is a new molecular entity inhibitor of PI3Kδ, the delta isoform of phosphatidylinositol 3-kinase. PI3Kδ is a downstream signal transducer for several receptors including B-cell receptor (BCR), CD40 receptor, chemokine receptor CXCR5, IL-6 receptor, and integrins. These pathways may be involved in B-cell proliferation, motility, and in homing to and maintenance of the tumor microenvironment in B-cell malignancies. There are no approved PI3K inhibitors.

The primary basis for the application are the results of clinical trial 312-0116, a randomized, double-blind, placebo-controlled trial of idelalisib in combination with rituximab in patients with relapsed chronic lymphocytic leukemia, for whom rituximab alone would be considered appropriate therapy due to other co-morbidities. Supportive clinical trials include single-arm trials of idelalisib combined with rituximab or chemo-immunotherapy regimens, and monotherapy idelalisib trials referenced in NDA 205858.

2. Background

Chronic Lymphocytic Leukemia (CLL) is a lymphoproliferative neoplasm characterized by the clonal proliferation and accumulation of mature B lymphocytes. It is the most common leukemia in the United States, accounting for 30% of all leukemias. It is estimated that there will be 15,680 new cases of CLL, and 4,580 deaths from CLL in the 2013. There is a slight male predominance (1.7:1), and the disease occurs more frequently in the elderly, with a median age at diagnosis between 67 and 72 years.

CLL is a heterogeneous disease with variable clinical course and outcome. Treatment may not be indicated in all patients with CLL; as benefit has not been established for treating early stage asymptomatic CLL. Treatment is typically reserved for those who are symptomatic, or have progressive disease.

CLL is not a curable disease, except in the rare setting of an allogeneic hematopoietic stem cell transplant. For physically fit patients, chemo-immunotherapy regimens (e.g., fludarabine, cyclophosphamide, and rituxumab (FCR); bendamustine and rituximab (BR); or pentostatin, cyclophosphamide, and rituximab (PCR)) are commonly used regimens. For patients that are physically unfit with significant comorbidity, treatment with chlorambucil with or without rituximab or rituximab alone is used. At the time of relapse, treatment with the initial regimen can be pursued if the treatment-free interval is longer than 2 years. If relapse occurs earlier, alternative therapies are used. Patients with del(17p) or TP53 mutation that achieve a CR or PR to first-line therapy, that are physically fit, are considered for stem cell transplantation. The table below lists the current FDA-approved drugs indicated for the treatment of CLL.

Table 1. FDA-Approved Drugs for CLL

Drug	Year Approved	Drug Class	Indication(s)
Chlorambucil	1957	Alkylating agent	CLL
Cyclophosphamide	1959	Alkylating agent	CLL
Fludarabine	1991	Purine analog	CLL patients who have not responded to or whose disease is progressed during treatment with at least one standard alkylating-agent containing regimen
Alemtuzumab	2001	Anti-CD52 monoclonal antibody	Single-agent for treatment of B-cell CLL
Bendamustine	2008	Alkylating agent	CLL. Efficacy relative to first line therapies other than chlorambucil has not been established
Ofatumumab	2009 (accelerated approval) 2014 (regular approval)	Anti-CD20 monoclonal antibody	Patients with CLL refractory to fludarabine and alemtuzumab In combination with chlorambucil, for the treatment of previously untreated patients with chronic lymphocytic leukemia (CLL) for whom fludarabine-based therapy is considered inappropriate
Rituximab	1997 (CLL approval-2010)	Anti-CD20 monoclonal antibody	In combination with fludarabine and cyclophosphamide, for the treatment of patients with previously untreated and previously treated CD20 positive CLL
Obinutuzumab	2013	CD20-directed cytolytic antibody	In combination with chlorambucil, for the treatment of patients with previously untreated CLL
Ibrutinib	2014 (accelerated approval)	Kinase inhibitor	Patients with CLL who have received at least one prior therapy

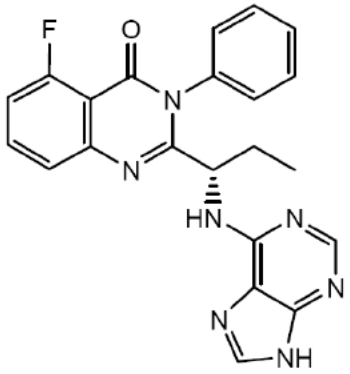
3. CMC/Device

Source: CMC tertiary review

- General product quality considerations

Drug Substance. The drug substance, idelalisib, a new molecular entity, is a (b) (4) It is a white to almost white (b) (4) substance. Idelalisib is designated as a BCS class II with low solubility and high permeability. Idelalisib can exist in two (b) (4) forms, Form I and Form II. (b) (4) is manufactured consistently and used for the manufacture of the drug product. (b) (4) (b) (4) Stability data has been provided which demonstrate that there is no (b) (4) on storage. Both forms have comparable solubility and other relevant physical properties. Because of (b) (4) and comparable solubility, the risk of product failure based on drug substance polymorphic form is acceptable. The drug substance synthesis is (b) (4) synthesis. The structure of the drug substance was adequately established using appropriate analytical techniques.

The chemical name for idelalisib is 5-fluoro-3-phenyl-2-[(1S)-1-(9H-purin-6-ylamino)propyl]quinazolin-4(3H)-one. It has a molecular formula of C22H18FN7O and a molecular weight of 415.42. Idelalisib has the following structural formula:



Idelalisib is a white to off-white solid with a pH-dependent aqueous solubility ranging from <0.1 mg/mL at pH 5-7 to over 1 mg/mL at pH 2 under ambient conditions.

The drug substance quality is ensured through quality control of all starting materials, in-process controls throughout the manufacturing process, appropriate quality control of the isolated intermediates and the appropriate final drug substance specification. The drug substance specification includes tests and acceptance criteria for drug substance critical quality attributes, e.g., identification, assay, impurities, enantiomeric purity, particle size distribution, residual solvents, and elemental impurities. The analytical procedures have been adequately described and validated to control the quality of the drug substance. The stability of the drug substance has been demonstrated through appropriate stability studies to support a retest period of (b) (4) months when stored (b) (4).

Drug product. Zydelig (idelalisib) tablets are an immediate release product to be marketed as 100 mg and 150 mg strengths. The drug product formulation uses standard compendial excipients. These are microcrystalline cellulose, hydroxypropyl cellulose,

croscarmellose sodium, sodium starch glycolate, and magnesium stearate. The manufacturing process includes (b) (4) The manufacturing process has appropriate in-process controls to ensure the quality of the drug product. The product quality is further ensured through end product testing. The end product specification includes testing for appearance, identification, assay, (b) (4), uniformity of dosage units, degradation products, dissolution, and microbial controls. All analytical procedures for the drug product are adequately described and validated. An expiration period of 24 months is granted for the product.

The drug product is stored at 25°C with excursions permitted 15-30ºC (59-86ºF).

- Facilities review/inspection

  Office of Compliance has issued an overall acceptable recommendation for this application dated 17-May-2014.

  Therefore, the NDA is recommended for approval from a CMC perspective.

- Other notable issues (resolved or outstanding)

  At the late cycle meeting on June 5, 2014, the Applicant and the Agency discussed (b) (4) of the tablets to allow for (b) (4). CMC commented that a CMC supplement can be submitted for (b) (4). CMC also referenced the FDA Guidance for Industry on (b) (4).

4. Nonclinical Pharmacology/Toxicology

Source: Primary pharmacology-toxicology review

- General nonclinical pharmacology/toxicology considerations (including pharmacologic properties of the product, both therapeutic and otherwise).

  Idelalisib (IDELA; GS-1101; CAL-101), is a kinase inhibitor with selectivity toward PI3Kδ. PI3Kδ is a downstream signal transducer for several receptors including B-cell receptor (BCR), CD40 receptor, chemokine receptor CXCR5, IL-6 receptor, and integrins. These pathways may be involved in B-cell proliferation, motility, and in homing to and maintenance of the tumor microenvironment in B-cell malignancies. The primary human metabolite of idelalisib, GS-563117, inhibits lymphocyte-oriented kinase (LOK) and Ste20-like kinase (SLK). According to the information at Cancer Genome Anatomy Project (CGAP), LOK is involved in lymphocyte migration and SLK is involved in apoptosis. GS-563117 is present in the plasma of healthy volunteers at higher levels (62% of drug-related material) than the parent drug (38% of drug-related material) following single oral dosing of idelalisib at 150 mg.

Idelalisib inhibits PI3K by binding to the ATP binding site of the catalytic subunit p110δ. P110δ is over-expressed in cell lines derived from patients with follicular lymphoma (small cleaved cell lymphoma or NHL). The (IC50) of idelalisib for PI3Kδ was 19 nM in an in vitro assay and the EC50 was 8.9 nM in a cell-based assay. The primary human metabolite, GS-563117, is an inhibitor of LOK and SLK kinases with IC50 values of 0.11 μM and 0.05 μM, respectively. Idelalisib inhibited cell viability and induced apoptosis in malignant B-cells. Idelalisib exhibited higher sensitivity for acute lymphoblastic leukemia (B-ALL) and CLL cells compared with acute myeloid leukemia (AML) and myeloproliferative neoplasm (MPN) cells, suggesting a greater activity potential for B-cell malignancies. Idelalisib inhibited CXCR4 and CXCR5 signaling and chemotaxis in CLL cells, as well as BCR signaling and chemokine secretion and CLL cell migration in an in vitro simulated tumor microenvironment.

In in vivo and in vitro safety pharmacology studies conducted, no clear drug-related effects were observed for idelalisib on neurological, cardiovascular, or respiratory function. However, drug-related cardiomyopathy and increased in the heart weight were observed in the rat in the repeat-dose toxicology studies (see below).
Orally administered idelalisib was absorbed rapidly (T_{max} 0.5 to 2 hours), with bioavailability less than 50% in the animals tested. Idelalisib was localized to most tissues in the rat, but was relatively excluded from bone, brain, spinal cord, and eye lens. In Long-Evans rats, pigmented skin and eye uvea showed higher concentrations of idelalisib than that observed for the similar tissues in Sprague-Dawley rats, suggesting some association of drug-derived radioactivity with melanin. The pharmacokinetics of idelalisib are similar between rats and dogs and humans, however, the plasma level of the metabolite GS-563117 was lower in dogs (34%) and rats (1.4%) than humans (62%). Idelalisib was the most abundant analyte in plasma of rats and dogs (~90% in rats and ~60% in dogs). Idelalisib exhibited moderately high plasma protein binding in all species with the average free fraction values of 19%, 21%, and 16% for rat, dog, and human respectively. The hepatobiliary route was the primary route of excretion within 24 to 48 hours in rats and dogs, with the majority of idelalisib being detected in the feces and 6% or less in the urine.

Toxicities following repeated dosing of idelalisib in rats and/or dogs included findings in the following tissues/organs:

- hematopoietic/lymphoid system (lymphoid depletion, reduced weight of spleen and thymus, thymic hemorrhage and necrosis, myeloid and granulopoeitic 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).

Inflammation was observed in several tissues (e.g. in the GI tract, pancreas, lungs, heart, and liver) and may be related to the inhibition of the CXCR5 pathway, involved in homing of B-cells. Skin may be also a target of idelalisib toxicity. In pigmented rats, idelalisib-related radioactivity was present in the eyes and skin at higher concentrations than what were reported for non-pigmented rats. Skin erythema, dryness, swelling, and redness have been observed in animals in toxicology studies.

An in vitro photo-toxicity study was conducted in the embryonic murine fibroblast BALB/c 3T3 cell line using Neutral Red uptake as a marker of cellular viability in the presence and absence of ultraviolet A (UVA) light exposure. The study was not reviewed by the Agency, however, based on the summary provided by the Applicant, results for idelalisib were inconclusive, while the primary human metabolite, GS-563117, induced photo-toxicity in the presence of UVA exposure.

General toxicology studies were done by the oral route and included 28-day studies in rats and dogs, a 13-week study in rats, a 6-month study in rats, and a 9-month study in dogs. There were mortalities in all rat studies with cause of deaths undetermined or related to liver toxicity. Cardiomyopathy was observed in unscheduled sacrifices and surviving rats in the 13-week and 6-month studies, with an increase in heart weight observed in the 13-week study. In the 9-month dog study, mortality was attributed to systemic inflammation, with no signs of hepatotoxicity in this study.

- Carcinogenicity

  Idelalisib did not induce mutations in the bacterial mutagenesis (Ames) assay and, was not clastogenic in the in vitro chromosome aberration assay using human peripheral blood lymphocytes. Idelalisib was genotoxic in males in the in vivo rat micronucleus study at a high dose of 2000 mg/kg. Carcinogenicity studies with idelalisib have not been conducted.

- Reproductive toxicology

  Idelalisib may impair fertility in humans. In a fertility study, treated male rats (25, 50, or 100 mg/kg/day of idelalisib) were mated with untreated females. Decreased epididymal and testicular weights were observed at all dose levels and reduced sperm concentration at the mid- and high doses; however, there were no adverse effects on fertility parameters. The low dose in males resulted in an exposure (AUC) that is approximately 50% of the exposure in patients at the recommended dose of 150 mg twice daily.

  In a separate fertility study, treated female rats (25, 50, or 100 mg/kg/day of idelalisib) were mated with untreated males. There were no adverse effects on fertility parameters; however, there was a decrease in the number of live embryos at the high dose. The high dose in females resulted in an exposure (AUC) that is approximately 17-fold the exposure in patients at the recommended dose of 150 mg twice daily.

Reproductive and developmental toxicology studies were conducted in rats to assess the effects of idelalisib on fertility and embryo-fetal development. In a fertility and early embryonic development study, idelalisib-treated male rats were mated to untreated female rats. In this study, idelalisib had no effect on reproductive function or fertility, despite decreased testis and epididymis weights, and reduced sperm counts. When idelalisib-treated female rats were paired with untreated male rats, there was an increase in pre-implantation and post-implantation loss, and early embryo-lethality, resulting in a 20% decrease in the number of live embryos at the high dose of 100 mg/kg (600 mg/m^2).

The embryo-fetal development effects of idelalisib were studied in the rat. Idelalisib produced post-implantation loss and was teratogenic. Idelalisib was maternally toxic based on reductions in net body weight gain > 10% at the mid and high doses (75 and 150 mg/kg/day; 450 and 900 mg/m^2/day) and clinical signs of maternal toxicity, most evident at the high dose. Adverse embryo-fetal findings at doses ≥ 75 mg/kg/day (450 mg/m^2/day) included decreased fetal weights, external malformations (short tail) and skeletal variations (delayed ossifications and/or unossification of the skull, vertebrae, and sternebrae). At 150 mg/kg/day (900 mg/m^2/day) dose, idelalisib resulted in spontaneous abortion (urogenital loss, complete resorption, increased post-implantation loss, and reduced mean litter size) and malformations (vertebral agenesis with anury, microphthalmia, anophthalmia, and hydrocephaly) in live fetuses. The dose of 75 and 150 mg/kg/day of idelalisib in rats resulted in exposures (AUC) of approximately 25 and 60 times, respectively, the human exposure at the recommended dose of 150 mg BID.

As a kinase inhibitor, the teratogenic effects of idelalisib were expected and observed in rats at the mid and high doses tested. Based on teratogenicity findings, an embryo-fetal developmental study in a second species is not needed and pregnancy category D is recommended.

- Other notable issues (resolved or outstanding)

  There are no outstanding issues with nonclinical pharmacology and toxicology.

5. Clinical Pharmacology/Biopharmaceutics

Source: Clinical pharmacology primary review

- General clinical pharmacology and biopharmaceutics considerations

  Absorption and Food Effect. Idelalisib exposure increased in a less than dose proportional manner with doses up to 350 mg in fasted conditions; it demonstrates dose-dependent absorption. The median T_{max} was observed at 1.5 h (range 0.5, 6 h) under fasted conditions. The administration of a single 400 mg dose of idelalisib with a high-fat meal resulted in a 1.4-fold increase in AUC. Idelalisib should be administered

without regard to food. In the NHL and CLL trials, idelalisib was administered without regard to food.

Metabolism and Half-Life. Idelalisib is metabolized to its major metabolite GS-563117 via aldehyde oxidase and CYP3A. GS-563117 is inactive against PI3Kδ in vitro. Idelalisib undergoes minor metabolism by UGT1A4.

The population apparent systemic clearance at steady-state is 14.9 L/hr. The population terminal elimination half-life of idelalisib is 8.2 hours.

Is the proposed starting dose of 150 mg BID reasonable? Yes. The maximum administered dose (MAD) was 350 mg BID and no maximum tolerated dose (MTD) was identified in the dose escalation phase. No exposure-response (E-R) relationships were observed for the primary endpoints in the NHL (101-09) and CLL (312-0116) trials and for selected safety endpoints, except for diarrhea in the NHL population. In these trials most patients administered a dose of 150 mg BID achieved minimal concentrations (C_{tau}) greater than the in vitro EC_{90} for PI3Kδ inhibition. A lower starting dose is not recommended, because the ER relationship with tumor size in the dose finding study (101-02) suggests that the lowest exposure is associated with less clinical activity. A higher starting dose is not recommended as idelalisib is associated with hepatotoxicity and higher exposures were associated with a greater incidence of diarrhea.

- Drug-drug interactions

  Rifampin decreased idelalisib AUC by 75%. Idelalisib should not be coadministered with strong CYP3A inducers. Ketoconazole increased idelalisib AUC by 1.8-fold. No dose adjustment is recommended for patients taking strong CYP3A inhibitors with idelalisib.

  Idelalisib or its metabolite inhibited CYP3A, CYP2C19, P-glycoprotein (P-gp), OATP1B1 and OATP1B3 in vitro. Idelalisib increased midazolam AUC by 5.4-fold; therefore, idelalisib should not be coadministered with sensitive CYP3A substrates. No changes in exposure to rosuvastatin (OAT1B1 and OATP1B3) or digoxin (P-gp) were observed.

  More diarrhea and rash were observed in patients taking idelalisib with proton pump inhibitors (PPI) (CYP2C19). Overlapping toxicities or a CYP-mediated drug interaction could be responsible for the additional adverse events.

- Pathway of elimination

  Approximately 78% and 14% of the radioactivity was excreted in feces and urine, respectively following a single 150 mg oral dose of [^{14}C]-labeled idelalisib. GS-563117 accounted for most of the radioactivity in plasma (62%), urine (49%) and feces (44%).

- Critical intrinsic factors potentially affecting elimination: age, gender, hepatic insufficiency and renal impairment.

  Body weight and hepatic impairment influence exposure to idelalisib. Body weight was maintained in the final population PK model, but body weight has no clinically meaningful effect on exposure. Hence, no dose adjustment is needed for body weight.

  No dose adjustment is needed for patients with creatinine clearance (CLcr) ≥ 15 mL/min, since the exposure was only increased 1.3-fold in patients with CLcr 15 to 29 mL/min.

  No dose modifications are recommended in patients with baseline hepatic impairment. The AUC increased up to 1.7-fold in subjects with ALT or AST or bilirubin greater than the ULN compared to healthy subjects. However, no exposure-response relationship was observed for selected safety endpoints with the exception of diarrhea in the NHL population.

  The remaining covariates assessed in the population PK model had no impact on exposure, including age, race, gender, background therapies, baseline serum creatinine, and CLcr.

- QT assessment

  Nonclinical. The IC_{50} for the hERG potassium current was estimated to be greater than 50 μM (BHR00004). No effects on electrocardiograms (ECGs) were observed in dogs treated with doses up to 20 mg/kg. The no observed adverse effect level (NOAEL) is 20 mg/kg (BHR00041).

  Clinical (Thorough QT Study). The effect of Zydelig (150 mg and 400 mg) on the QT/QTc interval was evaluated in a placebo- and positive-controlled (moxifloxacin 400 mg) crossover study in 46 healthy subjects. At a dose 2.7 times the maximum recommended dose, Zydelig did not prolong the QT/QTc interval (i.e., not greater than 10 ms).

6. Clinical Microbiology

The application did not include clinical microbiology information. Refer to Section 8 regarding infections in Zydelig-treated patients.

7. Clinical/Statistical- Efficacy

I agree with the conclusions of the clinical reviewer (Nicole Gormley) and statistical reviewer (Sirisha Mushti) on the efficacy of Zydelig for the following recommended indication:

- Treatment of patients with relapsed chronic lymphocytic leukemia (CLL), in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities.

The efficacy of Zydelig was evaluated in clinical trial 312-0116, in which 220 patients were randomized to receive either idelalisib 150 mg orally BID in combination with 8 doses of rituximab (first dose at 375 mg/m^2, subsequent doses at 500 mg/m^2 every 2 weeks for four infusions and every 4 weeks for an additional 4 infusion) or placebo in combination with rituximab. Subjects continued treatment with idelalisib or placebo until disease progression, unacceptable toxicity, or the end of study. The clinical trial was designed with progression free survival (PFS) as the primary endpoint and the secondary endpoints in the following order: objective response rate, lymph node response rate, and overall survival.

Eligible patients after screening were randomized in a 1:1 ratio to either the treatment arm (idelalisib + rituximab) or the control arm (placebo + rituximab) and randomization was stratified using the following factors:

- 17p deletion and/or p *TP53* mutation in CLL cells: either versus neither (or indeterminate)
- Immunoglobulin heavy chain variable region (*IGHV*) mutation: unmutated (or *IGHV*3-21) versus mutated (or indeterminate)
- Any prior therapy with an anti-CD20 therapeutic antibody: yes versus no.

Sample Size Calculations. A total of 220 patients were planned to be randomized to either of the treatment arms (110 patients to each treatment arm) to achieve an improvement in median PFS from 6 months to 10.5 months due to the addition of idelalisib to rituximab in the treatment arm. A total of 119 PFS events were required to detect a hazard ratio of 0.57 along with achieving a power of >0.85 based on a stratified log-rank test with a 2-sided significance level of 0.05. A planned accrual period of 12 months and a minimum follow-up period of 12 months was assumed with a 10% lost to follow-up (5% during the accrual period and 5% during the follow-up period).

Interim Efficacy Analyses. Two formal interim analyses of efficacy (~50% and ~75% of PFS events) were planned. The significance level for the first interim analysis will be 0.001 and for the second interim analysis will be 0.005. If a decision is made to stop the trial based on an interim analysis, the database will be cleaned and locked for the subsequent final analysis and the significance level of 0.044 will be used.

A Type A meeting was held between the Agency and the Applicant on October 7, 2013 to discuss early termination of clinical trial GS-US-312-0116 for efficacy based on the results of the first interim analysis (65 PFS events) with a data cutoff of August 30, 2013. The data

cutoff date for the efficacy analysis was October 9, 2013 and included a total of 75 PFS events. Breakthrough Therapy designation was granted on November 8, 2013 for Zydelig for the treatment of patients with relapsed chronic lymphocytic leukemia.

The median age was 71 (range 47, 92) with 78% over 65; 66% were male, 90% were Caucasian. The median time since diagnosis was 8.5 years. The median number of prior therapies was 3. Nearly all (96%) subjects had received prior anti-CD20 monoclonal antibodies. The most common (>15%) prior regimens were: bendamustine + rituximab (98 subjects, 45%), fludarabine + cyclophosphamide + rituximab (75 subjects, 34%), single-agent rituximab (67 subjects, 31%), fludarabine + rituximab (37 subjects, 17%), and chlorambucil (36 subjects, 16%).

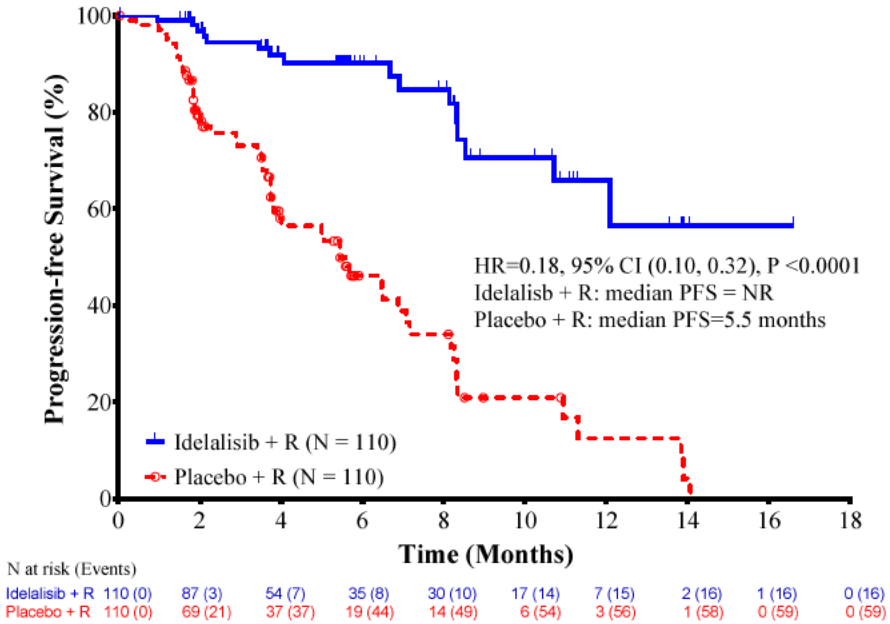
The primary endpoint was progression free survival (PFS), as assessed by an independent review committee (IRC). The trial was stopped for efficacy following the first pre-specified interim analysis. Results of a second interim analysis continued to show a statistically significant improvement for Zydelig + rituximab over placebo + rituximab for the primary endpoint of PFS (HR: 0.18, 95% CI (0.10, 0.32), $p < 0.0001$). The efficacy results are shown in Table 2 and the Kaplan-Meier curve for PFS is shown in Figure 1.

Table 2: Efficacy Results from Clinical Trial 312-0116

		Zydelig + R N=110	Placebo + R N=110
PFS	Median (months) (95% CI)	NR (10.7, NR)	5.5 (3.8, 7.1)
	Hazard ratio (95% CI)	0.18 (0.10, 0.32)	
	P-value	< 0.0001 †	

R: rituximab; PFS: progression-free survival; NR: not reached
† The P values for PFS was based on stratified log-rank test.

Figure 1: Kaplan-Meier Plot of IRC-Assessed PFS



Overall response rate was a secondary endpoint. There were no complete responses (CRs) in either treatment arm. There were 82 partial responses (PR) in the Idelalisib + rituximab arm (overall response rate-74.5%), and 16 partial responses in the placebo + rituximab arm (overall response rate- 14.5%).

CDTL Comment: Overall response rate was not included in the prescribing information due to extensive modifications to the CLL response criteria.

Overall survival was a secondary endpoint. The analysis of overall survival was limited by the small number of events (19 deaths). In addition, the significance level for interim analysis of overall survival was not specified in the protocol. The protocol and statistical analysis plan lacked detail whether the trial was powered for overall survival.

8. Safety

I agree with the clinical reviewer's conclusion regarding the safety of Zydelig.

Safety Summary

The safety profile of idelalisib is based on the safety profile observed in clinical trial 312-0116. As of the final data-cutoff date of October 9, 2013, 220 patients were randomized, of which 218 received at least one dose of idelalisib or placebo. The safety population for Study 312-0116 consists of 218 subjects who received at least 1 dose of study treatment. A summary of the key safety findings are listed below:

- The idelalisib dose was 150 mg orally BID. The median exposure duration to Idelalisib was 5.0 months (range: 0.3, 17.3).
- Thirty nine (39) subjects (35.5%) in the Idelalisib arm and 19 subjects (17.6%) in the placebo arm had a dose interruption due to adverse reactions or lab abnormalities. Sixteen (16) subjects in the idelalisib arm (14.5%) had a dose reduction due to adverse reactions or lab abnormalities. No subjects in the placebo arm required a dose reduction. Twelve (12) subjects in the idelalisib arm discontinued study drug due to an adverse event, and 12 subjects in the placebo arm discontinued due to an adverse event.
- Serious adverse reactions were reported in 54 (49.1%) subjects treated with idelalisib+ rituximab compared to 38 patients (35.2%) in the placebo arm. The most frequent serious adverse reactions that were observed more frequently in the idelalisib arm were pneumonia (13.6%), pyrexia (9.1%), sepsis (7.3%), pneumonitis (3.6%), and diarrhea (2.7%).
- Additional safety issues have been identified with the use of idelalisib including intestinal perforation, colitis, AST/ALT elevations, serious and fatal hepatotoxicity, and severe cutaneous skin reactions.

Overall, the safety profile of idelalisib 150 mg BID in combination with rituximab was similar to the safety profile of idelalisib 150 mg BID, which was marked by substantial toxicity. Refer also to the safety findings in the CDTL review for NDA 205858.

9. Advisory Committee Meeting

The application for Zydelig was not referred to an FDA advisory committee because the application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of a disease.

10. Pediatrics

Zydelig is exempt from the pediatric study requirements in 21 CFR 314.55. Zydelig was granted Orphan Drug Designation by the Office of Orphan Products Development for the following indications (date granted):

- Follicular lymphoma (September 26, 2013)
- Lymphoplasmacytic lymphoma with or without Waldenström's macroglobulinemia (September 26, 2013)
- Splenic marginal zone lymphoma (October 15, 2013)
- Nodal marginal zone lymphoma (October 15, 2013)
- Extranodal marginal zone lymphoma (October 15, 2013)
- Chronic lymphocytic leukemia and small lymphocytic leukemia (October 15, 2013)

Zydelig has not been evaluated in pediatric patients.

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP):** No issues.
- **Exclusivity or Patent Issues of Concern:** No issues. Refer to exclusivity review.
- **Financial Disclosures:** No issues. The Applicant provided a list of clinical investigators and financial disclosures for the pivotal and supporting clinical trials. None of the disclosures submitted revealed a potential conflict of interest.
- **Other GCP Issues:** None
- **Office of Scientific Investigation (OSI) Audits:** The following is from the overall assessment of findings and general recommendations:

  Three domestic clinical sites were selected for inspection of clinical trial 312-0116 supporting this NDA: John Pagel, M.D., Ph.D. (Fred Hutchinson Cancer Research Center), Bruce Cheson, M.D. (Georgetown University Medical Center/Lombardi Cancer Center), and Richard Furman, M.D (Cornell University Medical School). The Applicant (Gilead Sciences, Inc.) was also inspected.

  The final regulatory classification for Dr. Pagel is VAI (Voluntary Action Indicated).The preliminary regulatory classification for Dr. Cheson and Dr. Furman is

NAI (No Action Indicated). The preliminary classification for Gilead Sciences is VAI (Voluntary Action Indicated).

The study data collected from these clinical sites and submitted by the sponsor appear generally reliable in support of the requested indication.

- **Other discipline consults**: None
- **Other outstanding regulatory issues**: None

12. Labeling

- **Proprietary name.** On 3 October 2013, OSE/DMEPA concluded that the proposed proprietary name, Zydelig was conditionally acceptable.

- **OSE/DRISK.** DRISK and Division of Hematology Products have determined, if Zydelig is approved, a REMS (Risk Evaluation and Mitigation Strategy) that consists of a communication plan to address the risks of hepatotoxicity, intestinal perforation, colitis, and pneumonitis will be necessary to ensure that the benefits outweigh the risks of treatment. The Agency instructed the Applicant to submit a risk management plan that includes a proposed communication plan REMS.

  The Applicant submitted the proposed REMS including REMS materials and REMS supporting document on 21 May 2014. An amended version was submitted on 28 May 2014. In general, DRISK evaluation noted that the outline and layout of the proposed REMS, REMS Supporting Document, and REMS communication materials (REMS letter to healthcare providers, REMS letter to professional societies, REMS Fact sheet, REMS journal information piece, and REMS website) were acceptable. However, significant revisions to the language for these materials are needed based on the final version of the labeling.

- **OSE/DMEPA.** DMEPA participated in the labeling discussions and provided recommendations for the container labels, carton and insert labeling.

- **Patient Labeling Team.** The patient labeling group participated in the labeling discussions and reviewed the Medication Guide.

- **OPDP.** OPDP attended labeling meetings and provided input. Refer to OPDP review in DARRTS for OPDP labeling recommendations.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Regular Approval

- Risk Benefit Assessment

  The efficacy and safety results from clinical trial 312-0116 demonstrate an acceptable benefit-risk profile for the treatment of patients with relapsed chronic lymphocytic leukemia (CLL), in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities. All review team members recommend approval.

  Clinical trial 312-0116 was Zydelig was a randomized, double-blind, placebo-controlled study in 220 patients with relapsed CLL who required treatment and were unable to tolerate standard chemo-immunotherapy due to coexisting medical conditions, reduced renal function as measured by creatinine clearance < 60 mL/min, or NCI CTCAE Grade ≥ 3 neutropenia or Grade ≥ 3 thrombocytopenia resulting from myelotoxic effects of prior therapy with cytotoxic agents. Subjects were randomized 1:1 to receive 8 doses of rituximab (first dose at 375 mg/m^2, subsequent doses at 500 mg/m^2 every 2 weeks for four infusions and every 4 weeks for an additional 4 infusions) in combination with either an oral placebo twice daily or with Zydelig 150 mg taken twice daily until disease progression or unacceptable toxicity.

  The primary endpoint was progression free survival (PFS), as assessed by an independent review committee (IRC). Secondary endpoints were analyzed in the following order: objective response rate, lymph node response rate, and overall survival.

  The trial was sized at 220 patients randomized 1:1 to each arm to achieve an improvement in PFS from 6 months to 10.5 months due to the addition of idelalisib to rituximab in the treatment arm. A total of 119 PFS events were required to detect a hazard ratio of 0.57 along with achieving a power of >0.85 based on a stratified log-rank test with a 2-sided significance level of 0.05.

  The trial was stopped for efficacy following the first pre-specified interim analysis (65 PFS events). Results of a second interim analysis (75 PFS events) continued to show a statistically significant improvement for Zydelig + rituximab over placebo + rituximab for the primary endpoint of PFS (HR: 0.18, 95% CI (0.10, 0.32), $p < 0.0001$). Sensitivity analyses for PFS demonstrated that the PFS results were robust. Refer to Table 2 and Figure 1 in Section 7 for further details of the PFS analysis.

  The secondary endpoint of overall response rate could not be adequately evaluated due to extensive modifications to the response criteria. Interpretation of overall survival was limited by the small number of events (19 deaths). In addition, the significance level for interim analysis of overall survival was not specified in the protocol. The protocol and statistical analysis plan lacked detail whether the trial was powered for overall survival.

CDTL Comment: The indication granted reflects the actual population studied in the clinical trial. The use of a rituximab-only control arm limits the applicability of the trial results to the broader CLL population.

The safety profile for Zydelig (as monotherapy or in combination with rituximab) is notable for substantial toxicities, including fatalities. The labeling will include boxed warnings for the following fatal and serious toxicities: hepatotoxicity, diarrhea and colitis, pneumonitis, and intestinal perforation. Additional items in Warnings and Precautions include severe cutaneous reactions, neutropenia, and embryo-fetal toxicity. A Medication Guide will be required.

The above toxicities were likely 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. Hence, the Applicant was required to submit a REMS communication plan to address the risks of hepatotoxicity, intestinal perforation, colitis, and pneumonitis. The REMS will be necessary to ensure that the benefits outweigh the risks of treatment.

The short treatment duration for idelalisib is a limitation for clinical trial 312-0116, with a median treatment duration of 5.0 months. Whether patients will be able to tolerate longer treatment durations of idelalisib, given that none of the patients achieved a complete response, will be an important consideration in ongoing and future trials of idelalisib in the CLL population. The occurrence of significant toxicities with short (less than 6 months) duration of idelalisib treatment is concerning. Alternative dosing regimens for idelalisib will need to be explored.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

  As discussed above, the approval for this application will include a REMS communication plan. The final elements of the REMS are under negotiation: REMS letter to healthcare providers, REMS letter to professional societies, REMS Fact sheet, REMS journal information piece, REMS website, and a Patient Safety Information Card.

  Refer to the DRISK reviews for the final elements and details of the REMS.

- Recommendation for other Postmarketing Requirements and Commitments

  I agree with the following postmarketing requirements proposed by the review teams, and agreed upon with the Applicant. PMR 2180-9 and 2180-10 represent safety PMRs.

  PMR 2180-9 Conduct a trial to provide evidence sufficient to characterize the long-term safety of Zydelig when used in combination with an anti-

CD20 regimen. Submit the complete study report and data from trial GS-US-312-0119, a Phase 3, randomized, study of idelalisib in combination with ofatumumab in patients with previously treated CLL.

PMR 2180-10 Conduct a trial to provide evidence sufficient to characterize the long-term safety of Zydelig when used in a combination therapy regimen. Submit the complete study report and data showing long-term safety with 5 years of follow-up from trial GS-US-312-0117, a Phase 3, 2 arm, extension study of idelalisib in patients with previously treated CLL.

Refer to action letter for NDA 206545 for final wording and milestones of the post-marketing requirements. Refer also to action letter for NDA 205858 for other PMRs.

- Recommended Comments to Applicant

  None

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/s/

ROMEO A DE CLARO
07/07/2014