

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206545Orig1s000

MEDICAL REVIEW(S)

July 23, 2014

The PDUFA Goal Date on the first page of the below review is incorrect. The correct PDUFA Goal Date is August 6, 2014.

CLINICAL REVIEW

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| Application Type | NDA |
| Application Number(s) | 206545 |
| Priority or Standard | Priority |
| Submit Date(s) | December 6, 2013 |
| Received Date(s) | December 6, 2013 |
| PDUFA Goal Date | May 29, 2014 |
| Division / Office | Division of Hematology Products/ Office of Hematology and Oncology Products |
| Reviewer Name(s) | Nicole Gormley, MD |
| Review Completion Date | May 29, 2014 |
| Established Name | Idelalisib |
| (Proposed) Trade Name | Zydelig ® |
| Therapeutic Class | Kinase inhibitor |
| Applicant | Gilead Sciences, Inc. |
| Formulation(s) | Tablet (150 mg, 100 mg) |
| Dosing Regimen | 150 mg administered orally twice daily |
| Indication(s) | Relapsed Chronic Lymphocytic Leukemia |
| Intended Population(s) | ≥ 18 years of age |

Template Version: March 6, 2009

Table of Contents

| | | |
|----------|---|-----------|
| 1 | RECOMMENDATIONS/RISK BENEFIT ASSESSMENT | 9 |
| 1.1 | Recommendation on Regulatory Action | 9 |
| 1.2 | Risk Benefit Assessment..... | 9 |
| 1.3 | Recommendations for Postmarket Risk Evaluation and Mitigation Strategies . | 12 |
| 1.4 | Recommendations for Postmarket Requirements and Commitments | 12 |
| 1.5. | Recommendations for Labelling | 12 |
| 2 | INTRODUCTION AND REGULATORY BACKGROUND | 13 |
| 2.1 | Product Information | 13 |
| 2.2 | Tables of Currently Available Treatments for Proposed Indications | 13 |
| 2.3 | Availability of Proposed Active Ingredient in the United States | 15 |
| 2.4 | Important Safety Issues with Consideration to Related Drugs..... | 15 |
| 2.5 | Summary of Presubmission Regulatory Activity Related to Submission | 15 |
| 2.6 | Other Relevant Background Information | 16 |
| 3 | ETHICS AND GOOD CLINICAL PRACTICES..... | 16 |
| 3.1 | Submission Quality and Integrity | 16 |
| 3.2 | Compliance with Good Clinical Practices | 16 |
| 3.3 | Financial Disclosures..... | 17 |
| 4 | SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES | 17 |
| 4.1 | Chemistry Manufacturing and Controls | 17 |
| 4.2 | Clinical Microbiology..... | 18 |
| 4.3 | Preclinical Pharmacology/Toxicology | 18 |
| 4.4 | Clinical Pharmacology | 18 |
| 4.4.1 | Mechanism of Action..... | 18 |
| 4.4.2. | Pharmacodynamics..... | 18 |
| 4.4.3 | Pharmacokinetics..... | 18 |
| 5 | SOURCES OF CLINICAL DATA..... | 19 |
| 5.1 | Tables of Studies/Clinical Trials | 19 |
| 5.2 | Review Strategy | 20 |
| 5.3 | Discussion of Individual Studies/Clinical Trials..... | 20 |
| 6 | REVIEW OF EFFICACY | 34 |
| | Efficacy Summary..... | 34 |
| 6.1 | Indication | 34 |
| 6.1.1 | Methods | 34 |
| 6.1.2 | Demographics..... | 35 |
| 6.1.3 | Subject Disposition | 40 |
| 6.1.4 | Analysis of Primary Endpoint(s)..... | 41 |

| | | |
|----------|--|-----------|
| 6.1.5 | Analysis of Secondary Endpoints(s)..... | 42 |
| 6.1.6 | Other Endpoints | 43 |
| 6.1.7 | Subpopulations | 43 |
| 6.1.8 | Analysis of Clinical Information Relevant to Dosing Recommendations | 43 |
| 6.1.9 | Discussion of Persistence of Efficacy and/or Tolerance Effects..... | 44 |
| 6.1.10 | Additional Efficacy Issues/Analyses | 44 |
| 7 | REVIEW OF SAFETY..... | 45 |
| | Safety Summary | 45 |
| 7.1 | Methods..... | 45 |
| 7.1.1 | Studies/Clinical Trials Used to Evaluate Safety | 45 |
| 7.1.2 | Categorization of Adverse Events..... | 46 |
| 7.1.3 | Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence..... | 46 |
| 7.2 | Adequacy of Safety Assessments | 46 |
| 7.2.1 | Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations | 46 |
| 7.2.2 | Explorations for Dose Response..... | 47 |
| 7.2.3 | Special Animal and/or In Vitro Testing | 49 |
| 7.2.4 | Routine Clinical Testing | 49 |
| 7.2.5 | Metabolic, Clearance, and Interaction Workup | 49 |
| 7.2.6 | Evaluation for Potential Adverse Events for Similar Drugs in Drug Class .. | 49 |
| 7.3 | Major Safety Results | 49 |
| 7.3.1 | Deaths..... | 50 |
| 7.3.2 | Nonfatal Serious Adverse Events | 52 |
| 7.3.3 | Dropouts and/or Discontinuations | 53 |
| 7.3.4 | Significant Adverse Events | 54 |
| 7.3.5 | Submission Specific Primary Safety Concerns | 57 |
| 7.4 | Supportive Safety Results | 57 |
| 7.4.1 | Common Adverse Events | 57 |
| 7.4.2 | Laboratory Findings | 59 |
| 7.4.3 | Vital Signs | 60 |
| 7.4.4 | Electrocardiograms (ECGs) | 60 |
| 7.4.5 | Special Safety Studies/Clinical Trials | 61 |
| 7.4.6 | Immunogenicity | 63 |
| 7.5 | Other Safety Explorations..... | 63 |
| 7.5.1 | Dose Dependency for Adverse Events | 63 |
| 7.5.2 | Time Dependency for Adverse Events..... | 63 |
| 7.5.3 | Drug-Demographic Interactions | 63 |
| 7.5.4 | Drug-Disease Interactions..... | 64 |
| 7.5.5 | Drug-Drug Interactions..... | 64 |
| 7.6 | Additional Safety Evaluations | 64 |
| 7.6.1 | Human Carcinogenicity | 64 |
| 7.6.2 | Human Reproduction and Pregnancy Data..... | 64 |

| | | |
|----------|---|-----------|
| 7.6.3 | Pediatrics and Assessment of Effects on Growth | 65 |
| 7.6.4 | Overdose, Drug Abuse Potential, Withdrawal and Rebound..... | 65 |
| 7.7 | Additional Submissions / Safety Issues | 65 |
| 8 | POSTMARKET EXPERIENCE..... | 66 |
| 9 | APPENDICES | 67 |
| 9.1 | Literature Review/References | 67 |
| 9.2 | Labelling Recommendations..... | 68 |
| 9.3 | Advisory Committee Meeting..... | 68 |
| 9.4 | Clinical Investigator Financial Disclosure Review Template..... | 68 |

Table of Tables

| | |
|--|----|
| Table 1. List of Abbreviations | 7 |
| Table 2. Risk Benefit Assessment..... | 9 |
| Table 3. FDA-Approved Drugs for CLL | 14 |
| Table 4. Idelalisib Regulatory History | 15 |
| Table 5. Clinical Trials Reviewed | 19 |
| Table 6. Inclusion Criteria Baseline Lab Requirements..... | 23 |
| Table 7. Dose Modification Recommendations from Study 312-0116..... | 26 |
| Table 8. Schedule of Events for Study 312-0116 | 28 |
| Table 9. Baseline Demographics of the ITT population..... | 35 |
| Table 10. Baseline Disease and Comorbidity Characteristics of the ITT population | 35 |
| Table 11. CLL Conditions Indicating Treatment Need..... | 38 |
| Table 12. Number of Prior Therapies | 38 |
| Table 13. Subjects with stable or progressive disease in prior rituximab containing regimen | 39 |
| Table 14. Study 312-0116 Subject Disposition..... | 40 |
| Table 15. PFS assessment by IRC | 41 |
| Table 16. Secondary Endpoint Analyses..... | 43 |
| Table 17. Sensitivity Analyses of PFS Endpoint..... | 44 |
| Table 18. Baseline Demographics of the Safety Population..... | 46 |
| Table 19. Baseline Disease and Comorbidity Characteristics of the Safety Population | 47 |
| Table 20. Idelalisib or Placebo Exposure | 47 |
| Table 21. Rituximab Exposure | 48 |
| Table 22. Safety Summary for Study 312-0116 | 49 |
| Table 23. Deaths on study or within 30 days of discontinuation..... | 50 |
| Table 24. Deaths in Study 312-0117 | 51 |
| Table 25. Treatment- Emergent Serious Adverse Events in $\geq 2\%$ of Subjects in Study 312-0116 | 52 |
| Table 26. Adverse Events leading to Study Drug Withdrawal | 53 |
| Table 27. Treatment-Emergent Adverse Events of Any Grade in $\geq 5\%$ of Subjects..... | 57 |
| Table 28. Treatment-emergent AEs Grade 3-4 in $\geq 2\%$ of Subjects | 58 |
| Table 29. Laboratory Abnormalities of Any Grade in $\geq 10\%$ of Subjects | 59 |
| Table 30. Laboratory Abnormalities Grade 3-4 in $\geq 2\%$ of Subjects..... | 60 |
| Table 31. Cardiac Adverse Events..... | 60 |
| Table 32. Additional Studies in CLL Patient Populations..... | 61 |
| Table 33. Adverse Events of Any Grade in $\geq 10\%$ of Subjects based on Age..... | 63 |

Table of Figures

| | |
|--|----|
| Figure 1. Chemical Structure of Idelalisib..... | 17 |
| Figure 2. Study Design Study 312-0116..... | 20 |
| Figure 3. Kaplan-Meier Progression Free Survival ITT population..... | 42 |
| Figure 4. Duration of Exposure to Idelalisib in Months..... | 48 |
| Figure 5. Bilirubin and ALT elevations..... | 55 |

Table 1. List of Abbreviations

| | |
|----------|---|
| AE | Adverse Event |
| ALC | Absolute lymphocyte count |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| ANC | Absolute neutrophil count |
| AST | Aspartate aminotransferase |
| BID | Twice per day |
| BR | Bendamustine and rituximab |
| CBC | Complete Blood Count |
| CIRS | Cumulative Illness Rating Score |
| CLL | Chronic Lymphocytic Leukemia |
| CR | Complete response |
| CrCl | Creatinine Clearance |
| CSR | Clinical Study Report |
| CT | Computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| del(17p) | Deletion 17p |
| ECG | Electrocardiogram |
| eCTD | Electronic Common Technical Document |
| EQ-5D | EuroQoL Five-Dimension |
| FACT-Leu | Functional Assessment of Cancer Therapy- Leukemia |
| FCR | Fludarabine, cyclophosphamide, and rituximab |
| FDA | Food and Drug Administration |
| G-CSF | Granulocyte colony-stimulating factor |
| GGT | Gamma Glutamyl Transferase |
| HBV | Hepatitis B |
| HCV | Hepatitis C |
| HIV | Human immunodeficiency virus |
| HRQL | Health-related quality of life |
| ICH | International Conference on Harmonization |
| IEC | Independent Ethics Committee |
| Ig | Immunoglobulin |
| IGHV | Immunoglobulin heavy chain variable region |
| IND | Investigational New Drug |
| IRB | Institutional Review Board |
| IRC | Independent Review Committee |
| ITT | Intention-to-treat |
| IWCLL | International Workshop on CLL |
| IWRS | Interactive web response system |
| LD | Longest diameter |

| | |
|---------------|--|
| LPD | Longest perpendicular diameter |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | Magnetic resonance imaging |
| mTOR | Mammalian target of rapamycin |
| NCI | National Cancer Institute |
| ND | No Disease |
| NDA | New Drug Application |
| NE | Non-Evaluable |
| NHL | Non-Hodgkin Lymphoma |
| PCR | Pentostatin, cyclophosphamide, and rituximab |
| PD | Progressive Disease |
| PFS | Progression Free Survival |
| PI3K δ | Phosphatidylinositol 3-kinase p110 δ |
| PR | Partial Response |
| PRBC | Packed Red Blood Cell |
| SD | Stable Disease |
| SLL | Small Lymphocytic Lymphoma |
| SPD | Sum of the products of the perpendicular diameters of measured lymph nodes |
| ULN | Upper limit of normal |
| β -HCG | Beta human chorionic gonadotropin |

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend regular approval for Idelalisib in combination with rituximab for the treatment of adult patients with relapsed CLL, for whom rituximab alone would be considered appropriate therapy due to other co-morbidities.

1.2 Risk Benefit Assessment

The basis for regular approval is based on a single, randomized, placebo-controlled trial, Study 312-0116, which demonstrated an improvement in progression-free survival among patients with relapsed CLL that had comorbidities.

Table 2. Risk Benefit Assessment

| Decision Factor | Evidence and Uncertainties | Conclusions |
|-----------------------|--|---|
| Analysis of Condition | It is estimated that there will be 15,680 new cases of CLL, and 4,580 deaths from CLL in the year 2013. CLL is considered a serious and life-threatening condition. | Relapsed CLL is a serious and life-threatening condition. |
| Unmet Medical Need | CLL is not a curable disease, except in the setting of hematopoietic stem cell transplant. Patients who initially respond to initial therapy generally relapse and require subsequent therapy. The duration of response often shortens with subsequent therapies. | Relapsed CLL is a serious and life-threatening condition characterized by relapse and often refractory disease. Additional therapeutic agents are needed to treat relapsed CLL. |
| Clinical Benefit | <p>Study 312-0116 was a phase 3, randomized, placebo-controlled trial of Idelalisib 150 mg PO BID in combination with rituximab versus placebo in combination with rituximab in patients with relapsed CLL, that had a CIRS score ≥ 6, Grade ≥ 3 neutropenia or thrombocytopenia, or estimated creatinine clearance < 60 mL/min.</p> <ul style="list-style-type: none"> The PFS hazard ratio of the ITT population was 0.18 (95% CI: 0.10, 0.31) stratified log-rank p value <0.0001 Median PFS was not reached in the Idelalisib arm, and was 5.5 months in the placebo + rituximab arm The overall response rate was 74.5% in the Idelalisib + rituximab arm, compared to 14.5% in the placebo + rituximab arm. There were no complete responses. All the responses were partial responses. | Single-agent rituximab has limited clinical activity in patients with relapsed CLL and its use is generally reserved for those patients that are frail, elderly, or have comorbid conditions that preclude the use of more effective chemoimmunotherapy regimens. Idelalisib has demonstrated activity in patients with relapsed CLL. |

| | | |
|-------------------------------|--|--|
| <p>Risks</p> | <p>The safety population for study 312-0116 consisted of 218 subjects.</p> <ul style="list-style-type: none"> • The median duration of exposure to Idelalisib was 5 months. • Serious adverse reactions were reported in 54 (49.1%) subjects treated with Idelalisib+ rituximab compared to 38 patients (35.2%) in the placebo arm • Frequent AEs (≥ 10% incidence and >2% compared to placebo arm) included: pyrexia, neutropenia, nausea, chills, diarrhea, rash, vomiting, and headache. • Grade 3-4 AEs (≥2% incidence and ≥2% compared to placebo) included: Neutropenia, pneumonia, sepsis, pneumonitis, rash, colitis, and increased ALT. • There was 1 Hy's Law case identified. | <p>There were several safety concerns identified in the review. The Idelalisib safety profile could be deemed acceptable in patients that are unable to tolerate standard chemoimmunotherapy due to other medical comorbidities. However, prescribers should be aware of the risks of colitis, pneumonitis, hepatotoxicity, and severe skin reactions and monitor patients appropriately. Furthermore, the risks associated with long-term administration are unknown.</p> |
| <p>Risk Management</p> | <p>Prescribers should be aware of the risk of colitis, pneumonitis, hepatotoxicity and severe skin reactions. The proposed labeling includes warnings, precautions including recommended monitoring, and dose modifications, but safe use will require that both patients and healthcare providers are aware of these instructions.</p> | <p>It is recommended that the label contain a boxed warning for hepatotoxicity, bowel perforation, colitis, and pneumonitis. Additionally, a patient medication guide is required to inform and educate patients of treatment 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 expertise.</p> |

Clinical benefit. The efficacy of Idelalisib was evaluated in study 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/m², subsequent doses at 500 mg/m² 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. A Type A meeting was held between the Agency and the applicant on October 7, 2013 to discuss early termination of Study GS-US-312-0116 for efficacy based on the results of an interim analysis. The clinical trial was terminated early on October 9, 2013. A summary of the key efficacy findings are listed below. The data cutoff date for the efficacy analysis was October 9, 2013.

- The primary endpoint was PFS as assessed by the IRC. PFS between the two treatment arms was compared using a stratified log-rank test, adjusted for the stratification factors: 17p deletion and/or TP53 mutation status and IGHV

mutation status. The IRC assessed PFS hazard ratio of the ITT population was 0.18 (95% CI: 0.10, 0.31) stratified log-rank p value <0.0001.

- The median PFS was not reached in the Idelalisib + rituximab group at the time of the interim analysis, and was 5.5 months in the placebo + rituximab group.
- 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%).
- Overall survival was a secondary endpoint. The analysis of overall survival is limited by the small number of events (19 events).

Risk. The safety population for Study 312-0116 consisted of 218 subjects who received at least one dose of study drug. 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 bowel perforation, colitis, AST/ALT elevations, serious and fatal hepatotoxicity, and severe cutaneous skin reactions.

Benefit-Risk Assessment. In Study 312-0116, Idelalisib in combination with rituximab demonstrated a significant improvement in PFS compared to rituximab alone (+ placebo). Single-agent rituximab in patients with relapsed disease has limited clinical activity. It is difficult to confidently characterize the benefits of Idelalisib given the limitations of the control arm. Single-agent rituximab is generally restricted to those individuals that have serious comorbidities that would not tolerate standard immunochemotherapy. In study 312-0116, eligibility was based on CIRS scoring, which has not been validated in hematologic malignancies. It is not clear whether the trial adequately identified patients who could not tolerate standard immunochemotherapy. Given the safety findings noted in this potentially more fit patient population, the safety in a truly frail patient population is questionable. Additionally, it is difficult to assess the proposed indication of use of Idelalisib until

disease progression or unacceptable toxicity. Since there were no complete responses observed, only partial responses, it is expected that patients will remain on Idelalisib for extended durations. The median duration of Idelalisib exposure was only 5 months in Study 312-0116. Therefore, the safety of long-term administration of Idelalisib cannot be assessed. Idelalisib has demonstrated activity in relapsed CLL. However, the projected benefits outweigh the projected risks *only* if there are additional risk management strategies in place to ensure the safe use in the intended patient population.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The clinical team determined that Idelalisib would need a REMS to ensure the safe use of Idelalisib. The REMS should consist of a communication plan regarding boxed warning safety issues.

1.4 Recommendations for Postmarket Requirements and Commitments

At the time of the completion of this review, the clinical team determined the need for the following post-marketing requirements:

- Provide 5-year safety follow-up for Study 312-0117, the extension trial for study 312-0116.
- Conduct a clinical study to characterize the incidence, diagnosis and effective treatment of Idelalisib-related pneumonitis.
- Provide additional safety data, including long term safety data, for the use of Idelalisib in combination with anti-CD20 therapies, such as ofatumumab, Study 312-0119 may be used to provide this information.

1.5. Recommendations for Labelling

- The indication should be for patients with relapsed CLL in combination with rituximab for whom rituximab alone would be an appropriate therapy due to other comorbidities. Idelalisib should only be used in a patient population that is too frail or otherwise unable to tolerate standard chemoimmunotherapy due to the presence of serious co-existing medical comorbidities.
- The label should contain a boxed warning for hepatotoxicity, bowel perforation, colitis, and pneumonitis.
- Warning and Precautions should contain information about diarrhea, myelosuppression, and severe cutaneous reactions observed with Idelalisib.

2 Introduction and Regulatory 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 year 2013(Siegel *et al.*). 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- 72 years. Two thirds of cases are diagnosed among those aged ≥ 65 (Danilov, 2013).

CLL is a heterogeneous disease with variable clinical course and outcome. Treatment is not indicated in all patients with CLL; as there is no benefit for treating early stage asymptomatic CLL(Desablens *et al.*, 2013). Treatment is typically reserved for those that are symptomatic, or have progressive or high risk disease. CLL patients are categorized into risk groups based on the clinical staging systems, Rai and Binet. Other prognostic factors which help guide treatment include: lymphocyte doubling time, cytogenetic abnormalities, biological prognostic factors (IGHV), serum markers, and mutational status. A hierarchical model of risk in CLL based on common genetic abnormalities was developed by Döhner(Döhner *et al.*, 2000). This study demonstrated that individuals with deletion 17p and 11q have significantly shorter survival times and poorer response to treatment.

2.1 Product Information

Established Name: Idelalisib

Trade Name: Zydelig®

Chemical Class: New molecular entity

Pharmacologic Class: PI3K δ inhibitor

Proposed Indication: For the treatment of patients with relapsed chronic lymphocytic leukemia (CLL)

Proposed Dosage and Administration: 150 mg orally, twice daily

2.2 Tables of Currently Available Treatments for Proposed Indications

CLL is not a curable disease, except in the setting of hematopoietic stem cell transplant. For physically fit patients, chemoimmunotherapy regimens (eg. fludarabine, cyclophosphamide, and rituxumab (FCR); bendamustine and rituximab (BR); or pentostatin, cyclophosphamide, and rituximab (PCR)) are the standard of care. For patients that are physically unfit with significant comorbidity, treatment with chlorambucil

with or without rituximab or rituximab alone is the current standard of care (Zelenetz *et al.*, 2013). 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 should be used. Patients with del(17p) or TP53 mutation that achieve a CR or PR to first-line therapy, that are physically fit, should be considered for stem cell transplant (Hallek & Hallek, 2013; Zelenetz *et al.*, 2013). The table below lists the current FDA-approved drugs indicated for the treatment of CLL.

Table 3. FDA-Approved Drugs for CLL

| Drug | Year Approved | Type | 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 | Anti-CD20 monoclonal antibody | Patients with CLL refractory to fludarabine and alemtuzumab |
| 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 CD-20 positive CLL |
| Obinutuzumab | 2013 | CD20-directed cytolytic antibody | In combination with chlorambucil, for the treatment of patients with previously untreated CLL |
| Ibrutinib | 2014 | Bruton's tyrosine kinase (BTK) inhibitor | Patients with CLL who have received at least one prior therapy |

For relapsed disease, if the first-line therapy was well tolerated, and relapse occurs 24 months after initial treatment, first-line therapy may be repeated. Patients that experience relapse within a short time or have resistant disease do not respond to

standard chemotherapy, and are often referred for clinical trials or hematopoietic stem cell transplant if eligible.

Single-agent rituximab has been studied in patients with relapsed or refractory CLL. Response rates range between 25 and 45%, but most responses are only partial responses, and very few complete responses are observed (Robak, 2012). Given the relatively limited activity of single-agent rituximab in patients with relapsed disease, it is generally reserved for those patients that are frail, elderly, or have comorbid conditions that preclude the use of more toxic therapies (Zelenetz *et al.*, 2013).

2.3 Availability of Proposed Active Ingredient in the United States

Idelalisib is a new molecular entity and is not marketed in the United States or any other country at the time of this review.

2.4 Important Safety Issues with Consideration to Related Drugs

None.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

A summary of the regulatory history of Idelalisib is outlined in the table below.

Table 4. Idelalisib Regulatory History

| Date | Event Type | Purpose |
|-------------------|--|---|
| June 8, 2011 | Type B End-of Phase 1 Meeting | To discuss Phase 3 trial designs for CLL indication |
| August, 2011 | Orphan Designation Granted | |
| November 22, 2011 | Phase 3 Study in CLL (GS-US-312-0116) submitted to the IND | |
| January 30, 2012 | Fast Track Designation for CLL granted | |
| March 7, 2012 | Type C Meeting | To discuss the pharmacology development plan |
| July 1, 2013 | Type B Pre-NDA Meeting | To discuss the content for NDA submission for iNHL and obtain feedback on proposed CLL indication |
| October 7, 2013 | Type A Meeting | To discuss early termination of Study GS-US-312-0116 for efficacy based on interim analysis |

2.6 Other Relevant Background Information

The target patient population for study 312-0116 was subjects with previously treated recurrent CLL that required therapy for CLL and were not fit to receive cytotoxic therapy because of chemotherapy-induced bone marrow damage or other comorbid conditions. In standard practice, given the low response rates seen, single-agent rituximab is only used in patients that are too frail or are otherwise unfit to receive standard chemoimmunotherapy. The applicant planned to primarily use CIRS to identify a population that would not be appropriate for chemoimmunotherapy.

In correspondence sent to the applicant in August 2012 regarding Study GS-312-0116, the Agency reiterated that the “CIRS does not identify a population of patients who would not be eligible for standard chemotherapy. CIRS has not been validated for CLL or in any other cancer setting. In addition, the patient heterogeneity as a result of using CIRS would be a problem in labeling a patient population based on CIRS data.”

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was provided in accordance with the International Conference on Harmonization Electronic Common Technical Document (eCTD).

3.2 Compliance with Good Clinical Practices

Study 312-0116 was conducted under an IND application and in accordance with ICH guideline for Good Clinical Practice and the principles embodied in the Declaration of Helsinki. The protocol, protocol amendments, and consent forms were submitted by each investigator to an independent ethics committee (IEC) or institutional review board (IRB) for review and approval prior to study initiation.

There were 66 major protocol deviations in Study 312-0116. These deviations pertain to deviations in stratification, screening, eligibility criteria, SAE reporting timelines, and missed or delayed study procedures or deviations in dosing.

The following sites were inspected by the FDA Office of Scientific Investigations as part of the NDA review:

- Georgetown University (PI- Bruce Cheson, MD)
- Cornell University (PI- Richard Furman, MD)
- Fred Hutchinson Center (PI- John Pagel, MD, PhD)
- Gilead Sciences, Inc.

For the Fred Hutchinson Center study site, a Form FDA 483 was issued for failure to follow the study protocol according to the investigational plan and for failure to prepare and to maintain adequate records. It was felt that the regulatory deficiencies noted above were noncritical to determination of efficacy or subject safety. Sensitivity analyses were conducted by the statistical review team to evaluate the impact of this site on the trial primary efficacy results. The study data collected from this clinical site and data submitted by the sponsor were felt to appear generally reliable in support of the requested indication.

3.3 Financial Disclosures

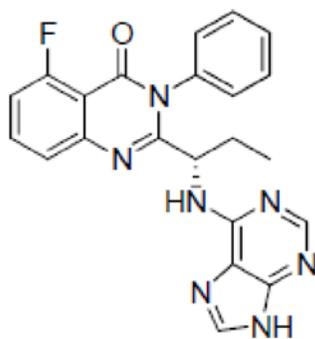
The applicant submitted financial disclosure information for investigators. There were no principal investigators or sub-investigators from Study 312-0116 who reported financial interest or arrangements as described in 21 CFR 54.4(a)(3).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Idelalisib is a phosphatidylinositol 3-kinase (PI3K) p110 δ inhibitor. The chemical name for Idelalisib is 5-Fluoro-3-phenyl-2-[(1S)-1-(9H-purin-6-ylamino)propyl]quinazolin-4(3H)-one. The molecular formula is C₂₂H₁₈FN₇O which corresponds to a formula weight of 415.42. The structure of Idelalisib is shown in the figure below.

Figure 1. Chemical Structure of Idelalisib



Idelalisib tablets, 100mg (orange color) and 150 mg (pink color) are oval-shaped, film-coated tablets. The core inactive excipients ingredients are microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, sodium starch glycolate, and magnesium stearate. The aqueous solubility of Idelalisib is pH dependent. It is soluble in acidic pH and insoluble in basic pH.

Refer to the CMC Review for further details.

4.2 Clinical Microbiology

The CMC Microbiological review indicated that the microbiological examination tests performed on the drug product packaged in the proposed commercial packaging stored at long-term and accelerated stability conditions establish low microbial burden in the Idelalisib tablets during storage.

4.3 Preclinical Pharmacology/Toxicology

Toxicology studies performed by the applicant include: 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 deaths in all rat studies, with the cause of death as undetermined or related to liver toxicity. Cardiomyopathy was observed in surviving rats in the 13-week and 6-month studies. The Clinical Pharmacology reviewers noted the following toxicities with repeat dosing of Idelalisib in the following tissues/organs: hematopoietic/lymphoid system (lymphoid depletion, reduced spleen and thymus weight, thymic hemorrhage and necrosis, myeloid and granulopoietic hyperplasia); liver (increased liver enzymes, increased liver weight, inflammation, hepatocellular necrosis); GI tract infiltration, hemorrhage, and ulceration; heart (in rats, myocardium infiltrate, fibrosis, increased heart rate); male reproductive systems (testicular seminiferous tubule degeneration, reduced testicular weight).

Refer to the Pharmacology-Toxicology Review for further details.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Idelalisib inhibits adenosine-5'-triphosphate (APT) binding to the catalytic domain of phosphatidylinositol 3-kinase (PI3K). PI3K δ is thought to modulate B-cell receptor signaling and signaling through cytokine, chemokine, and integrin receptors.

4.4.2 Pharmacodynamics

Refer to section 4.4.3 and the Clinical Pharmacology Review for further details.

4.4.3 Pharmacokinetics

The Clinical Pharmacology review noted that the absolute bioavailability of Idelalisib has not been evaluated in humans. The median t_{max} was 1.5 hours after a dose of Idelalisib under fasting conditions in patients with hematologic malignancies. Idelalisib and its metabolites are predominantly distributed to plasma. Idelalisib undergoes metabolism

by aldehyde oxidase and CYP3A4 to form its major metabolite GS-563117. The metabolism by aldehyde oxidase accounts for approximately 43% of the overall metabolism of Idelalisib and CYP3A4 accounts for approximately 19%. Hepatobiliary is the major route of elimination. The population estimated elimination half-life is 8.2 hours.

Refer to the Clinical Pharmacology Review for further details.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The efficacy and safety of Idelalisib is based on the results of Study 312-0116. This is a randomized, placebo-controlled trial of Idelalisib in combination with rituximab in patients with relapsed chronic lymphocytic leukemia.

The application contains efficacy results from 220 patients with relapsed CLL who were enrolled in Study 312-0116.

The safety analysis of Idelalisib is based on data from 218 subjects with relapsed CLL that were included in the safety population in Study 312-0116. Additional safety results were included from studies 312-0117, 101-07 and 101-08 where applicable. Pooled analyses were not conducted due to the disparate nature of the trials, treatment regimens used, and the patient populations studied.

Table 5. Clinical Trials Reviewed

| Clinical Trial ID | Study Design | Intervention | Number of Subjects | Patient Population | Status |
|-------------------|---|---|-------------------------------|------------------------|------------|
| 312-0116 | Phase 3, Randomized, double-blind, placebo-controlled | Idelalisib 150 mg BID plus rituximab vs. placebo plus rituximab | Planned: 200 Enrolled: 220 | Previously treated CLL | Terminated |
| 312-0117 | Phase 3, 2 arm, extension study | Idelalisib 150mg BID or Idelalisib 300 mg BID | Planned: up to 160 | Previously treated CLL | Ongoing |
| 101-07 | Phase I, Open-label | Idelalisib in combination with Rituximab, Bendamustine, Rituximab + | Planned: 210 Enrolled: 226 | CLL, iNHL, or MCL | Ongoing |

| | | | | | |
|--------|--------------------|---|-----------------------------|---|---------|
| | | Bendamustine, Ofatumumab, or Fludarabine | | | |
| 101-08 | Phase 2 Single-arm | Idelalisib 150 mg BID in combination with Rituximab | Planned: 59 Enrolled: 64 | Elderly Subjects with Previously untreated CLL or SLL | Ongoing |

5.2 Review Strategy

The clinical review was primarily based on the efficacy and safety data of Study 312-0116. The electronic submission, with the CSRs were reviewed and analyzed. The key review materials and activities are listed below:

- The electronic submission of the NDA;
- Relevant published literature
- Relevant prior regulatory history
- Relevant applicant submissions in response to the review team's information requests
- Sponsor presentations to the FDA
- Major efficacy and safety analyses were reproduced or audited

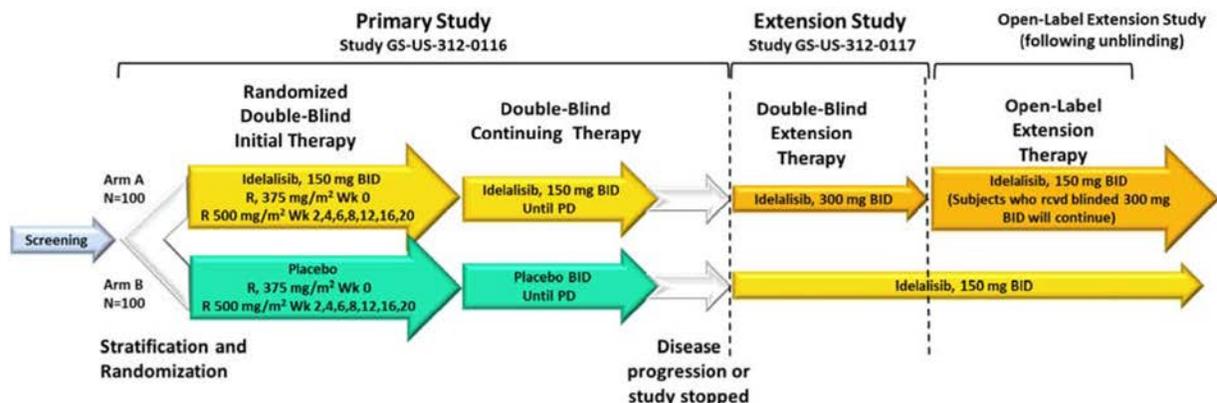
5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Study 312-0116

Study Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination with Rituximab for Previously Treated Chronic Lymphocytic Leukemia

Study Design: Study 312-0116 was a phase 3, multicenter, randomized, placebo-controlled trial of Idelalisib in combination with rituximab. Subjects were randomized to the two study arms in a 1:1 ratio. There were 3 stratification factors: 17p deletion and/or p53 mutation (either or neither); immunoglobulin heavy chain variable region (IgHV) mutation (unmutated or mutated); any prior therapy with an anti-CD20 antibody (yes or no). The study design for Study 312-0116 is included below.

Figure 2. Study Design Study 312-0116



Source: Sponsor's Second Interim Clinical Study Report, Section 16.1.1, Amendment 4 link, Clinical Protocol section 2.1

Trial Population: Eligible subjects were those with relapsed CLL that required treatment of CLL and had comorbidities that did not allow for treatment with standard chemotherapy based on one or more of the following: grade ≥ 3 neutropenia or thrombocytopenia attributable to myelotoxic effects of prior therapy, estimated CrCL ≤ 60 mL/min, or cumulative illness rating score (CIRS) > 6 .

Inclusion Criteria (summarized):

1. Male or female patients ≥ 18 years of age
2. Diagnosis of B-cell CLL, with diagnosis established according to International Workshop on CLL (IWCLL) criteria
3. CLL that warrants treatment (consistent with accepted IWCLL criteria for initiation of therapy). Any of the following conditions constitute CLL that warrants therapy:
 - Evidence of progressive marrow failure as manifested by the onset or worsening of anemia and/or thrombocytopenia
 - Massive (lower edge of spleen ≥ 6 cm below left costal margin), progressive, or symptomatic splenomegaly
 - Massive (≥ 10 cm in the longest diameter), progressive, or symptomatic lymphadenopathy
 - Progressive lymphocytosis in the absence of infection, with an increase in blood ALC $\geq 50\%$ over a 2 month period or lymphocyte doubling time of < 6 months (as long as initial ALC was $\geq 30,000/L$)

- Autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy
- Constitutional symptoms, defined as any one or more of the following disease-related symptoms or signs occurring in the absence of evidence of infection
 - Unintentional weight loss of $\geq 10\%$ within the previous 6 months
 - Significant fatigue \geq grade 2
 - Fevers $> 100.5^{\circ}$ F or 38.0° C for ≥ 2 weeks
 - Night sweats for > 1 month
- 4. Presence of measurable lymphadenopathy (defined as the presence of ≥ 1 nodal lesion that measures ≥ 2 cm in the longest diameter (LD) and ≥ 1 cm in the longest perpendicular diameter (LPD) as assessed by computed tomography [CT] or magnetic resonance imaging [MRI]).
- 5. Prior treatment for CLL comprised of any of the following
 - Prior treatment with ≥ 1 regimen containing a therapeutic anti-CD20 antibody (eg- rituximab, ofatumumab, GA-101) administered for ≥ 2 doses of antibody treatment or
 - Prior treatment with ≥ 2 regimens containing ≥ 1 cytotoxic agent (eg- fludarabine, pentostatin, cladribine, cyclophosphamide, chlorambucil, bendamustine) administered for ≥ 2 cycles of cytotoxic treatment

Note: Prior anti-CD20 antibody or cytotoxic drugs may have been administered as single agents or as components of combination therapies. Subjects may also have received other commercially available therapies (eg, alemtuzumab, lenalidomide, corticosteroids, or others) or non-excluded investigational therapies. Each repeated course of the same single-agent or combination is considered an independent regimen.

- 6. In a subject whose last prior therapy contained an anti-CD20 antibody, evidence of disease improvement during that therapy or documentation of CLL progression ≥ 6 months after completion of that therapy ***Note: Subjects who did not receive a therapeutic anti-CD-20 antibody (eg, rituximab, ofatumumab, GA-101) as a component of the last prior therapy need not have experienced disease***

improvement or may have relapsed <6 months from the completion of the prior regimen.

7. Documentation of CLL progression < 24 months since the completion of the last prior therapy for CLL.
8. Discontinuation of all therapy for the treatment of CLL ≥ 3 weeks before randomization
9. All acute toxicities from any prior antitumor therapy must have resolved to ≤ grade 1 before randomization (with the exception of alopecia [Grade 1 or 2 permitted], neurotoxicity [Grade 1 or 2 permitted], or bone marrow parameters [any of Grade 1, 2, 3, or 4 permitted]).
10. Karnofsky Performance score of ≥ 40
11. Appropriate for non-cytotoxic containing therapy based on at least one of the following criteria:
 - Grade ≥ 3 neutropenia or thrombocytopenia attributable to cumulative myelotoxicity from prior administration of cytotoxic agents (as documented by bone marrow biopsy obtained since last prior therapy)
 - Estimated CrCl < 60 mL/min (Cockcroft-Gault method)
 - Cumulative Illness Rating Scale (CIRS) score of > 6
12. Required baseline laboratory data Note: Confirmation should be considered for out-of-range values to determine if the abnormality is real or artifactual. Values should be obtained within the screening period and should generally be the most recent measurement obtained. Subjects with any degree of neutropenia, thrombocytopenia, or anemia due to CLL or prior therapy may enroll.

Table 6. Inclusion Criteria Baseline Lab Requirements

| Organ System | Parameter | Required Value |
|--------------|-------------------------------|--|
| Hepatic | Serum total bilirubin | ≤1.5 x ULN (unless elevated due to Gilbert's syndrome) |
| | Serum ALT | ≤2.5 x ULN |
| | Serum AST | |
| Renal | eC _{Cr} ^a | >30 ml/min |
| Pregnancy | β-HCG ^b | Negative |
| Infection | HIV | Negative HIV antibody |
| | HBV | Negative HBsAg and negative HBc antibody |
| | HCV | Negative viral RNA (if HCV antibody is positive) |

Source: Sponsor's Second Interim Clinical Study Report, Section 16.1.1, Amendment 4 link, Protocol section 4.2.1

13. For females of childbearing potential, willingness to use a protocol-recommended method of contraception
14. For males of childbearing potential and having intercourse with females of childbearing potential, willingness to use a protocol-recommended method of contraception
15. In the judgment of the investigator, the protocol offers an acceptable benefit-to-risk ratio
16. Willingness to comply with scheduled visits, drug administration plan, and other study procedures
17. Evidence of a signed informed consent form

Exclusion Criteria (summarized):

1. Known histologic transformation from CLL to an aggressive lymphoma (Richter transformation). **Note: Biopsy documentation of the absence or presence of transformation is not required.**
2. Presence of Intermediate- or high-grade myelodysplastic syndrome
3. History of a non-CLL malignancy except the following (basal or squamous cell carcinoma of skin, cervical carcinoma in situ, superficial bladder cancer, prostate cancer, or any other cancer that has been in complete remission for ≥ 5 years)
4. Evidence of ongoing systemic bacterial, fungal, or viral infection at the time of randomization
5. Ongoing drug-induced liver injury, chronic active hepatitis C, chronic active hepatitis B, alcoholic liver disease, non-alcoholic steatohepatitis, primary biliary cirrhosis, extrahepatic obstruction caused by cholelithiasis, cirrhosis of the liver, or portal hypertension
6. Ongoing drug-induced pneumonitis
7. Ongoing inflammatory bowel disease
8. Ongoing alcohol or drug addiction
9. Pregnant or breast feeding
10. History of prior allogeneic bone marrow progenitor cell or solid organ transplant

11. Ongoing immunosuppressive therapy, including systemic steroids for the treatment of CLL **Note: Subjects may use topical, enteric, or inhaled corticosteroids as therapy for comorbid conditions and systemic steroids for autoimmune anemia and/or thrombocytopenia. Ongoing use of low-dose systemic corticosteroids (≤ 5 mg/day of methylprednisolone or equivalent) for rheumatologic conditions is permitted. During study participation, subjects may receive systemic or other corticosteroids as pretreatment for rituximab infusions or as needed for treatment-emergent comorbid conditions.**
12. Prior therapy with any inhibitor of AKT, BTK, JAK, mTOR, PI3K, or spleen tyrosine kinase (Syk)
13. History of anaphylaxis in association with previous administration of monoclonal antibodies.
14. Concurrent participation in another therapeutic clinical trial
15. Prior ongoing clinically significant illness, medical condition, surgical history, physical finding, ECG finding, or lab abnormality that in the investigator's opinion could adversely affect the safety of the subject or impair the assessment of study results

Study Treatment: Eligible subjects received either placebo or Idelalisib in combination with rituximab. Idelalisib or placebo was administered at doses of 150 mg orally twice daily continuously until subject withdrawal, progression of CLL, or intolerable study drug-related toxicities, or met other subject withdrawal criteria. Rituximab was administered as a maximum 8 infusions over 6 months (every 2 weeks for 5 infusions then every 4 weeks for 3 infusions). Subjects were given Rituximab intravenously 375 mg/m² on Day 1 (week 0) and continued with a dose of 500 mg/m² on Day 15 (week 2), Day 29 (week 4), Day 43 (week 6), Day 57 (week 8), Day 85 (week 12), Day 113 (Week 16), Day 141 (week 20). Dose modifications and dose delays were permitted as part of the trial. In the event that an adverse event occurred, study drug administration was to be held until the adverse event resolved to grade ≤ 1 . Upon re-initiation of therapy, the dose was to be reduced to dose level -1 (100 mg/ dose BID). The following dose reduction recommendations were included in the protocol and were based on study drug-related toxicity, graded according to NCI CTCAE version 4.03.

Table 7. Dose Modification Recommendations from Study 312-0116

| NCI CTCAE Grade | Recommendation | |
|---|--|---|
| | Idelalisib | Rituximab |
| HEMATOLOGICAL ADVERSE EVENTS | | |
| Neutropenia | | |
| Grade ≤2 neutropenia | Maintain current dose level and schedule. | Maintain current dose level and schedule. |
| Grade ≤3 neutropenia | During combination or continuing single-agent therapy periods, maintain current idelalisib dose level and schedule. Consider G-CSF support. | Maintain current dose level and schedule. Consider G-CSF support. |
| Grade 4 neutropenia (or occurrence of neutropenic fever or infection) | During combination therapy period, consider G-CSF support and maintain current idelalisib dose level and schedule. During continuing single-agent idelalisib therapy period, consider G-CSF support and continue idelalisib at initial or lower dose level at investigator discretion. | Delay rituximab until Grade ≤3 (ANC ≥0.5 x 10 ⁹ /L) and/or neutropenic fever or infection is resolved; thereafter, resume at full dose. Consider G-CSF support to avoid delays. If delay is >4 weeks, discontinue rituximab. |
| Thrombocytopenia | | |
| Grade ≤3 | Maintain current dose level and schedule. | Maintain current dose level and schedule. |
| Grade 4 | During combination therapy period, maintain current idelalisib dose level and schedule. During continuing single-agent idelalisib therapy period, withhold for bruising or bleeding until Grade ≤3. May resume idelalisib at initial or lower dose level at investigator discretion. | Delay rituximab until Grade ≤3 (platelets ≥25 x 10 ⁹ /L); thereafter, resume at full dose. If delay is >4 weeks, discontinue rituximab. |
| NON-HEMATOLOGICAL ADVERSE EVENTS | | |
| Dermatological | | |
| Grade ≤1 | Maintain current dose level and schedule. | Maintain current dose level and schedule. |
| Grade 2 | Withhold idelalisib until Grade ≤1. Resume idelalisib at current dose level. If rechallenge at current dose level results in recurrence, may resume at same or lower idelalisib dose level at investigator discretion. | Delay rituximab until Grade ≤1; thereafter, resume at full dose. |
| Grade 3 or 4 | Withhold idelalisib until Grade ≤1. May resume at lower dose level or discontinue idelalisib at investigator discretion. | Delay rituximab until Grade ≤1; thereafter, may resume at full dose or discontinue rituximab at investigator discretion. |
| Gastrointestinal Inflammation/Diarrhea | | |
| Grade ≤1 | Provide anti-diarrheal (eg, loperamide) and maintain current idelalisib dose level and schedule | Maintain current dose level and schedule. |

| NCI CTCAE Grade | Recommendation | |
|--|---|---|
| | Idelalisib | Rituximab |
| Grade 2 | Provide anti-diarrheal (eg, loperamide). Withhold idelalisib until Grade ≤1. Resume idelalisib at current dose level. If rechallenge results in recurrence, may resume at initial or lower dose level at investigator discretion. Consider addition of anti-inflammatory (eg, sulfasalazine, budesonide). | Maintain current dose level and schedule. |
| Grade 3 | Provide anti-diarrheal (eg, loperamide). Withhold idelalisib until Grade ≤1. Resume at lower dose level. Consider addition of anti-inflammatory (eg, sulfasalazine, budesonide). | Delay rituximab as necessary to ensure subject is sufficiently stable to receive further treatment; thereafter maintain full dose and schedule. |
| Grade 4 | Provide anti-diarrheal (eg, loperamide). Withhold idelalisib until Grade ≤1. May resume at lower dose level or discontinue idelalisib at investigator discretion. Consider addition of anti-inflammatory (eg, sulfasalazine, budesonide). | Delay rituximab as necessary to ensure subject is sufficiently stable to receive further treatment; thereafter maintain full dose and schedule. |
| Hepatic Adverse Events (elevations in ALT, AST, or bilirubin) | | |
| Grade ≤1 (ALT/AST≤3xULN) (Bilirubin≤1.5xULN) | Maintain current dose level and schedule. | Maintain current dose level and schedule. |
| Grade 2 (ALT/AST>3-5xULN) (Bilirubin>1.5- ≤3xULN) | Maintain current dose level and schedule. Monitor ALT, AST, ALP, and bilirubin at least 1x per week. | Maintain current dose level and schedule. |
| Grade 3 (ALT/AST>5-20xULN) (Bilirubin>3-10xULN) | Withhold idelalisib. Monitor ALT, AST, ALP, and bilirubin at least 1x per week until all abnormalities are Grade ≤1. If bilirubin abnormality was Grade <3, resume idelalisib at same dose level. If bilirubin abnormality was Grade ≥3, resume at lower dose level. | Delay rituximab as necessary to ensure subject is sufficiently stable to receive further treatment; thereafter maintain full dose and schedule. |
| Grade 4 (ALT/AST>20xULN) (Bilirubin>10xULN) | Withhold idelalisib. Monitor ALT, AST, ALP, and bilirubin at least 1x per week until all abnormalities are Grade ≤1. If bilirubin abnormality was Grade <4, resume idelalisib at lower dose level. If bilirubin abnormality was Grade 4, discontinue idelalisib. | Delay rituximab as necessary to ensure subject is sufficiently stable to receive further treatment; thereafter maintain full dose and schedule. |
| Pneumonitis (dyspnea, cough, hypoxia and/or diffuse interstitial pattern or ground-glass opacities on chest CT and no obvious infectious cause) | | |
| Grade ≤1 | Maintain current dose level and schedule. Consider pneumocystis prophylaxis. | Maintain current dose level and schedule. |
| Grade 2 | Withhold idelalisib until Grade ≤1, consider systemic corticosteroids and pneumocystistreatment. May resume at initial or lower dose level at investigator discretion. | Delay rituximab as necessary to ensure subject is sufficiently stable to receive further treatment; thereafter maintain full dose and schedule. |

| NCI CTCAE Grade | Recommendation | |
|--|---|---|
| | Idelalisib | Rituximab |
| Grade ≥3 | Withhold idelalisib until Grade ≤1, consider systemic corticosteroids and consider pneumocystis treatment. May resume at lower dose level or discontinue idelalisib at investigator discretion. | Delay rituximab as necessary to ensure subject is sufficiently stable to receive further treatment; thereafter maintain full dose and schedule or discontinue rituximab at investigator discretion. |
| Other Nonhematological Adverse Events | | |
| Grade ≤2 | Maintain current dose level and schedule | Maintain current dose level and schedule. |
| Grade ≥3 | Withhold idelalisib until Grade ≤1. May resume idelalisib at initial or lower dose level or discontinue idelalisib at investigator discretion. | Delay rituximab as necessary to ensure subject is sufficiently stable to receive further treatment; thereafter maintain full dose and schedule or discontinue rituximab at investigator discretion. |

Source: Sponsor's Second Interim Clinical Study Report, Section 16.1.1, Amendment 4 link, Clinical Protocol section 5.3.1.6

Schedule of Events: The following assessments were performed as part of the screening, treatment, and follow-up periods of study 312-0116.

Table 8. Schedule of Events for Study 312-0116

| Period | Screen | | Treatment | | | | | | | | | | | | | | Follow-up | | |
|---|-----------------|---|-----------|----|----|----|----|----|-----|-----|-----|-----|-----|-----|-----|-----|--------------|-----------|-----------------|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16+ | End of study | 30 day | Long-term |
| Week | -4 | 0 | 2 | 4 | 6 | 8 | 10 | 12 | 16 | 20 | 24 | 30 | 36 | 42 | 48 | | | Q12 weeks | Within +30 days |
| Study Day | Within -28 days | 1 | 15 | 29 | 43 | 57 | 71 | 85 | 113 | 141 | 169 | 211 | 253 | 295 | 337 | | | | |
| Visit Window | | | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±7 | | | |
| Informed consent | X | | | | | | | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | | | | | | | |
| CIRS assessment | X | | | | | | | | | | | | | | | | | | |
| Serum virology | X | | | | | | | | | | | | | | | | | | |
| β-HCG (women of childbearing potential) | X | X | | X | | X | | X | X | X | X | X | X | X | X | X | X | | |
| CLL peripheral blood evaluation | X | | | | | | | | | | | | | | | | | X | |
| CLL serology | X | | | | | | | | | | | | | | | | | X | |
| Coagulation | X | | | | | | | | | | | | | | | | | | |
| Urinalysis | X | | | | | | | | | | | | | | | | | | |
| 12-lead ECG | X | | | | | | | | | | | | | | | | | | |
| IWRS | X | X | X | X | X | X | | X | X | X | X | X | X | X | X | X | X | | |
| Genotyping and expression analysis | | X | | | | | | | | | | | | | | | | X | |
| HRQL/healthy utility – FACT-Leu/EQ-5D | | 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 |
| Performance status | X | X | X | X | X | X | | X | X | X | X | X | X | X | X | X | X | | |
| Physical exam (includes nodes, liver, spleen) | X | X | | X | | X | | X | X | X | X | X | X | X | X | X | X | | |
| Oxygen saturation (by pulse oximetry) | 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 | | |
| Serum chemistry | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |

| Period | Screen | Treatment | | | | | | | | | | | | | | | Follow-up | | |
|---|-----------------|-----------|----|----|----|----|----|----|-----|-----|-----|-----|-----|-----|-----|-----------|--------------|-----------------|-------------|
| Visit | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16+ | End of study | 30 day | Long-term |
| Week | -4 | 0 | 2 | 4 | 6 | 8 | 10 | 12 | 16 | 20 | 24 | 30 | 36 | 42 | 48 | Q12 weeks | | Within +30 days | To +5 years |
| Study Day | Within -28 days | 1 | 15 | 29 | 43 | 57 | 71 | 85 | 113 | 141 | 169 | 211 | 253 | 295 | 337 | | | | |
| Visit Window | | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±7 | | | |
| Circulating cells | | X | X | X | | X | | X | X | X | X | X | X | X | X | X | X | | |
| Biomarkers | | X | X | X | | X | | X | X | X | X | X | X | X | X | X | X | | |
| Serum Igs | | X | X | X | | X | | X | X | X | X | X | X | X | X | X | X | | |
| Idelalisib/placebo administration in clinic | | X | X | X | | X | | X | X | X | X | | | | | | | | |
| Idelalisib pharmacokinetics | | X | X | X | | X | | X | X | X | X | | | | | | | | |
| Premedication and rituximab administration | | X | X | X | X | X | | X | X | X | | | | | | | | | |
| Infusion severity and duration assessment | | X | X | | | | | | | | | | | | | | | | |
| Idelalisib/placebo dispensing/accounting | | X | | X | | X | | X | X | X | X | | X | | X | X | X | | |
| Radiology assessment (CT/MRI) ^a | X ^b | | | | | X | | X | X | X | X | | X | | X | X | X | | |
| Bone marrow biopsy/aspirate ^c | X | | | | | X | | X | X | X | X | | X | | X | X | X | | |
| Post-treatment CLL therapy | | | | | | | | | | | | | | | | | | | X |
| Long-term follow-up | | | | | | | | | | | | | | | | | | | X |

Source: Sponsor's Second Interim Clinical Study Report, Section 16.1.1, Amendment 4 link, Protocol section 6.2, appendix 7

Statistics: The primary endpoint of Study 312-0116 was PFS, defined as the interval from randomization to the earlier of the first documentation of definitive disease progression or death from any cause. The analysis of PFS was adjudicated by the IRC and was based on the intention-to-treat analysis set, which included all subjects randomized regardless of whether subject received any study drug, or received a regimen different from that to which they were randomized. For the primary analysis, the difference in PFS between the two treatment arms was assessed using Kaplan-Meier methods and the stratified log-rank test adjusted for stratification factors. There were 4 secondary endpoints that were tested sequentially to control for Type I error. These endpoints were: overall response rate, lymph node response rate, complete response rate, and overall survival. If the primary efficacy hypothesis was rejected at the 2-sided 0.05 significance level, then the 4 secondary endpoints would be sequentially tested at the 2-sided 0.05 significance level in the order listed above.

For the primary analysis, the null hypothesis assumed a hazard ratio equal to 1 (no difference between treatment arms), while the alternative hypothesis posited a hazard ratio of 0.57 demonstrating superiority of the Idelalisib-containing arm. Based on these assumptions, 119 events (definitive CLL progressions) were required to achieve a power of > 0.85 based on a stratified log-rank test with a 2-sided significance level of 0.05. It was estimated that 100 subjects per treatment arm would yield the required number of events.

Criteria for Response: Response was categorized by the IRC as CR, PR, SD, or PD. Additionally, there were categories of not evaluable (NE) and no disease (ND). The definition for each of these responses is listed below.

Complete Response (CR): All of the following criteria must be met to satisfy criteria for a CR

- No evidence of new disease
- ALC in peripheral blood $< 4 \times 10^9/L$
- Regression of all index nodal masses to normal size ≤ 1.5 cm in the LD
- Normal spleen and liver size
- Regression to normal of all nodal non-index disease and disappearance of all detectable non-nodal, non-index disease
- Morphologically negative bone marrow defined as $< 30\%$ of nucleated cells being lymphoid cells and no lymphoid nodules in a bone marrow sample that is normocellular for age
- Peripheral blood counts meeting all the following criteria:
 - ANC $> 1.5 \times 10^9/L$ without need for exogenous growth factors
 - Platelet count $\geq 100 \times 10^9/L$ without need for exogenous growth factors
 - Hemoglobin ≥ 11.0 g/dL without need for red cell transfusions or the need for exogenous growth factors
- **Note: Subjects who fulfill all the criteria for a CR (including bone marrow criteria) but who have a persistent anemia, thrombocytopenia, or neutropenia or a hypocellular bone marrow that is related to prior or ongoing drug toxicity (and not to CLL) will be considered as a CR with incomplete marrow recovery (CRi).**

Partial Response (PR): All of the following criteria must be met to satisfy criteria for PR

- No evidence of new disease
- A change in the disease status meeting ≥ 2 of the following criteria, with 2 exceptions in which only 1 criterion is needed: (1) Only lymphadenopathy is present at baseline; (2) Only lymphadenopathy and lymphocytosis are present at baseline. In these 2 cases, only lymphadenopathy must improve to the extent specified below:
 - In a subject with baseline lymphocytosis (ALC $\geq 4 \times 10^9/L$), a decrease in peripheral blood ALC by $\geq 50\%$ from baseline or a decrease to $< 4 \times 10^9/L$
 - A decrease by $\geq 50\%$ from the baseline in the SPD of the index nodal lesions
 - In a subject with enlargement of the spleen at baseline, a splenomegaly response as defined by a 50% decrease (minimum 2 cm decrease) from baseline in the enlargement of the spleen in its LVD or decrease to ≤ 12 cm by imaging is required.
 - In a subject with enlargement of the liver at baseline, a hepatomegaly response as defined by a 50% decrease (minimum 2 cm decrease) from baseline in the enlargement of the liver in its LVD or decrease to ≤ 18 cm.
 - A decrease by $\geq 50\%$ from baseline in the CLL marrow infiltrate or in B-lymphoid nodules
- No index, splenic, liver or non-index disease with worsening that meets the criteria for definitive PD
- Peripheral blood counts meeting ≥ 1 of the following criteria:

- ANC $> 1.5 \times 10^9/L$ of $\geq 50\%$ increase over baseline without need for exogenous growth factors
- Platelet count $\geq 100 \times 10^9/L$ or $\geq 50\%$ increase over baseline without need for exogenous growth factors
- Hemoglobin ≥ 11.0 g/dL without need for red cell transfusions or the need for exogenous growth factors

Stable Disease: The following criteria must be met:

- No evidence of new disease
- There is neither sufficient evidence of tumor shrinkage to qualify for PR nor sufficient evidence of tumor growth to qualify for definitive PD

Definitive Progressive Disease: the occurrence of any of the following events indicates definitive PD

- Evidence of any new disease
 - A new node that measures > 1.5 cm in the LD and > 1.0 cm in the LPD
 - New or recurrent splenomegaly, with minimum LVD of 14 cm
 - New or recurrent hepatomegaly, with a minimum LVD of 20 cm
 - Unequivocal reappearance of an extra-nodal lesion of any size
 - A new unequivocal extra-nodal lesion of any size
 - New non-index disease (eg- effusions, ascites, or other organ abnormalities related to CLL)

Note: Isolated new effusions, ascites, or other organ abnormalities are not sufficient evidence alone of PD unless histologically confirmed. Thus, a declaration of PD should not be made if this is the only manifestation of apparently new disease.

- Evidence of worsening of index lesions, spleen, liver, or non-index disease:
 - Increase from the nadir by $\geq 50\%$ from the nadir in the SPD of index lesions
 - Increase from the nadir by $\geq 50\%$ in the LD of an individual node or extra-nodal mass that now has an LD of 1.5 cm and an LPD of > 1.0 cm
 - Splenic progression, defined as an increase in splenic enlargement by $\geq 50\%$ from nadir (with a minimum 2 cm increase and a minimum LVD of 14 cm)
 - Hepatic progression, defined as an increase in hepatic enlargement by $\geq 50\%$ from nadir (with a minimum 2 cm increase and minimum LVD of 20 cm)
 - Unequivocal increase in the size of non-index disease (eg, effusions, ascites, or other organ abnormalities related to CLL)
 - Transformation to a more aggressive histology (eg, Richter syndrome) as established by biopsy (with the date of the biopsy being considered the date of CLL progression is the subject has no earlier objective documentation of CLL progression)

- Decrease in platelet count or hemoglobin that is attributable to CLL, is not attributable to an autoimmune phenomenon, and is confirmed by bone marrow biopsy showing an infiltrate of clonal CLL cells
 - The current platelet count is $< 100 \times 10^9/L$ and there has been a decrease by $> 50\%$ from the highest on-study platelet count
 - The current hemoglobin is 11.0 g/dL and there has been a decrease by > 2 g/dL from the highest on-study hemoglobin

Note: If there is uncertainty regarding whether there is true progression, the subject should continue study treatment and remain under close observation pending confirmation of progression status by the IRC. In particular, worsening of constitutional symptoms in the absence of objective evidence of worsening CLL will not be considered definitive disease progression; in such subjects, both CLL-related and non-CLL-related causes for the constitutional symptoms should be considered. Worsening of disease during temporary interruption of study treatment (eg, for intercurrent illness) is not necessarily indicative of resistance to study treatment. In these instances, CT/MRI or other relevant evaluations should be considered in order to document whether definitive disease progression has occurred. If subsequent evaluations suggest that the subject has experienced persistent definitive CLL progression, then the date of progression should be the time point at which progression was first objectively documented.

Non-Evaluable: In a subject who does not have evidence of PD, the occurrence of any of the following conditions indicates a response status of NE.

- There are no images or inadequate or missing images
- Images of the liver and spleen are missing at that time point (with the exception that absence of splenic images will not result in an NE designation in a subject known to have undergone splenectomy)

Note: A time-point will be considered to have a response of NE if any index lesion is missing. PD may be assigned at any time point regardless of the extent of missing index or non-index lesions. Missing non-index lesions will not impact the ability to assess for response or disease progression.

No Disease: All of the following conditions are required for designation of ND

- No index disease noted at baseline or on-treatment
- No non-index disease noted at baseline or on-treatment

Amendments:

Four amendments were submitted to the IND containing revisions for study 312-0116. The most pertinent changes are described below:

- Amendment 1 (January 23, 1012):
 - The definition of splenomegaly response rate and hepatomegaly response rate were updated and added respectively.

- Spleen and liver assessments were updated to indicate that the nadir values would be used in addition to the baseline values in determination of tumor response and progression. The spleen and liver evaluations were revised to consider changes relative to the *enlargement* of the spleen or liver at baseline.
- It was added that non-index lesion measurements were not needed, and should be followed as present or absent.
- Added that lymphocytosis alone would not constitute disease progression.
- Amendment 2 (December 19, 2012)
 - Added that IRC findings would be considered primary for analyses of PFS and other tumor control endpoints
 - Statistical plan updated to include formal sequential testing for secondary endpoints
 - Confirmation of response at 8 weeks was removed from the response criteria
 - Dose Modifications updated
 - Information added regarding inhibitors and inducers of CYP3A4
 - Added that the nadir LD of individual lesions and the nadir of the SPD would be used as the references for characterization of CLL progression.
 - Added that the spleen would be considered enlarged if it was > 12 cm in the LVD
- Amendment 3 (June 21, 2013)
 - Two formal interim analyses were added to be conducted after ~ 50% and 75% of the expected number of 119 PFS events occurred. The significance levels were 0.001 and 0.005 respectively.
 - Spleen and liver response and progressions were changed such that minimum change of 2cm was removed.
- Amendment 4 (September 10, 2013)
 - The order of secondary endpoints was changed to place overall survival before complete response.
 - Splenomegaly and hepatomegaly response rate and disease progression criteria were changed to require minimum 2 cm change.
 - Splenic progression updated to require a minimum LVD of 14cm, hepatic progression updated to require a minimum LVD of 20 cm.
 - Information added regarding the possible early stopping of the study if there should be overwhelming efficacy noted at an interim analysis.

6 Review of Efficacy

Efficacy Summary

A summary of the key efficacy findings are listed below. The data cutoff date for the efficacy analysis was October 9, 2013.

- The primary endpoint was PFS as assessed by the IRC. PFS between the two treatment arms was compared using a stratified log-rank test, adjusted for the stratification factors: 17p deletion and/or TP53 mutation status and IGHV mutation status. The IRC assessed PFS hazard ratio of the ITT population was 0.18 (95% CI: 0.10, 0.31) stratified log-rank p value <0.0001.
- The median PFS was not reached in the Idelalisib + rituximab group at the time of the interim analysis, and was 5.5 months in the placebo + rituximab group.
- 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%).
- Overall survival was a secondary endpoint. The analysis of overall survival is limited by the small number of events (19 events).

6.1 Indication

The applicant's proposed indication is for the treatment of patients with relapsed chronic lymphocytic leukemia.

6.1.1 Methods

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

- First and second interim clinical Study Report for Study 312-0116
- Protocol, protocol amendments, and statistical analysis plan for Study 312-0116
- Raw and derived datasets for Study 312-0116
- Case Report forms for Study 312-0116
- Narratives for Study 312-0116
- Response to information requests
- Proposed labeling for Idelalisib

The data cutoff date for the efficacy analysis was October 9, 2013.

6.1.2 Demographics

Study 312-0116 randomized 220 patients from 57 clinical sites in 5 countries. Most patients (163, 74%) were enrolled from clinical sites within the US. The ITT population consisted of 220 patients, 110 per treatment group. The baseline demographics, disease history, and prior treatments are summarized in the tables below.

Table 9. Baseline Demographics of the ITT population

| | Idelalisib + R N (%) | Placebo + R N (%) |
|--------------------------------------|-------------------------|----------------------|
| N | 110 | 110 |
| Gender | | |
| Male | 76 (69.0) | 68 (61.8) |
| Female | 34 (30.9) | 42 (38.2) |
| Age (years) | | |
| Median | 71 | 71 |
| Range | 48, 90 | 47, 92 |
| < 65 | 21 (19.1) | 27 (25.0) |
| ≥ 65 | 89 (80.9) | 81 (75.0) |
| Race | | |
| White | 100 (90.9) | 96 (88.9) |
| Asian | 0 | 0 |
| African-American | 3 (2.7) | 3 (2.8) |
| Other or Unknown | 7 (6.4) | 9 (8.3) |
| Country | | |
| USA | 80 (72.7) | 83 (75.5) |
| UK | 18 (16.4) | 14 (12.7) |
| Germany | 7 (6.4) | 5 (4.5) |
| Italy | 2 (1.8) | 5 (4.5) |
| France | 3 (2.7) | 3 (2.7) |
| Karnofsky Performance Status, Median | 80 | 80 |

Table 10. Baseline Disease and Comorbidity Characteristics of the ITT population

| | Idelalisib + R N (%) | Placebo + R N (%) |
|---------------------------|-------------------------|----------------------|
| N | 110 | 110 |
| Deletion 17p | 26 (23.6) | 31 (28.1) |
| IGHV unmutated | 91 (82.7) | 93 (84.5) |
| Number of Prior Therapies | | |
| Median | 3 | 3 |
| Range | 1, 12 | 1, 10 |
| Prior Anti-CD20 therapy | 107 (97.3) | 104 (94.5) |

| | | |
|---|-------------|-----------|
| Prior Single-agent Ritux | 34 (30.9) | 33 (30.0) |
| Single-agent Ritux was prior therapy | 15 (13.6) | 11 (10.0) |
| CIRS Score | | |
| Median | 8.5 | 8 |
| Range | 3, 18 | 1, 18 |
| >6 | 97 (88.2) | 90 (81.8) |
| ≤6 | 13 (11.8) | 20 (18.2) |
| CrCl | | |
| Median | 61.2 | 66.5 |
| Range | 32.4, 160.6 | 21, 198.6 |
| < 60 mL/min | 49 (44.5) | 41 (37.3) |
| Baseline Cytopenias | | |
| Absolute neutrophil count < 1.0 x10 ⁹ /L | 14 (12.7) | 15 (13.6) |
| Platelet count < 50 x 10 ⁹ /L | 16 (14.5) | 27 (24.5) |

The target patient population for study 312-0116 was subjects with previously treated recurrent CLL that required therapy for CLL and were not fit to receive cytotoxic therapy because of chemotherapy-induced bone marrow damage or other comorbid conditions. In standard practice, given the low response rates seen, single-agent rituximab is only used in patients that are too frail or are otherwise unfit to receive standard chemoimmunotherapy. In an attempt to define a patient population that was appropriate for non-cytotoxic therapy, the trial inclusion criteria required that subjects have either:

- Grade ≥ 3 neutropenia or thrombocytopenia attributable to cumulative myelotoxicity from prior cytotoxic agents or
- Estimated creatinine clearance < 60 mL/min or
- A CIRS score > 6.

In correspondence sent to the applicant in August 2012 regarding Study GS-312-0116, the Agency reiterated that the “CIRS does not identify a population of patients who would not be eligible for standard chemotherapy. CIRS has not been validated for CLL or in any other cancer setting. In addition, the patient heterogeneity as a result of using CIRS would be a problem in labeling a patient population based on CIRS data.”

Among the three inclusion criteria listed above, a CIRS score > 6 was the criterion most frequently used for inclusion. One hundred eighty-seven (187) subjects (85%) were enrolled based on meeting the inclusion criterion of CIRS >6. Among those subjects enrolled based on a CIRS score > 6, the median CIRS score was 9 (range 6-18).

As an example, the CIRS criteria for subject 7136-10004 are described. This patient was given a CIRS score of 9. The underlying comorbidities (and scores) for which he was granted a score of 9 are: prostatic hypertrophy (2), loss of hearing (3), chronic bronchitis (recurring) (3), varicose vein discomfort (1). Another subject with a CIRS score of 9, subject 6708-10239, had the following comorbidities: common facial

dermatitis rosacea (1), vulvar dysplasia (2), hypercoagulability (Factor V Leiden) (3), cataract (s/p surgery) (2), GERD (1). Another subject with a CIRS score of 9, subject 6767-10634, had the following comorbidities: atrial fibrillation (1), chronic hives (3), Gilbert's (1), sore throat (2), hypercholesterolemia (2). These subjects had CIRS scores of 9, and this was used to justify their inclusion in the trial. Yet, while these subjects met the inclusion criteria, many of the comorbidities that allowed for their inclusion do not represent serious conditions that would preclude patients from receiving standard chemotherapy in clinical practice. Also of note, for the 3 subjects described above, the CIRS criterion was the only criterion met of the 3 for trial inclusion.

Estimated creatinine clearance <60 mL/min was the second most commonly cited justification for inclusion. Ninety-one (91) subjects (41%) were enrolled based on meeting the inclusion criterion of estimated creatinine clearance <60 mL/min. Among those subjects enrolled with a CrCl < 60ml/min, the median CrCl was 50.7 mL/min (range 21-60.3).

Only 5 subjects were enrolled based on meeting the criteria with grade \geq 3 neutropenia or thrombocytopenia attributable to cumulative myelotoxicity from prior cytotoxic agents.

Sixty-three (63) subjects met two of the three criteria for inclusion.

Subjects were also required to have CLL that warranted or necessitated initiation of treatment. Investigators selected among a pre-defined check list of reasons based on the IWCLL guidelines for the diagnosis and treatment of CLL (Hallek *et al.*, 2008).

Subjects had to meet one of the following criteria:

- Evidence of progressive marrow failure as manifested by the onset or worsening of anemia and/or thrombocytopenia
- Massive (lower edge of spleen \geq 6 cm below left costal margin), progressive, or symptomatic splenomegaly
- Massive (\geq 10 cm in the longest diameter), progressive, or symptomatic lymphadenopathy
- Progressive lymphocytosis in the absence of infection, with an increase in blood ALC \geq 50% over a 2 month period or lymphocyte doubling time of < 6 months (as long as initial ALC was \geq 30,000/L)
- Autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy
- Constitutional symptoms, defined as any one or more of the following disease-related symptoms or signs occurring in the absence of evidence of infection

- Unintentional weight loss of $\geq 10\%$ within the previous 6 months
- Significant fatigue \geq grade 2
- Fevers $> 100.5^{\circ}$ F or 38.0° C for ≥ 2 weeks
- Night sweats for > 1 month

The criteria that led to inclusion in the trial are included below. Subjects could have more than one condition that determined their CLL warranted therapy.

Table 11. CLL Conditions Indicating Treatment Need

| | Idelalisib + R N (%); N=110 | Placebo + R N (%); N=110 | Total N (%); N=220 |
|-----------------------------|--------------------------------|-----------------------------|-----------------------|
| Progressive Marrow Failure | 52 (47.3) | 41 (37.3) | 93 (42.3) |
| Symptomatic Splenomegaly | 21 (19.1) | 18 (16.4) | 39 (17.7) |
| Symptomatic Lymphadenopathy | 45 (40.9) | 47 (42.7) | 92 (41.8) |
| Progressive Lymphocytosis | 33 (30) | 35 (31.8) | 68 (30.9) |
| Autoimmune anemia | 4 (3.6) | 9 (8.2) | 13 (5.9) |
| Constitutional Symptoms | 49 (44.5) | 53 (48.2) | 102 (46.4) |

Subjects enrolled on Study 312-0116 had received a median of 3 prior therapies (range 1-12).

Table 12. Number of Prior Therapies

| | Idelalisib + R N (%) | Placebo + R N (%) | Total N (%) |
|---------------------------|-------------------------|----------------------|----------------|
| N | 110 | 110 | 220 |
| Number of Prior Therapies | | | |
| 1 | 16 (7.3) | 16 (7.3) | 32 (14.5) |
| 2 | 24 (10.9) | 28 (12.7) | 52 (23.6) |
| 3 | 17 (7.7) | 21 (9.5) | 38 (17.3) |
| 4 | 18 (8.2) | 16 (7.3) | 34 (15.5) |
| 5 | 10 (4.5) | 11 (5.0) | 21 (9.5) |
| 6 | 4 (1.8) | 10 (4.5) | 14 (6.4) |
| 7 | 11 (5.0) | 3 (1.4) | 14 (6.4) |
| 8 | 3 (1.4) | 1 (0.5) | 4 (1.8) |

| | | | |
|----|---------|---------|---------|
| 9 | 3 (1.4) | 3 (1.4) | 6 (2.7) |
| 10 | 2 (0.9) | 1 | 3 (1.4) |
| 11 | 1 (0.5) | 0 | 1 (0.5) |
| 12 | 1 (0.5) | 0 | 1 (0.5) |

One hundred ninety nine (199) subjects had received prior rituximab therapy, 101 randomized to the Idelalisib arm, and 98 to the placebo arm. One hundred forty one (141) subjects (65%) received rituximab either as a single-agent or as part of a combination regimen as their more recent prior therapy. Single-agent rituximab was the most recent prior therapy in 26 subjects.

Single-agent rituximab in the relapsed or refractory patient population has limited activity, with most commonly partial responses observed as the best response (Robak, 2012). Given the limited clinical activity of single-agent rituximab, its use is generally reserved for those patients that are frail, elderly, or have serious comorbid conditions that preclude the use of more toxic therapies. Furthermore, repeat treatment would not be an appropriate therapy in patients that have previously had an inadequate response or experienced early relapse. Among the 141 subjects that received rituximab as part of their most recent prior therapy, stable disease or progressive disease was the best response observed among 33 patients. In an attempt to exclude patients that were known to be refractory to monoclonal antibody therapy, the trial inclusion criteria required that if a patient received anti-CD20 therapy as part of their prior regimen, he or she would only be eligible if they had evidence of disease improvement during that therapy or documentation of CLL progression \geq 6 months after completion of that therapy. Fifteen subjects violated this inclusion criterion and are listed in the table below. These subjects had a poor response to a rituximab (or ofatumumab) containing regimen (or single-agent rituximab) and then were enrolled in a trial with a control arm consisting of single-agent rituximab.

Table 13. Subjects with stable or progressive disease in prior rituximab containing regimen

| Subject ID | Treatment Arm | Prior Treatment | Best Response | Time from prior therapy to Idelalisib (days) | Best Response on Study 312-0116 |
|------------|---------------|-----------------------------|---------------|--|---------------------------------|
| 6870-10408 | Idelalisib | Ritux Alone | SD | 49 | PR |
| 6708-10649 | Idelalisib | Ritux Alone | SD | 54 | PR |
| 7291-10686 | Idelalisib | Ritux Alone | SD | 59 | PR |
| 6870-10407 | Placebo | Ritux Alone | SD | 96 | SD |
| 5775-10223 | Idelalisib | Ritux Alone | SD | 135 | PR |
| 7064-10240 | Idelalisib | Ritux-Lenalidomide | PD | 81 | PD |
| 7067-10629 | Placebo | Ofatumumab-Lenalidomide-VCR | SD | 161 | SD |

| | | | | | |
|------------|------------|-------------------------|----|-----|----|
| 2882-10667 | Placebo | CVR-CAR T cells | SD | 150 | SD |
| 2882-10215 | Placebo | BR | SD | 127 | SD |
| 8453-10409 | Idelalisib | R-CV-Dox | SD | 123 | SD |
| 7067-10221 | Placebo | Ofatumumab-Lenalidomide | SD | 112 | SD |
| 2882-10623 | Placebo | R-CP | SD | 105 | SD |
| 8453-10638 | Idelalisib | BR | SD | 79 | SD |
| 7063-10208 | Placebo | BR | SD | 66 | SD |
| 5775-10229 | Placebo | BR | SD | 62 | PD |

6.1.3 Subject Disposition

Table 14. Study 312-0116 Subject Disposition

| | Idelalisib + R N (%); N=110 | Placebo + R N (%); N=110 | Overall N (%); N=220 |
|---|--------------------------------|-----------------------------|-------------------------|
| Treatment Ongoing | 80 (72.7) | 51 (46.4) | 131(59.5) |
| Discontinued | 30 (27.3) | 59 (53.6) | 89 (40.4) |
| Reason for Treatment Discontinuation | | | |
| Progressive Disease or Lack of Efficacy | 7 (6.4) | 42 (38.2) | 49 (22.3)* |
| Death | 2 (1.8) | 2 (1.8) | 4 (1.8) |
| Adverse Event | 12 (10.9) | 12 (10.9) | 24 (10.9) |
| Withdrawal by Subject | 8 (7.3) | 2 (1.8) | 10 (4.5) |
| Physician Decision | 1 (0.9) | 1 (0.9) | 2 (0.9) |

Source: FDA Reviewer's Analysis. Subject 6859-10225 (Idelalisib) was categorized as subject withdrawal, but the comments indicated that the subject withdrew due to adverse events and Subject 7130-10637 (Placebo) was categorized as physician decision, but the comments indicated that the patient's disease was progressing.

*The total number of subjects that had disease progression as a reason for treatment discontinuation on the CRF as indicated in the disposition dataset is 49, while there were 62 IRC adjudicated progression events.

Study 312-0117 was designed as a follow-up study to 312-0116, such that subjects that had disease progression on study 312-0116 were eligible for enrollment in study 312-0117. Study 312-0117 enrolled patients to either Idelalisib 300 mg BID or Idelalisib 150 mg BID depending on the treatment received in study 312-0117. At the time of the data cutoff (October 9, 2013), 44 subjects had rolled over to Study 312-0117. At the time of the second interim analysis of study 312-0116, 62 subjects had progressed, and 57 subjects chose to enroll on study 312-0117.

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint of Study 312-0116 was PFS as assessed by the IRC. PFS was defined as the interval from randomization to the earlier of the first documentation of definitive disease progression or death from any cause. PFS between the two treatment arms was compared using a stratified log-rank test, adjusted for the stratification factors: 17p deletion and/or TP53 mutation status and IGHV mutation status. Although prior anti-CD20 therapy was a randomization stratum, given the high percentage of subjects that had received prior anti-CD20 therapy, this was not included as a stratification factor for analyses.

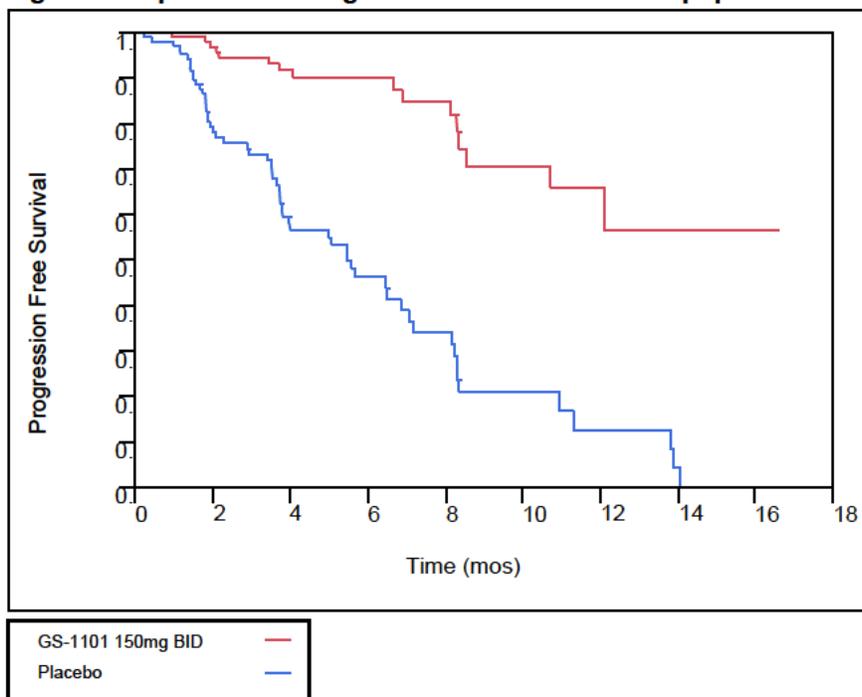
The IRC assessed PFS hazard ratio of the ITT population was 0.18 (95% CI: 0.10, 0.31) stratified log-rank p value <0.0001.

Table 15. PFS assessment by IRC

| | Idelalisib + R N (%); N=110 | Placebo + R N (%); N=110 | Overall N (%); N=220 |
|-------------------------------|---|-----------------------------|-------------------------|
| Subjects with an Event | 16 (14.5) | 59 (53.6) | 75 (34.1) |
| Disease Progression | 11 (10) | 51 (46.4) | 62 (28.2) |
| Death | 5 (4.5) | 8 (7.3) | 13 (5.9) |
| Subjects Censored | 94 (85.5) | 51 (46.4) | 145 (66.4) |
| Ongoing | 82 (74.5) | 46 (41.8) | 128 (58.2) |
| Discontinued without an Event | 12 (10.9) | 5 (4.5) | 17 (7.7) |
| KM Estimate of PFS (months) | | | |
| Median | Not Reached | 5.5 | |
| Adjusted Hazard Ratio | 0.18 (95% CI: 0.10, 0.31); p value < 0.0001 | | |

Source: FDA Reviewer's Analysis

Figure 3. Kaplan-Meier Progression Free Survival ITT population



Source: FDA reviewer's analysis

6.1.5 Analysis of Secondary Endpoints(s)

The secondary endpoints for Study 312-0116 were overall response rate, lymph node response rate, overall Survival, and complete response rate. An assessment of CR was not performed as there were no CRs at the time of the interim analysis. ORR, LNR, and OS were tested sequentially.

Below are the results of the ORR and LNR evaluations. ORR is the percentage of subjects that achieved a best overall response of CR or PR. LNR is defined as the percentage of subjects who achieved a $\geq 50\%$ decrease in the SPD of index lymph nodes. Overall Survival is not included in this review, as there were very few events (19 events) and there was not an adequate allotment of alpha. The applicant submitted simulation analyses to address the concerns pertaining to their calculations of overall survival. The biostatistics review team felt that the simulations did not conclusively show that type I error would be conserved for all possible scenarios that could occur as the data continue to accrue. Therefore, the analysis of overall survival was deemed not reliable. Please refer to the Biostatistics Review for further discussion.

Of note, the analysis of overall response rate consisted of only partial responses as there were no complete responses. Additionally, the assessment of response deviated from the accepted IWG CLL criteria in that confirmation of response at 8 weeks was removed as a requirement in amendment 2.

Table 16. Secondary Endpoint Analyses

| | Idelalisib + R N (%); N=110 | Placebo + R N (%); N=110 | Overall N (%); N=220 |
|-----------------------|--------------------------------|-----------------------------|-------------------------|
| Overall Response Rate | 82 (74.5) | 16 (14.5) | 98 (44.5) |
| Complete Response | 0 | 0 | 0 |
| Partial Response | 82 (74.5) | 16 (14.5) | 98 (44.5) |
| Stable Disease | 19 (17.3) | 68 (61.8) | 87 (39.5) |
| Progressive Disease | 1 (0.9) | 17 (15.5) | 18 (8.2) |
| Not Evaluable | 8 (7.3) | 9 (8.2) | 17 (7.7) |
| LNR | 94 (85.4) | 6 (5.4) | 100 (45.4) |

Source: FDA Reviewer's Analysis

6.1.6 Other Endpoints

An analysis of the duration of response was not performed as there were very few events. Ninety-eight (98) subjects achieved a PR; there were no CRs. Among those subjects that achieved a response, there were 11 events of progression or death after attainment of response (7 in the Idelalisib arm and 4 in the placebo arm). Given the small number of events, analyses of duration of response would be difficult to interpret.

Time to response was assessed among those patients that achieved a PR or CR. The time to response was defined as the time from randomization to date of first best PR or CR. Using a Kaplan-Meier method of analysis, the median time to response was 2.0 months in the Idelalisib arm (range 1.5, 13.9), compared to 3.2 months in the placebo arm (range 1.9, 8.5).

6.1.7 Subpopulations

Fifty-seven (57) subjects (26%) with 17p deletion and 184 (84%) subjects with IgHV unmutated status were enrolled in the trial. The PFS analyses for these subgroups were consistent with the findings observed in the ITT population. The PFS hazard ratio for those subjects with 17p deletion was 0.11 (95% CI: 0.03, 0.33) log-rank p value <0.0001. The PFS hazard ratio for those subjects with IgHV unmutated status was 0.14 (95% CI: 0.07, 0.26) log-rank p value <0.0001. The small number of subjects with 17p deletion limits the interpretation of these results.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The recommended dosing regimen of Idelalisib is based on the results from Study 312-0116. The only dose evaluated in this trial was 150 mg BID. As such, it is difficult to ascertain if lower doses would have a better safety profile and adequate efficacy.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Refer to sections 6.1.4 and 6.1.5.

6.1.10 Additional Efficacy Issues/Analyses

The following sensitivity analyses were conducted for the primary endpoint:

- Analysis of the impact of the inclusion of the subjects that did not meet inclusion criterion based on their prior poor response to an anti-CD20 containing regimen (see section 6.1.2).
- Analysis of the impact of inclusion of FDA identified individuals that did not meet criteria for disease progression. The FDA identified 5 subjects that did not meet criteria for progression; 4 subjects in the placebo arm and 1 in the Idelalisib arm. These 5 subjects met criteria for progression based on platelet or hemoglobin criteria alone. However, these subjects were receiving platelet and/or PRBC transfusions, complicating the interpretation of progression. The 5 subjects are as follows: 5883-10302, 5993-10256, 7061-10270, 7640-10655, 5776-10237.

The results of these analyses are shown in the table below.

Table 17. Sensitivity Analyses of PFS Endpoint

| Analysis excluding patients with poor response to prior anti-CD20 therapy | | | |
|---|---|-----------------------------|-------------------------|
| | Idelalisib + R N (%); N=103 | Placebo + R N (%); N=102 | Overall N (%); N=205 |
| Subjects with an Event | 14 (13.6) | 53 (52) | 67 (32.7) |
| Disease Progression | 10 (9.7) | 45 (44.1) | 55 (26.8) |
| Death | 4 (3.9) | 8 (7.8) | 12 (5.8) |
| KM Estimate of PFS (months) | | | |
| Median | Not Reached | 5.6 | |
| Adjusted Hazard Ratio | 0.17 (95% CI: 0.09, 0.29); p value < 0.0001 | | |
| Analysis excluding patients without progression based on FDA assessment | | | |
| | Idelalisib + R N (%); N=109 | Placebo + R N (%); N=106 | Overall N (%); N=215 |
| Subjects with an Event | 15 (13.8) | 55 (51.9) | 70 (32.6) |
| Disease Progression | 10 (9.2) | 47 (44.3) | 57 (26.5) |
| Death | 5 (4.6) | 8 (7.5) | 13 (6) |
| KM Estimate of PFS (months) | | | |
| Median | Not Reached | 5.7 | |
| Adjusted Hazard Ratio | 0.18 (95% CI: 0.10, 0.31); p value < 0.0001 | | |

Source: FDA reviewer's analysis

7 Review of Safety

Safety Summary

The safety profile of Idelalisib is based on the safety profile observed in Study 312-0116. As of the final data-cutoff date of October 9, 2013, 220 patients were randomized to study 312-0116, 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 bowel perforation, colitis, AST/ALT elevations, serious and fatal hepatotoxicity, and severe cutaneous skin reactions.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety review for Idelalisib included the review of the following items submitted by the Applicant (Gilead Sciences, Inc.):

- Clinical study report for Study 312-0116
- Clinical study report for Study 101-07
- Clinical study report for Study 101-08
- Protocol and statistical analysis plan for Study 312-0116, Study 101-07, and Study 101-08
- Raw and derived datasets for Study 312-0116, Study 101-07, and Study 101-08
- Case report forms for Study 312-0116, Study 101-07, and Study 101-08
- Narratives for Study 312-0116, Study 312-0117, Study 101-07, and Study 101-08
- Response to information requests
- Proposed labeling for Idelalisib

- Safety Reports submitted to the IND relevant to the proposed indication

7.1.2 Categorization of Adverse Events

Treatment-emergent adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 15.1. The severity of AEs was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

No data pooling was conducted due to the disparity between the patient populations and treatment regimens used in the various trials.

7.2 Adequacy of Safety Assessments

The datasets submitted to this NDA application are adequate to support the evaluation of safety. The duration of exposure to study drug was relatively short, with median exposure duration of 5.0 months. Given that the intended use of Idelalisib in combination with rituximab is until disease progression or unacceptable toxicity, 5 months is not adequate to fully characterize the long-term safety of treatment with Idelalisib.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Demographics of the Safety Population

The safety population for Study 312-0116 consists of 218 subjects who received at least 1 dose of study treatment. The patient demographics and baseline disease characteristics are presented in the table below.

Table 18. Baseline Demographics of the Safety Population

| | Idelalisib + R N (%) | Placebo + R N (%) |
|-------------|-------------------------|----------------------|
| N | 110 | 108 |
| Gender | | |
| Male | 76 (69.0) | 68 (63.0) |
| Female | 34 (30.9) | 40 (37.0) |
| Age (years) | | |
| Median | 71 | 71 |
| Range | 48, 90 | 47, 92 |

| | | |
|------------------|------------|-----------|
| < 65 | 21 (19.1) | 27 (25.0) |
| ≥ 65 | 89 (80.9) | 81 (75.0) |
| Race | | |
| White | 100 (90.9) | 96 (88.9) |
| Asian | 0 | 0 |
| African-American | 3 (2.7) | 3 (2.8) |
| Other or Unknown | 7 (6.4) | 9 (8.3) |

Baseline Disease and Comorbidity Characteristics of the Safety Population

The baseline disease characteristics and comorbidity characteristics of the safety population are presented in the table below.

Table 19. Baseline Disease and Comorbidity Characteristics of the Safety Population

| | Idelalisib + R N (%) | Placebo + R N (%) |
|---------------------------|-------------------------|----------------------|
| N | 110 | 108 |
| Deletion 17p | 26 (23.6) | 30 (27.8) |
| IGHV unmutated | 91 (82.7) | 91 (84.3) |
| Number of Prior Therapies | | |
| Median | 3 | 3 |
| Range | 1, 12 | 1, 10 |
| CIRS Score | | |
| Median | 8.5 | 8 |
| Range | 3, 18 | 1, 18 |
| >6 | 97 (88.2) | 88 (81.5) |
| ≤6 | 13 (11.8) | 20 (18.5) |
| CrCl | | |
| Median | 61.5 | 66.9 |
| Range | 32.4, 160.8 | 22.8, 198.6 |
| < 60 mL/min | 48 (43.6) | 38 (35.2) |

7.2.2 Explorations for Dose Response

The median exposure duration and cumulative exposure for the safety population are presented below. Patients treated with Idelalisib received treatment for a median of 5.0 months.

Table 20. Idelalisib or Placebo Exposure

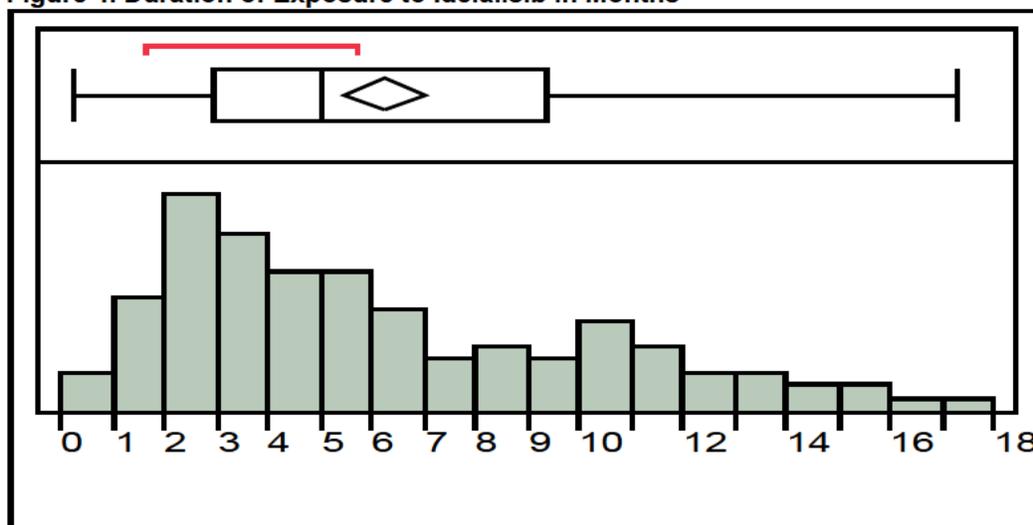
| | Idelalisib + R | Placebo + R |
|---|----------------|-------------|
| N | 110 | 108 |

| | | |
|--|-------------|-----------|
| Duration of Exposure to Idelalisib or placebo (months) | | |
| Median | 5.0 | 3.7 |
| Min, Max | 0.3, 17.3 | 0.1, 14.6 |
| Cumulative Exposure to Idelalisib or placebo (mg) | | |
| Median | 20925 | 16725 |
| Min, Max | 1350, 75600 | 600,65400 |
| Average Daily Dose (mg) | | |
| Median | 150 | 150 |
| Min, Max | 61.9, 150 | 89.8,150 |

Source: FDA reviewer's analysis

The duration of exposure to Idelalisib is included in the histogram below.

Figure 4. Duration of Exposure to Idelalisib in Months



Source: FDA reviewer's analysis

Three (3) subjects were treated with Idelalisib for less than 1 month, 12 subjects were treated for less than 2 months, 29 subjects were treated for less than 3 months, and 43 subjects were treated for less than 4 months, and 54 subjects were treated for less than 5 months duration.

Table 21. Rituximab Exposure

| | Idelalisib + R | Placebo + R |
|-----------------------------------|----------------|-------------|
| Duration of Exposure to Rituximab | | |
| N | 110 | 108 |
| Median number of doses | 8 | 6 |
| Min, Max | 1, 12 | 1, 15 |
| Total Rituximab doses | | |

| | | |
|----|----|----|
| 01 | 1 | 3 |
| 02 | 2 | 1 |
| 03 | 1 | 6 |
| 04 | 12 | 7 |
| 05 | 11 | 18 |
| 06 | 13 | 21 |
| 07 | 14 | 12 |
| 08 | 49 | 33 |
| 09 | 3 | 4 |
| 10 | 3 | 2 |
| 11 | 0 | 0 |
| 12 | 1 | 0 |
| 13 | 0 | 0 |
| 14 | 0 | 0 |
| 15 | 0 | 1 |

Source: FDA reviewer's analysis

Thirty- nine (39) subjects (35.5%) in the Idelalisib arm and 19 subjects (17.6%) in the placebo arm had a dose interruption. Sixteen (16) subjects in the Idelalisib arm (14.5%) had a dose reduction. No subjects in the placebo arm required a dose reduction. Explorations for dose response in study 312-0116 are not possible because all subjects were started at the 150 mg dose.

7.2.3 Special Animal and/or In Vitro Testing

Results of the relevant preclinical studies are summarized in section 4.2.

7.2.4 Routine Clinical Testing

Refer to section 5.3.1 for a detailed schedule of safety assessments.

7.2.5 Metabolic, Clearance, and Interaction Workup

Refer to the Clinical Pharmacology review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Idelalisib is a new molecular entity and is a first-in class agent. As such, there are no relevant approved drugs within this class.

7.3 Major Safety Results

Table 22. Safety Summary for Study 312-0116

| Event | Idelalisib + R | Placebo + R | Total |
|-------|----------------|-------------|-------|
|-------|----------------|-------------|-------|

| | n (%) | n (%) | n (%) |
|------------------------------|------------|------------|------------|
| N | 110 | 108 | 218 |
| Deaths | 6 (5.5) | 13 (12.0) | 19 (8.7) |
| Progressive Disease | 3 (2.7) | 2 (1.9) | 5 (2.3) |
| Adverse Event | 3 (2.7) | 11 (10.2) | 14 (6.4) |
| Serious TEAE | 54 (49.1) | 41 (38.0) | 95 (43.6) |
| Discontinuations due to TEAE | 12 (10.9) | 12 (11.1) | 24 (11.0) |
| Any Grade 3 or 4 TEAE | 70 (63.6) | 52 (48.1) | 122 (56.0) |
| Any TEAE | 106 (96.4) | 106 (98.1) | 212 (97.2) |

Source: FDA reviewer's analysis

7.3.1 Deaths

Nineteen (19) subjects (8.7%) died during the study or within 30 days of treatment discontinuation. Disease progression was the cause of death in 5 subjects, 3 in the Idelalisib plus rituximab arm, and 2 in the placebo/rituximab arm. There was one additional death in the follow-up period in a patient in the placebo/rituximab arm that was due to an adverse event of pneumonia. Deaths due to adverse events are shown in the table below.

In both the Idelalisib arm and the placebo arms, the most common cause of death due to adverse events was infections.

Table 23. Deaths on study or within 30 days of discontinuation

| Subject ID | Age/ Gender | AE Leading to Death | Days on Study when AE started | Other ongoing AEs at time of death |
|-----------------------------|----------------|---------------------------------------|--|---|
| Idelalisib/Rituximab | | | | |
| 1727-10670 | 82/F | Sepsis | 57 | Nausea, weight loss |
| 6708-10230 | 67/F | Fungal pneumonia | 53 | Anemia, Atrial septal defect, diarrhea, febrile neutropenia, hepatic enzyme increased, hyponatremia, hypotension, lung infiltration, metabolic acidosis |
| 7430-10272 | 69/M | Pneumocystis Jiroveci Pneumonia | 9 | Hypertension, Myocardial Infarction |
| Placebo/Rituximab | | | | |
| 5786-10658 | 74/F | Cardiac Failure | 37 | None |
| 6767-10622 | 77/M | Sepsis, Septic | 247 | CNS lesion, colitis, cough, |

| | | | | |
|------------|------|--|-----|--|
| | | Shock | | dyspnea, fatigue, hypotension, lung neoplasm, pain |
| 7063-10238 | 79/M | Chronic Obstructive Pulmonary Disease | 16 | None |
| 7066-10241 | 65/M | Acute Respiratory Failure | 58 | Anemia, asthenia, cough, epistaxis, groin pain, lethargy, musculoskeletal chest pain, musculoskeletal pain, edema peripheral, pneumocystis jiroveci pneumonia, pyrexia, rhinitis |
| 7130-10637 | 78/M | General physical health deterioration | 101 | Ascites, Escherichia infection, femur fracture |
| 7136-10004 | 69/M | Sepsis | 166 | Decubitus ulcer, femoral neck fracture, fracture pain |
| 7136-10209 | 53/F | Pneumonia | 117 | Ankle swelling |
| 7136-10224 | 73/F | Pulmonary edema and left ventricular failure | 5 | None |
| 7137-10233 | 66/M | Pneumonia | 39 | Fluid Overload, Hypotension, Wheezing |
| 7174-10303 | 70/M | Bacteremia | 43 | Asthenia, constipation, decreased appetite, weight decreased |
| 7503-10263 | 71/F | Multi-organ failure | 13 | Immunodeficiency, neutropenia, edema, petechiae, thrombocytopenia |

Deaths in the Extension Trial:

Subjects in study 312-0116 that had disease progression or at the completion of the trial were eligible to enroll in the extension study, 312-0117. At the time of the second interim analysis of study 312-0116, 62 subjects had progressed, and 57 subjects chose to enroll on study 312-0117. In study 312-0117, subjects were randomized to receive either Idelalisib 300mg BID or 150 BID, based on their prior treatment arm from study 312-0116.

Table 24. Deaths in Study 312-0117

| Subject ID | Age/ Gender | Cause of Death | Other Adverse Events |
|------------|----------------|----------------|----------------------|
|------------|----------------|----------------|----------------------|

| | | | |
|-------------|------|---|--|
| 5796-10402 | 56/M | GI hemorrhage/ Cardiac Arrest | Not reported |
| 6767-10612 | 75/M | Pseudomonas pneumonia | Diarrhea |
| 5993-10642 | 68/M | Neutropenic Fever, Pneumonia | CMV reactivation, C. Diff colitis, fungal lung infection |
| 5775-10229* | 72/M | Disease Progression | Not reported |
| 5775-10229* | 59/F | Disease Progression | Not reported |
| 7136-10703 | 65/F | Mycobacterial respiratory tract infection | Not reported |
| 6767-10204 | 83/M | Respiratory failure | Not reported |

* Information supplied by company indicated the same subject ID for 2 patients

7.3.2 Nonfatal Serious Adverse Events

Serious Adverse events occurred in 54 patients (49.1%) in the Idelalisib arm, compared to 38 patients (35.2%) in the placebo arm.

Table 25. Treatment- Emergent Serious Adverse Events in ≥ 2% of Subjects in Study 312-0116

| Treatment-Emergent Serious Adverse Events | Idelalisib+ R N (%); N=110 | Placebo + R N (%); N=108 |
|--|-------------------------------|-----------------------------|
| Infections and Infestations | | |
| Pneumonia* | 13 (11.8) | 11 (10.2) |
| Sepsis [‡] | 8 (7.3) | 2 (1.9) |
| Cellulitis | 1 (0.9) | 3 (2.8) |
| General Disorders | | |
| Pyrexia | 10 (9.1) | 3 (2.8) |
| Asthenia | 1 (0.9) | 3 (2.8) |
| Respiratory, thoracic and mediastinal disorders | | |
| Pneumonitis | 4 (3.6) | 1 (0.9) |
| Dyspnea | 1 (0.9) | 3 (2.8) |
| Gastrointestinal Disorders | | |
| Diarrhea | 3 (2.7) | 0 |
| Blood and Lymphatic System Disorders | | |
| Febrile Neutropenia | 5 (4.5) | 5 (4.6) |

Source: FDA Reviewer's Analysis.

* Pneumonia includes the terms: pneumonia, lung infection, Pneumocystis jiroveci pneumonia, pneumonia legionella, lung infection pseudomonal

‡ Sepsis includes the terms: Sepsis, septic shock, neutropenic sepsis, and sepsis syndrome

Refer to Section 7.3.4 for details of the serious adverse events presented in an issue-based format.

7.3.3 Dropouts and/or Discontinuations

Sixteen subjects (14.5%) had a dose reduction in the Idelalisib arm compared to 0 in the placebo arm. Thirty-nine subjects (35.5%) in the Idelalisib arm had a dose interruption, compared to 19 (17.6%) in the placebo arm. Adverse events led to study discontinuation in 12 subjects in the Idelalisib + Rituximab arm and in 12 subjects in the placebo + Rituximab arm. The adverse events which led to study drug discontinuation are listed in the table below.

Table 26. Adverse Events leading to Study Drug Withdrawal

| | Idelalisib + R N | Placebo + R N |
|---------------------------------------|---------------------|------------------|
| Arrhythmia | 1 | 0 |
| Bronchial Carcinoma | 1 | 0 |
| Colitis | 1 | 0 |
| Exfoliative dermatitis | 1 | 0 |
| Diarrhea | 1 | 0 |
| Febrile Neutropenia | 1 | 0 |
| Hemolytic Anemia | 1 | 0 |
| Hepatitis | 1 | 0 |
| Pneumocystis jiroveci pneumonia | 1 | 0 |
| Fungal pneumonia | 1 | 0 |
| Pneumonitis | 1 | 1 |
| Rash maculo-papular | 1 | 0 |
| Sepsis | 1 | 2 |
| Transaminases increased | 1 | 0 |
| Acute Respiratory Failure | 0 | 1 |
| Cardiac Failure | 0 | 1 |
| Chronic obstructive pulmonary disease | 0 | 1 |
| Eczema | 0 | 1 |
| Gastroenteritis | 0 | 1 |
| Left Ventricular Failure | 0 | 1 |
| Mucosal Infection | 0 | 1 |
| Multi-organ failure | 0 | 1 |
| Pancytopenia | 0 | 1 |
| Pneumonia | 0 | 2 |
| Pulmonary edema | 0 | 1 |

Source: FDA Reviewer's Analysis. Subject 6859-10225 was categorized as subject withdrawal, but the comments indicated that the subject withdrew due to adverse events. The Adverse events ongoing at the time of discontinuation were constipation, hypercalcemia, rash, and urticarial. Subject 7130-10637 was categorized as physician decision, but the comments indicated that the patient's disease was progressing.

7.3.4 Significant Adverse Events

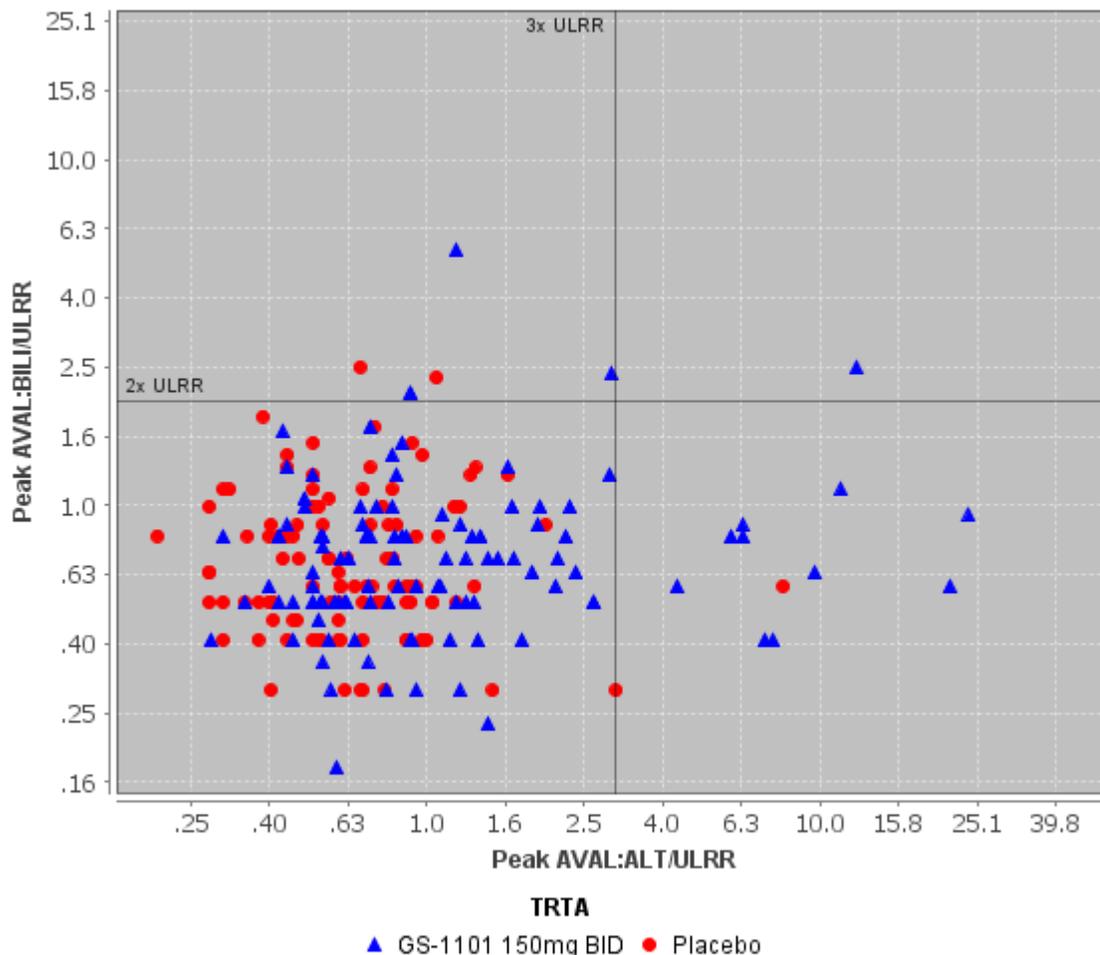
7.3.4.1 Hepatotoxicity

Idelalisib has been associated with significant hepatotoxicity. One Hy's law case was identified in the review of Study 312-0116. A case of fatal hepatotoxicity was observed with the use of Idelalisib in combination with ofatumumab in a patient with CLL. The hepatotoxicity that developed in this case was confounded by concurrent sepsis, acute renal failure, and paracetamol use.

ALT elevations that were treatment emergent occurred in 38 (34.5%) subjects in the Idelalisib arm compared to 11 subjects (10.2%) in the placebo arm based on analysis of the laboratory dataset. The median time to onset among the Idelalisib arm was 93 days (Range 15-308). AST Elevations occurred in 27 (24.5%) subjects in the Idelalisib arm compared with 16 (14.8%) subjects in the placebo arm. The median time to onset among the Idelalisib arm was 92 days (range 15-338).

Eleven (11) subjects in the Idelalisib arm had ALT elevations 3X ULN (CTCAE grade 2) compared to 2 subjects in the placebo arm, as shown in the figure below.

Figure 5. Bilirubin and ALT elevations



One Hy's laws case was observed in Study 312-0116. The Subject, 7064-10646, was a 69 year old female who began treatment with Idelalisib in combination with rituximab in April 2013. At baseline, the subject had normal ALT, AST, alkaline phosphatase, and total bilirubin values. On July 24, 2013, study day 106, the first elevation in ALT (101 U/L, grade 2), AST (77 U/L, grade 1), and bilirubin (31 μmol/L, grade 1) were reported. Study drug was interrupted on August 5, 2013, study day 118, due to transaminase elevation. On August 12, 2013, study day 125, the maximum reported values were obtained. The patient had an ALT of 445 U/L, grade 3; an AST of 234 U/L, grade 3; and a total bilirubin of 43 μmol/L, grade 2. The alkaline phosphatase was normal throughout this period. Other AEs ongoing during this time include erythema (grade 1), oral mucosa blistering (grade 1), pruritus (grade 1), hot skin sensation on hand (grade 1), and insomnia (grade 1). Idelalisib was reinitiated at the previously reduced of 100mg BID on September 2, 2013. Idelalisib was discontinued permanently on (b) (6) for AE of pain (grade 2) and subsequent sepsis, deep venous thrombosis, and cerebral vascular accident.

7.3.4.2 Diarrhea/Colitis

In study 312-0116, 21(19.1%) subjects in the Idelalisib + rituximab arm developed diarrhea compared with 16 subjects (14.8%) in the placebo + rituximab arm. The median toxicity grade for diarrhea was 2 (range 1-4) in the Idelalisib arm, compared to 1 (range 1-2) in the placebo arm. Four subjects had grade 3 or 4 diarrhea in the Idelalisib arm. The median time to development of symptoms was 20 days in the Idelalisib arm (range 1-220). The AE of diarrhea lasted a median of 7 days (range 0-98), with 2 subjects reported as having ongoing symptoms. Ten subjects required medication for management of symptoms, one required hospitalization. Study drug was interrupted in all 3 subjects with grade 3 diarrhea and withdrawn in the one subject with grade 4 diarrhea. Five subjects in the Idelalisib + rituximab arm also developed colitis, one subject in the placebo arm. The median toxicity grade for the colitis was 3 in the Idelalisib arm; and grade 2 in the placebo arm. Three subjects in the Idelalisib arm had grade 3 colitis toxicity. Study drug was interrupted or withdrawn for colitis in 3 subjects in the Idelalisib arm. In some subjects that were rechallenged with Idelalisib, diarrhea and/or colitis recurred. Several of the patients with colitis had biopsies performed. Pathologic findings included acute cryptitis, crypt abscess formation, loss of surface epithelium, aggregates of inflammatory exudates. Subjects were often treated with loperamide or budesonide. One subject (8453-10101) with intractable diarrhea, grade 3, was treated with loperamide, empiric flagyl, and empiric cholestyramine, with no improvement in symptoms. He was ultimately treated with intravenous high dose steroids with resolution of symptoms after 2 months.

7.3.4.3 Pneumonitis

Pneumonitis developed in 6 (5.4%) subjects in the Idelalisib + rituximab arm in Study 312-0116 and in 1 subject in the placebo + rituximab arm. Four subjects in the Idelalisib + Rituximab arm had prior respiratory conditions including: intermittent cough and dyspnea, COPD and history of pleurisy, baseline cough, and reactive airway disease. The 1 patient in the placebo arm that developed pneumonitis had a history of COPD. The median toxicity grade for the cases of pneumonitis in the Idelalisib arm was 3. The one case of pneumonitis in the placebo arm was also grade 3. Study drug was interrupted or withdrawn in 3 subjects. All patients required medication, frequently corticosteroids, for management of pneumonitis, 3 were hospitalized. The event of pneumonitis did not resolve in all cases, as some patients had residual sequela, such as new oxygen requirements. The incidence of pneumonitis may be under-reported, as the condition may be difficult to recognize in some cases.

7.3.4.4 Rash

Rash developed in 11 subjects (10%) in the Idelalisib arm compared to 5 subjects (4.6%) in the placebo arm. The term rash was expanded to include the following terms: Dermatitis exfoliative, dermatosis, erythema, pruritis, pruritis generalized, rash, rash macular, rash maculo-papular, rash papular, rash pruritic, skin disorder, and skin lesion. With the expanded term, there were 24 subjects (21.8%) with events in the Idelalisib

arm compared to 18 subjects (16.7%) in the placebo arm. The median toxicity grade was 1.5 in the Idelalisib arm and 1 in the placebo arm. There were 5 grade 3 events, 4 in the Idelalisib arm and 1 in the placebo arm. The grade 3 events in the Idelalisib arm were as follows: skin disorder, rash, rash maculo-papular, dermatitis exfoliative. In the placebo arm, there was a grade 3 rash macular in the placebo arm. All subjects who developed a grade 3 rash expanded term event were treated with steroids, either topical or oral. Two patients in the Idelalisib arm required hospitalization for the rash and 3 discontinued study medication as a result of the AE. Of note, one of the grade 3 rash events occurred in subject 7064-10646, the subject who met criteria for Hy's law. In this subject, the grade 3 rash event occurred on (b) (6), approximately 2 months prior to the development of the first LFT abnormalities.

7.3.5 Submission Specific Primary Safety Concerns

Refer to section 7.3.4

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The following treatment-emergent adverse events were reported in $\geq 5\%$ of subjects in either arm, summarized by preferred term.

Table 27. Treatment-Emergent Adverse Events of Any Grade in $\geq 5\%$ of Subjects

| Preferred Term N (%) | Idelalisib + R N=110 | Placebo + R N=108 |
|---------------------------|-------------------------|----------------------|
| Pyrexia | 38 (34.5) | 18 (16.7) |
| Neutropenia | 30 (27.3) | 18 (16.7) |
| Fatigue | 28 (25.5) | 30 (27.8) |
| Nausea | 28 (25.5) | 23 (21.3) |
| Chills | 23 (20.9) | 17 (15.7) |
| Infusion related reaction | 21 (19.1) | 32 (29.6) |
| Diarrhea | 21 (19.1) | 16 (14.8) |
| Rash [†] | 20 (18.2) | 7 (6.5) |
| Cough | 19 (17.3) | 30 (27.8) |
| Pneumonia* | 19 (17.3) | 19 (17.6) |
| Dyspnea | 14 (12.7) | 21 (19.4) |
| Constipation | 14 (12.7) | 12 (11.1) |
| Vomiting | 14 (12.7) | 9 (8.3) |
| Decreased Appetite | 13 (11.8) | 11 (10.2) |
| Night Sweats | 12 (10.9) | 11 (10.2) |
| Peripheral Edema | 11 (10) | 10 (9.3) |
| Headache | 11 (10) | 5 (4.6) |

| | | |
|-----------------------------------|----------|-----------|
| Anemia | 9 (8.2) | 11 (10.2) |
| Upper respiratory tract infection | 8 (7.3) | 12 (11.1) |
| Weight decreased | 10 (9.1) | 10 (9.3) |
| Sepsis [‡] | 9 (8.2) | 5 (5.6) |
| Sinusitis | 9 (8.2) | 4 (3.7) |
| Abdominal pain | 8 (7.3) | 10 (9.3) |
| Asthenia | 8 (7.3) | 10 (9.3) |
| Pain | 8 (7.3) | 2 (1.9) |
| Upper respiratory tract infection | 8 (7.3) | 12 (11.1) |
| Arthralgia | 8 (7.3) | 4 (3.7) |
| Thrombocytopenia | 7 (6.4) | 6 (5.6) |
| GERD | 7 (6.4) | 1 (0.9) |
| Stomatitis | 7 (6.4) | 2 (1.9) |
| Bronchitis | 7 (6.4) | 3 (2.8) |
| Cellulitis | 7 (6.4) | 5 (4.6) |
| Muscle Spasms | 7 (6.4) | 6 (5.6) |
| Insomnia | 7 (6.4) | 6 (5.6) |
| Urinary Tract Infection | 6 (5.5) | 3 (2.8) |
| Back Pain | 6 (5.5) | 4 (3.7) |
| Nasal Congestion | 6 (5.5) | 2 (1.9) |
| Oropharyngeal Pain | 6 (5.5) | 5 (4.6) |
| Pneumonitis | 6 (5.5) | 1 (0.9) |
| Dizziness | 5 (4.5) | 8 (7.4) |
| Hypotension | 5 (4.5) | 7 (6.5) |
| Skin Lesion | 2 (1.8) | 6 (5.6) |

Source: FDA Reviewer's Analysis.

‡ Rash includes the terms: Dermatitis exfoliative, rash, rash macular, rash maculo-papular, rash papular, rash pruritis, and skin disorder

* Pneumonia includes the terms: pneumonia, lung infection, Pneumocystis jiroveci pneumonia, legionella pneumonia, lung infection pseudomonal, pneumonia fungal

‡ Sepsis includes the terms: Sepsis, septic shock, neutropenic sepsis, and sepsis syndrome

The following treatment-emergent adverse events of grade 3-4 severity were reported in ≥ 2% of subjects in either arm.

Table 28. Treatment-emergent AEs Grade 3-4 in ≥ 2% of Subjects

| Preferred Term N (%) | Idelalisib + R N=110 | Placebo + R N=108 |
|-------------------------|-------------------------|----------------------|
| Neutropenia | 24 (21.8) | 13 (12) |
| Pneumonia* | 14 (12.7) | 11 (10.2) |
| Sepsis [‡] | 7 (6.4) | 2 (1.9) |
| Fatigue | 5 (4.5) | 3 (2.8) |

| | | |
|---------------------------|---------|---------|
| Febrile Neutropenia | 5 (4.5) | 4 (3.7) |
| Anemia | 5 (4.5) | 7 (6.5) |
| Diarrhea | 4 (3.6) | 0 |
| Pneumonitis | 4 (3.6) | 1 (0.9) |
| Rash* | 4 (3.6) | 1 (0.9) |
| Colitis | 3 (2.7) | 0 |
| ALT Increased | 3 (2.7) | 0 |
| Pyrexia | 3 (2.7) | 1 (0.9) |
| Transaminases Increased | 3 (2.7) | 1 (0.9) |
| Dyspnea | 3 (2.7) | 3 (2.8) |
| Thrombocytopenia | 3 (2.7) | 5 (4.6) |
| Asthenia | 1 (0.9) | 4 (3.7) |
| Infusion related reaction | 0 | 4 (3.7) |

Source: FDA Reviewer's Analysis.

* Pneumonia includes the terms: pneumonia, lung infection, Pneumocystis jiroveci pneumonia, legionella pneumonia, lung infection pseudomonal, pneumonia fungal

‡ Sepsis includes the terms: Sepsis, septic shock, neutropenic sepsis, and sepsis syndrome

¥ Rash includes the terms: Dermatitis exfoliative, rash, rash macular, rash maculo-papular, rash papular, rash pruritis, and skin disorder

7.4.2 Laboratory Findings

The following post-baseline through 30 days post last dose laboratory abnormalities of any grade were reported in ≥10% of subjects in Study 312-0116.

Table 29. Laboratory Abnormalities of Any Grade in ≥ 10% of Subjects

| Laboratory Parameter N (%) | Idelalisib + R N=110 | Placebo + R N=108 |
|-----------------------------------|-------------------------|----------------------|
| Neutropenia (ANC) | 66 (60) | 53 (49.1) |
| Hyperglycemia | 59 (53.6) | 50 (46.3) |
| ALT Increased | 38 (34.5) | 11 (10.2) |
| Hemoglobin Decreased | 32 (29.1) | 35 (32.4) |
| GGT Increased | 29 (26.4) | 15 (13.9) |
| Hypertriglyceridemia | 28 (25.5) | 16 (14.8) |
| Leukocytes Decreased | 28 (25.5) | 23 (21.3) |
| AST Increased | 27 (24.5) | 15 (13.9) |
| Lymphocytes Increased | 27 (24.5) | 10 (9.3) |
| Hyponatremia | 22 (20) | 16 (14.8) |
| Lymphocytes Decreased | 22 (20) | 13 (12) |
| Thrombocytopenia | 21 (19.1) | 34 (31.5) |
| Alkaline Phosphatase Increased | 19 (17.3) | 19 (17.6) |
| Albumin Decreased | 17 (15.5) | 19 (17.6) |

| | | |
|---------------------|-----------|-----------|
| Hypoglycemia | 12 (10.9) | 5 (4.6) |
| Hypokalemia | 11 (10) | 10 (9.3) |
| Uric Acid Increased | 8 (7.3) | 16 (14.8) |

Source: FDA Reviewer's Analysis.

The following post-baseline through 30 days post last dose laboratory abnormalities of grade 3-4 severity were reported in $\geq 2\%$ of subjects.

Table 30. Laboratory Abnormalities Grade 3-4 in $\geq 2\%$ of Subjects

| Laboratory Parameter N (%) | Idelalisib + R N=110 | Placebo + R N=108 |
|-------------------------------|-------------------------|----------------------|
| Neutropenia (ANC) | 39 (35.5) | 28 (25.9) |
| Lymphocytes Increased | 20 (18.2) | 5 (4.6) |
| Thrombocytopenia | 12 (10.9) | 19 (17.6) |
| Lymphocytes Decreased | 10 (9.1) | 4 (3.7) |
| ALT Increased | 9 (8.2) | 1 (0.9) |
| Hyperglycemia | 8 (7.3) | 2 (1.9) |
| Hemoglobin Decreased | 8 (7.3) | 18 (16.7) |
| Leukocytes Decreased | 7 (6.4) | 9 (8.3) |
| AST Increased | 6 (5.5) | 0 |
| Uric Acid Increased | 4 (3.6) | 5 (4.6) |
| Phosphate Decreased | 3 (2.7) | 1 (0.9) |
| Hypertriglyceridemia | 3 (2.7) | 0 |
| GGT Increased | 2 (1.8) | 3 (2.8) |
| Hyponatremia | 2 (1.8) | 7 (6.5) |
| Hypokalemia | 0 | 3 (2.8) |

Source: FDA Reviewer's Analysis.

7.4.3 Vital Signs

Height, weight and oxygen saturation were obtained in Study 312-0116.

7.4.4 Electrocardiograms (ECGs)

A thorough QT study was performed in healthy volunteers, Study 313-0117. Per the IRT review, no significant QTc prolongation effects of Idelalisib (150 mg and 400 mg) were detected. Please refer to the IRT Review for further details.

In Study 312-0116, ECGs were only obtained at the screening visit.

The following Cardiac AEs were reported in study 312-0116.

Table 31. Cardiac Adverse Events

| Adverse Event | Idelalisib + R | Placebo + R |
|---------------|----------------|-------------|
|---------------|----------------|-------------|

| N (%) | N=110 | N=108 |
|------------------------------|---------|---------|
| Tachycardia | 4 (3.6) | 3 (2.8) |
| Arrhythmia | 2 (1.8) | 0 |
| Cardiac Congestive Failure | 2 (1.8) | 0 |
| Atrial Fibrillation | 1 (0.9) | 1 (0.9) |
| Atrial Flutter | 1 (0.9) | 0 |
| Bradycardia | 1 (0.9) | 0 |
| Myocardial Infarction | 1 (0.9) | 1 (0.9) |
| Right atrial dilation | 1 (0.9) | 0 |
| Right ventricular failure | 1 (0.9) | 0 |
| Supraventricular tachycardia | 1 (0.9) | 0 |
| Cardiac Failure | 0 | 1 (0.9) |
| Left Ventricular Failure | 0 | 1 (0.9) |
| Palpitations | 0 | 2 (1.8) |

Source: FDA Reviewer's Analysis.

7.4.5 Special Safety Studies/Clinical Trials

The following studies were submitted with the NDA application and included CLL patients.

Table 32. Additional Studies in CLL Patient Populations

| Study Identifier | Study Design | Intervention | Number of Subjects | Patient Population | Status |
|------------------|---------------------|--|-------------------------------|---|---------|
| 101-07 | Phase I, Open-label | Idelalisib in combination with Rituximab, Bendamustine, Rituximab + Bendamustine, Ofatumumab, or Fludarabine | Planned: 210 Enrolled: 226 | CLL, iNHL, or MCL | Ongoing |
| 101-08 | Phase 2 Single-arm | Idelalisib 150 mg BID in combination with Rituximab | Planned: 59 Enrolled: 64 | Elderly Subjects with Previously untreated CLL or SLL | Ongoing |

Study 101-07 is an ongoing, phase I trial designed to investigate the safety of Idelalisib in combination with an anti-CD20 monoclonal antibody, a chemotherapeutic agent, a mTOR inhibitor, and/or proteasome inhibitor in subject with relapsed or refractory indolent CLL, NHL, or mantle cell lymphoma. Six dosing cohorts were evaluated in the

trial. A formal interim analysis was performed for cohorts 1-4 in all subjects who completed cycle 12 or end-of-study evaluation by the time of the interim analysis. An interim safety analysis was performed on all subjects. The safety results that are relevant to the CLL indication are discussed below.

In Study 101-07, 114 subjects with CLL were enrolled in the trial. One hundred subject started Idelalisib at a dose of 150 mg BID; 8 subjects started at 100 mg BID. Among those with CLL, starting at 150 mg BID, 29 subjects (25.4%) had a dose reduction to 100 mg BID. The median duration of exposure to Idelalisib was 10.1 months, (range-0.3, 13.6). Nineteen (19) subjects with CLL were treated with Idelalisib + rituximab. All 19 subjects experienced a TEAE. Eleven subjects (57.9%) experienced a \geq grade 3 TEAE. SAEs occurred in 9 subjects (47.4%).

Fifty-one subjects of all eligible disease types were treated with Idelalisib in combination with rituximab. Among all disease types treated with Idelalisib in combination with rituximab, the most frequently reported AEs were diarrhea in 22 subjects (43.1%); pyrexia, cough, and fatigue in 18 subjects each (35.3%); neutropenia in 15 subjects (29.4%); rash and headache in 12 subjects each (23.5%); and abdominal pain in 11 subjects (21.6%).

Study 101-08 is an ongoing, phase II, single-arm trial, designed to investigate the safety and clinical activity of Idelalisib in combination with rituximab in elderly patients with previously untreated CLL or SLL. Subjects were eligible for enrollment if they were age \geq 65 years, and had CLL or SLL and had not received any prior therapy. Subjects also were required to have Binet stage C or Rai Stage III or IV or active disease. Eligible subjects received Idelalisib 150 mg BID and rituximab 375 mg/m² weekly for 8 doses. Treatment continued until disease progression or unacceptable toxicity, up to a maximum of 48 weeks.

Sixty-four (64) subjects were enrolled in Study 101-08. The median age was 71 years (range-65, 90). Fifty-nine (59) subjects (92.2%) had CLL, 5 subjects (7.8%) had a diagnosis of SLL. The applicant reports that the overall response rate was 96.9%. Nine subjects had a CR (14.1%), 53 subjects (82.8%) had a partial response. The efficacy evaluations were not verified, as the study is ongoing.

Subjects received Idelalisib for a median of 10.8 months (range- 0.8, 12.3). Twenty-eight subjects (43.8%) were dose reduced to 100 mg BID. Six subjects (9.4%) were further dose-reduced to 75 mg BID. All subjects (100%) had a TEAE. Forty-nine subjects (76.6%) had a grade \geq 3 TEAE. Thirty-one subjects (48.8%) had a SAE. The most frequent TEAEs were: diarrhea in 34 subjects (53.1%); pyrexia in 27 subjects (42.2%); nausea and rash in 24 subjects each (37.5%); chills in 23 subjects (35.9%); cough in 21 subjects (28.1%); AST increased in 17 subjects (26.6%); dyspnea, headache, and pneumonia in 15 subjects each (23.4%); vomiting in 14 subjects (21.9%); and insomnia in 13 subjects (20.3%).

7.4.6 Immunogenicity

Immunogenicity studies were not conducted.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

In Study 312-0116, all subjects were started at a dose of 150 mg BID. This limits the dose dependency evaluations that can be performed. Please see Clinical Pharmacology review and the review of NDA 205858.

7.5.2 Time Dependency for Adverse Events

Time- to-event analyses were integrated into Section 7.3.4 where appropriate.

7.5.3 Drug-Demographic Interactions

Subgroup analyses based on age were conducted to evaluate for safety and the occurrence of specific adverse events. The results are included in the table below. Notably, dyspnea, rash, vomiting, peripheral edema, and pneumonia occurred in a greater percentage in the age ≥ 65 group compared to the < 65 age group in the Idelalisib arm, with the reverse trend noted in the placebo arms.

Table 33. Adverse Events of Any Grade in ≥ 10% of Subjects based on Age

| Preferred Term N (%) | Idelalisib + R N=110 | | Placebo + R N=108 | |
|-------------------------|-------------------------|--------------------|----------------------|--------------------|
| | Age < 65 (N=21) | Age ≥ 65 (N=89) | Age < 65 (N=27) | Age ≥ 65 (N=81) |
| Fatigue | 8 (38.1) | 20 (22.5) | 10 (37) | 20 (24.7) |
| Neutropenia | 7 (33.3) | 23 (25.8) | 3 (11.1) | 15 (18.5) |
| Pyrexia | 7 (33.3) | 31 (34.8) | 7 (25.9) | 11 (13.6) |
| Constipation | 6 (28.6) | 8 (9) | 4 (14.8) | 8 (9.9) |
| Nausea | 6 (28.6) | 22 (24.7) | 8 (29.6) | 15 (18.5) |
| Chills | 6 (28.6) | 17 (19.1) | 3 (11.1) | 14 (17.3) |
| Diarrhea | 5 (23.8) | 16 (18) | 2 (7.4) | 14 (17.3) |
| Cough | 5 (23.8) | 14 (15.7) | 6 (22.2) | 24 (29.6) |
| Urinary Tract Infection | 4 (19) | 2 (2.2) | 0 | 3 (3.7) |
| Dizziness | 4 (19) | 1 (1.1) | 5 (18.5) | 3 (3.7) |
| Anemia | 3 (14.3) | 6 (6.7) | 6 (22.2) | 5 (6.2) |
| Abdominal Pain Upper | 3 (14.3) | 1 (1.1) | 2 (7.4) | 2 (2.5) |

| | | | | |
|-----------------------------|----------|-----------|----------|-----------|
| Chest Discomfort | 3 (14.3) | 2 (2.2) | 0 | 0 |
| Sinusitis | 3 (14.3) | 6 (6.7) | 1 (3.7) | 3 (3.7) |
| Infusion related reaction | 3 (14.3) | 18 (20.2) | 10 (37) | 22 (27.2) |
| Night Sweats | 3 (14.3) | 9 (10.1) | 5 (18.5) | 6 (7.4) |
| Decreased appetite | 1 (4.8) | 12 (13.5) | 1 (3.7) | 10 (12.3) |
| Dyspnea | 2 (9.5) | 12 (13.5) | 9 (33.3) | 12 (14.8) |
| Vomiting | 2 (9.5) | 12 (13.5) | 4 (14.8) | 5 (6.2) |
| Peripheral Edema | 1 (4.8) | 10 (11.2) | 3 (11.1) | 7 (8.6) |
| Pneumonia | 1 (4.8) | 10 (11.2) | 4 (14.8) | 10 (12.3) |
| Rash | 1 (4.8) | 10 (11.2) | 0 | 5 (6.2) |
| Headache | 2 (9.5) | 9 (10.1) | 3 (11.1) | 2 (2.5) |
| Abdominal Pain | 2 (9.5) | 6 (6.7) | 3 (11.1) | 7 (8.6) |
| Upper Respiratory Infection | 2 (9.5) | 6 (6.7) | 4 (14.8) | 8 (9.9) |
| Asthenia | 2 (9.5) | 6 (6.7) | 3 (11.1) | 7 (8.6) |
| Febrile Neutropenia | 1 (4.8) | 4 (4.5) | 3 (11.1) | 2 (2.5) |

Source: FDA Reviewer's Analysis.

7.5.4 Drug-Disease Interactions

Relevant analyses of pre-existing conditions were included in section 7.4.

7.5.5 Drug-Drug Interactions

Refer to the Clinical Pharmacology Review.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Refer to the Pharmacology-Toxicology review for discussion of nonclinical studies for assessment of carcinogenicity.

7.6.2 Human Reproduction and Pregnancy Data

No pregnancies occurred on Study 312-0116.

7.6.3 Pediatrics and Assessment of Effects on Growth

No children were enrolled on Study 312-0116.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No overdoses were reported. Idelalisib is not pharmacologically or structurally related to drugs known to have abuse potential.

7.7 Additional Submissions / Safety Issues

After the second interim report, additional safety reports describing episodes of death and serious adverse events from Study 312-0116 and study 312-0117 were reported to the IND.

One death event from study 312-0117 occurred in a 68 year old female. The subject was treated with Idelalisib 150 mg BID. She developed Influenza Type A pneumonia and died. The cause of death was noted to be pneumonia.

Several SAEs were also reported and are described below:

- 76 year-old Hispanic male was randomized to receive Idelalisib 150mg BID in combination with rituximab on study 312-0116. The subject began treatment in August 2013. In (b) (6), he was hospitalized for stomatitis aphthosa for 2 weeks. In (b) (6), he was hospitalized for erythema of gastric mucosa. In (b) (6) he was hospitalized for colitis. He experienced nausea, vomiting, diarrhea, weight loss, and anorexia. In January 2014, the event of colitis was assessed as ongoing, and assessed as related to study drug by the investigator.
- 69 year-old Caucasian female was randomized to receive Idelalisib 150mg BID in combination with rituximab on study 312-0116. The subject began treatment in July 2013. In (b) (6), study drug was interrupted for diarrhea. The patient was admitted in (b) (6) for diarrhea. In (b) (6), the patient was admitted for weakness, rhabdomyolysis, and severe diarrhea. The subject was found to have underlying colitis and myopathy/myositis. The patient remained dependent on steroids, diphenoxylate/atropine and loperamide. In (b) (6), the patient was readmitted for severe abdominal pain, and was found to have pneumoperitoneum, due to bowel perforation. She underwent an exploratory laparotomy, and required a left hemicolectomy and colostomy. The surgical pathology from the resected colon noted diffuse ulceration of the mucosa. These events were assessed as serious and related to study drug by the investigator. Of note, 5 other cases of bowel perforation have been noted in the clinical development program evaluating the use of Idelalisib. Another case involved a 66 year-old male treated with Idelalisib and Ofatumumab. He initiated treatment with Idelalisib 150 mg BID on (b) (6). He had been receiving treatment for 16.3 months, when he was hospitalized on (b) (6) for a 6 week history of diarrhea. He was found to have colitis with ileum and colon biopsy

findings consistent with drug induced injury. He was discharged to home on oral prednisone. On [REDACTED] (b) (6), he was hospitalized for sepsis and bowel micro-perforation. After a prolonged and complicated hospitalization, he ultimately died from complications related to sepsis in [REDACTED] (b) (6).

8 Postmarket Experience

Idelalisib is a new molecular entity. There is no postmarket experience with Idelalisib at this time.

9 Appendices

9.1 Literature Review/References

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Clinical Review
 Nicole Gormley, MD
 NDA 206545
 Zydelig® (Idelalisib)

9.2 Labelling Recommendations

See Section 1.5

9.3 Advisory Committee Meeting

This application was not taken to an Oncologic Drugs Advisory Committee.

9.4 Clinical Investigator Financial Disclosure Review Template

Application Number: 206545
 Submission Date: 12/6/2013
 Applicant: Gilead Sciences, Inc.
 Product: Idelalisib
 Reviewer: Nicole Gormley, MD
 Date of Review: 1/9/2014

| | | |
|--|---|-----------------------------|
| 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 | | |
| 101-07 | 11 | 107 |
| 101-08 | 5 | 74 |
| GS-US-312-0116 | 57 | 646 |
| GS-US-312-0117 | 9 | 91 |
| 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> | | |

Clinical Review
Nicole Gormley, MD
NDA 206545
Zydelig® (Idelalisib)

| | | |
|--|---|-----------------------------|
| Is an attachment provided with the reason: | Yes <input type="checkbox"/> <u>N/A</u> | No <input type="checkbox"/> |
|--|---|-----------------------------|

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NICOLE J GORMLEY
06/03/2014

ROMEO A DE CLARO
06/03/2014

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 206545 **Applicant:** Gilead Sciences **Stamp Date:** 12/6/2013

Drug Name: Zydelig® (Idelalisib) **NDA/BLA Type:** Original

On initial overview of the NDA/BLA application for filing:

| | Content Parameter | Yes | No | NA | Comment |
|---------------------------------------|---|-----|----|----|--|
| FORMAT/ORGANIZATION/LEGIBILITY | | | | | |
| 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 | | | |
| LABELING | | | | | |
| 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 | | | |
| SUMMARIES | | | | | |
| 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 | | | |
| 10. | Has the applicant submitted the integrated summary of efficacy (ISE)? | x | | | |
| 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) |
| DOSE | | | | | |
| 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 | x | | | Additional PK data was obtained from sub-sampling from study 312-0116 |
| EFFICACY | | | | | |
| 14. | Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: 312-0116 Proposed Indication: For the treatment of relapsed and | x | | | Study 312-0116 was a double-blind, randomized, placebo-controlled trial evaluating Idelalisib in |

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

| | Content Parameter | Yes | No | NA | Comment |
|---------------|---|-----|----|----|--|
| | refractory chronic lymphocytic leukemia (CLL) Pivotal Study #2 Indication: | | | | combination with rituximab |
| 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 | | | |
| 17. | Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission? | x | | | |
| SAFETY | | | | | |
| 18. | 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 | | | |
| 19. | Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)? | x | | | Study 313-0117- A Phase 1, placebo and positive-controlled study to evaluate the effect of Idelalisib on the QT/QTc Interval in healthy subjects |
| 20. | Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product? | x | | | |
| 21. | For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious? | | | x | |
| 22. | For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division? | x | | | MedDRA version 15.1 |
| 23. | Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms? | x | | | |
| 24. | Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the | | | x | |

¹ 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.

² 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).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

| | Content Parameter | Yes | No | NA | Comment |
|-------------------------------|---|-----|----|----|---|
| | new drug belongs? | | | | |
| 25. | Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)? | x | | | |
| OTHER STUDIES | | | | | |
| 26. | Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions? | x | | | |
| 27. | For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)? | | | x | |
| PEDIATRIC USE | | | | | |
| 28. | Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral? | x | | | Idelalisib was granted orphan designation for the CLL indication, and as such is exempt |
| ABUSE LIABILITY | | | | | |
| 29. | If relevant, has the applicant submitted information to assess the abuse liability of the product? | | | x | |
| FOREIGN STUDIES | | | | | |
| 30. | Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population? | x | | | |
| DATASETS | | | | | |
| 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 | | | |
| CASE REPORT FORMS | | | | | |
| 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 | | | |
| FINANCIAL DISCLOSURE | | | | | |
| 38. | Has the applicant submitted the required Financial Disclosure information? | x | | | |
| GOOD CLINICAL PRACTICE | | | | | |
| 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 | | | Second Interim Clinical Study Report, section 5 |

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

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

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

None

| | |
|---------------------------|-----------|
| Nicole J. Gormley, MD | 1/13/2014 |
| Reviewing Medical Officer | Date |
| R. Angelo de Claro, MD | 1/13/2014 |
| Clinical Team Leader | Date |

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NICOLE J GORMLEY
01/13/2014

ROMEO A DE CLARO
01/14/2014