FINAL CLINICAL STUDY REPORT

Study Title:	A Phase I Study to Investigate the Safety and Clinical Activity of Idelalisib in Combination with Chemotherapeutic Agents, Immunomodulatory Agents and Anti-CD20 mAb in Subjects with Relapsed or Refractory Indolent B-cell Non-Hodgkin Lymphoma, Mantle Cell Lymphoma or Chronic Lymphocytic Leukemia
Name of Test Drug:	Idelalisib (GS-1101, formerly CAL-101)
Dose and Formulation:	50-, 75-, or 100-mg capsule or 75-, 100-, or 150-mg tablet
Indication:	Relapsed or refractory indolent B-cell non-Hodgkin lymphoma, mantle cell lymphoma, or chronic lymphocytic leukemia
Sponsor:	Gilead Sciences, Inc. 199 East Blaine Street Seattle, WA 98102 USA
Study No.:	101-07
Phase of Development:	Phase 1
IND No.:	101254
EudraCT No.:	Not Applicable
ClinicalTrials.gov Identifier:	NCT01088048
Study Start Date:	25 March 2010 (First Subject Screened)
Study End Date:	28 April 2015 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Sven de Vos, MD, PhD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Gary Jones, MD Telephone: PPD Fax: PPD
Report Date:	02 October 2015
Previous Report Date(s):	18 September 2013 (Addendum) 24 July 2013 (Interim 1) 17 February 2015 (Interim 2)

STUDY SYNOPSIS

Study 101-07
Gilead Sciences, Inc.
199 East Blaine Street
Seattle, WA 98102
USA

Title of Study: A Phase I Study to Investigate the Safety and Clinical Activity of Idelalisib in Combination with Chemotherapeutic Agents, Immunomodulatory Agents and Anti CD20 mAb in Subjects with Relapsed or Refractory Indolent B cell Non-Hodgkin Lymphoma, Mantle Cell Lymphoma or Chronic Lymphocytic Leukemia

Investigators: This was a multicenter study. The coordinating investigator was Sven de Vos, MD, PhD, PPD .

Study Centers: A total of 11 study centers in the United States participated in the study. Subjects in Cohort 7 were enrolled only at one of the study centers PPD .

Publications:

Barrientos JC, Coutre SE, de Vos S, et al. Long-term follow-up of a Phase 1b trial of idelalisib in combination with chemoimmunotherapy in patients with relapsed/refractory chronic lymphocytic leukemia including patients with del17p/TP53 mutation. 51st Annual Meeting of the American Society of Clinical Oncology (ASCO). 29 May-02 June 2015; Chicago, IL, USA. [Poster 7011].

Barrientos J, Coutre S, de Vos S, et al. Long-term follow-up of a Phase 1 study evaluating the selective PI3K-delta inhibitor idelalisib in combination with bendamustine (B), bendamustine/rituximab (BR), fludarabine (F), chlorambucil (Chl), Or chlorambucil/rituximab (ChlR) in patients with relapsed or refractory chronic lymphocytic leukemia. Society of Hematology (ASH) Annual Meeting. December 6-9, 2014; San Francisco, CA, USA. Poster 3343.

de Vos S, Wagner-Johnston N, Coutre S, et al. Durable responses following treatment with the PI3K-delta inhibitor idelalisib in combination with rituximab, bendamustine, or both, in recurrent indolent non-Hodgkin lymphoma: Phase I/II results. Society of Hematology (ASH) Annual Meeting. December 6-9, 2014; San Francisco, CA, USA. Poster 3063.

Barrientos J, Leonard J, Furman R, Flinn I, De Vos S, Coutre S, et al. Phase 1b study of idelalisib (GS-1101) plus chlorambucil ± rituximab in patients with relapsed and refractory chronic lymphocytic leukemia (CLL). European Hematology Association (EHA) 2013 Congress, 13-16 June 2013; Stockholm, Sweden. Abstract P100.

Barrientos J, Sharman J, De Vos S, et al. GS-1101 (CAL-101), selective phosphatidylinositol 3-Kinase inhibitor, in combination with ofatumumab for treatment of relapsed/refractory chronic lymphocytic leukemia. European Hematology Association (EHA) 2012 Congress, 14-17 June 2012; Amsterdam, The Netherlands. Abstract 1062.

Coutre S, Leonard J, Furman R, et al. Combinations of the selective phosphatidylinositol 3 Kinase-delta (PI3Kd) inhibitor GS-1101 (CAL-101) with rituximab and/or bendamustine are tolerable and highly active in patients with relapsed or refractory chronic lymphocytic leukemia (CLL): results from a phase 1 study. American Society of Hematology (ASH) Annual Meeting. 8-11 December 2012; Atlanta, GA, USA. Abstract 642.

de Vos S, Schreeder M, Finn I, et al. A phase 1 study of the selective phosphatidylinositol 3 Kinase-delta (PI3Kd) inhibitor CAL-101 (GS-1101) in combination with rituximab and/or bendamustine in patients with relapsed or refractory indolent non-Hodgkin lymphoma (iNHL). American Society of Hematology (ASH) 2011 Annual Meeting, 10-13 December 2011; San Diego, CA, USA. Abstract 2699.

Flinn I, Schreeder M, Wagner-Johnson N, et al. A phase 1 study of CAL-101, an isoform-selective inhibitor of phosphatidylinositol 3-Kinase P110δ, in combination with rituximab and/or bendamustine in patients with relapsed or refractory B-cell malignancies. American Society of Hematology (ASH) 2010 Annual Meeting, 04-07 December 2010; Orlando, FL, USA. Blood (ASH Annual Meeting Abstracts) 2010 116: Abstract 2832.

Flinn I, Schreeder M, Coutre S, et al. A phase 1 study of CAL-101, an isoform-selective inhibitor of phosphatidylinositol 3-Kinase P110δ, in combination with anti-CD20 monoclonal antibody therapy and/or bendamustine in patients with previously treated B-cell malignancies. 47th Annual Meeting of the American Society of Clinical Oncology (ASCO). 04-08 June 2011; Chicago, IL, USA. [Poster 3064].

Fowler N, de Vos S, Schreeder M, et al. Combinations of the phosphatidylinositol 3 Kinase delta (PI3Kd) inhibitor idelalisib (GS-1101) with rituximab and/or bendamustine are tolerable and highly active in previously treated, indolent non-Hodgkin lymphoma: results from a phase 1 study. American Society of Hematology (ASH) 2012.

Furman R, Barrientos J, Sharman J, et al. A phase 1/2 study of the selective phosphatidylinositol 3-Kinase-delta (PI3Kd) inhibitor CAL-101 (GS-1101) with ofatumumab in patients with previously treated chronic lymphocytic leukemia (CLL). [Poster 6518] 2012 American Society of Clinical Oncology (ASCO) Annual Meeting; 01 05 June, 2012; Chicago, IL, USA. Gilead Sciences, Inc. [Poster 6518].

Sharman J, de Vos S, Leonard J, et al. A phase 1 study of the selective phosphatidylinositol 3-Kinase-delta (PI3Kd) inhibitor CAL-101 (GS-1101) in combination with rituximab and/or bendamustine in patients with relapsed or refractory chronic lymphocytic leukemia. American Society of Hematology (ASH) 2011 Annual Meeting, 10-13 December 2011; San Diego, CA, USA. Abstract 1787.

Wagner-Johnston ND, De Vos S, Leonard J, Sharman JP, Schreeder MT, Boccia RV, et al. Preliminary results of PI3Kδ inhibitor idelalisib (GS-1101) treatment in combination with everolimus, bortezomib, or bendamustine/rituximab in patients with previously treated mantle cell lymphoma (MCL) [Abstract 8501]. J Clin Oncol (ASCO Annual Meeting Abstracts) 2013;31 (suppl).

Study Period:

25 March 2010 (First Subject Screened)
28 April 2015 (Last Subject Observation)

Phase of Development: Phase 1

Objectives:

The primary objective of this study was to investigate the safety of idelalisib (GS-1101, formerly CAL-101) in combination with an anti-CD20 monoclonal antibody (mAb), a chemotherapeutic agent, a mammalian target of rapamycin (mTOR) inhibitor, a proteasome inhibitor, an angiogenic agent, and/or an immunomodulatory agent in subjects with relapsed or refractory B cell chronic lymphocytic leukemia (CLL), indolent non-Hodgkin lymphoma (iNHL), or mantle cell lymphoma (MCL).

The secondary objectives of this study were as follows:

- To evaluate the clinical activity of idelalisib combined with an anti-CD20 mAb, a chemotherapeutic agent, an mTOR inhibitor, and/or a proteasome inhibitor in subjects with relapsed or refractory CLL, iNHL, or MCL
- To determine the plasma concentrations of idelalisib combined with an anti-CD20 mAb, a chemotherapeutic agent, an mTOR inhibitor, a proteasome inhibitor, an antiangiogenic agent, and/or an immunomodulatory agent in subjects with relapsed or refractory CLL, iNHL, or MCL
- Substudy: to determine the plasma concentrations of a chemotherapeutic agent combined with idelalisib and an anti-CD20 mAb, an angiogenic agent, or an immunomodulatory agent in subjects with relapsed or refractory CLL or iNHL
- To investigate the pharmacodynamic effects of idelalisib treatment
- To determine the plasma concentrations of the mTOR inhibitor, everolimus, when combined with idelalisib in subjects with relapsed or refractory MCL

Methodology: This was a Phase 1, open-label study of idelalisib in subjects with relapsed or refractory CLL, iNHL, or MCL.

Subjects were enrolled into 7 cohorts and multiple subcohorts as described in the protocol (Appendix 16.1.1). Study treatment consisted of continuous administration of idelalisib (Id) combined with 1 or more of the following drugs administered in 28-day cycles: rituximab (R), bendamustine (B), everolimus (E), bortezomib (Bo), ofatumumab (O), fludarabine (F), chlorambucil (Ch), or lenalidomide (L). The Ch-, O-, and F-containing regimens were restricted to CLL subjects. The E- and Bo-containing regimens were restricted to MCL subjects. The L-containing regimen was restricted to CLL and iNHL subjects. Subjects were evaluated for response after Cycles 2 (Week 8), 4 (Week 16), 6 (Week 24), 9 (Week 36), and 12 (Week 48) according to standard criteria. Treatment continued until disease progression or unacceptable toxicity, up to a maximum of 12 cycles. Subjects completing Cycle 12 (Week 48) were eligible to continue idelalisib treatment under a long-term extension protocol (Study 101-99).

Safety parameters were evaluated on an ongoing basis by the Gilead Sciences, Inc. (Gilead) medical monitor. Dose-limiting toxicity (DLT) for each regimen was assessed after Cycle 1 following Cohort 1, Cohort 2 (Regimens 2a and 2b), Cohort 5 (following enrollment of 6 subjects in each regimen), Cohort 6 (Regimen 6a), and Cohort 7.

Dose-limiting toxicity was defined as Grade ≥ 3 nonhematologic toxicity or Grade 4 hematologic toxicity persisting for at least 7 days, considered to be related to 1 or more drugs in the regimen.

A substudy involving serial pharmacokinetic (PK) sampling on Day 1 of Cycle 1 was offered to subjects with CLL or iNHL.

Number of Subjects (Planned and Analyzed):

Planned: 200 subjects (24 subjects in the PK substudy)

Analyzed: A total of 241 subjects were analyzed in the Intent-to-Treat (ITT) Analysis Set for this final clinical study report: 115 with CLL, 86 with iNHL, and 40 with MCL. Of the subjects in the ITT Analysis Set: 161 subjects in Cohorts 1 to 4 were analyzed for PK concentration data with results presented in the first interim report; 29 subjects in Cohort 5 and 25 subjects in Cohort 6 were analyzed for PK concentration data with results presented in the second interim report; and 7 subjects in Cohort 7 were analyzed for PK concentration data with results presented in this final report. Thus, the current report includes safety and efficacy data for all subjects in Cohorts 1-7 and PK data for subjects in Cohort 7.

Diagnosis and Main Criteria for Inclusion: Subjects with a documented diagnosis of histologically or cytologically confirmed select types of B-cell CLL, iNHL, or MCL were eligible for the study. Men and women of at least 18 years of age at Visit 1 with a World Health Organization (WHO) performance status of ≤ 2 who were previously treated with relapsed or refractory disease (refractory defined as not responding to a standard regimen or progressing within 6 months of the last course of a standard regimen) could be enrolled.

Subjects who were not good candidates to receive any of the drugs administered in the study for a given disease, according to the clinical judgment of the investigator, were excluded. The following subjects were also excluded: subjects with atypical immunophenotype with t(11:14) translocation or cyclin D1 overexpression (CLL subjects only), those who had radiotherapy, radioimmunotherapy, biological therapy, chemotherapy or treatment with study drug within 4 weeks prior to baseline disease status tests, treatment with a short course of corticosteroids within 1 week prior to baseline disease status tests, an allogenic hematopoietic stem cell transplant, known active nervous system involvement, or active, serious infection requiring systemic treatment. Subjects must also have had laboratory test results within ranges specified in the protocol.

Duration of Treatment: Subjects received study treatment until disease progression or unacceptable toxicity, up to a maximum of twelve 28-day cycles.

Test Product, Dose, Mode of Administration, and Lot No.: Idelalisib was administered to subjects orally twice daily at approximately 12-hour intervals. Idelalisib was supplied in bottles containing 50-, 75-, or 100-mg capsules or 75-, 100-, or 150-mg tablets.

Lot numbers for 50-mg capsules:	B090558, B090692
Lot numbers for 75-mg capsules:	B090671, B090690
Lot numbers for 75-mg tablets:	B100793, B100653, CV1103B1
Lot numbers for 100-mg capsules:	B090393
Lot numbers for 100-mg tablets:	B100172, CV1106B1, CV1102B1, CV1107B2, CY1201B1
Lot numbers for 150-mg tablets:	B110067, 22071001-01K001, CV1101B1, CV1105B1, CV1104D1, CV1107D2, CV1110D2, CV1205D1

Reference Therapy, Dose, Mode of Administration, and Lot No.: None

Criteria for Evaluation:

Efficacy: Clinical activity was evaluated by an investigator-derived assessment, as defined according to standard criteria for each indication (CLL: International Workshop on CLL criteria; iNHL: International Harmonization Project criteria). The clinical response was classified as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The best overall response was the best response recorded from the start of treatment until PD or early discontinuation. The best overall response was summarized by each response category as CR, PR, SD, PD, and not done (ND). Subjects' best overall response with a CR or PR was counted as responders, and all other subjects (including those with missing response information or ND) were included in the denominators for overall response rate (ORR) calculation.

The following clinical responses were assessed: ORR, duration of response (DOR), progression-free survival (PFS), time to response (TTR), percent change in lymph node area, lymph node response rate, splenomegaly response rate, hepatomegaly response rate, B symptoms, and overall survival (OS). Absolute lymphocyte count (ALC) response rate, platelet response rate, hemoglobin response rate, and absolute neutrophil count (ANC) response rate were assessed only for subjects with CLL.

Pharmacokinetics: Plasma concentrations of idelalisib were assessed, and the following PK parameters were estimated: the maximum observed concentration of drug in plasma (C_{max}), the time (observed time point) of C_{max} (T_{max}), the area under the plasma concentration-versus-time curve from time zero to the last quantifiable concentration (AUC_{last}), and the area under the plasma concentration-versus-time curve from time 0 to 6 hours (AUC_{0-6}).

Additional secondary endpoints included a substudy to assess the plasma concentration of chemotherapeutic agents, exploratory analysis of pharmacodynamic measures, and plasma concentrations of E.

Safety: Safety was assessed by the extent of exposure to idelalisib, adverse events (AEs) graded according to the Common Terminology Criteria for Adverse Events version 4.02, clinical laboratory observations (hematology, serum chemistry, coagulation, urinalysis, CLL immunophenotyping, and immunofixation), physical examinations, vital sign measurements, and electrocardiogram (ECG) results.

Statistical Methods: The final study analysis was conducted after all subjects completed Cycle 12 or end of study evaluations. Subjects were grouped by disease (CLL, iNHL, or MCL) and by treatment regimen. Summaries are presented by disease, by regimen, and overall by disease.

Efficacy: All efficacy endpoints were analyzed using the ITT Analysis Set (all subjects who received at least 1 dose of study drug [idelalisib or combination therapy]).

The ORR was calculated as the proportion of subjects whose best overall response was a CR or PR and presented with a 2-sided 95% exact confidence interval (CI). Clinical response was evaluated based on the investigator-derived assessment.

Duration of response, PFS, and OS were summarized using Kaplan-Meier (KM) methods. Survival curves were plotted based on the KM method. Descriptive statistics are presented for TTR. Duration of response and TTR were evaluated for subjects who achieved a response of CR or PR. For surviving and subjects without PD, data was censored on the date of the last tumor assessment for DOR and PFS calculations.

The sum of the products of the greatest perpendicular diameter (SPD) and percent change in SPD from baseline to each subsequent assessment time point were summarized. The best percent change from baseline during the study was also summarized. The on-treatment values were compared with the baseline values using a paired t-test. A waterfall plot of best on-treatment percent change in SPD based on the investigator's assessments was provided.

B symptoms at baseline and postbaseline visits were summarized. Only those subjects who had B symptoms at baseline were followed for postbaseline changes. The same summary is presented for the proportion of subjects with at least 1 B symptom.

Pharmacokinetics: The PK Analysis Sets include data from subjects in the ITT Analysis Set who had the necessary baseline and on-study measurements to provide interpretable results for the specific parameters of interest. These analysis sets were used for the tabulation of idelalisib plasma concentrations for subjects in Cohort 7; results for subjects in Cohorts 1 through 6 were presented in the previous interim reports.

Pharmacokinetic parameters were estimated for the PK substudy using WinNonlin® software 6.3 by application of a nonlinear model using standard noncompartmental methods. The linear up/log down trapezoidal rule was used in conjunction with the appropriate noncompartmental model, with input values for dose, time of dose, plasma concentration, and corresponding real time values, based on drug dosing times whenever possible. All predose sample times of less than time-zero were converted to zero. Samples below the limit of quantification (BLQ) of the bioanalytical assays that occurred prior to the achievement of the first quantifiable concentration were assigned a concentration value of zero to prevent overestimation of the initial AUC. Samples that were BLQ at all other time points were treated as missing data. The nominal time point for a key event (eg, urine collection) or dosing interval (τ) may have been used to permit direct calculation of AUC over specific time intervals. The appropriateness of this approach was assessed by the pharmacokineticist on a profile-by-profile basis.

Safety: Safety analyses were conducted using the ITT Analysis Set for the following categories: AEs, clinical laboratory test results, physical examinations, vital signs, and ECGs. Adverse events were summarized overall and for the following subgroups: sex, age group (< 65 years or ≥ 65 years), and race (white or nonwhite). Descriptive statistics of actual and change from baseline values were provided for each laboratory test, and the mean values of change from baseline for laboratory values were plotted over time. Physical examination, vital sign data, and ECG results were summarized.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: Overall, 115 subjects with CLL, 86 subjects with iNHL, and 40 subjects with MCL were enrolled in the study.

Of the 115 subjects with CLL in the ITT Analysis Set, 93.0% completed Cycle 2, 55.7% completed the study, and 44.3% discontinued the study. The most common reasons for discontinuation from the study were AE (13.0%), disease progression (9.6%), and death (8.7%).

Of the 86 subjects with iNHL in the ITT Analysis Set, 94.2% completed Cycle 2, 47.7% completed the study, and 52.3% discontinued the study. The most common reasons for discontinuation from the study were AE (19.8%), disease progression (10.5%), and other (7.0%).

Of the 40 subjects with MCL in the ITT Analysis Set, 70.0% completed Cycle 2, 22.5% completed the study, and 77.5% discontinued the study. The most common reasons for discontinuation from the study were AE (30.0%), disease progression (20.0%), and death (15.0%).

Of the subjects with CLL, 67.8% were male and 32.2% were female; most subjects (92.2%) were white. The mean (standard deviation [StD]) age was 65 (9.4) years, with a range of 41 to 87 years. Approximately half of subjects (51.3%) were ≥ 65 years of age. The majority of subjects had a WHO performance status of 0 or 1 (55.7% and 40.9%, respectively). Nearly two-thirds of the subjects (59.1%) had bulky adenopathy.

Of the subjects with iNHL, 66.3% were male and 33.7% were female; most subjects (80.2%) were white. The mean (StD) age was 61 (10.4) years, with a range of 37 to 84 years. Among these subjects, (40.7%) were ≥ 65 years of age. The majority of subjects had a WHO performance status of 0 or 1 (59.3% and 38.4%, respectively). Half of the subjects with iNHL (50.0%) had bulky adenopathy.

Of the subjects with MCL, 75.0% were male and 25.0% were female; most subjects (85.0%) were white. The mean (StD) age was 70 (7.5) years, with a range of 47 to 80 years. Most subjects (77.5%) were ≥ 65 years of age. The majority of subjects had a WHO performance status of 0 or 1 (37.5% and 50.0%, respectively). Of the subjects with MCL, 62.5% had bulky adenopathy.

The median (range) number of prior therapies was 3 (1 to 9) for subjects with CLL, 3 (1 to 11) for subjects with iNHL, and 3 (1 to 7) for subjects with MCL.

Efficacy Results: All efficacy analyses were performed on the ITT Analysis Set.

Overall Response Rates: For subjects with CLL across all treatment regimens, the ORR (95% CI) was 80.9% (72.5%, 87.6%). Overall, 7 subjects (6.1%) with CLL achieved a CR and 86 subjects (74.8%) achieved a PR; 14 subjects (12.2%) had SD. The ORR (95% CI) was 66.7% (48.2%, 82.0%) for subjects with either TP53 mutation or 17p deletion.

For subjects with iNHL across all treatment regimens, the ORR (95% CI) was 79.1% (69.0%, 87.1%). Overall, 23 subjects (26.7%) with iNHL achieved a CR and 45 subjects (52.3%) achieved a PR; 10 subjects (11.6%) had SD.

For subjects with MCL across all treatment regimens, the ORR (95% CI) was 57.5% (40.9%, 73.0%). Overall, 6 subjects (15.0%) with MCL achieved a CR and 17 subjects (42.5%) achieved a PR; 6 subjects (15.0%) had SD.

Duration of Response: Duration of response analyses were based on subjects who achieved a CR or PR. The median KM estimate of DOR was not reached for subjects with CLL or iNHL, and was 9.3 months for subjects with MCL.

Time to Response: For subjects with CLL who achieved a CR or PR, the median TTR was 1.9 months, with a minimum of 1.4 months and maximum of 8.3 months. For subjects with iNHL who achieved a CR or PR, the median TTR was 1.9 months, with a minimum of 1.0 month and maximum of 8.3 months. For subjects with MCL who achieved a CR or PR, the median TTR was 1.9 months, with a minimum of 1.7 months and a maximum of 5.5 months.

Progression-free Survival: The median KM estimate of DOR was not reached for subjects with CLL or iNHL, and was 11.1 months for subjects with MCL.

Overall Survival: For all subjects across all treatment regimens, the median KM estimate of OS was not reached.

Other Response Rates: For subjects with CLL, the overall lymph node response rate (95% CI) was 80.9% (72.5%, 87.6%). The overall splenomegaly response rate (95% CI) was 57.6% (44.8%, 69.7%), and the overall hepatomegaly response rate (95% CI) was 60.0% (32.3%, 83.7%).

For subjects with iNHL, the overall lymph node response rate (95% CI) was 77.9% (67.7%, 86.1%). The overall splenomegaly response rate (95% CI) was 90.9% (58.7%, 99.8%). For subjects with iNHL, the hepatomegaly response analysis included only 1 subject in the Id+B treatment group, and this subject had a response.

For subjects with MCL, the overall lymph node response rate (95% CI) was 60.0% (43.3%, 75.1%). The overall splenomegaly response rate (95% CI) was 66.7% (22.3%, 95.7%). For subjects with MCL, the hepatomegaly response analysis included 1 subject in the Id+Bo treatment group, and this subject had a response.

Additional CLL Hematologic Criteria Response Rates: For subjects with CLL across all treatment regimens, the ALC response rate (95% CI) was 89.1% (80.9%, 94.7%), the platelet response rate (95% CI) was 86.8% (74.7%, 94.5%), the hemoglobin response rate (95% CI) was 66.7% (52.5%, 78.9%), and the ANC response rate (95% CI) was 77.8% (52.4%, 93.6%).

B Symptoms: At baseline, 45 subjects (39.1%) with CLL had at least 1 B symptom. B symptoms generally resolved with idelalisib treatment. By Week 48, 1 subject (11.1%) who received Id+RCh had at least 1 B symptom and 1 subject (16.7%) who received Id+RCh had at least 1 B symptom excluding fatigue; no other subjects reported any continuing B symptoms by Week 48.

At baseline, 19 subjects (22.1%) with iNHL had at least 1 B symptom. B symptoms resolved with idelalisib treatment; no subjects reported any continuing B symptoms by Week 36.

At baseline, 9 subjects (22.5%) with MCL had at least 1 B symptom. B symptoms resolved with idelalisib treatment; no subjects reported any continuing B symptoms by Week 36.

Pharmacokinetics Results: All PK analyses were performed on the PK analysis set.

Overall, idelalisib plasma concentrations were comparable to those observed in other idelalisib CLL/iNHL monotherapy studies (eg, Study 101-02) and in prior cohorts receiving idelalisib combination therapy in this study, suggesting a lack of effect of L coadministration on idelalisib PK.

Safety Results: All safety analyses were performed on the ITT Analysis Set.

AEs, Overall: A total of 238 subjects (98.8%) experienced at least 1 TEAE. The most frequently reported AEs by PT (reported for ≥ 20% of the subjects) included pyrexia (103 subjects [42.7%]), diarrhea (101 subjects [41.9%]), neutropenia (99 subjects [41.1%]), fatigue (87 subjects [36.1%]), cough (80 subjects [33.2%]), nausea (79 subjects [32.8%]), rash (65 subjects [27.0%]), constipation (49 subjects [24.1%]), ALT increased (54 subjects [22.4%]), thrombocytopenia (53 subjects [22.2%]), and anemia (49 subjects [20.3%]).

The most frequently reported AEs by PT (reported for ≥ 20% of the subjects) in each treatment regimen were as follows:

- Id+R: diarrhea (21 subjects [41.2%]), cough, fatigue, and pyrexia (18 subjects [35.3%] each), nausea (17 subjects [33.3%]), neutropenia (15 subjects [29.4%]), headache and rash (12 subjects [23.5%] each), and abdominal pain (11 subjects [21.6%])
- Id+B: pyrexia (31 subjects [60.8%]), neutropenia (28 subjects [54.9%]), fatigue (24 subjects [47.1%]), nausea (19 subjects [37.3%]), ALT increased and cough (18 subjects [35.3%] each), rash (16 subjects [31.4%]), AST increased, diarrhea, and thrombocytopenia (15 subjects [29.4%] each), anemia (14 subjects [27.5%]), and constipation, insomnia, and upper respiratory infection (11 subjects [21.6%] each)
- Id+E: thrombocytopenia (12 subjects [66.7%]), diarrhea (9 subjects [50.0%]), cough, epistaxis, and neutropenia (7 subjects [38.9%] each), anemia, decreased appetite, and hypokalemia (6 subjects [33.3%] each), fatigue, pyrexia, and rash (5 subjects [27.8%] each), and pruritus and renal failure acute (4 subjects [22.2%] each)
- Id+Bo: diarrhea (8 subjects [44.4%]), ALT increased, anemia, AST increased, and rash (5 subjects [27.8%] each), and dizziness, fatigue, hypokalemia, neutropenia, and thrombocytopenia (4 subjects [22.2%] each)
- Id+BR: pyrexia (19 subjects [57.6%]), nausea and neutropenia (14 subjects [42.4%] each), rash (13 subjects [39.4%]), diarrhea and fatigue (12 subjects [36.4%] each), cough (9 subjects [27.3%]), constipation (8 subjects [24.2%]), and vomiting (7 subjects [21.2%])

- Id+O: diarrhea (11 subjects [52.4%]), cough (9 subjects [42.9%]), dyspnea and pyrexia (7 subjects [33.3%] each), nausea and neutropenia (6 subjects [28.6%] each), and decreased appetite (5 subjects [23.8%])
- Id+F: neutropenia (7 subjects [58.3%]), cough and diarrhea (6 subjects [50.0%] each), decreased appetite, fatigue, and pyrexia (5 subjects [41.7%] each), anemia and nausea (4 subjects [33.3%] each), and ALT increased, anxiety, AST increased, hyperglycemia, rhinorrhea, and vomiting (3 subjects [25.0%] each)
- Id+Ch: neutropenia (9 subjects [60.0%]), cough and diarrhea (7 subjects [46.7%] each), febrile neutropenia and thrombocytopenia (5 subjects [33.3%]), fatigue, insomnia, leukopenia, nausea, pyrexia, and vomiting (4 subjects [26.7%] each), and anemia, anxiety, dyspnea, edema peripheral, night sweats, pain, pneumonia, and rash (3 subjects [20.0%] each)
- Id+RCh: diarrhea (10 subjects [66.7%]), pyrexia (8 subjects [53.3%]), neutropenia (7 subjects [46.7%]), constipation, fatigue, and nausea (6 subjects [40.0%] each), hypokalemia and rash (5 subjects [33.3%] each), ALT increased, anemia, cough, and pneumonia (4 subjects [26.7%] each), and abdominal pain, AST increased, decreased appetite, dysgeusia, dyspnea, insomnia, thrombocytopenia, and upper respiratory tract infection (3 subjects [20.0%] each)
- Id+RL: constipation (6 subjects [85.7%]), ALT increased, AST increased, blood lactate dehydrogenase increased, and fatigue (5 subjects [71.4%] each), nausea (4 subjects [57.1%]), pyrexia (3 subjects [42.9%]), and cough, diarrhea, dizziness, dyspnea, headache, neutropenia, stomatitis, and vomiting (2 subjects [28.6%] each) (note that dosing of L in this group was discontinued due to ALT and AST elevations)

AEs, Severity: The most frequently reported PTs (≥ 5% of subjects overall) for TEAEs Grade ≥ 3 were neutropenia (79 subjects [32.8%]), ALT increased (37 subjects [15.4%]), thrombocytopenia (34 subjects [14.1%]), pneumonia (25 subjects [10.4%]), febrile neutropenia (23 subjects [9.5%]), anemia and AST increased (22 subjects [9.1%] each), diarrhea (20 subjects [8.3%]), and rash (12 subjects [5.0%]).

AEs, Relationship to Study Drug as Reported by Investigators: The most frequently reported Grade ≥ 3 TEAEs (≥ 5% of subjects overall) considered by the investigator to be related to idelalisib by PT were neutropenia (37 subjects [15.4%]), ALT increased (35 subjects [14.5%]), thrombocytopenia (23 subjects [9.5%]), AST increased (20 subjects [8.3%]), and diarrhea (15 subjects [6.2%]).

Deaths: Twenty subjects died on study or within 30 days of last treatment dose: 10 subjects with CLL (subdural hematoma; acute hypoxic respiratory failure; *Pneumocystis jirovecii* pneumonia; tumor lysis syndrome; secondary acute myeloid leukemia; gastrointestinal bleeding; multi organ failure and septic shock; neutropenic sepsis; *Pseudomonas bacteremia* and *Aspergillus* infection; and disease progression), 3 subjects with iNHL (cardiac arrest, sepsis, and disease progression), and 7 subjects with MCL (respiratory distress; asystolic arrest, respiratory failure, and sepsis; neutropenic fever; pneumonia; fall; acute kidney injury; and disease progression).

Serious Adverse Events (SAEs): Overall, 137 subjects (56.8%) experienced at least 1 SAE. The most frequently occurring SAEs (≥ 5% of subjects) overall were pyrexia (24 subjects [10.0%]), pneumonia (23 subjects [9.5%]), and febrile neutropenia (19 subjects [7.9%]).

The incidence of pyrexia, the most frequently reported SAE, ranged from 0% (in the Id+RCh group) to 28.6% (2 subjects in the Id+RL group). For the other frequently reported SAEs, pneumonia occurred with an incidence ranging from 0% (in the Id+Bo and Id+RL groups) to 19.6% (10 subjects in the Id+B group), and febrile neutropenia occurred with an incidence ranging from 0% (in the Id+Bo and Id+RL groups) to 26.7% (4 subjects in the Id+Ch group).

Discontinuations Due to AEs: Adverse events leading to idelalisib discontinuation reported for at least 2 subjects each (0.8%) included diarrhea (6 subjects [2.5%]), ALT increased (4 subjects [1.7%]), AST increased, colitis, pneumonia, pneumonitis, rash, sepsis, and vomiting (3 subjects [1.2%] each), and anemia, febrile neutropenia, nausea, rash macular, acute kidney failure, and thrombocytopenia (2 subjects [0.8%] each).

Adverse events of diarrhea leading to discontinuation were reported for 2 subjects (13.3%) in the Id+RCh group and for 1 subject each in the Id+R (2.0%), Id+B (2.0%), Id+Bo (5.6%), and Id+F (8.3%) groups. ALT increased was reported for 2 subjects (3.9%) each in the Id+R and Id+B groups. AST increased was reported for 2 subjects (3.9%) in the Id+R group and for 1 subject (14.3%) in the Id+RL group. Sepsis was reported for 2 subjects (3.9%) in the Id+B group and for 1 subject (5.6%) in the Id+Bo group. Rash macular was reported for 2 subjects (11.1%) in the Id+E group. All other PTs were reported for no more than a single subject in each treatment group.

Clinical Laboratory Evaluations: Among all subjects with CLL, mean hemoglobin and platelet counts generally improved with administration of idelalisib; mean neutrophil counts remained relatively stable.

Among subjects with iNHL, mean hemoglobin and platelet counts were decreased from baseline in the Id+B and Id+BR groups. For subjects who received the Id+R and Id+RCh regimens, mean hemoglobin and platelet counts showed only minor fluctations. Mean neutrophil counts showed only minor fluctuations in all groups.

Among subjects with MCL, mean hemoglobin, platelet counts, and neutrophil counts at Week 48 remained similar to baseline.

Grade 3 or 4 decreases in hemoglobin, neutrophils, and platelets occurred most frequently in cohorts that included combinations of idelalisib with drugs such as alkylating agents (eg, B) or purine analogs (eg, F) that have well recognized side effects of myelosupression and neutropenia.

Overall, mean ALT and AST values increased initially for most cohorts, returned to baseline levels by Week 16, and generally remained at or near baseline levels for the remainder of the study. Alkaline phosphatase, total bilirubin, and creatinine generally remained stable at or near baseline levels throughout the study, regardless of disease or treatment regimen. The incidence of Grade 3 or 4 ALT or AST elevation was low, and both ALT and AST resolved to ≤ Grade 1 for most subjects.

Due to ALT and AST elevations in the first 4 subjects in the Id+RL group, dosing of the Id+RL combination was terminated in Cohort 7. Subjects who remained in this cohort at the time the termination decision was made were switched to receive Id+R.

Vital Signs: There were no clinically meaningful changes in temperature, blood pressure, or heart rate during the study. No subject had a shift from normal ECG results to a clinically significant ECG abnormality. No subject had a QTc interval (Fridericia formula) > 500 msec at baseline, but 2 subjects (0.8%) had a QTc interval (Fridericia formula) > 500 msec at Week 48.

CONCLUSIONS:

- In subjects with relapsed/refractory CLL who had been heavily pretreated, remarkably high overall response rates (ORR of 80.9%) were achieved, including responses occurring after cessation of the combination drugs. Substantial improvements were achieved in all individual response criteria: lymph nodes (response rate of 80.9%, mean best percent change in area from baseline of −72.0), spleen (response rate of 57.6%), and liver (response rate of 60.0%). Rapid reductions in lymphadenopathy (median TTR of 1.9 months) and durable tumor control (median KM estimates of DOR and PFS were not reached) were observed. Improvements in hematologic parameters were noted in subjects with CLL who had abnormal hematologic parameters at baseline.
- In subjects with relapsed/refractory iNHL who had been heavily pretreated, high overall response rates (ORR of 79.1%) were achieved, including responses occurring after cessation of the combination drugs. Idelalisib in combination with R and/or B induced rapid reductions in lymphadenopathy (median TTR of 1.9 months) and durable tumor control (median KM estimates of DOR and PFS were not reached). Improvements in hematologic parameters were noted in subjects with iNHL who had abnormal hematologic parameters at baseline.
- In subjects with relapsed/refractory MCL who were heavily pretreated, remarkably high overall response rates (ORR of 57.5%) were achieved with idelalisib-based combination therapies, including responses occurring after completion of the combination drugs. Idelalisib in combination with BR induced rapid reductions in lymphadenopathy (median TTR of 1.9 months) and durable tumor control (median KM estimates of DOR and PFS were 9.3 and 11.1 months, respectively). Improvements in hematologic parameters were noted in subjects with MCL who had abnormal hematologic parameters at baseline.
- Rapid control of B symptoms in symptomatic patients was also demonstrated in all cohorts.
- With the exception of the Id+RL combination, idelalisib had a managable safety profile when administered in combination therapy with agents used routinely in clinical practice. The safety data suggest that idelalisib may lead to an increased risk of hepatotoxicity when used in combination with R and L at this dose and schedule. Excluding the Id+RL combination, the absence of overlapping toxicities allowed the administration of idelalisib and combination therapies at the planned doses of each. Diarrhea, neutropenia, pyrexia, rash, and transaminase elevations were similar to what has been observed with idelalisib monotherapy. Idelalisib did not exacerbate the known safety profile of any of the combination drugs, except possibly for E. Everolimus is a CYP3A substrate and, after the Id+E treatment cohort completed, it was established that the primary idelalisib metabolite is a CYP3A inhibitor, which may account for the comparatively high incidence of SAEs (77.8%) and AEs leading to discontinuation of idelalisib (55.6%).

- Overall, the AE profile was consistent with that expected for a heavily pretreated, relapsed/refractory hematologic cancer population receiving combination immunochemotherapy agents. The most frequently reported TEAE was pyrexia (42.7% of all subjects). The most frequently reported Grade ≥ 3 TEAE was neutropenia (32.8% of all subjects). Grade ≥ 3 rash occurred in 5.0% of subjects, including subjects receiving bendamustine.
- Early transaminase elevations that occurred were generally asymptomatic and transient. Overall, a Grade 3 or 4 ALT or AST elevation was reported for 30 subjects (12.4%); 29 subjects (12.0%) had a dose interruption due to a Grade 3 or 4 ALT or AST elevation. The overall median time to onset of Grade 3 or 4 ALT/AST elevation was 6.1 weeks and the overall time to resolution of the first Grade 3 or 4 ALT/AST elevation was 2.1 weeks.
- There were no clinically meaningful changes in blood pressure, heart rate, or ECG results during the study.
- The efficacy and overall consistent safety results in this study supported the further evaluation of idelalisib in combination with many of the studied drugs, including R and B, in the Phase 3 program.