FINAL ABBREVIATED CLINICAL STUDY REPORT

Study Title:	A Phase 2, Single Arm Study Evaluating the Efficacy and Safety of Idelalisib in Combination with Rituximab in Patients with Previously Untreated Chronic Lymphocytic Leukemia with 17p Deletion
Name of Test Drug:	Idelalisib (IDL, Zydelig®)
Dose and Formulation:	Idelalisib 150-mg tablets
Indication:	Chronic Lymphocytic Leukemia with 17p deletion
Sponsor:	Gilead Sciences, Inc. 199 East Blaine Street Seattle, WA 98102 USA Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-312-0133
Phase of Development:	Phase 2
IND No.: **EudraCT No.:**	101254 2013-003314-41
ClinicalTrials.gov Identifier	NCT02044822
Study Start Date:	06 August 2014 (First Subject Screened)
Study End Date:	17 May 2016 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Professor Peter Hillmen Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Ronald Dubowy, MD Telephone: PPD Fax: PPD
Report Date:	18 April 2017

CONFIDENTIAL AND PROPRIETARY INFORMATION

This study was conducted in accordance with the guidelines of Good Clinical Practice, including archiving of essential documents.

STUDY SYNOPSIS
Study GS-US-312-0133
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 2, Single Arm Study Evaluating the Efficacy and Safety of Idelalisib in Combination with Rituximab in Patients with Previously Untreated Chronic Lymphocytic Leukemia with 17p Deletion

Investigators: This was a global multicenter study.

Study Centers: A total of 100 study sites were activated, of which 56 enrolled subjects in Australia, Austria, Belgium, Czech Republic, Denmark, France, Hungary, Italy, Poland, Portugal, Romania, Spain, United Kingdom (UK), and United States (US)

Publications: There were no publications based on the study at the time of writing this study report.

Study Period:

06 August 2014 (First Subject Screened)
17 May 2016 (Last Subject Observation)

Phase of Development: Phase 2

Objectives:

The primary objective of this study was as follows:

- To evaluate the overall response rate (ORR) following treatment with idelalisib (IDL) plus rituximab (R) (IDL + R) in subjects with previously untreated chronic lymphocytic leukemia (CLL) with 17p deletion

The secondary objectives of this study were as follows:

- To evaluate the effect of IDL + R on the onset, magnitude, and duration of disease control, including duration of response (DOR), progression-free survival (PFS), and overall survival (OS)
- To evaluate the effect of IDL + R on minimal residual disease (MRD)
- To describe the safety profile observed with IDL + R
- To characterize exposure to study treatment with IDL + R as determined by treatment administration and evaluation of IDL plasma concentrations over time

Methodology: Study GS-US-312-0133 was a Phase 2, single arm, open-label clinical study of IDL given in combination with rituximab in subjects with previously untreated CLL with 17p deletion. During screening, confirmation of 17p deletion status by central laboratory fluorescence in-situ hybridization (FISH) testing was required for enrollment.

Subjects received IDL 150 mg twice daily, taken orally continuously until progression of CLL or intolerable toxicity. Study drug included both IDL and rituximab. IDL was supplied by Gilead.

Subjects received rituximab 375 mg/m^2 administered intravenously on Day 1 (Week 0), Day 8 (Week 1), Day 15 (Week 2), Day 22 (Week 3), Day 29 (Week 4), Day 36 (Week 5), Day 43 (Week 6), and Day 50 (Week 7) for a total of 8 infusions. Gilead provided rituximab to study sites in Europe and Australia.

The screening period was up to 28 days and treatment duration with rituximab was up to 8 weeks. Subjects were to remain on either IDL or rituximab, even if the other agent was discontinued due to agent-specific toxicity. Study assessments continued until study discontinuation due to confirmed disease progression or other reasons. Upon study discontinuation, an end-of-study (EOS) visit was conducted. After the EOS, there was a safety follow-up period of 30 days, leading into annual long-term follow-up visits.

Number of Subjects (Planned and Analyzed):
Planned: 100 subjects
Analyzed: 102 subjects were enrolled as the Intent-to-Treat (ITT) population at the time of early termination of the study; all 102 subjects were included in the Pharmacokinetic (PK) Analysis Set

Diagnosis and Main Criteria for Inclusion: The target population consisted of adult subjects with previously untreated CLL with 17p deletion documented by FISH assay, measurable lymphadenopathy, and who required treatment for their CLL. Inclusion criteria to be eligible for participation in this study were as follows:

1) Male or female ≥ 18 years of age
2) Documented diagnosis of B-cell CLL, according to International Workshop on Chronic Lymphocytic Leukemia (IWCLL) 2008
3) Presence of 17p deletion in CLL cells as demonstrated by FISH testing performed at a central laboratory
4) No prior therapy for CLL other than corticosteroids for disease complications
5) CLL that warranted treatment based on any of the following criteria:
    a) Evidence of progressive marrow failure as manifested by the onset or worsening of anemia and/or thrombocytopenia
    b) Progressive or symptomatic or massive splenomegaly (ie, lower edge of spleen ≥ 6 cm below the left costal margin)
    c) Progressive or symptomatic or massive lymphadenopathy (ie, ≥ 10 cm in the longest diameter)

d) Progressive lymphocytosis in the absence of infection, with an increase in blood absolute lymphocyte count (ALC) ≥ 50% over a 2-month period or lymphocyte doubling time of < 6 months (as long as initial ALC was ≥ 30,000/μL)

e) Autoimmune anemia and/or thrombocytopenia that was poorly responsive to corticosteroids, or other standard therapy

f) Constitutional symptoms, as evidenced by any of the following:

i) Unintentional weight loss of ≥ 10% within the previous 6 months

ii) Significant fatigue (Eastern Cooperative Oncology Group [ECOG] performance status of 2: inability to work or perform usual activities)

iii) Fevers > 100.5°F or 38.0°C for ≥ 2 weeks without evidence of infection

iv) Night sweats for > 1 month without evidence of infection

6) Presence of measurable lymphadenopathy confirmed by the Independent Review Committee (IRC) (defined as the presence of ≥ 1 nodal lesion that measures ≥ 2.0 cm in the longest dimension [LD] and ≥ 1.0 cm in the longest perpendicular dimension [LPD] as assessed by computed tomography [CT] or magnetic resonance imaging [MRI]).

7) ECOG performance status of ≤ 2

8) Required screening laboratory data (within 28 days prior to enrollment) as shown in the table below:

Organ System	Parameter	Required Value
Hematopoietic	ANC	$\geq 1 \times 10^9$/L[a]
	Platelet	$\geq 75 \times 10^9$/L[a]
	Hemoglobin	≥ 100 g/L (10.0 g/dL or 6.2 mmol/L)[a]
Hepatic	Serum total bilirubin	≤ 1.5 × ULN (unless elevated due to Gilbert's syndrome or hemolysis)
	Serum ALT	≤ 2.5 × ULN
	Serum AST	
Renal	eC_{Cr}[b]	≥ 30 mL/min
Pregnancy	β-hCG[c]	Negative
Infection	HIV	Negative HIV antibody
	HBV	Negative HBsAg and negative HBc antibody, or positive HBc antibody and negative for HBV DNA by quantitative PCR
	HCV	Negative viral RNA (if HCV antibody is positive)

β-hCG = beta human chorionic gonadotropin, ALT = alanine aminotransferase, AST = aspartate aminotransferase, DNA = deoxyribonucleic acid, eC_{Cr} = estimated creatinine clearance, HBc antibody = anti-hepatitis B core antibody, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, HCV = hepatitis C virus, HIV = human immunodeficiency virus, Ig = immunoglobulin, PCR = polymerase chain reaction, RNA = ribonucleic acid, ULN = upper limit of normal

a Grade ≥ 2 neutropenia, thrombocytopenia, or anemia was permitted if abnormality was related to bone marrow involvement with CLL (as documented by bone marrow biopsy/aspirate).

b As calculated by the Cockcroft-Gault formula or measured.

c For women of child-bearing potential only; serum β-hCG must have been negative during screening and urine pregnancy test must have been negative at enrollment (Visit 2)

9) For female subjects of childbearing potential, willing to use a protocol-recommended method of contraception from the signing of informed consent throughout the study treatment period and 30 days from the last dose of IDL or 12 months from the last dose of R, whichever was later.
10) Male subjects of reproductive potential who had intercourse with females of childbearing potential, must have agreed to utilize protocol specified methods of contraception and refrain from sperm donation from the enrollment visit throughout the study treatment period and up to 3 months from the last dose of IDL or 12 months from the last dose of R, whichever was later.
11) Lactating females must have agreed to discontinue nursing before study drug administration.
12) Willing and able to comply with scheduled visits, drug administration plan, imaging studies, laboratory tests, other study procedures, and study restrictions
13) Evidence of a signed informed consent

Subjects who met any of the following exclusion criteria were not to be enrolled in this study:

1) Known histological transformation from CLL to an aggressive lymphoma (ie, Richter transformation)
2) Known presence of myelodysplastic syndrome
3) History of a non-CLL malignancy, with the following exceptions:
    a) The malignancy had been in remission without treatment for ≥ 5 years prior to enrollment
    b) Carcinoma in situ of the cervix
    c) Adequately treated basal or squamous cell skin cancer or other localized non-melanoma skin cancer
    d) Asymptomatic prostate cancer without known metastatic disease and with no current requirement for therapy or requiring only hormonal therapy and with normal prostate-specific antigen for ≥ 1 year prior to enrollment
    e) Ductal carcinoma in situ (DCIS) of the breast treated with lumpectomy alone
    f) Other adequately treated Stage 1 or 2 cancer currently in complete remission
4) Known hypersensitivity or intolerance to any of the active substances or excipients in the formulations for IDL or R
5) Evidence of ongoing systemic bacterial, fungal, or viral infection at the time of enrollment
6) Ongoing drug-induced liver injury, alcoholic liver disease, nonalcoholic steatohepatitis, primary biliary cirrhosis, extrahepatic obstruction caused by cholelithiasis, cirrhosis of the liver, or portal hypertension
7) History of noninfectious pneumonitis
8) Ongoing inflammatory bowel disease
9) History of prior allogeneic bone marrow progenitor cell or solid organ transplantation

10) Ongoing immunosuppressive therapy other than corticosteroids

11) Received last dose of study drug on another therapeutic clinical trial within 30 days prior to enrollment

12) Prior or ongoing clinically significant illness, medical condition, surgical history, physical finding, electrocardiogram (ECG) finding, or laboratory abnormality that, in the investigator's opinion, could have adversely affected the safety of the subject or have impaired the assessment of study results

13) Subject had undergone major surgery other than diagnosis surgery within 30 days prior to enrollment

Duration of Treatment: Idelalisib was administered twice daily in a continuous manner until progression of CLL or intolerable toxicity. Rituximab was administered weekly for a total of 8 infusions. Subjects were to remain on either component of study treatment even if the other agent had to be discontinued due to agent-specific toxicity. The overall duration of the study was expected to be approximately 10 years, including long-term follow-up.

Test Product, Dose, Mode of Administration, and Lot No.:

Idelalisib: 150 mg orally twice daily starting on Day 1 and administered continuously

Lot Numbers: CV1301D1, CV1402B1, NSZV

The dose could be decreased to 100 mg twice daily if the subject experienced a toxicity requiring dose adjustment.

Lot Numbers: CV1304D1, CV1301C1, NSZS

The dose could be increased back to 150 mg twice daily if the subject tolerated the lower dose level for ≥ 4 weeks, at the discretion of the investigator.

Reference Therapy, Dose, Mode of Administration, and Lot No.:

Rituximab: 375 mg/m² intravenously (IV) on Day 1 (Week 0), Day 8 (Week 1), Day 15 (Week 2), Day 22 (Week 3), Day 29 (Week 4), Day 36 (Week 5), Day 43 (Week 6), and Day 50 (Week 7) for a total of 8 infusions. Missed doses could be made up through Week 11.

Lot Numbers: H0710B03, H0740B04, N7004B04, N7004B09, N7008B09, N7011B02, N7027B04, N7035B02

In March 2016, a safety signal of increased rate of deaths and serious adverse events (SAEs) was observed in subjects with early-line indolent non-Hodgkin lymphoma (iNHL) and front-line CLL receiving IDL with standard therapy versus standard therapy alone in a pooled analysis of 3 Phase 3 placebo-controlled studies (Studies GS-US-312-0123, GS-US-313-0124, and GS-US-313-0125). Gilead reviewed the unblinded data and terminated those studies in agreement with the data monitoring committee (DMC) recommendation and in consultation with the US Food and Drug Administration (FDA). All front-line studies evaluating IDL, including this study, were also terminated. A letter to investigators was issued globally on 11 March 2016, providing written notification of the safety findings and decision to terminate this study. The last dose of study drug was administered on 31 March 2016 and the last subject observation occurred on 17 May 2016.

Criteria for Evaluation:

Efficacy: Due to early study termination, the efficacy analyses were not conducted.

Pharmacokinetics: Trough (predose) and peak (1.5-hour samples) plasma concentrations of IDL and its metabolite, GS-563117, were assessed by a validated bioanalytical method.

Safety: The overall safety profile was characterized by the type, frequency, severity, timing of onset, duration, and relationship to study therapy of any adverse events (AEs) or abnormalities of laboratory tests, SAEs, or AEs leading to discontinuation of study treatment.

Statistical Methods:

The ITT Analysis Set was used in the analyses of all safety endpoints. The ITT Analysis Set comprised data from subjects who received ≥ 1 dose of study drug.

Efficacy: No efficacy analyses were performed.

Pharmacokinetics: Plasma concentrations of IDL and its major metabolite were listed and summarized using descriptive statistics (eg, sample size, arithmetic mean, % coefficient of variation, standard deviation [StD], median, minimum, first quartile [Q1], third quartile [Q3], and maximum). No pharmacodynamics analyses were performed.

Safety: Adverse event data were listed by subject. Treatment-emergent AEs, treatment-related AEs, SAEs, and AEs leading to permanent study drug discontinuation were summarized by system organ class (SOC), and preferred term (PT) using the current version of the Medical Dictionary for Regulatory Activities, Version 19.0. Listings of individual subject laboratory results were provided. Laboratory results and change from baseline values for selected laboratory tests were summarized at scheduled visits. The incidence of treatment-emergent laboratory abnormalities and vital signs were also summarized.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: This study was fully enrolled at the time it was terminated based on a safety signal identified in a similar study population. A total of 102 subjects were included in the ITT Analysis Set, which included all the subjects who received ≥ 1 dose of study drug. Overall, 9 subjects (8.8%) met the primary endpoint of the study (disease progression by investigator assessment or death), 10 subjects (9.8%) were withdrawn by the investigator, 3 subjects (2.9%) withdrew consent, 2 subjects (2.0%) discontinued the study due to initiation of new anticancer therapy, and 1 subject (1.0%) was lost to follow up. The remaining 77 subjects (75.5%) were discontinued when the study was terminated by the sponsor.

Most subjects (59.8%) were ≥ 65 years of age, with a median (Q1, Q3) age of 66 (61, 72) years and range of 37 to 86 years. The majority of subjects (56.9%) were male and most (92.2%) were white. The median (Q1, Q3) baseline body mass index (BMI) was 25.6 (23.0, 30.0) kg/m^2. Most subjects (92 subjects; 90.2%) had an ECOG Performance Status of 0 or 1.

Prior to study entry, the subject population had presented with CLL for a median (Q1, Q3) of 1.33 (0.36, 2.01) years with a range of 0.04 to 32.04 years. At study screening, 44.1% of subjects had Rai disease stages III/IV.

Efficacy Results: Efficacy analyses were not performed for this study.

Pharmacokinetics Results: In general, IDL and GS-563117 plasma concentrations were comparable at predose or 1.5 hours postdose between Week 2 and Week 20. Trough concentrations of IDL were similar to those observed in other monotherapy studies (eg, Study 101-02) and to population PK modeling estimates following IDL 150 mg twice daily monotherapy. These results suggest that there was no significant change in the PK of IDL or GS-563117 when coadministered with rituximab.

Safety Results: In the ITT Analysis Set, the median (Q1, Q3) duration of exposure to IDL was 6.4 (3.0, 9.5) months, with a range of 0.7 to 17.0 months. The median (Q1, Q3) duration of exposure to rituximab was 1.6 (1.6, 1.8) months, with a range of 0.7 to 2.6 months.

Key safety findings are as follows:

Adverse Events: Adverse events occurred in 99.0% (101 subjects). The most commonly reported AEs were alanine aminotransferase (ALT) increased (38.2%, 39 subjects), diarrhea (37.3%, 38 subjects), and pyrexia (29.4%, 30 subjects). The AEs (any grade) with the highest incidence rates were ALT increased (0.85 events/subject-year), diarrhea (0.81 events/subject-year), and pyrexia (0.58 events/subject-year).

Adverse Events of Interest: AEs of interest for IDL were any grade bowel perforation, ≥ Grade 3 diarrhea and/or colitis, any grade PML, any grade pneumonitis, and ≥ Grade 3 rash by MST. Following from safety findings identified in March 2016, the AEI list was expanded to include infection (specifically ≥ Grade 3 infection, ≥ Grade 3 febrile neutropenia, any grade CMV infection, and any grade *Pneumocystis jirovecii* pneumonia [PJP]).

No subjects reported PML or any form of bowel perforation.

Diarrhea/Colitis

The analysis of diarrhea and/or colitis utilized the combined PTs of diarrhea and colitis. In this study, 16 subjects (15.7%) had ≥ Grade 3 diarrhea and/or colitis. The exposure-adjusted incidence rate for ≥ Grade 3 diarrhea and/or colitis was 0.27 events/subject-year. Overall, no subjects had IDL dose reduced, 9 subjects (8.8%) had IDL interruption, and 2 subjects (2.0%) discontinued IDL due to ≥ Grade 3 diarrhea and/or colitis. No deaths due to diarrhea and/or colitis were reported.

Pneumonitis

The analysis of pneumonitis utilized the single PT pneumonitis. In this study, 5 subjects (4.9%) had pneumonitis of any grade. The exposure-adjusted incidence rate for pneumonitis was 0.08 events/subject-year. Overall, no subjects had IDL dose reduced, 2 subjects (2.0%) had IDL interruption, and no subjects discontinued IDL due to pneumonitis. No deaths due to pneumonitis were reported.

Rash

Rash was defined per the Gilead MST. In this study, 15 subjects (14.7%) had ≥ Grade 3 rash. The exposure-adjusted incidence rate for ≥ Grade 3 rash was 0.25 events/subject-year. Overall, no subject had IDL dose reduced, 7 subjects (6.9%) had IDL interruption, and 4 subjects (3.9%) discontinued IDL due to ≥ Grade 3 rash. No deaths due to ≥ Grade 3 rash were reported. There were no cases of Stevens-Johnson syndrome or toxic epidermal necrolysis reported.

Infections

The analysis of ≥ Grade 3 infection utilized the SOC of infections and infestations and the PT of febrile neutropenia. A total of 20 subjects (19.6%) had ≥ Grade 3 infections. The exposure-adjusted incidence rate for ≥ Grade 3 infection was 0.34 events/subject-year. Overall, no subject had IDL dose reduced, 8 subjects (7.8%) had IDL interruption, and 2 subjects (2.0%) discontinued IDL due to ≥ Grade 3 infection. A total of 2 subjects (2.0%) had infectious events leading to death.

Febrile Neutropenia

Five subjects (4.9%) had ≥ Grade 3 febrile neutropenia. The exposure-adjusted incidence rate for ≥ Grade 3 febrile neutropenia was 0.08 events/subject-year. Overall, no subject had IDL dose reduced, IDL interruption, or discontinued IDL due to ≥ Grade 3 febrile neutropenia. No deaths due to ≥ Grade 3 febrile neutropenia were reported.

CMV Infection

The analysis of cytomegalovirus (CMV) infection utilized either the high-level term (HLT) of CMV infections or the PT of CMV test positive. Three subjects (2.9%) had CMV infection of any grade. The exposure-adjusted incidence rate for CMV infection was 0.05 events/subject-year. Overall, no subject had IDL dose reduced, IDL interruption, or discontinued IDL due to CMV infection. No deaths due to CMV infection were reported.

PJP

The analysis of PJP utilized the HLT of *Pneumocystis* infections. Three subjects (2.9%) had PJP of any grade. One subject had PJP with an onset date of 12 November 2015, and was treated with Bactrim for PJP from 23 May 2015 to 22 June 2015, and again on 12 November 2015 that was ongoing at data collection for this CSR. The exposure-adjusted incidence rate for PJP was 0.05 events/subject-year. Overall, no subjects had IDL dose reduced, 1 subject (1.0%) had IDL interruption, and no subjects discontinued IDL due to PJP. No deaths due to PJP were reported.

Deaths: A total of 6 subject deaths were reported. The causes of death were infectious events for 2 subjects (1 each due to pneumonia and sepsis), worsening or progressive CLL in 2 subjects, progressive clinical deterioration in 1 subject, and heart failure in 1 subject. No events other than CLL progression led to death in more than 1 subject.

SAEs: Serious AEs were reported for 45.1% (46 subjects). Serious AEs occurred most commonly in the SOC of infections and infestations (18 subjects, 17.6%) followed by gastrointestinal disorders (14 subjects, 13.7%). The most frequently reported SAEs by PT were pyrexia (11 subjects, 10.8%), colitis (6 subjects, 5.9%), and diarrhea (6 subjects, 5.9%).

AEs Leading to Discontinuation of Study Drug: Overall, 28 subjects (27.5%) discontinued IDL due to an AE. Overall, ALT increased and/or AST increased, hepatotoxicity, transaminases increased, or liver function test abnormal led to IDL discontinuation in 10 subjects (9.8%).

Laboratory Evaluations of Interest:

A total of 78 subjects (76.5%) had treatment-emergent ALT laboratory abnormalities of any grade (40.2% [41 subjects] with ≥ Grade 3 abnormalities). For AST, 62.7% (64 subjects) had treatment-emergent abnormalities of any grade (18.6% [19 subjects] with ≥ Grade 3 abnormalities).

A total of 17.6% (18 subjects) had treatment-emergent Grade 3 or 4 ALT and AST increases. The exposure-adjusted incidence rate of treatment-emergent laboratory abnormalities of any grade ALT increase was 2.50 events/subject-year. The exposure-adjusted incidence rate of treatment-emergent laboratory abnormalities of any grade AST increase was 1.83 events/subject-year.

For the 42 subjects (41.2%) with Grade 3 or 4 ALT and/or AST elevations, the median (minimum, maximum) time to onset of the first Grade 3 or 4 events was 8.14 (4.1, 24.1) weeks. Overall, the Grade 3 or 4 ALT and/or AST elevations resolved in 40 of the 42 subjects (95.2%), with a median (minimum, maximum) time to resolution (≤ Grade 1) of 3.14 (1.1, 16.0) weeks. No subject experienced AST or ALT > 3 × upper limit of normal (ULN) with concurrent elevation of bilirubin > 2 × ULN and elevated (> 1.5 ULN) alkaline phosphatase.

A total of 68 subjects (66.7%) had treatment-emergent laboratory assessments of decreased neutrophil count. Overall, 37.3% (38 subjects) had ≥ Grade 3 treatment-emergent decreased neutrophil count. The exposure-adjusted incidence rate of laboratory abnormalities of any grade neutropenia was 2.53 events/subject-year.

Other Clinical Laboratory Evaluations: Hemoglobin concentrations and platelet counts trended upward with time.

CONCLUSIONS: This study was terminated early due to a safety signal observed in ongoing studies evaluating a similar patient population. An increased rate of deaths and SAEs in subjects with early-line iNHL and front-line CLL receiving IDL with standard therapy versus standard therapy alone was observed by the DMC during review of 3 Gilead Phase 3 studies. Gilead reviewed the unblinded data and terminated those studies in agreement with the DMC recommendation and in consultation with the US FDA. All front-line studies of IDL, including this study, were also terminated. Due to early study termination, data were premature to draw conclusions about the efficacy of treatment and the prespecified efficacy analyses were not conducted. The safety conclusions from this study are as follows:

- The incidences of AEI related to infections were as follows: ≥ Grade 3 infection (19.6%, 20 subjects), ≥ Grade 3 febrile neutropenia (4.9%, 5 subjects), CMV infection of any grade (2.9%, 3 subjects), and PJP of any grade (2.9%, 3 subjects).

- Serious AEs occurred in 45.1% of subjects (46 of 102), with events occurring most commonly in the SOC of infections and infestations (17.6% [18 subjects]) followed by gastrointestinal disorders (13.7% [14 subjects]).

- Through the 09 December 2016 database finalization date, 6 subjects died. Four subjects (3.9%) experienced TEAEs that led to death, including infectious events for 2 subjects (1 each due to pneumonia and sepsis), worsening CLL in 1 subject, and heart failure in 1 subject. Two additional deaths occurred due to progression of CLL (1 subject) and progressive clinical deterioration (1 subject).