GILEAD

FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	A Phase 1b Study to Investigate the Safety, Tolerability, and Pharmacokinetics of Idelalisib in Japanese Subjects with Relapsed or Refractory Indolent B-Cell Non-Hodgkin Lymphomas or Chronic Lymphocytic Leukemia
Name of Test Drug:	Idelalisib (Zydelig®)
Dose and Formulation:	150-mg tablets, twice daily 100-mg tablets, twice daily, for subjects requiring dose reduction
Indication:	Chronic Lymphocytic Leukemia Indolent Non-Hodgkin Lymphomas • Follicular Lymphoma • Small Lymphocytic Lymphoma • Lymphoplasmacytic Lymphoma with or without Waldenstrom Macroglobulinemia • Marginal Zone Lymphoma
Sponsor:	Gilead Sciences, Inc. 199 E Blaine St Seattle, WA 98102 USA Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-313-1380
Phase of Development:	Phase 1b
IND No.:	101254
EudraCT No.:	Not Applicable
ClinicalTrials.gov Identifier:	NCT02242045
Study Start Date:	01 October 2014 (First Subject Screened)
Study End Date:	17 October 2017 (Last Subject Last Visit)
Principal or Coordinating Investigator:	Name: Dr. Kazuhito Yamamoto Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Pankaj Bhargava, MD Telephone: PPD Fax: PPD
Report Date:	14 May 2018

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-313-1380

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Seattle, WA 98102
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Title of Study: A Phase 1b Study to Investigate the Safety, Tolerability, and Pharmacokinetics of Idelalisib in Japanese Subjects with Relapsed or Refractory Indolent B-Cell Non-Hodgkin Lymphomas or Chronic Lymphocytic Leukemia

Investigators: This was a multicenter study.

Study Centers: 6 sites in Japan

Publications: Kinoshita T, Fukuhara N, Nagai H, Izutsu K, Kobayashi Y, et al. Phase 1b and Pharmacokinetic Study of Idelalisib in Japanese Patients with Relapsed or Refractory (R/R) Indolent B-Cell Non-Hodgkin Lymphoma (iNHL) or Chronic Lymphocytic Leukemia (CLL) [Abstract 85914]. Blood 2015;126:5089

Study Period:

01 October 2014 (First Subject Screened)
17 October 2017 (Last Subject Last Visit)

Phase of Development: Phase 1b

Objectives:

The primary objectives of this study were as follows:

- To evaluate the 28-day safety and tolerability of idelalisib (Zydelig®) in Japanese subjects with relapsed or refractory indolent non-Hodgkin lymphoma (iNHL) or chronic lympocytic leukemia (CLL)
- To determine the pharmacokinetics (PK) of idelalisib in Japanese subjects with relapsed or refractory iNHL or CLL

The secondary objective of this study was as follows:

- To evaluate the safety of continuous daily administration of idelalisib to Japanese subjects with relapsed or refractory iNHL or CLL beyond 28 days

Methodology: This was a Phase 1b, open-label study of continuous daily administration of idelalisib to Japanese adults with relapsed or refractory iNHL or CLL. The study utilized a 6+6 design.

Cohort A1 was planned to include 6 subjects treated with idelalisib 150 mg twice daily. The safety and tolerability of idelalisib would be evaluated by the safety review team after the sixth subject had been on study for at least 28 days.

Cohort A2 was planned to include 6 subjects treated with idelalisib 150 mg twice daily. This cohort would open for enrollment only if an unexpected treatment-related adverse event (AE) was observed in Cohort A1. The safety and tolerability of idelalisib would be evaluated by the safety review team after the sixth subject had been on study for at least 28 days.

Cohort B was planned to include 6 subjects treated with idelalisib 100 mg twice daily. This cohort would open for enrollment only if an unexpected treatment-related AE was observed in Cohort A2. The safety and tolerability of idelalisib would be evaluated by the safety review team after the sixth subject had been on study for at least 28 days.

Cohort C was planned to include 6 subjects with CLL treated with idelalisib 150 mg twice daily. This cohort would open for enrollment if Cohort A1 enrolled ≤ 2 CLL subjects or Cohorts A1 and A2 combined enrolled ≤ 4 CLL subjects. If Cohort B was open to enrollment, Cohort C would not be opened in order to prevent dose discrepancies. If Cohort C opened and there was an unexpected treatment-related AE, Cohort B would not open.

For all cohorts, treatment with idelalisib was planned to continue until unacceptable toxicity, substantial noncompliance, disease progression, pregnancy, initiation of another anticancer or experimental therapy, investigator discretion, or idelalisib discontinuation.

Six subjects were enrolled in Cohort A1, including 3 subjects with CLL, and all discontinued the study after Day 28, therefore Cohorts A2, B, and C did not meet criteria for opening. As a result, this study was completed with only 1 treatment group (Cohort A1).

Number of Subjects (Planned and Analyzed):

Planned: A minimum of 6 subjects, up to 18 subjects if needed.

Analyzed:
Full Analysis Set: 6 subjects
PK Analysis Set: 6 subjects

Diagnosis and Main Criteria for Inclusion: This study included Japanese male and nonpregnant, nonlactating female subjects aged ≥ 20 years with relapsed or refractory iNHL or CLL. All therapy (including radiotherapy, chemotherapy, immunotherapy, or investigational therapy) for the treatment of iNHL or CLL must have been discontinued ≥ 4 weeks prior to Day 1 and all acute toxic effects of any prior antitumor therapy must have resolved to Grade ≤ 1 before Day 1 (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, or 3 permitted]). The Eastern Cooperative Oncology Group performance status must have been 0 or 1.

Duration of Treatment: Idelalisib was taken continuously until the earliest of the following: unacceptable toxicity, substantial noncompliance, disease progression, pregnancy, initiation of another anticancer or experimental therapy, investigator discretion, or idelalisib discontinuation.

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

Idelalisib was taken orally twice daily starting on Day 1 and taken continuously thereafter.

The batch numbers were as follows:

Idelalisib 150 mg: CV1308B1, CV1402B1

Idelalisib 100 mg (for subjects requiring dose reduction): CV1302C1, PCZX, NSZP

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

Criteria for Evaluation:

Efficacy: Due to the completion of the study with only 1 treatment group (Cohort A1), the prespecified efficacy analyses could not be conducted.

Pharmacokinetics: Plasma samples were collected and analyzed for concentrations of idelalisib and its primary metabolite, GS-563117, using validated bioanalytical methods. PK samples were collected at predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours postdose on Days 1 and 29. PK samples were also collected on Days 8, 15, and 22 at pre-AM dose and 1.5 hours post dose.

Safety: Safety was assessed during the study through the reporting of AEs, and by clinical laboratory tests, physical examinations, and vital signs at various time points. Concomitant medication usage was assessed throughout the study.

Statistical Methods:

Efficacy:

Due to the completion of the study with only 1 treatment group (Cohort A1), the prespecified efficacy analyses could not be conducted.

Pharmacokinetics:

Individual subject concentration data for idelalisib, and its metabolite GS-563117, were assessed and summarized using descriptive statistics. Summary statistics (sample size [n], mean, standard deviation [StD], coefficient of variation [CV], median, minimum, maximum, first quartile [Q1], and third quartile [Q3]) were presented for individual subject concentration data by visit and time point.

Safety:

Safety data were described and summarized through the idelalisib treatment period and for 30 days following the last dose. All AEs and laboratory abnormalities presented in this report were treatment emergent and are referred to as AEs and laboratory abnormalities throughout this report.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1. System organ class, high level group term, high level term, preferred term, and lower level term were provided in the AE dataset.

The severity of AEs was graded by the investigator according to the National Cancer Institutes' Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03, whenever possible. Severity grades were categorized as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life threatening), or Grade 5 (fatal).

The relationship of the AE to study drug was categorized as related or unrelated. Events for which the investigator did not record a relationship to study drug were considered related and data listings showed the relationship as missing.

A treatment-emergent laboratory abnormality was defined as an abnormality that, compared with baseline, worsened by ≥ 1 grade in the period from the first dose of study treatment to 30 days after the last dose of study treatment. If baseline data were missing, then any graded abnormality ≥ Grade 1 in severity was considered treatment-emergent.

Hematologic and serum biochemistry data were programmatically graded according to the NCI CTCAE, Version 4.03. Severity grades were categorized as Grade 0, Grade 1, Grade 2, Grade 3, or Grade 4. Grade 0 included all values that did not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with both increased and decreased levels, analyses for each direction (ie, increased, decreased) were presented separately.

Descriptive statistics (n, mean, StD, median, Q1, Q3, minimum, and maximum) were provided for each laboratory test specified in the study protocol.

SUMMARY OF RESULTS:

All subjects were enrolled in Cohort A1 and discontinued the study after Day 28, and the study was completed without enrolling further cohorts.

Subject Disposition: A total of 6 subjects were screened for study participation, enrolled into Cohort A1, and received at least 1 dose of study drug. All subjects received idelalisib 150 mg twice daily for a minimum of 28 days, thus meeting the primary objective for safety evaluation. Beyond the 28 day period, all subjects discontinued study drug: 1 subject due to an AE, 2 subjects due to progressive disease, 1 subject due to an inability to tolerate rechallenge with idelalisib, and 2 subjects due to initiation of another anticancer or experimental therapy. All subjects also discontinued the study for the same reasons with the exception of the subject who discontinued study drug due to an AE. This subject discontinued the study due to investigator's discretion.

Demographics and Disease Characteristics: All subjects were Japanese males with a median (Q1, Q3) age of 64.0 (52.0, 71.0) years and an age range of 49 to 74 years. Three subjects had a disease history of CLL and 3 subjects had a history of iNHL with a median (Q1, Q3) time since diagnosis of 7.7 (7.1, 7.8) years and a range of 5.5 to 8.8 years. One of the 6 subjects had relapsed disease and 5 had refractory disease. The median (Q1, Q3) time since the most recent relapse/refractory diagnosis was 5.3 (1.6, 8.5) months. The median (Q1, Q3) number of prior therapy regimens was 3.5 (3.0, 4.0) and the median (Q1, Q3) time since completion of the last regimen was 8.9 (2.5, 16.2) months.

Efficacy Results: Due to the completion of the study with only 1 treatment group (Cohort A1), the prespecified efficacy analyses could not be conducted.

Pharmacokinetics Results: The plasma concentrations of idelalisib and its primary metabolite, GS-563117, observed in this study were similar to those observed in other idelalisib studies. Individual plasma concentrations, summary statistics, and PK sampling details can be found in Table 15.10.1.1, Table 15.10.1.2, and Listing 16.2.5.3.

Safety Results:

Exposure

All 6 subjects enrolled into the study received at least 1 dose of idelalisib and were evaluable for safety. The median (Q1, Q3) duration of exposure to study drug was 16.0 (7.6, 28.0) months, with a range of 1.3 to 35.0 months.

Adverse Events

Adverse events were consistent for a heavily pretreated, relapsed or refractory iNHL or CLL population receiving immunochemotherapeutic agents and with the established safety profile of idelalisib. Within the first 28 days of treatment, AEs were reported in 4 (66.7%) subjects. Of the reported AEs, none were experienced by more than 1 subject. Of these AEs, the only ≥ Grade 3 AE was decreased appetite (Grade 3).

Over the entire duration of treatment, AEs were reported in all 6 subjects. The most commonly reported AEs were diarrhea (5 subjects, 83.3%), and gastritis, insomnia, and pyrexia (3 subjects [50%] each). The most commonly reported ≥ Grade 3 AEs were diarrhea, increased transaminases, and decreased appetite, which were reported in 2 subjects (33.3%) each.

Adverse Events Related to Idelalisib

Within the first 28 days of treatment, no subject experienced an AE that was assessed by the investigator as related to idelalisib.

Over the entire duration of treatment, 5 subjects (83.3%) experienced AEs that were assessed by the investigator as related to idelalisib. The most frequently reported treatment-related AEs were diarrhea (3 subjects, 50%) and insomnia (2 subjects, 33.3%). All other treatment-related AEs were reported in no more than 1 subject.

Adverse Events of Interest

Adverse events of interest for idelalisib were ≥ Grade 3 diarrhea and/or colitis, ≥ Grade 3 rash by medical search term, any grade pneumonitis, any grade organizing pneumonia, any grade bowel perforation, any grade progressive multifocal leukoencephalopathy, ≥ Grade 3 febrile neutropenia, ≥ Grade 3 infection, any grade *Pneumocystis jirovecii* pneumonia, and any grade cytomegalovirus infection.

Within the first 28 days of treatment, no subject experienced an AE of interest.

Over the entire duration of treatment, 4 AEs of interest, assessed as related to idelalisib, occurred in 3 subjects as follows:

- Grade 4 diarrhea occurred in 1subject, which led to discontinuation of idelalisib on Day 498. This subject also experienced Grade 3 pneumonia.
- Grade 3 diarrhea occurred in 1 subject, which led to interruption of idelalisib, and later on, to dose reduction of idelalisib. This subject also experienced Grade 3 infection.
- Grade 1 pneumonitis occurred in 1 subject, which led to a dose reduction of idelalisib.

Deaths

No deaths were reported during this study.

Serious Adverse Events

Within the first 28 days of treatment, 1 subject (16.7%) experienced a serious adverse event (SAE) of decreased appetite, which was assessed by the investigator as not related to idelalisib.

Over the entire duration of treatment, SAEs were reported in 5 subjects (83.3%). The most commonly reported SAE was diarrhea (3 subjects, 50.0%). All other SAEs (pneumonia, increased transaminases, decreased appetite, pyrexia, and infection) were reported in no more than 1 subject. Three subjects (50.0%) experienced SAEs that were assessed by the investigator as related to idelalisib: 1 subject with pneumonia and diarrhea, 1 subject with increased transaminases, and 1 subject with diarrhea and infection.

Idelalisib Discontinuations Due to Adverse Events

Within the first 28 days of treatment, no subject experienced an AE that led to discontinuation of idelalisib.

Over the entire duration of treatment, 1 subject discontinued idelalisib due to a Grade 4 AE of diarrhea.

Idelalisib Dose Reductions or Interruptions Due to Adverse Events

Within the first 28 days of treatment, no subject experienced an AE that led to dose reduction or interruption of idelalisib.

Over the entire duration of treatment, 4 subjects experienced AEs that led to dose reduction or interruption of idelalisib: 1 subject due to AEs of otitis media, decreased appetite, pneumonia, and diarrhea; 1 subject due to AEs of increased transaminases and allergic rhinitis; 1 subject due to AEs of pneumonitis and gastritis; and 1 subject due to an AE of diarrhea. All subjects resumed dosing with either the same or reduced dose.

Clinical Laboratory Evaluations

Within the first 28 days of treatment, no subjects had transaminase elevations. No ≥ Grade 3 hematology abnormalities occurred in more than 1 subject, and there were no ≥ Grade 3 chemistry abnormalities.

Over the entire duration of treatment, 3 subjects (50.0%) had increased alanine aminotransferase (ALT) of any grade; 1 subject had increased ALT of Grade 4 and 2 subjects of Grade 1. Three subjects (50.0%) had increased aspartate aminotransferase (AST) of any grade; 1 subject had increased AST of Grade 3 and 2 subjects of Grade 1. The subject with Grade 4 ALT elevation also had the Grade 3 AST elevation. ALT and AST for this subject resolved to Grade 1 by the end of the study. The most common ≥ Grade 3 hematology or chemistry abnormalities (≥ 2 subjects) over the entire duration of treatment were decreased neutrophils (2 subjects, Grade 3), decreased phosphate (2 subjects, Grade 3), decreased potassium (1 subject, Grade 3; 1 subject, Grade 4), and increased triglycerides (2 subjects, Grade 3).

Hemoglobin concentrations trended upward with time.

CONCLUSIONS:

Due to the completion of the study with only 1 treatment group (Cohort A1), the prespecified efficacy analyses were not conducted.

The PK and safety conclusions from this study are as follows:

- The plasma concentrations of idelalisib and its primary metabolite GS-563117 observed in this study were consistent with those established by previous studies.
- Idelalisib was generally well tolerated and had a manageable safety profile consistent with the known safety profile of idelalisib. Most AEs were as expected for a heavily pretreated, relapsed or refractory iNHL or CLL population.