PROTOCOL SYNOPSIS
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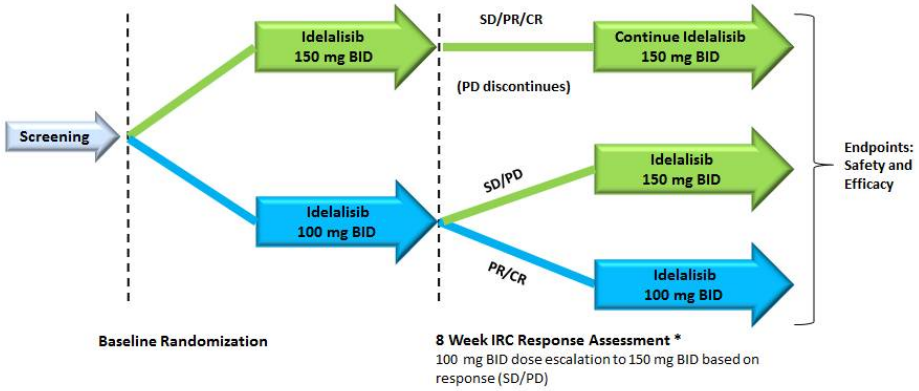
Study Title:	Dose Optimization Study of Idelalisib in Follicular Lymphoma
IND Number:	101254
EudraCT Number:	2015-000366-66
Clinical Trials.gov Identifier:	02536300
Study Centers Planned:	Approximately 90 centers globally
Objectives:	The primary objective of this study is: • To optimize the safety and efficacy of chronic administration of idelalisib in subjects with follicular lymphoma (FL) who are randomized to treatment with idelalisib at 150 mg twice daily (BID) or 100 mg BID — To evaluate the overall safety profile of idelalisib — To evaluate the overall response rate (ORR) by Week 24 The secondary objectives of this study are: • To assess the frequency, severity, timing, and drug interruptions for adverse events (AEs) of interest (≥ Grade 3 diarrhea/colitis, ≥ Grade 3 transaminase elevations, pneumonitis, and rash) • To evaluate progression-free survival (PFS), duration of response (DOR), and overall survival (OS) • To determine the pharmacokinetics (PK) of idelalisib and its major metabolite (GS-563117) The exploratory objective of this study is: • To evaluate the relationship between idelalisib and/or GS-563117 exposure versus efficacy and safety parameters

Study Design:

The study will evaluate the safety, efficacy, and PK of idelalisib in subjects randomized to either 150 mg BID or 100 mg BID idelalisib. Based on the 8-week blinded independent review committee (IRC) response assessment, subjects with stable disease (SD) or progressive disease (PD) will be unblinded in both arms. Subjects with a partial response (PR) or complete response (CR) will maintain the blind and continue at the randomized dose level. Subjects randomized to 100 mg BID with SD or PD may be dose escalated to 150 mg BID. Subjects randomized to 150 mg BID with SD will continue open-label idelalisib at 150 mg BID. Subjects randomized to 150 mg BID with PD will be discontinued from study. These same unblinding and dose modification details may also apply at any time throughout study participation when disease progression is suspected and confirmed by IRC assessment.



* Unblinding and dose modification may occur at any time during study participation if the IRC Assessment confirms progressive disease.

Number of Subjects Planned:

A sample size of 240 subjects randomized to 2 arms with a 1:1 ratio (~120 subjects in 150 mg BID arm; ~120 subjects in 100 mg BID arm).

Target Population:

The target population comprises adults who have received at least 2 lines of prior therapy for FL, demonstrated disease progression within 6 months from the last dose of at least 2 prior therapies, have measurable lymphadenopathy, and require therapy according to standard response criteria.

Duration of Treatment:

Idelalisib will be administered continuously until the earliest of: disease progression, unacceptable toxicity, substantial noncompliance with study procedures or study drug, initiation of another anti-cancer or experimental therapy, study discontinuation, or withdrawal from study.

Duration of Study:

The overall duration of the trial is expected to be approximately 5 years.

Eligibility Criteria:

Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study:

1) Male or female ≥18 years of age
2) Histologically confirmed diagnosis of B-cell FL, and grade limited to 1, 2, or 3a based on criteria established by the World Health Organization (WHO) 2008 classification of tumors of hematopoietic and lymphoid tissues
3) Refractory to and disease progression within 6 months from the last dose of at least 2 lines of prior therapy
4) Ann-Arbor Stage 2 (non-contiguous), 3, or 4 disease per Lugano Classification
5) Radiographically measurable lymphadenopathy or extranodal lymphoid malignancy as determined by the IRC (defined as the presence of ≥ 1 lesion that measures ≥ 1.5 cm in the longest dimension [LD] and ≥ 1.0 cm in the longest perpendicular dimension [LPD] as assessed by positron emission tomography–computed tomography [PET-CT], computed tomography [CT] or magnetic resonance imaging [MRI])
6) Has adequate performance status (such as Eastern Cooperative Oncology Group [ECOG] Performance Status of ≤ 2 or Karnofsky Performance Status of ≥ 60)
7) Required baseline central laboratory data (within 4 weeks prior to start of study therapy) as shown in the table.
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.

Organ System	Parameter	Required Value
Hematopoietic[a]	ANC	≥ 1,000/ul
	Platelet	≥ 50,000/uL
	Hemoglobin	≥ 8g/dL
Hepatic	Serum total bilirubin	≤ 1.5 x ULN (unless elevated due to Gilbert syndrome)
	Serum ALT	≤ 2.5 x ULN
	Serum AST	
Renal	Serum Creatinine	≤ 1.5 x ULN Calculated or Estimated CrCL > 30 mL/min
Pregnancy	β-hCG[b]	Negative
Infection	HIV	Negative HIV antibody[c]
	HBV	Negative HBsAg and negative HBc[d] antibody
	HCV	Negative viral RNA (if HCV antibody is positive)
	CMV	Negative CMV pp65 antigenemia study or negative CMV PCR[e]

ANC=absolute neutrophil count, β-hCG= beta human chorionic gonadotropin, ALT=alanine aminotransferase, AST=aspartate aminotransferase, CMV=cytomegalovirus, CrCL= 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, RNA=ribonucleic acid, ULN=upper limit of normal

a Grade ≥ 3 neutropenia, thrombocytopenia, or anemia is permitted if abnormality is related to bone marrow involvement with FL (as documented by bone marrow biopsy/aspirate obtained since the last prior therapy)

b For women of child-bearing potential only; serum β-hCG must be negative during screening and urine dipstick pregnancy test must be negative at enrollment

c If screening test is positive, a negative confirmatory test will be required for eligibility.

d Subjects who have positive HBc antibody may be enrolled if HBV DNA is undetectable by quantitative PCR

e CMV screening and surveillance for active disease

8) For female subjects of childbearing potential, willingness to use a protocol-recommended method of contraception during heterosexual intercourse from the signing of informed consent throughout the study treatment period and up to 30 days from the last dose of idelalisib (see Appendix 4)

9) For male subjects of reproductive potential having intercourse with females of childbearing potential, willing to use a protocol-recommended method of contraception during heterosexual intercourse and to refrain from sperm donation throughout the study treatment period and for 90 days following discontinuation of idelalisib (see Appendix 4)

10) Lactating females must agree to discontinue nursing before study drug administration and at least 30 days following last dose of idelalisib

11) Indicate willingness to comply with scheduled visits, drug administration plan, imaging studies, laboratory tests, other study procedures, and study restrictions, including mandatory prophylaxis for PJP

12) Evidence of a signed informed consent indicating that the subject is aware of the neoplastic nature of their disease and has been informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential benefits, possible side effects, potential risks and discomforts, and other pertinent aspects of study participation

Exclusion Criteria

Subjects who meet *any* of the following exclusion criteria are not to be enrolled in this study:

1) History of lymphoid malignancy other than FL (eg, DLBCL)
Note: Biopsy documentation of the absence or presence of high grade lymphoma is not required

2) Known history of, or clinically apparent, central nervous system (CNS) lymphoma or leptomeningeal lymphoma.
Note: Imaging documentation of the absence or presence of central nervous system disease is not required

3) Known presence of intermediate or high-grade myelodysplastic syndrome. Note: intermediate or high-grade myelodysplasia is defined as the presence of ≥5% bone marrow blasts; karotypic abnormalities other than normal, Y deletion, 5q deletion, or 20q deletion; or ≥ 2 lineages of cytopenias due to myelodysplasia

4) Known history of serious allergic reaction including anaphylaxis or Stevens-Johnson syndrome/toxic epidermal necrolysis

5) History of a non-lymphoid malignancy except for the following: adequately treated local basal cell or squamous cell carcinoma of the skin, cervical carcinoma *in situ*, superficial bladder cancer, asymptomatic prostate cancer without known metastatic disease and with no requirement for therapy or requiring only hormonal therapy and with normal prostate-specific antigen for ≥1 year prior to enrollment, or any other cancer or malignancy that has been in complete remission for ≥ 5 years

6) Evidence of ongoing systemic infection (eg, bacterial, fungal, viral) at the time of enrollment

7) Known history of drug-induced liver injury, chronic active hepatitis B (HBV), chronic active hepatitis C (HCV), alcoholic liver disease, non-alcoholic steatohepatitis, cirrhosis of the liver, portal hypertension, primary biliary cirrhosis, or ongoing extrahepatic obstruction caused by cholelithiasis
8) History of or ongoing drug-induced pneumonitis
9) History of or ongoing inflammatory bowel disease
10) Known human immunodeficiency virus (HIV) infection
11) CMV: Ongoing infection, treatment, or prophylaxis within the past 28 days
12) Presence of any condition that could, in the opinion of the investigator, compromise the subject's ability to participate in the study, such as history of substance abuse, alcoholism, or a psychiatric condition
13) History of prior allogeneic bone marrow progenitor cell or solid organ transplantation
14) Ongoing immunosuppressive therapy, including systemic corticosteroids (> 10 mg prednisone or equivalent/day) with the exception of the use of topical, enteric, or inhaled corticosteroids as therapy for comorbid conditions or systemic corticosteroids for autoimmune anemia and/or thrombocytopenia
15) Concurrent participation in another therapeutic clinical trial
16) 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 adversely affect the safety of the subject or impair the assessment of study results
17) Prior treatment with PI3K delta inhibitors, BTK inhibitors, JAK inhibitors, mTOR inhibitors, or Syk inhibitors

Study Visits: Subjects will be randomized in a 1:1 ratio to receive either idelalisib 150 mg BID or 100 mg BID orally starting on Day 1.

Clinic visits will occur every 2 weeks through Week 12, every 4 weeks through Week 24, every 8 weeks through Week 48, and every 12 weeks through end of study (EOS). Subjects will be assessed for safety at each visit. Additional visits will be required between protocol-specified visits for laboratory testing only.

Subjects will be assessed for FL disease status by continuous utilization of a single modality including PET-CT, CT, or MRI at baseline and at Weeks 8, 16, 24, and every 24 weeks thereafter until disease progression.

	Following the 8-week response assessment or at any time during study participation when disease progression is confirmed by IRC assessment, subjects with SD or PD confirmed by IRC will be unblinded.
Study Drug, Dose, and Mode of Administration:	Idelalisib 150 mg BID arm: 150 mg will be taken twice daily orally starting on Day 1 and administered continuously. Dose reduction to 100 mg BID is available, if required. Idelalisib 100 mg BID arm: 100 mg will be taken twice daily orally starting on Day 1 and administered continuously. Dose reductions are not available.
Criteria for Evaluation:	
Safety/Efficacy Primary Endpoints:	• Overall safety profile of idelalisib, including the incidence of adverse events (AEs) and clinically significant laboratory abnormalities, severity, timing, and relationship to idelalisib of any AEs; serious adverse events (SAEs); or AEs leading to interruption of idelalisib • ORR by Week 24 defined as the proportion of subjects who achieve a PR or CR by Week 24
Secondary Endpoints:	• Time to onset of AEs of interest (Grade ≥ 3 diarrhea/colitis, pneumonitis, ≥ Grade 3 transaminase elevations, and rash) defined as the interval from the start of idelalisib treatment to the first documentation of start of AE of interest • Rate of AE of interest defined as the number of subjects with AE of interest • Rate of drug interruptions for the number of subjects with AE of interest • PFS defined as the interval from randomization to the earlier of the first documentation of disease progression by IRC or death from any cause • DOR defined as the interval from the first documentation of CR or PR to the earlier of the first documentation of disease progression by IRC or death from any cause • OS defined as the interval from randomization to death from any cause • Idelalisib trough (pre-dose) and peak (1.5-hour samples) plasma concentrations assessed by a validated bioanalytical method

Exploratory Endpoint:	• Idelalisib exposure-response relationship between efficacy (such as PFS, DOR, ORR), safety (such as Grade $\geq$ 3 of ALT/AST, neutropenia, diarrhea, rash, infection, pneumonitis) parameters and idelalisib exposure (such as AUC, C_{max}, C_{tau})

Statistical Methods:

Analysis Data Set

The Intent-to-treat (ITT) Analysis Set will include all subjects who are randomized regardless of whether subjects receive any study drug, or receive a different regimen from which they were randomized. Treatment assignment will be designated according to randomization (randomized to 150 mg BID or 100 mg BID).

The Safety Analysis Set will include data from all subjects who receive at least 1 dose of study treatment, with treatment assignments designated according to the actual treatment received. All safety analyses will be performed based on the Safety Analysis Set by treatment arms: 150 mg BID, 100 mg BID.

The PK/Biomarker Analysis Set will include data from subjects in the Safety Analysis Set who have the necessary baseline and on-study samples/measurements to provide interpretable results for the specific parameters of interest.

An IRC will review radiographic data and pertinent clinical data in order to provide expert evaluation of tumor status, in a blinded manner. The findings of the IRC will be considered primary for analyses of the primary efficacy endpoints and other tumor control endpoints. Tumor response status and progression will be assessed by the IRC using standard response criteria.

Subject characteristics and study results will be described and summarized by treatment arm. Formal hypothesis testing will not be performed. In general, for data summaries involving continuous variables, data tables will typically contain the following information: sample size, mean, standard deviation (StD), standard error, median, minimum, and maximum. For categorical variables, the following information will typically be presented: sample size, proportion, and 95% confidence intervals (CIs) based on exact binomial proportion.

Efficacy Analysis

For the primary efficacy analysis, the ORR will be estimated with 95% Clopper-Pearson exact CI provided. The estimation will also be done for subgroups including potential predictors of response. Subjects who do not have sufficient baseline or on-study tumor assessment to characterize response will be counted as failures. Differences between the arms for ORR might be compared using the Cochran-Mantel-Haenszel (CMH)

Chi-square test for association between treatment and response and odds ratios with the corresponding 95% CIs might be presented. The potential influence of subject baseline characteristics and treatment response rates will be explored with logistic regression modeling. For the analyses of PFS/OS, the Kaplan-Meier (KM) method will be used based on the ITT Analysis Set. Median ranges, the proportion of subjects who are progression-free/alive from first dose of study drug (based on KM estimates), hazard ratios, and corresponding 95% CIs (as calculated using a Cox proportional hazards regression model) will be presented.

For the analyses of DOR, the KM method will be used. Subjects who achieve a PR or CR will be included in the DOR analyses.

Safety Analysis

Safety will be assessed via clinical laboratory tests (hematology, serum chemistry, coagulation, and urinalysis), concomitant medications, and AEs. Information regarding study drug administration, study drug compliance, and other safety variables will be described and summarized. The frequency, severity, timing, and drug interruptions for the AEs of interest (≥ Grade 3 diarrhea/colitis, pneumonitis, ≥ Grade 3 transaminase elevations, and rash) will be summarized using descriptive statistics. Incidence rates of the AEs of interest will be summarized with estimates and 95% exact CI provided. The estimation will also be done for subgroups including potential predictors of safety. Differences in incidence rates of AEs of interest will be analyzed using a CMH Chi-square test. Time to onset and resolution of AEs of interest will be analyzed using KM methods and descriptive statistics.

PK Analysis

Using data from the PK Analysis Set, idelalisib/metabolite plasma concentrations will be described and summarized. A logistic regression model will be applied to explore the relationship between drug exposure and efficacy or safety will be explored.

Sample Size Calculation

A total of 240 subjects will be randomized to 2 arms with a 1:1 ratio. Based on the prior idelalisib studies, the rate of Grade ≥3 diarrhea/colitis is ~15%. A sample size of 120 subjects per arm would provide a 73% chance to detect a reduction of 10% (ie, 15% incidence in the 150 mg BID arm versus 5% incidence in the 100 mg BID arm) using a 2-sided Chisq test with an alpha level of 0.05.

This study will be conducted in accordance with the guidelines of Good Clinical Practices (GCPs) including archiving of essential documents.