Clinical trial results:
A Phase 2 Study to Assess the Efficacy and Safety of Idelalisib in Subjects with Indolent B-Cell Non-Hodgkin Lymphomas Refractory to Rituximab and Alkylating Agents

Summary

EudraCT number	2010-022155-33
Trial protocol	DE GB IT
Global end of trial date	16 May 2018

Results information

Result version number	v2 (current)
This version publication date	30 June 2019
First version publication date	30 May 2019
Version creation reason	• Correction of full data set Update to study start date, primary completion date, time frames for some endpoints, and death (all causes) data.

Trial information

Trial identification

Sponsor protocol code	101-09

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01282424
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Gilead Sciences
Sponsor organisation address	333 Lakeside Drive, Foster City, CA, United States, 94404
Public contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com
Scientific contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 May 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 May 2018
Global end of trial reached?	Yes
Global end of trial date	16 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to assess the overall response rate and to evaluate the efficacy and safety of idelalisib (IDELA; GS-1101) in participants with previously treated indolent Non-Hodgkin Lymphoma (iNHL) that was refractory both to rituximab and to alkylating-agent-containing chemotherapy.

Eligible participants initiated oral therapy with idelalisib at a starting dose of 150 mg taken twice per day. Treatment with idelalisib continued in compliant participants as long as the study was still ongoing and the participants appear to be benefiting from treatment with acceptable safety.

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.
This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 March 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 8
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	United States: 83
Worldwide total number of subjects	125
EEA total number of subjects	42

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	69
From 65 to 84 years	54
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at a total of 54 study sites in North America and Europe. The first participant was screened on 04 March 2011. The last participant observation was on 16 May 2018.

Pre-assignment

Screening details:

125 participants were enrolled and treated and comprise the Intent-to-Treat (ITT) Analysis Set.

Period 1

Period 1 title	Treatment Period (TP) (81 months)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Idelalisib

Arm description:

Idelalisib 150 mg tablet administered orally twice daily until tumor progression or development of unacceptable toxicity.

Arm type	Experimental
Investigational medicinal product name	Idelalisib
Investigational medicinal product code	GS-1101
Other name	IDELA, formerly CAL-101
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Idelalisib 150 mg administered twice daily until tumor progression or development of unacceptable toxicity.

Number of subjects in period 1	Idelalisib
Started	125
Completed: Disease Progression	70 [1]
Completed: Death	9 [2]
Completed	79
Not completed	46
Withdrew Consent	6
Adverse Event	30
Investigator Request	7
Other (Unknown)	3

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: 70 participants with disease progression is a subcategory for the number of participants

who completed the TP overall.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: 9 participants who died during the study is a subcategory for the number of participants who completed the TP overall.

Period 2

Period 2 title	Long-term Follow-up Period (5 years)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Idelalisib

Arm description:

Idelalisib 150 mg tablet administered orally twice daily until tumor progression or development of unacceptable toxicity.

Arm type	Experimental
Investigational medicinal product name	Idelalisib
Investigational medicinal product code	GS-1101
Other name	IDELA, formerly CAL-101
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Idelalisib 150 mg administered twice daily until tumor progression or development of unacceptable toxicity.

Number of subjects in period 2[3]	Idelalisib
Started	54
Completed	20
Not completed	64
Withdrew Consent	2
Other (Unknown)	21
Death	40
Lost to follow-up	1
Joined	30
Discontinued TP but joined Long-term Follow-up	30

Notes:

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: 54 of 79 participants who completed the TP entered the Long-term Follow up Period. 30 additional participants who discontinued the TP also joined the Long-term Follow-up Period. Therefore, a total of 84 participants entered the Long-term Follow up Period.

Baseline characteristics

Reporting groups	
Reporting group title	Idelalisib
Reporting group description:	
Idelalisib 150 mg tablet administered orally twice daily until tumor progression or development of unacceptable toxicity.	

Reporting group values	Idelalisib	Total	
Number of subjects	125	125	
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	62		
standard deviation	± 11.4	-	
Gender categorical			
Units: Subjects			
Female	45	45	
Male	80	80	
Race/Ethnicity, Customized			
Units: Subjects			
Ethnicity: Hispanic or Latino	6	6	
Ethnicity: Not Hispanic or Latino	117	117	
Ethnicity: Missing	2	2	
Race/Ethnicity, Customized			
Units: Subjects			
Race: White/Caucasian	110	110	
Race: Black or African American	2	2	
Race: Asian	3	3	
Race: American Indian or Alaska Native	1	1	
Race: Other	8	8	
Race: Missing	1	1	
Karnofsky Performance Status			
Karnofsky performance status classified participants according to their functional impairment. Scores ranged from 0-100, the lower the score, the worse the survival for most serious illnesses.			
Units: Subjects			
Score = 60	2	2	
Score = 70	6	6	
Score = 80	27	27	
Score = 90	44	44	
Score = 100	46	46	
Baseline Disease History			
LPL/WM: Lymphoplasmacytic lymphoma/Waldenström macroglobulinemia			
Units: Subjects			
Folicular lymphoma	72	72	
Small lymphocytic lymphoma	28	28	

LPL/WM	10	10	
Marginal zone lymphoma	15	15	

End points

End points reporting groups

Reporting group title	Idelalisib

Reporting group description:

Idelalisib 150 mg tablet administered orally twice daily until tumor progression or development of unacceptable toxicity.

Reporting group title	Idelalisib

Reporting group description:

Idelalisib 150 mg tablet administered orally twice daily until tumor progression or development of unacceptable toxicity.

Primary: Overall Response Rate

End point title	Overall Response Rate[1]

End point description:

Overall response rate (ORR) was assessed based on the International Working Group Revised Response Criteria for Malignant Lymphoma (Cheson, 2007), and was defined as the percentage of participants achieving a complete response (CR) or partial response (PR; or minor response [MR] for participants with WM) as assessed by the study independent review committee (IRC).
CR was defined as the complete resolution of all disease-related radiological abnormalities and the disappearance of all signs and symptoms related to the disease.
PR was defined as a ≥ 50% reduction in the sum of the products of the longest perpendicular diameters of all index lesions, with no new lesions.
For WM only, response was defined as a reduction in immunoglobulin M (IgM) of ≥ 50% decrease for PR, and ≥ 25% decrease for MR; no increase from baseline in the sum of the products of the longest perpendicular diameters of all index lesions, with no new lesions or signs and symptoms of active disease (Owen, 2013)

End point type	Primary

End point timeframe:

Start of Treatment to End of Treatment (up to 81 months)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The statistical analysis of this primary endpoint is provided in the attachment.

End point values	Idelalisib			
Subject group type	Reporting group			
Number of subjects analysed	125[2]			
Units: Percentage of participants				
number (confidence interval 95%)	57.6 (48.4 to 66.4)			

Notes:

[2] - ITT Analysis Set included enrolled participants who received at least one dose of study drug.

Attachments (see zip file)	Statistical Analysis/101-09_Primary_Endpoint_StatsAnalysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response

End point description:

Duration of Response (DOR) was defined as the interval from the first documentation of CR or PR (or MR for participants with WM) to the earlier of the first documentation of disease progression as assessed by the study IRC or death from any cause. DOR was analyzed using Kaplan-Meier (KM) estimates. Participants in ITT Analysis Set who achieved a CR or PR (or MR for participants with WM) were analyzed.

End point type	Secondary

End point timeframe:

Start of Treatment to End of Treatment (up to 81 months)

End point values	Idelalisib			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: months				
median (inter-quartile range (Q1-Q3))	12.5 (6.2 to 28.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Lymph Node Response Rate

End point title	Lymph Node Response Rate

End point description:

Lymph node response (LNR) was defined as the percentage of participants who achieved a ≥ 50% decrease from baseline in the sum of the product of the perpendicular diameters (SPD) of measurable index lesions as assessed by the study IRC. Participants in the ITT Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Start of Treatment to End of Treatment (up to 81 months)

End point values	Idelalisib			
Subject group type	Reporting group			
Number of subjects analysed	125			
Units: percentage of participants				
number (confidence interval 95%)	56.8 (47.6 to 65.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response

End point title	Time to Response

End point description:

Time to response (TTR) was defined as the interval from the start of idelalisib treatment to the first documentation of CR or PR (or MR for participants with WM) as assessed by the study IRC. Participants in the ITT Analysis Set who achieved a CR or PR (or MR for participants with WM) were analyzed.

End point type	Secondary

End point timeframe:

Start of Treatment to End of Treatment (up to 81 months)

End point values	Idelalisib			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: months				
median (inter-quartile range (Q1-Q3))	2.0 (1.8 to 4.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival

End point title	Progression-Free Survival

End point description:

Progression-free survival (PFS) was defined as the interval from the start of idelalisib treatment to the earlier of the first documentation of disease progression as assessed by the study IRC or death from any cause. PFS was analyzed using KM estimates. Participants in the ITT Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Start of Treatment to End of Treatment (up to 81 months)

End point values	Idelalisib			
Subject group type	Reporting group			
Number of subjects analysed	125			
Units: months				
median (confidence interval 95%)	11.1 (8.3 to 14.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival (OS) was defined as the time interval from the start of idelalisib treatment to death from any cause. OS was analyzed using KM estimates. Participants in the ITT Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Start of Treatment to Last Long-Term Follow-Up Visit (up to maximum of 7 years)

End point values	Idelalisib			
Subject group type	Reporting group			
Number of subjects analysed	125			
Units: months				
median (confidence interval 95%)	48.6 (33.9 to 71.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Health-Related Quality of Life Using the Functional Assessment of Cancer Therapy: Lymphoma Subscale (FACT-LymS)

End point title	Change in Health-Related Quality of Life Using the Functional Assessment of Cancer Therapy: Lymphoma Subscale (FACT-LymS)

End point description:

Change in health-related quality of life events were reported by participants using the Functional Assessment of Cancer Therapy: Lymphoma Subscale (FACT-LymS) assessment tool. Results are presented as the mean (SD) best change from baseline. The best change from baseline was defined as the highest change score (improvement) after baseline.
The FACT-LymS is on a scale from 0-60, with higher scores associated with a better quality of life. It incorporates values from 15 questions, each rated 0-4, related to study indications. Participants in the ITT Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline to End of Treatment (up to 81 months)

End point values	Idelalisib			
Subject group type	Reporting group			
Number of subjects analysed	113			
Units: units on a scale				
arithmetic mean (standard deviation)	10.3 (± 17.08)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Karnofsky Performance Status

End point title	Change in Karnofsky Performance Status

End point description:

The change in Karnofsky performance status was reported as the best (highest change score) and worst (lowest change score) change from baseline using the Karnofsky performance criteria. The Karnofsky score classified participants according to their functional impairment. Scores are on a scale from 0-100, the lower the score, the worse the survival for most serious illnesses. Participants in the ITT Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline to End of Treatment (up to 81 months)

End point values	Idelalisib			
Subject group type	Reporting group			
Number of subjects analysed	122			
Units: units on a scale				
arithmetic mean (standard deviation)				
Best change	3.0 (± 8.71)			
Worst change	-10.7 (± 12.61)			

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in Plasma Concentrations of Disease-Associated Chemokines and Cytokines

End point title	Changes in Plasma Concentrations of Disease-Associated Chemokines and Cytokines

End point description:

Analysis of the cytokine/chemokine was planned to be performed on a subset of samples from this study along with a subset of samples from other studies. Therefore, data for this endpoint are not reported here because the analysis population includes participants who were not enrolled in this study.

End point type	Secondary

End point timeframe:

Enrollment to End of Treatment (up to 81 months)

End point values	Idelalisib			
Subject group type	Reporting group			
Number of subjects analysed	0[3]			
Units: pg/mL				
arithmetic mean (standard deviation)	()			

Notes:

[3] - Data not reported

Statistical analyses

No statistical analyses for this end point

Secondary: Safety and Tolerability of Idelalisib Assessed as the Number of Participants Experiencing Adverse Events (AEs) or Abnormalities in Vital Signs, Laboratory Tests, or Electrocardiograms

End point title	Safety and Tolerability of Idelalisib Assessed as the Number of Participants Experiencing Adverse Events (AEs) or Abnormalities in Vital Signs, Laboratory Tests, or Electrocardiograms

End point description:

This composite endpoint measured the safety and tolerability profile of idelalisib. "Clinically meaningful" abnormalities in vital signs and electrocardiograms (ECG) were as determined by the investigator. Participants in the ITT Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Start of Treatment to End of Treatment (up to 81 months) plus 30 days

End point values	Idelalisib			
Subject group type	Reporting group			
Number of subjects analysed	125			
Units: participants				
Any AE	123			
AE leading to drug discontinuation	35			
Serious AE	72			
Vital signs abnormal – clinically meaningful	0			
ECG abnormal – clinically meaningful	0			
Grade 3 or 4 hemoglobin	2			
Grade 3 or 4 neutrophils	35			
Grade 3 or 4 platelets	9			
Grade 3 or 4 alanine aminotransferase	16			
Grade 3 or 4 aspartate aminotransferase	11			

Statistical analyses

No statistical analyses for this end point

Secondary: Study Drug Exposure

End point title	Study Drug Exposure

End point description:

The average idelalisib exposure was summarized. Participants in the ITT Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Start of Treatment to End of Treatment (up to 81 months)

End point values	Idelalisib			
Subject group type	Reporting group			
Number of subjects analysed	125			
Units: months				
arithmetic mean (standard deviation)	13.2 (± 15.08)			

Statistical analyses

No statistical analyses for this end point

Secondary: Idelalisib Plasma Concentration

End point title	Idelalisib Plasma Concentration

End point description:

Pharmacokinetic (PK) Analysis Set included participants in the ITT Analysis Set who had the necessary baseline and on-study measurements.

End point type	Secondary

End point timeframe:

Predose and at 1.5 hours (± 5 minutes) postdose on Day 29

End point values	Idelalisib			
Subject group type	Reporting group			
Number of subjects analysed	125			
Units: ng/mL				
arithmetic mean (standard deviation)				
Predose (n = 108)	471.6 (± 486.53)			
Postdose (n =106)	2187.7 (± 1050.76)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter: Cmax

End point title	PK Parameter: Cmax

End point description:

Cmax at Days 1 and 29 was analyzed. Cmax is defined as the maximum concentration of drug. Participants in the PK Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours postdose on Days 1 and 29

End point values	Idelalisib			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: ng/mL				
arithmetic mean (standard deviation)				
Cmax at Day 1	2647.5 (± 1084.99)			
Cmax at Day 29	2258.8 (± 809.61)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter: Tmax

End point title	PK Parameter: Tmax

End point description:

Tmax at Days 1 and 29 was analyzed. Tmax is defined as the time of Cmax (the maximum concentration of drug). Participants in the PK Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours postdose on Days 1 and 29

End point values	Idelalisib			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: hours				
arithmetic mean (inter-quartile range (Q1-Q3))				
Tmax at Day 1	1.00 (0.99 to 1.04)			

Tmax at Day 29	1.00 (0.95 to 2.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter: AUClast

End point title	PK Parameter: AUClast

End point description:

AUClast at Days 1 and 29 was analyzed. AUClast is defined as the concentration of drug from time zero to the last observable concentration. Participants in the PK Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours postdose on Days 1 and 29

End point values	Idelalisib			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: hours x ng/mL				
arithmetic mean (standard deviation)				
AUClast at Day 1	9094.76 (± 2960.391)			
AUClast at Day 29	9293.39 (± 3996.826)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events: Start of Treatment to End of Treatment (up to 81 months) plus 30 days; All-Cause Mortality: Baseline to Last Long-Term Follow-Up Visit (up to maximum of 7 years)

Adverse event reporting additional description:

ITT Analysis Set included enrolled participants who received at least one dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Idelalisib

Reporting group description:

Idelalisib 150 mg tablet administered orally twice daily until tumor progression or development of unacceptable toxicity.

Serious adverse events	Idelalisib		
Total subjects affected by serious adverse events			
subjects affected / exposed	72 / 125 (57.60%)		
number of deaths (all causes)	64		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma			
subjects affected / exposed	2 / 125 (1.60%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Adenocarcinoma			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Basal cell carcinoma			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric cancer			

subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin cancer				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Hypotension				
subjects affected / exposed	2 / 125 (1.60%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Deep vein thrombosis				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lymphorrhoea				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Pyrexia				
subjects affected / exposed	15 / 125 (12.00%)			
occurrences causally related to treatment / all	0 / 16			
deaths causally related to treatment / all	0 / 0			
Peripheral swelling				
subjects affected / exposed	3 / 125 (2.40%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Asthenia				
subjects affected / exposed	2 / 125 (1.60%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			

Chest pain				
subjects affected / exposed	2 / 125 (1.60%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Multiple organ dysfunction syndrome				
subjects affected / exposed	2 / 125 (1.60%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Death				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Immune system disorders				
Anaphylactic reaction				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Autoimmune disorder				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Dyspnoea				
subjects affected / exposed	3 / 125 (2.40%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	3 / 125 (2.40%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Acute respiratory distress syndrome				
subjects affected / exposed	2 / 125 (1.60%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			

Pleural effusion				
subjects affected / exposed	2 / 125 (1.60%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	2 / 125 (1.60%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Interstitial lung disease				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung infiltration				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Anxiety				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Fall				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fracture				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Head injury				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hip fracture				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Limb injury				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Cardiac failure				
subjects affected / exposed	2 / 125 (1.60%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Acute myocardial infarction				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cardiomyopathy				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sinus tachycardia				

subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Supraventricular tachycardia				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cerebral ischaemia				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Paraplegia				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Febrile neutropenia				
subjects affected / exposed	5 / 125 (4.00%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	3 / 125 (2.40%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Anaemia				
subjects affected / exposed	2 / 125 (1.60%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Autoimmune haemolytic anaemia				

subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Splenic infarction				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Thrombocytopenia				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Visual impairment				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Diarrhoea				
subjects affected / exposed	11 / 125 (8.80%)			
occurrences causally related to treatment / all	0 / 14			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	5 / 125 (4.00%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Melaena				
subjects affected / exposed	2 / 125 (1.60%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	2 / 125 (1.60%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				

subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute abdomen			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Autoimmune colitis			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Enteritis			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Enterocolitis			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhoids			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mouth haemorrhage			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			

subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oesophagitis			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rectal haemorrhage			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Stomatitis			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic function abnormal			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			

Dermatitis exfoliative generalised				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Erythema				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rash				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	4 / 125 (3.20%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Hydronephrosis				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Back pain				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Pneumonia				
subjects affected / exposed	15 / 125 (12.00%)			
occurrences causally related to treatment / all	0 / 21			
deaths causally related to treatment / all	0 / 3			
Cytomegalovirus colitis				

subjects affected / exposed	2 / 125 (1.60%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	2 / 125 (1.60%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Perirectal abscess				
subjects affected / exposed	2 / 125 (1.60%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumocystis jirovecii pneumonia				
subjects affected / exposed	2 / 125 (1.60%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Sepsis				
subjects affected / exposed	2 / 125 (1.60%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Septic shock				
subjects affected / exposed	2 / 125 (1.60%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Urinary tract infection				
subjects affected / exposed	2 / 125 (1.60%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				

subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infective exacerbation of chronic obstructive airways disease				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung infection				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pharyngitis				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia cytomegaloviral				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia necrotising				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia pneumococcal				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia pseudomonal				

subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumonia staphylococcal				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia streptococcal				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis syndrome				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sinusitis				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Soft tissue infection				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Staphylococcal infection				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Toxoplasmosis				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Varicella zoster virus infection				

subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Wound infection				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				
subjects affected / exposed	4 / 125 (3.20%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Hypercalcaemia				
subjects affected / exposed	2 / 125 (1.60%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hypokalaemia				
subjects affected / exposed	2 / 125 (1.60%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Decreased appetite				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Failure to thrive				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolic acidosis				

subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Idelalisib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	123 / 125 (98.40%)		
Investigations			
Weight decreased			
subjects affected / exposed	19 / 125 (15.20%)		
occurrences (all)	21		
Alanine aminotransferase increased			
subjects affected / exposed	18 / 125 (14.40%)		
occurrences (all)	22		
Aspartate aminotransferase increased			
subjects affected / exposed	16 / 125 (12.80%)		
occurrences (all)	20		
Blood creatinine increased			
subjects affected / exposed	9 / 125 (7.20%)		
occurrences (all)	10		
Blood lactate dehydrogenase increased			
subjects affected / exposed	7 / 125 (5.60%)		
occurrences (all)	9		
Vascular disorders			
Hypertension			
subjects affected / exposed	9 / 125 (7.20%)		
occurrences (all)	9		
Hypotension			
subjects affected / exposed	8 / 125 (6.40%)		
occurrences (all)	11		
Nervous system disorders			
Headache			

subjects affected / exposed	17 / 125 (13.60%)		
occurrences (all)	18		
Dizziness			
subjects affected / exposed	11 / 125 (8.80%)		
occurrences (all)	14		
Dysgeusia			
subjects affected / exposed	7 / 125 (5.60%)		
occurrences (all)	7		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	35 / 125 (28.00%)		
occurrences (all)	69		
Thrombocytopenia			
subjects affected / exposed	23 / 125 (18.40%)		
occurrences (all)	28		
Anaemia			
subjects affected / exposed	18 / 125 (14.40%)		
occurrences (all)	21		
Leukopenia			
subjects affected / exposed	9 / 125 (7.20%)		
occurrences (all)	11		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	40 / 125 (32.00%)		
occurrences (all)	48		
Pyrexia			
subjects affected / exposed	34 / 125 (27.20%)		
occurrences (all)	59		
Asthenia			
subjects affected / exposed	14 / 125 (11.20%)		
occurrences (all)	14		
Oedema peripheral			
subjects affected / exposed	13 / 125 (10.40%)		
occurrences (all)	13		
Chills			

subjects affected / exposed	11 / 125 (8.80%)		
occurrences (all)	13		
Pain			
subjects affected / exposed	9 / 125 (7.20%)		
occurrences (all)	11		
Mucosal inflammation			
subjects affected / exposed	8 / 125 (6.40%)		
occurrences (all)	9		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	59 / 125 (47.20%)		
occurrences (all)	95		
Nausea			
subjects affected / exposed	38 / 125 (30.40%)		
occurrences (all)	50		
Abdominal pain			
subjects affected / exposed	21 / 125 (16.80%)		
occurrences (all)	22		
Vomiting			
subjects affected / exposed	20 / 125 (16.00%)		
occurrences (all)	22		
Constipation			
subjects affected / exposed	11 / 125 (8.80%)		
occurrences (all)	14		
Abdominal pain upper			
subjects affected / exposed	10 / 125 (8.00%)		
occurrences (all)	10		
Stomatitis			
subjects affected / exposed	8 / 125 (6.40%)		
occurrences (all)	8		
Dysphagia			
subjects affected / exposed	7 / 125 (5.60%)		
occurrences (all)	7		
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all)	40 / 125 (32.00%) 55		
Dyspnoea subjects affected / exposed occurrences (all)	22 / 125 (17.60%) 26		
Oropharyngeal pain subjects affected / exposed occurrences (all)	11 / 125 (8.80%) 12		
Pleural effusion subjects affected / exposed occurrences (all)	7 / 125 (5.60%) 7		
Skin and subcutaneous tissue disorders Night sweats subjects affected / exposed occurrences (all)	18 / 125 (14.40%) 25		
Rash subjects affected / exposed occurrences (all)	18 / 125 (14.40%) 19		
Dry skin subjects affected / exposed occurrences (all)	9 / 125 (7.20%) 9		
Pruritus subjects affected / exposed occurrences (all)	9 / 125 (7.20%) 12		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	12 / 125 (9.60%) 12		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	13 / 125 (10.40%) 13		
Arthralgia subjects affected / exposed occurrences (all)	8 / 125 (6.40%) 10		

Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	23 / 125 (18.40%)		
occurrences (all)	33		
Pneumonia			
subjects affected / exposed	8 / 125 (6.40%)		
occurrences (all)	10		
Urinary tract infection			
subjects affected / exposed	8 / 125 (6.40%)		
occurrences (all)	10		
Bronchitis			
subjects affected / exposed	7 / 125 (5.60%)		
occurrences (all)	8		
Herpes zoster			
subjects affected / exposed	7 / 125 (5.60%)		
occurrences (all)	7		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	23 / 125 (18.40%)		
occurrences (all)	28		
Hypokalaemia			
subjects affected / exposed	15 / 125 (12.00%)		
occurrences (all)	19		
Hyperglycaemia			
subjects affected / exposed	11 / 125 (8.80%)		
occurrences (all)	15		
Dehydration			
subjects affected / exposed	10 / 125 (8.00%)		
occurrences (all)	12		
Hypocalcaemia			
subjects affected / exposed	7 / 125 (5.60%)		
occurrences (all)	10		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 December 2010	• Clarified inclusion criteria for participants with Grade 3 FL to enroll only participants with Grades 1, 2, or 3a FL (not Grade 3b), ie, only participants with indolent FL. • Amended storage and stability to allow brief excursions of IDELA down to 5°C. • Clarified the response definition in the event that PET scans were obtained for participants with a PR
24 January 2011	• Amended inclusion criteria to ensure all participants were of legal age (≥ 18 years of age) at the time of entry into the study. • Removed the statement that idelalisib would be shipped at controlled room temperature, as this was not required.
23 April 2012	• Updated toxicology section to include findings available from 13-week toxicology studies. • Included a new section to provide new reproductive toxicity findings received from a definitive embryo-fetal development toxicity study. • Provided clarification regarding the inclusion of participants with SLL to state that the allogeneic lymphocyte cytotoxicity must be ≤ 5 × 10^9/L at the time of diagnosis and at the time of study entry. This clarification was made to ensure that participants with CLL were excluded. • Clarified the inclusion criteria regarding presence of radiographically measurable lymphadenopathy description and included a requirement for the length of longest perpendicular diameter. This provided enhanced clarity regarding the definition of measurable disease for study inclusion. • Revised inclusion criteria to ensure resolution of all acute toxicities to Grade ≤1 before the initiation of study treatment (exception of alopecia, neurotoxicity, and bone marrow parameters with resolution to Grade ≤ 2). • Removed the treatment stratification enrollment limit for participants who had received prior bendamustine. • Further defined the criteria for lesion selection and tumor response. This aligned the protocol with central imaging methods. • Provided time window surrounding the collection of PK samples to minimize deviations. • Added the requirement for collection and consideration for overall response of IgM serum monoclonal protein levels assessed by serum protein electrophoresis (SPEP) for participants with WM. • Included the provision "as allowed by local law" in the event of potential transition of participants from study treatment to commercial supply, should study drug become approved in the country in which the participant lives. • Changed the Stage 1 ORR analysis to be based on investigator response assessment instead of IRC assessment.
23 May 2013	• Established storage of biological samples (with participant's informed consent) for future studies. • Clarified that final efficacy analysis occurs ≥ 24 weeks after the last participant enrolls. • Aligned the clinical response section with the criteria for the IRC. • Removed stratification analysis. • Revised dose modifications to no longer include reductions below 100 mg BID (based on PK data and exposure-response analysis for safety and efficacy). • Updated the pregnancy risk language, based on current animal studies data.

18 July 2013	• Modified the definition of SAE to exclude untoward medical occurrences which resulted in death due to disease progression. • Modified the definition of SAE to include CLL progression or death due to CLL progression only if assessed that study drug caused or contributed to the disease progression.
28 October 2014	• Updated the general information on idelalisib to reflect approval status in the United States and European Union • Align the following information with Investigator's Brochure Edition 11 -Guidance to investigators for evaluation, intervention, and drug interruption/discontinuation for specific adverse events (AEs) -Information regarding the interaction of idelalisib with CYP3A inhibitors, inducers, and substrates
25 March 2016	• Updated the safety information and guidelines for toxicity management to be consistent across idelalisib study protocols. These changes included mandated prophylaxis for Pneumocystis jirovecii pneumonia (PJP), cytomegalovirus (CMV) surveillance, and increased monitoring. • Removed references to 75 mg tablets, as this dose strength was no longer formulated
22 August 2016	• Updated the recommended and required guidelines for toxicity management to be consistent across idelalisib study protocols• Updated the recommended and required guidelines for toxicity management to be consistent across idelalisib study protocols
13 October 2016	• In order to provide clear guidance for idelalisib administration in the event of pneumonitis, the language around actions to be taken was revised.
23 November 2016	• It was a France-only version which included additional information, per the request of the health authority, concerning discontinuation of idelalisib following an event of Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) and management of co-administered medications.
05 September 2017	• Organizing pneumonia emerged as a potential safety signal during Gilead routine signal detection monitoring. This risk was added to the protocol.
06 October 2017	• Organizing pneumonia emerged as a potential safety signal during Gilead routine signal detection monitoring. This risk was added to the protocol. • It was a France-only version, which included information, per the request of the health authority, concerning discontinuation of idelalisib following an event of SJS or TEN and management of co-administered medications.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/24450858