Clinical trial results:
An Expanded Access Protocol for Idelalisib in Combination with Rituximab for Relapsed, Previously Treated Subjects with Chronic Lymphocytic Leukemia

Summary

EudraCT number	2013-005343-82
Trial protocol	IT IE GB
Global end of trial date	15 August 2017

Results information

Result version number	v1 (current)
This version publication date	30 August 2018
First version publication date	30 August 2018

Trial information

Trial identification

Sponsor protocol code	GS-US-312-1325

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02136511
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	15 August 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 August 2017
Global end of trial reached?	Yes
Global end of trial date	15 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To provide idelalisib in an open-label format to eligible participants with relapsed chronic lymphocytic leukemia (CLL) who have limited treatment options.

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	19 May 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Ireland: 2
Country: Number of subjects enrolled	Italy: 20
Country: Number of subjects enrolled	United States: 6
Worldwide total number of subjects	31
EEA total number of subjects	25

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)	20
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in the United States and Europe. The first participant was screened on 19 May 2014. The last study visit occurred on 15 August 2017.

Pre-assignment

Screening details:

31 participants were screened.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Idelalisib + rituximab

Arm description:

Idelalisib + rituximab until unacceptable toxicity, disease progression, study discontinuation, or death occurs.

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

Dosage and administration details:

150 mg twice per day (or 100 mg twice per day if dose was modified)

Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Starting at a dose of 375 mg/m^2 on Week 0 and continuing with a dose of 500 mg/m^2 on Weeks 2, 4, 6, 8, 12, 16, and 20 for a total of 8 infusions

Number of subjects in period 1	Idelalisib + rituximab
Started	31
Completed	0
Not completed	31
Adverse event, non-fatal	6
Protocol violation	1
Death	9

Study terminated by sponsor	6
Unacceptable toxicity	1
Progressive disease	6
Investigator's discretion	1
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Idelalisib + rituximab

Reporting group description:

Idelalisib + rituximab until unacceptable toxicity, disease progression, study discontinuation, or death occurs.

Reporting group values	Idelalisib + rituximab	Total	
Number of subjects	31	31	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 63 ± 9.8	 -	
Gender categorical Units: Subjects			
Female	10	10	
Male	21	21	
Race Units: Subjects			
White	30	30	
Other	1	1	
Ethnicity Units: Subjects			
Not Hispanic or Latino	31	31	

End points

End points reporting groups

Reporting group title	Idelalisib + rituximab

Reporting group description:

Idelalisib + rituximab until unacceptable toxicity, disease progression, study discontinuation, or death occurs.

Primary: Progression-Free Survival

End point title	Progression-Free Survival[1]

End point description:

Progression-free survival (PFS) was defined as the interval from the initial study dosing date to the first documentation of disease progression or death from any cause. The primary analysis of PFS was performed using the Kaplan-Meier method. Participants in the Full Analysis Set (participants who took at least 1 dose of study drug) were analyzed.

99999 = Not reached.

End point type	Primary

End point timeframe:

Baseline to end of study (maximum exposure to idelalisib: 156.1 weeks)

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: Because there was only one treatment arm, no statistical comparison was planned or performed.

End point values	Idelalisib + rituximab			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: months				
median (confidence interval 95%)	21.8 (7.2 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Safety as Assessed by the Incidence of Serious Adverse Events (SAEs) ≥ Grade 3 and Deaths

End point title	Safety as Assessed by the Incidence of Serious Adverse Events (SAEs) ≥ Grade 3 and Deaths

End point description:

The percentage of participants experiencing SAEs ≥ Grade 3 and the percentage of participants that died during the study are presented. Participants in the Full Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

First dose date to end of study (maximum exposure to idelalisib: 156.1 weeks)

End point values	Idelalisib + rituximab			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: percentage of participants				
number (not applicable)				
SAEs ≥ Grade 3	64.5			
Death (all causes)	32.3			
Death (treatment-emergent AE leading to death)	25.8			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First dose date to end of study (maximum exposure to idelalisib: 156.1 weeks)

Adverse event reporting additional description:

Full Analysis Set: participants who took at least 1 dose of study drug

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Idelalisib + rituximab

Reporting group description:

Idelalisib + rituximab until unacceptable toxicity, disease progression, study discontinuation, or death occurs.

Serious adverse events	Idelalisib + rituximab		
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 31 (70.97%)		
number of deaths (all causes)	10		
number of deaths resulting from adverse events	8		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 31 (3.23%)		
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	4 / 31 (12.90%)		
occurrences causally related to treatment / all	3 / 5		
deaths causally related to treatment / all	1 / 1		
Anaemia			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			

subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Condition aggravated			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hernia			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 31 (12.90%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Enteritis			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Enterocolitis				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal haemorrhage				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Large intestinal obstruction				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Vomiting				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Respiratory failure				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Renal and urinary disorders				
Nephrolithiasis				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Pneumonia				

subjects affected / exposed	5 / 31 (16.13%)			
occurrences causally related to treatment / all	1 / 6			
deaths causally related to treatment / all	0 / 2			
Sepsis				
subjects affected / exposed	4 / 31 (12.90%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 2			
Escherichia sepsis				
subjects affected / exposed	2 / 31 (6.45%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Bacterial sepsis				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cytomegalovirus infection				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infective exacerbation of bronchiectasis				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection bacterial				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Periorbital cellulitis				

subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumococcal sepsis			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia pneumococcal			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Progressive multifocal leukoencephalopathy			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	1 / 1		
Staphylococcal sepsis			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 31 (3.23%)		
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 + rituximab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 31 (93.55%)		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	21 / 31 (67.74%)		
occurrences (all)	47		
Asthenia			
subjects affected / exposed	6 / 31 (19.35%)		
occurrences (all)	7		
Oedema peripheral			
subjects affected / exposed	6 / 31 (19.35%)		
occurrences (all)	7		
Fatigue			
subjects affected / exposed	4 / 31 (12.90%)		
occurrences (all)	6		
Pain			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	3		
Chest pain			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Malaise			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	10 / 31 (32.26%)		
occurrences (all)	12		
Rhinorrhoea			
subjects affected / exposed	5 / 31 (16.13%)		
occurrences (all)	6		
Dyspnoea			

subjects affected / exposed	4 / 31 (12.90%)		
occurrences (all)	6		
Productive cough			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	4		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	4 / 31 (12.90%)		
occurrences (all)	4		
Investigations			
Platelet count decreased			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	5		
Weight decreased			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	3		
Alanine aminotransferase increased			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Neutrophil count decreased			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Transaminases increased			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	4		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	3		
Cardiac disorders			
Palpitations			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	3		

Nervous system disorders			
Headache			
subjects affected / exposed	5 / 31 (16.13%)		
occurrences (all)	6		
Dysgeusia			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Neuralgia			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Presyncope			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	13 / 31 (41.94%)		
occurrences (all)	46		
Anaemia			
subjects affected / exposed	9 / 31 (29.03%)		
occurrences (all)	15		
Febrile neutropenia			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Thrombocytopenia			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Eye disorders			
Cataract			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	19 / 31 (61.29%)		
occurrences (all)	42		
Nausea			
subjects affected / exposed	11 / 31 (35.48%)		
occurrences (all)	12		

Vomiting subjects affected / exposed occurrences (all)	9 / 31 (29.03%) 10		
Abdominal pain subjects affected / exposed occurrences (all)	8 / 31 (25.81%) 15		
Constipation subjects affected / exposed occurrences (all)	7 / 31 (22.58%) 8		
Abdominal pain upper subjects affected / exposed occurrences (all)	5 / 31 (16.13%) 7		
Stomatitis subjects affected / exposed occurrences (all)	4 / 31 (12.90%) 5		
Inguinal hernia subjects affected / exposed occurrences (all)	3 / 31 (9.68%) 3		
Odynophagia subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2		
Oral pain subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	7 / 31 (22.58%) 8		
Night sweats subjects affected / exposed occurrences (all)	3 / 31 (9.68%) 4		
Dry skin subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2		
Endocrine disorders			

Hypothyroidism			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	4		
Back pain			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	4		
Musculoskeletal pain			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Osteoporosis			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Infections and infestations			
Herpes zoster			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	3		
Urinary tract infection			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	5		
Bronchitis			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	4		
Helicobacter infection			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Herpes virus infection			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Influenza			

subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Nasopharyngitis			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Oesophageal candidiasis			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Oral fungal infection			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Oral herpes			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Sinusitis			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Skin infection			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Upper respiratory tract infection			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	5 / 31 (16.13%)		
occurrences (all)	10		
Hypocalcaemia			
subjects affected / exposed	4 / 31 (12.90%)		
occurrences (all)	4		
Decreased appetite			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	3		
Hyperglycaemia			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	4		

Hyperuricaemia subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 3		
Hypoglycaemia subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 February 2014	Specified safety monitoring for ALT, AST, and total bilirubin as occurring in all patients every 2 weeks for the first 3 months of treatment, then every 2 to 3 months thereafter and clarified the medications listed to treat AE diarrhea.
10 October 2014	Updated the general information on idelalisib to reflect approval status in the US and EU; Updated information on guidance to investigators for evaluation, intervention, and drug interruption/discontinuation for specific adverse events and information on the interaction of idelalisib with CYP3A inhibitors, inducers, and substrates
25 March 2016	Updated the safety information and guidelines for toxicity management. These changes include mandated prophylaxis for PJP, CMV surveillance and increased monitoring.
23 August 2016	Updated to align with Urgent Safety Measures, clarification on the definition of recommended vs. required treatment for adverse events, and added safety measure for subjects to be monitored for PJP prophylaxis 2-6 months after last idelalisib dose.
24 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. Based on clinical trial data indicating the risk for PJP infection exceeds the time of idelalisib dosing, modification was made to the protocol instructions implementing PJP prophylaxis for a period of 2-6 months following discontinuation of idelalisib.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported