Clinical trial results:
A Phase 3, Randomized, Open-Label Study Evaluating the Efficacy and Safety of Idelalisib in Combination with Obinutuzumab Compared to Chlorambucil in Combination with Obinutuzumab for Previously Untreated Chronic Lymphocytic Leukemia

Summary

EudraCT number	2013-004551-20
Trial protocol	GB PT HU ES BE BG HR IT
Global end of trial date	13 May 2016

Results information

Result version number	v1 (current)
This version publication date	15 April 2017
First version publication date	15 April 2017

Trial information

Trial identification

Sponsor protocol code	GS-US-312-0118

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01980875
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	Clinical Trials Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.com
Scientific contact	Clinical Trials Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@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	13 May 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 May 2016
Global end of trial reached?	Yes
Global end of trial date	13 May 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the effects of idelalisib with obinutuzumab versus the combination of chlorambucil and obinutuzumab on progression-free survival (PFS) in participants with previously untreated chronic lymphocytic leukemia (CLL).

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	21 April 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 28
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	United States: 12
Country: Number of subjects enrolled	Australia: 4
Worldwide total number of subjects	57
EEA total number of subjects	39

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)	12
From 65 to 84 years	40
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in Australia, Europe, and North America. The first participant was screened on 05 May 2015. The last study visit occurred on 13 May 2016.

Pre-assignment

Screening details:

80 participants were screened.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Safety Run-In: Idelalisib +Obinutuzumab

Arm description:

Participants received idelalisib for up to 96 weeks and obinutuzumab over 21 weeks. Following 4 weeks of treatment, safety data was reviewed by an independent data monitoring committee (DMC). If acceptable tolerability was observed, the randomized portion of the study would begin.

Arm type	Experimental
Investigational medicinal product name	Idelalisib
Investigational medicinal product code	
Other name	Zydelig®, GS-1101, CAL-101
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

150 mg tablet administered orally twice daily

Investigational medicinal product name	Obinutuzumab
Investigational medicinal product code	
Other name	Gazyvaro, Gazyva
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1000 mg for a total of 8 doses

Arm title	Randomized: Idelalisib +Obinutuzumab

Arm description:

Participants received idelalisib for up to 96 weeks and obinutuzumab over 21 weeks

Arm type	Experimental
Investigational medicinal product name	Idelalisib
Investigational medicinal product code	
Other name	Zydelig®, GS-1101, CAL-101
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

150 mg tablet administered orally twice daily

Investigational medicinal product name	Obinutuzumab
Investigational medicinal product code	
Other name	Gazyvaro, Gazyva
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1000 mg for a total of 8 doses

Arm title	Randomized: Obinutuzumab +Chlorambucil

Arm description:

Participants received obinutuzumab over 21 weeks and chlorambucil over 23 weeks.

Arm type	Active comparator
Investigational medicinal product name	Obinutuzumab
Investigational medicinal product code	
Other name	Gazyvaro, Gazyva
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1000 mg for a total of 8 doses

Investigational medicinal product name	Chlorambucil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

2 mg tablets administered at a dose of 0.5 mg/kg every other week for a total of 12 doses

Number of subjects in period 1	Safety Run-In: Idelalisib +Obinutuzumab	Randomized: Idelalisib +Obinutuzumab	Randomized: Obinutuzumab +Chlorambucil
Started	8	25	24
Completed	0	0	0
Not completed	8	25	24
Withdrew Consent	1	1	1
Study Terminated by Sponsor	7	24	22
Lost to follow-up	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Safety Run-In: Idelalisib +Obinutuzumab
Reporting group description:	
Participants received idelalisib for up to 96 weeks and obinutuzumab over 21 weeks. Following 4 weeks of treatment, safety data was reviewed by an independent data monitoring committee (DMC). If acceptable tolerability was observed, the randomized portion of the study would begin.	
Reporting group title	Randomized: Idelalisib +Obinutuzumab
Reporting group description:	
Participants received idelalisib for up to 96 weeks and obinutuzumab over 21 weeks	
Reporting group title	Randomized: Obinutuzumab +Chlorambucil
Reporting group description:	
Participants received obinutuzumab over 21 weeks and chlorambucil over 23 weeks.	

Reporting group values	Safety Run-In: Idelalisib +Obinutuzumab	Randomized: Idelalisib +Obinutuzumab	Randomized: Obinutuzumab +Chlorambucil
Number of subjects	8	25	24
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	67.1	72.2	71.1
standard deviation	± 8.1	± 8.23	± 6.84
Gender categorical			
Units: Subjects			
Female	3	8	9
Male	5	17	15
Race			
Units: Subjects			
Black or African American	1	0	0
White	7	22	21
Other	0	1	0
Not Permitted	0	2	3
Rai Stage			
Rai staging is a way to categorize the disease progression of chronic lymphocytic leukemia (CLL) with higher stages reflecting increasing severity. Rai Stage 0: Lymphocytosis only, Rai Stage I: Lymphocytosis with lymphadenopathy, Rai Stage II: Lymphocytosis with hepatomegaly or splenomegaly, Rai Stage III: Lymphocytosis with anemia, Rai Stage IV: Lymphocytosis with thrombocytopenia.			
Units: Subjects			
Stage I-II	3	11	9
Stage III-IV	5	14	15
IgHV Mutation			
The mutation status of the unique immunoglobulin gene (IgHV) rearrangement in the monoclonal proliferation of B-cells in CLL can be used to predict aggressiveness of the disease. Participants with a mutated IgHV gene usually have a less aggressive and more indolent disease, with longer overall survival. Participants with an unmutated IgHV gene usually have a more aggressive disease and shorter overall survival.			

Units: Subjects			
Unmutated	5	16	17
Mutated	3	9	7
17p Deletion in CLL Cells			
Participants with CLL who have deletion of 17p, a portion of the chromosome that acts to suppress cancer growth and is a recognized negative prognostic risk factor.			
Units: Subjects			
Present	0	3	3
Absent	8	22	21

Reporting group values	Total		
Number of subjects	57		
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	20		
Male	37		
Race Units: Subjects			
Black or African American	1		
White	50		
Other	1		
Not Permitted	5		
Rai Stage			
Rai staging is a way to categorize the disease progression of chronic lymphocytic leukemia (CLL) with higher stages reflecting increasing severity. Rai Stage 0: Lymphocytosis only, Rai Stage I: Lymphocytosis with lymphadenopathy, Rai Stage II: Lymphocytosis with hepatomegaly or splenomegaly, Rai Stage III: Lymphocytosis with anemia, Rai Stage IV: Lymphocytosis with thrombocytopenia.			
Units: Subjects			
Stage I-II	23		
Stage III-IV	34		
IgHV Mutation			
The mutation status of the unique immunoglobulin gene (IgHV) rearrangement in the monoclonal proliferation of B-cells in CLL can be used to predict aggressiveness of the disease. Participants with a mutated IgHV gene usually have a less aggressive and more indolent disease, with longer overall survival. Participants with an unmutated IgHV gene usually have a more aggressive disease and shorter overall survival.			
Units: Subjects			
Unmutated	38		
Mutated	19		
17p Deletion in CLL Cells			
Participants with CLL who have deletion of 17p, a portion of the chromosome that acts to suppress cancer growth and is a recognized negative prognostic risk factor.			
Units: Subjects			
Present	6		

Absent	51		

End points

End points reporting groups

Reporting group title	Safety Run-In: Idelalisib +Obinutuzumab
Reporting group description:	
Participants received idelalisib for up to 96 weeks and obinutuzumab over 21 weeks. Following 4 weeks of treatment, safety data was reviewed by an independent data monitoring committee (DMC). If acceptable tolerability was observed, the randomized portion of the study would begin.	
Reporting group title	Randomized: Idelalisib +Obinutuzumab
Reporting group description:	
Participants received idelalisib for up to 96 weeks and obinutuzumab over 21 weeks	
Reporting group title	Randomized: Obinutuzumab +Chlorambucil
Reporting group description:	
Participants received obinutuzumab over 21 weeks and chlorambucil over 23 weeks.	

Primary: Progression-Free Survival

End point title	Progression-Free Survival[1]
End point description:	
Progression-free survival (PFS) is defined as the interval from randomization to the first documentation of definitive disease progression or death from any cause. Definitive disease progression is CLL progression based on standard criteria, excluding lymphocytosis alone. PFS was to be assessed by an independent review committee (IRC). Due to the early termination of the study, efficacy data were not available for all participants, and therefore the prespecified analyses were not conducted.	
End point type	Primary
End point timeframe:	
Not applicable	

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: Due to the early termination of the study, efficacy data were not available for all participants, and therefore the prespecified analyses were not conducted.

End point values	Safety Run-In: Idelalisib +Obinutuzumab	Randomized: Idelalisib +Obinutuzumab	Randomized: Obinutuzumab +Chlorambucil	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[2]	0[3]	0[4]	
Units: Not applicable				

Notes:

[2] - Analysis was not performed due to early study termination.

[3] - Analysis was not performed due to early study termination.

[4] - Analysis was not performed due to early study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate

End point title	Overall Response Rate
End point description:	
Overall response rate (ORR) is defined as the proportion of participants who achieve a confirmed	

complete or partial response. ORR was to be assessed by an IRC. Due to the early termination of the study, efficacy data were not available for all participants, and therefore the prespecified analyses were not conducted.

End point type	Secondary

End point timeframe:

Not applicable

End point values	Safety Run-In: Idelalisib +Obinutuzumab	Randomized: Idelalisib +Obinutuzumab	Randomized: Obinutuzumab +Chlorambucil	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[5]	0[6]	0[7]	
Units: Not applicable				

Notes:

[5] - Analysis was not performed due to early study termination.

[6] - Analysis was not performed due to early study termination.

[7] - Analysis was not performed due to early study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Nodal Response Rate

End point title	Nodal Response Rate

End point description:

Nodal response rate is defined as the proportion of participants who achieve a 50% decrease from baseline in the sum of the products of the greatest perpendicular diameters of index lesions. Nodal response rate was to be assessed by an IRC. Due to the early termination of the study, efficacy data were not available for all participants, and therefore the prespecified analyses were not conducted.

End point type	Secondary

End point timeframe:

Not applicable

End point values	Safety Run-In: Idelalisib +Obinutuzumab	Randomized: Idelalisib +Obinutuzumab	Randomized: Obinutuzumab +Chlorambucil	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[8]	0[9]	0[10]	
Units: Not applicable				

Notes:

[8] - Analysis was not performed due to early study termination.

[9] - Analysis was not performed due to early study termination.

[10] - Analysis was not performed due to early study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Response Rate

End point title	Complete Response Rate

End point description:

Complete response rate is defined as the proportion of participants who achieve a confirmed complete response. Complete response rate was to be assessed by an IRC. Due to the early termination of the study, efficacy data were not available for all participants, and therefore the prespecified analyses were not conducted.

End point type	Secondary

End point timeframe:

Not applicable

End point values	Safety Run-In: Idelalisib +Obinutuzumab	Randomized: Idelalisib +Obinutuzumab	Randomized: Obinutuzumab +Chlorambucil	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[11]	0[12]	0[13]	
Units: Not applicable				

Notes:

[11] - Analysis was not performed due to early study termination.

[12] - Analysis was not performed due to early study termination.

[13] - Analysis was not performed due to early study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival is defined as the interval from randomization to death from any cause. Due to the early termination of the study, efficacy data were not mature for all participants, and therefore the prespecified analyses were not conducted.

End point type	Secondary

End point timeframe:

Not applicable

End point values	Safety Run-In: Idelalisib +Obinutuzumab	Randomized: Idelalisib +Obinutuzumab	Randomized: Obinutuzumab +Chlorambucil	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[14]	0[15]	0[16]	
Units: Not applicable				

Notes:

[14] - Analysis was not performed due to early study termination.

[15] - Analysis was not performed due to early study termination.

[16] - Analysis was not performed due to early study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Minimal Residual Disease Negativity Rate at Week 36

End point title	Minimal Residual Disease Negativity Rate at Week 36

End point description:

Minimal residual disease (MRD) negativity rate is defined as the proportion of participants with MRD < 10^-4 assessed by flow cytometry in bone marrow at Week 36 after therapy initiation. For participants receiving the final dose of obinutuzumab after the original scheduled date, the MRD assessment was performed no less than 12 weeks after the last dose of obinutuzumab. MRD negativity rate was to be assessed by an IRC. Due to the early termination of the study, efficacy data were not available for all participants, and therefore the prespecified analyses were not conducted.

End point type	Secondary

End point timeframe:

Not applicable

End point values	Safety Run-In: Idelalisib +Obinutuzumab	Randomized: Idelalisib +Obinutuzumab	Randomized: Obinutuzumab +Chlorambucil	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[17]	0[18]	0[19]	
Units: Not applicable				

Notes:

[17] - Analysis was not performed due to early study termination.

[18] - Analysis was not performed due to early study termination.

[19] - Analysis was not performed due to early study termination.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to the last dose date plus 30 days (maximum: 12 months)

Adverse event reporting additional description:

Safety Analysis Set: participants who received at least 1 dose of study drug, with treatment group designated according to actual treatment received.

NOTE: Serious adverse events and deaths causally related to "treatment" refers to events deemed related to idelalisib treatment per investigator assessment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Safety Run-In: Idelalisib +Obinutuzumab

Reporting group description:

Participants received idelalisib for 96 weeks and obinutuzumab over 21 weeks. Following 4 weeks of treatment, safety data was reviewed by an independent data monitoring committee (DMC). If acceptable tolerability was observed, the randomized portion of the study would begin.

Reporting group title	Randomized: Idelalisib +Obinutuzumab

Reporting group description:

Participants received idelalisib for 96 weeks and obinutuzumab over 21 weeks

Reporting group title	Randomized: Obinutuzumab +Chlorambucil

Reporting group description:

Participants received obinutuzumab over 21 weeks and chlorambucil over 23 weeks.

Serious adverse events	Safety Run-In: Idelalisib +Obinutuzumab	Randomized: Idelalisib +Obinutuzumab	Randomized: Obinutuzumab +Chlorambucil
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 8 (25.00%)	12 / 24 (50.00%)	8 / 23 (34.78%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Richter's syndrome			
subjects affected / exposed	0 / 8 (0.00%)	0 / 24 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Infusion related reaction			

subjects affected / exposed	0 / 8 (0.00%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 8 (0.00%)	0 / 24 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Leukoencephalopathy			
subjects affected / exposed	1 / 8 (12.50%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 8 (0.00%)	2 / 24 (8.33%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 24 (4.17%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 8 (0.00%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			

subjects affected / exposed	0 / 8 (0.00%)	0 / 24 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Secondary immunodeficiency			
subjects affected / exposed	0 / 8 (0.00%)	0 / 24 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 8 (12.50%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 8 (0.00%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 8 (0.00%)	2 / 24 (8.33%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 8 (0.00%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			

subjects affected / exposed	0 / 8 (0.00%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 24 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 8 (0.00%)	0 / 24 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 24 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 24 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 24 (4.17%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Tumour lysis syndromerome			

subjects affected / exposed	0 / 8 (0.00%)	0 / 24 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Safety Run-In: Idelalisib +Obinutuzumab	Randomized: Idelalisib +Obinutuzumab	Randomized: Obinutuzumab +Chlorambucil
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)	19 / 24 (79.17%)	17 / 23 (73.91%)
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 8 (12.50%)	0 / 24 (0.00%)	1 / 23 (4.35%)
occurrences (all)	1	0	1
Hypertension			
subjects affected / exposed	0 / 8 (0.00%)	2 / 24 (8.33%)	1 / 23 (4.35%)
occurrences (all)	0	2	1
Orthostatic hypotension			
subjects affected / exposed	1 / 8 (12.50%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 8 (12.50%)	2 / 24 (8.33%)	0 / 23 (0.00%)
occurrences (all)	1	2	0
Face oedema			
subjects affected / exposed	1 / 8 (12.50%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	1 / 8 (12.50%)	3 / 24 (12.50%)	2 / 23 (8.70%)
occurrences (all)	1	3	2
Influenza like illness			
subjects affected / exposed	2 / 8 (25.00%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	3	0	0
Oedema peripheral			

subjects affected / exposed	1 / 8 (12.50%)	3 / 24 (12.50%)	1 / 23 (4.35%)
occurrences (all)	1	3	1
Pyrexia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 24 (4.17%)	4 / 23 (17.39%)
occurrences (all)	1	2	4
Reproductive system and breast disorders			
Penile pain			
subjects affected / exposed	0 / 8 (0.00%)	2 / 24 (8.33%)	0 / 23 (0.00%)
occurrences (all)	0	2	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 8 (0.00%)	2 / 24 (8.33%)	0 / 23 (0.00%)
occurrences (all)	0	2	0
Dyspnoea			
subjects affected / exposed	1 / 8 (12.50%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	2	0	0
Hypoxia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 8 (12.50%)	0 / 24 (0.00%)	1 / 23 (4.35%)
occurrences (all)	1	0	1
Insomnia			
subjects affected / exposed	2 / 8 (25.00%)	2 / 24 (8.33%)	0 / 23 (0.00%)
occurrences (all)	3	2	0
Restlessness			
subjects affected / exposed	2 / 8 (25.00%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	2	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	7 / 8 (87.50%)	5 / 24 (20.83%)	1 / 23 (4.35%)
occurrences (all)	8	6	1
Aspartate aminotransferase increased			

subjects affected / exposed	7 / 8 (87.50%)	5 / 24 (20.83%)	1 / 23 (4.35%)
occurrences (all)	7	6	1
Blood creatinine increased			
subjects affected / exposed	0 / 8 (0.00%)	2 / 24 (8.33%)	0 / 23 (0.00%)
occurrences (all)	0	2	0
Heart rate increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	2 / 8 (25.00%)	3 / 24 (12.50%)	14 / 23 (60.87%)
occurrences (all)	2	3	14
Muscle strain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Cerebellar syndrome			
subjects affected / exposed	1 / 8 (12.50%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	2	0	0
Circadian rhythm sleep disorder			
subjects affected / exposed	1 / 8 (12.50%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Dementia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Dizziness			
subjects affected / exposed	1 / 8 (12.50%)	2 / 24 (8.33%)	0 / 23 (0.00%)
occurrences (all)	1	2	0
Dizziness postural			
subjects affected / exposed	1 / 8 (12.50%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	1 / 8 (12.50%)	2 / 24 (8.33%)	2 / 23 (8.70%)
occurrences (all)	1	2	3
Psychomotor skills impaired			

subjects affected / exposed	1 / 8 (12.50%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Somnolence			
subjects affected / exposed	1 / 8 (12.50%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Tremor			
subjects affected / exposed	1 / 8 (12.50%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	2	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 8 (25.00%)	6 / 24 (25.00%)	2 / 23 (8.70%)
occurrences (all)	2	6	2
Neutropenia			
subjects affected / exposed	4 / 8 (50.00%)	6 / 24 (25.00%)	9 / 23 (39.13%)
occurrences (all)	8	10	11
Thrombocytopenia			
subjects affected / exposed	3 / 8 (37.50%)	2 / 24 (8.33%)	1 / 23 (4.35%)
occurrences (all)	3	3	1
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 8 (12.50%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Eye swelling			
subjects affected / exposed	1 / 8 (12.50%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 8 (12.50%)	1 / 24 (4.17%)	1 / 23 (4.35%)
occurrences (all)	1	1	1
Autoimmune colitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	2 / 8 (25.00%)	2 / 24 (8.33%)	1 / 23 (4.35%)
occurrences (all)	2	2	1
Diarrhoea			

subjects affected / exposed	4 / 8 (50.00%)	4 / 24 (16.67%)	1 / 23 (4.35%)
occurrences (all)	4	4	1
Flatulence			
subjects affected / exposed	1 / 8 (12.50%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	2	0	0
Nausea			
subjects affected / exposed	2 / 8 (25.00%)	2 / 24 (8.33%)	4 / 23 (17.39%)
occurrences (all)	3	2	4
Stomatitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Ecchymosis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Night sweats			
subjects affected / exposed	2 / 8 (25.00%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	2	0	0
Rash			
subjects affected / exposed	1 / 8 (12.50%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences (all)	1	1	0
Rash macular			
subjects affected / exposed	1 / 8 (12.50%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	2	0	0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 8 (0.00%)	0 / 24 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	2
Urinary retention			
subjects affected / exposed	1 / 8 (12.50%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 8 (12.50%)	2 / 24 (8.33%)	0 / 23 (0.00%)
occurrences (all)	1	2	0
Back pain			

subjects affected / exposed	0 / 8 (0.00%)	2 / 24 (8.33%)	1 / 23 (4.35%)
occurrences (all)	0	2	1
Neck pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Clostridium difficile colitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Lower respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 24 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	2
Pneumonia			
subjects affected / exposed	0 / 8 (0.00%)	2 / 24 (8.33%)	1 / 23 (4.35%)
occurrences (all)	0	2	1
Upper respiratory tract infection bacterial			
subjects affected / exposed	1 / 8 (12.50%)	2 / 24 (8.33%)	2 / 23 (8.70%)
occurrences (all)	3	2	2
Urinary tract infection			
subjects affected / exposed	1 / 8 (12.50%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences (all)	1	1	0
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 8 (12.50%)	0 / 24 (0.00%)	1 / 23 (4.35%)
occurrences (all)	2	0	1
Hyperglycaemia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences (all)	1	1	0
Hyperuricaemia			
subjects affected / exposed	0 / 8 (0.00%)	3 / 24 (12.50%)	0 / 23 (0.00%)
occurrences (all)	0	4	0
Hypocalcaemia			

subjects affected / exposed	1 / 8 (12.50%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Hypokalaemia			
subjects affected / exposed	1 / 8 (12.50%)	2 / 24 (8.33%)	0 / 23 (0.00%)
occurrences (all)	1	2	0
Hyponatraemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Tetany			
subjects affected / exposed	0 / 8 (0.00%)	0 / 24 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	2
Tumour lysis syndrome			
subjects affected / exposed	0 / 8 (0.00%)	0 / 24 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 November 2014	– Updated the study design and background therapy in order to better align with current clinical trial results in frontline CLL. These recent results suggest new standards of care for patients not suitable for intensive chemoimmunotherapy. The design has been amended to an open-label study comparing idelalisib + obinutuzumab vs chlorambucil + obinutuzumab. – Clarified and edited the procedures section as applicable to the new therapies used in this study and to align all procedures to the schedule of assessments in the appendix. – Allowed for approximately 130 additional subjects to be enrolled to support design and statistical assumption changes.
06 March 2015	– Updated contraception requirements and guidance for management of tumor lysis syndrome.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
11 March 2016	An increased rate of deaths and serious adverse events (SAEs) among participants with front-line CLL and early-line iNHL treated with idelalisib in combination with standard therapies was observed by the independent data monitoring committee (DMC) during regular review of 3 Gilead Phase 3 studies. Gilead reviewed the unblinded data and terminated those studies in agreement with the DMC recommendation and in consultation with the US Food and Drug Administration (FDA). All front-line studies of idelalisib, including this study, were also terminated.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to the early termination of the study, efficacy data were not available for all participants, and therefore the prespecified analyses were not conducted.

Notes: