Clinical trial results:
A Prospective, Open-Label, Multicenter, Phase 2 Trial to Evaluate the Safety and Efficacy of the Combination of Tirabrutinib (GS-4059) and Idelalisib With and Without Obinutuzumab in Subjects with Chronic Lymphocytic Leukemia

Summary

EudraCT number	2015-003909-42
Trial protocol	DE
Global end of trial date	14 January 2021

Results information

Result version number	v1 (current)
This version publication date	11 January 2022
First version publication date	11 January 2022

Trial information

Trial identification

Sponsor protocol code	GS-US-401-1958

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02968563
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	14 January 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 June 2019
Global end of trial reached?	Yes
Global end of trial date	14 January 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to determine the preliminary efficacy of the combination of tirabrutinib and idelalisib with
obinutuzumab in adults with relapsed or refractory chronic lymphocytic leukemia (CLL).

The study had a 6 participant per arm safety run-in to evaluate safety prior to the enrollment of subsequent participants. The treatment period was adaptive, with a duration of active treatment up to two years and a total follow-up on study for up to 30 days
post end of treatment, or up to Week 25 should a participant discontinue treatment prior to Week 25 for reasons other than disease progression.

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	13 December 2016
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	Germany: 35
Worldwide total number of subjects	35
EEA total number of subjects	35

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)	15
From 65 to 84 years	20
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in Germany. The first participant was screened on 13 December 2016. The last study visit occurred on 14 January 2021.

Pre-assignment

Screening details:

35 participants were screened. Randomization was discontinued after implementation of Protocol Amendment 3; all additional participants were enrolled to Arm: Tirabrutinib + Idelalisib + Obinutuzumab.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Tirabrutinib + Idelalisib

Arm description:

Tirabrutinib 80 mg (4 x 20 mg tablets/2 x 40 mg tablets/1 x 80 mg tablet) orally once daily + idelalisib 100 mg (1 x 100 mg tablet) orally once daily for up to 104 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:

100 mg administered once daily

Investigational medicinal product name	Tirabrutinib
Investigational medicinal product code	
Other name	GS-4059
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

80 mg administered once daily

Arm title	Tirabrutinib + Idelalisib + Obinutuzumab

Arm description:

Tirabrutinib 80 mg (4 x 20 mg tablets/ 2 x 40 mg tablets/ 1 x 80 mg tablet) orally once daily + idelalisib 100 mg (1 x 100 mg tablet) orally once daily for up to 104 weeks + obinutuzumab 100 mg on Day 1, 900 mg on Day 1 or 2, and 1000 mg subsequently for up to 8 doses on Day 1 of Weeks 2, 3, 5, and then every 4 weeks through Week 21.

Arm type	Experimental
Investigational medicinal product name	Tirabrutinib
Investigational medicinal product code	
Other name	GS-4059
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

80 mg administered once daily

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

Dosage and administration details:

100 mg on day 1, 900 mg on day 1 or 2, and 1000 mg administered intravenously

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:

100 mg administered once daily

Number of subjects in period 1	Tirabrutinib + Idelalisib	Tirabrutinib + Idelalisib + Obinutuzumab
Started	5	30
Completed	4	22
Not completed	1	8
Death	1	1
Adverse event	-	6
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Tirabrutinib + Idelalisib
Reporting group description:	
Tirabrutinib 80 mg (4 x 20 mg tablets/2 x 40 mg tablets/1 x 80 mg tablet) orally once daily + idelalisib 100 mg (1 x 100 mg tablet) orally once daily for up to 104 weeks.	
Reporting group title	Tirabrutinib + Idelalisib + Obinutuzumab
Reporting group description:	
Tirabrutinib 80 mg (4 x 20 mg tablets/ 2 x 40 mg tablets/ 1 x 80 mg tablet) orally once daily + idelalisib 100 mg (1 x 100 mg tablet) orally once daily for up to 104 weeks + obinutuzumab 100 mg on Day 1, 900 mg on Day 1 or 2, and 1000 mg subsequently for up to 8 doses on Day 1 of Weeks 2, 3, 5, and then every 4 weeks through Week 21.	

Reporting group values	Tirabrutinib + Idelalisib	Tirabrutinib + Idelalisib + Obinutuzumab	Total
Number of subjects	5	30	35
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	62	65	
standard deviation	± 4.7	± 9.4	-
Gender categorical			
Units: Subjects			
Female	3	10	13
Male	2	20	22
Race			
Not Permitted = local regulators did not allow collection of race information.			
Units: Subjects			
White	5	29	34
Not Permitted	0	1	1
Ethnicity			
Not Permitted = local regulators did not allow collection of ethnicity information.			
Units: Subjects			
Not Hispanic or Latino	5	29	34
Not Permitted	0	1	1

End points

End points reporting groups

Reporting group title	Tirabrutinib + Idelalisib
Reporting group description:	
Tirabrutinib 80 mg (4 x 20 mg tablets/2 x 40 mg tablets/1 x 80 mg tablet) orally once daily + idelalisib 100 mg (1 x 100 mg tablet) orally once daily for up to 104 weeks.	
Reporting group title	Tirabrutinib + Idelalisib + Obinutuzumab
Reporting group description:	
Tirabrutinib 80 mg (4 x 20 mg tablets/ 2 x 40 mg tablets/ 1 x 80 mg tablet) orally once daily + idelalisib 100 mg (1 x 100 mg tablet) orally once daily for up to 104 weeks + obinutuzumab 100 mg on Day 1, 900 mg on Day 1 or 2, and 1000 mg subsequently for up to 8 doses on Day 1 of Weeks 2, 3, 5, and then every 4 weeks through Week 21.	

Primary: Rate of Complete Response/Complete Remission (CR), as Assessed by Investigator Using Modified International Workshop on Chronic Lymphocytic Leukemia (IWCLL) 2008 Criteria at Week 25

End point title	Rate of Complete Response/Complete Remission (CR), as Assessed by Investigator Using Modified International Workshop on Chronic Lymphocytic Leukemia (IWCLL) 2008 Criteria at Week 25[1]
End point description:	
Rate of CR per modified IWCLL 2008 criteria at Week 25 was defined as the percentage of participants who achieved CR/complete remission with incomplete recovery of the bone marrow (CRi) at Week 25. CR: meeting following criteria and no disease related symptoms: no lymphadenopathy > 1.5 cm/hepatomegaly/splenomegaly; lymphocytes < 4000/µL; bone marrow sample must be normocellular with 30% lymphocytes and no B-lymphoid nodules; platelets > 100,000/µL; hemoglobin > 11 g/dL; and neutrophils > 1500/µL. CRi: CR criteria (no lymphadenopathy > 1.5 cm/hepatomegaly/splenomegaly; lymphocytes < 4000/µL; bone marrow [hypocellular] with 30% lymphocytes and no B-lymphoid nodules), persistent anemia/thrombocytopenia/neutropenia unrelated to CLL but related to drug toxicity. Analysis Population Description: The Full Analysis Set included all randomized or enrolled participants who received at least 1 dose of any study drug.	
End point type	Primary
End point timeframe:	
Week 25	
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: No statistical comparison was planned or performed.	

End point values	Tirabrutinib + Idelalisib	Tirabrutinib + Idelalisib + Obinutuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	30		
Units: percentage of participants				
number (confidence interval 90%)	0 (0 to 45.1)	6.7 (1.2 to 19.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of CR With Bone Marrow Minimal Residual Disease (CR/BM MRD) Negativity, as Assessed by the Investigator Using the Modified IWCLL 2008 Criteria at Week 25

End point title	Rate of CR With Bone Marrow Minimal Residual Disease (CR/BM MRD) Negativity, as Assessed by the Investigator Using the Modified IWCLL 2008 Criteria at Week 25

End point description:

Rate of CR/BM MRD at Week 25: percentage of participants who achieved CR/CRi per modified IWCLL 2008 criteria and achieved BM MRD negativity at Week 25. CR:meeting following criteria and no disease related symptoms:no lymphadenopathy >1.5 cm/hepatomegaly/splenomegaly;lymphocytes <4000/µL;bone marrow sample must be normocellular with 30% lymphocytes and no B-lymphoid nodules;platelets >100,000/µL;hemoglobin >11 g/dL;and neutrophils >1500/µL. CRi:CR criteria (no lymphadenopathy >1.5 cm/hepatomegaly/splenomegaly;lymphocytes <4000/µL;bone marrow [hypocellular] with 30% lymphocytes and no B-lymphoid nodules),persistent anemia/thrombocytopenia/neutropenia unrelated to CLL but related to drug toxicity. MRD response was assessed with four-color-flow cytometry (FACS) and MRD negativity was defined as one CLL cell per 10,000 leukocytes [0.01%], ie,<10^-4 and participants were defined as MRD negative if their disease burden was below threshold.Participants in the Full Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Week 25

End point values	Tirabrutinib + Idelalisib	Tirabrutinib + Idelalisib + Obinutuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	30		
Units: percentage of participants				
number (confidence interval 90%)	0 (0 to 45.1)	0 (0 to 9.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of CR With Peripheral Minimal Residual Disease (CR/PB MRD) Negativity, as Assessed by the Investigator Using the Modified IWCLL 2008 Criteria at Week 25

End point title	Rate of CR With Peripheral Minimal Residual Disease (CR/PB MRD) Negativity, as Assessed by the Investigator Using the Modified IWCLL 2008 Criteria at Week 25

End point description:

Rate of CR/PB MRD at Week 25:percentage of participants who achieved CR/CRi per modified IWCLL 2008 criteria and also achieved PB MRD negativity at Week 25. CR: meeting following criteria and no disease related symptoms: no lymphadenopathy > 1.5 cm/hepatomegaly/splenomegaly; lymphocytes < 4000/µL; bone marrow sample must be normocellular with 30% lymphocytes and no B-lymphoid nodules; platelets > 100,000/µL; hemoglobin > 11 g/dL; and neutrophils > 1500/µL. CRi: CR criteria (no lymphadenopathy > 1.5 cm/hepatomegaly/splenomegaly; lymphocytes < 4000/µL; bone marrow [hypocellular] with 30% lymphocytes and no B-lymphoid nodules), persistent anemia/thrombocytopenia/neutropenia unrelated to CLL but related to drug toxicity. MRD response was assessed with FACS and MRD negativity was defined as one CLL cell per 10,000 leukocytes [0.01%], ie,<10^-4 and participants were defined as MRD negative if their disease burden was below this threshold.Participants in the Full Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Week 25

End point values	Tirabrutinib + Idelalisib	Tirabrutinib + Idelalisib + Obinutuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	30		
Units: percentage of participants				
number (confidence interval 90%)	0 (0 to 45.1)	0 (0 to 9.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR), as Assessed by the Investigator Using the Modified IWCLL 2008 Criteria at Week 25

End point title	Overall Response Rate (ORR), as Assessed by the Investigator Using the Modified IWCLL 2008 Criteria at Week 25

End point description:

ORR was assessed based on modified IWCLL 2008 criteria and was defined as percentage of participants achieving a CR, CRi, partial remission (PR; including nodular partial response [nPR]), and PR with lymphocytosis (PR-L). CR and CRi: meeting all the criteria that have been defined in Outcome measures 1, 2 and 3. PR: ≥ 2 of these: ≥ 50% decrease in lymphocytes, lymphadenopathy, size of liver, size of spleen, and 50% decrease in bone marrow infiltrates; and ≥ 1 of these: neutrophils > 1500/µL or ≥ 50% increase from Baseline, platelets ≥ 100,000/µL or ≥ 50% increase from Baseline, hemoglobin >11 g/dL or ≥ 50% increase from Baseline. PR-L: meeting PR criteria; however, a lymphocytosis related to treatment may be present. nPR: All criteria for a CR/CRi were fulfilled, but the bone marrow showed lymphoid nodules. Participants in the Full Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Week 25

End point values	Tirabrutinib + Idelalisib	Tirabrutinib + Idelalisib + Obinutuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	30		
Units: percentage of participants				
number (confidence interval 90%)	60.0 (18.9 to 92.4)	93.3 (80.5 to 98.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Experiencing Any Treatment-Emergent Adverse Events (AEs) and Treatment-Emergent Serious Adverse Events (SAEs)

End point title	Percentage of Participants Experiencing Any Treatment-Emergent Adverse Events (AEs) and Treatment-Emergent Serious Adverse Events (SAEs)

End point description:

Treatment-emergent AEs are defined as 1 or both of the following:
- Any AEs with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug
- Any AEs leading to discontinuation of study drug

A SAE is defined as an event that, at any dose, resulted in any of the following: death, life-threatening, in-patient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, a congenital anomaly/birth defect, or a medically important event or reaction.

The Safety Analysis Set included all randomized or enrolled participants who received at least 1 dose of any study drug.

End point type	Secondary

End point timeframe:

First dose date up to the last dose date (maximum: 105 weeks) plus 30 days

End point values	Tirabrutinib + Idelalisib	Tirabrutinib + Idelalisib + Obinutuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	30		
Units: percentage of participants				
number (not applicable)				
Any Treatment-Emergent AEs	100	100		
Treatment-Emergent SAEs	60.0	46.7		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events: First dose date up to last dose date (maximum: 105 weeks) plus 30 days;

All-Cause Mortality: Enrollment up to 31 months

Adverse event reporting additional description:

Adverse Events: The Safety Analysis Set included all randomized or enrolled participants who received at least 1 dose of any study drug.

All-Cause Mortality: The All Enrolled Analysis Set included all participants who received a study participant identification number in the study after screening.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Tirabrutinib + Idelalisib

Reporting group description:

Tirabrutinib 80 mg (4 x 20 mg tablets/2 x 40 mg tablets/1 x 80 mg tablet) orally once daily + idelalisib 100 mg (1 x 100 mg tablet) orally once daily for up to 104 weeks.

Reporting group title	Tirabrutinib + Idelalisib + Obinutuzumab

Reporting group description:

Tirabrutinib 80 mg (4 x 20 mg tablets/ 2 x 40 mg tablets/ 1 x 80 mg tablet) orally once daily + idelalisib 100 mg (1 x 100 mg tablet) orally once daily for up to 104 weeks + obinutuzumab 100 mg on Day 1, 900 mg on Day 1 or 2, and 1000 mg subsequently for up to 8 doses administered intravenously over 21 weeks.

Serious adverse events	Tirabrutinib + Idelalisib	Tirabrutinib + Idelalisib + Obinutuzumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 5 (60.00%)	14 / 30 (46.67%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events			
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigation			
subjects affected / exposed	0 / 5 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Neutrophil count decreased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 5 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure acute			
subjects affected / exposed	1 / 5 (20.00%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 5 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			

subjects affected / exposed	0 / 5 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 5 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 5 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	1 / 5 (20.00%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Atypical pneumonia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			

subjects affected / exposed	0 / 5 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 5 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Tumour lysis syndrome			
subjects affected / exposed	0 / 5 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Tirabrutinib + Idelalisib	Tirabrutinib + Idelalisib + Obinutuzumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)	29 / 30 (96.67%)	
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 5 (20.00%)	6 / 30 (20.00%)	
occurrences (all)	1	16	
Hypertension			
subjects affected / exposed	0 / 5 (0.00%)	5 / 30 (16.67%)	
occurrences (all)	0	5	
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	1 / 5 (20.00%)	10 / 30 (33.33%)	
occurrences (all)	1	11	
Pyrexia			
subjects affected / exposed	1 / 5 (20.00%)	7 / 30 (23.33%)	
occurrences (all)	3	7	
Chills			
subjects affected / exposed	1 / 5 (20.00%)	6 / 30 (20.00%)	
occurrences (all)	1	7	
Feeling cold			
subjects affected / exposed	0 / 5 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Influenza like illness			
subjects affected / exposed	0 / 5 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	3	
Oedema peripheral			
subjects affected / exposed	0 / 5 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Medical device pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 5 (0.00%)	8 / 30 (26.67%)	
occurrences (all)	0	12	
Epistaxis			
subjects affected / exposed	0 / 5 (0.00%)	4 / 30 (13.33%)	
occurrences (all)	0	6	
Dysphonia			
subjects affected / exposed	0 / 5 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Haemoptysis			
subjects affected / exposed	0 / 5 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Nasal mucosal disorder			

subjects affected / exposed	0 / 5 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 5 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Insomnia			
subjects affected / exposed	1 / 5 (20.00%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Sleep disorder			
subjects affected / exposed	0 / 5 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	0 / 5 (0.00%)	4 / 30 (13.33%)	
occurrences (all)	0	9	
Alanine aminotransferase increased			
subjects affected / exposed	1 / 5 (20.00%)	2 / 30 (6.67%)	
occurrences (all)	2	4	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 5 (20.00%)	2 / 30 (6.67%)	
occurrences (all)	2	3	
C-reactive protein increased			
subjects affected / exposed	0 / 5 (0.00%)	3 / 30 (10.00%)	
occurrences (all)	0	5	
Hepatic enzyme increased			
subjects affected / exposed	0 / 5 (0.00%)	3 / 30 (10.00%)	
occurrences (all)	0	4	
Platelet count decreased			
subjects affected / exposed	0 / 5 (0.00%)	3 / 30 (10.00%)	
occurrences (all)	0	3	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 5 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Weight decreased			

subjects affected / exposed	0 / 5 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 5 (0.00%)	5 / 30 (16.67%)	
occurrences (all)	0	6	
Foot fracture			
subjects affected / exposed	1 / 5 (20.00%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 5 (20.00%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 5 (40.00%)	3 / 30 (10.00%)	
occurrences (all)	3	4	
Memory impairment			
subjects affected / exposed	0 / 5 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Headache			
subjects affected / exposed	1 / 5 (20.00%)	4 / 30 (13.33%)	
occurrences (all)	2	6	
Restless legs syndrome			
subjects affected / exposed	0 / 5 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Syncope			
subjects affected / exposed	1 / 5 (20.00%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 5 (0.00%)	8 / 30 (26.67%)	
occurrences (all)	0	8	
Neutropenia			
subjects affected / exposed	0 / 5 (0.00%)	11 / 30 (36.67%)	
occurrences (all)	0	18	

Anaemia			
subjects affected / exposed	0 / 5 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Leukopenia			
subjects affected / exposed	0 / 5 (0.00%)	4 / 30 (13.33%)	
occurrences (all)	0	5	
Lymphopenia			
subjects affected / exposed	0 / 5 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	3	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 5 (0.00%)	6 / 30 (20.00%)	
occurrences (all)	0	6	
Eye disorders			
Vision blurred			
subjects affected / exposed	1 / 5 (20.00%)	2 / 30 (6.67%)	
occurrences (all)	1	2	
Visual impairment			
subjects affected / exposed	0 / 5 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Lacrimation increased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 5 (40.00%)	10 / 30 (33.33%)	
occurrences (all)	7	17	
Nausea			
subjects affected / exposed	2 / 5 (40.00%)	7 / 30 (23.33%)	
occurrences (all)	7	10	
Vomiting			
subjects affected / exposed	1 / 5 (20.00%)	4 / 30 (13.33%)	
occurrences (all)	3	4	
Constipation			
subjects affected / exposed	1 / 5 (20.00%)	2 / 30 (6.67%)	
occurrences (all)	1	3	
Flatulence			

subjects affected / exposed	0 / 5 (0.00%)	3 / 30 (10.00%)	
occurrences (all)	0	4	
Abdominal distension			
subjects affected / exposed	0 / 5 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Abdominal pain			
subjects affected / exposed	0 / 5 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Abdominal pain upper			
subjects affected / exposed	0 / 5 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	3	
Colitis			
subjects affected / exposed	0 / 5 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Gastritis			
subjects affected / exposed	0 / 5 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Diverticulum intestinal			
subjects affected / exposed	1 / 5 (20.00%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 5 (0.00%)	8 / 30 (26.67%)	
occurrences (all)	0	12	
Rash maculo-papular			
subjects affected / exposed	2 / 5 (40.00%)	3 / 30 (10.00%)	
occurrences (all)	2	4	
Pruritus			
subjects affected / exposed	0 / 5 (0.00%)	4 / 30 (13.33%)	
occurrences (all)	0	5	
Dry skin			
subjects affected / exposed	0 / 5 (0.00%)	3 / 30 (10.00%)	
occurrences (all)	0	3	
Ecchymosis			
subjects affected / exposed	0 / 5 (0.00%)	3 / 30 (10.00%)	
occurrences (all)	0	3	

Night sweats			
subjects affected / exposed	0 / 5 (0.00%)	3 / 30 (10.00%)	
occurrences (all)	0	3	
Skin lesion			
subjects affected / exposed	0 / 5 (0.00%)	3 / 30 (10.00%)	
occurrences (all)	0	3	
Petechiae			
subjects affected / exposed	0 / 5 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Skin exfoliation			
subjects affected / exposed	0 / 5 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	4	
Dermatitis allergic			
subjects affected / exposed	1 / 5 (20.00%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 5 (20.00%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 5 (20.00%)	7 / 30 (23.33%)	
occurrences (all)	1	9	
Arthralgia			
subjects affected / exposed	0 / 5 (0.00%)	4 / 30 (13.33%)	
occurrences (all)	0	6	
Muscle spasms			
subjects affected / exposed	0 / 5 (0.00%)	3 / 30 (10.00%)	
occurrences (all)	0	4	
Flank pain			
subjects affected / exposed	1 / 5 (20.00%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Myalgia			
subjects affected / exposed	1 / 5 (20.00%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Osteoarthritis			

subjects affected / exposed	0 / 5 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Pain in extremity			
subjects affected / exposed	0 / 5 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Spinal pain			
subjects affected / exposed	0 / 5 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Groin pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 5 (0.00%)	10 / 30 (33.33%)	
occurrences (all)	0	19	
Upper respiratory tract infection			
subjects affected / exposed	2 / 5 (40.00%)	7 / 30 (23.33%)	
occurrences (all)	11	9	
Bronchitis			
subjects affected / exposed	0 / 5 (0.00%)	6 / 30 (20.00%)	
occurrences (all)	0	8	
Sinusitis			
subjects affected / exposed	0 / 5 (0.00%)	4 / 30 (13.33%)	
occurrences (all)	0	5	
Influenza			
subjects affected / exposed	1 / 5 (20.00%)	2 / 30 (6.67%)	
occurrences (all)	1	2	
Pneumonia			
subjects affected / exposed	0 / 5 (0.00%)	3 / 30 (10.00%)	
occurrences (all)	0	4	
Urinary tract infection			
subjects affected / exposed	0 / 5 (0.00%)	3 / 30 (10.00%)	
occurrences (all)	0	4	
Conjunctivitis			
subjects affected / exposed	0 / 5 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	

Cystitis			
subjects affected / exposed	0 / 5 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Cytomegalovirus infection			
subjects affected / exposed	0 / 5 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Cytomegalovirus infection reactivation			
subjects affected / exposed	0 / 5 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Febrile infection			
subjects affected / exposed	1 / 5 (20.00%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Fungal infection			
subjects affected / exposed	0 / 5 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Herpes virus infection			
subjects affected / exposed	0 / 5 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	7	
Herpes zoster			
subjects affected / exposed	1 / 5 (20.00%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Oral pustule			
subjects affected / exposed	1 / 5 (20.00%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 5 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	3	
Hyperkalaemia			
subjects affected / exposed	0 / 5 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	4	
Hyperuricaemia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 30 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 August 2016	• Update to benefit-risk assessment to include data on adverse events (AEs) that occurred in the idelalisib + obinutuzumab treatment arm of Study GS-US-312-0118 • Update to dose rationale for the combination treatment • Addition of weekly clinic visits and lab monitoring for the first 28 days of treatment • Inclusion of statement specifying that results from the safety cohort was provided to BfArM • Specification of safety monitoring throughout the duration of the study • Clarification that restaging radiologic evaluation was limited to affected areas identified at the time of the screening evaluation • Inclusion of statement that imaging assessments are in accordance with European Society for Medical Oncology (ESMO) guidelines • Update to instructions for safety reporting to clarify that serious adverse events (SAEs), regardless of cause or relationship, was reported from the time of informed consent throughout the duration of the trial, which is inclusive of the post-treatment period
16 September 2016	• Replaced idelalisib 50 mg twice daily (BID) with 100 mg once daily dosing regimen and updated the dose rationale language accordingly • Added requirement for evaluation for gastrointestinal events/colitis in alignment with updated idelalisib safety information • Revised dose adjustment guidelines and requirements in alignment with updated idelalisib safety information
24 August 2017	• Further enrollment into Arm A was discontinued. All additional participants were enrolled to Arm B. A total of approximately 6 participants were enrolled in Arm A and 30 participants in Arm B, thus the total sample size for the study was reduced from 60 participants to approximately 36 participants • The requirement for a bone marrow biopsy at Week 25 was limited to participants who otherwise would meet criteria for a CR or complete remission with incomplete bone marrow recovery (CRi). For participants without radiographic evidence of disease at screening, a bone marrow biopsy including aspirate was required at screening. In the presence of systemic disease, the bone marrow result was only critical for assessing a complete remission or progressive disease per International Workshop on Chronic Lymphocytic Leukemia (IWCLL) 2008 guidelines. As bone marrow evaluation in the case of progressive disease was performed only when clinical progression was suspected, the scheduled bone marrow assessment was only necessary to evaluate patients who did not have a radiographically evident change in disease assessment. This change did not preclude investigator assessment of disease response per IWCLL 2008 criteria and should decrease the burden of bone marrow biopsies to the overall cohort of participants enrolled.
15 January 2019	• The post treatment follow up period was removed. All subjects completed the study at the End of Treatment visit, or at the Week 25 visit, should treatment have discontinued prior to Week 25 • Based on ongoing study data that indicate minimal residual disease (MRD) negativity may be achieved post Week 25, additional exploratory endpoints were added to allow for analysis at later time points
19 November 2019	• The risk of progressive multifocal leukoencephalopathy was added as discontinuation and dose interruption criteria
28 May 2020	• The risk of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) was added as per Company Core Data Sheet (CCDS), the Idealisib IB edition 21 dated 02-Apr-2020 was updated to reflect this new information

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported