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 Entospletinib With and Without Obinutuzumab in Subjects With Chronic Lymphocytic Leukemia

Summary

EudraCT number	2016-002768-15
Trial protocol	DE
Global end of trial date	01 October 2020

Results information

Result version number	v1 (current)
This version publication date	16 October 2021
First version publication date	16 October 2021

Trial information

Trial identification

Sponsor protocol code	GS-US-401-2076

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02983617
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	01 October 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 February 2019
Global end of trial reached?	Yes
Global end of trial date	01 October 2020
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 (formerly GS-4059) and entospletinib with obinutuzumab in adults with relapsed or refractory 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	06 April 2017
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: 36
Worldwide total number of subjects	36
EEA total number of subjects	36

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	21
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in Germany. The first participant was screened on 06 April 2017. The last study visit occurred on 01 October 2020.

Pre-assignment

Screening details:

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

Arm description:

Tirabrutinib 80 mg (4 x 20 mg tablets/2 x 40 mg tablets/1 x 80 mg tablet) orally once daily + entospletinib 400 mg (2 x 200 mg tablets) orally once daily for up to 104 weeks.

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

Dosage and administration details:

80 mg administered once daily

Investigational medicinal product name	Entospletinib
Investigational medicinal product code	
Other name	GS-9973
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

400 mg administered once daily

Arm title	Tirabrutinib + Entospletinib + Obinutuzumab

Arm description:

Tirabrutinib 80 mg (4 x 20 mg tablets/ 2 x 40 mg tablets/ 1 x 80 mg tablet) orally once daily + entospletinib 400 mg (2 x 200 mg tablets) 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 on Day 1 of Weeks 2, 3, 5, 9, 13, 17 and 21.

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

Dosage and administration details:

80 mg administered once daily

Investigational medicinal product name	Entospletinib
Investigational medicinal product code	
Other name	GS-9973
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:
400 mg administered once daily

Investigational medicinal product name	Obinutuzumab
Investigational medicinal product code	
Other name	Gazyvaro®, Gazyva®, GA101
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:
100 mg, 900 mg, and 1000 mg administered over 21 weeks

Number of subjects in period 1	Tirabrutinib + Entospletinib	Tirabrutinib + Entospletinib + Obinutuzumab
Started	6	30
Completed	6	21
Not completed	0	9
Adverse Event	-	7
Death	-	1
Investigator`s Discretion	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Tirabrutinib + Entospletinib
Reporting group description:	
Tirabrutinib 80 mg (4 x 20 mg tablets/2 x 40 mg tablets/1 x 80 mg tablet) orally once daily + entospletinib 400 mg (2 x 200 mg tablets) orally once daily for up to 104 weeks.	
Reporting group title	Tirabrutinib + Entospletinib + 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 + entospletinib 400 mg (2 x 200 mg tablets) 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 on Day 1 of Weeks 2, 3, 5, 9, 13, 17 and 21.	

Reporting group values	Tirabrutinib + Entospletinib	Tirabrutinib + Entospletinib + Obinutuzumab	Total
Number of subjects	6	30	36
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	61	67	
standard deviation	± 8.3	± 9.9	-
Gender categorical			
Units: Subjects			
Female	2	7	9
Male	4	23	27
Ethnicity			
Not Permitted = local regulators did not allow collection of ethnicity information.			
Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	4	29	33
Not Permitted	2	1	3
Race			
Not Permitted = local regulators did not allow collection of race information.			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Black	0	0	0
Native Hawaiian or Pacific Islander	0	0	0
White	4	29	33
Other	0	0	0
Not Permitted	2	1	3

End points

End points reporting groups

Reporting group title	Tirabrutinib + Entospletinib
Reporting group description:	
Tirabrutinib 80 mg (4 x 20 mg tablets/2 x 40 mg tablets/1 x 80 mg tablet) orally once daily + entospletinib 400 mg (2 x 200 mg tablets) orally once daily for up to 104 weeks.	

Reporting group title	Tirabrutinib + Entospletinib + 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 + entospletinib 400 mg (2 x 200 mg tablets) 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 on Day 1 of Weeks 2, 3, 5, 9, 13, 17 and 21.	

Primary: Rate of Complete Remission/Complete Remission with Incomplete Recovery of the Bone Marrow (CR/CRi), as Assessed by Investigator Using Modified International Workshop on Chronic Lymphocytic Leukemia (IWCLL) 2008 Criteria at Week 25

End point title	Rate of Complete Remission/Complete Remission with Incomplete Recovery of the Bone Marrow (CR/CRi), 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 lymphoidnodules), persistent anemia/thrombocytopenia/neutropenia unrelated to CLL but related to drug toxicity. 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 + Entospletinib	Tirabrutinib + Entospletinib + Obinutuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	30		
Units: percentage of participants				
number (confidence interval 90%)	0 (0 to 39.3)	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 was defined as percentage of participants who achieved CR/CRi per modified IWCLL 2008 criteria and also achieved BM MRD negativity at Week 25. CR, CRi: meeting all the criteria that have been defined in end point 1. 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 this threshold. Participants in the Full Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Week 25

End point values	Tirabrutinib + Entospletinib	Tirabrutinib + Entospletinib + Obinutuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	30		
Units: percentage of participants				
number (confidence interval 90%)	0 (0 to 39.3)	3.3 (0.2 to 14.9)		

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 was defined as the percentage of participants who achieved CR/CRi per modified IWCLL 2008 criteria and also achieved PB MRD negativity at Week 25. CR, CRi: meeting all the criteria that have been defined in end point 1. 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 + Entospletinib	Tirabrutinib + Entospletinib + Obinutuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	30		
Units: percentage of participants				
number (confidence interval 90%)	0 (0 to 39.3)	3.3 (0.2 to 14.9)		

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 end point 1. 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 + Entospletinib	Tirabrutinib + Entospletinib + Obinutuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	30		
Units: percentage of participants				
number (confidence interval 90%)	100.0 (60.7 to 100.0)	90.0 (76.1 to 97.2)		

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:

A treatment emergent AE is defined as an AE that occurs or worsens in severity on or after the date of the first dose of study drug but no later than 30 days after the permanent discontinuation of study drug or an AE 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. 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: 105.9 weeks) plus 30 days

End point values	Tirabrutinib + Entospletinib	Tirabrutinib + Entospletinib + Obinutuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	30		
Units: percentage of participants				
number (not applicable)				
Any Treatment-Emergent AEs	100.0	100.0		
Treatment-Emergent SAEs	16.7	50.0		

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: 105.9 weeks) plus 30 days;
All-Cause Mortality: Enrollment up to 42 months

Adverse event reporting additional description:

Adverse Events: Safety Analysis Set included all randomized or enrolled participants who received at least 1 dose of any study drug;
All-cause mortality: 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 + Entospletinib + 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 + entospletinib 400 mg (2 x 200 mg tablets) 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 on Day 1 of Weeks 2, 3, 5, 9, 13, 17 and 21.

Reporting group title	Tirabrutinib + Entospletinib

Reporting group description:

Tirabrutinib 80 mg (4 x 20 mg tablets/2 x 40 mg tablets/1 x 80 mg tablet) orally once daily + entospletinib 400 mg (2 x 200 mg tablets) orally once daily for up to 104 weeks.

Serious adverse events	Tirabrutinib + Entospletinib + Obinutuzumab	Tirabrutinib + Entospletinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 30 (50.00%)	1 / 6 (16.67%)	
number of deaths (all causes)	4	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural haemorrhage			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			

subjects affected / exposed	1 / 30 (3.33%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	1 / 30 (3.33%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 30 (3.33%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 30 (3.33%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	1 / 30 (3.33%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			

subjects affected / exposed	1 / 30 (3.33%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 30 (3.33%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Pemphigoid			
subjects affected / exposed	1 / 30 (3.33%)	0 / 6 (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			
Renal impairment			
subjects affected / exposed	1 / 30 (3.33%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral caruncle			
subjects affected / exposed	1 / 30 (3.33%)	0 / 6 (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			
Pneumonia			

subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	3 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Covid-19 pneumonia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonsillitis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	1 / 30 (3.33%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 30 (3.33%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Tirabrutinib + Entospletinib + Obinutuzumab	Tirabrutinib + Entospletinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 30 (96.67%)	6 / 6 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Richter's syndrome			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Vascular disorders			
Haematoma			
subjects affected / exposed	6 / 30 (20.00%)	2 / 6 (33.33%)	
occurrences (all)	9	2	
Hypotension			
subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	10 / 30 (33.33%)	2 / 6 (33.33%)	
occurrences (all)	11	4	
Pyrexia			
subjects affected / exposed	10 / 30 (33.33%)	1 / 6 (16.67%)	
occurrences (all)	22	7	
Chills			
subjects affected / exposed	7 / 30 (23.33%)	0 / 6 (0.00%)	
occurrences (all)	9	0	
Oedema peripheral			
subjects affected / exposed	6 / 30 (20.00%)	1 / 6 (16.67%)	
occurrences (all)	6	1	
Asthenia			
subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Chest pain			
subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	3	0	

Mucosal inflammation			
subjects affected / exposed	1 / 30 (3.33%)	1 / 6 (16.67%)	
occurrences (all)	2	2	
Impaired healing			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Erectile dysfunction			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	9 / 30 (30.00%)	1 / 6 (16.67%)	
occurrences (all)	11	1	
Oropharyngeal pain			
subjects affected / exposed	1 / 30 (3.33%)	1 / 6 (16.67%)	
occurrences (all)	1	2	
Pleural effusion			
subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	4 / 30 (13.33%)	0 / 6 (0.00%)	
occurrences (all)	6	0	
Lipase increased			
subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Immunoglobulins decreased			

subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Platelet count decreased			
subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Weight increased			
subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Blood glucose increased			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Haemoglobin urine present			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Red blood cells urine positive			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	2	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	4 / 30 (13.33%)	0 / 6 (0.00%)	
occurrences (all)	4	0	
Arthropod bite			
subjects affected / exposed	3 / 30 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Contusion			
subjects affected / exposed	1 / 30 (3.33%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Cardiac disorders			
Palpitations			
subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Tachycardia			
subjects affected / exposed	1 / 30 (3.33%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Aortic valve incompetence			

subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 30 (10.00%)	1 / 6 (16.67%)	
occurrences (all)	3	4	
Headache			
subjects affected / exposed	6 / 30 (20.00%)	1 / 6 (16.67%)	
occurrences (all)	7	2	
Polyneuropathy			
subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Paraesthesia			
subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	4	0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	14 / 30 (46.67%)	0 / 6 (0.00%)	
occurrences (all)	28	0	
Anaemia			
subjects affected / exposed	3 / 30 (10.00%)	1 / 6 (16.67%)	
occurrences (all)	3	2	
Leukopenia			
subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Thrombocytopenia			
subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Tinnitus			
subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Eye disorders			

Conjunctival haemorrhage			
subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	9 / 30 (30.00%)	2 / 6 (33.33%)	
occurrences (all)	16	4	
Diarrhoea			
subjects affected / exposed	7 / 30 (23.33%)	1 / 6 (16.67%)	
occurrences (all)	15	8	
Constipation			
subjects affected / exposed	8 / 30 (26.67%)	0 / 6 (0.00%)	
occurrences (all)	9	0	
Flatulence			
subjects affected / exposed	3 / 30 (10.00%)	1 / 6 (16.67%)	
occurrences (all)	3	1	
Vomiting			
subjects affected / exposed	5 / 30 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	5	0	
Abdominal pain			
subjects affected / exposed	3 / 30 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Gastritis			
subjects affected / exposed	3 / 30 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Abdominal pain upper			
subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Dry mouth			
subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	5	0	
Dyspepsia			
subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorder			

subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Stomatitis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	5 / 30 (16.67%)	2 / 6 (33.33%)	
occurrences (all)	6	2	
Pruritus			
subjects affected / exposed	5 / 30 (16.67%)	1 / 6 (16.67%)	
occurrences (all)	5	1	
Night sweats			
subjects affected / exposed	3 / 30 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Petechiae			
subjects affected / exposed	3 / 30 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Urticaria			
subjects affected / exposed	3 / 30 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Eczema			
subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Rash papular			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Purpura			
subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	4 / 30 (13.33%)	2 / 6 (33.33%)	
occurrences (all)	5	5	
Arthralgia			
subjects affected / exposed	4 / 30 (13.33%)	0 / 6 (0.00%)	
occurrences (all)	6	0	
Muscle spasms			
subjects affected / exposed	3 / 30 (10.00%)	1 / 6 (16.67%)	
occurrences (all)	3	1	
Pain in extremity			
subjects affected / exposed	4 / 30 (13.33%)	0 / 6 (0.00%)	
occurrences (all)	4	0	
Neck pain			
subjects affected / exposed	3 / 30 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	4	0	
Musculoskeletal pain			
subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Osteoarthritis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Osteoporotic fracture			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	10 / 30 (33.33%)	4 / 6 (66.67%)	
occurrences (all)	20	8	
Oral herpes			
subjects affected / exposed	5 / 30 (16.67%)	2 / 6 (33.33%)	
occurrences (all)	6	5	
Urinary tract infection			
subjects affected / exposed	6 / 30 (20.00%)	1 / 6 (16.67%)	
occurrences (all)	11	1	
Bronchitis			

subjects affected / exposed	6 / 30 (20.00%)	0 / 6 (0.00%)	
occurrences (all)	8	0	
Upper respiratory tract infection			
subjects affected / exposed	3 / 30 (10.00%)	1 / 6 (16.67%)	
occurrences (all)	3	1	
Sinusitis			
subjects affected / exposed	3 / 30 (10.00%)	1 / 6 (16.67%)	
occurrences (all)	3	1	
Herpes virus infection			
subjects affected / exposed	2 / 30 (6.67%)	1 / 6 (16.67%)	
occurrences (all)	3	1	
Gastroenteritis			
subjects affected / exposed	1 / 30 (3.33%)	2 / 6 (33.33%)	
occurrences (all)	1	3	
Herpes zoster			
subjects affected / exposed	3 / 30 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Pneumonia			
subjects affected / exposed	3 / 30 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	4	0	
Conjunctivitis			
subjects affected / exposed	1 / 30 (3.33%)	1 / 6 (16.67%)	
occurrences (all)	1	2	
Cystitis			
subjects affected / exposed	1 / 30 (3.33%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Periodontitis			
subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Rhinitis			
subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Folliculitis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Respiratory tract infection			

subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Root canal infection			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Folate deficiency			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Hypertriglyceridaemia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 November 2016	• Added study flow chart to reflect stratification by mutation, treatment of an early safety cohort, and review of 28-day safety data from the safety cohort by the Safety Review Team (SRT) • Included additional details on sample size determination • Incorporated recommendations from the Summary of Product Characteristics (SmPC) for Gazyvaro® (obinutuzumab) in the event of suspicion of progressive multifocal leukoencephalopathy (PML)
02 February 2017	• Updated entospletinib formulation information • Revised the recommendations for concomitant medications with entospletinib • Updated the study procedures for CLL immunophenotyping at disease progression
24 August 2017	• Further enrollment into Arm A was discontinued. All additional subjects were enrolled to Arm B. A total of approximately 6 subjects were enrolled in Arm A and 30 subjects in Arm B, thus the total sample size for the study was reduced from 60 subjects to approximately 36 subjects. • As of 07 June 2017, 10 subjects with CLL were treated on Phase 1b Study GS-US-401-1757 with the combination of tirabrutinib and entospletinib with a median exposure of 43 weeks (range: 18-55). All 10 subjects continued on study and treatment however no CLL subjects have achieved a complete remission (CR). Given the lack of CRs seen in the ongoing treatment experience with the combination of tirabrutinib and entospletinib and the primary endpoint of CR in this protocol (GS-US-401-2076), with Amendment 3, enrollment into the doublet combination of tirabrutinib and entospletinib without obinutuzumab was discontinued. Arm B continued enrollment as the safety and preliminary efficacy of the combination with the addition of obinutuzumab retained the potential to be safe and achieve a high rate and depth of response. • The requirement for a bone marrow biopsy at Week 25 was limited to subjects who otherwise would meet criteria for a CR or complete remission with incomplete bone marrow recovery (CRi). For subjects 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 a critical study for assessing a complete remission or progressive disease per IWCLL 2008 guidelines. As evaluation of the bone marrow in the case of progressive disease was performed only when clinical progression was suspected, the scheduled bone marrow assessment was only necessary to evaluate subjects who do not have radiographically evident disease. This change did not impact disease response assessment and should decrease the burden of bone marrow biopsies at the cohort level.

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. • The primary endpoint of complete remission (CR) and secondary endpoints of rate of CR with bone marrow minimal residual disease (MRD) negativity (CR/BM MRD-) and the rate of CR with MRD negativity (<10-4) in peripheral blood (CR/PB MRD-) at Week 25 were not met, based on data from the ongoing study with the combination of tirabrutinib, entospletinib and obinutuzumab. Therefore, post-treatment disease assessments were no longer conducted. • Based on ongoing study data that indicate MRD negativity may be achieved post Week 25, additional exploratory endpoints were added to allow for analysis at later time points. • The lots of tirabrutinib 20 mg tablets expired in Feb 2020 and it was unknown if the shelf-life was extended, therefore the 20 mg tablets were replaced with 40 mg tablets. Data supporting the tablet formulation was contained within the protocol and supporting documents.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported