Clinical trial results:
A Phase 1b-2, Open-Label, Dose Escalation and Expansion Study Evaluating the Safety and Efficacy of Entospletinib (ENTO [GS-9973]) combined with Vincristine (VCR) in Adult Subjects with Relapsed or Refractory B-cell Non-Hodgkin Lymphoma (NHL)

Summary

EudraCT number	2015-002731-17
Trial protocol	HU GB ES
Global end of trial date	22 June 2017

Results information

Result version number	v1 (current)
This version publication date	06 July 2018
First version publication date	06 July 2018

Trial information

Trial identification

Sponsor protocol code	GS-US-339-1562

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02568683
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	22 June 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 October 2016
Global end of trial reached?	Yes
Global end of trial date	22 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial was to evaluate the safety of entospletinib (ENTO) with vincristine (VCR) in adults with relapsed or refractory B-cell non-Hodgkin lymphoma (NHL).

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	11 February 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	France: 6
Country: Number of subjects enrolled	United States: 4
Worldwide total number of subjects	10
EEA total number of subjects	6

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)	4
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in the United States and France. The first participant was screened on 11 February 2016. The last study visit occurred on 22 June 2017.

Pre-assignment

Screening details:

13 participants were screened.

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	ENTO 200 mg

Arm description:

ENTO 200 mg + VCR

Arm type	Experimental
Investigational medicinal product name	Entospletinib
Investigational medicinal product code	
Other name	GS-9973, ENTO
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

200 mg tablet administered orally twice daily under fasted conditions

Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	VCR
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1.0 mg/m^2 administered via intravenous infusion every 14 days

Arm title	ENTO 400 mg

Arm description:

ENTO 400 mg + VCR

Arm type	Experimental
Investigational medicinal product name	Entospletinib
Investigational medicinal product code	
Other name	GS-9973, ENTO
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

400 mg tablet administered orally twice daily under fasted conditions

Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	VCR
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1.0 mg/m^2 administered via intravenous infusion every 14 days

Number of subjects in period 1	ENTO 200 mg	ENTO 400 mg
Started	6	4
Completed	0	0
Not completed	6	4
Withdrew Consent	1	-
Study Terminated By Sponsor	5	2
Death	-	2

Baseline characteristics

Reporting groups	
Reporting group title	ENTO 200 mg
Reporting group description: ENTO 200 mg + VCR	
Reporting group title	ENTO 400 mg
Reporting group description: ENTO 400 mg + VCR	

Reporting group values	ENTO 200 mg	ENTO 400 mg	Total
Number of subjects	6	4	10
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	62	69	
standard deviation	± 13.6	± 8.1	-
Gender categorical Units: Subjects			
Female	3	1	4
Male	3	3	6
Race Units: Subjects			
White	4	1	5
Not Permitted	2	3	5
Ethnicity Units: Subjects			
Not Hispanic or Latino	4	1	5
Not Permitted	2	3	5

End points

End points reporting groups

Reporting group title	ENTO 200 mg
Reporting group description: ENTO 200 mg + VCR	
Reporting group title	ENTO 400 mg
Reporting group description: ENTO 400 mg + VCR	

Primary: Occurrence of adverse events and laboratory abnormalities defined as dose limiting toxicities (DLTs) for ENTO in combination with VCR in participants in the dose escalation stage with relapsed or refractory B-cell NHL

End point title	Occurrence of adverse events and laboratory abnormalities defined as dose limiting toxicities (DLTs) for ENTO in combination with VCR in participants in the dose escalation stage with relapsed or refractory B-cell NHL[1]

End point description:

DLT Analysis Set: participants in the Full Analysis Set (participants receiving at least 1 dose of ENTO) who received 37 of 56 Cycle 1 doses of ENTO for dose level 1-4 and completed the full Cycle 1 dose of VCR or who experienced a DLT during the DLT assessment window.

End point type	Primary

End point timeframe:

Up to 28 days

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	ENTO 200 mg	ENTO 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	3		
Units: participants				
number (not applicable)	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of adverse events and laboratory abnormalities not defined as DLTs for ENTO with VCR in participants in the dose escalation stage with relapsed or refractory B-cell NHL

End point title	Occurrence of adverse events and laboratory abnormalities not defined as DLTs for ENTO with VCR in participants in the dose escalation stage with relapsed or refractory B-cell NHL

End point description:

Participants in the Full Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Up to 28 days

End point values	ENTO 200 mg	ENTO 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	4		
Units: participants				
number (not applicable)				
AEs not defined as DLTs	6	4		
Lab abnormalities not defined as DLTs	5	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Exposure to Entospletinib

End point title	Duration of Exposure to Entospletinib

End point description:

Participants in the Full Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Baseline to End of Study (maximum: 24 weeks)

End point values	ENTO 200 mg	ENTO 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	4		
Units: weeks				
arithmetic mean (standard deviation)	17.7 (± 6.09)	4.3 (± 2.68)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Exposure to Vincristine

End point title	Duration of Exposure to Vincristine

End point description:

Participants in the Full Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Baseline to End of Study (maximum: 24 weeks)

End point values	ENTO 200 mg	ENTO 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	4		
Units: doses				
arithmetic mean (standard deviation)	8.7 (± 3.27)	2.3 (± 1.50)		

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 exposure: 200 mg ENTO = 24 weeks; 400 mg ENTO = 8 weeks). Any adverse events or deaths occurring outside of this time frame were not included.

Adverse event reporting additional description:

Safety Analysis Set: all participants who received at least 1 dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20

Reporting groups

Reporting group title	ENTO 200 mg

Reporting group description:

ENTO 200 mg + VCR

Reporting group title	ENTO 400 mg

Reporting group description:

ENTO 400 mg + VCR

Serious adverse events	ENTO 200 mg	ENTO 400 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 6 (16.67%)	1 / 4 (25.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (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			
Sinus pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	ENTO 200 mg	ENTO 400 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	4 / 4 (100.00%)	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 4 (25.00%)	
occurrences (all)	1	1	
Fatigue			
subjects affected / exposed	2 / 6 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Feeling drunk			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Ill-defined disorder			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Malaise			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Oedema peripheral			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	2 / 6 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Hiccups			

subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Rhinorrhoea			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Confusional state			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Mental status changes			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 6 (16.67%)	1 / 4 (25.00%)	
occurrences (all)	2	1	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 6 (16.67%)	1 / 4 (25.00%)	
occurrences (all)	2	1	
Weight decreased			
subjects affected / exposed	1 / 6 (16.67%)	1 / 4 (25.00%)	
occurrences (all)	1	1	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Blood creatinine increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Gamma-glutamyltransferase increased			

subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Dehydration			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Disturbance in attention			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Hypoaesthesia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Neuropathy peripheral			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Paraesthesia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Neutropenia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 6 (50.00%)	1 / 4 (25.00%)	
occurrences (all)	3	1	
Nausea			
subjects affected / exposed	2 / 6 (33.33%)	2 / 4 (50.00%)	
occurrences (all)	2	2	
Abdominal pain upper			

subjects affected / exposed	2 / 6 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Constipation			
subjects affected / exposed	1 / 6 (16.67%)	1 / 4 (25.00%)	
occurrences (all)	1	1	
Abdominal pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Dysphagia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Ileus			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Odynophagia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Night sweats			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Urticaria			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Pollakiuria			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			

Arthralgia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 4 (0.00%) 0	
Groin pain subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 4 (0.00%) 0	
Musculoskeletal pain subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 4 (0.00%) 0	
Pain in extremity subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 4 (0.00%) 0	
Infections and infestations Sepsis subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 4 (25.00%) 1	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 4 (25.00%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 August 2015	Revision of the scan frequency during the long term follow-up to align with European Society for Medical Oncology (ESMO) guidelines for follow-up of subjects with diffuse large B-cell lymphoma
15 October 2015	Updated inclusion criterion for acute toxic effects and added text regarding excluded medications
18 February 2016	• Revised study title to include full name of Entospletinib as well as addition of "relapsed or refractory B-cell" • Standardized dose escalation levels and dose expansion cohort wording • Removed language regarding R-CHOP, EPOCH, their components, and combination therapy references • Updated number of subjects participating in the study

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
22 June 2017	Upon review of the clinical data, Gilead decided not to proceed with the dose expansion stage given the minimal treatment effect observed, and the study was terminated. This decision was not based upon any safety concerns.	-

Notes:

Limitations and caveats

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

Because the study was terminated after enrolling only 10 subjects, the planned efficacy analyses were not conducted.

Notes: