Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of IPI-145 in Combination with Rituximab vs Rituximab in Subjects with Previously-Treated Follicular Lymphoma

Summary

EudraCT number	2013-002406-31
Trial protocol	IT GB HU ES BE AT PL DE DK
Global end of trial date	05 October 2016

Results information

Result version number	v1
This version publication date	19 October 2017
First version publication date	19 October 2017

Trial information

Trial identification

Sponsor protocol code	IPI-145-08

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1158-1596
Other trial identifiers	IND Number: 112,486

Notes:

Sponsors

Sponsor organisation name	Infinity Pharmaceuticals, Inc.
Sponsor organisation address	780 Memorial Drive, Cambridge, MA, United States, 02139
Public contact	Brenda Jeglinski, Verastem, Inc., 001 781 292 4200, bjeglinski@verastem.com
Scientific contact	Brenda Jeglinski, Verastem, Inc., 001 781 292 4200, bjeglinski@verastem.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	21 December 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 October 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

to evaluate the efficacy of duvelisib (IPI-145) administered in combination with rituximab (D+R) vs placebo in combination with rituximab (PBO+R) in subjects with previously-treated CD20-positive follicular lymphoma (FL)

Protection of trial subjects:

Prior to screening for enrollment into the clinical trial, all patients were provided detailed information about the investigational product and the trial. During the informed consent process, patients were allowed to ask questions and have a conversation with the study staff providing consent. The informed consent form (ICF) included all elements required by ICH, GCP, and adhered to the IRB/IEC requirements and the ethical principles that have their origin in the Declaration of Helsinki. It was explained to patients during this conversation that they have the right to withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. The ICF was updated when important new information became available, and all patients still receiving treatment in the trial were re-consented on the new information.

During the trial, protection of trial subjects took the form of adverse event and concomitant medication monitoring, and disease response monitoring. Adverse events (AEs) were monitored from the time of signing the ICF. The Protocol provided information on what concomitant medication and therapies were either not allowed or should be used with caution. An assessment of these medications and therapies was performed at every clinic visit. Lastly, disease response assessments were performed according to the scheduled stipulated in the Protocol. If a study subject progressed, appropriate conversations were had with their study investigator to determine the best course of action for further treatment or management of their disease, outside of the clinical trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 March 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	7 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 3
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	United States: 2
Country: Number of subjects enrolled	Australia: 1

Worldwide total number of subjects	13
EEA total number of subjects	9

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)	6
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening will be performed ≤30 days from randomization.

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Duvelisib 25 mg BID and Rituximab

Arm description:

IPI-145 (25 mg BID) administered orally in 28-day continuous treatment cycles + IV infusion of rituximab (375 mg/m2) once weekly for 4 weeks during Cycle 1, then once on Day 1 of Cycles 4, 6, 8, and 10.

Arm type	Experimental
Investigational medicinal product name	Duvelisib
Investigational medicinal product code	IPI-145
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The blinded study drug should be swallowed whole with a glass of water (approximately 8 ounces or 240 mL) at approximately the same time(s) each day.

Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Rituximab will be administered via infusion. Premedication consisting of an anti-pyretic and an antihistaminic should always be administered before each infusion of rituximab. Premedication with glucocorticoids should also be considered.

Arm title	Placebo and Rituximab

Arm description:

Matching Placebo administered orally in 28-day continuous treatment cycles + IV infusion of rituximab (375 mg/m2) once weekly for 4 weeks during Cycle 1, then once on Day 1 of Cycles 4, 6, 8, and 10.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The blinded study drug should be swallowed whole with a glass of water (approximately 8 ounces or 240 mL) at approximately the same time(s) each day.

Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Rituximab will be administered via infusion. Premedication consisting of an anti-pyretic and an antihistaminic should always be administered before each infusion of rituximab. Premedication with glucocorticoids should also be considered.

Number of subjects in period 1	Duvelisib 25 mg BID and Rituximab	Placebo and Rituximab
Started	6	7
Completed	2	0
Not completed	4	7
IP discontinuation due to SAE	1	-
Patient progression disease	-	1
Termination of Study by Sponsor	2	6
Patient deemed ineligible	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Duvelisib 25 mg BID and Rituximab
Reporting group description:	
IPI-145 (25 mg BID) administered orally in 28-day continuous treatment cycles + IV infusion of rituximab (375 mg/m2) once weekly for 4 weeks during Cycle 1, then once on Day 1 of Cycles 4, 6, 8, and 10.	
Reporting group title	Placebo and Rituximab
Reporting group description:	
Matching Placebo administered orally in 28-day continuous treatment cycles + IV infusion of rituximab (375 mg/m2) once weekly for 4 weeks during Cycle 1, then once on Day 1 of Cycles 4, 6, 8, and 10.	

Reporting group values	Duvelisib 25 mg BID and Rituximab	Placebo and Rituximab	Total
Number of subjects	6	7	13
Age categorical Units: Subjects			
Adults (18-64 years)	4	2	6
From 65-84 years	2	5	7
Age continuous Units: years			
arithmetic mean	62.7	65.4	
full range (min-max)	50 to 81	42 to 79	-
Gender categorical Units: Subjects			
Female	4	1	5
Male	2	6	8

End points

End points reporting groups

Reporting group title	Duvelisib 25 mg BID and Rituximab

Reporting group description:

IPI-145 (25 mg BID) administered orally in 28-day continuous treatment cycles + IV infusion of rituximab (375 mg/m2) once weekly for 4 weeks during Cycle 1, then once on Day 1 of Cycles 4, 6, 8, and 10.

Reporting group title	Placebo and Rituximab

Reporting group description:

Matching Placebo administered orally in 28-day continuous treatment cycles + IV infusion of rituximab (375 mg/m2) once weekly for 4 weeks during Cycle 1, then once on Day 1 of Cycles 4, 6, 8, and 10.

Primary: Death due to any cause

End point title	Death due to any cause[1]

End point description:

End point type	Primary

End point timeframe:

Throughout the study

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to the small number of evaluable subjects, the pre-planned analyses supporting the endpoints were not amenable to analyses.

End point values	Duvelisib 25 mg BID and Rituximab	Placebo and Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	7		
Units: Number of subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response Rate (ORR) - Partial response (PR)

End point title	Best Overall Response Rate (ORR) - Partial response (PR)

End point description:

ORR was performed based on investigator analyses

End point type	Secondary

End point timeframe:

Throughout the study

End point values	Duvelisib 25 mg BID and Rituximab	Placebo and Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	6		
Units: Number of subjects	2	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response Rate (ORR) - Complete response (CR)

End point title	Best Overall Response Rate (ORR) - Complete response (CR)

End point description:

ORR was performed based on investigator analyses

End point type	Secondary

End point timeframe:

Throughout the study

End point values	Duvelisib 25 mg BID and Rituximab	Placebo and Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	6		
Units: Number of subjects	3	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response Rate (ORR) - Stable disease (SD)

End point title	Best Overall Response Rate (ORR) - Stable disease (SD)

End point description:

ORR was performed based on investigator analyses

End point type	Secondary

End point timeframe:

Throughout the study

End point values	Duvelisib 25 mg BID and Rituximab	Placebo and Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	6		
Units: Number of subjects	0	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response Rate (ORR) - Progressive disease (PD)

End point title	Best Overall Response Rate (ORR) - Progressive disease (PD)

End point description:

ORR was performed based on investigator analyses

End point type	Secondary

End point timeframe:

Throughout the study

End point values	Duvelisib 25 mg BID and Rituximab	Placebo and Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	6		
Units: Number of subjects	0	2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For randomized subjects, AEs will be collected on the eCRF from signing of the ICF through 30 days after the final dose of either the blinded study drug or rituximab (whichever is later).

Adverse event reporting additional description:

The SAEs and AEs have been recorded until the data base lock. At this time, there were 2 subjects remaining on study. The SAEs covering the time from the data cut to the date of the last subject last visit in this study are included here as well.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Duvelisib 25 mg BID and Rituximab

Reporting group description:

IPI-145 (25 mg BID) administered orally in 28-day continuous treatment cycles + IV infusion of rituximab (375 mg/m2) once weekly for 4 weeks during Cycle 1, then once on Day 1 of Cycles 4, 6, 8, and 10.

Reporting group title	Placebo and Rituximab

Reporting group description:

Matching Placebo administered orally in 28-day continuous treatment cycles + IV infusion of rituximab (375 mg/m2) once weekly for 4 weeks during Cycle 1, then once on Day 1 of Cycles 4, 6, 8, and 10.

Serious adverse events	Duvelisib 25 mg BID and Rituximab	Placebo and Rituximab	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 6 (83.33%)	0 / 7 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	10 / 13	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal inflammation			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	10 / 13	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			

Interstitial lung disease			
subjects affected / exposed	2 / 6 (33.33%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	10 / 13	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	10 / 13	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	10 / 13	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	10 / 13	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 6 (50.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	10 / 13	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia cytomegaloviral			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	10 / 13	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Duvelisib 25 mg BID and Rituximab	Placebo and Rituximab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	7 / 7 (100.00%)	
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	2 / 6 (33.33%)	2 / 7 (28.57%)	
occurrences (all)	6	7	
Chest pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	6	7	
Oedema peripheral			
subjects affected / exposed	1 / 6 (16.67%)	1 / 7 (14.29%)	
occurrences (all)	6	7	
Pyrexia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 7 (14.29%)	
occurrences (all)	6	7	
Chills			
subjects affected / exposed	0 / 6 (0.00%)	2 / 7 (28.57%)	
occurrences (all)	6	7	
Fatigue			
subjects affected / exposed	0 / 6 (0.00%)	2 / 7 (28.57%)	
occurrences (all)	6	7	
Influenza like illness			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	6	7	
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease			
subjects affected / exposed	2 / 6 (33.33%)	0 / 7 (0.00%)	
occurrences (all)	6	7	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	6	7	
Cough			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	6	7	
Dyspnoea			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	6	7	
Hypoventilation			

subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	6	7	
Pneumonitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	6	7	
Respiratory failure			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	6	7	
Productive cough			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	6	7	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 6 (0.00%)	2 / 7 (28.57%)	
occurrences (all)	6	7	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 6 (50.00%)	0 / 7 (0.00%)	
occurrences (all)	6	7	
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 6 (50.00%)	0 / 7 (0.00%)	
occurrences (all)	6	7	
Amylase increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	6	7	
Blood cholesterol increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	6	7	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	6	7	
Lipase increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	6	7	
Weight decreased			

subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	6	7	
Blood uric acid increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	6	7	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 6 (0.00%)	2 / 7 (28.57%)	
occurrences (all)	6	7	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	6	7	
Hypoaesthesia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	6	7	
Balance disorder			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	6	7	
Sciatica			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	6	7	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	2 / 6 (33.33%)	0 / 7 (0.00%)	
occurrences (all)	6	7	
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	6	7	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 6 (16.67%)	1 / 7 (14.29%)	
occurrences (all)	6	7	
Abdominal pain upper			

subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	6	7	
Constipation			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	6	7	
Dysphagia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	6	7	
Gastrointestinal inflammation			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	6	7	
Mouth ulceration			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	6	7	
Nausea			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	6	7	
Abdominal distension			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	6	7	
Dry mouth			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	6	7	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	6	7	
Pruritus			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	6	7	
Skin discolouration			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	6	7	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	6	7	
Metatarsalgia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	6	7	
Muscle spasms			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	6	7	
Pain in extremity			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	6	7	
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 6 (33.33%)	0 / 7 (0.00%)	
occurrences (all)	6	7	
Gastroenteritis			
subjects affected / exposed	1 / 6 (16.67%)	1 / 7 (14.29%)	
occurrences (all)	6	7	
Pneumonia cytomegaloviral			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	6	7	
Bronchitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	6	7	
Bronchitis viral			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	6	7	
Nasopharyngitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	6	7	
Oral herpes			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	6	7	
Upper respiratory tract infection			

subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	6	7	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	6	7	
Hypertriglyceridaemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	6	7	
Hyperuricaemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	6	7	
Hypokalaemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	6	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
05 October 2016	This study was terminated early due to enrolment challenges. Two patients in Italy remained on study at the time of the data cut (05 October 2016) and were rolled over into the extension study IPI-145-23. The Last Subject Last Visit (LSLV) date for this trial was 03 March 2017. Due to the small number of evaluable subjects, many of the endpoints were not amenable to analyses. Only ORR and the safety analyses are available for this report.	-

Notes:

Limitations and caveats

None reported