Clinical trial results:
A Phase III, randomized, double-blind, multi-center, multi-national trial to evaluate efficacy and safety of BI 695500 versus rituximab as a first-line immunotherapy treatment in patients with low tumor burden follicular lymphoma

Summary

EudraCT number	2014-004544-36
Trial protocol	BE ES
Global end of trial date	07 December 2015

Results information

Result version number	v1 (current)
This version publication date	21 December 2016
First version publication date	21 December 2016

Trial information

Trial identification

Sponsor protocol code	1301.6

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02417129
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, +1 800 243 0127 , clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, +1 800 243 0127 , clintriage.rdg@boehringer-ingelheim.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	08 January 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 December 2015
Global end of trial reached?	Yes
Global end of trial date	07 December 2015
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 statistical equivalence of efficacy as assessed by Overall Response (measured as Overall Response Rate) at Week 30 for treatment with BI 695500 versus rituximab (Rituxan®) in patients with untreated low tumor burden follicular lymphoma (LTBFL).

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct. Rescue medication was allowed for all patients as required.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 April 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 2
Worldwide total number of subjects	2
EEA total number of subjects	0

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)	2
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

It was planned to randomize approximately 250 patients (125 in each treatment group). Actually two patients were randomized, an additional patient was enrolled but not randomized. Two patient were randomised to BI 695500, thus no patient was treated with rituximab in this trial.

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects attended specialist sites which would then ensure that the subject met all strictly implemented inclusion/exclusion criteria. Subjects were not to be randomised to trial treatment if any one of the specific entry criteria were violated.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Arm title	BI 695500

Arm description:

Patients received an infusion of 375 milligram (mg)/square meter (m2) of BI 695500 once a week intravenously for 4 weeks treatment. These 4 dosages were administered on Days 1, 8, 15, and 22 with 26 weeks follow-up.

Arm type	Experimental
Investigational medicinal product name	BI 695500
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients received an infusion of 375 milligram (mg)/square meter (m2) of BI 695500 once a week intravenously for 4 weeks treatment. These 4 dosages were administered on Days 1, 8, 15, and 22 with 26 weeks follow-up.

Number of subjects in period 1	BI 695500
Started	2
Completed	2

Baseline characteristics

Reporting groups	
Reporting group title	BI 695500
Reporting group description:	
Patients received an infusion of 375 milligram (mg)/square meter (m2) of BI 695500 once a week intravenously for 4 weeks treatment. These 4 dosages were administered on Days 1, 8, 15, and 22 with 26 weeks follow-up.	

Reporting group values	BI 695500	Total	
Number of subjects	2	2	
Age categorical Units: Subjects			
Age Continuous Units: Years			
arithmetic mean	45.5		
standard deviation	± 3.54	-	
Gender, Male/Female Units: Participants			
Female	2	2	
Male	0	0	

End points

End points reporting groups

Reporting group title	BI 695500

Reporting group description:

Patients received an infusion of 375 milligram (mg)/square meter (m2) of BI 695500 once a week intravenously for 4 weeks treatment. These 4 dosages were administered on Days 1, 8, 15, and 22 with 26 weeks follow-up.

Primary: Overall response measured as overall response rate (ORR) at week 30 for BI 695500 versus rituximab

End point title	Overall response measured as overall response rate (ORR) at week 30 for BI 695500 versus rituximab[1]

End point description:

The primary objective of this trial was to evaluate statistical equivalence of efficacy as assessed by Overall Response (measured as Overall Response Rate (ORR)) at Week 30 for treatment with BI 695500 versus rituximab (Rituxan®) in patients with untreated low tumor burden follicular lymphoma (LTBFL). The overall response measured as Overall Response Rate (ORR), which is the completed response (CR) and the partial response (PR) at Week 30, approximately 26 weeks after the completion of study treatment, as defined by International Working Group (IWG) criteria 2007 via an independent radiology assessment.
This endpoint was not summarized for arm ' rituximab ', as two patient were randomized and treated with BI 695500, whereas no patient was treated with rituximab in this trial.

End point type	Primary

End point timeframe:

From first administration of study medication until 30 weeks thereafter.

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: As the program was prematurely discontinued and only two patient were randomized and treated with BI 695500. No patient was treated with rituximab. Therefore comparisons cannot be made between treatment groups, thus the planned statistical analysis was not performed.

End point values	BI 695500			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: participants				
CR	0			
PR	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Extrapolated area under the concentration-time curve of BI 695500 or rituximab at steady state over the interval 0 hour (h) to the next dose of trial medication (AUC0-τ, ss)

End point title	Extrapolated area under the concentration-time curve of BI 695500 or rituximab at steady state over the interval 0 hour (h) to the next dose of trial medication (AUC0-τ, ss)

End point description:

Extrapolated area under the concentration-time curve of BI 695500 or rituximab in plasma at steady state over the interval 0 hour (h) to the next dose of trial medication (AUC0-τ, ss) establised by population pharmacokinetics.
This endpoint was not summarized for arm ' rituximab ', as two patient were randomized and treated with BI 695500, thus no patient was treated with rituximab in this trial. Therefore, no pharmacokinetic data analysis was performed.

End point type	Secondary

End point timeframe:

Sample timepoints Day 1, 8, 22, 23-24 (24-48 hours from start of Cycle 4 infusion), 24-26 (48-96 hours from start of Cycle 4 infusion), 26-36 (96-336 hours from start of Cycle 4 infusion), 78, 134, 204

End point values	BI 695500			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: NA				
number (not applicable)				

Notes:

[2] - As the program was prematurely discontinued and only two patients were randomized and treated.

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity at Week 30

End point title	Immunogenicity at Week 30

End point description:

Immunogenicity (rate of anti-drug antibodies) at Week 30 presented as the number of participants having Immunogenicity at Week 30.
This endpoint was not summarized for arm ' rituximab ', as two patient were randomized and treated with BI 695500, thus no patient was treated with rituximab in this trial.
As the program was prematurely discontinued and only two patients were randomized at the time of discontinuation, the planned statistical analysis was not performed.

End point type	Secondary

End point timeframe:

Day 204 or end of study

End point values	BI 695500			
Subject group type	Reporting group			
Number of subjects analysed	2[3]			
Units: participants				
number (not applicable)	0			

Notes:

[3] - Safety analysis set.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first administration of study medication until 26 weeks after last administration of study medication up to 204 days.

Adverse event reporting additional description:

When the program was prematurely discontinued only two patients were randomized to the arm "BI 695500". There were no patients included in the "Rituximab (US-licensed Rituxan)" arm. It is not possible to add an arm into the adverse event section by entering the number of patient "0" within this arm. Therefore this arm is not presented here.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	BI 695500

Reporting group description:

Patients received an infusion of 375 milligram (mg)/square meter (m2) of BI 695500 once a week intravenously for 4 weeks treatment. These 4 dosages were administered on Days 1, 8, 15, and 22 with 26 weeks follow-up.

Serious adverse events	BI 695500		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	BI 695500		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Nervous system disorders			
Headache			

subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	2		
Paraesthesia			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Feeling cold			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	2 / 2 (100.00%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 2 (100.00%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Infections and infestations			
Nasopharyngitis			

subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 February 2015	Title Page and Synopsis: Name of the Coordinating Investigator was corrected.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
08 September 2015	Program was terminated.	-

Notes:

Limitations and caveats

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

When the program was prematurely discontinued only 2 patients were randomized to the arm "BI 695500", no patient to the "Rituximab (US-licensed Rituxan)" arm. The planned statistical analysis was not performed.

Notes: