Clinical trial results:
An open label multicenter Phase Ib/II trial to determine the dose of BI 836826 in combination with gemcitabine and oxaliplatin (GemOx) and the efficacy of BI 836826-GemOx versus rituximab (R)- GemOx (R-GemOx) in patients with relapsed/ refractory diffuse large B-cell lymphoma (DLBCL) who are not eligible for, or have relapsed/progressed after autologous/allogeneic stem cell transplant

Summary

EudraCT number	2014-004794-16
Trial protocol	BE IT
Global end of trial date	16 March 2018

Results information

Result version number	v1
This version publication date	29 March 2019
First version publication date	29 March 2019

Trial information

Trial identification

Sponsor protocol code	1270.11

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02624492
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 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, +1 8002430127, 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	28 June 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 March 2018
Global end of trial reached?	Yes
Global end of trial date	16 March 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of Phase Ib of the trial was to investigate the maximum tolerated dose (MTD), safety and tolerability, pharmacokinetics (PK), and preliminary efficacy of BI 836826 in combination with GemOx in patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL).

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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 January 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	Belgium: 1
Country: Number of subjects enrolled	Italy: 20
Country: Number of subjects enrolled	Spain: 14
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)	22
From 65 to 84 years	12
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

This trial was designed to consist of 2 parts. First part was an open-label, non-randomised, Phase Ib dose-escalation trial according to a standard 3+3 design to determine the maximum tolerated dose (MTD) of BI 836286 in combination with gemcitabine and oxaliplatin. Second part of the trial, an open-label randomised Phase II, was not conducted.

Pre-assignment

Screening details:

All patients were screened for eligibility to participate in the trial. Patients attended specialist sites which would then ensure that they (the patients) met all inclusion/exclusion criteria. Patients were not to be randomized 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	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Open label trial

Arms

Are arms mutually exclusive?	Yes
Arm title	BI 836826 25 milligram (mg) + GemOx

Arm description:

Patients were administered (intravenous infusion) BI 836826 25 mg on Day 8 and GemOx (gemcitabine 1000 mg/metre square (m^2) plus oxaliplatin 100 mg/m^2) on Day 1 (up to 6 cycles of treatment); the duration of each cycle was 14 days.

Arm type	Experimental
Investigational medicinal product name	BI 836826
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients were administered (intravenous infusion) BI 836826 25 mg on Day 8 and GemOx (gemcitabine 1000
mg/metre square (m^2) plus oxaliplatin 100 mg/m^2) on Day 1 (up to 6 cycles of treatment); the duration of
each cycle was 14 days.

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

Dosage and administration details:

Patients were administered (intravenous infusion) BI 836826 25 mg on Day 8 and GemOx (gemcitabine 1000
mg/metre square (m^2) plus oxaliplatin 100 mg/m^2) on Day 1 (up to 6 cycles of treatment); the duration of
each cycle was 14 days.

Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients were administered (intravenous infusion) BI 836826 25 mg on Day 8 and GemOx (gemcitabine 1000
mg/metre square (m^2) plus oxaliplatin 100 mg/m^2) on Day 1 (up to 6 cycles of treatment); the duration of
each cycle was 14 days.

Arm title	BI 836826 50 mg + GemOx

Arm description:

Patients were administered (intravenous infusion) BI 836826 50 mg on Day 8 and GemOx (gemcitabine 1000 mg/m^2 plus oxaliplatin 100 mg/m^2) on Day 1 (up to 6 cycles of treatment); the duration of each cycle was 14 days.

Arm type	Experimental
Investigational medicinal product name	BI 836826
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients were administered (intravenous infusion) BI 836826 50 mg on Day 8 and GemOx (gemcitabine 1000
mg/metre square (m^2) plus oxaliplatin 100 mg/m^2) on Day 1 (up to 6 cycles of treatment); the duration of
each cycle was 14 days.

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

Dosage and administration details:

Patients were administered (intravenous infusion) BI 836826 50 mg on Day 8 and GemOx (gemcitabine 1000
mg/metre square (m^2) plus oxaliplatin 100 mg/m^2) on Day 1 (up to 6 cycles of treatment); the duration of
each cycle was 14 days.

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

Dosage and administration details:

Patients were administered (intravenous infusion) BI 836826 50 mg on Day 8 and GemOx (gemcitabine 1000
mg/metre square (m^2) plus oxaliplatin 100 mg/m^2) on Day 1 (up to 6 cycles of treatment); the duration of
each cycle was 14 days.

Arm title	BI 836826 100 mg + GemOx

Arm description:

Patients were administered (intravenous infusion) BI 836826 100 mg on Day 8 and GemOx (gemcitabine 1000 mg/m^2 plus oxaliplatin 100 mg/m^2) on Day 1 (up to 6 cycles of treatment); the duration of each cycle was 14 days.

Arm type	Experimental

Investigational medicinal product name	BI 836826
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients were administered (intravenous infusion) BI 836826 100 mg on Day 8 and GemOx (gemcitabine 1000
mg/metre square (m^2) plus oxaliplatin 100 mg/m^2) on Day 1 (up to 6 cycles of treatment); the duration of
each cycle was 14 days.

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

Dosage and administration details:

Patients were administered (intravenous infusion) BI 836826 100 mg on Day 8 and GemOx (gemcitabine 1000
mg/metre square (m^2) plus oxaliplatin 100 mg/m^2) on Day 1 (up to 6 cycles of treatment); the duration of
each cycle was 14 days.

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

Dosage and administration details:

Patients were administered (intravenous infusion) BI 836826 100 mg on Day 8 and GemOx (gemcitabine 1000
mg/metre square (m^2) plus oxaliplatin 100 mg/m^2) on Day 1 (up to 6 cycles of treatment); the duration of
each cycle was 14 days.

Number of subjects in period 1[1]	BI 836826 25 milligram (mg) + GemOx	BI 836826 50 mg + GemOx	BI 836826 100 mg + GemOx
Started	5	8	8
Completed	3	4	3
Not completed	2	4	5
Adverse event, serious fatal	-	1	-
Adverse event, non-fatal	2	1	2
Progressive disease	-	2	3

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Baseline characteristics are based on patients who were randomised after successfully completing the screening period and received at least one dose of the trial medication.

Baseline characteristics

Reporting groups	
Reporting group title	BI 836826 25 milligram (mg) + GemOx
Reporting group description:	
Patients were administered (intravenous infusion) BI 836826 25 mg on Day 8 and GemOx (gemcitabine 1000 mg/metre square (m^2) plus oxaliplatin 100 mg/m^2) on Day 1 (up to 6 cycles of treatment); the duration of each cycle was 14 days.	
Reporting group title	BI 836826 50 mg + GemOx
Reporting group description:	
Patients were administered (intravenous infusion) BI 836826 50 mg on Day 8 and GemOx (gemcitabine 1000 mg/m^2 plus oxaliplatin 100 mg/m^2) on Day 1 (up to 6 cycles of treatment); the duration of each cycle was 14 days.	
Reporting group title	BI 836826 100 mg + GemOx
Reporting group description:	
Patients were administered (intravenous infusion) BI 836826 100 mg on Day 8 and GemOx (gemcitabine 1000 mg/m^2 plus oxaliplatin 100 mg/m^2) on Day 1 (up to 6 cycles of treatment); the duration of each cycle was 14 days.	

Reporting group values	BI 836826 25 milligram (mg) + GemOx	BI 836826 50 mg + GemOx	BI 836826 100 mg + GemOx
Number of subjects	5	8	8
Age categorical			
Units: Subjects			
Age Continuous			
The treated set (TS) includes all randomised patients who received at least 1 dose of trial medication.			
Units: years			
arithmetic mean	62.4	56.5	57.9
standard deviation	± 26.6	± 14.3	± 14.0
Sex: Female, Male			
The treated set (TS) includes all randomised patients who received at least 1 dose of trial medication.			
Units: Subjects			
Female	4	4	3
Male	1	4	5
Race (NIH/OMB)			
The treated set (TS) includes all randomised patients who received at least 1 dose of trial medication.			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	5	8	8
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB)			
The treated set (TS) includes all randomised patients who received at least 1 dose of trial medication.			
Units: Subjects			
Hispanic or Latino	0	3	4
Not Hispanic or Latino	5	5	4

Unknown or Not Reported	0	0	0

Reporting group values	Total		
Number of subjects	21		
Age categorical Units: Subjects			

Age Continuous			
The treated set (TS) includes all randomised patients who received at least 1 dose of trial medication.			
Units: years arithmetic mean standard deviation	- -		
Sex: Female, Male			
The treated set (TS) includes all randomised patients who received at least 1 dose of trial medication.			
Units: Subjects			
Female	11		
Male	10		
Race (NIH/OMB)			
The treated set (TS) includes all randomised patients who received at least 1 dose of trial medication.			
Units: Subjects			
American Indian or Alaska Native	0		
Asian	0		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	0		
White	21		
More than one race	0		
Unknown or Not Reported	0		
Ethnicity (NIH/OMB)			
The treated set (TS) includes all randomised patients who received at least 1 dose of trial medication.			
Units: Subjects			
Hispanic or Latino	7		
Not Hispanic or Latino	14		
Unknown or Not Reported	0		

End points

End points reporting groups

Reporting group title	BI 836826 25 milligram (mg) + GemOx

Reporting group description:

Patients were administered (intravenous infusion) BI 836826 25 mg on Day 8 and GemOx (gemcitabine 1000 mg/metre square (m^2) plus oxaliplatin 100 mg/m^2) on Day 1 (up to 6 cycles of treatment); the duration of each cycle was 14 days.

Reporting group title	BI 836826 50 mg + GemOx

Reporting group description:

Patients were administered (intravenous infusion) BI 836826 50 mg on Day 8 and GemOx (gemcitabine 1000 mg/m^2 plus oxaliplatin 100 mg/m^2) on Day 1 (up to 6 cycles of treatment); the duration of each cycle was 14 days.

Reporting group title	BI 836826 100 mg + GemOx

Reporting group description:

Patients were administered (intravenous infusion) BI 836826 100 mg on Day 8 and GemOx (gemcitabine 1000 mg/m^2 plus oxaliplatin 100 mg/m^2) on Day 1 (up to 6 cycles of treatment); the duration of each cycle was 14 days.

Primary: Number of patients with Dose Limiting Toxicities (DLTs) in the maximum tolerated dose (MTD) evaluation period- Phase 1b

End point title	Number of patients with Dose Limiting Toxicities (DLTs) in the maximum tolerated dose (MTD) evaluation period- Phase 1b[1]

End point description:

DLT (non-haematologic & haematologic drug-related adverse events (AEs)).Non-haematologic AEs of Common Toxicity Criteria for AEs Grade 3 or higher qualified for DLTs with following exceptions: laboratory abnormalities (corrected with treatment within 48 h);nausea, vomiting, or diarrhoea(resolved within 48 h with adequate treatment); neuropathy (related to oxaliplatin);or an infusion-related reactions.For haematologic AEs, DLTs: Grade 4 neutropenia lasting >7 days (d) despite growth factors support;any febrile neutropenia(not resolved within 48 hours with appropriate treatment);Grade 4 thrombocytopenia lasting >7 d or Grade 3/4 thrombocytopenia clinically significant bleeding; failure to recover platelets ≥75*10^9/litres (L) by 4 weeks after start of cycle;or failure to recover neutrophils ≥1.0*10^9/L by 4 weeks after start of cycle.MTD evaluation set:All patients who were documented to have received at least 1 dose of BI 836826 and were not replaced for the MTD evaluation.

End point type	Primary

End point timeframe:

14 days from first trial medication

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: This endpoint was evaluated only descriptively. Thus, no statistical hypothesis were tested.

End point values	BI 836826 25 milligram (mg) + GemOx	BI 836826 50 mg + GemOx	BI 836826 100 mg + GemOx	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3[2]	6[3]	6[4]	
Units: participants	0	1	1	

Notes:

[2] - MTD set

[3] - MTD set

[4] - MTD set

Statistical analyses

No statistical analyses for this end point

Primary: The MTD of BI 836826 with GemOx- Phase 1b

End point title	The MTD of BI 836826 with GemOx- Phase 1b[5]

End point description:

MTD defined as the highest dose studied for which the number of patients with dose-limiting toxicity (DLT) was 17% or less (i.e. not more than 1 of 6 patients) during the MTD evaluation period (Cycle 1). The trial was discontinued prematurely before the MTD based on the frequency of patients with DLTs in the MTD evaluation period, i.e. the 1st treatment cycle, was reached.

End point type	Primary

End point timeframe:

14 days from first trial medication

Notes:

[5] - 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: This endpoint was evaluated only descriptively. Thus, no statistical hypothesis were tested.

End point values	BI 836826 25 milligram (mg) + GemOx	BI 836826 50 mg + GemOx	BI 836826 100 mg + GemOx	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[6]	0[7]	0[8]	
Units: mg				

Notes:

[6] - Trial was discontinued prematurely before the MTD in MTD evaluation period was reached

[7] - Trial was discontinued prematurely before the MTD in MTD evaluation period was reached

[8] - Trial was discontinued prematurely before the MTD in MTD evaluation period was reached

Statistical analyses

No statistical analyses for this end point

Primary: Overall response, i.e. CR and PR, by central review assessment- Phase II

End point title	Overall response, i.e. CR and PR, by central review assessment- Phase II[9]

End point description:

Overall response based on central review assessment, i.e. CR and PR by central review assessment; CR: Disappearance of all evidence of disease PR: Regression of measurable disease and no new sites. Sponsor discontinued the trial for strategic reasons. Consequently, Phase II of the trial was not conducted and hence the endpoint is not evaluated.

End point type	Primary

End point timeframe:

up to 32 weeks from first trial medication administration

Notes:

[9] - 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: This endpoint was evaluated only descriptively. Thus, no statistical hypothesis were tested.

End point values	BI 836826 25 milligram (mg) + GemOx	BI 836826 50 mg + GemOx	BI 836826 100 mg + GemOx	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[10]	0[11]	0[12]	
Units: participants				

Notes:

[10] - Primary & secondary endpoints of Phase II are not applicable since Phase II has not been conducted

[11] - Primary & secondary endpoints of Phase II are not applicable since Phase II has not been conducted

[12] - Primary & secondary endpoints of Phase II are not applicable since Phase II has not been conducted

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response based on investigator's assessment- Phase 1b

End point title	Overall response based on investigator's assessment- Phase 1b

End point description:

Overall response based on investigator's assessment, i.e. partial remission (PR) and complete remission (CR) by investigator assessment; CR: Disappearance of all evidence of disease PR: Regression of measurable disease and no new sites

End point type	Secondary

End point timeframe:

up to 32 weeks from first trial medication administration.

End point values	BI 836826 25 milligram (mg) + GemOx	BI 836826 50 mg + GemOx	BI 836826 100 mg + GemOx	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5[13]	8[14]	8[15]	
Units: participants				
CR|	1	0	1	
PR|	2	3	1	

Notes:

[13] - Treated set

[14] - Treated set

[15] - Treated set

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the plasma concentration-time curve over the time interval from 0 to the time of the last quantifiable data point after drug administration (AUC0-tz) of BI 836826- Phase 1b

End point title	Area under the plasma concentration-time curve over the time interval from 0 to the time of the last quantifiable data point after drug administration (AUC0-tz) of BI 836826- Phase 1b

End point description:

Pharmacokinetic analyses were planned to be performed. However, after encountering technical difficulties and discontinuation of the BI 836826 programme, the sponsor decided not to re-analyse the samples.

End point type	Secondary

End point timeframe:

up to 32 weeks from first trial medication administration.

End point values	BI 836826 25 milligram (mg) + GemOx	BI 836826 50 mg + GemOx	BI 836826 100 mg + GemOx	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[16]	0[17]	0[18]	
Units: nanomole*hours/litre (nmol*h/L)				
geometric mean (geometric coefficient of variation)	()	()	()	

Notes:

[16] - PK parameters were not calculated because the sponsor discontinued development of BI 836826

[17] - PK parameters were not calculated because the sponsor discontinued development of BI 836826

[18] - PK parameters were not calculated because the sponsor discontinued development of BI 836826

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum measured plasma concentration of BI 836826 (Cmax)- Phase 1b

End point title	Maximum measured plasma concentration of BI 836826 (Cmax)- Phase 1b

End point description:

Pharmacokinetic analyses were planned to be performed. However, after encountering technical difficulties and discontinuation of the BI 836826 programme, the sponsor decided not to re-analyse the samples.

End point type	Secondary

End point timeframe:

up to 32 weeks from first trial medication administration.

End point values	BI 836826 25 milligram (mg) + GemOx	BI 836826 50 mg + GemOx	BI 836826 100 mg + GemOx	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[19]	0[20]	0[21]	
Units: nmol/L				
geometric mean (geometric coefficient of variation)	()	()	()	

Notes:

[19] - PK parameters were not calculated because the sponsor discontinued development of BI 836826

[20] - PK parameters were not calculated because the sponsor discontinued development of BI 836826

[21] - PK parameters were not calculated because the sponsor discontinued development of BI 836826

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Response (CR) by central review assessment- Phase II

End point title	Complete Response (CR) by central review assessment- Phase II

End point description:

Complete Response (CR) by central review assessment- Phase II; CR: Disappearance of all evidence of disease. Sponsor discontinued the trial for strategic reasons. Consequently, Phase II of the trial was not conducted and hence the endpoint is not evaluated.

End point type	Secondary

End point timeframe:

up to 32 weeks from first trial medication administration.

End point values	BI 836826 25 milligram (mg) + GemOx	BI 836826 50 mg + GemOx	BI 836826 100 mg + GemOx	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[22]	0[23]	0[24]	
Units: participants				

Notes:

[22] - Primary & secondary endpoints of Phase II are not applicable since Phase II has not been conducted
[23] - Primary & secondary endpoints of Phase II are not applicable since Phase II has not been conducted
[24] - Primary & secondary endpoints of Phase II are not applicable since Phase II has not been conducted

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events that started from the first administration of any trial medication to 30 days after the last administration; up to 114 days

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	BI 836826 25 milligram (mg) + GemOx

Reporting group description:

Patients were administered (intravenous infusion) BI 836826 25 mg on Day 8 and GemOx (gemcitabine 1000 mg/metre square (m^2) plus oxaliplatin 100 mg/m^2) on Day 1 (up to 6 cycles of treatment); the duration of each cycle was 14 days.

Reporting group title	BI 836826 50 mg + GemOx

Reporting group description:

Patients were administered (intravenous infusion) BI 836826 50 mg on Day 8 and GemOx (gemcitabine 1000 mg/m^2 plus oxaliplatin 100 mg/m^2) on Day 1 (up to 6 cycles of treatment); the duration of each cycle was 14 days.

Reporting group title	BI 836826 100 mg + GemOx

Reporting group description:

Patients were administered (intravenous infusion) BI 836826 100 mg on Day 8 and GemOx (gemcitabine 1000 mg/m^2 plus oxaliplatin 100 mg/m^2) on Day 1 (up to 6 cycles of treatment); the duration of each cycle was 14 days.

Serious adverse events	BI 836826 25 milligram (mg) + GemOx	BI 836826 50 mg + GemOx	BI 836826 100 mg + GemOx
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 5 (80.00%)	5 / 8 (62.50%)	3 / 8 (37.50%)
number of deaths (all causes)	0	2	1
number of deaths resulting from adverse events	0	1	0
Investigations			
White blood cell count decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Febrile nonhaemolytic transfusion reaction			

subjects affected / exposed	1 / 5 (20.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion related reaction			
subjects affected / exposed	1 / 5 (20.00%)	2 / 8 (25.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	2 / 5 (40.00%)	1 / 8 (12.50%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	3 / 3	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Pleural effusion			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Aspergillus infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Device related infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 5 (0.00%)	2 / 8 (25.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Tumour lysis syndrome			
subjects affected / exposed	0 / 5 (0.00%)	2 / 8 (25.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0

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

Non-serious adverse events	BI 836826 25 milligram (mg) + GemOx	BI 836826 50 mg + GemOx	BI 836826 100 mg + GemOx
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)	8 / 8 (100.00%)	8 / 8 (100.00%)
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Pallor			

subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 5 (60.00%)	2 / 8 (25.00%)	3 / 8 (37.50%)
occurrences (all)	5	2	3
Chest pain			
subjects affected / exposed	0 / 5 (0.00%)	2 / 8 (25.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Chills			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Fatigue			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Infusion site extravasation			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Oedema peripheral			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	1 / 5 (20.00%)	4 / 8 (50.00%)	5 / 8 (62.50%)
occurrences (all)	3	6	5
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 5 (20.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Cough			
subjects affected / exposed	2 / 5 (40.00%)	4 / 8 (50.00%)	0 / 8 (0.00%)
occurrences (all)	2	4	0
Dyspnoea			

subjects affected / exposed	0 / 5 (0.00%)	2 / 8 (25.00%)	1 / 8 (12.50%)
occurrences (all)	0	3	1
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Insomnia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 5 (20.00%)	1 / 8 (12.50%)	3 / 8 (37.50%)
occurrences (all)	1	1	7
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 5 (20.00%)	1 / 8 (12.50%)	3 / 8 (37.50%)
occurrences (all)	1	1	9
Blood creatinine increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 5 (20.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	5
Platelet count decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	3
Transaminases increased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Weight decreased			
subjects affected / exposed	0 / 5 (0.00%)	2 / 8 (25.00%)	1 / 8 (12.50%)
occurrences (all)	0	2	1
White blood cell count decreased			

subjects affected / exposed	1 / 5 (20.00%)	3 / 8 (37.50%)	3 / 8 (37.50%)
occurrences (all)	8	8	9
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	1 / 5 (20.00%)	3 / 8 (37.50%)	3 / 8 (37.50%)
occurrences (all)	1	7	4
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Dysaesthesia			
subjects affected / exposed	1 / 5 (20.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Dysarthria			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	2 / 5 (40.00%)	2 / 8 (25.00%)	0 / 8 (0.00%)
occurrences (all)	2	2	0
Neuropathy peripheral			
subjects affected / exposed	1 / 5 (20.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Paraesthesia			
subjects affected / exposed	1 / 5 (20.00%)	2 / 8 (25.00%)	1 / 8 (12.50%)
occurrences (all)	1	2	1
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Syncope			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Tremor			

subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 5 (60.00%)	4 / 8 (50.00%)	7 / 8 (87.50%)
occurrences (all)	13	7	14
Leukocytosis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Leukopenia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	4
Lymphopenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	3 / 8 (37.50%)
occurrences (all)	0	0	7
Neutropenia			
subjects affected / exposed	4 / 5 (80.00%)	4 / 8 (50.00%)	8 / 8 (100.00%)
occurrences (all)	17	16	21
Thrombocytopenia			
subjects affected / exposed	3 / 5 (60.00%)	4 / 8 (50.00%)	7 / 8 (87.50%)
occurrences (all)	10	12	12
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Constipation			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	1 / 5 (20.00%)	3 / 8 (37.50%)	2 / 8 (25.00%)
occurrences (all)	1	3	3
Dyspepsia			
subjects affected / exposed	2 / 5 (40.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Melaena			

subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	2 / 5 (40.00%)	2 / 8 (25.00%)	3 / 8 (37.50%)
occurrences (all)	2	4	7
Oral dysaesthesia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Stomatitis			
subjects affected / exposed	2 / 5 (40.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	3	0	0
Vomiting			
subjects affected / exposed	0 / 5 (0.00%)	2 / 8 (25.00%)	1 / 8 (12.50%)
occurrences (all)	0	3	3
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Night sweats			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Urinary incontinence			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	3 / 8 (37.50%)
occurrences (all)	0	0	5

Muscle spasms			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Neck pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Cytomegalovirus infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Influenza			
subjects affected / exposed	1 / 5 (20.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Oral candidiasis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Hyperglycaemia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Hyperkalaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Hyperuricaemia			
subjects affected / exposed	1 / 5 (20.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	2
Hypocalcaemia			

subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	2
Hypokalaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	1 / 8 (12.50%)
occurrences (all)	0	1	2
Hypomagnesaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	2 / 8 (25.00%)
occurrences (all)	0	1	2
Hypophosphataemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Tetany			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 October 2016	- Biochemistry test was added on Day 1 of Cycle 1 on request of Belgian health authority - Other changes were made to make the protocol more clear, correct some mistakes, as well as add consistency and clarity
03 November 2016	- Weight assessment was moved to End of Treatment Visit because of an error in a previous version of the Clinical trial Protocol (CTP) - Regular Hepatitis B Virus (HBV) Deoxyribonucleic Acid (DNA) tests were required in case a patient was positive for Hepatitis B surface antigen (HBsAg) or anti- HBc at screening
10 January 2017	A clarification was added that the MTD can only be determined based on 'evaluable' patients
09 June 2017	- Two additional dose cohorts (150 and 200 mg) were added - Six to 9 patients were to be recruited at the established MTD to have a total of 12 patients treated at this MTD
14 September 2017	Inclusion criterion 4 was changed to allow patients with 1 large single lesion to participate to the trial

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Because of discontinuation of BI 836826 programme, Phase II of the trial and PK analysis in Phase Ib were not conducted.

Notes: