Clinical trial results:
Open, non-controlled, multicentre, first-in-man study using escalating doses of LFB-R603 in patients with advanced stage B-Chronic lymphocytic leukemia.

Summary

EudraCT number	2008-002601-40
Trial protocol	FR
Global end of trial date	23 August 2011

Results information

Result version number	v1 (current)
This version publication date	31 December 2016
First version publication date	31 December 2016

Trial information

Trial identification

Sponsor protocol code	CD20-0703

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	LFB Biotechnologies
Sponsor organisation address	3 Avenue des Tropiques, COURTABOEUF, France, 91953
Public contact	Global Clinical Development Leader, LFB Biotechonologies, 33 169825656,
Scientific contact	Global Clinical Development Leader, LFB Biotechonologies, 33 169825656,

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	11 April 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 August 2011
Global end of trial reached?	Yes
Global end of trial date	23 August 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective is to assess the safety of LFB-R603 administered to patients suffering from advanced B-CLL, relapsed or refractory after at least one prior course of fludarabin.

Protection of trial subjects:

The Safety Committee was due to meet systematically within a maximum of 24 hours before each new cohort began treatment to analyse all potential AEs/SAEs and review, if necessary, the recommendations made during the previous meeting(s).
The Safety Committee made recommendation whether or not it was possible to escalate the dose to a higher dose level as per the dose administration rules.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 November 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 33
Worldwide total number of subjects	33
EEA total number of subjects	33

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)	18

From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Of the 41 patients screened between November 2008 and September 2010, 33 were eligible (IS population) and received treatment (TTS population); 21 in Part I: 6 at 75 mg, 3 each at 200 mg, 510 mg, 1050 mg, 6 at 1650 mg; 12 in Part II at 3300 mg.

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	41[1]
Number of subjects completed	33

Pre-assignment subject non-completion reasons

Reason: Number of subjects	screening failure: 8

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Of the 41 patients screened between November 2008 and September 2010, 33 were eligible and were enrolled in the trial.

Period 1

Period 1 title	Baseline period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Total Patients

Arm description:

A total of 33 patients were included to receive study treatment, 21 in the Part I dose escalation phase (75 mg to 1650 mg) and 12 in Part II (3300 mg). An additional patient was included in Part II compared to the 11 planned inclusions due to concomitant inclusion processes in two Investigational Centres.

Arm type	Experimental
Investigational medicinal product name	LFB-R603
Investigational medicinal product code	anti-CD20
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Part I:
Five consecutive cohorts of 3 to 6 patients were planned. In each cohort, patients received once weekly infusions of LFB-R603 for 4 weeks at doses ranging from 5 to 450 mg as follows:
Cohort A: 5 mg, 10 mg, 20 mg and 40 mg for infusions 1, 2, 3 and 4, respectively
Cohort B: 20 mg for the 1st infusion and 60 mg for the next 3 infusions
Cohort C: 60 mg for the 1st infusion and 150 mg for the next 3 infusions
Cohort D: 150 mg for the 1st infusion and 300 mg for the next 3 infusions
Cohort E: 300 mg for the 1st infusion and 450 mg for the next 3 infusions

Part II:
Cohort F: 12 patients received once- weekly infusions of LFB-R603 for 8 weeks. For each patient, the first dose was 150 mg and each subsequent dose (from 2 to 8) was 450 mg.

Number of subjects in period 1	Total Patients
Started	33
Completed	33

Period 2

Period 2 title	Treatment period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Total Patients

Arm description:

A total of 33 patients were included to receive study treatment, 21 in the Part I dose escalation phase (75 mg to 1650 mg) and 12 in Part II (3300 mg). An additional patient was included in Part II compared to the 11 planned inclusions due to concomitant inclusion processes in two Investigational Centres.

Arm type	Experimental
Investigational medicinal product name	LFB-R603
Investigational medicinal product code	anti-CD20
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Part I:
Five consecutive cohorts of 3 to 6 patients were planned. In each cohort, patients received once weekly infusions of LFB-R603 for 4 weeks at doses ranging from 5 to 450 mg as follows:
Cohort A: 5 mg, 10 mg, 20 mg and 40 mg for infusions 1, 2, 3 and 4, respectively
Cohort B: 20 mg for the 1st infusion and 60 mg for the next 3 infusions
Cohort C: 60 mg for the 1st infusion and 150 mg for the next 3 infusions
Cohort D: 150 mg for the 1st infusion and 300 mg for the next 3 infusions
Cohort E: 300 mg for the 1st infusion and 450 mg for the next 3 infusions

Part II:
Cohort F: 12 patients received once- weekly infusions of LFB-R603 for 8 weeks. For each patient, the first dose was 150 mg and each subsequent dose (from 2 to 8) was 450 mg.

Number of subjects in period 2	Total Patients
Started	33
Completed	32
Not completed	1
Adverse event, non-fatal	1

Period 3

Period 3 title	follow-up period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Total Patients

Arm description:

A total of 33 patients were included to receive study treatment, 21 in the Part I dose escalation phase (75 mg to 1650 mg) and 12 in Part II (3300 mg). An additional patient was included in Part II compared to the 11 planned inclusions due to concomitant inclusion processes in two Investigational Centres.

Arm type	Experimental
Investigational medicinal product name	LFB-R603
Investigational medicinal product code	anti-CD20
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

No administration during follow-up period.

Number of subjects in period 3	Total Patients
Started	32
Completed	15
Not completed	17
Consent withdrawn by subject	1
Physician decision	2
Adverse event, non-fatal	1
Lack of efficacy	13

Baseline characteristics

Reporting groups

Reporting group title	Baseline period

Reporting group description: -

Reporting group values	Baseline period	Total	
Number of subjects	33	33	
Age categorical Units: Subjects			
Adults (18-80 years)	33	33	
Age continuous Units: years median full range (min-max)	 64 43 to 77	 -	
Gender categorical Units: Subjects			
Female Male	6 27	6 27	

Subject analysis sets

Subject analysis set title	Part I
Subject analysis set type	Full analysis
Subject analysis set description: subjects included in the Part I	
Subject analysis set title	part II
Subject analysis set type	Full analysis
Subject analysis set description: Subjects included in the part II	

Reporting group values	Part I	part II	
Number of subjects	21	12	
Age categorical Units: Subjects			
Adults (18-80 years)	21	12	
Age continuous Units: years median full range (min-max)	 62 43 to 76	 69.5 62 to 77	
Gender categorical Units: Subjects			
Female Male	4 17	2 10	

End points

End points reporting groups

Reporting group title	Total Patients

Reporting group description:

A total of 33 patients were included to receive study treatment, 21 in the Part I dose escalation phase (75 mg to 1650 mg) and 12 in Part II (3300 mg). An additional patient was included in Part II compared to the 11 planned inclusions due to concomitant inclusion processes in two Investigational Centres.

Reporting group title	Total Patients

Reporting group description:

A total of 33 patients were included to receive study treatment, 21 in the Part I dose escalation phase (75 mg to 1650 mg) and 12 in Part II (3300 mg). An additional patient was included in Part II compared to the 11 planned inclusions due to concomitant inclusion processes in two Investigational Centres.

Reporting group title	Total Patients

Reporting group description:

A total of 33 patients were included to receive study treatment, 21 in the Part I dose escalation phase (75 mg to 1650 mg) and 12 in Part II (3300 mg). An additional patient was included in Part II compared to the 11 planned inclusions due to concomitant inclusion processes in two Investigational Centres.

Subject analysis set title	Part I
Subject analysis set type	Full analysis

Subject analysis set description:

subjects included in the Part I

Subject analysis set title	part II
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects included in the part II

Primary: adverse events occurrence

End point title	adverse events occurrence[1]

End point description:

End point type	Primary

End point timeframe:

12 months

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: descriptive analysis.

End point values	Total Patients			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: number	332			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Throughout the study.	
Adverse event reporting additional description:	
TEAEs reporting below occured in ≥4 patients.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	11.1

Reporting groups	
Reporting group title	Total Patients

Reporting group description:

A total of 33 patients were included to receive study treatment, 21 in the Part I dose escalation phase (75 mg to 1650 mg) and 12 in Part II (3300 mg). An additional patient was included in Part II compared to the 11 planned inclusions due to concomitant inclusion processes in two Investigational Centres.

Serious adverse events	Total Patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 33 (72.73%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Ischaemic stroke			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrioventricular block complete			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Endocarditis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia haemolytic autoimmune			

subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	2 / 33 (6.06%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Pancytopenia				
subjects affected / exposed	2 / 33 (6.06%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Leukaemia				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	3 / 33 (9.09%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Infusion related reaction				
subjects affected / exposed	6 / 33 (18.18%)			
occurrences causally related to treatment / all	6 / 6			
deaths causally related to treatment / all	0 / 0			
Wrong technique in product usage process				
subjects affected / exposed	3 / 33 (9.09%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Pyrexia				

subjects affected / exposed	4 / 33 (12.12%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
Streptococcal sepsis				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Staphylococcal sepsis				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Listeriosis				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Bronchopulmonary aspergillosis				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung infection				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Bronchopneumopathy				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
hepatititis C				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cytolitic hepatitis				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cholecystitis acute				
subjects affected / exposed	2 / 33 (6.06%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Neuroendocrine carcinoma of the skin				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma				
subjects affected / exposed	2 / 33 (6.06%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Basal cell carcinoma				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Varicella				

subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Total Patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 33 (100.00%)		
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 33 (27.27%)		
occurrences (all)	15		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	21 / 33 (63.64%)		
occurrences (all)	32		
Infusion related reaction			
subjects affected / exposed	20 / 33 (60.61%)		
occurrences (all)	23		
Asthenia			
subjects affected / exposed	9 / 33 (27.27%)		
occurrences (all)	10		
Chills			
subjects affected / exposed	7 / 33 (21.21%)		
occurrences (all)	8		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	15 / 33 (45.45%)		
occurrences (all)	20		
Thrombocytopenia			
subjects affected / exposed	13 / 33 (39.39%)		
occurrences (all)	15		
Gastrointestinal disorders			
Nausea			

subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	5		
Respiratory, thoracic and mediastinal disorders			
Bronchitis			
subjects affected / exposed	12 / 33 (36.36%)		
occurrences (all)	17		
Nasopharyngitis			
subjects affected / exposed	7 / 33 (21.21%)		
occurrences (all)	8		
Rhinitis			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	5		
Cough			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	4		
Sinusitis			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	4		
Hepatobiliary disorders			
Cytolytic hepatitis			
subjects affected / exposed	7 / 33 (21.21%)		
occurrences (all)	7		
Gamma-glutamyltransferase increased			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	4		
Infections and infestations			
oral herpes			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 December 2008	- To notify a change in a prohibited prior and/or concomitant medication. Prior and concomitant IV or subcutaneous immunoglobulin infusion was prohibited during the study treatment. However, since LFB-R603 may increase the risk of infections, especially serious bacterial infections in this selected population of patients, the use of IV or subcutaneous immunoglobulins was authorised if deemed necessary for patient's welfare. - To notify a correction made in the flow rate of administration for infusions 3 and 4 of LFB-R603.
20 January 2009	To specify the modality of administration of LFB-R603. For the dose between 5 and 150 mg, in order to maintain the permeability during the infusion, a concomitant administration of NaCl 0.9% was recommended.
07 May 2009	- To specify the wash-out period of any other medication for CLL required prior to study entry. - To specify that progression of the disease was to be evaluated according to the NCI-WG criteria 2008. - To add premedication with methylprednisolone for infusions 3 and 4 of LFB-R603 in all cohorts. - To extend the duration of Part I of the study from 7.5 months to 10 months and to delay the first patient in Part II.
14 August 2009	- To notify the change in the modality of administration of LFB-R603 infusion.
28 January 2010	-To notify the recommended dose escalation regimen to be used in Part II of the study. - To specify the total of 11 additional patients were to be treated in part II in order to determine the recommended dose for subsequent clinical trials. - To specify the role of the Safety Committee in Part II of the study. - To add a thoracic, abdominal and pelvic CT-scan at M2 in order to evaluate the tumour burden and assess the relationship between tumour burden and lymphocyte depletion.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported