Clinical trial results:
A phase II multicentric study in adults with acute myelogenous leukaemia (AML) in first complete remission (CR1) using IV BuCy2 in a once daily Bu regimen targeting a narrow therapeutic window prior to hematopoietic stem cell transplantation.

Summary

EudraCT number	2009-016601-42
Trial protocol	FR ES IT
Global end of trial date	19 June 2014

Results information

Result version number	v1 (current)
This version publication date	09 March 2017
First version publication date	09 March 2017

Trial information

Trial identification

Sponsor protocol code	F60002 IN 202 G0

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	PIERRE FABRE MEDICAMENT
Sponsor organisation address	45 Place Abel Gance, Boulogne, France, 92654
Public contact	Ta Thanh Minh Christine, PIERRE FABRE MEDICAMENT, 33 0149108000, christine.ta.thanh.minh@pierre-fabre.com
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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	30 September 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 June 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To target the upper range of the busulfan therapeutic window (AUC from 4400 to 6000 µM.min) from a once daily myeloablative regimen in adult patients with AML in CR1 receiving the IV BuCy2 regimen.

Protection of trial subjects:

Before enrolment in the study trial, the patient was examined by an experienced physician in charge of the study; some routine tests, including usual blood tests for pre-transplant check-up, a chest X-ray, echocardiogram and pulmonary tests function were carried out in order to assess vital functions and monitor the disease. Results of these tests were documented by the physician and the specialized team in charge of performing the hematopoietic stem cell transplantation. The patient was hospitalized 8 days before the transplantation in a bone marrow unit. The entire procedure of transplantation including administration of the conditioning regimen was supervised by a specialized physician. The patient was isolated in a sterile environment. The conditioning regimen consisted of intravenous busulfan over 4 days followed by a day of rest and followed by infusion of cyclophosphamide over 2 days (60 mg/kg/d); there was a day of rest after the last day of cyclophosphamide, then on the following day (Day0) the graft was infused to the patient. During the administration of the conditioning therapy, the dose level of intravenous busulfan were adjusted as it was an objective of the trial . Twelve plasma samples were collected over 4 days. The duration of the initial hospitalization lasted between four and six weeks until complete recovery. The follow-up, the treatments, the transplantation procedure were performed by the physician in charge of the study. He was also responsible of reviewing the patient information sheet and obtaining the patient's agreement. Women of childbearing potential had to have negative serum or urine pregnancy test within 72 hours prior to the start of study treatment. Fertile men and women of childbearing potential were expected to use an effective method of contraception during the 2 months preceding the start of study treatment, during treatment and at least 6 months following the last dose of study treatment.

Background therapy:

Allogeneic Hematopoietic Stem Cell transplantation (HSCT) is a curative therapy and is widely used in the treatment of various haematological and non-haematological malignancies. The conditioning therapy is a key point in this procedure. Apart from the conditioning regimen, during the allogeneic procedure, many concomitant treatments are usually administered before or after infusion of the graft as prophylaxis to prevent occurrence of side effects or as part of supportive care. The graft was administered after the end of the conditioning therapy. Oral phenytoin was used as seizure prophylaxis. The prophylaxis to prevent the occurrence of veno-occlusive disease was based on heparin. The prophylaxis for prevention of the graft-versus-host-disease could have combined antithymoglobuline (if indicated) and ciclosporin and methotrexate. The recommended doses and duration of the graft-versus-host-disease prophylaxis was to be adapted based on local institutional guidelines. Hydration with glucose serum or chloride serum, uromitexan and anti-emetic therapies were recommended and adjusted according to the local institutional guidelines. Others medications such as blood transfusions, platelet transfusions, growth factor, antibiotics, antifungal treatment were given according to institutional guidelines.

Evidence for comparator:

not applicable. The study was a phase multicentric study, open-label

Actual start date of recruitment	17 May 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	France: 22
Country: Number of subjects enrolled	Italy: 6
Worldwide total number of subjects	30
EEA total number of subjects	30

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)	30
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

30 patients were enrolled from 8 active centers in 3 countries. The patient's eligibilty was assessed by an experienced physician within four weeks before the start of conditioning regimen. First patient enrolled on the 17th May 2010; last patient enrolled on the 21th May 2012.

Pre-assignment

Screening details:

Patient eligibility was assessed from Day-36 to Day-9 (the period before the day of transplantation was counted as negative). Patient's informed consent was signed. Parameters: demographics, disease, organ functions, laboratory tests, eligibility for transplantation, compatible donor, no exclusion criteria. Assignement of patient number.

Pre-assignment period milestones

Number of subjects started	30
Intermediate milestone: Number of subjects	pre study screeening period: 30
Number of subjects completed	30

Period 1

Period 1 title	study treatment period-follow-up periods (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

not applicable

Arms

Arm title	overall cohort-study treatment period and follow-up periods

Arm description:

The study was split in study treatment period and study follow-up periods. The reference day was Day0 the day of transplantation. After Day0 the number of days was counted as positive. Before Day0, the days was counted as negative. The study treatment period started from Day-8 up to Day+28: 30 patients (overall cohort) were enrolled and treated with IV BuCy2 as conditioning regimen prior to allogeneic hematopoietic stem cell transplantation. During this period, in-patients evaluations for safety and efficacy were done until Day+28. Follow-up period 1 : Day+29 up to Day+100; Follow-up period 2: Day+101 up to Day+365; Follow-up period 3: Day+366 up to Day+730. During the 3 study follow-up periods, the patients could have received additional therapies as part of the transplantation procedure, and the clinical evaluations with safety and efficacy parameters were collected. All 30 patients were evaluable for pharmacokinetic, safety and efficacy analysis.

Arm type	Investigational arm
Investigational medicinal product name	Busilvex
Investigational medicinal product code	F60002
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

First administered dose (Day-8) was 3.2 mg/kg according to either actual body weight (ABW) for normal patients or to adjusted ideal body weight (AIBW) for obese patients. Then subsequent doses (Day-7 to Day-5) were adjusted according to the targeted AUC (i.e.: 5200 µM.min), corresponding to the middle of the therapeutic window (i.e.: 4400-6000 µM.min) and based on prior PK information collected from the dose before. One-day rest (Day-4) followed the last administration of IV Bu before cyclophosphamide treatment.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	cyclophosphamide
Other name	Cytoxan; Endoxan
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

One-day rest (Day-4) followed the last administration of IV Bu before cyclophosphamide administered at a dose of 60 mg/kg over two to four hours for two consecutive days (total dose 120 mg/kg) (Day-3 toDay-2). One-day rest (Day-1) followed the IV BuCy2 regimen before Stem Cell Infusion on Day0.

Number of subjects in period 1	overall cohort-study treatment period and follow-up periods
Started	30
Completed	30

Baseline characteristics

Reporting groups	
Reporting group title	study treatment period-follow-up periods

Reporting group description:

Overall cohort: 30 adult patients diagnosed with acute myelogenous leukemia in first complete remission. The characteristics of patients at baseline (diagnosis, prior medical history, prior treatment, clinical and biological tests for eligibility) were collected during visits before enrolment and start of the conditioning therapy.

Reporting group values	study treatment period-follow-up periods	Total	
Number of subjects	30	30	
Age categorical Units: Subjects			
Adults (18-64 years)	30	30	
Age continuous Units: years median full range (min-max)	 43.5 19.3 to 55.5	 -	
Gender categorical Units: Subjects			
Female Male	9 21	9 21	
disease			
AML in first complete remission			
Units: Subjects			
disease	30	30	
height Units: centimeter median full range (min-max)	 174.5 155 to 186	 -	
Weight Units: kilo units median full range (min-max)	 75.5 47 to 99	 -	
karnofsky performance status			
General status score			
Units: score median full range (min-max)	 100 90 to 100	 -	

End points

End points reporting groups

Reporting group title	overall cohort-study treatment period and follow-up periods

Reporting group description:

The study was split in study treatment period and study follow-up periods. The reference day was Day0 the day of transplantation. After Day0 the number of days was counted as positive. Before Day0, the days was counted as negative. The study treatment period started from Day-8 up to Day+28: 30 patients (overall cohort) were enrolled and treated with IV BuCy2 as conditioning regimen prior to allogeneic hematopoietic stem cell transplantation. During this period, in-patients evaluations for safety and efficacy were done until Day+28. Follow-up period 1 : Day+29 up to Day+100; Follow-up period 2: Day+101 up to Day+365; Follow-up period 3: Day+366 up to Day+730. During the 3 study follow-up periods, the patients could have received additional therapies as part of the transplantation procedure, and the clinical evaluations with safety and efficacy parameters were collected. All 30 patients were evaluable for pharmacokinetic, safety and efficacy analysis.

Primary: Number of patients in Bu therapeutic window

End point title	Number of patients in Bu therapeutic window[1]

End point description:

To target the upper range of the busulfan therapeutic window (AUC from 4400 to 6000 µM.min) from a once daily myeloablative regimen in adult patients with AML inCR1 receiving the IV BuCy2 regimen. A daily PK guided dose adjustment from Day-7 (Dose 2) to Day-5 (Dose 4) of Bu treatment was expected to enable the same targeting performance (≥ 70 to 80% ofpatients within the therapeutic window) as that achieved for the larger therapeutic window (i.e.: 3600 – 6000 µM.min) without dose adjustment. The endpoint value was expressed by the number of subjects within the Bu therapeutic window (AUC from 4400 to 6000 µM.min).

End point type	Primary

End point timeframe:

Blood sampling for pharmacokinetic analysis performed over 4 days from Day-8 (dose 1) to Day-5 (dose 4) in order to calculate daily busulfan plasma exposure (AUC). Doses were ajusted from Day-7 (dose 2) to Day-5 (dose 4).

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: The endpoint number of patients in Bu therapeutic window was calculated and reported as absolute count. No statistical test was performed for this endpoint

End point values	overall cohort-study treatment period and follow-up periods			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: subjects	27			

Statistical analyses

No statistical analyses for this end point

Secondary: intrapatient variability of clearance

End point title	intrapatient variability of clearance

End point description:

To confirm the narrow intra-patient variability of once daily busulfan pharmacokinetics already demonstrated on a q.i.d. dosing regimen.

End point type	Secondary

End point timeframe:

For once-daily busulfan infusion over four days of treatment from Day-8 to Day-5 (dose 1 to dose 4)

End point values	overall cohort-study treatment period and follow-up periods			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: percentage				
number (not applicable)	14			

Statistical analyses

No statistical analyses for this end point

Secondary: number of patients alive during study treatment period

End point title	number of patients alive during study treatment period

End point description:

proportion of patients alive at the end of the study treatment period (Day+28).

End point type	Secondary

End point timeframe:

from Day-8 up to Day+28

End point values	overall cohort-study treatment period and follow-up periods			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: subjects	30			

Statistical analyses

No statistical analyses for this end point

Secondary: number of patients with engraftment during study treatment period

End point title	number of patients with engraftment during study treatment period

End point description:

End point type	Secondary

End point timeframe:

from Day-8 up to Day+28

End point values	overall cohort-study treatment period and follow-up periods			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: subjects	30			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients alive at Day+100

End point title	Number of patients alive at Day+100

End point description:

End point type	Secondary

End point timeframe:

From Day-8 up to Day+28 (study treatment period) and Day+29 up to Day+100 (Follow-up period 1)

End point values	overall cohort-study treatment period and follow-up periods			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: subjects	30			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with TRM at Day+100

End point title	Number of patients with TRM at Day+100

End point description:

TRM: transplant-related mortality; TRM was expressed as a number of patients who died from causes other than relapse of the underlying hematological malignancy.

End point type	Secondary

End point timeframe:

Study treatment period and follow-up period 1 (Day-8 up to Day+28 and Day+29 up to Day+100)

End point values	overall cohort-study treatment period and follow-up periods			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients alive at Day+365

End point title	Number of patients alive at Day+365

End point description:

End point type	Secondary

End point timeframe:

From Day-8 up to Day+365: study treatment period, follow-up period 1 and follow-up period 2

End point values	overall cohort-study treatment period and follow-up periods			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: subjects	22			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with TRM at Day+365

End point title	Number of patients with TRM at Day+365

End point description:

TRM: transplant-related mortality; TRM was expressed as a number of patients who died from causes other than relapse of the underlying hematological malignancy.

End point type	Secondary

End point timeframe:

From Day-8 up to Day+365: study treatment period, follow-up period 1 and follow-up period 2

End point values	overall cohort-study treatment period and follow-up periods			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: subjects	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients alive at Day+730

End point title	Number of patients alive at Day+730

End point description:

End point type	Secondary

End point timeframe:

From Day-8 up to Day+730: study treatment period and the 3 follow-up periods.

End point values	overall cohort-study treatment period and follow-up periods			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: subjects	19			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with TRM at Day+730

End point title	Number of patients with TRM at Day+730

End point description:

End point type	Secondary

End point timeframe:

From Day-8 up to Day+730: study treatment period and the 3 follow-up periods

End point values	overall cohort-study treatment period and follow-up periods			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: subjects	5			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with relapse at Day+365

End point title	Number of patients with relapse at Day+365

End point description:

End point type	Secondary

End point timeframe:

From Day-8 up to Day+365: study treatment period, follow-up period 1 and follow-up period 2

End point values	overall cohort-study treatment period and follow-up periods			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: subjects	5			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with relapse at Day+730

End point title	Number of patients with relapse at Day+730

End point description:

End point type	Secondary

End point timeframe:

From Day-8 up to Day+730: study treatment period, and the 3 follow-up periods.

End point values	overall cohort-study treatment period and follow-up periods			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: subjects	6			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with VOD

End point title	Number of patients with VOD

End point description:

VOD: veno-occlusive disease. Diagnosis defined by Jones criteria and severity according to McDonald criteria.
Overall 3 episodes of VOD in 2 patients.

End point type	Secondary

End point timeframe:

From Day-8 up to Day+365

End point values	overall cohort-study treatment period and follow-up periods			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: subjects	2			

Statistical analyses

No statistical analyses for this end point

Secondary: number of patients with acute GVHD grade III-IV at Day+100

End point title	number of patients with acute GVHD grade III-IV at Day+100

End point description:

GVHD: graft-versus-host-disease. Grading according to Glucksberg criteria.
No patient developed acute GVHD of grade IV.

End point type	Secondary

End point timeframe:

From Day0 up to Day+100: study treatment period and follow-up period 1

End point values	overall cohort-study treatment period and follow-up periods			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: subjects	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Myeloablation

End point title	Myeloablation

End point description:

Expected effect of conditioning regimen. number of patients with profound cytopenia after administration of the conditioning regimen (Bucy2)

End point type	Secondary

End point timeframe:
study treatment period (Day-8 to D+28) post-HSCT

End point values	overall cohort-study treatment period and follow-up periods			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: subject	30			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Day-8 to Day+365

Adverse event reporting additional description:

Grading of severity according NCI-CTC v.3 for AEs except for VOD, GVHD, infections and febrile neutropenia. Assessment by physician, collected through the case report form.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13

Reporting groups

Reporting group title	overall cohort-study treatment period-follow-up periods

Reporting group description:

Reporting period for SAEs and non serious AEs: from Day-8 up to Day+365.
Reported: related SAEs by patient and related non serious AEs (grade 4) by patient during the period defined above.

Serious adverse events	overall cohort-study treatment period-follow-up periods		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 30 (13.33%)		
number of deaths (all causes)	11		
number of deaths resulting from adverse events	1		
Cardiac disorders			
Left ventricular dysfunction			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Bone marrow failure			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			

Stomatitis			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
veno-occlusive disease	Additional description: diagnosis according to Jones criteria and grading according to McDonald criteria		
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Interstitial lung disease			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Haemorrgagic cystitis with BK virus			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			

subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infection	Additional description: Gastro intestinal-clostridium difficile		
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia	Additional description: sepsis		
subjects affected / exposed	1 / 30 (3.33%)		
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	overall cohort-study treatment period-follow-up periods		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 30 (13.33%)		
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	4		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 February 2011	The end of the period of inclusion was extended to Q2 2012.
21 June 2011	The amendment modified the planned list of centers and investigators with addition of new center as the accrual was slow. The procedure of IV Bu administration was modified to allow more flexibility to each participating center.
18 November 2011	Update of the manufacturer site for Busilvex.There was no consequence for the certification of the finished product. The corresponding section in the protocol was updated.

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.

not applicable

Notes: