



Clinical trial results:

Phase I-II study of low dose CdA combined with valproic acid (VPA) in previously treated B-cell chronic lymphocytic leukemia (CLL) patients.

Summary

EudraCT number	2010-019983-35
Trial protocol	BE
Global end of trial date	18 September 2013

Results information

Result version number	v1 (current)
This version publication date	17 March 2021
First version publication date	17 March 2021

Trial information

Trial identification

Sponsor protocol code	VPA-CdA
-----------------------	---------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01295593
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cliniques universitaires Saint-Luc- Université Catholique de Louvain
Sponsor organisation address	Avenue Hippocrate 10, Brussels, Belgium, 1200
Public contact	Eric Van Den Neste, Cliniques universitaires Saint-Luc- Université Catholique de Louvain, 0032 27641875, eric.vandenneste@uclouvain.be
Scientific contact	Eric Van Den Neste, Cliniques universitaires Saint-Luc- Université Catholique de Louvain, 0032 27641875, eric.vandenneste@uclouvain.be

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	18 September 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 September 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine the tolerability of VPA in combination with low dose CdA in patients with advanced B-CLL

Protection of trial subjects:

This study will be conducted according to the principles of the "Helsinki Declaration", of the, International Conference on Harmonization (ICH)'s Good Clinical Practice Guidelines, national law and reglementation pertaining to clinical studies.

Background therapy:

VPA : daily, oral, starting dose 10mg/kg/day total dose, taken in 2 separate administrations of around 5 mg/kg/day each, for a maximum of 6 months.

CdA : 5.6 mg/m²/day IV during 3 days, every 28 days, for a maximum of 4 cycles.

Evidence for comparator:

Not applicable

Actual start date of recruitment	24 November 2010
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: 10
Worldwide total number of subjects	10
EEA total number of subjects	10

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)	3
From 65 to 84 years	7

85 years and over	0
-------------------	---

Subject disposition

Recruitment

Recruitment details:

A total of 11 patients were included between March 2011 and August 2013 in several centers in Brussels. In Luxembourg, no patient was included. The eleventh patient was included on August 23, 2013, only this patient was not included in the analyzes. Ten patients can be analyzed after a median follow-up of 10.6 months.

Pre-assignment

Screening details:

All patients had given written informed consent prior to any study-specific examination or procedure. Patients were evaluated within 28 days of the first administration of the study treatment. However, hematology and blood chemistry tests (including creatinine clearance) have been carried out within 7 days of the first day of treatment.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Valproic acid and 2-chlorodeoxyadenosine
------------------	--

Arm description:

VPA : daily, oral, starting dose 10mg/kg/day total dose, taken in 2 separate administrations of around 5 mg/kg/day each, for a maximum of 6 months.

CdA : 5.6 mg/m²/day IV during 3 days, every 28 days, for a maximum of 4 cycles.

Arm type	Experimental
Investigational medicinal product name	Valproic acid
Investigational medicinal product code	VPA
Other name	Depakine
Pharmaceutical forms	Cachet
Routes of administration	Oral use

Dosage and administration details:

VPA / 5/mg /kg twice a day, per os

Investigational medicinal product name	2-chlorodeoxyadenosine
Investigational medicinal product code	CdA
Other name	Cladribine
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

CdA / 5,6 mg/m²/day during 3 days, every 28 days, IV, for 4 cycles

Number of subjects in period 1	Valproic acid and 2-chlorodeoxyadenosine
Started	10
Completed	10

Baseline characteristics

Reporting groups

Reporting group title	Overall trial
Reporting group description:	
Patients receiving VPA / 5/mg /kg twice a day, per os and CdA / 5,6 mg/m ² /day during 3 days, every 28 days, IV, for 4 cycles	

Reporting group values	Overall trial	Total	
Number of subjects	10	10	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	3	3	
From 65-84 years	7	7	
85 years and over	0	0	
Age continuous			
Units: years			
median	68.5		
inter-quartile range (Q1-Q3)	64.25 to 76.75	-	
Gender categorical			
Units: Subjects			
Female	4	4	
Male	6	6	

End points

End points reporting groups

Reporting group title	Valproic acid and 2-chlorodeoxyadenosine
Reporting group description:	
VPA : daily, oral, starting dose 10mg/kg/day total dose, taken in 2 separate administrations of around 5 mg/kg/day each, for a maximum of 6 months.	
CdA : 5.6 mg/m ² /day IV during 3 days, every 28 days, for a maximum of 4 cycles.	

Primary: To determine the tolerability of VPA in combination with low dose CdA in patients with advanced B- Chronic Lymphocytic Leukemia

End point title	To determine the tolerability of VPA in combination with low dose CdA in patients with advanced B- Chronic Lymphocytic Leukemia ^[1]
-----------------	--

End point description:

The primary endpoint was defined as the rate of patients developing toxicities during combination therapy with valproic acid and low dose CdA2-chlorodeoxyadenosine.

End point type	Primary
----------------	---------

End point timeframe:

After 7 months of treatment

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 primary endpoint for sample size estimation has been defined as the rate of patients developing toxicities under the combined treatment. A two-stages Simon design was used. In the first step, 10 patients needed to be included. If strictly less than 6 patients are free of toxicity, the trial would be stopped prematurely. Otherwise, the study would go on until 33 patients will have been treated by the combination.

End point values	Valproic acid and 2-chlorodeoxyadenosine			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Number				
number (not applicable)	6			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival

End point title	Progression free survival
-----------------	---------------------------

End point description:

End point type	Secondary
----------------	-----------

End point timeframe:

PFS was the time interval between the date of inclusion and the date of progressive disease or death

from any cause.

End point values	Valproic acid and 2-chlorodeoxyadenosine			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Months				
median (full range (min-max))	7.6 (2.5 to 26.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: overall survival (OS)

End point title	overall survival (OS)
-----------------	-----------------------

End point description:

End point type	Secondary
----------------	-----------

End point timeframe:

OS was defined as the time interval between the date of inclusion and the date of death

End point values	Valproic acid and 2-chlorodeoxyadenosine			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Months				
median (full range (min-max))	17.8 (3.7 to 26.1)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Any AE occurring during study AND within 12 months after the last administration of CdA, and within 3 months of the last administration of VPA, have been reported on the AE form of the CRF, regardless of its relationship to study. Any AE was documented an

Adverse event reporting additional description:

Any type of adverse event possibly linked to the IMP will be collected at each visit and graded according to NCIC-CTC version 3.0.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	CTCAE GRADE
Dictionary version	3.0

Reporting groups

Reporting group title	Valproic acid combined with CdA
-----------------------	---------------------------------

Reporting group description:

Patients receiving VPA / 5/mg /kg twice a day, per os and CdA / 5,6 mg/m²/day during 3 days, every 28 days, IV, for 4 cycles

Serious adverse events	Valproic acid combined with CdA		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 10 (50.00%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Cardiac disorders			
NSTEMI			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	4 / 10 (40.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pansinusitis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Septicemia with E coli			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	1 / 1		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Valproic acid combined with CdA		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)		
Nervous system disorders			
Neurologic symptoms			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
paresthesia hands			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	6 / 10 (60.00%)		
occurrences (all)	1		
Thrombocytopenia			
subjects affected / exposed	3 / 10 (30.00%)		
occurrences (all)	1		
Anemia			
subjects affected / exposed	5 / 10 (50.00%)		
occurrences (all)	1		
Hematoma on left arm			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue and Fever			
subjects affected / exposed	4 / 10 (40.00%)		
occurrences (all)	1		
Gastrointestinal disorders			

nausea subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 1		
diarrhea subjects affected / exposed occurrences (all)	3 / 10 (30.00%) 1		
Respiratory, thoracic and mediastinal disorders Bronchitis subjects affected / exposed occurrences (all) Pulmonary embolism subjects affected / exposed occurrences (all) dyspnoea subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 1 1 / 10 (10.00%) 1 2 / 10 (20.00%) 1		
Psychiatric disorders Insomnia confusion, hallucination, cramps ,Depression subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Renal and urinary disorders Renal insufficiency subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
18 September 2013	This study was stopped for excessive toxicity of the combination as defined per protocol.	-

Notes:

Limitations and caveats

None reported