Clinical trial results:
Phase II study of High-Dose Rituximab in High Risk Chronic Lymphocytic Leukemia in Suboptimal Response after Induction Immunochemotherapy

Summary

EudraCT number	2011-005174-27
Trial protocol	BE
Global end of trial date	30 May 2015

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	HYDRIC

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01625741
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, 32 27641875, eric.vandenneste@uclouvain.be
Scientific contact	Eric Van Den Neste, Cliniques universitaires Saint Luc, 32 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	30 May 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 May 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Evaluate the rate of conversion into MRD negativity 3 months after the administration of 4 monthly courses of high-dose (2000 mg) rituximab in high-risk CLL patients with suboptimal response after ICT, or MRD relapse after ICT.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines, United States Food and Drug Administration (FDA) regulations/guidelines, and country-specific national and local laws. A copy of the protocol proposed informed consent form (ICF), other written subject information, and any proposed advertising material was submitted to the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for written approval. A copy of the IEC/IRB approval was received by the sponsor before recruitment of subjects into the study. All subjects provided written informed consent before undergoing any study-related procedures, including screening procedures.

Background therapy:

Rituximab was administered intravenously monthly, for four months, at a dose of 2000 mg total (total of 4 doses of 2000 mg each), starting within one month of signing the ICF.

Evidence for comparator:

Not applicable

Actual start date of recruitment	01 March 2012
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: 6
Worldwide total number of subjects	6
EEA total number of subjects	6

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)	4
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The subjects were recruited from eleven sites in Belgium between July 2012 and January 2013.13 patients in total have ben screened for inclusion. Six patients have been included and treated. The remainder had negative MRD (n=4), positive MRD but with exclusion criteria (n=1), or refused inclusion (n=2).

Pre-assignment

Screening details:

This study is reserved for patients with residual disease at the end of therapy at the level of Minimal Residual Disease (MRD-positive either in the peripheral blood at least 6 months after the last dose of rituximab-containing immunochemotherapy or in the bone marrow at least 3 months after the last dose of rituximab-containing immunochemotherapy)

Period 1

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

Arms

Arm title	RITUXIMAB

Arm description:

Patients receiving rituximab 2000 mg intravenously once a month for 4 months (with a total of 4 doses).

Arm type	Experimental
Investigational medicinal product name	RITUXIMAB
Investigational medicinal product code	SUB12570MIG
Other name	MABTHERA
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Rituximab is given intravenously at a monthly dose of 2000 mg for four months (a total of 4 doses of 2000 mg each).
*First infusion (approximately 8 hours infusion): The infusions were administered at an initial rate of 50 mg / hr and increased in 50 mg / hr increments at 30 minutes intervals, depending on tolerance, up to a maximum rate of 400 mg / hr.
*Second and following infusions (approximately 6 hours infusion): The infusions were administered at an initial rate of 100 mg / hr and increased in increments of 100 mg / hr at 30 minute intervals, depending on tolerance, up to a maximum rate of 400 mg / hr.

Number of subjects in period 1	RITUXIMAB
Started	6
Completed	6

Baseline characteristics

Reporting groups	
Reporting group title	RITUXIMAB
Reporting group description:	
Patients receiving rituximab 2000 mg intravenously once a month for 4 months (with a total of 4 doses)	

Reporting group values	RITUXIMAB	Total	
Number of subjects	6	6	
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)	4	4	
From 65-84 years	2	2	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	63		
standard deviation	± 4.6	-	
Gender categorical Units: Subjects			
Female	2	2	
Male	4	4	

End points

End points reporting groups

Reporting group title	RITUXIMAB

Reporting group description:

Patients receiving rituximab 2000 mg intravenously once a month for 4 months (with a total of 4 doses).

Primary: Rate of conversion of MRD-positivity into eradication of MRD (MRD-negative) using sensitive flow cytometry at 3 months after 4 courses of high-dose rituximab

End point title	Rate of conversion of MRD-positivity into eradication of MRD (MRD-negative) using sensitive flow cytometry at 3 months after 4 courses of high-dose rituximab[1]

End point description:

The primary endpoint was the Rate of conversion of MRD-positivity into eradication of MRD (MRD-negative) using sensitive flow cytometry at 3 months after 4 courses of high-dose rituximab.
The assessment of this endpoint was performed during administration of rituximab therapy and follow-up visits.

End point type	Primary

End point timeframe:

3 months after 4 courses of high-dose rituximab.

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: A Fleming’s Single Stage Phase II Procedure was used to determine patient need. Descriptive statistics were performed on the primary and secondary endpoints.

End point values	RITUXIMAB			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Number				
number (not applicable)	3			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events have been reported from the first dose of rituximab up to 3 months after the last administration.

Adverse event reporting additional description:

All grade 2 to 4 infectious events occurring in the year following the last administration of rituximab were recorded, unless they are clearly related to the initiation of a new treatment.
Any AEs that occurred during study treatment AND up to the last follow-up visit were reported on the CRF AE form.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE GRADE
Dictionary version	4.03

Reporting groups

Reporting group title	RITUXIMAB

Reporting group description:

Patients receiving rituximab 2000 mg intravenously once a month for 4 months (with a total of 4 doses)

Serious adverse events	RITUXIMAB		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 6 (33.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Progressive multifocal leucoencephalopathy			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	RITUXIMAB		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Bronchitis			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	1		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Upper air way infection			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	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
04 May 2015	It was decided to close the study because it was not possible to recruit patients in a reasonable time (inclusion rate 3/ years) for several reasons.	-

Notes:

Limitations and caveats

None reported