Clinical trial results:
Preclinical phase 0 micro dose study to evaluate the effekt of R-CHOP chemotherapy on cellular gene-expression.
- Establisment of a preclinical model for in vivo evaluation of molecular biological efects.

Summary

EudraCT number	2011-002677-30
Trial protocol	DK
Global end of trial date	11 May 2016

Results information

Result version number	v1 (current)
This version publication date	18 December 2019
First version publication date	18 December 2019

Trial information

Trial identification

Sponsor protocol code	KFE2011.04

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Department of Haematology, Aalborg Hospital
Sponsor organisation address	Sdr. Skovvej 15, Aalborg, Denmark, 9000
Public contact	Hæmatologisk Forskningsafsnit, Professor Tarec C. El-Galaly, MD, DMSc, Department of Haematology, Aalborg Hospital, 45 97663869, lit@rn.dk
Scientific contact	Hæmatologisk Forskningsafsnit, Professor Tarec C. El-Galaly, MD, DMSc, Department of Haematology, Aalborg Hospital, 45 97663869, lit@rn.dk

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 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 May 2016
Global end of trial reached?	Yes
Global end of trial date	11 May 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To establish a clinical method for phase 0 studies with the combination chemotherapy R-CHOP as focal-point.

Protection of trial subjects:

Data are pseudo-anonymized in downstream handling.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 July 2014
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	Denmark: 9
Worldwide total number of subjects	9
EEA total number of subjects	9

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)	5
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study treatment constitutes 1% of the planned standard R-CHOP treatment and will be given two hours prior to standard treatment. Blood samples are taken at baseline, 15, 30, 60 and 120 minutes for microarray analysis. Subjects are included with informed consent.

Pre-assignment

Screening details:

Planned treatment with R-CHOP for a hematologic disease in accordance with current guidelines at Aalborg Hospital.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Rituximab

Arm description:

Rituximab 0,1 mg administered and blood samples drawn at 0, 30, 60, 90, 120 minutes

Arm type	Experimental
Investigational medicinal product name	MabThera (rituximab)
Investigational medicinal product code	SUB12570MIG
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

0,1 mg

Arm title	Doxorubicin

Arm description:

Doxorubicin 0,1 mg administered and blood samples drawn after 0, 30, 30, 90, 120 minutes.

Arm type	Experimental
Investigational medicinal product name	Adriamycin
Investigational medicinal product code	SUB06391MIG
Other name	Doxorubicin
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

0,1 mg

Number of subjects in period 1	Rituximab	Doxorubicin
Started	6	3
Completed	6	3

Baseline characteristics

Reporting groups	
Reporting group title	Overall period
Reporting group description:	
All subjects	

Reporting group values	Overall period	Total	
Number of subjects	9	9	
Age categorical			
All subjects were above 18 years.			
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)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
From 18-84 years	9	9	
Gender categorical Units: Subjects			
Female	4	4	
Male	5	5	

Subject analysis sets	
Subject analysis set title	All subjects
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects	

Reporting group values	All subjects		
Number of subjects	9		
Age categorical			
All subjects were above 18 years.			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	0		

From 65-84 years	0		
85 years and over	0		
From 18-84 years	9		
Gender categorical Units: Subjects			
Female	4		
Male	5		

End points

End points reporting groups

Reporting group title	Rituximab
Reporting group description:	
Rituximab 0,1 mg administered and blood samples drawn at 0, 30, 60, 90, 120 minutes	
Reporting group title	Doxorubicin
Reporting group description:	
Doxorubicin 0,1 mg administered and blood samples drawn after 0, 30, 30, 90, 120 minutes.	
Subject analysis set title	All subjects
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects	

Primary: Establish a clinical method for a phase 0 trial with R-CHOP as a focal point

End point title	Establish a clinical method for a phase 0 trial with R-CHOP as a focal point[1]
End point description:	
10 subjects were included in the study and 1 was subsequently excluded.	
End point type	Primary
End point timeframe:	
4 November 2014 - 11 May 2016	

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: We have successfully included and analyzed data from 9 subjects illustrating that our setup supports the primary endpoint.

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

Statistical analyses

No statistical analyses for this end point

Secondary: To identify a genetic profile of genes that are up- or downregulated during R-CHOP treatment, and through these data identify specifik pathways for each drug individually and for the entire combinaiton therapy.

End point title	To identify a genetic profile of genes that are up- or downregulated during R-CHOP treatment, and through these data identify specifik pathways for each drug individually and for the entire combinaiton therapy.
End point description:	
End point type	Secondary
End point timeframe:	
Before 31 December 2016.	

End point values	Rituximab	Doxorubicin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	3		
Units: Differential gene expression	6	3		

Statistical analyses

Statistical analysis title	Linear models
Statistical analysis description: Global GEP.	
Comparison groups	Doxorubicin v Rituximab
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	< 0.05
Method	ANOVA
Parameter estimate	Differentially expressed genes
Confidence interval	
level	95 %
sides	2-sided

Notes:

[2] - The analysis on the significant genes included unsupervised clustering and it was assessed whether clustering based on time or patient occurred. Detection of patterns across time by inspecting the PCA trajectories over time of all the significant genes, in both 2 and 3-dimensions were conducted. Finally, detection of change in patterns of gene expression over time by applying self-organizing maps (SOMS) was pursued. By unsupervised clustering, data did not cluster by patients nor time.

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 2 hours	
Adverse event reporting additional description: Facial heat flush and chills to Rituximab.	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	3.0

Reporting groups	
Reporting group title	Rituximab
Reporting group description: Subjects included in the Rituximab arm.	
Reporting group title	Doxorubicin
Reporting group description: Subjects in the Doxorubicin arm.	

Serious adverse events	Rituximab	Doxorubicin	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Rituximab	Doxorubicin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 6 (66.67%)	0 / 3 (0.00%)	
Skin and subcutaneous tissue disorders			
Flushing			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Chills	Additional description: Cold chills		
subjects affected / exposed	3 / 6 (50.00%)	0 / 3 (0.00%)	
occurrences (all)	3	0	

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
11 May 2016	Due to AE (heat flush and chills) in 4 subjects in the Rituximab arm, the trial was interrupted.	-

Notes:

Limitations and caveats

None reported