Clinical trial results:
Therapy for chronic cold agglutinin disease: A prospective, non-randomized international multicenter trial on the safety and efficacy of bendamustine and rituximab combination therapy.

Summary

EudraCT number	2011-004835-30
Trial protocol	NO DK FI
Global end of trial date	22 May 2017

Results information

Result version number	v1 (current)
This version publication date	22 February 2021
First version publication date	22 February 2021
Summary attachment (see zip file)	Berentsen et al_Blood 2017 (2017_Berentsen et al_BR in CAD_Blood.pdf)

Trial information

Trial identification

Sponsor protocol code	CAD5

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02689986
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Haugesund Hospital, Helse Fonna
Sponsor organisation address	Karmsundgata 128, Haugeusnd, Norway, 5504
Public contact	Sigbjorn Berentsen, Department of Medicine, 47 52732000, sigbjorn.berentsen@haugnett.no
Scientific contact	Sigbjorn Berentsen, Department of Research and Innovation, 47 52732000, sigbjorn.berentsen@haugnett.no

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	22 May 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 May 2017
Global end of trial reached?	Yes
Global end of trial date	22 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Rate of complete and partial responses, respectively.

Protection of trial subjects:

Trial including protection of trial subjects was performed in accordance with REK (Regional Committee for Medical and Health Research Ethichs) approval, NoMi (Norwegian Medicines Agency) approval, and the Declaration of Helsinki.

Background therapy:

None.

Evidence for comparator:

No comparator(s).

Actual start date of recruitment	01 August 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety, Scientific research
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 38
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	Finland: 5
Worldwide total number of subjects	45
EEA total number of subjects	45

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)	19
From 65 to 84 years	23
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Patients had to be diagnosed with CAD and require therapy. Criteria for CAD: hemolysis combined, CA titer>64, DAT + for C3d, confirmation of bone marrow clonal B-cell lymphoproliferative disorder. Exclusion criteria as per protocol.

Pre-assignment

Screening details:

History, clinical examination, blood trests and bone marrow examination as per protocol See protocol chapter 4.2-4.4 or attached publication.

Period 1

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

Blinding implementation details:

Not blinded

Arms

Arm title	All patients

Arm description:

All patients

Arm type	Experimental
Investigational medicinal product name	bendamustine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

90 mg/sqm /1 hr infusion days 1-2 for 4 cycles at 20 d interval. Dose reduction allowed as per protocol. Administered as combination therapy which also includes rituximab 375 mg/sqm day 1 at the same intevals.

Number of subjects in period 1	All patients
Started	45
Completed	45

Period 2

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

Blinding implementation details:

Non-randomized trial

Arms

Arm title	All patients

Arm description:

All patients

Arm type	Experimental
Investigational medicinal product name	bendamustine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

90 mg/sqm /1 hr infusion days 1-2 for 4 cycles at 20 d interval. Dose reduction allowed as per protocol. Administered as combination therapy which also includes rituximab 375 mg/sqm day 1 at the same intevals.

Number of subjects in period 2	All patients
Started	45
Completed	45

Baseline characteristics

Reporting groups	
Reporting group title	Baseline
Reporting group description:	
All patients at baseline	

Reporting group values	Baseline	Total	
Number of subjects	45	45	
Age categorical			
Adults 18-64 years: 19 From 65-84 years: 23 85 years and over: 3			
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)	19	19	
From 65-84 years	23	23	
85 years and over	3	3	
Age continuous			
Units: years			
median	74		
full range (min-max)	48 to 86	-	
Gender categorical			
Males and females, respectively.			
Units: Subjects			
Female	25	25	
Male	20	20	
All patients			
Units: Subjects			
All	45	45	
All patients			
All patients			
Units: Subjects			
All	45	45	
Not recorded	0	0	

Subject analysis sets	
Subject analysis set title	Basline characteristics
Subject analysis set type	Per protocol
Subject analysis set description:	
Baseline characteristics	
Subject analysis set title	End of trial

Subject analysis set type	Per protocol

Subject analysis set description:

All patients who completed the trial

Reporting group values	Basline characteristics	End of trial	
Number of subjects	45	45	
Age categorical			
Adults 18-64 years: 19 From 65-84 years: 23 85 years and over: 3			
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)	19		
From 65-84 years	23		
85 years and over	3		
Age continuous			
Units: years			
median	74		
full range (min-max)	48 to 86		
Gender categorical			
Males and females, respectively.			
Units: Subjects			
Female	25		
Male	20		
All patients			
Units: Subjects			
All	45		
All patients			
All patients			
Units: Subjects			
All	45		
Not recorded	0		

End points

End points reporting groups

Reporting group title	All patients
Reporting group description: All patients	
Reporting group title	All patients
Reporting group description: All patients	
Subject analysis set title	Basline characteristics
Subject analysis set type	Per protocol
Subject analysis set description: Baseline characteristics	
Subject analysis set title	End of trial
Subject analysis set type	Per protocol
Subject analysis set description: All patients who completed the trial	

Primary: Complete + partial responses (CR + PR)

End point title	Complete + partial responses (CR + PR)
End point description: Complete and partial responses, repectively, as define per protocol.	
End point type	Primary
End point timeframe: Any	

End point values	All patients	Basline characteristics	End of trial	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	45	45	45	
Units: patients				
Complete responses (CR)	18	0	18	
Partial responses (PR)	14	0	14	

Statistical analyses

Statistical analysis title	Not relevant
Statistical analysis description: Not relevant	
Comparison groups	Basline characteristics v End of trial

Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	95
Confidence interval	
level	95 %
sides	2-sided
lower limit	90
upper limit	99
Variability estimate	Standard error of the mean

Statistical analysis title	Not relevant
Comparison groups	Basline characteristics v End of trial
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	95
Confidence interval	
level	95 %
sides	2-sided
lower limit	90
upper limit	99
Variability estimate	Standard error of the mean

Secondary: Hemoglobin increase	
End point title	Hemoglobin increase
End point description:	
Increase in hemoglobin level at response or at the end of study.	
End point type	Secondary
End point timeframe:	
Any	

End point values	All patients	All patients	Basline characteristics	End of trial
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	45	0[1]	45	45
Units: g/dL				
median (full range (min-max))				
CR	4.4 (0.1 to 11.8)	(to)	0 (0 to 0)	4.4 (0.1 to 11.8)
PR	3.9 (0 to 7.6)	(to)	0 (0 to 0)	3.9 (0 to 7.6)
All patients	3.6 (0 to 11.8)	(to)	0 (0 to 0)	3.6 (0 to 11.8)

Notes:

[1] - Only one reporting group

Statistical analyses

Statistical analysis title	Not relevant
Statistical analysis description: Not relevant	
Comparison groups	All patients v End of trial
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.05 [3]
Method	Not relevant
Parameter estimate	Not relevant
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard error of the mean

Notes:

[2] - No comparison

[3] - Not relevant; single-armed trial

Statistical analysis title	Not relevant
Comparison groups	Basline characteristics v End of trial
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)
Point estimate	95
Confidence interval	
level	95 %
sides	2-sided
lower limit	90
upper limit	99
Variability estimate	Standard error of the mean

Notes:

[4] - Non-randomized study

Secondary: Time to response (TTR)

End point title	Time to response (TTR)
End point description:	
Time from start of treatment to achievement of any degree of response.	
End point type	Secondary
End point timeframe:	
Any	

End point values	All patients	Basline characteristics		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	45	45[5]		
Units: months				
median (full range (min-max))	1.9 (0.25 to 12)	1.9 (0.25 to 12)		

Notes:

[5] - All responders

Statistical analyses

Statistical analysis title	Not relevant
Statistical analysis description:	
Not relevant	
Comparison groups	All patients v Basline characteristics
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	95
Confidence interval	
level	95 %
sides	2-sided
lower limit	90
upper limit	99
Variability estimate	Standard error of the mean

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Whole study period	
Adverse event reporting additional description:	
As per observations during follow-up according to protocol.	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups	
Reporting group title	All patients
Reporting group description:	
All patients	

Serious adverse events	All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 45 (11.11%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	1		
Blood and lymphatic system disorders			
Neutropenia requiring hospitalization	Additional description: Neutropenia requiring hospitalization		
subjects affected / exposed	5 / 45 (11.11%)		
occurrences causally related to treatment / all	7 / 7		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Generalized weakness and hypothermia	Additional description: An 80 year-old man died 3 weeks after developing generalized weakness and hypothermia immediately after administration of rituximab. We considered his death related to rituximab (standard therapy) but not bendamustine (study drug).		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	All patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 45 (37.78%)		
General disorders and administration site conditions			
Non-hematologic AEs	Additional description: Gastrointestinal discomfort (mostly mild nausea) (5 events), rash (4), non-neutropenic infection (2), atrial fibrillation (1). Manageable in all cases.		
subjects affected / exposed	17 / 45 (37.78%)		
occurrences (all)	17		

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? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28533306

http://www.ncbi.nlm.nih.gov/pubmed/32374875