Clinical trial results:
Phase II study of carfilzomib- cyclophosphamide-dexamethasone and high-dose melphalan followed by randomization between observa-tion or maintenance with carfil-zomib and dexamethasone in pa-tients with relapsed multiple myeloma after high-dose melphalan with autologous stem cell support

Summary

EudraCT number	2013-003789-15
Trial protocol	DK FI SE NO LT
Global end of trial date	01 September 2019

Results information

Result version number	v1 (current)
This version publication date	10 May 2021
First version publication date	10 May 2021

Trial information

Trial identification

Sponsor protocol code	NMSG#20/13

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02572492
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Nordic Myeloma Study Group
Sponsor organisation address	Mølleparkvej 4, Aalborg, Denmark, 9000
Public contact	Clinical Trial Unit Hematology Aalborg University Hospital Mølleparkvej 4 9000 Aalborg Denmark, Nordic Myeloma Study Group, 0045 97663884, henrik.gregersen@rn.dk
Scientific contact	Clinical Trial Unit Hematology Aalborg University Hospital Mølleparkvej 4 9000 Aalborg Denmark, Nordic Myeloma Study Group, 0045 97663884, henrik.gregersen@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	06 April 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 September 2019
Global end of trial reached?	Yes
Global end of trial date	01 September 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of our study is to evaluate the effect of the combination of carfilzomib, cyclophosphamide and dexamethasone in the induction regimen and carfilzomib in the conditioning regimen of salvage HDT. In addition to evaluate the potential effect of carfilzomib/dexamethasone maintenance treatment.

Protection of trial subjects:

Exclusion criteria regarding heart disease e.g. exclusion of patients with uncontrolled or severe cardiovascular disease including myocardial infarction within 6 months of enrolment, NYHA Class III or IV heart failure, uncontrolled angina, clinically significant pericardial disease, uncontrolled severe arrhytmias, or cardiac amyloidosis. In addition LVEF <40%, determined by 2-D transthoracic echocardiogram (ECHO) or Multigated Acquisition Scan (MUGA)

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 January 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	Norway: 58
Country: Number of subjects enrolled	Sweden: 50
Country: Number of subjects enrolled	Denmark: 66
Country: Number of subjects enrolled	Finland: 10
Country: Number of subjects enrolled	Lithuania: 16
Worldwide total number of subjects	200
EEA total number of subjects	200

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	138
From 65 to 84 years	62
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from NMSG centers in Denmark, Sweden, Norway, Finland and Lithuania

Pre-assignment

Screening details:

Multiple myeloma patients with first relapse more than one year after single or double high-dose melphalan with stem cell support

Period 1

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

Arms

Arm title	CA-CY-DEX and salvage ASCT

Arm description:

Included patients received:
Four cycles of CAR-CY-DEX (iv carfilzomib, p.o. cyclophosphamide and p.o. dexamethasone
Conditioning regimen: Iv carfilzomib on day –2 and –1 and iv melphalan 200 mg/sqm on day –2.

Arm type	Experimental
Investigational medicinal product name	Carfilzomib
Investigational medicinal product code	L01XG02
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Induction regime:
Four cycles of CAR-CY-DEX (Cycle 1 with iv carfilzomib 20 mg/sqm on days 1 and 2, and iv carfilzomib 36 mg/sqm on days 8, 9, 15 and 16. Cycle 2 - 4 with iv carfilzomib 36 mg/sqm on days 1, 2, 8, 9, 15 and 16. P.o. cyclophosphamide 300 mg/sqm on days 1, 8 and 15 and p.o. dexamethasone 20 mg on days 1, 2, 8, 9, 15 and 16 in each 28-days cycle).

Conditioning regimen:
Iv carfilzomib 27 mg/sqm on day –2 and –1
Iv melphalan 200 mg/sqm on day –2
> 2.0 x 106 CD34+ stem cells/kg body weight on day 0

Number of subjects in period 1	CA-CY-DEX and salvage ASCT
Started	200
Completed	168
Not completed	32
Adverse event, serious fatal	5
Consent withdrawn by subject	7
Physician decision	1
Adverse event, non-fatal	8

Broken bag af stem cells	1
Non-compliance	1
Progression af myeloma	8
Lost to follow-up	1

Baseline characteristics

Reporting groups

Reporting group title	Induction and salvage ASCT

Reporting group description: -

Reporting group values	Induction and salvage ASCT	Total	
Number of subjects	200	200	
Age categorical			
Age distribution			
Units: Subjects			
Adults (18-64 years)	138	138	
From 65-84 years	62	62	
Gender categorical Units: Subjects			
Female	84	84	
Male	116	116	

Subject analysis sets

Subject analysis set title	CAR-CY-DEX and salvage ASCT
Subject analysis set type	Intention-to-treat

Subject analysis set description:
CAR-CY-DEX and salvage ASCT

Reporting group values	CAR-CY-DEX and salvage ASCT		
Number of subjects	200		
Age categorical			
Age distribution			
Units: Subjects			
Adults (18-64 years)			
From 65-84 years			
Gender categorical Units: Subjects			
Female	84		
Male	116		

End points

End points reporting groups

Reporting group title	CA-CY-DEX and salvage ASCT
Reporting group description: Included patients received: Four cycles of CAR-CY-DEX (iv carfilzomib, p.o. cyclophosphamide and p.o. dexamethasone Conditioning regimen: Iv carfilzomib on day –2 and –1 and iv melphalan 200 mg/sqm on day –2.	
Subject analysis set title	CAR-CY-DEX and salvage ASCT
Subject analysis set type	Intention-to-treat
Subject analysis set description: CAR-CY-DEX and salvage ASCT	

Primary: Comparison of time to progression (TTP) after first high-dose melphalan with stem cell support (HDT) and TTP after a second HDT combined with carfilzomib-cyclophosphamide-dexamethasone (CAR-CY-DEX)

End point title	Comparison of time to progression (TTP) after first high-dose melphalan with stem cell support (HDT) and TTP after a second HDT combined with carfilzomib-cyclophosphamide-dexamethasone (CAR-CY-DEX)
End point description:	
End point type	Primary
End point timeframe: From inclusion until end of study	

End point values	CA-CY-DEX and salvage ASCT	CAR-CY-DEX and salvage ASCT		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	168	168		
Units: Months				
median (inter-quartile range (Q1-Q3))				
TTP after upfront ASCT	33.2 (30.4 to 37.7)	33.2 (30.4 to 37.7)		
TTP after salvage ASCT	26.7 (24.2 to 30.7)	26.7 (24.2 to 30.7)		

Statistical analyses

Statistical analysis title	Comparison of TTP
Statistical analysis description: Mann-Whitney test	
Comparison groups	CA-CY-DEX and salvage ASCT v CAR-CY-DEX and salvage ASCT

Number of subjects included in analysis	336
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)

Secondary: Treatment response after four cycles of CAR-CY-DEX induction

End point title	Treatment response after four cycles of CAR-CY-DEX induction

End point description:

No difference compared with VGPR, CR or sCR after induction therapy after up-front ASCT

End point type	Secondary

End point timeframe:

VGPR, CR or sCR after CAR-CY-DEX induction before salvage ASCT

End point values	CA-CY-DEX and salvage ASCT			
Subject group type	Reporting group			
Number of subjects analysed	200			
Units: Patients with VGPR, CR or sCR				
number (not applicable)	200			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to marrow regeneration (neutrophil- and platelet recovery) after the salvage ASCT

End point title	Time to marrow regeneration (neutrophil- and platelet recovery) after the salvage ASCT

End point description:

Mean time to neutrophils above 1.0 × bn/L after salvage ASCT and mean time to thrombocytes above 100 × 10 bn/L after salvage ASCT.

End point type	Secondary

End point timeframe:

Time to marrow regeneration (neutrophil- and platelet recovery) after the HDT

End point values	CA-CY-DEX and salvage ASCT			
Subject group type	Reporting group			
Number of subjects analysed	168			
Units: Days				
arithmetic mean (standard deviation)				
Neutrophile recovery	13.4 (± 3.5)			
Thrombocyte recovery	21.1 (± 8.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Response rates of induction therapy and HDT

End point title	Response rates of induction therapy and HDT

End point description:

End point type	Secondary

End point timeframe:

Treatment response after CAR-CY-DEX induction and salvage ASCT

End point values	CA-CY-DEX and salvage ASCT			
Subject group type	Reporting group			
Number of subjects analysed	168			
Units: Different levels of response				
sCR	19			
CR	19			
VGPR	82			
PR	45			
SD	2			
PD	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From inclusion until 60 days after salvage ASCT	
Assessment type	Systematic

Dictionary used	
Dictionary name	NCI CTC
Dictionary version	4.0

Reporting groups	
Reporting group title	CAR-CY-DEX and salvage ASCT

Reporting group description:

Included patients received:
Four cycles of CAR-CY-DEX (iv carfilzomib, p.o. cyclophosphamide and p.o. dexamethasone
Conditioning regimen: Iv carfilzomib on day –2 and –1 and iv melphalan 200 mg/sqm on day –2.

Serious adverse events	CAR-CY-DEX and salvage ASCT		
Total subjects affected by serious adverse events			
subjects affected / exposed	87 / 200 (43.50%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events	1		
Vascular disorders			
Venous thromboembolism	Additional description: Deep vein thrombosis and pulmonary embolism		
subjects affected / exposed	3 / 200 (1.50%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Transient ischemic attack			
subjects affected / exposed	2 / 200 (1.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Intracerebral hemorrhage			
subjects affected / exposed	1 / 200 (0.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac failure			

subjects affected / exposed	3 / 200 (1.50%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
Acute myocardial infarction				
subjects affected / exposed	2 / 200 (1.00%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	1 / 200 (0.50%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	2 / 200 (1.00%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Diarrhea				
subjects affected / exposed	3 / 200 (1.50%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Nausea and vomiting				
subjects affected / exposed	4 / 200 (2.00%)			
occurrences causally related to treatment / all	1 / 5			
deaths causally related to treatment / all	0 / 0			
Thyphilitis				
subjects affected / exposed	2 / 200 (1.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	2 / 200 (1.00%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				

subjects affected / exposed	3 / 200 (1.50%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	2 / 200 (1.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Electrolyte disorder			
subjects affected / exposed	3 / 200 (1.50%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Septicemia			
subjects affected / exposed	14 / 200 (7.00%)		
occurrences causally related to treatment / all	6 / 14		
deaths causally related to treatment / all	1 / 4		
Other bacterial infection			
subjects affected / exposed	51 / 200 (25.50%)		
occurrences causally related to treatment / all	33 / 65		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	8 / 200 (4.00%)		
occurrences causally related to treatment / all	1 / 9		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	CAR-CY-DEX and salvage ASCT		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	181 / 200 (90.50%)		
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	176 / 200 (88.00%)		
occurrences (all)	176		
Thrombocytopenia			
subjects affected / exposed	181 / 200 (90.50%)		
occurrences (all)	181		
Neutropenia			
subjects affected / exposed	160 / 200 (80.00%)		
occurrences (all)	160		

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.

No

Notes: