Clinical trial results:
A multicentre open randomized phase II study of the efficacy and safety of azacitidine alone or in combination with lenalidomide in high-risk myeloid disease (high-risk MDS and AML) with a karyotype including del (5q)

Summary

EudraCT number	2011-001639-21
Trial protocol	SE FI NO DK
Global end of trial date	29 August 2020

Results information

Result version number	v1 (current)
This version publication date	12 June 2024
First version publication date	12 June 2024

Trial information

Trial identification

Sponsor protocol code	NMDSG10B

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01556477
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Nordic MDS Group
Sponsor organisation address	Karolinska University Hospital Huddinge, Stockholm, Sweden, 14186
Public contact	Lars Möllgård, Sahlgrenska University Hospital, Postcode 41345, Gothenburg, Sweden, , +46 31 3420000, lars.mollgard@vgregion.se
Scientific contact	Eva Hellström-Lindberg, Karolinska University Hospital Huddinge, +46 8 858580000, lars.mollgard@karolinska.se

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	20 August 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 August 2017
Global end of trial reached?	Yes
Global end of trial date	29 August 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To study the efficacy of azacitidine with or without the additioiin of lenalidomide in high-risk MDS (IPSS Int-2 or high) and AML (multilineage dysplasia and 20-30% marrow blasts) with a karyotype oncluding del(5q)

Protection of trial subjects:

For the experimental arm with azacitidine + lenalidomide ther we were aware of a higher risk of inectious complications. To avoid this there was a possibility to add GCS-F treatment if neutrofils were low.

Background therapy:

All patients received the standard treatment for this group of patient with sc azacitidine.

Evidence for comparator:

Azacitidine i standard treatment for patients with both MDS and AML

Actual start date of recruitment	01 December 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
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: 7
Country: Number of subjects enrolled	Sweden: 53
Country: Number of subjects enrolled	Denmark: 11
Country: Number of subjects enrolled	Finland: 1
Worldwide total number of subjects	72
EEA total number of subjects	72

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)	21
From 65 to 84 years	51
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The patients were recruited between 7 March 2012 and 29 August 2017 in Sweden, Denmark, Norway and Finland.

Pre-assignment

Screening details:

The patients were screened during a 28 days period. There were 19 screen failures (8 patients with >30% blasts in the bone marrow, 6 patients with no 5q deletion, 2 patients with IPSS score intremediate 1, 2 patients with rapid progression and 1 patient due to patient request.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	azacitidine

Arm description:

Standard dose of azacitidine 5-2-2 (75 mg/m2/day subcutaneously12) with a total cycle length of 4 weeks and 6 cycles

Arm type	Active comparator
Investigational medicinal product name	azacitidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

azacitidine 5-2-2 (75 mg/m2/day subcutaneously12) with a total cycle length of 4 weeks

Arm title	azacitidine + lenalidomide

Arm description:

Standard dose of AZA 5-2-2 (75 mg/m2/day subcutaneously12) with a total cycle length of 4 weeks + lenalidomide 10 mg, oral, daily, 21/28 days, starting day one in each azacitidine cycle and leaving the last week free of treatment. If tolerated, the dose was escalated to 25 mg daily during cycle four to six.

Arm type	Experimental
Investigational medicinal product name	azacitidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

azacitidine 5-2-2 (75 mg/m2/day subcutaneously12) with a total cycle length of 4 weeks

Investigational medicinal product name	lenalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The initial dose of lenalidomide was 10 mg, oral, daily, 21/28 days, starting day one in each azacitidine cycle and leaving the last week free of treatment. If tolerated, the dose was escalated to 25 mg daily

during cycle four to six.

Number of subjects in period 1	azacitidine	azacitidine + lenalidomide
Started	36	36
Completed	21	19
Not completed	15	17
Treatment not started	3	-
Consent withdrawn by subject	-	2
Disease progression	6	2
Adverse Event	6	10
Did not start tretament	-	3

Baseline characteristics

Reporting groups	
Reporting group title	azacitidine
Reporting group description:	
Standard dose of azacitidine 5-2-2 (75 mg/m2/day subcutaneously12) with a total cycle length of 4 weeks and 6 cycles	
Reporting group title	azacitidine + lenalidomide
Reporting group description:	
Standard dose of AZA 5-2-2 (75 mg/m2/day subcutaneously12) with a total cycle length of 4 weeks + lenalidomide 10 mg, oral, daily, 21/28 days, starting day one in each azacitidine cycle and leaving the last week free of treatment. If tolerated, the dose was escalated to 25 mg daily during cycle four to six.	

Reporting group values	azacitidine	azacitidine + lenalidomide	Total
Number of subjects	36	36	72
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	11	10	21
From 65-84 years	25	26	51
85 years and over	0	0	0
Age continuous Units: years			
median	73	70	
full range (min-max)	35 to 82	37 to 84	-
Gender categorical Units: Subjects			
Female	16	14	30
Male	20	22	42

Subject analysis sets	
Subject analysis set title	Intention to treat group
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The subjects who were included in the study on an intentions to treat basis	

Reporting group values	Intention to treat group		
Number of subjects	72		
Age categorical 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)	21		
From 65-84 years	51		
85 years and over	0		
Age continuous			
Units: years			
median	71		
full range (min-max)	35 to 84		
Gender categorical			
Units: Subjects			
Female	30		
Male	42		

End points

End points reporting groups

Reporting group title	azacitidine
Reporting group description:	
Standard dose of azacitidine 5-2-2 (75 mg/m2/day subcutaneously12) with a total cycle length of 4 weeks and 6 cycles	
Reporting group title	azacitidine + lenalidomide
Reporting group description:	
Standard dose of AZA 5-2-2 (75 mg/m2/day subcutaneously12) with a total cycle length of 4 weeks + lenalidomide 10 mg, oral, daily, 21/28 days, starting day one in each azacitidine cycle and leaving the last week free of treatment. If tolerated, the dose was escalated to 25 mg daily during cycle four to six.	
Subject analysis set title	Intention to treat group
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The subjects who were included in the study on an intentions to treat basis	

Primary: response according to 2006 International Working Group (IWG) criteria for MDS13

End point title	response according to 2006 International Working Group (IWG) criteria for MDS13
End point description:	
The primary endpoint, was response according to 2006 International Working Group (IWG) criteria for MDS13, was assessed by two independent observers after six cycles of AZA or AZA+LEN treatment, or at end of study if this occurred at an earlier time point.	
End point type	Primary
End point timeframe:	
The Primary endpoint was assessed after six cycles of azacitidine or azacitidine+lenalidmode treatment, or at end of study if this occurred at an earlier time point.	

End point values	azacitidine	azacitidine + lenalidomide	Intention to treat group	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	33	33	66	
Units: Number of patients				
number (not applicable)	14	16	30	

Statistical analyses

Statistical analysis title	Statistical evaluation of response
Statistical analysis description:	
Continuous data were described by mean and median (range) values depending on the distribution of data. 2- or Fisher´s exact tests were used to measure the difference between responders and non-responders.	
Comparison groups	azacitidine v azacitidine + lenalidomide

Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.62
Method	Fisher exact

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs will be recorded by the Investigator(s) from the time the subject signs informed consent through the end of the designated follow-up period

Assessment type	Non-systematic

Dictionary used

Dictionary name	NCI CTCAE
Dictionary version	4.03

Reporting groups

Reporting group title	Azacitidine arm
Reporting group description: -	
Reporting group title	Azacitidin + lenalidomide arm

Reporting group description: -

Serious adverse events	Azacitidine arm	Azacitidin + lenalidomide arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	33 / 33 (100.00%)	33 / 33 (100.00%)	
number of deaths (all causes)	6	0	
number of deaths resulting from adverse events	2	0	
Cardiac disorders			
Heart failure			
subjects affected / exposed	0 / 33 (0.00%)	4 / 33 (12.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
Nervous system disorders			
Subarachnoid haematoma, cerebral hematoma			
subjects affected / exposed	1 / 33 (3.03%)	2 / 33 (6.06%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 1	
Blood and lymphatic system disorders			
Severe myelosupression			
subjects affected / exposed	28 / 33 (84.85%)	31 / 33 (93.94%)	
occurrences causally related to treatment / all	28 / 28	31 / 31	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			

subjects affected / exposed	27 / 33 (81.82%)	24 / 33 (72.73%)	
occurrences causally related to treatment / all	27 / 27	24 / 24	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anemia			
subjects affected / exposed	16 / 33 (48.48%)	13 / 33 (39.39%)	
occurrences causally related to treatment / all	16 / 16	13 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	25 / 33 (75.76%)	18 / 33 (54.55%)	
occurrences causally related to treatment / all	25 / 25	18 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fever			
subjects affected / exposed	2 / 33 (6.06%)	4 / 33 (12.12%)	
occurrences causally related to treatment / all	2 / 2	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 33 (6.06%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 33 (3.03%)	2 / 33 (6.06%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sweets syndrome			
subjects affected / exposed	2 / 33 (6.06%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Febrile neutropenia			

subjects affected / exposed	11 / 33 (33.33%)	15 / 33 (45.45%)	
occurrences causally related to treatment / all	11 / 11	15 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	8 / 33 (24.24%)	7 / 33 (21.21%)	
occurrences causally related to treatment / all	8 / 8	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 33 (3.03%)	5 / 33 (15.15%)	
occurrences causally related to treatment / all	1 / 1	5 / 5	
deaths causally related to treatment / all	1 / 1	4 / 4	
Sepsis			
subjects affected / exposed	3 / 33 (9.09%)	6 / 33 (18.18%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 4	
Fungal infection			
subjects affected / exposed	3 / 33 (9.09%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
perianal infection			
subjects affected / exposed	0 / 33 (0.00%)	2 / 33 (6.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary aspergillosis			
subjects affected / exposed	0 / 33 (0.00%)	2 / 33 (6.06%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Azacitidine arm	Azacitidin + lenalidomide arm	
Total subjects affected by non-serious adverse events subjects affected / exposed	33 / 33 (100.00%)	33 / 33 (100.00%)	
Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all)	29 / 33 (87.88%) 29	26 / 33 (78.79%) 26	
Anemia subjects affected / exposed occurrences (all)	26 / 33 (78.79%) 26	29 / 33 (87.88%) 29	
Thrombocytopenia subjects affected / exposed occurrences (all)	21 / 33 (63.64%) 21	28 / 33 (84.85%) 28	
General disorders and administration site conditions Nausea subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 3	9 / 33 (27.27%) 9	
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)	8 / 33 (24.24%) 8	13 / 33 (39.39%) 13	
Diarrhoea subjects affected / exposed occurrences (all)	5 / 33 (15.15%) 5	7 / 33 (21.21%) 7	
Skin and subcutaneous tissue disorders Injection site reaction subjects affected / exposed occurrences (all)	7 / 33 (21.21%) 7	6 / 33 (18.18%) 6	
Rash subjects affected / exposed occurrences (all)	4 / 33 (12.12%) 4	7 / 33 (21.21%) 7	
Infections and infestations Febrile neutropenia subjects affected / exposed occurrences (all)	11 / 33 (33.33%) 11	15 / 33 (45.45%) 15	
Pneumonia			

subjects affected / exposed	9 / 33 (27.27%)	9 / 33 (27.27%)	
occurrences (all)	9	9	
Infection			
subjects affected / exposed	1 / 33 (3.03%)	8 / 33 (24.24%)	
occurrences (all)	1	8	
Sepsis			
subjects affected / exposed	3 / 33 (9.09%)	6 / 33 (18.18%)	
occurrences (all)	3	6	
Urinary tract infection			
subjects affected / exposed	6 / 33 (18.18%)	2 / 33 (6.06%)	
occurrences (all)	6	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 November 2011	The approved CTA contains only one dose, 10 mg, of the comparator IMP, lenalidomide. According to the approved study protocol, a 25 mg dose of lenalidomide will also be used. The CTA has therefore been amended accordingly with acorrected MA number for the 10 mg
23 April 2012	The manufacturer of Lenalidomide has changed from Fischer to Almac and the package has changed from bottles to blisters, now available as a market product. The corresponding changes have been added to a revised CTA form (EudraCT v8).
13 June 2016	Due to slow inclusion rate we have decided during the last year to include patients who have had a maximum of 1 cycle of azacitidine before inclusion. So far every potential study object in that situation has been discussed with the study committee and noted as protocol violence in the CRF. In amendment 4 the exclusion criteria will be changed from: "Prior therapy with azacitidine" to "Prior therapy with >1 cycle of azacitidine".

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/35277655