Clinical trial results:
GHSG-AFM13
An open-label, randomized, multicenter phase II trial with AFM13 in patients with relapsed or refractory Hodgkin Lymphoma

Summary

EudraCT number	2014-004036-19
Trial protocol	DE
Global end of trial date	28 November 2019

Results information

Result version number	v1 (current)
This version publication date	19 September 2020
First version publication date	19 September 2020

Trial information

Trial identification

Sponsor protocol code	Uni-Koeln-1754

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02321592
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Cologne
Sponsor organisation address	Albertus-Magnus-Platz, Cologne, Germany, 50923
Public contact	German Hodgkin Study Group, German Hodgkin Study Group, 0049 22147888200, ghsg@uk-koeln.de
Scientific contact	German Hodgkin Study Group, German Hodgkin Study Group, 0049 22147888200, ghsg@uk-koeln.de

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	31 January 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 November 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Primary aim of the AFM13 trial was to demonstrate efficacy of AFM13 with an optimized treatment schedule. This phase II trial also aimed at selecting a treatment schedule, which warrants further investigation in a phase III clinical trial. The primary objectives of the AFM13 trial were to evaluate the tumor response to one 8-week cycle of AFM13 and to select one out of three therapeutic regimens of AFM13 for a potential phase III trial.

Further efficacy assessment, evaluation of safety and feasibility and assessment of patient reported outcomes were the secondary objectives of the trial.

Protection of trial subjects:

Written informed consent prior to study entry; Premedication with paracetamol, dimetindene, ranitidine, and prednisone; Reduced infusion rate for the first infusion and hospitalization during days 1-3 of weeks 1-2 to ensure that adequate measures can be taken in case of adverse events. Management of AFM13-associated infusion-related reactions and other AFM13-related side effects are described in the trial protocol; frequent mandatory safety laboratory examinations during therapy.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 June 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 25
Worldwide total number of subjects	25
EEA total number of subjects	25

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)	20
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment details:
Between June 26, 2015 and May 31, 2019, 25 adult patients with relapsed or refractory classical Hodgkin lymphoma were randomized or assigned to receive AFM13 treatment with the regimen specified for arms A (n=5), B (n=12), or C (n=8), respectively. The trial was terminated before stage-1 analysis.

Pre-assignment

Screening details:

Medical history (all clinical Symptoms, serious concurrent diseases); physical measurements (ECOG Performance Status, cardial, pulmonary, and thyroid function); laboratory diagnostics; pregnancy test; CT or MRI of neck, thorax and abdomen (obligatory); PET-CT (strongly recommended)

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

Patients were treated in each cycle with 1.5 mg/kg AFM13 three times per week over 8 weeks.
Patients were randomly assigned to receive treatment according to arm A or arm B

Arm type	Experimental
Investigational medicinal product name	AFM13
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1-2 cycles of AFM13 according to the regimen specified for Arm A

Arm title	Arm B

Arm description:

Patients received 1.5 mg/kg AFM13 three times per week for 2 weeks, followed by once Weekly administrations of 7.0 mg/kg over 6 weeks.
Patients were randomly assigned to receive treatment according to arm A or arm B.

Arm type	Experimental
Investigational medicinal product name	AFM13
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1-2 cycles of AFM13 according to the regimen specified for Arm B

Arm title	Arm C

Arm description:

Patients received a loading dose of 1 mg/kg administered over 1 hour followed by a 5-day continuous Infusion of 6 mg/kg, resulting in a total dose of 7 mg/kg per week.

After randomization into arms A and B had been postponed, arm C was introduced and all new patients were allocated to this arm.

Arm type	Experimental
Investigational medicinal product name	AFM13
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1-2 eight-week cycles of AFM13 according to the regimen specified for Arm B

Number of subjects in period 1	Arm A	Arm B	Arm C
Started	5	12	8
Completed	5	12	8

Period 2

Period 2 title	Stage 1 (overall period)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	All study patients

Arm description: -

Arm type	Experimental
Investigational medicinal product name	AFM13
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1-2 cycles of AFM13 according to the regimens specified for Arms A, B, and C

Number of subjects in period 2	All study patients
Started	25
Completed	25

Baseline characteristics

Reporting groups	
Reporting group title	Recruitment groups
Reporting group description: -	

Reporting group values	Recruitment groups	Total	
Number of subjects	25	25	
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)	20	20	
From 65-84 years	5	5	
85 years and over	0	0	
Age continuous Units: years			
median	45		
full range (min-max)	21 to 73	-	
Gender categorical Units: Subjects			
Female	1	1	
Male	24	24	
ECOG Performance Status Units: Subjects			
ECOG 0-1	24	24	
ECOG 2	1	1	
Time since first HL diagnosis			
Years between Primary Hodgkin diagnosis and registration for the GHSG-AFM13 trial			
Units: years			
median	7.2		
full range (min-max)	0.2 to 40.3	-	
HL therapies after first-line Units: number			
median	3		
full range (min-max)	1 to 11	-	

Subject analysis sets	
Subject analysis set title	Arm A
Subject analysis set type	Full analysis
Subject analysis set description: Trial subjects randomised to Arm A	

Subject analysis set title	Arm B
Subject analysis set type	Full analysis
Subject analysis set description: Subjects randomised to Arm B	
Subject analysis set title	Arm C
Subject analysis set type	Full analysis
Subject analysis set description: Subjects assigned to Arm C	

Reporting group values	Arm A	Arm B	Arm C
Number of subjects	5	12	8
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)	4	9	7
From 65-84 years	1	3	1
85 years and over	0	0	0
Age continuous Units: years			
median	48	43	41
full range (min-max)	23 to 73	21 to 72	24 to 64
Gender categorical Units: Subjects			
Female	0	0	1
Male	5	12	7
ECOG Performance Status Units: Subjects			
ECOG 0-1	5	11	8
ECOG 2	0	1	0
Time since first HL diagnosis			
Years between Primary Hodgkin diagnosis and registration for the GHSG-AFM13 trial			
Units: years			
median	13.7	6.8	4.9
full range (min-max)	4.2 to 40.3	3.6 to 14.9	0.2 to 35.8
HL therapies after first-line Units: number			
median	4	3	3
full range (min-max)	2 to 6	2 to 6	1 to 11

End points

End points reporting groups

Reporting group title	Arm A

Reporting group description:

Patients were treated in each cycle with 1.5 mg/kg AFM13 three times per week over 8 weeks.
Patients were randomly assigned to receive treatment according to arm A or arm B

Reporting group title	Arm B

Reporting group description:

Patients received 1.5 mg/kg AFM13 three times per week for 2 weeks, followed by once Weekly administrations of 7.0 mg/kg over 6 weeks.
Patients were randomly assigned to receive treatment according to arm A or arm B.

Reporting group title	Arm C

Reporting group description:

Patients received a loading dose of 1 mg/kg administered over 1 hour followed by a 5-day continuous Infusion of 6 mg/kg, resulting in a total dose of 7 mg/kg per week.
After randomization into arms A and B had been postponed, arm C was introduced and all new patients were allocated to this arm.

Reporting group title	All study patients

Reporting group description: -

Subject analysis set title	Arm A
Subject analysis set type	Full analysis

Subject analysis set description:

Trial subjects randomised to Arm A

Subject analysis set title	Arm B
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects randomised to Arm B

Subject analysis set title	Arm C
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects assigned to Arm C

Primary: Objective response rate (ORR) after 1 cycle

End point title	Objective response rate (ORR) after 1 cycle[1]

End point description:

Objective response was defined as complete or partial remission in the centrally reviewed restaging after 1 cycle of AFM13.

According to the protocol, the null hypothesis H0: ORR <= 10% was to be tested in a 2-stage design. The trial was terminated during stage 1 due to lack of recruitment. Thus, only descriptive analyses of the primary endpoint in the stage-1 intention-to-treat Population were performed.

End point type	Primary

End point timeframe:

PET/CT-based restaging was performed 20 to 22 (arms A and C) or 24 to 26 days (arm B) after the last day with AFM13 infusion in cycle 1.

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: No confirmative test was performed for the primary endpoint since no trial arm was carried into stage-2. Therefore, only a descriptive analysis of the primary endpoint in the stage-1 population was done. The objective response rate was estimated at 16.6%, 95%-confidence interval [4.5% - 36.1%].

End point values	All study patients	Arm A	Arm B	Arm C
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25	5	12	8
Units: subjects				
Objective response (Complete or Partial Remission)	4	1	1	2
No objective response (No Change or Progression)	20	4	10	6
not evaluated	1	0	1	0

Statistical analyses

No statistical analyses for this end point

Secondary: PET/CT-based remission status after cycle 1

End point title	PET/CT-based remission status after cycle 1

End point description:

End point type	Secondary

End point timeframe:

PET/CT-based restaging was performed 20 to 22 (arms A and C) or 24 to 26 days (arm B) after the last day with AFM13 infusion in cycles 1 and 2.

End point values	All study patients	Arm A	Arm B	Arm C
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25	5	12	8
Units: subjects				
Complete Remission	2	0	1	1
Partial Remission	2	1	0	1
Stable Disease	3	1	1	1
Progression	14	3	6	5
not evaluated	4	0	4	0

Statistical analyses

No statistical analyses for this end point

Secondary: PET/CT-base remission status after cycle 2

End point title	PET/CT-base remission status after cycle 2

End point description:

End point type	Secondary

End point timeframe:

PET/CT-based restaging was performed 20 to 22 (arms A and C) or 24 to 26 days (arm B) after the last day with AFM13 infusion in cycles 1 and 2.

End point values	All study patients	Arm A	Arm B	Arm C
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	2	2	1
Units: subjects				
Complete Remission	1	0	0	1
Partial Remission	1	1	0	0
Stable Disease	1	0	1	0
Progression	2	1	1	0
not evaluated	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Time to next salvage therapy

End point title	Time to next salvage therapy

End point description:

First and second new anticancer therapy after the last dose of study drug were to be recorded with the follow-up assessments.

End point type	Secondary

End point timeframe:

The follow-up period was one year measured from the restaging after the last AFM13 cycle. Within the scope of amendment 10 it was decided to shorten the follow-up period for the last arm C patient to 3 months.

End point values	All study patients	Arm A	Arm B	Arm C
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	19	4	9	6
Units: months				
median (full range (min-max))	3.2 (0.2 to 11.2)	4.9 (3.0 to 11.2)	2.1 (0.2 to 6.8)	3.2 (1.0 to 6.3)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were assessed during study treatment and within 28 days after end of study treatment or until the first day of a new HL therapy, whatever occurred first.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.2

Reporting groups

Reporting group title	Stage I - Overall period

Reporting group description:

All trial subjects

Serious adverse events	Stage I - Overall period		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 25 (20.00%)		
number of deaths (all causes)	9		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Generall physical health deterioration			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Pyloric stenosis			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			

Hypercalcemia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0.01 %

Non-serious adverse events	Stage I - Overall period		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 25 (40.00%)		
Investigations			
CPK increase	Additional description: All non-serious grade III-IV AEs		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Aspartate aminotransferase increased	Additional description: All non-serious grade III-IV AEs		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Lipase increased	Additional description: All non-serious grade III-IV AEs		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
White blood cell decreased	Additional description: All non-serious grade III-IV AEs		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Neutrophil count decreased	Additional description: All non-serious grade III-IV AEs		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Lymphocyte count decreased	Additional description: All non-serious grade III-IV AEs		
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anemia	Additional description: All grade III-IV non-serious AEs		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	6		
Leukopenia	Additional description: All non-serious grade III-IV AEs		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Lymphopenia	Additional description: All non-serious grade III-IV AEs		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Back pain	Additional description: All non-serious grade III-IV AEs		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 July 2015	Current Information regarding trial medication were taken into account and editorial changes were implemented.
20 August 2015	Current Information regarding trial medication were taken into account and editorial changes were implemented.
22 December 2015	Specifications of E-Data-Capture procedures were made and some assessment times were adapted and described in a more detailed way.
12 July 2016	Update of the Investigational Medicinal Product Dossier
10 May 2017	Within the Framework of the 5th, 6th, and 7th Amendment tretment arm C with continuous AFM13 Infusion over 5 days was introduced, while randomization into arms A and B is postponed.
24 April 2019	A mandatory premedication with Paracetamol, dimetindene, ranitidine and prednisone before the first Administration of AFM13 was included.
26 November 2019	Recruitment was terminated earlier than planned and with no continuation in stage II due to lack of recruitment. It was also decided to shorten the follow-up period to three months from restaging for the last patient of the trial.

Notes:

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.

The trial was terminated without continuation in stage II. All statistical analyses of primary and secondary endpoints are of descriptive nature. A reliable estimate of the ORR cannot be obtained for any arm.

Notes: