Clinical trial results:
A Phase II Open-label Multicenter Study to Assess the Efficacy and Safety of AFM13 in Patients with Relapsed or Refractory CD30-positive Peripheral T-cell Lymphoma or Transformed Mycosis Fungoides (REDIRECT).

Summary

EudraCT number	2019-001003-20
Trial protocol	ES DE PL IT
Global end of trial date	

Results information

Result version number	v1
This version publication date	24 May 2023
First version publication date	24 May 2023

Trial information

Trial identification

Sponsor protocol code	AFM13-202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04101331
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Affimed GmbH
Sponsor organisation address	Im Neuenheimer Feld 582, Heidelberg, Germany, 69120
Public contact	Clinical Operations, Affimed GmbH, +49 62216530770, trials@affimed.com
Scientific contact	Clinical Operations, Affimed GmbH, +49 62216530770, trials@affimed.com

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	Interim
Date of interim/final analysis	13 October 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 May 2022
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the antitumor activity of AFM13 by Independent Review Committee confirmed overall response rate (ORR)

Protection of trial subjects:

Only eligible subjects that met all the study inclusion and none of the exclusion criteria could enter the study. Subjects could withdraw from the study at any time without stating a reason and without prejudice to further treatment. The investigator may have withdrawn a subject from the study and discontinued study drug and assessments at any time. The sponsor reserved the right to request withdrawal of a subject because of protocol violation or any other significant reason.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 October 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Korea, Republic of: 13
Country: Number of subjects enrolled	Spain: 19
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Italy: 12
Country: Number of subjects enrolled	United States: 16
Country: Number of subjects enrolled	Australia: 21
Country: Number of subjects enrolled	Turkey: 7
Country: Number of subjects enrolled	Russian Federation: 11
Worldwide total number of subjects	108
EEA total number of subjects	40

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	58
From 65 to 84 years	49
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

This study was a Phase II open-label multicenter study to assess the efficacy and safety of AFM13 in subjects with relapsed or refractory CD30-positive peripheral T-cell lymphoma.

Pre-assignment

Screening details:

All the subjects were screened for CD30 expression. Investigators assessed the subjects, and they were enrolled in the study if they met all inclusion criteria and none of the exclusion criteria.

Period 1

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

Arms

Arm title	Cohort A

Arm description:

Subjects with Relapsed or Refractory CD30 positive Peripheral T-cell Lymphoma (PTCL).

Arm type	Experimental
Investigational medicinal product name	AFM13
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous AFM13 administered 200 milligram weekly until disease progression, unacceptable toxicity, Investigator discretion or withdrawal of consent.

Number of subjects in period 1	Cohort A
Started	108
Completed	8
Not completed	100
Consent withdrawn by subject	1
Disease progression	79
Allogenic transplant	1
Adverse event, non-fatal	7
Death	6
Investigator decision	6

Baseline characteristics

Reporting groups

Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	108	108	
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)	58	58	
From 65-84 years	49	49	
85 years and over	1	1	
Age continuous Units: years			
arithmetic mean	61.1		
standard deviation	± 13.98	-	
Gender categorical Units: Subjects			
Female	42	42	
Male	66	66	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	5	5	
Not Hispanic or Latino	90	90	
Unknown or Not Reported	13	13	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	15	15	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	5	5	
White	75	75	
More than one race	0	0	
Unknown or Not Reported	13	13	

End points

End points reporting groups

Reporting group title	Cohort A

Reporting group description:

Subjects with Relapsed or Refractory CD30 positive Peripheral T-cell Lymphoma (PTCL).

Primary: Overall Response Rate Assessed by Independent Review Committee Based on PET-CT

End point title	Overall Response Rate Assessed by Independent Review Committee Based on PET-CT[1]

End point description:

Overall response by Positron Emission Tomography-Computed Tomography (PET-CT) as defined by achieving complete response and/or partial response assessed by an Independent Review Committee (IRC) utilizing the modified Lugano Classification Revised Staging System for malignant lymphoma (Cheson, 2014).

End point type	Primary

End point timeframe:

Tumor assessment performed every 8 weeks for first 3 assessments, then every 12 weeks until documented disease progression (up to 28 months).

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: Statistical analysis is included as a comment, no group comparison was made.

End point values	Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	108[2]			
Units: Percentage				
number (confidence interval 95%)	32.4 (23.7 to 42.1)			

Notes:

[2] - One side P-value for exact binomial test = 0.051.

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Response Rate, Partial Response Rate and Overall Response Rate Assessed by Independent Review Committee Based on CT

End point title	Complete Response Rate, Partial Response Rate and Overall Response Rate Assessed by Independent Review Committee Based on CT

End point description:

Overall response by Computed Tomography (CT) as defined by achieving complete response and/or partial response assessed by an Independent Review Committee (IRC) utilizing the modified Lugano Classification Revised Staging System for malignant lymphoma (Cheson, 2014).

End point type	Secondary

End point timeframe:

Tumor assessment performed every 8 weeks for first 3 assessments, then every 12 weeks until documented disease progression (up to 28 months).

End point values	Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	108[3]			
Units: Percentage				
number (confidence interval 95%)				
Overall response rate (ORR)	24.1 (16.4 to 33.3)			
Complete response rate (CR rate)	8.3 (3.9 to 15.2)			
Partial response rate (PR rate)	15.7 (9.4 to 24.0)			

Notes:

[3] - One side P-value for exact binomial test = 0.537.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Overall Response Assessed by Independent Review Committee Based on PET-CT

End point title	Duration of Overall Response Assessed by Independent Review Committee Based on PET-CT

End point description:

Duration of response (DOR) defined as the period from first Partial Response (PR) and Complete Response (CR) assessment till first assessment of progressive disease or death. Response assessed by Positron Emission Tomography-Computed Tomography (PET-CT) by Independent Review Committee (IRC).

End point type	Secondary

End point timeframe:

Tumor assessment performed every 8 weeks for first 3 assessments, then every 12 weeks until documented disease progression (up to 26 months).

End point values	Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: Months				
median (confidence interval 95%)	2.3 (1.9 to 6.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment Related Adverse Event

End point title	Number of Subjects With Treatment Related Adverse Event

End point description:

Number of subjects who had treatment (AFM13) related Adverse Events.

The safety set consisted of all subjects who received at least one dose of AFM13 and had at least one post-baseline safety assessment.

End point type	Secondary

End point timeframe:

From the date of first treatment until the date of the last treatment + 37 days, up to 138 weeks.

End point values	Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	108			
Units: Participants	79			

Statistical analyses

No statistical analyses for this end point

Secondary: European Quality of Life 5-dimensional Pain/Discomfort Score (EQ-5D)

End point title	European Quality of Life 5-dimensional Pain/Discomfort Score (EQ-5D)

End point description:

Quality of Life (QoL) as measured by the European QoL 5-dimensional questionnaire (EQ-5D) for Cohorts A. The EQ-5D comprises asks for the current health state in the five dimensions: mobility, self care, usual activities, pain/discomfort, and anxiety/depression. Pain/discomfort scores assessed based on questionnaire. The categories of the response offer three levels pain/discomfort score: "no pain or discomfort" (score of 1), "moderate pain or discomfort" (score of 2), and "extreme pain and discomfort" (score of 3). Scores are presented from baseline to each visit for Cohort A.

The full analysis set (FAS) followed the intent to treat principle and consisted of all subjects who received at least one dose of AFM13.

End point type	Secondary

End point timeframe:

At baseline and final study visit, up to 138 weeks.

End point values	Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	108			
Units: Participants				
Baseline/No pain or discomfort	41			
Baseline/Moderate pain or discomfort	55			
Baseline/Extreme pain or discomfort	9			
Baseline/Missing	3			
Final study visit/No pain or discomfort	17			

Final study visit/Moderate pain or discomfort	36			
Final study visit/Extreme pain or discomfort	4			
Final study visit/Missing	51			

Statistical analyses

No statistical analyses for this end point

Secondary: European Quality of Life 5-dimensional Visual Analogue Scale Scores (EQ-5D)

End point title	European Quality of Life 5-dimensional Visual Analogue Scale Scores (EQ-5D)

End point description:

Quality of Life (QoL) as measured by the European Quality of Life 5-dimensional questionnaire (EQ-5D) for Cohorts A. Visual Analogue Scale scores assessed based on drawn scale from 0(worst imaginable state) to 100(best imaginable state). Subjects chose their health state on scale based on their situation by themselves.

The full analysis set (FAS) followed the intent to treat principle and consisted of all subjects who received at least one dose of AFM13.

End point type	Secondary

End point timeframe:

From baseline until final study visit, up to 138 weeks.

End point values	Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	108			
Units: Score on a scale				
arithmetic mean (standard deviation)	-6.8 (± 23.36)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate Assessed by Investigator Based on PET-CT

End point title	Overall Response Rate Assessed by Investigator Based on PET-CT

End point description:

Overall response by Positron Emission Tomography-Computed Tomography (PET-CT) as defined by achieving complete response and/or partial response assessed by the investigator utilizing the modified Lugano Classification Revised Staging System for malignant lymphoma (Cheson, 2014).

End point type	Secondary

End point timeframe:

Tumor assessment performed every 8 weeks for first 3 assessments, then every 12 weeks until documented disease progression (up to 28 months).

End point values	Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	108[4]			
Units: Percentage				
number (confidence interval 95%)	31.5 (22.9 to 41.1)			

Notes:

[4] - One side P-value for exact binomial test = 0.077

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate Assessed by Investigator Based on CT

End point title	Overall Response Rate Assessed by Investigator Based on CT

End point description:

Overall response by Computed Tomography (CT) as defined by achieving complete response and/or partial response assessed by the investigator utilizing the modified Lugano Classification Revised Staging System for malignant lymphoma (Cheson, 2014).

End point type	Secondary

End point timeframe:

Tumor assessment performed every 8 weeks for first 3 assessments, then every 12 weeks until documented disease progression (up to 28 months).

End point values	Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	108[5]			
Units: Percentage				
number (confidence interval 95%)	29.6 (21.2 to 39.2)			

Notes:

[5] - One side P-value for exact binomial test = 0.159

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Overall Response Assessed by Independent Review Committee Based on CT

End point title	Duration of Overall Response Assessed by Independent Review Committee Based on CT

End point description:

Duration of response (DOR) defined as the period from first Partial Response (PR) and Complete Response (CR) assessment till first assessment of progressive disease or death. Response assessed by Computed Tomography (CT) by Independent Review Committee (IRC).

End point type	Secondary

End point timeframe:

Tumor assessment performed every 8 weeks for first 3 assessments, then every 12 weeks until documented disease progression (up to 26 months).

End point values	Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: Months				
median (confidence interval 95%)	2.1 (1.9 to 7.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Response Rate and Partial Response Rate Assessed by Independent Review Committee Based on PET-CT

End point title	Complete Response Rate and Partial Response Rate Assessed by Independent Review Committee Based on PET-CT

End point description:

Complete response and/or partial response by Positron Emission Tomography-Computed Tomography (PET-CT) assessed by an Independent Review Committee (IRC) utilizing the modified Lugano Classification Revised Staging System for malignant lymphoma (Cheson, 2014).

End point type	Secondary

End point timeframe:

Tumor assessment performed every 8 weeks for first 3 assessments, then every 12 weeks until documented disease progression (up to 28 months).

End point values	Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	108			
Units: percentage				
number (confidence interval 95%)				
Complete response rate (CR rate)	10.2 (5.2 to 17.5)			
Partial response rate (PR rate)	22.2 (14.8 to 31.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Overall Response Assessed by Investigator Based on PET-CT

End point title	Duration of Overall Response Assessed by Investigator Based on PET-CT

End point description:

Duration of response (DOR) defined as the period from first Partial Response (PR) and Complete Response (CR) assessment till first assessment of progressive disease or death. Response assessed by Positron Emission Tomography-Computed Tomography (PET-CT) by the investigator.

End point type	Secondary

End point timeframe:

Tumor assessment performed every 8 weeks for first 3 assessments, then every 12 weeks until documented disease progression (up to 26 months).

End point values	Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: months				
median (confidence interval 95%)	2.2 (1.9 to 9.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Overall Response Assessed by Investigator Based on CT

End point title	Duration of Overall Response Assessed by Investigator Based on CT

End point description:

Duration of response (DOR) defined as the period from first Partial Response (PR) and Complete Response (CR) assessment till first assessment of progressive disease or death. Response assessed by Computed Tomography (CT) by the investigator.

End point type	Secondary

End point timeframe:

Tumor assessment performed every 8 weeks for first 3 assessments, then every 12 weeks until documented disease progression (up to 26 months).

End point values	Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: months				
median (confidence interval 95%)	5.9 (1.9 to 9.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Measured Concentration (Cmax) of AFM13 at Cycle 1/Day 1

End point title	Maximum Measured Concentration (Cmax) of AFM13 at Cycle 1/Day 1

End point description:

Maximum measured concentration (Cmax) of the AFM13 in plasma.

The pharmacokinetic set (PK) consists of subjects who have at least received one dose of study drug and have at least one post dose PK measurement.

End point type	Secondary

End point timeframe:

Predose and 1 hour after start of infusion, end of injection (EOI) and 1 hour, 2 hours, 3 hours, 24 hours and 48 hours after EOI on Cycle 1 Day 1.

End point values	Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	26232 (± 270)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Measured Concentration (Cmax) of AFM13 at Cycle 1/Day 29

End point title	Maximum Measured Concentration (Cmax) of AFM13 at Cycle 1/Day 29

End point description:

Maximum measured concentration (Cmax) of the AFM13 in plasma.

The pharmacokinetic set (PK) consists of subjects who have at least received one dose of study drug and have at least one post dose PK measurement.

End point type	Secondary

End point timeframe:

Predose and 1 hour after start of infusion, end of injection (EOI) and 1 hour, 2 hours, 3 hours, 24 hours and 48 hours after EOI on Cycle 1 Day 29.

End point values	Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	24435 (± 364)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-Time Curve of AFM13 From 0 to Infinity (AUC 0-∞) at Cycle 1/Day 1

End point title	Area Under the Concentration-Time Curve of AFM13 From 0 to Infinity (AUC 0-∞) at Cycle 1/Day 1

End point description:

Area under concentration (AUC) versus time curve of the AFM13 in plasma over time interval from 0 extrapolated to infinity.

The pharmacokinetic set (PK) consists of subjects who have at least received one dose of study drug and have at least one post dose PK measurement.

End point type	Secondary

End point timeframe:

Predose and 1 hour after start of infusion, end of injection (EOI) and 1 hour, 2 hours, 3 hours, 24 hours and 48 hours after EOI on Cycle 1 Day 1.

End point values	Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: ng.h/mL				
geometric mean (geometric coefficient of variation)	612361 (± 60.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-Time Curve of AFM13 From 0 to Infinity (AUC 0-∞) at Cycle 1/Day 29

End point title	Area Under the Concentration-Time Curve of AFM13 From 0 to Infinity (AUC 0-∞) at Cycle 1/Day 29

End point description:

Area under concentration (AUC) versus time curve of the AFM13 in plasma over time interval from 0 extrapolated to infinity.

The pharmacokinetic set (PK) consists of subjects who have at least received one dose of study drug and have at least one post dose PK measurement.

End point type	Secondary

End point timeframe:

Predose and 1 hour after start of infusion, end of injection (EOI) and 1 hour, 2 hours, 3 hours, 24 hours and 48 hours after EOI on Cycle 1 Day 29.

End point values	Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: ng.h/mL				
geometric mean (geometric coefficient of variation)	749717 (± 35)			

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Distribution at Steady State (Vss) of AFM13 at Cycle 1/Day 1

End point title	Volume of Distribution at Steady State (Vss) of AFM13 at Cycle 1/Day 1

End point description:

Volume of distribution at steady state (Vss) of the AFM13.

The pharmacokinetic set (PK) consists of subjects who have at least received one dose of study drug and have at least one post dose PK measurement.

End point type	Secondary

End point timeframe:

Predose and 1 hour after start of infusion, end of injection (EOI) and 1 hour, 2 hours, 3 hours, 24 hours and 48 hours after EOI on Cycle 1 Day 1.

End point values	Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Liter				
geometric mean (geometric coefficient of variation)	7.46 (± 41.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Distribution at Steady State (Vss) of AFM13 at Cycle 1/Day 29

End point title	Volume of Distribution at Steady State (Vss) of AFM13 at Cycle 1/Day 29

End point description:

Volume of distribution at steady state (Vss) of the AFM13.

The pharmacokinetic set (PK) consists of subjects who have at least received one dose of study drug and have at least one post dose PK measurement.

End point type	Secondary

End point timeframe:

Predose and 1 hour after start of infusion, end of injection (EOI) and 1 hour, 2 hours, 3 hours, 24 hours and 48 hours after EOI on Cycle 1 Day 29.

End point values	Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: Liter				
geometric mean (geometric coefficient of variation)	5.1 (± 58.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: The Terminal Half-life (t1/2) of AFM13 at Cycle 1/Day 1

End point title	The Terminal Half-life (t1/2) of AFM13 at Cycle 1/Day 1

End point description:

The terminal half-life (t1/2) of the AFM13.

The pharmacokinetic set (PK) consists of subjects who have at least received one dose of study drug and have at least one post dose PK measurement.

End point type	Secondary

End point timeframe:

Predose and 1 hour after start of infusion, end of injection (EOI) and 1 hour, 2 hours, 3 hours, 24 hours and 48 hours after EOI on Cycle 1 Day 1.

End point values	Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: hours				
geometric mean (geometric coefficient of variation)	20.7 (± 35.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: The Terminal Half-life (t1/2) of AFM13 at Cycle 1/Day 29

End point title	The Terminal Half-life (t1/2) of AFM13 at Cycle 1/Day 29

End point description:

The terminal half-life (t1/2) of the AFM13.

The pharmacokinetic set (PK) consists of subjects who have at least received one dose of study drug and have at least one post dose PK measurement.

End point type	Secondary

End point timeframe:

Predose and 1 hour after start of infusion, end of injection (EOI) and 1 hour, 2 hours, 3 hours, 24 hours and 48 hours after EOI on Cycle 1 Day 29.

End point values	Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: hours				
geometric mean (geometric coefficient of variation)	19.6 (± 47.4)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the date of first treatment till the date of the last treatment + 37 days, up to 138 weeks.

Adverse event reporting additional description:

The safety set consisted of all subjects who received at least one dose of AFM13 and had at least one post-baseline safety assessment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Cohort A

Reporting group description:

Subjects with Relapsed or Refractory CD30 positive Peripheral T-cell Lymphoma (PTCL).

Serious adverse events	Cohort A		
Total subjects affected by serious adverse events			
subjects affected / exposed	43 / 108 (39.81%)		
number of deaths (all causes)	46		
number of deaths resulting from adverse events	6		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diffuse large B-cell lymphoma			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Superior vena cava syndrome			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	2 / 108 (1.85%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Chills			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	2 / 108 (1.85%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Dyspnoea			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemoptysis			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Pulmonary haemorrhage				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pulmonary oedema				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Investigations				
Hepatic enzyme increased				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
International normalised ratio increased				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Infusion related reaction				
subjects affected / exposed	5 / 108 (4.63%)			
occurrences causally related to treatment / all	8 / 8			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute left ventricular failure				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiomyopathy				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Nervous system disorders				
Ischaemic cerebral infarction				

subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 108 (2.78%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
COVID-19			
subjects affected / exposed	9 / 108 (8.33%)		
occurrences causally related to treatment / all	0 / 33		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	5 / 108 (4.63%)		
occurrences causally related to treatment / all	2 / 5		
deaths causally related to treatment / all	0 / 2		
Herpes zoster			
subjects affected / exposed	2 / 108 (1.85%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Septic shock			

subjects affected / exposed	2 / 108 (1.85%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
COVID-19 pneumonia				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile colitis				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Cytomegalovirus infection reactivation				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enterococcal bacteraemia				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Orchitis				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Periodontitis				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				

subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Rhinovirus infection			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Soft tissue infection			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular access site infection			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Cohort A		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	95 / 108 (87.96%)		
Investigations			
Blood lactate dehydrogenase increased			
subjects affected / exposed	6 / 108 (5.56%)		
occurrences (all)	8		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	25 / 108 (23.15%)		
occurrences (all)	67		
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 108 (9.26%)		
occurrences (all)	12		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	16 / 108 (14.81%)		
occurrences (all)	24		
Neutropenia			
subjects affected / exposed	14 / 108 (12.96%)		
occurrences (all)	53		
Thrombocytopenia			
subjects affected / exposed	13 / 108 (12.04%)		
occurrences (all)	28		
Lymphopenia			
subjects affected / exposed	6 / 108 (5.56%)		
occurrences (all)	13		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	20 / 108 (18.52%)		
occurrences (all)	27		
Asthenia			
subjects affected / exposed	9 / 108 (8.33%)		
occurrences (all)	14		
Chills			

subjects affected / exposed occurrences (all)	7 / 108 (6.48%) 9		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all)	 13 / 108 (12.04%) 13 12 / 108 (11.11%) 18 11 / 108 (10.19%) 13 10 / 108 (9.26%) 10 8 / 108 (7.41%) 9 6 / 108 (5.56%) 7		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all)	 9 / 108 (8.33%) 10 8 / 108 (7.41%) 10 8 / 108 (7.41%) 12		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) Erythema	 17 / 108 (15.74%) 26		

subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all)	10 / 108 (9.26%) 12 7 / 108 (6.48%) 9		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	 8 / 108 (7.41%) 9		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	 9 / 108 (8.33%) 11		
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	 6 / 108 (5.56%) 6		
Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all) Decreased appetite subjects affected / exposed occurrences (all) Hypomagnesaemia subjects affected / exposed occurrences (all)	 8 / 108 (7.41%) 10 7 / 108 (6.48%) 8 7 / 108 (6.48%) 11		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 March 2019	Global Protocol Amendment 1, Final Version 2.0 Clarification on PTCL (Peripheral T-cell Lymphoma) and TMF (Transformed Mycosis Fungoides) definition to include Ber-H2 targeted IHC (Immunohistochemistry) using Ber-H2 targeted assay. Photography for Cohort C was updated in different sections of the protocol to clarify that it referred to whole body photography. Addition of the ALK (Anaplastic Lymphoma Kinase) status to be also performed centrally as well as information on the allowable age of tumor slides. Update to the timeframe for blood sampling and ECG (Electrocardiogram) performance, cytokine testing time points and PK (Pharmocokinetics) sampling windows. Definition of premedication timeframe and addition of timeframe information on assessment around EOI (End of Infusion).

07 June 2019	Global Protocol Amendment 2, Final Version 3.0 part 1/2 Redefinition of CD30 cut-offs for each cohort based on IHC validation levels. Removal of 4 weeks confirmation criteria for Cohort A and B based on standard of care assessment criteria for PTCL (Peripheral T-cell Lymphoma) and update of study objectives to reflect the new requirement of 8 weeks for the definition of confirmed response for subjects in Cohort C. Change of the secondary and exploratory objectives by inclusion of PET-CT (Positron emission tomography–computed tomography)-based ORR (Objective Response Rate) (secondary), and PFS (Progression-free Survival) and OS (Overall Survival) (exploratory); removal of the exploratory objective for the serum albumin levels. Change of dosing schedule to weekly dosing for all treatment cycles based on FDA (Food and Drug Administration) feedback. Specification on the allowed PTCL subtypes based on the FDA feedback and clarification on eligibility based on central testing with local results being allowed from sites with validated CD30 IHC assay only. Updated measurable disease definition for Cohorts A and B to include FDG (Fluorodeoxyglucose) avid disease by PET. Updated subject population definition and definition of intolerance and specified requirement for documentation of intolerance. Updated laboratory functional parameters for inclusion/exclusion criteria so that PT (Preferred Term) and aPTT (Activated Partial Thromboplastin Time) were no longer specified as well as on exclusion of specific subtypes of lymphoma. Reduced time from organ transplant prior study entry from 5 to 3 years. Removal of the information that ventricular cardiovascular physiology was allowed. Removal of impaired lung function as an exclusion criterion and change on Hepatitis B and C exclusion criteria language. Removal of language that subjects with a CR (Complete Response) were allowed to have their AFM13 dosing held per FDA feedback.

07 June 2019	Global Protocol Amendment 2, Final Version 3.0 part 2/2 Updated definition of variable estimand based on the new requirement of 8 weeks for the definition of confirmed response for subjects in Cohort C. Addition of a Pre-screening period to determine the suitability of subjects to enter the Screening Period based on their CD30 expression results and a requirement for subjects to sign a Pre-screening ICF (Informed Consent Form). Addition of the modified Lugano Classification. Replacement of mandatory premedication with recommended premedication and removal of NSAIDs (Non-steroidal Anti-inflammatory Drugs) as a part of the regimen. Addition of new separate analyses of CR and PR independently in Section 8.5.1 and censoring rules for the DOR (Duration of Response) calculation in Section 8.6.1.2 of the protocol. Addition of a plan to analyze the data if Cohort B had more than 4 responses, but Cohort A failed at stage 1 in Section 8.9 of the protocol. Minor updates of the Schedule of Assessment (footnotes 2, 9-10, 12-13, 19-20). Addition of serology and pathology testing to be performed by sites locally in Appendix D of the protocol. Updated response criteria for PTCL to clarify that CT-based response will guide both the clinical decisions and the Overall Response assessment for subjects in Cohorts A and B.
02 July 2020	Global Protocol Amendment 3, Final Version 4.0 part 1/5 The overall rationale for this amendment was to update the protocol to introduce changes made to the premedication regimen for administration of AFM13, as well as the guidance for the management of AFM13 related IRRs and other AEs (Adverse Events). Results of the recently completed study AFM13-103 were added to update current information about clinical studies conducted with AFM13. PK considerations were updated based on results from previous AFM-13 studies that have shown that AUC0-∞ (Area Unver Curve) of at least 100,000 h*ng/mL (hours*nanogram/milligram) was important to increase the likelihood of achieving clinical benefit of AFM-13 treatment. Studies have also shown that lower albumin levels led to faster clearance, which impacted AUC. Modelling projections have shown that chosen AFM-13 dose for this study (200 milligram weekly) provided required exposure margin needed for clinical efficacy even in subjects with low albumin. Language for endpoints was made more specific. Some of the secondary endpoints were moved to exploratory endpoints. Redundant language for some of the endpoints was removed. Of note, there was no impact on the overall scientific value of the study. Considering the current COVID-19 pandemic situation, the sponsor recognized there could have been a situation where subject may have had to withdraw due to direct/indirect impact of COVID-19. A criterion for subject replacement was added for those subjects who dropped-out prior to their first post-baseline efficacy assessment. Also, impact of subjects dropping-out due to COVID-19 pandemic on sensitivity analysis was clarified. For this protocol, to cover the pandemic situation, up to 10 additional patients were allowed to be enrolled for Cohort A and 2 additional patients for Cohort C.

02 July 2020	Global Protocol Amendment 3, Final Version 4.0 part 2/5 Language in Section 3.1 (inclusion criteria) was amended to clarify the importance of central CD30 testing to determine eligibility in order to provide consistency in evaluation of CD30 expression in subjects across study sites. Inclusion criterion # 5 was amended. The Sponsor recognized that the subject population for this study may have needed radiation therapy because of their disease condition. The criterion was added such that subjects who may have required radiation therapy for palliative intent to a single cutaneous lesion or single nodal lesion may have been enrolled in this study after agreement with the Sponsor. Inclusion criterion #7 was amended. Alopecia is a common side effect of anti-cancer therapies. It was clarified that subjects who may have experienced alopecia (of any grade) with prior anti-cancer therapy were allowed to participate in the study. Inclusion criterion #10 was amended. The Sponsor recognized that given the disease state under study in a R/R (Relapsed or Refractory) setting, there may have been subjects who had a compromised bone marrow but who could be reasonably supported medically in this regard. This text was added to provide clarification on when such may be considered for enrollment in the trial. Exclusion criterion #6 was amended. Active Hepatitis B and Hepatitis C were broad exclusion criteria. In addition, the Sponsor recognized that there were some subjects with chronic hepatitis B who were effectively managed with antiviral prophylaxis to prevent reactivation in the setting of immunosuppression due to malignancy and the associated treatments. The language in this exclusion criteria was amended to reflect this understanding and provide further guidance on the eligibility or ineligibility of subjects who lived with this comorbidity.
02 July 2020	Global Protocol Amendment 3, Final Version 4.0 part 3/5 Details about process for subject enrollment were removed from protocol and a cross-reference was included to a separate document ‘Enrollment process’, which covered these details. Published FDA guidance recognized that the COVID-19 pandemic may have affected the conduct of clinical trials. Special focus was therefore placed on the safety of trial subjects with modification of the study conduct accordingly. As such, in agreement with this guidance, the protocol was amended to include a criterion of withdrawing a subject from study upon a benefit-risk analysis, should that patient be directly or indirectly impacted due to pandemic. In addition, the Sponsor recognized that for some subjects it may have been clinically beneficial to transition to stem cell transplant once they had achieved durable response in the study. The amended language clarified that these subjects were to be withdrawn from the study. Language on Pre-screening was amended to clarify that CD30 expression levels for all subjects were to be confirmed centrally to avoid any potential inter-site variance. Text was updated to clarify that hepatitis serology was to be confirmed during screening period by laboratory tests, and HIV (Human Immunodeficiency Virus) serology was to be repeated only if the status was unknown. Results from completed studies have shown that overall AFM-13 had low toxic potential as it related to adverse hematological events. However, evaluation of hematological parameters both pre-dose and now at the end of infusion may assist in the investigation of any potential hematological predictors of IRR (Infusion-related Reaction). In this regard, the Sponsor has updated the current protocol to clarify that hematological parameters were to be monitored closely during start of treatment in Cycle 1 Day 1, and results were to be collected and analyzed predose and end of infusion.

02 July 2020	Global Protocol Amendment 3, Final Version 4.0 part 4/5 Clarification on Exploratory Biomarker Flow Cytometry that samples could only be taken at sites that had the respective capabilities to cryopreserve them. Clarification that CD30 positivity was to be evaluated centrally to determine study eligibility and that local IHC (Immunohistochemistry) results were not be used for this purpose. In addition, since this was trial in subjects with R/R disease, many of whom would have received multiple prior therapies, the protocol was also amended to state that biopsy samples older than 90 days prior to pre-screening were not allowed. This would better ensure that the CD30 expression at study entry was truly representative of the current status. In addition, it was further clarified that bone marrow biopsies were not accepted to enroll subjects in Cohorts A and B. The primary endpoint for these cohorts was to be assessed by CT scan, and similar to cutaneous lesions (cutaneous biopsies also not allowed to determine eligibility for Cohorts A and B), bone marrow responses were not assessed by CT scan. To allow testing per local country specific requirements, text was updated to state that FSH (Follicle-stimulating Hormone) testing was allowed in blood or urine. However, it was clarified that if the results of urine test were not clear then the test was to be done with blood sample. The sponsor recognized that due to current COVID-19 pandemic situation, there could have been operational challenges at different sites in different countries. It was recognized that a more intensive PK sampling schedule could be potentially more burdensome to trial subjects and site staff in the setting of this pandemic. As such, the criteria that mandated completing PK sampling in Group 1 prior to Group 2 were changed to state that Group 2 sampling (less intensive) could be commenced prior to completion of PK sampling in Group 1 (more intensive). This would not impact overall PK anal
02 July 2020	Global Protocol Amendment 3, Final Version 4.0 part 5/5 To improve the subjects' tolerability to AFM13 while participating in the study and to maintain the planned dose intensity, which was assumed to improve antitumor activity, the sponsor issued a letter of amendment (LOA) mandating premedication with a regimen that included steroids. The LOA also included revisions for the management of IRR. The protocol was amended in alignment with the LOA including suggested revisions from the FDA. AFM-13 infusion rate was specified in mg/hr instead of total infusion time to provide greater clarity, especially in the setting of infusion rate adjustments for IRRs, per FDA guidance. Clarification that preventive hospitalizations due to COVID-19 situation were not to be categorized as SAEs (Serious Adverse Events). Positive results for COVID-19 were considered an important medical situation and the criteria for immediate reporting were included in the protocol. Guidance for Industry about sensitivity analysis was followed. Text was added to state that additional analyses might be needed due to current COVID-19 pandemic. This addition was in alignment to the following guidance: EMA/CHMP/ICH/436221/2017 Committee for Medicinal Products for Human Use ICH (International Council for Harmonisation) E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials (17 February 2020). Text clarified for the intent behind the interim analyses. Cohort C was not intended to have an interim analysis due to its size of 20 patients and the exploratory nature and the interim analysis was removed. Additional subgroup analysis was introduced to evaluate the potentially combined Cohort A and B as subgroups at the final analysis. Substantive changes made to Table 2 and Table 4 of the protocol, Version 3.0 (see Appendix 16.1.1).

29 June 2021	Global Protocol Amendment 4, Final Version 5.0 The overall rationale for this amendment was to update the protocol to change the primary form of assessment from CT scan to PET/CT based on updated NCCN (National Comprehensive Cancer Network) guidelines. Please note that Global Final Version 5.0 was signed but not distributed.
12 July 2021	Global Protocol Amendment 5, Final Version 6.0 The overall rationale for this amendment was to update the protocol to change the primary form of assessment from CT scan to PET/CT based on updated NCCN guidelines. This change was introduced in Version 5.0 from 29 June 2021. Prior to distribution of Version 5.0, additional changes for clarification of Inclusion Criteria #5 and #10 and an update of the shelf life as per the most recent IB update were added in Version 6.0 (12 July 2021). Clarification on the premedication regimen language: The intent was to include at least an H1 antagonist with the option to also include an H2 antagonist. Based on the recommendation of the Independent Safety Review Committee, the Sponsor provided more specific guidance for Investigators should their subjects have experienced treatment related adverse events.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported