



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, cardiac, 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 | | | |
| General 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 treatment 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: