# Clinical trial results:
# Dose Finding safety run in Phase followed by a randomized Phase II Trial of Intensive Chemotherapy With or Without Volasertib (BI 6727) Administered Prior or After Chemotherapy in Patients With Newly Diagnosed High-Risk Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML)

## Summary

| | |
|---|---|
| EudraCT number | 2014-000477-39 |
| Trial protocol | DE |
| Global end of trial date | 28 November 2016 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 12 June 2021 |
| First version publication date | 12 June 2021 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | AMLSG20-13 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02198482 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | University Hospital Ulm |
| Sponsor organisation address | Albert-Einstein-Allee 23, Ulm, Germany, 89081 |
| Public contact | Hartmut Döhner, University Hospital Ulm, +49 73150045521, hartmut.doehner@uniklinik-ulm.de |
| Scientific contact | Hartmut Döhner, University Hospital Ulm, +49 73150045521, hartmut.doehner@uniklinik-ulm.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 | 13 November 2017 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 28 November 2016 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

Primary efficacy objective
- To evaluate efficacy (CR/CRi rate) of the combination of intensive chemo-therapy with volasertib administered prior or after chemotherapy

Secondary efficacy objectives
- To evaluate cumulative incidence of relapse (CIR) and death (CID), relapse-free survival (RFS), event-free survival (EFS), overall survival (OS) of the combination of intensive chemotherapy with volasertib administered prior or after chemotherapy

Safety objectives
- To evaluate incidence and intensity of adverse events (AEs) according to Common Terminology Criteria for Adverse Events (CTCAE) version v4.03 of the combination of intensive chemotherapy with Volasertib administered prior or after chemotherapy.

Protection of trial subjects:

In this study, safety was assessed by evaluating the following: reported adverse events, clinical laboratory test results, vital signs measurements, ECG findings, chest X-ray, echo scan, physical examination findings, monitoring of concomitant therapy. For each safety parameter, all findings (whether normal or abnormal) were recorded in the eCRF.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 29 March 2016 |
| 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 | Germany: 6 |
| Worldwide total number of subjects | 6 |
| EEA total number of subjects | 6 |

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) | 4 |
| From 65 to 84 years | 2 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

First patient in: 29.03.2016
Early termination date: 28.11.2016
On 22.11.2016 Boehringer Ingelheim decided to discontinue the development of Volasertib due to manufacturing problems. Recruitment of patients was already suspended since 01.06.2016 due to the manufacturing problems mentioned above.

### Pre-assignment

Screening details:

Molecular genetic analysis (central AMLSG reference lab) of blood and bone marrow was performed at baseline within 48 hours to make an enrollment possible.

### Period 1

| | |
|---|---|
| Period 1 title | Safety Run-in Phase (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Volasertib prior chemotherapy |

Arm description: -

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Volasertib |
| Investigational medicinal product code | BI6727 |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Each vial of Volasertib contained 350 mg (vial with 175 ml, 2.0 mg/ml) and was ad-ministered as intravenous infusion over 2 hours in a total volume of 500 ml 0.9% physiological sodium chloride (NaCl). An initial safety run-in study was planned administering intensive induction therapy as well as consolidation therapy with the study drug Volasertib administered prior or after chemotherapy. A modified Fibonacci design had to be followed for the dose escalation; Volasertib dose levels were defined at level 0 of 170 mg/m2 BSA, level +1 of 200 mg/m2 BSA, and level -1 of 140 mg/m2 BSA. After establishing the Volasertib dose, a randomized Phase II portion of the trial was planned.

| | |
|---|---|
| **Arm title** | Volasertib after chemotherapy |

Arm description: -

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Volasertib |
| Investigational medicinal product code | BI6727 |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Each vial of Volasertib contained 350 mg (vial with 175 ml, 2.0 mg/ml) and was ad-ministered as intravenous infusion over 2 hours in a total volume of 500 ml 0.9% physiological sodium chloride (NaCl). An initial safety run-in study was planned administering intensive induction therapy as well as consolidation therapy with the study drug Volasertib administered prior or after chemotherapy. A modified Fibonacci design had to be followed for the dose escalation; Volasertib dose levels were defined at level 0 of 170 mg/m2 BSA, level +1 of 200 mg/m2 BSA, and level -1 of 140 mg/m2 BSA. After establishing the Volasertib dose, a randomized Phase II portion of the trial was planned.

| **Number of subjects in period 1** | Volasertib prior chemotherapy | Volasertib after chemotherapy |
|---|---|---|
| Started | 4 | 2 |
| Completed | 2 | 1 |
| Not completed | 2 | 1 |
| Adverse event, serious fatal | 1 | - |
| Consent withdrawn by subject | 1 | - |
| Lack of efficacy | - | 1 |

## Baseline characteristics

### Reporting groups

| Reporting group title | Safety Run-in Phase (overall period) |
|---|---|

Reporting group description: -

| Reporting group values | Safety Run-in Phase (overall period) | Total | |
|---|---|---|---|
| Number of subjects | 6 | 6 | |
| Age categorical<br>Units: Subjects | | | |
| Age <=60 years | 4 | 4 | |
| Age >60 years | 2 | 2 | |
| Age continuous<br>Units: years | | | |
| median | 53 | | |
| full range (min-max) | 42 to 75 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 1 | 1 | |
| Male | 5 | 5 | |

### Subject analysis sets

| Subject analysis set title | Analysis data set |
|---|---|
| Subject analysis set type | Per protocol |

Subject analysis set description:

The analysis set contains all subjects which received at least one dose of study medication within the trial.

| Reporting group values | Analysis data set | | |
|---|---|---|---|
| Number of subjects | 5 | | |
| Age categorical<br>Units: Subjects | | | |
| Age <=60 years | 3 | | |
| Age >60 years | 2 | | |
| Age continuous<br>Units: years | | | |
| median | 53 | | |
| full range (min-max) | 42 to 75 | | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 1 | | |
| Male | 4 | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Volasertib prior chemotherapy |
| Reporting group description: - | |
| Reporting group title | Volasertib after chemotherapy |
| Reporting group description: - | |
| Subject analysis set title | Analysis data set |
| Subject analysis set type | Per protocol |

Subject analysis set description:

The analysis set contains all subjects which received at least one dose of study medication within the trial.

### Primary: Rate of complete remission / complete remission with incomplete hematological recovery

| | |
|---|---|
| End point title | Rate of complete remission / complete remission with incomplete hematological recovery[1] |

End point description:

| | |
|---|---|
| End point type | Primary |

End point timeframe:

after induction therapy (within two 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: Since the trial was discontinued prematurely during the safety run-in phase after treatment of 5 patients, primary and secondary efficacy endpoints were not analyzed and follow-up of patients was terminated.

| End point values | Analysis data set | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | | | | |
| Units: Patients with CR/CRi | | | | |
| CR/CRi | 3 | | | |
| no CR/CRi | 2 | | | |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

The adverse event reporting period for this trial began upon signing of informed consent and ended 28 days after the last treatment administration or until all study drug-related toxicities are resolved, whichever is later.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | CTCAE |
| Dictionary version | 4.03 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Overall treatment period |

Reporting group description: -

| Serious adverse events | Overall treatment period | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 5 (40.00%) | | |
| number of deaths (all causes) | 1 | | |
| number of deaths resulting from adverse events | 1 | | |
| Infections and infestations | | | |
| Soft tissue infection | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |

Frequency threshold for reporting non-serious adverse events: 1 %

| Non-serious adverse events | Overall treatment period | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 5 / 5 (100.00%) | | |
| Vascular disorders | | | |
| hematoma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 5 (20.00%) | | |
| occurrences (all) | 1 | | |
| Hypertension | | | |
| subjects affected / exposed | 2 / 5 (40.00%) | | |
| occurrences (all) | 2 | | |
| General disorders and administration site conditions | | | |
| Chills | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | | |
| occurrences (all) | 2 | | |
| Edema limbs | | | |
| subjects affected / exposed | 3 / 5 (60.00%) | | |
| occurrences (all) | 5 | | |
| Fatigue | | | |
| subjects affected / exposed | 3 / 5 (60.00%) | | |
| occurrences (all) | 4 | | |
| Fever | | | |
| subjects affected / exposed | 2 / 5 (40.00%) | | |
| occurrences (all) | 2 | | |
| Injection site reaction | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | | |
| occurrences (all) | 3 | | |
| Localised oedema | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | | |
| occurrences (all) | 2 | | |
| Pain | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | | |
| occurrences (all) | 2 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | | |
| occurrences (all) | 1 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | | |
| occurrences (all) | 1 | | |
| Epistaxis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 5 (20.00%) | | |
| occurrences (all) | 1 | | |
| Sore throat | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | | |
| occurrences (all) | 1 | | |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | | |
| occurrences (all) | 1 | | |
| Investigations | | | |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 3 / 5 (60.00%) | | |
| occurrences (all) | 5 | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 4 / 5 (80.00%) | | |
| occurrences (all) | 8 | | |
| Platelet count decreased | | | |
| subjects affected / exposed | 4 / 5 (80.00%) | | |
| occurrences (all) | 8 | | |
| Weight gain | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | | |
| occurrences (all) | 1 | | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 4 / 5 (80.00%) | | |
| occurrences (all) | 8 | | |
| Cardiac disorders | | | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | | |
| occurrences (all) | 1 | | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 2 / 5 (40.00%) | | |
| occurrences (all) | 3 | | |
| Dysgeusia | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | | |
| occurrences (all) | 1 | | |
| Headache | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 5 (20.00%) | | |
| occurrences (all) | 2 | | |
| Syncope | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | | |
| occurrences (all) | 1 | | |
| Blood and lymphatic system disorders | | | |
| Anemia | | | |
| subjects affected / exposed | 4 / 5 (80.00%) | | |
| occurrences (all) | 9 | | |
| Blood and lymphatic system disorders - Other | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | | |
| occurrences (all) | 1 | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 2 / 5 (40.00%) | | |
| occurrences (all) | 2 | | |
| Lymph node pain | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | | |
| occurrences (all) | 1 | | |
| Eye disorders | | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | | |
| occurrences (all) | 1 | | |
| Dry eye | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | | |
| occurrences (all) | 1 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | | |
| occurrences (all) | 3 | | |
| Constipation | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | | |
| occurrences (all) | 1 | | |
| Diarrhea | | | |
| subjects affected / exposed | 3 / 5 (60.00%) | | |
| occurrences (all) | 3 | | |
| Gastrooesophageal reflux disease | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 5 (20.00%) | | |
| occurrences (all) | 1 | | |
| Gastrointestinal pain | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | | |
| occurrences (all) | 1 | | |
| Mucositis oral | | | |
| subjects affected / exposed | 3 / 5 (60.00%) | | |
| occurrences (all) | 3 | | |
| Nausea | | | |
| subjects affected / exposed | 3 / 5 (60.00%) | | |
| occurrences (all) | 5 | | |
| Periodontal disease | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | | |
| occurrences (all) | 1 | | |
| Small intestinal mucositis | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | | |
| occurrences (all) | 1 | | |
| Vomiting | | | |
| subjects affected / exposed | 2 / 5 (40.00%) | | |
| occurrences (all) | 2 | | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | | |
| occurrences (all) | 2 | | |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | | |
| occurrences (all) | 1 | | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | | |
| occurrences (all) | 2 | | |
| Skin and subcutaneous tissue disorder - Other | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | | |
| occurrences (all) | 1 | | |
| Renal and urinary disorders | | | |

| | | | |
|---|---|---|---|
| Urinary frequency<br>subjects affected / exposed<br>occurrences (all)<br><br>Urinary retention<br>subjects affected / exposed<br>occurrences (all) | 2 / 5 (40.00%)<br>2<br><br>1 / 5 (20.00%)<br>1 | | |
| Endocrine disorders<br>Hypoparathyroidism<br>subjects affected / exposed<br>occurrences (all) | 1 / 5 (20.00%)<br>3 | | |
| Musculoskeletal and connective tissue disorders<br>Pain in extremity<br>subjects affected / exposed<br>occurrences (all) | 1 / 5 (20.00%)<br>1 | | |
| Infections and infestations<br>Lip infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Mucosal infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Sinusitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Tooth infection<br>subjects affected / exposed<br>occurrences (all) | 1 / 5 (20.00%)<br>1<br><br>1 / 5 (20.00%)<br>2<br><br>1 / 5 (20.00%)<br>1<br><br>1 / 5 (20.00%)<br>1 | | |
| Metabolism and nutrition disorders<br>Anorexia<br>subjects affected / exposed<br>occurrences (all)<br><br>Hypercalcemia<br>subjects affected / exposed<br>occurrences (all)<br><br>Hypokalemia | 2 / 5 (40.00%)<br>3<br><br>1 / 5 (20.00%)<br>1 | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 5 (40.00%) | | |
| occurrences (all) | 2 | | |
| Metabolism and nutrition disorders - Other | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | | |
| occurrences (all) | 1 | | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

## Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|---|---|---|
| 01 June 2016 | Recruitment of patients was suspended due to manufacturing problems regarding the IMP. | - |

Notes:

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Since the trial was discontinued prematurely during the safety run-in phase after treatment of 5 patients, primary and secondary efficacy endpoints were not analyzed and follow-up of patients was terminated.

Notes: