



## 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
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##### **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
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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
<b>Arm title</b>	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/m<sup>2</sup> BSA, level +1 of 200 mg/m<sup>2</sup> BSA, and level -1 of 140 mg/m<sup>2</sup> BSA. After establishing the Volasertib dose, a randomized Phase II portion of the trial was planned.

<b>Arm title</b>	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/m<sup>2</sup> BSA, level +1 of 200 mg/m<sup>2</sup> BSA, and level -1 of 140 mg/m<sup>2</sup> BSA. After establishing the Volasertib dose, a randomized Phase II portion of the trial was planned.

<b>Number of subjects in period 1</b>	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)
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Reporting group description: -

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

### Subject analysis sets

Subject analysis set title	Analysis data set
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Subject analysis set type	Per protocol
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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			
Units: Subjects			
Age ≤60 years	3		
Age >60 years	2		
Age continuous			
Units: years			
median	53		
full range (min-max)	42 to 75		
Gender categorical			
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 <sup>[1]</sup>
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
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### Dictionary used

Dictionary name	CTCAE
Dictionary version	4.03

### Reporting groups

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

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

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

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

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### 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: