



## Clinical trial results:

**Multicenter, open-label single arm phase II study testing the tolerability and the efficacy of Bosutinib step-in dosing in Chronic Phase CML patients intolerant or refractory to previous Imatinib, Nilotinib or Dasatinib therapy, "Bosutinib Dose Optimization Study - BODO-Study"**  
**Summary**

EudraCT number	2014-005531-13
Trial protocol	DE
Global end of trial date	23 June 2020

### Results information

Result version number	v1 (current)
This version publication date	30 March 2022
First version publication date	30 March 2022

### Trial information

#### Trial identification

Sponsor protocol code	MED3-201401
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#### Additional study identifiers

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

Notes:

### Sponsors

Sponsor organisation name	Universitätsklinikum Bonn
Sponsor organisation address	Venusberg-Campus 1, Bonn, Germany, 53127
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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:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	10 February 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 June 2020
Global end of trial reached?	Yes
Global end of trial date	23 June 2020
Was the trial ended prematurely?	Yes

Notes:

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**General information about the trial**

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Main objective of the trial:

The objective of the BODO trial is to assess the tolerability and efficacy of a step-in dosing concept of the dual SRC-ABL kinase inhibitor Bosutinib in CP-CML patients who either developed intolerance or treatment failure to previous Imatinib, Dasatinib or Nilotinib as 1st or 2nd line therapy

Protection of trial subjects:

The study medication has already been authorized for the treatment of CP-CML. The investigator informed the patient about the study in detail and both signed the informed consent form. A patient insurance was in place. Adverse events were documented regularly and a data safety monitoring board did assess the safety status of the trial regularly.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 April 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	Germany: 57
Worldwide total number of subjects	57
EEA total number of subjects	57

Notes:

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**Subjects enrolled per age group**

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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)	47
From 65 to 84 years	10

85 years and over	0
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## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

After obtaining the signed written informed consent from a potential CML patient, centers will perform screening examinations and will check inclusion/exclusion criteria. After all data is collected the BODO trial screening form will be send via fax to the Study Center Bonn (SCB). The Study Center Bonn (SCB) will get in contact to the BODO Medical

### Period 1

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

### Arms

Arm title	Bosotinib
Arm description: -	
Arm type	single
Investigational medicinal product name	Bosutinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

step-in dosage of 300, 400 or 500 mg per day orally

<b>Number of subjects in period 1</b>	Bosotinib
Started	57
Completed	57

## Baseline characteristics

### Reporting groups

Reporting group title	overall trial
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Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	57	57	
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)	47	47	
From 65-84 years	10	10	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	25	25	
Male	32	32	

### Subject analysis sets

Subject analysis set title	full analysis data
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Subject analysis set type	Full analysis
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Subject analysis set description:

A total of n=57 patients were eligible to participate in the study. All n=57 patients started the bosutinib therapy and were included in the full analysis data set.

Reporting group values	full analysis data		
Number of subjects	57		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	47		
From 65-84 years	10		
85 years and over	0		

Gender categorical			
Units: Subjects			
Female			
Male			

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## End points

### End points reporting groups

Reporting group title	Bosotinib
Reporting group description: -	
Subject analysis set title	full analysis data
Subject analysis set type	Full analysis
Subject analysis set description:	
A total of n=57 patients were eligible to participate in the study. All n=57 patients started the bosutinib therapy and were included in the full analysis data set.	

### Primary: Rate of GI-Toxicity (i.e. incidence and severity of grade 2 to 4 toxicities) within the first 6 months of treatment

End point title	Rate of GI-Toxicity (i.e. incidence and severity of grade 2 to 4 toxicities) within the first 6 months of treatment
End point description:	
End point type	Primary
End point timeframe:	
baseline to 6 month	

End point values	Bosotinib	full analysis data		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	57	57		
Units: whole	57	57		

Attachments (see zip file)	BODO_results toxicity.docx
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### Statistical analyses

Statistical analysis title	rate of GI toxicity within first 6 months
Statistical analysis description:	
The primary endpoint was to be evaluated by calculation of the incidence rate of grade 2 to 4 gastrointestinal (GI) toxicity adverse events (AEs) within 6 months after registration. The null hypothesis for the primary endpoint was given by: "The proportion of 2-4 GI toxicity will be at least P = 0.40 within the first six months of therapy." It was to be tested against the alternative hypothesis "The proportion of 2-4 GI toxicity will be less than P = 0.40 within the first six months of therapy."	
Comparison groups	Bosotinib v full analysis data
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	other <sup>[1]</sup>
Method	Aalen-Johansen estimator
Parameter estimate	Risk ratio (RR)
Point estimate	59.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	45.1
upper limit	70.8

Notes:

[1] - In this non-randomized phase II study, we chose grade 2-4 GI toxicity at 6 months as the primary endpoint. This primary endpoint will be confirmatively tested.

Null hypothesis H0: The proportion of 2-4 GI toxicity will be at least  $P = 0.40$  within the first six months of therapy.

Alternative hypothesis H1: The proportion of 2-4 GI toxicity will be less than  $P = 0.40$  within the first six months of therapy.

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### Secondary: Tolerability (i.e. all grade, grade 2 to 4 and grade 3 and 4 toxicities) at month 6, 12 and 24

End point title	Tolerability (i.e. all grade, grade 2 to 4 and grade 3 and 4 toxicities) at month 6, 12 and 24
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End point description:

End point type	Secondary
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End point timeframe:

month 6, 12 and 24

<b>End point values</b>	Bosotinib			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: whole	57			

<b>Attachments (see zip file)</b>	BODO_results toxicity.docx AE listing BODO study.docx
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### Statistical analyses

No statistical analyses for this end point

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### Secondary: Efficacy parameters: CCyR, MMR, MR4 and MR4.5 rate at month 3, 6, 12, 18 and 24

End point title	Efficacy parameters: CCyR, MMR, MR4 and MR4.5 rate at month 3, 6, 12, 18 and 24
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End point description:

End point type	Secondary
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End point timeframe:

month 3, 6, 12, 18, 24



<b>End point values</b>	Bosotinib			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: whole	57			

<b>Attachments (see zip file)</b>	BODO_results efficacy.docx
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### Statistical analyses

No statistical analyses for this end point

### Secondary: Patient-reported outcome measures (QoL)

End point title	Patient-reported outcome measures (QoL)
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End point description:

End point type	Secondary
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End point timeframe:

whole study period

<b>End point values</b>	Bosotinib			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: whole	57			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)
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End point description:

End point type	Secondary
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End point timeframe:

whole study period

<b>End point values</b>	Bosotinib			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: whole	57			

<b>Attachments (see zip file)</b>	BODO_results PFS OS.docx
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### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall survival (OS)

End point title	Overall survival (OS)
End point description:	
End point type	Secondary
End point timeframe: whole study period	

<b>End point values</b>	Bosotinib			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: whole	57			

<b>Attachments (see zip file)</b>	BODO_results PFS OS.docx
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### Statistical analyses

No statistical analyses for this end point

### Secondary: The rate of emerging mutations during Bosutinib treatment

End point title	The rate of emerging mutations during Bosutinib treatment
End point description:	
End point type	Secondary
End point timeframe: whole study period	

<b>End point values</b>	Bosotinib			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: whole	57			

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

whole study period

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	23
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### Reporting groups

Reporting group title	bosutinib
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Reporting group description:

The safety analysis dataset contained all patients who received at least one dose of the investigational drug and consisted of all 57 registered patients. Time under risk for an adverse event was defined as the time while receiving study medication plus 30 days thereafter or until change of the TKI, if realized within these 30 days

Serious adverse events	bosutinib		
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 57 (28.07%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	1		
Investigations			
Catheterisation cardiac			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Coronary artery restenosis	Additional description: MedDRA preferred Term was used		
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Peripheral arterial occlusive disease	Additional description: MedDRA preferred Term was used		
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Embolism	Additional description: MedDRA preferred Term was used		

subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphatic fistula	Additional description: MedDRA preferred Term was used		
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphocele	Additional description: MedDRA preferred Term was used		
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina pectoris	Additional description: MedDRA preferred Term was used		
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Coronary artery disease	Additional description: MedDRA preferred Term was used		
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mitral valve incompetence			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pericardial effusion	Additional description: MedDRA preferred Term was used		
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			

Cerebral haemorrhage	Additional description: MedDRA preferred Term was used		
	subjects affected / exposed	1 / 57 (1.75%)	
	occurrences causally related to treatment / all	1 / 1	
	deaths causally related to treatment / all	1 / 1	
Cerebrovascular accident	Additional description: MedDRA preferred Term was used		
	subjects affected / exposed	1 / 57 (1.75%)	
	occurrences causally related to treatment / all	0 / 1	
	deaths causally related to treatment / all	0 / 0	
Syncope	Additional description: MedDRA preferred Term was used		
	subjects affected / exposed	1 / 57 (1.75%)	
	occurrences causally related to treatment / all	0 / 1	
	deaths causally related to treatment / all	0 / 0	
Eye disorders			
	Papilloedema	Additional description: MedDRA preferred Term was used	
	subjects affected / exposed	1 / 57 (1.75%)	
	occurrences causally related to treatment / all	1 / 1	
Gastrointestinal disorders			
	Abdominal pain upper	Additional description: MedDRA preferred Term was used	
	subjects affected / exposed	1 / 57 (1.75%)	
	occurrences causally related to treatment / all	1 / 1	
Diarrhoea	Additional description: MedDRA preferred Term was used		
	subjects affected / exposed	1 / 57 (1.75%)	
	occurrences causally related to treatment / all	2 / 2	
	deaths causally related to treatment / all	0 / 0	
Respiratory, thoracic and mediastinal disorders			
	Pleural effusion	Additional description: MedDRA preferred Term was used,	
	subjects affected / exposed	1 / 57 (1.75%)	
	occurrences causally related to treatment / all	3 / 3	
Skin and subcutaneous tissue disorders			
	Skin ulcer	Additional description: MedDRA preferred Term was used	

subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury	Additional description: MedDRA preferred Term was used		
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal artery stenosis	Additional description: MedDRA preferred Term was used		
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Lung infection	Additional description: MedDRA preferred Term was used, 3 such SAEs were reported		
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Erysipelas	Additional description: MedDRA preferred Term was used, 1 such SAE was reported		
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis norovirus	Additional description: MedDRA preferred Term was used, 1 such SAE was reported		
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal infection			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Tooth abscess	Additional description: MedDRA preferred Term was used		
	subjects affected / exposed	1 / 57 (1.75%)	
	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 %

<b>Non-serious adverse events</b>	bosutinib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	57 / 57 (100.00%)		
Gastrointestinal disorders			
Diarrhoea	Additional description: This AE is exemplary for all AEs. A complete listing of the AEs has been uploaded as a chart at endpoint tolerability		
subjects affected / exposed	57 / 57 (100.00%)		
occurrences (all)	57		



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 August 2016	Addition of pre-treatment with the first-generation TKI imatinib for inclusion Addition of follow-up visits at three-month intervals following the 24-month treatment phase until the end of the BODO study. Additional screening of patients for hepatitis B prior to initiation of treatment with tyrosine kinase inhibitors (TKIs) Bone marrow aspiration (BMP) is now only mandatory at screening/ inclusion.
16 May 2018	Inclusion criterion changed: pre-treated with one or two different TKIs (imatinib, dasatinib, or nilotinib) possible, i.e., bosutinib as a 2nd- or 3rd-line TKI. The definition of intolerance has been changed so that the degree of toxicity leading to treatment switch is not the sole criterion. The recruitment period has been extended by 1 year.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported