



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 |
|-----------------------|-------------|

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 |
| Public contact | Dr. Mareille Warnken-Uhlich, Studienzentrale Studienzentrum Bonn (SZB), 49 22828716040, verena.dykstra@gmx.de |
| Scientific contact | Dr. Mareille Warnken-Uhlich, Studienzentrale Studienzentrum Bonn (SZB), 5208835336 22828716040, verena.dykstra@gmx.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 | 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:

General information about the trial

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:

Population of trial subjects

Subjects enrolled per country

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

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) | 47 |
| From 65 to 84 years | 10 |

| | |
|-------------------|---|
| 85 years and over | 0 |
|-------------------|---|

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

| | |
|---------------------------------------|-----------|
| Number of subjects in period 1 | Bosotinib |
| Started | 57 |
| Completed | 57 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | overall trial |
|-----------------------|---------------|

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 |
|----------------------------|--------------------|

| | |
|---------------------------|---------------|
| 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.

| 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 | | | |

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 |
|----------------------------|----------------------------|

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 ^[1] |
| 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.

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 |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

month 6, 12 and 24

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | Bosotinib | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 57 | | | |
| Units: whole | 57 | | | |

| | |
|-----------------------------------|--|
| Attachments (see zip file) | BODO_results toxicity.docx AE listing BODO study.docx |
|-----------------------------------|--|

Statistical analyses

No statistical analyses for this end point

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 |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

month 3, 6, 12, 18, 24

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | Bosotinib | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 57 | | | |
| Units: whole | 57 | | | |

| | |
|-----------------------------------|----------------------------|
| Attachments (see zip file) | BODO_results efficacy.docx |
|-----------------------------------|----------------------------|

Statistical analyses

No statistical analyses for this end point

Secondary: Patient-reported outcome measures (QoL)

| | |
|-----------------|---|
| End point title | Patient-reported outcome measures (QoL) |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

whole study period

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | 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) |
|-----------------|---------------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

whole study period

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | Bosotinib | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 57 | | | |
| Units: whole | 57 | | | |

| | |
|-----------------------------------|--------------------------|
| Attachments (see zip file) | BODO_results PFS OS.docx |
|-----------------------------------|--------------------------|

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 | |

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | Bosotinib | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 57 | | | |
| Units: whole | 57 | | | |

| | |
|-----------------------------------|--------------------------|
| Attachments (see zip file) | BODO_results PFS OS.docx |
|-----------------------------------|--------------------------|

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 | |

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | Bosotinib | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 57 | | | |
| Units: whole | 57 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

whole study period

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

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|----|
| Dictionary version | 23 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | bosutinib |
|-----------------------|-----------|

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 %

| | | | |
|---|---|--|--|
| Non-serious adverse events | 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:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported