



## Clinical trial results:

### An open-label, two-stage Phase I/IIa dose escalation study of BT062 in metastatic triple receptor-negative breast cancer and in metastatic transitional cell carcinoma of the urinary bladder

#### Summary

EudraCT number	2013-003252-20
Trial protocol	DE BE
Global end of trial date	05 July 2017

#### Results information

Result version number	v1 (current)
This version publication date	08 October 2021
First version publication date	08 October 2021

#### Trial information

##### Trial identification

Sponsor protocol code	989
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##### Additional study identifiers

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

Notes:

##### Sponsors

Sponsor organisation name	Biotest AG
Sponsor organisation address	Landsteinerstr. 5, Dreieich, Germany, 63303
Public contact	Dr. Iris Bobenhausen, Biotest AG, iris.bobenhausen@biotest.com
Scientific contact	Dr. Iris Bobenhausen, Biotest AG, iris.bobenhausen@biotest.com

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	05 July 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 October 2016
Global end of trial reached?	Yes
Global end of trial date	05 July 2017
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

Phase I Part (Dose Escalation): To determine the dose-limiting toxicities (DLTs), the maximum tolerated dose (MTD) and the recommended Phase II dose (RPTD) of BT062 in patients with metastatic triple-negative breast cancer (TNBC) or metastatic transitional cell carcinoma of the urinary bladder ((TCCUB).

Phase IIa Part (Cohort Expansion): To assess the proportion of patients experiencing disease control (SD, PR or CR) according to RECIST criteria during the first 3 treatment cycles.

Protection of trial subjects:

Patients who experience progression disease (PD) are not eligible for further treatment cycles and will complete the study according to the protocol. If a patient experiences a DLT, the study treatment must be stopped in this particular patient. In case of toxicity other than DLT, the Investigator will decide whether the patient is eligible for further treatment cycles. No patient will receive more than 3 doses of BT062 during a 28-day treatment cycle. Patients initially treated at a dose level higher than the finally defined RPTD, and who did not experience unacceptable toxicity or PD, may continue treatment at this dose level or below unless unacceptable BT062-related toxicity or PD is detected. A dose of BT062 higher than the MAD will never be permitted to be administered. A DLT is always considered as an AE. For safety monitoring, physical examinations, vital signs, ECG, pregnancy test, Fecal Occult Blood and safety laboratory parameters and Eastern Cooperative Oncology Group Performance Status. Any unfavorable or unintended sign, symptom, or disease that appears or worsens in a study subject during the period of observation in a clinical study were reported as an AE.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 March 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	8 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 20
Country: Number of subjects enrolled	Germany: 19
Worldwide total number of subjects	39
EEA total number of subjects	39

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)	25
From 65 to 84 years	14
85 years and over	0

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## Subject disposition

### Recruitment

Recruitment details:

Recruitment period: 11-Mar-2014 to 15-Jul-2016 (27 months)

Countries: Belgium and Germany

Subjects with metastatic TNBC (stage IV) with histochemical confirmation of the absence (<1%) of progesterone receptors, estrogen receptors, and human epidermal growth factor receptors or with metastatic TCCUB (stage IV).

### Pre-assignment

Screening details:

- Subject aged  $\geq 18$  with relapsed and/or refractory disease at a stage that could not be controlled adequately by surgery, radiotherapy, or standard chemotherapy.
- Measurable disease acc. to RECIST v1.1 with at least 1 measurable lesion and at least 1 tumor biopsy with histologically confirmed.
- Estimated life expectancy  $\geq 12$  weeks and ECOG $\leq 2$ .

### Period 1

Period 1 title	Phase I
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	100 mg/m <sup>2</sup>
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	BT062 100 mg / m <sup>2</sup> BSA
Investigational medicinal product code	
Other name	Indatuximab ravtansine
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

BT062 has been provided as a pre-filled, single-use vial containing 25 mg BT062 in 5 mL solution (5 mg / mL). The dose was calculated as mg / m<sup>2</sup> BSA.

BT062 will be administered intravenously at Days 1, 8 and 15 during a 28-day treatment cycle.

<b>Arm title</b>	120 mg / m <sup>2</sup>
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	BT062 120 mg / m <sup>2</sup> BSA
Investigational medicinal product code	
Other name	Indatuximab ravtansine
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

BT062 has been provided as a pre-filled, single-use vial containing 25 mg BT062 in 5 mL solution (5 mg / mL). The dose was calculated as mg / m<sup>2</sup> BSA.

BT062 will be administered intravenously at Days 1, 8 and 15 during a 28-day treatment cycle.

<b>Arm title</b>	140 mg/m <sup>2</sup>
Arm description: -	
Arm type	Experimental

Investigational medicinal product name	BT062 140 mg / m <sup>2</sup> BSA
Investigational medicinal product code	
Other name	Indatuximab ravtansine
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

BT062 has been provided as a pre-filled, single-use vial containing 25 mg BT062 in 5 mL solution (5 mg / mL). The dose was calculated as mg / m<sup>2</sup> BSA.

BT062 will be administered intravenously at Days 1, 8 and 15 during a 28-day treatment cycle.

Number of subjects in period 1 <sup>[1]</sup>	100 mg/m <sup>2</sup>	120 mg / m <sup>2</sup>	140 mg/m <sup>2</sup>
Started	6	4	4
Completed	5	3	3
Not completed	1	1	1
no post dose safety/RECIST assessment	1	1	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Of the 20 subjects screened for Phase I, 14 subjects received at least 1 of 3 dose levels (100, 120, or 140 mg/m<sup>2</sup>) of BT062. 6 screened subjects were screen failures. 6 subjects continued Phase IIa

36 subjects were directly screened for Phase IIa. Therefore in total 56 subjects were screened in this trial.

**Period 2**

Period 2 title	Phase IIa
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

**Arms**

Are arms mutually exclusive?	No
<b>Arm title</b>	TNBC

Arm description:

subjects with triple-negative breast cancer

Arm type	Experimental
Investigational medicinal product name	BT062 100 mg / m <sup>2</sup> BSA
Investigational medicinal product code	
Other name	Indatuximab ravtansine
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

BT062 has been provided as a pre-filled, single-use vial containing 25 mg BT062 in 5 mL solution (5 mg / mL). The dose was calculated as mg / m<sup>2</sup> BSA.

BT062 will be administered intravenously at Days 1, 8 and 15 during a 28-day treatment cycle.

<b>Arm title</b>	TCCUB
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Arm description:

Subjects with transitional cell cancer of the urinary bladder

Arm type	Experimental
Investigational medicinal product name	BT062 100 mg / m <sup>2</sup> BSA
Investigational medicinal product code	
Other name	Indatuximab ravtansine
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

BT062 has been provided as a pre-filled, single-use vial containing 25 mg BT062 in 5 mL solution (5 mg / mL). The dose was calculated as mg / m<sup>2</sup> BSA.

BT062 will be administered intravenously at Days 1, 8 and 15 during a 28-day treatment cycle.

<b>Number of subjects in period 2</b>	TNBC	TCCUB
Started	15	16
Completed	13	14
Not completed	2	2
no post dose safety/RECIST assessment	2	2

## Baseline characteristics

### Reporting groups

Reporting group title	100 mg/m2
Reporting group description: -	
Reporting group title	120 mg / m <sup>2</sup>
Reporting group description: -	
Reporting group title	140 mg/m2
Reporting group description: -	

Reporting group values	100 mg/m2	120 mg / m <sup>2</sup>	140 mg/m2
Number of subjects	6	4	4
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	56.3	54.8	67.5
standard deviation	± 11.5	± 7.63	± 5.45
Gender categorical Units: Subjects			
Female	2	4	3
Male	4	0	1

Reporting group values	Total		
Number of subjects	14		
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over	0 0 0 0 0 0 0 0 0		

Age continuous Units: years arithmetic mean standard deviation		-	
Gender categorical Units: Subjects			
Female		9	
Male		5	

### Subject analysis sets

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population will include all patients who were administered at least 1 dose of study medication. The safety population will be used for all analyses of safety endpoints. The safety population will be used for the presentation of patients in all patient listings (except disposition).

Subject analysis set title	ENROLLED POPULATION
Subject analysis set type	Full analysis

Subject analysis set description:

The enrolled population will include all patients enrolled. Enrolled is defined as informed consent given. Unless specified otherwise, this enrolled population will be used for listings and summaries of patient disposition.

Here as a workaround enrolled population entered is number of patients randomized to avoid errors.

Subject analysis set title	INTENTION-TO-TREAT POPULATION
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The intention-to-treat (ITT) population (both phases) will include all patients enrolled, who have received at least one dose of BT062, have both a post-dose safety assessment, e.g. AE, vital sign and a post-dose RECIST assessment.

Subject analysis set title	PER PROTOCOL POPULATION
Subject analysis set type	Per protocol

Subject analysis set description:

The per-protocol population (PP) will include patients from the ITT population who have completed the study without major protocol deviation.

Subject analysis set title	PHARMACOKINETIC POPULATION
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The PK population is defined as all patients who received any amount of study medication and who had at least one measurement of BT062 or derivative component of BT062 in plasma or urine.

Reporting group values	Safety Population	ENROLLED POPULATION	INTENTION-TO-TREAT POPULATION
Number of subjects	39	39	33
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			

From 65-84 years 85 years and over			
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Age continuous Units: years arithmetic mean standard deviation	57.3 ± 13.85	±	±
Gender categorical Units: Subjects			
Female	24		
Male	15		

<b>Reporting group values</b>	PER PROTOCOL POPULATION	PHARMACOKINETIC POPULATION	
Number of subjects	28	38	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years arithmetic mean standard deviation	±	±	
Gender categorical Units: Subjects			
Female			
Male			

## End points

### End points reporting groups

Reporting group title	100 mg/m <sup>2</sup>
Reporting group description: -	
Reporting group title	120 mg / m <sup>2</sup>
Reporting group description: -	
Reporting group title	140 mg/m <sup>2</sup>
Reporting group description: -	
Reporting group title	TNBC
Reporting group description: subjects with triple-negative breast cancer	
Reporting group title	TCCUB
Reporting group description: Subjects with transitional cell cancer of the urinary bladder	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description: The safety population will include all patients who were administered at least 1 dose of study medication. The safety population will be used for all analyses of safety endpoints. The safety population will be used for the presentation of patients in all patient listings (except disposition).	
Subject analysis set title	ENROLLED POPULATION
Subject analysis set type	Full analysis
Subject analysis set description: The enrolled population will include all patients enrolled. Enrolled is defined as informed consent given. Unless specified otherwise, this enrolled population will be used for listings and summaries of patient disposition. Here as a workaround enrolled population entered is number of patients randomized to avoid errors.	
Subject analysis set title	INTENTION-TO-TREAT POPULATION
Subject analysis set type	Intention-to-treat
Subject analysis set description: The intention-to-treat (ITT) population (both phases) will include all patients enrolled, who have received at least one dose of BT062, have both a post-dose safety assessment, e.g. AE, vital sign and a post-dose RECIST assessment.	
Subject analysis set title	PER PROTOCOL POPULATION
Subject analysis set type	Per protocol
Subject analysis set description: The per-protocol population (PP) will include patients from the ITT population who have completed the study without major protocol deviation.	
Subject analysis set title	PHARMACOKINETIC POPULATION
Subject analysis set type	Sub-group analysis
Subject analysis set description: The PK population is defined as all patients who received any amount of study medication and who had at least one measurement of BT062 or derivative component of BT062 in plasma or urine.	

### Primary: Proportion of disease control (SD, PR, or CR) during the first 3 treatment cycles

End point title	Proportion of disease control (SD, PR, or CR) during the first 3 treatment cycles <sup>[1]</sup>
End point description: The primary efficacy endpoint in Phase IIa is the proportion of patients experiencing disease control (stable disease, partial response, or complete response) defined by Response Criteria in Solid Tumors (RECIST) v1.1 criteria for each tumor entity during the first 3 treatment cycles.	
End point type	Primary

End point timeframe:

during the first 3 treatment cycles ( up to 3 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: Categorical variables will be summarized using number of observations (n), frequency, and percentages of patients, unless stated otherwise. Unless stated otherwise, the calculation of percentages will be based on the total number of patients in the population of interest.

End point values	100 mg/m <sup>2</sup>	120 mg / m <sup>2</sup>	140 mg/m <sup>2</sup>	TNBC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	3	3	13
Units: subjects				
Disease Control - Yes	0	1	1	3
Disease Control - No	5	2	2	10

End point values	TCCUB	INTENTION-TO-TREAT POPULATION		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	14	33		
Units: subjects				
Disease Control - Yes	4	9		
Disease Control - No	10	24		

## Statistical analyses

No statistical analyses for this end point

## Primary: Dose-Limiting Toxicities

End point title | Dose-Limiting Toxicities<sup>[2]</sup>

End point description:

The primary objective of the phase I part is to determine the dose-limiting toxicities (DLTs).

A DLT is always considered as an AE. The following criteria should be checked:

1. SAE or AE of severity Grade 3 or higher, which is related to BT062.
2. The following AEs will be considered as DLTs, if pre-specified criteria are fulfilled:
  - Grade 3-4 nausea and vomiting, if lasting longer than 3 days despite optimal antiemetic medication;
  - Grade 3-4 diarrhea, if lasting longer than 3 days despite optimal antidiarrheal medication;
  - Grade 4 neutropenia, if lasting longer than 7 days;
  - Grade 3-4 neutropenia\*, if the body core temperature is higher than or equal 38.3°C;
  - Grade 3 thrombocytopenia\*, if platelet count is < 30,000 /  $\mu$ L
  - Grade 3 thrombocytopenia, if associated with clinically significant bleeding
  - Grade 4 thrombocytopenia.

End point type | Primary

End point timeframe:

From Baseline to the end of Phase I

Notes:

[2] - 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: Categorical variables will be summarized using number of observations (n), frequency, and percentages of patients, unless stated otherwise. Unless stated

otherwise, the calculation of percentages will be based on the total number of patients in the population of interest.

<b>End point values</b>	100 mg/m <sup>2</sup>	120 mg / m <sup>2</sup>	140 mg/m <sup>2</sup>	Safety Population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	6	4	4	14
Units: subjects				
Subject with at least 1 DLT	0	2	1	4
Skin and Subcutaneous Tissue Disorders	0	2	1	3
Dermatitis Exfoliative	0	1	0	1
Palmar-Plantar Erythrodysesthesia Syndrome	0	0	0	1
Rash	0	0	1	0
Rash Maculo-Papular	0	1	0	1
Gastrointestinal Disorders	0	0	0	1
Stomatitis	0	0	0	1

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Lesion Response Defined by RECIST v1.1

End point title	Overall Lesion Response Defined by RECIST v1.1
End point description:	A patient will be counted only once for their best overall lesion response. The order from best to worse is Complete Response (CR) > Partial Response (PR) > Stable disease (SD) > Progression disease (PD) > NE (NE = Not Evaluable).
End point type	Secondary
End point timeframe:	from baseline to end of study

<b>End point values</b>	100 mg/m <sup>2</sup>	120 mg / m <sup>2</sup>	140 mg/m <sup>2</sup>	TNBC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	3	3	13
Units: subjects				
CR	0	0	0	0
PR	0	1	0	1
SD	0	0	1	2
PD	5	2	2	10

<b>End point values</b>	TCCUB	INTENTION-TO-TREAT POPULATION		

Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	14	33		
Units: subjects				
CR	0	0		
PR	1	3		
SD	3	6		
PD	10	24		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Progression free survival

End point title	Progression free survival
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End point description:

Progression free survival is defined as the duration from start of the treatment to disease progression or death (regardless of cause of death), whichever is earlier. If the patient does not have a documented date of progression or death, PFS will be censored at the date of the last adequate assessment.  
PFS (weeks) = ([Date of progression / death - date of first dose] + 1) / 7

PFS will be analyzed using Kaplan Meier quartile estimates along with 2-sided 95% CIs.

End point type	Secondary
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End point timeframe:

From Baseline to the end of study

End point values	100 mg/m <sup>2</sup>	120 mg / m <sup>2</sup>	140 mg/m <sup>2</sup>	TNBC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	3	3	13
Units: Week				
median (confidence interval 95%)	10.1 (5.3 to 13.3)	9.9 (7.1 to 13.6)	10.7 (9.1 to 14.4)	8.0 (5.1 to 12.7)

End point values	TCCUB	INTENTION-TO-TREAT POPULATION		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	14	33		
Units: Week				
median (confidence interval 95%)	11.6 (8.0 to 31.9)	10.7 (8.0 to 12.1)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Survival

End point title	Overall Survival
End point description:	
Overall survival (OS) is defined as the time from the start of the treatment to death from any cause. If the patient does not have a documented date of death, OS will be censored at the date of the patient was last known to be alive.	
OS (weeks) = ([Date of death – date of first dose] + 1) / 7	
OS will be analyzed using Kaplan Meier quartile estimates along with 2-sided 95% CIs.	
For Reporting Group 2 the upper limit of the Confidence Interval 95% is non-estimable. Therefore the longest overall survival was entered to avoid errors. The longest overall survival reported was 110.6 weeks. The subject was still alive after 110.6 weeks at study end.	
End point type	Secondary
End point timeframe:	
From Baseline to the end of study	

End point values	100 mg/m <sup>2</sup>	120 mg / m <sup>2</sup>	140 mg/m <sup>2</sup>	TNBC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	3	3	13
Units: week				
median (confidence interval 95%)	26.9 (16.3 to 50.7)	32.6 (28.6 to 110.6)	40.9 (31.9 to 52.6)	24.1 (12.0 to 44.9)

End point values	TCCUB	INTENTION-TO-TREAT POPULATION		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	14	33		
Units: week				
median (confidence interval 95%)	28.6 (18.3 to 50.7)	31.9 (24.1 to 42.4)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of Stable Disease

End point title	Duration of Stable Disease
End point description:	
Duration of stable disease will be assessed following the RECIST v1.1 criteria. The DSD is measured from the start of the treatment until the criteria for progression are met, or until death of the patient from any cause. Stable disease will therefore be assumed from the start of treatment until the criteria for disease progression are first met. If the patient does not have a documented date of progression or death, DSD will be censored at the date of the last adequate assessment.	
DSD (weeks) = ([Date of progression/death {where cause is not PD} – date of first dose] + 1) / 7	
DSD has been presented as a swimmer plot with DSD on the Y axis and patient number on the X axis.	

No summary data is available for this end point.

In the attached figure, all subject numbers were deleted due to data privacy protection.  
The best result (longest duration of stable disease) was entered in the corresponding result value field).

End point type	Secondary
End point timeframe:	
From Baseline to the end of study	

<b>End point values</b>	100 mg/m <sup>2</sup>	120 mg / m <sup>2</sup>	140 mg/m <sup>2</sup>	TNBC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	3	3	13
Units: week				
number (not applicable)	13.3	13.6	14.4	27.3

<b>End point values</b>	TCCUB	INTENTION-TO-TREAT POPULATION		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	14	33		
Units: week				
number (not applicable)	60	60		

<b>Attachments (see zip file)</b>	Duration of stable disease of individual subjects/f-14-02-02-04.
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### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse Events were documented after written consent has been obtained until patient's exit from the study.

Adverse event reporting additional description:

Non-treatment emergent AEs (after written consent has been obtained, but before the first dose of study drug started), and not related AEs after patient's Exit from the study were not considered here.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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### Reporting groups

Reporting group title	Safety population
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Reporting group description:

The safety population included all enrolled subjects who were administered at least 1 dose of BT062.

<b>Serious adverse events</b>	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 39 (48.72%)		
number of deaths (all causes)	9		
number of deaths resulting from adverse events	9		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain	Additional description: Resolved, not related to study drug.		
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant neoplasm progression			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Investigations			
Electrocardiogram QT prolonged	Additional description: Resolved, not related to study drug.		
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			

Cerebral haemorrhage subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Fatal outcome, not related to study drug.		
	1 / 39 (2.56%)		
	0 / 1		
	0 / 1		
General disorders and administration site conditions General physical health deterioration subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all			
	2 / 39 (5.13%)		
	0 / 2		
	0 / 2		
Disease progression subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all			
	2 / 39 (5.13%)		
	0 / 2		
	0 / 2		
Infusion site extravasation subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Resolving, no Action with study drug, related to study drug.		
	1 / 39 (2.56%)		
	1 / 1		
	0 / 0		
Gastrointestinal disorders Stomatitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Resolving, drug withdrawn, related to study drug.		
	1 / 39 (2.56%)		
	1 / 1		
	0 / 0		
Gastrointestinal haemorrhage subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Fatal outcome, not related to study drug.		
	1 / 39 (2.56%)		
	0 / 1		
	0 / 1		
Intestinal obstruction subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Resolved, not related to study drug.		
	1 / 39 (2.56%)		
	0 / 1		
	0 / 0		
Respiratory, thoracic and mediastinal disorders Pleural effusion			

subjects affected / exposed	2 / 39 (5.13%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
<b>Skin and subcutaneous tissue disorders</b>			
Dermatitis exfoliative			
Additional description: Resolving, dose reduction, related to study drug.			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Palmar-plantar erythrodysesthesia syndrome			
Additional description: Resolving, study drug temporarily stopped, related to study drug.			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Rash			
Additional description: Resolving, dose reduced, related to study drug.			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Psychiatric disorders</b>			
Disorientation			
Additional description: Resolved, not related to study drug.			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Renal and urinary disorders</b>			
Acute kidney injury			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
<b>Musculoskeletal and connective tissue disorders</b>			
Soft tissue necrosis			
Additional description: Resolved, not related to study drug.			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
Additional description: Resolving, not related to study drug.			

subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Infections and infestations</b>			
<b>Pneumonia</b>	Additional description: Resolved, not related to study medication.		
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Febrile infection</b>	Additional description: Resolved, not related.		
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Cystitis</b>	Additional description: Resolved, not related to study drug.		
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Pyelonephritis acute</b>	Additional description: Resolved, not related to study drug.		
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Infusion site cellulitis</b>	Additional description: Resolving, study drug temporarily interrupted, related to study drug.		
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Sepsis</b>	Additional description: Not resolved, , not related to study drug, subject died 4 days later due to gastrointestinal haemorrhage.		
subjects affected / exposed	1 / 39 (2.56%)		
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>	Safety population		
Total subjects affected by non-serious adverse events subjects affected / exposed	39 / 39 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Cancer pain subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 3		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)  Hypotension subjects affected / exposed occurrences (all)	3 / 39 (7.69%) 9  3 / 39 (7.69%) 4		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)  Oedema peripheral subjects affected / exposed occurrences (all)  Pyrexia subjects affected / exposed occurrences (all)  Chest pain subjects affected / exposed occurrences (all)  Pain subjects affected / exposed occurrences (all)  Chills subjects affected / exposed occurrences (all)  Feeling cold subjects affected / exposed occurrences (all)	21 / 39 (53.85%) 40  6 / 39 (15.38%) 15  4 / 39 (10.26%) 8  3 / 39 (7.69%) 3  3 / 39 (7.69%) 3  2 / 39 (5.13%) 2  2 / 39 (5.13%) 2		

Mucosal inflammation subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 3		
Reproductive system and breast disorders Breast pain subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 3		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)  Cough subjects affected / exposed occurrences (all)  Pleural effusion subjects affected / exposed occurrences (all)  Rhinorrhoea subjects affected / exposed occurrences (all)	9 / 39 (23.08%) 26  6 / 39 (15.38%) 8  4 / 39 (10.26%) 8  2 / 39 (5.13%) 2		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)  Anxiety subjects affected / exposed occurrences (all)  Sleep disorder subjects affected / exposed occurrences (all)  Confusional state subjects affected / exposed occurrences (all)  Depression subjects affected / exposed occurrences (all)	5 / 39 (12.82%) 6  3 / 39 (7.69%) 3  3 / 39 (7.69%) 3  2 / 39 (5.13%) 2  2 / 39 (5.13%) 2		

Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	8 / 39 (20.51%) 13		
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	7 / 39 (17.95%) 12		
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	5 / 39 (12.82%) 9		
Weight decreased subjects affected / exposed occurrences (all)	4 / 39 (10.26%) 5		
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	3 / 39 (7.69%) 5		
Blood creatinine increased subjects affected / exposed occurrences (all)	3 / 39 (7.69%) 10		
Electrocardiogram QT prolonged subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2		
Blood lactate dehydrogenase increased subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2		
Glomerular filtration rate decreased subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 5		
Lipase increased subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2		
Injury, poisoning and procedural complications Infusion related reaction			

subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 7		
Cardiac disorders Tachycardia subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2		
Nervous system disorders Headache subjects affected / exposed occurrences (all)  Dizziness subjects affected / exposed occurrences (all)  Dysgeusia subjects affected / exposed occurrences (all)  Paraesthesia subjects affected / exposed occurrences (all)  Polyneuropathy subjects affected / exposed occurrences (all)  Peripheral sensory neuropathy subjects affected / exposed occurrences (all)  Dysaesthesia subjects affected / exposed occurrences (all)	5 / 39 (12.82%) 7  4 / 39 (10.26%) 4  4 / 39 (10.26%) 4  4 / 39 (10.26%) 4  4 / 39 (10.26%) 5  3 / 39 (7.69%) 7  2 / 39 (5.13%) 2		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)  Lymphadenopathy subjects affected / exposed occurrences (all)	8 / 39 (20.51%) 20  2 / 39 (5.13%) 2		
Ear and labyrinth disorders			

Ear pain			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	20 / 39 (51.28%)		
occurrences (all)	33		
Nausea			
subjects affected / exposed	14 / 39 (35.90%)		
occurrences (all)	20		
Constipation			
subjects affected / exposed	11 / 39 (28.21%)		
occurrences (all)	16		
Stomatitis			
subjects affected / exposed	7 / 39 (17.95%)		
occurrences (all)	11		
Vomiting			
subjects affected / exposed	7 / 39 (17.95%)		
occurrences (all)	10		
Abdominal pain upper			
subjects affected / exposed	4 / 39 (10.26%)		
occurrences (all)	6		
Dry mouth			
subjects affected / exposed	4 / 39 (10.26%)		
occurrences (all)	4		
Abdominal pain			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	6		
Dyspepsia			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Gastrointestinal motility disorder			

subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2		
<b>Skin and subcutaneous tissue disorders</b>			
<b>Dry skin</b>			
subjects affected / exposed occurrences (all)	5 / 39 (12.82%) 5		
<b>Palmar-plantar erythrodysesthesia syndrome</b>			
subjects affected / exposed occurrences (all)	5 / 39 (12.82%) 9		
<b>Pruritus</b>			
subjects affected / exposed occurrences (all)	5 / 39 (12.82%) 7		
<b>Rash</b>			
subjects affected / exposed occurrences (all)	5 / 39 (12.82%) 16		
<b>Rash maculo-papular</b>			
subjects affected / exposed occurrences (all)	3 / 39 (7.69%) 8		
<b>Dermatitis bullous</b>			
subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2		
<b>Night sweats</b>			
subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2		
<b>Skin ulcer</b>			
subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2		
<b>Renal and urinary disorders</b>			
<b>Acute kidney injury</b>			
subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 3		
<b>Dysuria</b>			
subjects affected / exposed occurrences (all)	4 / 39 (10.26%) 4		
<b>Haematuria</b>			

<p>subjects affected / exposed occurrences (all)</p> <p>Pollakiuria subjects affected / exposed occurrences (all)</p> <p>Urinary incontinence subjects affected / exposed occurrences (all)</p>	<p>3 / 39 (7.69%) 5</p> <p>2 / 39 (5.13%) 2</p> <p>2 / 39 (5.13%) 3</p>		
<p>Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)</p>	<p>2 / 39 (5.13%) 3</p>		
<p>Musculoskeletal and connective tissue disorders</p> <p>Back pain subjects affected / exposed occurrences (all)</p> <p>Muscle spasms subjects affected / exposed occurrences (all)</p> <p>Musculoskeletal pain subjects affected / exposed occurrences (all)</p> <p>Pain in extremity subjects affected / exposed occurrences (all)</p> <p>Arthralgia subjects affected / exposed occurrences (all)</p> <p>Myalgia subjects affected / exposed occurrences (all)</p>	<p>6 / 39 (15.38%) 10</p> <p>4 / 39 (10.26%) 4</p> <p>4 / 39 (10.26%) 5</p> <p>4 / 39 (10.26%) 8</p> <p>3 / 39 (7.69%) 5</p> <p>2 / 39 (5.13%) 2</p>		
<p>Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)</p> <p>Cystitis</p>	<p>4 / 39 (10.26%) 5</p>		

subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 3		
Bronchitis subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2		
Skin infection subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 3		
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	12 / 39 (30.77%) 20		
Hypokalaemia subjects affected / exposed occurrences (all)	9 / 39 (23.08%) 20		
Dehydration subjects affected / exposed occurrences (all)	5 / 39 (12.82%) 5		
Hypoalbuminaemia subjects affected / exposed occurrences (all)	5 / 39 (12.82%) 9		
Hypomagnesaemia subjects affected / exposed occurrences (all)	5 / 39 (12.82%) 6		
Hypophosphataemia subjects affected / exposed occurrences (all)	5 / 39 (12.82%) 15		
Hypocalcaemia subjects affected / exposed occurrences (all)	4 / 39 (10.26%) 6		
Hyperglycaemia subjects affected / exposed occurrences (all)	3 / 39 (7.69%) 4		
Hyponatraemia subjects affected / exposed occurrences (all)	3 / 39 (7.69%) 8		

Hyperuricaemia subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2		
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## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 December 2013	<p>Protocol amendment 1 dated 05-DEC-2013 introduced the following changes:</p> <ul style="list-style-type: none"><li>• The recruitment timeline and assumed duration of the study were adapted.</li><li>• The FACT GOG-Ntx questionnaire was added.</li><li>• Minor clarifications to the flowchart were made.</li><li>• The DLT definition of thrombocytopenia was re-worded to make it clearer without changing the criteria.</li><li>• More emphasis was put on the recommendation to conduct further unscheduled visits if AEs were still ongoing at study end.</li><li>• The number of cases with SAEs and the cut-off date to determine this number of cases in the benefit-risk evaluation section of the protocol (Section 12.5.2) were updated, on the basis of data updates from other ongoing studies with BT062.</li><li>• The option to have CD138 assessed on historic biopsies, while a fresh biopsy still remained mandatory, was added.</li><li>• Wording saying CA 15-3 and carcinoembryonic antigen (CEA) levels in breast cancer patients were to be assessed at baseline in addition to screening was removed to correct a discrepancy with the flow chart.</li><li>• The description on optimal biomarker time points was corrected to match the flowchart.</li><li>• It was further clarified that biological samples to be used for PK analysis consisted of sodium heparin plasma samples.</li><li>• Blood gas analyses were removed from the clinical chemistry panel as it had been included in error.</li><li>• A reminder on the limitations of the Cockcroft-Gault equation in showing the true glomerular filtration rate was included.</li><li>• It was further clarified in the statistical section of the protocol that further recruitment was to be stopped if insufficient efficacy was found. The term 'disease control or better' was corrected into 'disease control' because disease control also included the best possible outcome CR.</li></ul>

11 March 2015	<p>The major changes:</p> <ul style="list-style-type: none"> <li>• Estimated end dates of enrollment and data cut-off were updated.</li> <li>• Enrollment of subjects who were scheduled to continue an ongoing denosumab treatment as concomitant medication during treatment with BT062 was permitted under certain restrictions and denosumab PK-specific time points were added to the description of the study visits.</li> <li>• Collection of denosumab PK samples and instructions for administering BT062 and denosumab as co-medication were added. In addition, all screening results had to be completed before the first dose of BT062 and it was explained that informed consent and biopsy collection could take place even before screening period.</li> <li>• In breast cancer subjects who failed more than 2 treatment regimens, the requirement to be eligible for the current study was that no PD was observed earlier than 9 weeks of the start of the last unsuccessful treatment. Treatments of a short duration &lt; 9weeks due to insufficient tolerability or other reasons, with absence of disease progression did not have to lead to exclusion of a subject.</li> <li>• In case participation ended for a reason other than PD and the subject had received at least 2 cycles of BT062, the first tumor staging data from routine diagnostics after discontinuation were to be captured in the eCRF.</li> <li>• Previous chemotherapies, including adjuvant therapies, sequential regimens, and in-situ therapies were provided.</li> <li>• Guidance on the timing of written informed consent was provided.</li> <li>• Guidance on the timing of the 30-day follow-up depending on the reason of study discontinuation was provided.</li> <li>• A brief description of extravasation as a potential source of risk or discomfort was added.</li> <li>• A more detailed description of molecular parameters related to PK was added to clarify the aim to also analyze potential BT062 metabolites.</li> <li>• suspicion of a technical complaint or product complaint in a Biotest product which caused an infection in a subject, represented an IRAE.</li> </ul>
02 June 2016	<p>Protocol amendment 3, dated 02-JUN-2016 introduced the following changes:</p> <ul style="list-style-type: none"> <li>• It was clarified that disease control observation was done during the first 3 cycles.</li> <li>• The ITT population and subsequently also the subject replacement section were adapted according to RECIST criteria. Every subject treated with BT062 who had 1 post-treatment tumor staging or DLT/intolerabilities was to be included in the ITT population. Subjects, who discontinued the treatment before the first post-dose tumor staging and for whom no DLT or other sign of insufficient tolerability was observed, needed to be replaced. In case of SD, the minimum time interval between baseline tumor staging and first post-dose tumor staging was defined as 6 weeks.</li> <li>• It was clarified that tumor staging was planned after every third treatment cycle, but could be performed at any time during the study, if clinically indicated.</li> <li>• The number of PK parameters analyzed was reduced for Phase I of the study.</li> <li>• Certain other sections were amended for clarification.</li> </ul>

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
15 July 2016	<p>Recruitment was stopped prematurely during Stage 1 of Phase IIa because of a low recruitment rate, an unacceptably large number of subjects prematurely terminating the study, and limited monotherapeutic efficacy in these indications with end-stage patients and exhausted treatment options.</p>	-

Notes:

## Limitations and caveats

None reported