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

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:

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

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 ≥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 ≥ 12 weeks and ECOG≤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
Arm title	100 mg/m2

Arm description: -

Arm type	Experimental
Investigational medicinal product name	BT062 100 mg / m² 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 / m2 BSA.
BT062 will be administered intravenously at Days 1, 8 and 15 during a 28-day treatment cycle.

Arm title	120 mg / m²

Arm description: -

Arm type	Experimental
Investigational medicinal product name	BT062 120 mg / m² 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 / m2 BSA.
BT062 will be administered intravenously at Days 1, 8 and 15 during a 28-day treatment cycle.

Arm title	140 mg/m2

Arm description: -

Arm type	Experimental

Investigational medicinal product name	BT062 140 mg / m² 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 / m2 BSA.
BT062 will be administered intravenously at Days 1, 8 and 15 during a 28-day treatment cycle.

Number of subjects in period 1[1]	100 mg/m2	120 mg / m²	140 mg/m2
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/m2) 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
Arm title	TNBC

Arm description:

subjects with triple-negative breast cancer

Arm type	Experimental
Investigational medicinal product name	BT062 100 mg / m² 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 / m2 BSA.
BT062 will be administered intravenously at Days 1, 8 and 15 during a 28-day treatment cycle.

Arm title	TCCUB

Arm description:

Subjects with transitional cell cancer of the urinary bladder

Arm type	Experimental
Investigational medicinal product name	BT062 100 mg / m² 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 / m2 BSA.
BT062 will be administered intravenously at Days 1, 8 and 15 during a 28-day treatment cycle.

Number of subjects in period 2	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 / m²
Reporting group description: -	
Reporting group title	140 mg/m2
Reporting group description: -	

Reporting group values	100 mg/m2	120 mg / m²	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	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)	0		
From 65-84 years	0		
85 years and over	0		

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

Age continuous			
Units: years			
arithmetic mean	57.3		
standard deviation	± 13.85	±	±
Gender categorical			
Units: Subjects			
Female	24		
Male	15		

Reporting group values	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/m2
Reporting group description: -	
Reporting group title	120 mg / m²
Reporting group description: -	
Reporting group title	140 mg/m2
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[1]
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/m2	120 mg / m²	140 mg/m2	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[2]

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 / µL
• 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.

End point values	100 mg/m2	120 mg / m²	140 mg/m2	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 Erythrodysaesthesia 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

End point values	100 mg/m2	120 mg / m²	140 mg/m2	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

End point values	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

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

End point timeframe:

From Baseline to the end of study

End point values	100 mg/m2	120 mg / m²	140 mg/m2	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/m2	120 mg / m²	140 mg/m2	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

End point values	100 mg/m2	120 mg / m²	140 mg/m2	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

End point values	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		

Attachments (see zip file)	Duration of stable disease of individual subjects/f-14-02-02-04.

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

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Safety population

Reporting group description:

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

Serious adverse events	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	Additional description: Fatal outcome, 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 / 1		
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Disease progression			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Infusion site extravasation	Additional description: Resolving, no Action with study drug, 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		
Gastrointestinal disorders			
Stomatitis	Additional description: Resolving, drug withdrawn, 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		
Gastrointestinal haemorrhage	Additional description: Fatal outcome, 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 / 1		
Intestinal obstruction	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		
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		
Skin and subcutaneous tissue disorders			
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 erythrodysaesthesia 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		
Psychiatric disorders			
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		
Renal and urinary disorders			
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		
Musculoskeletal and connective tissue disorders			
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		
Infections and infestations			
Pneumonia	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		
Febrile infection	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		
Cystitis	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		
Pyelonephritis acute	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		
Infusion site cellulitis	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		
Sepsis	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 %

Non-serious adverse events	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	2 / 39 (5.13%)		
occurrences (all)	3		
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	9		
Hypotension			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	4		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	21 / 39 (53.85%)		
occurrences (all)	40		
Oedema peripheral			
subjects affected / exposed	6 / 39 (15.38%)		
occurrences (all)	15		
Pyrexia			
subjects affected / exposed	4 / 39 (10.26%)		
occurrences (all)	8		
Chest pain			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Pain			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Chills			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Feeling cold			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		

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

Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	8 / 39 (20.51%)		
occurrences (all)	13		
Gamma-glutamyltransferase increased			
subjects affected / exposed	7 / 39 (17.95%)		
occurrences (all)	12		
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 39 (12.82%)		
occurrences (all)	9		
Weight decreased			
subjects affected / exposed	4 / 39 (10.26%)		
occurrences (all)	5		
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	5		
Blood creatinine increased			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	10		
Electrocardiogram QT prolonged			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Blood lactate dehydrogenase increased			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Glomerular filtration rate decreased			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	5		
Lipase increased			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	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	2 / 39 (5.13%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	5 / 39 (12.82%)		
occurrences (all)	5		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	5 / 39 (12.82%)		
occurrences (all)	9		
Pruritus			
subjects affected / exposed	5 / 39 (12.82%)		
occurrences (all)	7		
Rash			
subjects affected / exposed	5 / 39 (12.82%)		
occurrences (all)	16		
Rash maculo-papular			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	8		
Dermatitis bullous			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Night sweats			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Skin ulcer			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	3		
Dysuria			
subjects affected / exposed	4 / 39 (10.26%)		
occurrences (all)	4		
Haematuria			

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 December 2013	Protocol amendment 1 dated 05-DEC-2013 introduced the following changes: •The recruitment timeline and assumed duration of the study were adapted. • The FACT GOG-Ntx questionnaire was added. • Minor clarifications to the flowchart were made. • The DLT definition of thrombocytopenia was re-worded to make it clearer without changing the criteria. • More emphasis was put on the recommendation to conduct further unscheduled visits if AEs were still ongoing at study end. • 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. • The option to have CD138 assessed on historic biopsies, while a fresh biopsy still remained mandatory, was added. • 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. • The description on optimal biomarker time points was corrected to match the flowchart. • It was further clarified that biological samples to be used for PK analysis consisted of sodium heparin plasma samples. • Blood gas analyses were removed from the clinical chemistry panel as it had been included in error. • A reminder on the limitations of the Cockcroft-Gault equation in showing the true glomerular filtration rate was included. • 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.

11 March 2015	The major changes: • Estimated end dates of enrollment and data cut-off were updated. • 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. • 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. • 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 < 9weeks due to insufficient tolerability or other reasons, with absence of disease progression did not have to lead to exclusion of a subject. • 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. • Previous chemotherapies, including adjuvant therapies, sequential regimens, and in-situ therapies were provided. • Guidance on the timing of written informed consent was provided. • Guidance on the timing of the 30-day follow-up depending on the reason of study discontinuation was provided. • A brief description of extravasation as a potential source of risk or discomfort was added. • A more detailed description of molecular parameters related to PK was added to clarify the aim to also analyze potential BT062 metabolites. • suspicion of a technical complaint or product complaint in a Biotest product which caused an infection in a subject, represented an IRAE.
02 June 2016	Protocol amendment 3, dated 02-JUN-2016 introduced the following changes: • It was clarified that disease control observation was done during the first 3 cycles. • 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. • 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. • The number of PK parameters analyzed was reduced for Phase I of the study. • Certain other sections were amended for clarification.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
15 July 2016	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.	-

Notes:

Limitations and caveats

None reported