Clinical trial results:
A Double-blind Randomised, Parallel Phase I/IIb Study to Evaluate Initial Safety and Efficacy, Comparative Pharmacokinetics and Immunogenicity for CT-P6 and Herceptin in Metastatic Breast Cancer

Summary

EudraCT number	2009-014463-39
Trial protocol	LV BG GB
Global end of trial date	29 December 2023

Results information

Result version number	v1 (current)
This version publication date	24 August 2024
First version publication date	24 August 2024

Trial information

Trial identification

Sponsor protocol code	1.1

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Celltrion, Inc.
Sponsor organisation address	23, Academy-ro, Yeonsu-gu, Incheon, Korea, Republic of, 22014, Incheon, Korea, Republic of,
Public contact	Celltrion, Inc., Celltrion, Inc., 82 850 5000, contact@celltrion.com, Celltrion, Inc., 82 8505000,
Scientific contact	Celltrion, Inc., Celltrion, Inc., 82 850 5000, contact@celltrion.com, Celltrion, Inc., 82 8505000,

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	18 March 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 June 2012
Global end of trial reached?	Yes
Global end of trial date	29 December 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to demonstrate equivalent PK in terms of area under the curve at steady state (AUCSS) between CT-P6 and the comparator Herceptin in patients with metastatic breast cancer.

Protection of trial subjects:

The study was conducted according to the protocol and in compliance with Good Clinical Practice (GCP) and other applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 February 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	14 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 10
Country: Number of subjects enrolled	Latvia: 15
Country: Number of subjects enrolled	Serbia: 11
Country: Number of subjects enrolled	Ukraine: 29
Country: Number of subjects enrolled	Korea, Republic of: 63
Country: Number of subjects enrolled	Russian Federation: 45
Country: Number of subjects enrolled	Taiwan: 1
Worldwide total number of subjects	174
EEA total number of subjects	25

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)	150
From 65 to 84 years	24
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were enrolled at 7 sites across Bulgaria, Korea, Republic of, Latvia, Russian Federation, Serbia, Taiwan, and Ukraine.

Pre-assignment

Screening details:

This study included females 18 years of age or older with HER-2 positive metastatic breast cancer who had not been treated in the first line metastatic setting.

Pre-assignment period milestones

Number of subjects started	174
Number of subjects completed	143

Pre-assignment subject non-completion reasons

Reason: Number of subjects	excluded from Full Analysis Set (FAS): 31

Period 1

Period 1 title	Main Study Treatment Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	CT-P6

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Trastuzumab (CT-P6, Herzuma)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

8 mg/kg body weight on Day 1, Cycle 1, followed by 6 mg/kg body weight repeated at every 3 weeks until disease progression, death, or discontinuation.

Arm title	Herceptin

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Trastuzumab (Herceptin)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

8 mg/kg body weight on Day 1, Cycle 1, followed by 6 mg/kg body weight repeated at every 3 weeks until disease progression, death, or discontinuation.

Number of subjects in period 1[1]	CT-P6	Herceptin
Started	76	67
Completed	60	56
Not completed	16	11
Disease progression	11	7
Adverse Event	5	3
Other reason	-	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: Overall, 31 enrolled patients who did not met definition of FAS was excluded.

Period 2

Period 2 title	Treatment Period Beyond Cycle 8
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	CT-P6

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Trastuzumab (CT-P6, Herzuma)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

8 mg/kg body weight on Day 1, Cycle 1, followed by 6 mg/kg body weight repeated at every 3 weeks until disease progression, death, or discontinuation.

Arm title	Herceptin

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Trastuzumab (Herceptin)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

8 mg/kg body weight on Day 1, Cycle 1, followed by 6 mg/kg body weight repeated at every 3 weeks until disease progression, death, or discontinuation.

Number of subjects in period 2	CT-P6	Herceptin
Started	60	56
Discontinued treatment after Cycle 8	60	56
Completed	0	0
Not completed	60	56
Consent withdrawn by subject	4	4
Physician decision	2	4
Disease progression	51	45
Adverse Event	1	-
Unknown	-	1
Other reason	2	2

Baseline characteristics

Reporting groups	
Reporting group title	CT-P6
Reporting group description: -	
Reporting group title	Herceptin
Reporting group description: -	

Reporting group values	CT-P6	Herceptin	Total
Number of subjects	76	67	143
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	63	59	122
From 65-84 years	13	8	21
85 years and over	0	0	0
Age continuous Units: years			
median	56.0	56.0	
full range (min-max)	33 to 75	28 to 76	-
Gender categorical Units: Subjects			
Female	76	67	143
Male	0	0	0

Subject analysis sets	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

All randomized patients who received any study drug and had at least one post-baseline assessment, with the exception of the patients who violated against Herceptin indication. Patients were analyzed according to the treatment to which they were randomized and not according to what they actually received, in the event there will be a discrepancy between the actual treatment received and the randomized treatment. All summaries of study population data, including disposition of patients, major protocol deviations, and analysis sets, as well as demographic and baseline characteristics were performed using the FAS. Also, all efficacy analysis were performed using the FAS.

Subject analysis set title	PK Analysis Set – Global (PKASg)
Subject analysis set type	Full analysis

Subject analysis set description:

All FAS patients who had achieved steady state by the 8th cycle, which required 3 consecutive similar trough concentrations. Patients were analyzed according to the study drug they actually received. All summaries of PK parameter were performed using the PKASg.

Reporting group values	Full Analysis Set (FAS)	PK Analysis Set – Global (PKASg)	
Number of subjects	143	100	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	122	83	
From 65-84 years	21	17	
85 years and over	0	0	
Age continuous Units: years			
median	56.0	56.0	
full range (min-max)	28 to 76	28 to 76	
Gender categorical Units: Subjects			
Female	143	100	
Male	0	0	

End points

End points reporting groups

Reporting group title	CT-P6
Reporting group description: -	
Reporting group title	Herceptin
Reporting group description: -	
Reporting group title	CT-P6
Reporting group description: -	
Reporting group title	Herceptin
Reporting group description: -	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

All randomized patients who received any study drug and had at least one post-baseline assessment, with the exception of the patients who violated against Herceptin indication. Patients were analyzed according to the treatment to which they were randomized and not according to what they actually received, in the event there will be a discrepancy between the actual treatment received and the randomized treatment. All summaries of study population data, including disposition of patients, major protocol deviations, and analysis sets, as well as demographic and baseline characteristics were performed using the FAS. Also, all efficacy analysis were performed using the FAS.

Subject analysis set title	PK Analysis Set – Global (PKASg)
Subject analysis set type	Full analysis

Subject analysis set description:

All FAS patients who had achieved steady state by the 8th cycle, which required 3 consecutive similar trough concentrations. Patients were analyzed according to the study drug they actually received. All summaries of PK parameter were performed using the PKASg.

Primary: AUCss at 6 months (8 treatment cycles).

End point title	AUCss at 6 months (8 treatment cycles).

End point description:

The primary endpoint was to demonstrate PK equivalence in terms of area under the concentration time curve at steady state (AUCss) between CT-P6 and the comparator. The primary endpoint was reached at 6 months (8 treatment cycle; Main Study Treatment Period).

End point type	Primary

End point timeframe:

6 months

End point values	CT-P6	Herceptin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	49		
Units: ug*h/mL				
arithmetic mean (standard deviation)	34400 (± 15000)	31800 (± 9820)		

Statistical analyses

Statistical analysis title	Geometric Mean Ratio
Comparison groups	Herceptin v CT-P6
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Geometric Mean Ratio
Point estimate	104.57
Confidence interval	
level	90 %
sides	2-sided
lower limit	93.64
upper limit	116.78

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 14 years.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups

Reporting group title	CT-P6
Reporting group description: -	
Reporting group title	Herceptin

Reporting group description: -

Serious adverse events	CT-P6	Herceptin	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 76 (15.79%)	19 / 67 (28.36%)	
number of deaths (all causes)	2	3	
number of deaths resulting from adverse events	0	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 76 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Biliary drainage			
subjects affected / exposed	0 / 76 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	1 / 76 (1.32%)	5 / 67 (7.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 2	
Infusion related reaction			

subjects affected / exposed	1 / 76 (1.32%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 76 (1.32%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 76 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Endoscopic retrograde cholangiopancreatography			
subjects affected / exposed	0 / 76 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 76 (1.32%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Spinal fracture			
subjects affected / exposed	0 / 76 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure acute			
subjects affected / exposed	0 / 76 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Nervous system disorders			
Brain oedema			

subjects affected / exposed	0 / 76 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 76 (1.32%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	2 / 76 (2.63%)	3 / 67 (4.48%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 76 (0.00%)	3 / 67 (4.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 76 (1.32%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 76 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cholecystitis acute			
subjects affected / exposed	0 / 76 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis cholestatic			
subjects affected / exposed	0 / 76 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 76 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Acute tonsillitis			
subjects affected / exposed	1 / 76 (1.32%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	2 / 76 (2.63%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	1 / 76 (1.32%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic infection			
subjects affected / exposed	0 / 76 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 76 (1.32%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Sepsis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 76 (1.32%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 76 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 76 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	CT-P6	Herceptin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	75 / 76 (98.68%)	65 / 67 (97.01%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	7 / 76 (9.21%)	8 / 67 (11.94%)	
occurrences (all)	12	19	
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 76 (7.89%)	7 / 67 (10.45%)	
occurrences (all)	8	16	
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 76 (6.58%)	4 / 67 (5.97%)	
occurrences (all)	6	9	
Nervous system disorders			

Peripheral sensory neuropathy			
subjects affected / exposed	21 / 76 (27.63%)	27 / 67 (40.30%)	
occurrences (all)	79	50	
Neuropathy peripheral			
subjects affected / exposed	23 / 76 (30.26%)	21 / 67 (31.34%)	
occurrences (all)	46	54	
Headache			
subjects affected / exposed	11 / 76 (14.47%)	13 / 67 (19.40%)	
occurrences (all)	16	18	
Dizziness			
subjects affected / exposed	6 / 76 (7.89%)	13 / 67 (19.40%)	
occurrences (all)	11	23	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	32 / 76 (42.11%)	33 / 67 (49.25%)	
occurrences (all)	59	85	
Leukopenia			
subjects affected / exposed	8 / 76 (10.53%)	12 / 67 (17.91%)	
occurrences (all)	10	28	
Anaemia			
subjects affected / exposed	9 / 76 (11.84%)	5 / 67 (7.46%)	
occurrences (all)	19	9	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	24 / 76 (31.58%)	10 / 67 (14.93%)	
occurrences (all)	52	14	
Fatigue			
subjects affected / exposed	10 / 76 (13.16%)	10 / 67 (14.93%)	
occurrences (all)	27	31	
Pyrexia			
subjects affected / exposed	10 / 76 (13.16%)	10 / 67 (14.93%)	
occurrences (all)	18	18	
Oedema peripheral			
subjects affected / exposed	8 / 76 (10.53%)	8 / 67 (11.94%)	
occurrences (all)	10	12	
Chills			

subjects affected / exposed	6 / 76 (7.89%)	7 / 67 (10.45%)	
occurrences (all)	11	8	
Mucosal inflammation			
subjects affected / exposed	4 / 76 (5.26%)	5 / 67 (7.46%)	
occurrences (all)	5	6	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	13 / 76 (17.11%)	18 / 67 (26.87%)	
occurrences (all)	23	38	
Stomatitis			
subjects affected / exposed	6 / 76 (7.89%)	11 / 67 (16.42%)	
occurrences (all)	13	14	
Constipation			
subjects affected / exposed	4 / 76 (5.26%)	10 / 67 (14.93%)	
occurrences (all)	6	14	
Abdominal pain upper			
subjects affected / exposed	4 / 76 (5.26%)	8 / 67 (11.94%)	
occurrences (all)	4	13	
Dyspepsia			
subjects affected / exposed	5 / 76 (6.58%)	3 / 67 (4.48%)	
occurrences (all)	6	3	
Nausea			
subjects affected / exposed	19 / 76 (25.00%)	17 / 67 (25.37%)	
occurrences (all)	51	41	
Vomiting			
subjects affected / exposed	5 / 76 (6.58%)	9 / 67 (13.43%)	
occurrences (all)	10	14	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	11 / 76 (14.47%)	8 / 67 (11.94%)	
occurrences (all)	13	11	
Dyspnoea			
subjects affected / exposed	8 / 76 (10.53%)	5 / 67 (7.46%)	
occurrences (all)	11	7	
Oropharyngeal pain			

subjects affected / exposed	3 / 76 (3.95%)	5 / 67 (7.46%)	
occurrences (all)	4	6	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	47 / 76 (61.84%)	44 / 67 (65.67%)	
occurrences (all)	59	50	
Rash			
subjects affected / exposed	10 / 76 (13.16%)	12 / 67 (17.91%)	
occurrences (all)	16	29	
Pruritus			
subjects affected / exposed	7 / 76 (9.21%)	12 / 67 (17.91%)	
occurrences (all)	11	18	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	7 / 76 (9.21%)	13 / 67 (19.40%)	
occurrences (all)	14	16	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	31 / 76 (40.79%)	31 / 67 (46.27%)	
occurrences (all)	134	127	
Arthralgia			
subjects affected / exposed	10 / 76 (13.16%)	15 / 67 (22.39%)	
occurrences (all)	33	29	
Pain in extremity			
subjects affected / exposed	10 / 76 (13.16%)	17 / 67 (25.37%)	
occurrences (all)	14	32	
Bone pain			
subjects affected / exposed	13 / 76 (17.11%)	6 / 67 (8.96%)	
occurrences (all)	22	10	
Back pain			
subjects affected / exposed	5 / 76 (6.58%)	11 / 67 (16.42%)	
occurrences (all)	7	19	
Musculoskeletal pain			
subjects affected / exposed	6 / 76 (7.89%)	7 / 67 (10.45%)	
occurrences (all)	7	9	
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	7 / 76 (9.21%)	3 / 67 (4.48%)	
occurrences (all)	11	9	
Upper respiratory tract infection			
subjects affected / exposed	3 / 76 (3.95%)	6 / 67 (8.96%)	
occurrences (all)	3	10	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	7 / 76 (9.21%)	8 / 67 (11.94%)	
occurrences (all)	12	22	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 May 2010	Amendments in the eligibility crieria and procedures
02 December 2010	Amendments in the sample size calculation
23 February 2012	Clarification in determination of disease progression related to follow-up of patient was moved to the Investigator from ITRC
03 July 2013	Amendments in study duration and updated study protocol to open-label study

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported