Clinical trial results:
A multi-center, open label, uncontrolled, Phase IIa clinical trial evaluating the safety and efficacy of NOX-A12 in combination with a background therapy of bortezomib and dexamethasone (VD) in previously treated patients with multiple myeloma (MM)

Summary

EudraCT number	2011-004651-40
Trial protocol	DE AT IT
Global end of trial date	30 September 2015

Results information

Result version number	v1 (current)
This version publication date	30 September 2016
First version publication date	30 September 2016

Trial information

Trial identification

Sponsor protocol code	SNOXA12C301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01521533
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	NOXXON Pharma AG
Sponsor organisation address	Max-Dohrn-Strasse 8-10, Berlin, Germany, 10589
Public contact	Clinical Trial Disclosure Desk NOXXON, NOXXON Pharma AG, clinicaltrialdisclosuredesk@noxxon.com
Scientific contact	Clinical Trial Disclosure Desk NOXXON, NOXXON Pharma AG, clinicaltrialdisclosuredesk@noxxon.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	26 April 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 September 2015
Global end of trial reached?	Yes
Global end of trial date	30 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety and tolerability of olaptesed pegol alone (pilot group only) and in combination with VD

To determine the overall response rate according to IMWG uniform response criteria (ORR = best response at least partial response(PR))

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, ICH GCP Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, 2005/28/EC, and 2003/63/EC and relevant national and local legislations, and with the ethical principles that have their origin in the Declaration of Helsinki. Only subjects that met all the study inclusion and none of the exclusion criteria were randomized. Study drug administrations were performed by qualified and trained study personnel. Patient who received treatment were closely followed by means of adverse event reporting and vital signs. In the event of a study related adverse event, patients were monitored to determine the outcome. The clinical course of the AE was followed up according to accepted standards of medical practice, even after the end of the period of observation, until a satisfactory explanation is found or the Investigator considered it medically justifiable to terminate follow-up.

Background therapy:

bortezomib and dexamethasone

Evidence for comparator: -

Actual start date of recruitment	20 July 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 12
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Italy: 7
Worldwide total number of subjects	28
EEA total number of subjects	28

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)	11
From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

32 patients with diagnosis of relapsed and refractory multiple myeloma for which bortezomib / dexamethasone would be given as standard of care were screened; 4 patients were screening failure. After a screening period of 2 weeks 28 patients were enrolled.

Period 1

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

Arms

Arm title	Olaptesed pegol + VD

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Olaptesed pegol
Investigational medicinal product code	NOX-A12
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Pilot group: 1, 2, or 4 mg/kg body weight olaptesed pegol given as single i.v. injections on Day -14. If no DLT occurred, doses given on Days 1, 4, 8 and 11 of each 21-day cycle were 1 mg/kg for Cycle 1, 2 mg/kg for Cycle 2 and 4 mg/kg for Cycle 3 and the highest individually titrated doses through cycles 4 to 8.
Expansion group: i.v. injections of 1 mg/kg body weight olaptesed pegol for Cycle 1, 2 mg/kg for Cycle 2 and 4 mg/kg for Cycle 3 given on Days 1, 4, 8 and 11 of each 21-day cycle and the highest individually titrated doses through cycles 4 - 8.
Doses were calculated according to screening body weight. In case body weight changed by more than 10%, the dose was re-calculated.
Single-use, preservative-free, sterile solution of olaptesed pegol in an aqueous glucose solution for adjustment of tonicity to physiological levels.

Number of subjects in period 1	Olaptesed pegol + VD
Started	28
Completed	16
Not completed	12
Consent withdrawn by subject	3
Adverse event, non-fatal	1
progressive disease	7
Lack of efficacy	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	28	28	
Age categorical Units: Subjects			
Adults (18-64 years)	11	11	
From 65-84 years	17	17	
Age continuous Units: years			
arithmetic mean	66.3		
full range (min-max)	47 to 79	-	
Gender categorical Units: Subjects			
Female	14	14	
Male	14	14	

End points

End points reporting groups

Reporting group title	Olaptesed pegol + VD

Reporting group description: -

Primary: Overall response

End point title	Overall response[1]

End point description:

The primary efficacy parameter was to determine the overall response rate according to IMWG uniform response criteria (ORR = best response at least partial response (PR))

End point type	Primary

End point timeframe:

Eight 21-day cycles of treatment

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: Treatment with olaptesed pegol + VD resulted in an ORR of 68%. These results compare favorably with the 40%, 50% and 53% obtained in the RETRIEVE (Petrucci 2013), MMY-3021 (Arnulf 2012), and BoMER study (Harrison 2015). The PANORAMA1 study reported an ORR of 55% for the VD control group (San-Miguel 2015). Importantly, the patient population on which the approval of panobinostat is based (at least 2 prior regimens, including bortezomib and an IMiD), showed an ORR of approx. 40% (Richardson 2015).

End point values	Olaptesed pegol + VD			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: patients				
Overall response	19			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From time the patient gives informed consent until 30 days after the last NOX-A12 administration

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Olaptesed pegol + VD

Reporting group description: -

Serious adverse events	Olaptesed pegol + VD		
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 28 (50.00%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			

subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea exertional			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subdural haematoma			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Brain compression			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Paraesthesia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Polyneuropathy			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Enteritis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			

subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 3.6 %

Non-serious adverse events	Olaptesed pegol + VD		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 28 (100.00%)		
Vascular disorders			
Haematoma			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Hypertension			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	5		
Orthostatic hypotension			

subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Phlebitis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 28 (17.86%)		
occurrences (all)	7		
Catheter site pain			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Chest discomfort			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Chest pain			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	5 / 28 (17.86%)		
occurrences (all)	5		
Gait disturbance			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
General physical health deterioration			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	7 / 28 (25.00%)		
occurrences (all)	9		
Pain			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Pyrexia			

subjects affected / exposed	5 / 28 (17.86%)		
occurrences (all)	6		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Cough			
subjects affected / exposed	6 / 28 (21.43%)		
occurrences (all)	10		
Dyspnoea			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	4		
Dyspnoea exertional			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Pulmonary congestion			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Pulmonary embolism			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Psychiatric disorders			
Agitation			

subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Anxiety			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Confusional state			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Depression			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Nervousness			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Investigations			
Blast cell count decreased			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Blast cells present			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Body temperature increased			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
C-reactive protein increased			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Electrocardiogram QT prolonged			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		

Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Hepatic enzyme increased			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Vitamin D decreased			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
White blood cell count decreased			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Fall			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Hand fracture			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Limb injury			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Subdural haematoma			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Cardiac failure			

subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Cardiac failure congestive			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Palpitations			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Sinus tachycardia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Nervous system disorders			
Brain compression			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Dizziness postural			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	2		
Dysgeusia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	4		
Hypoaesthesia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Neuralgia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Neuropathy peripheral			
subjects affected / exposed	5 / 28 (17.86%)		
occurrences (all)	5		
Orthostatic intolerance			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		

Paraesthesia subjects affected / exposed occurrences (all)	5 / 28 (17.86%) 5		
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1		
Polyneuropathy subjects affected / exposed occurrences (all)	5 / 28 (17.86%) 7		
Post herpetic neuralgia subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	11 / 28 (39.29%) 15		
Leukocytosis subjects affected / exposed occurrences (all)	4 / 28 (14.29%) 11		
Leukopenia subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 2		
Lymphopenia subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1		
Neutropenia subjects affected / exposed occurrences (all)	5 / 28 (17.86%) 8		
Thrombocytopenia subjects affected / exposed occurrences (all)	11 / 28 (39.29%) 19		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	3 / 28 (10.71%) 6		
Eye disorders			

Cataract subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1		
Conjunctivitis subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1		
Diplopia subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1		
Meibomianitis subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1		
Retinal vascular occlusion subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1		
Scotoma subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1		
Vision blurred subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1		
Visual impairment subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	3 / 28 (10.71%) 5		
Abdominal pain upper subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2		
Aerophagia subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1		
Constipation			

subjects affected / exposed	9 / 28 (32.14%)		
occurrences (all)	10		
Diarrhoea			
subjects affected / exposed	14 / 28 (50.00%)		
occurrences (all)	23		
Dyspepsia			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Enteritis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Gastritis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Lip dry			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	3		
Rectal haemorrhage			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Reflux gastritis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	3		
Vomiting			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	2		
Hepatobiliary disorders			

Bile duct stone			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Decubitus ulcer			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Dermatitis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Dermatitis exfoliative			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Erythema			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	2		
Pruritus			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	5		
Rash macular			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Skin hyperpigmentation			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Swelling face			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Renal failure			

subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Bone pain			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Musculoskeletal pain			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	4		
Pain in extremity			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Infections and infestations			
Abscess			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Bronchitis			
subjects affected / exposed	5 / 28 (17.86%)		
occurrences (all)	5		
Candidiasis			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Cystitis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Gingival infection			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Herpes simplex			

subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Herpes zoster			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Hordeolum			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Infection			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Influenza			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	2		
Nasopharyngitis			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	5		
Pneumonia			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	4		
Pulpitis dental			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Upper respiratory tract infection			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		

Dehydration			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Hypercalcaemia			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	4		
Hyperglycaemia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Hyperkalaemia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Hypocalcaemia			
subjects affected / exposed	6 / 28 (21.43%)		
occurrences (all)	9		
Hypokalaemia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Hypomagnesaemia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	2		
Hyponatraemia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Hypophosphataemia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 March 2012	Amendment 1 DE: administrative: to clarify that quantitation of immunoglobulins is part of tumor assessment only; clarification that ECGs, vitals & samples for PK/SDF-1, CD34+, plasma & myeloma cell analysis that are taken 1 h after olaptesed pegol, should be taken before BTZ-DEX; reduction in time period between olaptesed i.v. bolus and bortezomib i.v. bolus injection to improve alignment of the olaptesed PK/PD profiles with BTZ PK/PD profiles Amendment 1 AT & IT: implementation of changes required by BfArM in other countries further specification of Inclusion Criterion #7: details of permissible forms of reliable contraceptive methods are included; further specification of Inclusion Criterion #8: acceptable liver function is documented, in accordance with the bortezomib SPC; further specification of Inclusion Criterion #11: excluding patients with concomitant diseases; e.g. heart diseases; impaired liver function is included as a separate DLT due to increased liver values noted during the early development of olaptesed and in accordance with requirements to monitor liver values closely in order to adjust the dosage of BTZ and thus prevent any decrease in efficacy; hematological toxicity associated with olaptesed alone or olaptesed & BTZ-DEX in combination is included as a DLT to safeguard patient safety; time window & examination hierarchy: administrative correction to allow more time for pre-dose assessments; administrative: to provide further details of the ultrasound assessments of liver

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported