Clinical trial results:
A Phase I/II, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial Evaluating the Efficacy and Safety of Nintedanib/Vargatef in Combination With Paclitaxel Chemotherapy for Treatment of Patients with BRAF Wildtype Metastatic Melanoma

Summary

EudraCT number	2013-004458-34
Trial protocol	DE
Global end of trial date	17 October 2019

Results information

Result version number	v1 (current)
This version publication date	17 November 2021
First version publication date	17 November 2021
Summary attachment (see zip file)	CSR_synopsis (NIPAWILMA_CSR_V1.0_final_2020-07-21_Synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	Nipawilma_2013

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02308553
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Essen
Sponsor organisation address	Hufelandstr. 55, Essen, Germany, 45147
Public contact	Department of Dermatology, University of Essen, 0049 2017234345, dirk.schadendorf@uk-essen.de
Scientific contact	Department of Dermatology, University of Essen, 0049 2017234345, dirk.schadendorf@uk-essen.de

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 April 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 October 2019
Global end of trial reached?	Yes
Global end of trial date	17 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objectives of this study are to characterize the safety and to estimate the efficacy of nintedanib when combined with paclitaxel
chemotherapy compared with paclitaxel chemotherapy alone in patients with BRAF wildtype metastatic melanoma not previously
treated with taxanes or kinase inhibitors.
The primary endpoint of Phase I is the definition of the Maximum Tolerable Dose (MTD) of the nintedanib/paclitaxel combination treatment.
The primary endpoint of Phase II is the progression-free survival (PFS) according to RECIST v1.1.

Protection of trial subjects:

The treatment should be conducted exactly as described in the protocol. Any protocl deviations were reported. The recommendations of Good Clinical Practice (ICH-GCP: International Conference on Harmonisation - Good Clinical Practice), valid since 17.1.1997, were observed.
The phase I/phase II study design ensured that the best tolerated doses of the nintedanib/paclitaxel combination therapy as established in phase I part were administerd to patients of phase II. A formal assessment of the phase I results was done by the sponsor in cooperation with 1-2 independent experts. This interim analysis including determination of the Maximal Tolerated Dose was submitted to the higher competent authority and to the ethics committees. After approval, the phase II part started.
During phase I/II, dose reductions and treatment interuptions were permitted and specified requirements for continuation had to be observed. Liver enzymes were followed closely during treatment with nintedanib.
Since intedanib could have a potential risk of phototoxicity (skin and eyes), patients were advised to avoid sun exposure or artificial UVA/UVB radiation in solaria or tanning booths and to use protective clothing and broad spectrum (UVA/UVB) sunscreens if exposure to sunlight could not be avoided.
At the beginning of the study and in regular intervals thereafter, patients received little bottles with enough nintedanib capsules for a treatment period of approximately 8 weeks. Patients had to bring these bottles to every doctor's visit so that the intake of nintedanib during the period could be tracked.

Background therapy:

Sedatives, antibiotics, analgesics, antihistamines, steroids, granulocyte-colony stimulating factor, erythropoetin, or other medications as well as red blood cells, platelets or fresh frozen plasma transfusions could be given to assist in the management of pain, infection, and other complications of the malignancy.
Standard premedication according to the current Summary of Product Characteristics for paclitaxel was required prior to administration of paclitaxel to prevent severe hypersensitivity reactions.
Such premedication could consist of dexamethasone or methyl prednisone orally administered approximately 12 hours before paclitaxel, diphenhydramine i.v. 30 to 60 minutes prior to paclitaxel and cimetidine or ranitidine i.v. 30 to 60 minutes prior to administration. As anti-emetic 5HT-3 antagonists i.v. or per os (e.g., ondansetron, granisetron) could be given.

Evidence for comparator:

In the double-blinded phase II part of the study, patients were randomized 1:1 to receive either nintedanib or placebo each in combination with paclitaxel (Placebo Comparator).
Nintedanib or a placebo (matching the nintedanib capsules) was used in combination with paclitaxel, in order to assess the efficacy of a nintedanib-paclitaxel combination therapy compared to pactlitaxel alone.

Actual start date of recruitment	17 March 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 32
Worldwide total number of subjects	32
EEA total number of subjects	32

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)	23
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

After obtaining informed consent, screening evaluations were performed to confirm eligibiliy and to obtain baseline safety data.
From 17-Mar-2015 (first patient in) up to 15- Oct-2018 (last patient in), 34 patients were registered by 10 hospitals in Germany; thereof 10 patients were registered into phase I-part from 17-Mar-2015 to 07-Mar-2016.

Pre-assignment

Screening details:

The selection of patients occurred by the investigators according to the inclusion and exclusion criteria. After having informed the patient orally and in writiing about the study and after obtaining the patient's informed consent, screening evaluations and procedures had to be performed within 21 days prior to initiating study drug treatment.

Period 1

Period 1 title	Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Placebo contained 0 mg of nintedanib in capsules matching 100 mg and 150 mg of nintedanib capsules

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase I

Arm description:

Finding of maximal tolerated dose of nintedanib in combiantion with paclitaxel

Arm type	Experimental
Investigational medicinal product name	Nintedanib
Investigational medicinal product code	
Other name	Vargatef
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Intake of 1 x 150 mg twice daily (corresponded to a daily dose of 300 mg) or 2 x 100 mg twice daily (corresponded to a daily dose of 400 mg); on days of paclitaxel infusion, no intake of nintedanib

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	Taxomedac
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Paclitaxel 90mg/m2 was administered intravenously over a period of one hour on day 1, 8, and 15 during 4-week cycles.

Arm title	Phase II_Arm A

Arm description:

Nintedanib in combination with paclitaxel

Arm type	Experimental

Investigational medicinal product name	Nintedanib
Investigational medicinal product code	
Other name	Vargatef
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Patients had to swallow 2 x 100 mg capsules twice daily (= 400 mg daily); on days of paclitaxel infusion, no intake of nintedanib

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	Taxomedac
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

90mg/m2 paclitaxel adminitered intravenously on day 1, 8, and 15 during six 4-week cycles

Arm title	Phase II_Arm B

Arm description:

Placebo in combination with paclitaxel

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Patients had to swallow 2 x 100 mg capsules twice daily (= 400 mg daily); on days of paclitaxel infusion, no intake of placebo capsules

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	Taxomedac
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

90mg/m2 paclitaxel administered intravenously on day 1, 8, and 15 during six 4-week cycles

Number of subjects in period 1	Phase I	Phase II_Arm A	Phase II_Arm B
Started	10	9	13
Completed	10	9	13

Baseline characteristics

Reporting groups	
Reporting group title	Phase I
Reporting group description:	
Finding of maximal tolerated dose of nintedanib in combiantion with paclitaxel	
Reporting group title	Phase II_Arm A
Reporting group description:	
Nintedanib in combination with paclitaxel	
Reporting group title	Phase II_Arm B
Reporting group description:	
Placebo in combination with paclitaxel	

Reporting group values	Phase I	Phase II_Arm A	Phase II_Arm B
Number of subjects	10	9	13
Age categorical			
Patients aged 18 years or older could be enrolled. There was no maximum age limit. Age was calculated as Year of registration (phase I-part) or randomisation (phase II-part) minus year of birth.			
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)	8	6	9
From 65-84 years	2	3	4
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	56.80	58.89	58.23
standard deviation	± 13.80	± 7.75	± 11.62
Gender categorical			
There was no preferrred enrolment of men or women; however, pregnant or breast-feeding women were excluded from participation.			
Units: Subjects			
Female	4	2	5
Male	6	7	8

Reporting group values	Total		
Number of subjects	32		
Age categorical			
Patients aged 18 years or older could be enrolled. There was no maximum age limit. Age was calculated as Year of registration (phase I-part) or randomisation (phase II-part) minus year of birth.			
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)	23		
From 65-84 years	9		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
There was no preferrred enrolment of men or women; however, pregnant or breast-feeding women were excluded from participation.			
Units: Subjects			
Female	11		
Male	21		

Subject analysis sets

Subject analysis set title	Phase I
Subject analysis set type	Full analysis

Subject analysis set description:

All patients enrolled in phase I who fulfilled the inclusion and exclusion criteria with at least one administration of study treatment

Subject analysis set title	Phase II_Arm A
Subject analysis set type	Full analysis

Subject analysis set description:

Patients randomized into Arm A who fullfilled all eligibility criteria and who received at least one administration of study drugs

Subject analysis set title	Phase II_Arm B
Subject analysis set type	Full analysis

Subject analysis set description:

Patients randomized to Arm B and who received at least one administration of study drugs

Reporting group values	Phase I	Phase II_Arm A	Phase II_Arm B
Number of subjects	10	9	13
Age categorical			
Patients aged 18 years or older could be enrolled. There was no maximum age limit. Age was calculated as Year of registration (phase I-part) or randomisation (phase II-part) minus year of birth.			
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)	8	6	9
From 65-84 years	2	3	4
85 years and over	0	0	0

Age continuous			
Units: years			
arithmetic mean	56.80	58.89	58.23
standard deviation	± 13.80	± 7.75	± 11.62
Gender categorical			
There was no preferrred enrolment of men or women; however, pregnant or breast-feeding women were excluded from participation.			
Units: Subjects			
Female	4	2	5
Male	6	7	8

End points

End points reporting groups

Reporting group title	Phase I
Reporting group description:	
Finding of maximal tolerated dose of nintedanib in combiantion with paclitaxel	
Reporting group title	Phase II_Arm A
Reporting group description:	
Nintedanib in combination with paclitaxel	
Reporting group title	Phase II_Arm B
Reporting group description:	
Placebo in combination with paclitaxel	
Subject analysis set title	Phase I
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients enrolled in phase I who fulfilled the inclusion and exclusion criteria with at least one administration of study treatment	
Subject analysis set title	Phase II_Arm A
Subject analysis set type	Full analysis
Subject analysis set description:	
Patients randomized into Arm A who fullfilled all eligibility criteria and who received at least one administration of study drugs	
Subject analysis set title	Phase II_Arm B
Subject analysis set type	Full analysis
Subject analysis set description:	
Patients randomized to Arm B and who received at least one administration of study drugs	

Primary: Progression-free survival

End point title	Progression-free survival
End point description:	
Progression was determined according to RECIST v1.1 criteria by the respective trial sites. Progression-free survival was calculated by Kaplan-Meier-Analysis. For patients without progress and not known to have died, PFS time was censored at the date of last contact.	
End point type	Primary
End point timeframe:	
From start of study therapy until progression or death of any cause, whatever occurred first.	

End point values	Phase I	Phase II_Arm A	Phase II_Arm B	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	10	9	13	
Units: months				
median (confidence interval 95%)	6.99 (1.61 to 10.46)	3.47 (1.32 to 5.23)	1.64 (1.58 to 5.30)	

Statistical analyses

Statistical analysis title	PFS_Test
Statistical analysis description: Kaplan-Meier-estimates	
Comparison groups	Phase II_Arm A v Phase II_Arm B
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6282
Method	Logrank

Primary: Maximal tolerated dose

End point title	Maximal tolerated dose[1][2]
End point description: Dose finding will proceed in a classical 3+3, open-label, single arm design (phase I).	
End point type	Primary
End point timeframe: First treatment cycle of 28 days plus one week washout	

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: No statistical analysis was performed for this endpoint.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was performed for this endpoint.

End point values	Phase I	Phase I		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	10	10		
Units: mg twice daily				
number (not applicable)	200	200		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival rates

End point title	Progression-free survival rates
End point description: Progression-free survival (PFS) rates defined as number of patients alive and without progression at 6, 12, 18 and 24 months after start of therapy was derived by Kaplan-Meier methods for patients of Arm A and Arm B of phase II. PFS rates were analysed for Arm A and Arm B of phase II.	
End point type	Secondary
End point timeframe: 6, 12, 18 and 24 months after start of study therapy.	

End point values	Phase II_Arm A	Phase II_Arm B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	13		
Units: Number of patients alive and without PD				
6 months	1	3		
12 months	1	2		
18 months	1	2		
24 months	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

Overall survival (OS) was measured from start of therapy until death occurred due to any cause. OS was estmated by Kaplan-meier-method. OS for patients not known to have died were censored at the date of last contact.

End point type	Secondary

End point timeframe:

From start of study therapy until death occurred due to any cause.

End point values	Phase I	Phase II_Arm A	Phase II_Arm B	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	10	9	13	
Units: months				
median (confidence interval 95%)	19.64 (7.30 to 999.99)	20.63 (4.31 to 999.99)	19.31 (3.59 to 999.99)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events occurring from signing the informed consent onwards until 30 days after last administration of nintedanib/placebo

Adverse event reporting additional description:

Recurrence of disease or death due to underlying metastatic melanoma or findings that are clearly consistent with the expected progression of the underlying cancer should not be reported as an adverse event or a serious adverse event.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Safety analysis phase I

Reporting group description:

Patients who were registered into phase I and who received at least one administration of study medication

Reporting group title	Safety analysis phase II_Arm A

Reporting group description:

All patients who were randomised into Arm A and who received at least one administration of study treatment.

Reporting group title	Safety analysis phase II_Arm B

Reporting group description:

Patients who were randomised into Arm B (placebo control) and who received at least one administration of study therapy.

Serious adverse events	Safety analysis phase I	Safety analysis phase II_Arm A	Safety analysis phase II_Arm B
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 10 (20.00%)	2 / 9 (22.22%)	9 / 13 (69.23%)
number of deaths (all causes)	6	3	6
number of deaths resulting from adverse events	1	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to meninges			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Seizure			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			

Anaphylactic reaction			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	2 / 13 (15.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Large intestinal stenosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			

subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Safety analysis phase I	Safety analysis phase II_Arm A	Safety analysis phase II_Arm B
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)	9 / 9 (100.00%)	13 / 13 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Ganglioneuroma			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Tumour haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Tumour pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 13 (0.00%)
occurrences (all)	0	4	0
Haematoma			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Hypertension			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Lymphoedema			

subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 10 (10.00%)	1 / 9 (11.11%)	1 / 13 (7.69%)
occurrences (all)	2	1	1
Complication associated with device			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	8 / 10 (80.00%)	6 / 9 (66.67%)	1 / 13 (7.69%)
occurrences (all)	14	7	1
General physical health deterioration			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Influenza like illness			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Infusion site extravasation			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Localised oedema			
subjects affected / exposed	2 / 10 (20.00%)	0 / 9 (0.00%)	0 / 13 (0.00%)
occurrences (all)	2	0	0
Oedema peripheral			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 9 (11.11%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Immune system disorders			

Hypersensitivity			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 10 (0.00%)	2 / 9 (22.22%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Dyspnoea			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	2 / 13 (15.38%)
occurrences (all)	0	1	2
Epistaxis			
subjects affected / exposed	0 / 10 (0.00%)	2 / 9 (22.22%)	1 / 13 (7.69%)
occurrences (all)	0	2	1
Oropharyngeal pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Productive cough			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	2 / 13 (15.38%)
occurrences (all)	0	0	2
Rash maculo-papular			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	1 / 13 (7.69%)
occurrences (all)	0	3	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 10 (10.00%)	2 / 9 (22.22%)	0 / 13 (0.00%)
occurrences (all)	1	2	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 10 (20.00%)	3 / 9 (33.33%)	2 / 13 (15.38%)
occurrences (all)	5	6	2
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 10 (10.00%)	2 / 9 (22.22%)	1 / 13 (7.69%)
occurrences (all)	1	2	1
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 10 (10.00%)	1 / 9 (11.11%)	0 / 13 (0.00%)
occurrences (all)	1	1	0

Blood bilirubin increased			
subjects affected / exposed	1 / 10 (10.00%)	1 / 9 (11.11%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 10 (10.00%)	1 / 9 (11.11%)	1 / 13 (7.69%)
occurrences (all)	1	1	1
CD4 lymphocytes decreased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Electrocardiogram T wave inversion			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 10 (10.00%)	2 / 9 (22.22%)	1 / 13 (7.69%)
occurrences (all)	3	4	2
Granulocyte count increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 10 (0.00%)	2 / 9 (22.22%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Monocyte count increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Neutrophil count decreased			
subjects affected / exposed	4 / 10 (40.00%)	1 / 9 (11.11%)	0 / 13 (0.00%)
occurrences (all)	10	1	0
Platelet count increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Protein total decreased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Troponin T increased			

subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Vitamin D decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Weight decreased			
subjects affected / exposed	2 / 10 (20.00%)	0 / 9 (0.00%)	1 / 13 (7.69%)
occurrences (all)	2	0	1
White blood cell count decreased			
subjects affected / exposed	4 / 10 (40.00%)	2 / 9 (22.22%)	2 / 13 (15.38%)
occurrences (all)	13	2	5
Injury, poisoning and procedural complications			
Skin abrasion			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Wound complication			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Congenital, familial and genetic disorders			
Hypertrophic cardiomyopathy			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Cardiac disorders			
Atrial tachycardia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Conduction disorder			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Tachycardia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1

Dysgeusia			
subjects affected / exposed	2 / 10 (20.00%)	2 / 9 (22.22%)	1 / 13 (7.69%)
occurrences (all)	2	2	1
Headache			
subjects affected / exposed	2 / 10 (20.00%)	0 / 9 (0.00%)	0 / 13 (0.00%)
occurrences (all)	2	0	0
Hypoglossal nerve disorder			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Monoparesis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Paraesthesia			
subjects affected / exposed	3 / 10 (30.00%)	2 / 9 (22.22%)	1 / 13 (7.69%)
occurrences (all)	4	2	1
Peripheral sensory neuropathy			
subjects affected / exposed	2 / 10 (20.00%)	1 / 9 (11.11%)	0 / 13 (0.00%)
occurrences (all)	3	1	0
Restless legs syndrome			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Seizure			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Syncope			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Vagus nerve disorder			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 10 (20.00%)	2 / 9 (22.22%)	2 / 13 (15.38%)
occurrences (all)	3	2	2
Bone marrow failure			

subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 10 (10.00%)	1 / 9 (11.11%)	1 / 13 (7.69%)
occurrences (all)	1	1	1
Eye disorders			
Vision blurred			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	1 / 13 (7.69%)
occurrences (all)	2	0	1
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Abdominal distension			
subjects affected / exposed	0 / 10 (0.00%)	2 / 9 (22.22%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Abdominal pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Abdominal pain upper			
subjects affected / exposed	1 / 10 (10.00%)	1 / 9 (11.11%)	0 / 13 (0.00%)
occurrences (all)	2	1	0
Anal eczema			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Anal ulcer			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Angular cheilitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Constipation			

subjects affected / exposed	3 / 10 (30.00%)	0 / 9 (0.00%)	1 / 13 (7.69%)
occurrences (all)	4	0	1
Diarrhoea			
subjects affected / exposed	8 / 10 (80.00%)	6 / 9 (66.67%)	3 / 13 (23.08%)
occurrences (all)	10	13	3
Dry mouth			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Eructation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Flatulence			
subjects affected / exposed	0 / 10 (0.00%)	2 / 9 (22.22%)	0 / 13 (0.00%)
occurrences (all)	0	3	0
Gastritis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Glossitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	4 / 10 (40.00%)	6 / 9 (66.67%)	1 / 13 (7.69%)
occurrences (all)	6	9	1
Pancreatitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Tongue coated			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	2 / 10 (20.00%)	2 / 9 (22.22%)	0 / 13 (0.00%)
occurrences (all)	3	2	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	10 / 10 (100.00%)	5 / 9 (55.56%)	3 / 13 (23.08%)
occurrences (all)	11	6	3

Dermatitis acneiform			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Dry skin			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
Eczema			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Eczema asteatotic			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Erythema			
subjects affected / exposed	1 / 10 (10.00%)	1 / 9 (11.11%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Erythema multiforme			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Hair colour changes			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Hyperhidrosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	3 / 13 (23.08%)
occurrences (all)	0	0	4
Intertrigo			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Nail discolouration			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Papule			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1

Rosacea			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Glycosuria			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	2 / 13 (15.38%)
occurrences (all)	0	1	2
Bone pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Body tinea			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Bronchitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Conjunctivitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Folliculitis			
subjects affected / exposed	1 / 10 (10.00%)	2 / 9 (22.22%)	0 / 13 (0.00%)
occurrences (all)	1	2	0
Mucosal infection			

subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
Rash pustular			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
Skin infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	2 / 13 (15.38%)
occurrences (all)	0	0	4
Upper respiratory tract infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
Urinary tract infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Viral infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Diabetes mellitus			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Hyperuricaemia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 9 (11.11%)	0 / 13 (0.00%)
occurrences (all)	1	2	0
Hypokalaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Hypomagnesaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1

Hyponatraemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Hypophosphataemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	2
Iron deficiency			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 13 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 June 2016	Maximal tolerated dose determined in phase I was included in treatment description for phase II patients and timelines due to delay in recruitment during phase I part were adapted.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported