



Clinical trial results:

A Phase 2, Single-arm, Open-label, Multicenter Study of the Histone Deacetylase Inhibitor (HDACi) JNJ-26481585 in Subjects With Previously Treated Stage Ib-IVa Cutaneous T-cell Lymphoma

Summary

EudraCT number	2011-001076-18
Trial protocol	DE GB ES PT IT
Global end of trial date	22 July 2016

Results information

Result version number	v1 (current)
This version publication date	13 July 2017
First version publication date	13 July 2017

Trial information

Trial identification

Sponsor protocol code	26481585LYM2001
-----------------------	-----------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01486277
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen-Cilag International N.V.
Sponsor organisation address	Turnhoutseweg 30, Beerse, Belgium, B-2340
Public contact	Clinical Registry Group, Janssen-Cilag International NV, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen-Cilag International NV, ClinicalTrialsEU@its.jnj.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	22 July 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 July 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to determine the overall cutaneous response rate (RR) based on the modified Severity Weighted Assessment Tool (mSWAT) criteria.

Protection of trial subjects:

The safety assessments included monitoring of adverse events (AEs), changes in clinical laboratory test values (serum chemistry, hematology, pregnancy test), physical examination results and electrocardiogram (ECG).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 November 2011
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: 4
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Portugal: 3
Country: Number of subjects enrolled	United States: 1
Worldwide total number of subjects	26
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)	15
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted from 30 November 2011 to 22 July 2016 at 17 sites in 7 countries.

Pre-assignment

Screening details:

A total of 26 subjects were enrolled in study; out of these 25 subjects were evaluable for response and 1 subject discontinued the study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Quisinostat 8 milligram (mg)

Arm description:

Subjects with Stage Ib to IVa cutaneous T-cell lymphoma (CTCL) received quisinostat 8 mg orally on Days 1, 3, and 5 of each week in 21-day treatment cycles until disease progression, toxicity, availability of other effective drugs that the subject may receive, or treating physician advice. Subjects who were initially randomized to the JNJ-26481585 (quisinostat) 8 mg dose cohort were allowed to have their dose increased to 12 mg after study was amended to remove 8 mg arm.

Arm type	Experimental
Investigational medicinal product name	Quisinostat 8 mg
Investigational medicinal product code	JNJ-26481585
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received quisinostat 8 mg orally on Days 1, 3, and 5 of each week in 21-day treatment cycles.

Arm title	Quisinostat 12 mg
------------------	-------------------

Arm description:

Subjects with Stage Ib to IVa cutaneous T-cell lymphoma (CTCL) received JNJ-26481585 (quisinostat) 12 mg orally on Days 1, 3, and 5 of each week in 21-day treatment cycles until disease progression, toxicity, availability of other effective drugs that the subject may receive, or treating physician advice.

Arm type	Experimental
Investigational medicinal product name	Quisinostat 12 mg
Investigational medicinal product code	JNJ-26481585
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received quisinostat 12 mg orally on Days 1, 3, and 5 of each week in 21-day treatment cycle.

Number of subjects in period 1	Quisinostat 8 milligram (mg)	Quisinostat 12 mg
Started	6	20
Completed	2	3
Not completed	4	17
Adverse event, serious fatal	1	3
Physician decision	-	2
Other	3	10
Lost to follow-up	-	2

Baseline characteristics

Reporting groups

Reporting group title	Quisinostat 8 milligram (mg)
Reporting group description: Subjects with Stage Ib to IVa cutaneous T-cell lymphoma (CTCL) received quisinostat 8 mg orally on Days 1, 3, and 5 of each week in 21-day treatment cycles until disease progression, toxicity, availability of other effective drugs that the subject may receive, or treating physician advice. Subjects who were initially randomized to the JNJ-26481585 (quisinostat) 8 mg dose cohort were allowed to have their dose increased to 12 mg after study was amended to remove 8 mg arm.	
Reporting group title	Quisinostat 12 mg
Reporting group description: Subjects with Stage Ib to IVa cutaneous T-cell lymphoma (CTCL) received JNJ-26481585 (quisinostat) 12 mg orally on Days 1, 3, and 5 of each week in 21-day treatment cycles until disease progression, toxicity, availability of other effective drugs that the subject may receive, or treating physician advice.	

Reporting group values	Quisinostat 8 milligram (mg)	Quisinostat 12 mg	Total
Number of subjects	6	20	26
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	3	12	15
From 65 to 84 years	3	8	11
85 years and over	0	0	0
Title for AgeContinuous Units: years			
arithmetic mean	62.2	57	
standard deviation	± 15.37	± 14.02	-
Title for Gender Units: subjects			
Female	1	4	5
Male	5	16	21

End points

End points reporting groups

Reporting group title	Quisinostat 8 milligram (mg)
Reporting group description:	
Subjects with Stage Ib to IVa cutaneous T-cell lymphoma (CTCL) received quisinostat 8 mg orally on Days 1, 3, and 5 of each week in 21-day treatment cycles until disease progression, toxicity, availability of other effective drugs that the subject may receive, or treating physician advice. Subjects who were initially randomized to the JNJ-26481585 (quisinostat) 8 mg dose cohort were allowed to have their dose increased to 12 mg after study was amended to remove 8 mg arm.	
Reporting group title	Quisinostat 12 mg
Reporting group description:	
Subjects with Stage Ib to IVa cutaneous T-cell lymphoma (CTCL) received JNJ-26481585 (quisinostat) 12 mg orally on Days 1, 3, and 5 of each week in 21-day treatment cycles until disease progression, toxicity, availability of other effective drugs that the subject may receive, or treating physician advice.	

Primary: Percentage of Subjects Who Achieved Overall Cutaneous Response Based on Modified Severity Weighted Assessment Tool (mSWAT) Criteria

End point title	Percentage of Subjects Who Achieved Overall Cutaneous Response Based on Modified Severity Weighted Assessment Tool (mSWAT) Criteria ^[1]
End point description:	
Overall cutaneous response rate (RR) is defined as the percentage of evaluable subjects who achieved a complete response {CR (complete disappearance of all cutaneous disease)} or partial response (PR {greater than or equal to [\geq] 50 percent (%) reduction in mSWAT score compared with baseline}). mSWAT criteria was used to evaluate the skin tumor burden. The investigator was determine the percentage of total body surface area (TBSA) affected by patches, plaques or tumors in 12 body regions, using the subject's palm and fingers representing 1% of TBSA. The response evaluable population consisted of all subjects who received at least 1 dose of study drug and had a posttreatment disease assessment to allow for comparison to the baseline assessment.	
End point type	Primary
End point timeframe:	
From screening until progressive disease or confirmed lost to follow-up or death from any cause or start of alternate therapy, or withdrawal from the study (up to 6 months after the enrollment of the last subject)	
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: Only descriptive data was reported and no statistical analysis was performed for this specific end point.	

End point values	Quisinostat 8 milligram (mg)	Quisinostat 12 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	19		
Units: Percentage of subjects				
number (confidence interval 95%)	16.7 (0.4 to 64.1)	26.3 (9.2 to 51.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Achieved Overall Global RR Based on The Consensus Global Response Score

End point title	Percentage of Subjects Who Achieved Overall Global RR Based on The Consensus Global Response Score
-----------------	--

End point description:

Overall global RR is defined as the percentage of subjects who achieved CR (complete response) or PR (partial response) based on the consensus global response score for mycosis fungoides/ Sezary Syndrome (MF/SS) [defined as the total score of tumor, lymph nodes, metastasis, blood (TNMB) staging, ie, cutaneous disease, lymph nodes, viscera and blood. Complete response is defined as complete disappearance of all clinical evidence of disease (all categories have CR/ non-involved [NI]) and PR is defined as regression of measurable disease (all categories do not have a CR/NI and no category has a PD and if any other category involved at baseline, at least one has a CR or PR). The response evaluable population consisted of all subjects who received at least 1 dose of study drug and had a posttreatment disease assessment to allow for comparison to the baseline assessment.

End point type	Secondary
----------------	-----------

End point timeframe:

From screening until progressive disease or confirmed lost to follow-up or death from any cause or start of alternate therapy, or withdrawal from the study (up to 6 months after the enrollment of the last subject)

End point values	Quisinostat 8 milligram (mg)	Quisinostat 12 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	19		
Units: Percentage of subjects				
number (not applicable)	0	13.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)
-----------------	---------------------------------

End point description:

PFS is defined as the interval between the date of administration of the first dose of study drug and the date of disease progression or death from any cause, whichever occurred first. PFS is estimated by Kaplan-Meier (K-M) method. Here, '99999' for upper limit of CI represents that data was not estimable due to low number of events observed during the short follow-up duration. The subjects treated analysis set consisted of all subjects who received at least 1 dose of study drug.

End point type	Secondary
----------------	-----------

End point timeframe:

From the date of administration of the first dose of study medication until progressive disease or death from any cause, whichever occurs first (up to 6 months after the enrollment of the last subject)

End point values	Quisinostat 8 milligram (mg)	Quisinostat 12 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	20		
Units: months				
median (confidence interval 95%)	3.83 (0.72 to 99999)	5.09 (2.1 to 8.31)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)
-----------------	----------------------------

End point description:

Duration of response was defined only for subjects who have CR or PR as best overall response in skin based on mSWAT and is defined as the date from the first documentation of CR or PR until the date of first documentation of progressive disease (PD), or death from any cause. Here 'N' represents the number of subjects who received at least 1 dose of study drug and who achieved a response. '99999' for median and CI represents data was not estimable because the 1 subject in this arm was censored from the analysis (Quisinostat 8 mg) and for upper limit of CI (Quisinostat 12 mg) due to low number of events observed during the follow-up.

End point type	Secondary
----------------	-----------

End point timeframe:

First documentation of CR or PR until the date of first documentation of progressive disease, or death from any cause; as assessed for approximately 6 months after the enrollment of the last subject

End point values	Quisinostat 8 milligram (mg)	Quisinostat 12 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	5		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	4.86 (3.02 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: 9-Month Overall Survival (OS) Rate

End point title	9-Month Overall Survival (OS) Rate
-----------------	------------------------------------

End point description:

The 9-month OS rate was defined as the K-M estimate of the proportion of subjects surviving at least 9 months after the date of administration of the first dose of study drug. The subjects treated analysis set consisted of all subjects who received at least 1 dose of study drug.

End point type	Secondary
----------------	-----------

End point timeframe:

Month 9

End point values	Quisinostat 8 milligram (mg)	Quisinostat 12 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	20		
Units: proportion of subjects				
number (confidence interval 95%)	0.83 (0.27 to 0.97)	0.83 (0.57 to 0.94)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Pruritus Relief Measured by Pruritus Intensity Assessment (PIA) Questionnaire Scale Scores

End point title	Number of Subjects with Pruritus Relief Measured by Pruritus Intensity Assessment (PIA) Questionnaire Scale Scores
-----------------	--

End point description:

Pruritus relief was defined as a reduction from baseline of equal or greater than (\geq) 3 points on the 11 point PIA numeric rating scale or complete resolution for ≥ 3 continuous weeks. The PIA scores ranges from '0= no pruritus; 10 = worst imaginable'. The response evaluable population consisted of all subjects who received at least 1 dose of study drug and had a posttreatment disease assessment to allow for comparison to the baseline assessment.

End point type	Secondary
----------------	-----------

End point timeframe:

From screening until progressive disease or confirmed lost to follow-up or death from any cause or start of alternate therapy, or withdrawal from the study (up to 6 months after the enrollment of the last subject)

End point values	Quisinostat 8 milligram (mg)	Quisinostat 12 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	19		
Units: subjects	3	7		

Statistical analyses

No statistical analyses for this end point

Secondary: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Score

End point title	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Score
-----------------	--

End point description:

EORTC QLQ-C30 is a questionnaire to assess quality of life of cancer patients. For the multiple item

measure, 100-point scale is used. For Global Health the functional scales (physical, role, emotional, cognitive and social functioning), higher scores represent better health. The subjects treated analysis set consisted of all subjects who received at least 1 dose of study drug. Here 'n' represents the number of subjects analyzed for this specific category for this endpoint. '99999' for standard deviation represents that data could not be estimated and '99999' for follow up categories of quisinostat 8 mg reporting group represents that data was not analyzed as subjects were moved to quisinostat 12 mg group after amendment.

End point type	Secondary
----------------	-----------

End point timeframe:

From screening until progressive disease or confirmed lost to follow-up or death from any cause or start of alternate therapy, or withdrawal from the study (up to 6 months after the enrollment of the last subject)

End point values	Quisinostat 8 milligram (mg)	Quisinostat 12 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	20		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Physical functioning: Cycle 16 (n=1,1)	100 (± 99999)	100 (± 99999)		
Physical functioning: Follow up (n=0,2)	99999 (± 99999)	100 (± 0)		
Role functioning: Cycle 16 (n=1,1)	100 (± 99999)	100 (± 99999)		
Role functioning: Follow up (n=0,2)	99999 (± 99999)	91.7 (± 11.79)		
Emotional functioning: Cycle 16 (n=1,1)	100 (± 99999)	91.7 (± 99999)		
Emotional functioning: Follow up (n=0,2)	99999 (± 99999)	91.7 (± 11.79)		
Cognitive functioning: Cycle 16 (n=1,1)	100 (± 99999)	100 (± 99999)		
Cognitive functioning: Follow up (n=0,2)	99999 (± 99999)	100 (± 0)		
Social functioning: Cycle 16 (n=1,1)	100 (± 99999)	100 (± 99999)		
Social functioning: Follow up (n=0,2)	99999 (± 99999)	91.7 (± 11.79)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Approximately 5 years

Assessment type	Non-systematic
-----------------	----------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	15.0
--------------------	------

Reporting groups

Reporting group title	Quisinostat 8 mg
-----------------------	------------------

Reporting group description:

Subjects with Stage Ib to IVa cutaneous T-cell lymphoma (CTCL) received quisinostat 8 mg orally on Days 1, 3, and 5 of each week in 21-day treatment cycles until disease progression, toxicity, availability of other effective drugs that the subject may receive, or treating physician advice. Subjects who were initially randomized to the JNJ-26481585 (quisinostat) 8 mg dose cohort were allowed to have their dose increased to 12 mg after study was amended to remove 8 mg arm.

Reporting group title	Quisinostat 12 mg
-----------------------	-------------------

Reporting group description:

Subjects with Stage Ib to IVa cutaneous T-cell lymphoma (CTCL) received quisinostat 8 mg orally on Days 1, 3, and 5 of each week in 21-day treatment cycles until disease progression, toxicity, availability of other effective drugs that the subject may receive, or treating physician advice. Subjects who were initially randomized to the JNJ-26481585 (quisinostat) 8 mg dose cohort were allowed to have their dose increased to 12 mg after study was amended to remove 8 mg arm.

Serious adverse events	Quisinostat 8 mg	Quisinostat 12 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 6 (16.67%)	7 / 20 (35.00%)	
number of deaths (all causes)	1	3	
number of deaths resulting from adverse events			
Investigations			
Troponin T Increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Lymphoedema			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Hospitalisation			

subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 6 (16.67%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden Death			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Impairment			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			

subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Tract Infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
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 / 6 (16.67%)	0 / 20 (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			
Hyperkalaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Quisinostat 8 mg	Quisinostat 12 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	20 / 20 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	3	
Infected Neoplasm			
subjects affected / exposed	0 / 6 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Vascular disorders			

Hypertension			
subjects affected / exposed	1 / 6 (16.67%)	2 / 20 (10.00%)	
occurrences (all)	1	2	
Lymphoedema			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 6 (33.33%)	2 / 20 (10.00%)	
occurrences (all)	3	2	
Chills			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Cyst			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Face Oedema			
subjects affected / exposed	1 / 6 (16.67%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Fatigue			
subjects affected / exposed	1 / 6 (16.67%)	3 / 20 (15.00%)	
occurrences (all)	1	3	
Feeling Cold			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Feeling Hot			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Influenza Like Illness			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Irritability			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Malaise			

subjects affected / exposed	1 / 6 (16.67%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Oedema Peripheral			
subjects affected / exposed	0 / 6 (0.00%)	3 / 20 (15.00%)	
occurrences (all)	0	3	
Pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	2 / 6 (33.33%)	1 / 20 (5.00%)	
occurrences (all)	2	1	
Temperature Regulation Disorder			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Penile Oedema			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	2	
Balanitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	2	
Scrotal Ulcer			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Testicular Oedema			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	3	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 6 (16.67%)	2 / 20 (10.00%)	
occurrences (all)	1	2	
Oropharyngeal Pain			
subjects affected / exposed	0 / 6 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Productive Cough			

subjects affected / exposed	0 / 6 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Vocal Cord Inflammation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 6 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Insomnia			
subjects affected / exposed	0 / 6 (0.00%)	3 / 20 (15.00%)	
occurrences (all)	0	3	
Mood Swings			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Sleep Disorder			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Investigations			
Blood Urine Present			
subjects affected / exposed	1 / 6 (16.67%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Grip Strength Decreased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Glomerular Filtration Rate Decreased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Weight Decreased			
subjects affected / exposed	0 / 6 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Weight Increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			

Foot Fracture subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 20 (5.00%) 1	
Laceration subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 20 (5.00%) 1	
Procedural Pain subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 20 (5.00%) 1	
Cardiac disorders Cyanosis subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 20 (0.00%) 0	
Palpitations subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	2 / 20 (10.00%) 2	
Hepatojugular Reflux subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 20 (5.00%) 1	
Sinus Bradycardia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 20 (5.00%) 1	
Tachycardia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 2	0 / 20 (0.00%) 0	
Ventricular Extrasystoles subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 20 (5.00%) 1	
Nervous system disorders Cluster Headache subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 20 (5.00%) 1	
Dizziness subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	2 / 20 (10.00%) 3	
Dysgeusia			

subjects affected / exposed	1 / 6 (16.67%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	0 / 6 (0.00%)	5 / 20 (25.00%)	
occurrences (all)	0	5	
Lethargy			
subjects affected / exposed	0 / 6 (0.00%)	3 / 20 (15.00%)	
occurrences (all)	0	5	
Hypoaesthesia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 20 (5.00%)	
occurrences (all)	2	1	
Memory Impairment			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Tremor			
subjects affected / exposed	1 / 6 (16.67%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Migraine			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Lymphadenopathy			
subjects affected / exposed	0 / 6 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Thrombocytopenia			
subjects affected / exposed	0 / 6 (0.00%)	4 / 20 (20.00%)	
occurrences (all)	0	4	
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 6 (16.67%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Hypoacusis			

subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 20 (0.00%) 0	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Eye Irritation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Eye Swelling			
subjects affected / exposed	1 / 6 (16.67%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Eyelid Pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Lacrimation Increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	3	
Visual Acuity Reduced			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal Discomfort			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Abdominal Distension			
subjects affected / exposed	1 / 6 (16.67%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Abdominal Pain			
subjects affected / exposed	0 / 6 (0.00%)	4 / 20 (20.00%)	
occurrences (all)	0	6	
Abdominal Pain Upper			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Change of Bowel Habit			

subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	2 / 6 (33.33%)	5 / 20 (25.00%)	
occurrences (all)	2	7	
Faeces Discoloured			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Flatulence			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Gastritis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Lip Dry			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	2 / 6 (33.33%)	7 / 20 (35.00%)	
occurrences (all)	2	8	
Umbilical Hernia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	1 / 6 (16.67%)	2 / 20 (10.00%)	
occurrences (all)	1	4	
Hepatobiliary disorders			
Hepatic Function Abnormal			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	3	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	

Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	1 / 6 (16.67%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Dermatitis Exfoliative			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Dry Skin			
subjects affected / exposed	1 / 6 (16.67%)	2 / 20 (10.00%)	
occurrences (all)	2	2	
Eczema			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Erythema			
subjects affected / exposed	1 / 6 (16.67%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Hyperhidrosis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Pain of Skin			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	3 / 6 (50.00%)	7 / 20 (35.00%)	
occurrences (all)	5	10	
Scab			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Skin Exfoliation			
subjects affected / exposed	1 / 6 (16.67%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Skin Fissures			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Skin Irritation			

subjects affected / exposed	1 / 6 (16.67%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Skin Plaque			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	2	
Telangiectasia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Anuria			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Azotaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Nocturia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Renal Impairment			
subjects affected / exposed	0 / 6 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	2	
Groin Pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Back Pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Musculoskeletal Pain			

subjects affected / exposed	1 / 6 (16.67%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Pain in Extremity			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Infections and infestations			
Ear Infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Impetigo			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	2	
Influenza			
subjects affected / exposed	1 / 6 (16.67%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Localised Infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Lung Infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	1 / 6 (16.67%)	2 / 20 (10.00%)	
occurrences (all)	1	3	
Onychomycosis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Oral Candidiasis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	2	
Otitis Externa			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Respiratory Tract Infection			
subjects affected / exposed	1 / 6 (16.67%)	1 / 20 (5.00%)	
occurrences (all)	1	1	

Sinusitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Urinary Tract Infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	1 / 6 (16.67%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Hypercholesterolaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Hyperglycaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	2	
Hyperkalaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Hypertriglyceridaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Hyperuricaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Hypoalbuminaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Hypomagnesaemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Hypophosphataemia			

subjects affected / exposed	0 / 6 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 November 2011	Amendment included that the 8 milligram (mg) dose cohort and randomization procedure was removed. Subjects enrolled in the 8 mg cohort was allowed to receive the 12 mg dose without evidence of disease progression. The Simon 2-stage Minimax Design was no longer be incorporated because the 8 mg dose cohort has been eliminated. The sample size for the study was adjusted because of the removal of the low-dose cohort and elimination of the 2-stage design. The primary purpose of the interim analysis was to provide an early assessment of safety and efficacy of the recommended Phase 2 dose and a lower dose in order to minimize exposing subjects to an ineffective treatment. It is expected that accrual and treatment was proceeded quickly relative to the data available to base decisions on risk and benefit, thus eliminating the need for an interim analysis. Any exploratory statistical comparisons between the 2 treatment groups are no longer relevant because of the elimination of the 8 mg dose cohort. The lymph node classification international society for cutaneous lymphomas/european organization for research and treatment of cancer (ISCL/EORTC) has been modified to include central lymph nodes. A concern of repeated radiological assessment (CT/MRI) over a short time period was raised by investigators. This change allows the use of data obtained before informed consent if the tests were performed within a reasonable timeframe before the first dose of study medication. Reducing the recovery time following prior systemic therapy from at least 3 weeks to 2 weeks gave more flexibility in enrolling subjects to this study. Clarification of dose modification for toxicity in response to suggestions by health authorities and investigators. Clarification that biomarker analyses are dependent on the availability of assays. Biomarker analyses may not be performed if it is considered they was provided no useful scientific information. Minor errors were noted.
03 September 2014	Amendment was done to modify the long-term extension phase to allow subjects who were on study to continue receiving treatment beyond the 2-year clinical cutoff.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Study was amended to remove the 8 mg dose level arm and subjects enrolled at 8 mg were allowed to dose escalate to 12 mg. The removal of the 8 mg dose arm eliminated the potential for assessment of a dose response relationship on efficacy and safety.

Notes: