Clinical trial results:
A Phase Ib/II, open-label, multi-center, dose-finding study to assess the safety and efficacy of the oral combination of LDE225 and INC424 (Ruxolitinib) in subjects with myelofibrosis

Summary

EudraCT number	2012-004023-20
Trial protocol	ES GB IE IT DE NL FR DK BE
Global end of trial date	10 April 2018

Results information

Result version number	v1 (current)
This version publication date	25 April 2019
First version publication date	25 April 2019

Trial information

Trial identification

Sponsor protocol code	CLDE225X2116

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01787552
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.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	10 April 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 April 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Primary objective : (Phase Ib) To establish the MTD and/or RPIID of the co-administration of LDE225 and INC424 in subjects with MF, who have not previously received therapy with a JAK inhibitor. (Phase II) To assess the efficacy of the co-administration of LDE225 and INC424 on spleen volume reduction as determined by centrally reviewed magnetic resonance imaging (MRI)/ computed tomography (CT).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 May 2013
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	Australia: 3
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	Denmark: 4
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	Ireland: 1
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Spain: 4
Worldwide total number of subjects	50
EEA total number of subjects	36

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)	18
From 65 to 84 years	32
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 50 subjects were enrolled in the study, of which 23 subjects were enrolled in Phase Ib part of dose-escalation phase and 27 subjects were enrolled in Phase Ib dose-expansion phase and Phase II Stage 1.

Pre-assignment

Screening details:

A total of 50 subjects were enrolled in the study, of which 23 subjects were enrolled in Phase Ib part of dose-escalation phase and 27 subjects were enrolled in Phase Ib dose-expansion phase and Phase II Stage 1.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	LDE225 400mg + INC424 10mg (dose escalation phase)

Arm description:

Participants who took a combination of LDE225 400mg and INC424 10mg in the dose escalation phase.

Arm type	Experimental
Investigational medicinal product name	INC424
Investigational medicinal product code	INC424
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants who took a combination of LDE225 400mg and INC424 10mg in the dose escalation phase.

Investigational medicinal product name	LDE225
Investigational medicinal product code	LDE225
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants who took a combination of LDE225 400mg and INC424 10mg in the dose escalation phase.

Arm title	LDE225 400mg + INC424 15 mg (dose escalation phase)

Arm description:

Participants who took a combination of LDED225 400mg and INC424 15mg in the dose escalation phase

Arm type	Experimental
Investigational medicinal product name	INC424
Investigational medicinal product code	INC424
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants who took a combination of LDE225 400mg and INC424 10mg in the dose escalation phase.

Investigational medicinal product name	LDE225
Investigational medicinal product code	LDE225
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants who took a combination of LDE225 400mg and INC424 10mg in the dose escalation phase.

Arm title	LDE225 400mg + INC424 20mg (dose escalation phase)

Arm description:

Participants who took a combination of LDED225 400mg and INC424 20mg in the dose escalation phase

Arm type	Experimental
Investigational medicinal product name	LDE225
Investigational medicinal product code	LDE225
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants who took a combination of LDE225 400mg and INC424 10mg in the dose escalation phase.

Investigational medicinal product name	INC424
Investigational medicinal product code	INC424
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants who took a combination of LDE225 400mg and INC424 10mg in the dose escalation phase.

Arm title	LDED225 400mg + INC424 20mg (dose expansion phase)

Arm description:

Participants who took a combination of LDED225 400mg and INC424 20mg in the dose expansion phase

Arm type	Experimental
Investigational medicinal product name	INC424
Investigational medicinal product code	INC424
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants who took a combination of LDE225 400mg and INC424 10mg in the dose escalation phase.

Investigational medicinal product name	LDE225
Investigational medicinal product code	LDE225
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants who took a combination of LDE225 400mg and INC424 10mg in the dose escalation phase.

Number of subjects in period 1	LDE225 400mg + INC424 10mg (dose escalation phase)	LDE225 400mg + INC424 15 mg (dose escalation phase)	LDE225 400mg + INC424 20mg (dose escalation phase)
Started	8	10	5
Completed	0	1	0
Not completed	8	9	5
Adverse event, serious fatal	-	-	-
Consent withdrawn by subject	2	-	-
Physician decision	2	2	1
Study terminated by Sponsor	-	-	1
Adverse event, non-fatal	2	5	2
Progressive Disease	2	2	1

Number of subjects in period 1	LDED225 400mg + INC424 20mg (dose expansion phase)
Started	27
Completed	0
Not completed	27
Adverse event, serious fatal	1
Consent withdrawn by subject	4
Physician decision	2
Study terminated by Sponsor	3
Adverse event, non-fatal	16
Progressive Disease	1

Baseline characteristics

Reporting groups	
Reporting group title	LDE225 400mg + INC424 10mg (dose escalation phase)
Reporting group description:	
Participants who took a combination of LDE225 400mg and INC424 10mg in the dose escalation phase.	
Reporting group title	LDE225 400mg + INC424 15 mg (dose escalation phase)
Reporting group description:	
Participants who took a combination of LDED225 400mg and INC424 15mg in the dose escalation phase	
Reporting group title	LDE225 400mg + INC424 20mg (dose escalation phase)
Reporting group description:	
Participants who took a combination of LDED225 400mg and INC424 20mg in the dose escalation phase	
Reporting group title	LDED225 400mg + INC424 20mg (dose expansion phase)
Reporting group description:	
Participants who took a combination of LDED225 400mg and INC424 20mg in the dose expansion phase	

Reporting group values	LDE225 400mg + INC424 10mg (dose escalation phase)	LDE225 400mg + INC424 15 mg (dose escalation phase)	LDE225 400mg + INC424 20mg (dose escalation phase)
Number of subjects	8	10	5
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	1	6	2
From 65-84 years	7	4	3
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	70.9	59.9	64.6
standard deviation	± 5.19	± 11.59	± 13.18
Sex: Female, Male Units: Subjects			
Female	1	5	1
Male	7	5	4
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	2	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	6	10	5
More than one race	0	0	0
Unknown or Not Reported	0	0	0

Reporting group values	LDED225 400mg + INC424 20mg (dose expansion phase)	Total	
Number of subjects	27	50	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	9	18	
From 65-84 years	18	32	
85 years and over	0	0	
Age Continuous Units: Years			
arithmetic mean	67.4		
standard deviation	± 10.02	-	
Sex: Female, Male Units: Subjects			
Female	8	15	
Male	19	35	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	1	3	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	26	47	
More than one race	0	0	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	LDE225 400mg + INC424 10mg (dose escalation phase)
Reporting group description:	
Participants who took a combination of LDE225 400mg and INC424 10mg in the dose escalation phase.	
Reporting group title	LDE225 400mg + INC424 15 mg (dose escalation phase)
Reporting group description:	
Participants who took a combination of LDED225 400mg and INC424 15mg in the dose escalation phase	
Reporting group title	LDE225 400mg + INC424 20mg (dose escalation phase)
Reporting group description:	
Participants who took a combination of LDED225 400mg and INC424 20mg in the dose escalation phase	
Reporting group title	LDED225 400mg + INC424 20mg (dose expansion phase)
Reporting group description:	
Participants who took a combination of LDED225 400mg and INC424 20mg in the dose expansion phase	

Primary: Number of participants with Dose Limiting Toxicities (DLTs). (Phase 1b)

End point title	Number of participants with Dose Limiting Toxicities (DLTs). (Phase 1b)[1]
End point description:	
Established the maximum tolerated dose (MTD) and/or recommended phase II dose (RPIID) of LDE225 in combination with INC424	
End point type	Primary
End point timeframe:	
6 weeks (42 days)	

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 planned for this primary outcome.

End point values	LDE225 400mg + INC424 10mg (dose escalation phase)	LDE225 400mg + INC424 15 mg (dose escalation phase)	LDE225 400mg + INC424 20mg (dose escalation phase)	LDED225 400mg + INC424 20mg (dose expansion phase)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	10	5	27
Units: Participants				
Blood creatine phosphokinase increased	0	2	0	1

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of patients achieving >= 35% reduction in spleen volume

End point title	Percentage of patients achieving >= 35% reduction in spleen volume[2][3]

End point description:

Reduction in spleen volume as measured by magnetic resonance imaging/Cat Scan (MRI/CT).

End point type	Primary

End point timeframe:

Week 24 and Week 48

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned for this primary outcome.

[3] - 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: This Outcome Measure was only collected on the LDE225 400mg +INC424 20mg (dose expansion phase) arm, N=27).

End point values	LDED225 400mg + INC424 20mg (dose expansion phase)			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: Percentage of Participants				
number (not applicable)				
Week 24	44.4			
Week 48	29.6			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib and Phase II: Plasma pharmacokinetics (PK) parameters: Maximum Plasma Concentration(Cmax)

End point title	Phase Ib and Phase II: Plasma pharmacokinetics (PK) parameters: Maximum Plasma Concentration(Cmax)

End point description:

LDE225 and INC424 PK parameters: Maximum Plasma Concentration (Cmax)

End point type	Secondary

End point timeframe:

Week 1 Day 1, Week 9 Day 1

End point values	LDE225 400mg + INC424 10mg (dose escalation phase)	LDE225 400mg + INC424 15 mg (dose escalation phase)	LDE225 400mg + INC424 20mg (dose escalation phase)	LDED225 400mg + INC424 20mg (dose expansion phase)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8[4]	10[5]	5[6]	27[7]
Units: Unit by PK Parameter (ng/mL)				
arithmetic mean (standard deviation)				

LDE225 (Week 1, Day 1)	326 (± 102)	307 (± 275)	205 (± 149)	328 (± 266)
LDE225 (Week 9, Day 1)	933 (± 351)	831 (± 537)	1020 (± 429)	1070 (± 572)
INC424 (Week 1, Day 1)	159 (± 48.0)	263 (± 115)	361 (± 94.8)	364 (± 148)
INC424 (Week 9, Day 1)	178 (± 58.8)	283 (± 97.0)	295 (± 102)	371 (± 129)

Notes:

[4] - (n=6,8,8,8)

[5] - (n=10,8,10,9)

[6] - (n=5,5,5,4)

[7] - (n=26,20,27,20)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib and Phase II: Plasma pharmacokinetics (PK) parameters: Time to Maximum Plasma Concentration(Tmax)

End point title	Phase Ib and Phase II: Plasma pharmacokinetics (PK) parameters: Time to Maximum Plasma Concentration(Tmax)

End point description:

LDE225 and INC424 PK parameters:Time to Maximum Plasma Concentration (Tmax)

End point type	Secondary

End point timeframe:

Week 1 Day 1, Week 9 Day 1

End point values	LDE225 400mg + INC424 10mg (dose escalation phase)	LDE225 400mg + INC424 15 mg (dose escalation phase)	LDE225 400mg + INC424 20mg (dose escalation phase)	LDED225 400mg + INC424 20mg (dose expansion phase)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8[8]	10[9]	5[10]	27[11]
Units: Unit by PK Parameter (hr)				
median (full range (min-max))				
LDE225 (Week 1, Day 1)	3.01 (2.00 to 4.00)	2.08 (1.50 to 4.22)	2.00 (1.50 to 8.00)	2.00 (1.00 to 6.00)
LDE225 (Week 9, Day 1)	1.79 (0.170 to 4.00)	2.00 (1.50 to 4.00)	2.00 (1.50 to 6.00)	3.21 (1.50 to 23.9)
INC424 (Week 1, Day 1)	0.500 (0.500 to 2.00)	0.575 (0.330 to 2.03)	0.500 (0.500 to 0.970)	0.580 (0.420 to 4.00)
INC424 (Week 9, Day 1)	0.875 (0.170 to 1.50)	0.500 (0.500 to 1.52)	1.00 (0.500 to 1.00)	1.00 (0.330 to 2.00)

Notes:

[8] - (n=6,8,8,8)

[9] - (n=10,8,10,9)

[10] - (n=5,5,5,4)

[11] - (n=26,20,27,20)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib and Phase II: Plasma pharmacokinetics (PK) parameters: Area under the Curve(AUC)

End point title	Phase Ib and Phase II: Plasma pharmacokinetics (PK) parameters: Area under the Curve(AUC)

End point description:

LDE225 and INC424 PK parameters: Plasma Concentration Time Curve (AUC).

End point type	Secondary

End point timeframe:

Week 1 Day 1, Week 9 Day 1

End point values	LDE225 400mg + INC424 10mg (dose escalation phase)	LDE225 400mg + INC424 15 mg (dose escalation phase)	LDE225 400mg + INC424 20mg (dose escalation phase)	LDED225 400mg + INC424 20mg (dose expansion phase)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8[12]	10[13]	5[14]	27[15]
Units: Unit by PK Parameter (ng*hr/mL))				
median (full range (min-max))				
LDE225 (Week 1, Day 1)	2400 (1990 to 4930)	1640 (630 to 7720)	1060 (505 to 2720)	1770 (755 to 7290)
LDE225 (Week 9, Day 1)	14500 (11200 to 26800)	11600 (6420 to 31000)	16100 (13000 to 25900)	14800 (7030 to 31800)
INC424 (Week 1, Day 1)	416 (369 to 791)	795 (384 to 1550)	1200 (766 to 1390)	1200 (561 to 2590)
INC424 (Week 9, Day 1)	511 (271 to 803)	945 (449 to 1650)	1040 (692 to 1140)	1360 (420 to 2290)

Notes:

[12] - (n=6,6,8,8)

[13] - (n=10,6,10,9)

[14] - (n=4,4,5,4)

[15] - (n=24,14,25,20)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib and Phase II: Percentage of patients experiencing improvement in bone marrow fibrosis by at least one grade

End point title	Phase Ib and Phase II: Percentage of patients experiencing improvement in bone marrow fibrosis by at least one grade

End point description:

The number of patients experiencing improvement in their bone marrow fibrosis by at least one grade and assessment of cellularity.

End point type	Secondary

End point timeframe:

Baseline, Week 24, Week 48

End point values	LDE225 400mg + INC424 10mg (dose escalation phase)	LDE225 400mg + INC424 15 mg (dose escalation phase)	LDE225 400mg + INC424 20mg (dose escalation phase)	LDED225 400mg + INC424 20mg (dose expansion phase)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8[16]	10[17]	5[18]	27[19]
Units: Percentage of Participants				
number (not applicable)				
Baseline	0	10.0	0	14.8
Week 24	12.5	10.0	0	3.7
Week 48	0	0	0	3.7

Notes:

[16] - n=(0,1,0)

[17] - (n=1,1,0)

[18] - (n=0,0,0)

[19] - (n=4,1,1)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib and Phase II: Change in Pharmacodynamic Biomarkers: JAK2V617F allele burden

End point title	Phase Ib and Phase II: Change in Pharmacodynamic Biomarkers: JAK2V617F allele burden

End point description:

Change in Pharmacodynamic Biomarkers: JAK2V617F allele burden were compared from Baseline to Week 24 and Week 48

End point type	Secondary

End point timeframe:

Baseline, Week 24, Week 48

End point values	LDE225 400mg + INC424 10mg (dose escalation phase)	LDE225 400mg + INC424 15 mg (dose escalation phase)	LDE225 400mg + INC424 20mg (dose escalation phase)	LDED225 400mg + INC424 20mg (dose expansion phase)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8[20]	10[21]	5[22]	27[23]
Units: JAK2V617F allele burden				
median (full range (min-max))				
Baseline	84.7 (48.4 to 95.1)	61.7 (2.5 to 92.1)	88.3 (52.7 to 94.4)	55.4 (2.5 to 93.5)
Week 24	88.6 (49.8 to 94.1)	48.0 (2.5 to 78.4)	74.9 (52.1 to 89.6)	43.8 (2.5 to 93.9)
Week 48	86.0 (20.1 to 94.1)	54.3 (2.5 to 80.0)	75.7 (56.9 to 90.0)	46.1 (2.5 to 85.6)

Notes:

[20] - (n=8,7,4)

[21] - (n=10,6,3)

[22] - (n=5,5,4)
[23] - (n=27,21,13)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib and Phase II: Change in Pharmacodynamic Biomarkers: Cytokine Levels

End point title	Phase Ib and Phase II: Change in Pharmacodynamic Biomarkers: Cytokine Levels

End point description:

Change in Pharmacodynamic Biomarkers: Cytokine levels were compared from Baseline to Week 24 and Week 48

End point type	Secondary

End point timeframe:

Baseline, Week 24, Week 48

End point values	LDE225 400mg + INC424 10mg (dose escalation phase)	LDE225 400mg + INC424 15 mg (dose escalation phase)	LDE225 400mg + INC424 20mg (dose escalation phase)	LDED225 400mg + INC424 20mg (dose expansion phase)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8[24]	10[25]	5[26]	27[27]
Units: Level of Cytokine				
median (full range (min-max))				
Baseline	0.80 (0.3 to 2.3)	1.00 (0.6 to 1.5)	0.588 (0.3 to 1.7)	0.74 (0.3 to 3.7)
Week 24	0.75 (0.3 to 2.5)	0.79 (0.3 to 1.4)	1.10 (0.3 to 2.2)	0.49 (0.49 to 2.0)
Week 48	0.68 (0.3 to 1.6)	0.60 (0.5 to 0.9)	0.49 (0.49 to 1.1)	0.49 (0.49 to 2.6)

Notes:

[24] - (n=8,7,4)
[25] - (n=10,8,3)
[26] - (n=5,5,4)
[27] - (n=27,22,14)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib and Phase II: Change from Baseline in Percentage of patients having >= 50% reduction in total symptom score

End point title	Phase Ib and Phase II: Change from Baseline in Percentage of patients having >= 50% reduction in total symptom score[28]

End point description:

Change from Baseline in total symptom score as measured by the modified MFSAF (Myelofibrosis Symptom Assessment Form)

End point type	Secondary

End point timeframe:

Baseline, Week 24, Week 48

Notes:

[28] - 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: This Outcome Measure was only collected on the LDE225 400mg +INC424 20mg (dose expansion phase) arm, N=27).

End point values	LDED225 400mg + INC424 20mg (dose expansion phase)			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: Percentage				
number (not applicable)				
Week 24	48.1			
Week 48	22.2			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib andPhase II: Change from Baseline in total symptom score

End point title	Phase Ib andPhase II: Change from Baseline in total symptom score[29]

End point description:

Change from Baseline measured by the modified MFSAF (Myelofibrosis Symptom Assessment Form)

End point type	Secondary

End point timeframe:

Baseline, Week 24, Week 48

Notes:

[29] - 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: This Outcome Measure was only collected on the LDE225 400mg +INC424 20mg (dose expansion phase) arm, N=27).

End point values	LDED225 400mg + INC424 20mg (dose expansion phase)			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: Percentage				
number (not applicable)				

Week 24	22.2			
Week 48	14.8			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase I and Phase II: Change in EORTC QLQ-C30 scores from Baseline (increase in best change)

End point title	Phase I and Phase II: Change in EORTC QLQ-C30 scores from Baseline (increase in best change)[30]

End point description:

Change in EORTC QLQ-C30 scores from Baseline. EORTC QLQ-C30 is the European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire

End point type	Secondary

End point timeframe:

Baseline, Week 24, Week 48

Notes:

[30] - 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: This Outcome Measure was only collected on the LDE225 400mg +INC424 20mg (dose expansion phase) arm, N=27).

End point values	LDED225 400mg + INC424 20mg (dose expansion phase)			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: Percentage				
number (not applicable)				
Week 24	14.8			
Week 48	11.1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	LDE225 400 mg + INC424 10 mg
Reporting group description:	
LDE225 400 mg + INC424 10 mg	
Reporting group title	LDE225 400 mg + INC424 15 mg
Reporting group description:	
LDE225 400 mg + INC424 15 mg	
Reporting group title	LDE225 400 mg + INC424 20 mg
Reporting group description:	
LDE225 400 mg + INC424 20 mg	
Reporting group title	LDE225 400 mg + INC424 20 mg
Reporting group description:	
LDE225 400 mg + INC424 20 mg	
Reporting group title	All Patients
Reporting group description:	
All Patients	

Serious adverse events	LDE225 400 mg + INC424 10 mg	LDE225 400 mg + INC424 15 mg	LDE225 400 mg + INC424 20 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 8 (62.50%)	6 / 10 (60.00%)	2 / 5 (40.00%)
number of deaths (all causes)	1	1	1
number of deaths resulting from adverse events	0	0	0
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatine phosphokinase increased			

subjects affected / exposed	0 / 8 (0.00%)	2 / 10 (20.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myoglobin blood increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
B-cell lymphoma			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangiocarcinoma			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (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
Chronic myeloid leukaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (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
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (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

Meniscus injury			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (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
Post procedural haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (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
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (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
Right ventricular failure			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (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
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extramedullary haemopoiesis			

subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (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			
Face oedema			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (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
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	2 / 8 (25.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (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
Gastric ulcer			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastric ulcer haemorrhage			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (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
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	2 / 10 (20.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myositis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Diverticulitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastroenteritis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (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
Infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (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

Serious adverse events	LDE225 400 mg + INC424 20 mg	All Patients	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 27 (48.15%)	26 / 50 (52.00%)	
number of deaths (all causes)	1	4	
number of deaths resulting from adverse events	0	0	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 27 (3.70%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine phosphokinase increased			
subjects affected / exposed	3 / 27 (11.11%)	5 / 50 (10.00%)	
occurrences causally related to treatment / all	3 / 3	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myoglobin blood increased			

subjects affected / exposed	1 / 27 (3.70%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 27 (3.70%)	2 / 50 (4.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
B-cell lymphoma			
subjects affected / exposed	1 / 27 (3.70%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangiocarcinoma			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic myeloid leukaemia			
subjects affected / exposed	1 / 27 (3.70%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Post procedural haemorrhage			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 27 (3.70%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
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	2 / 27 (7.41%)	2 / 50 (4.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extramedullary haemopoiesis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Face oedema			

subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 27 (3.70%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pyrexia			
subjects affected / exposed	3 / 27 (11.11%)	5 / 50 (10.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 27 (3.70%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 27 (7.41%)	2 / 50 (4.00%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			

subjects affected / exposed	0 / 27 (0.00%)	2 / 50 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 27 (3.70%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	1 / 27 (3.70%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			
subjects affected / exposed	1 / 27 (3.70%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Diverticulitis			
subjects affected / exposed	1 / 27 (3.70%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 27 (3.70%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infection			
subjects affected / exposed	2 / 27 (7.41%)	2 / 50 (4.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	1 / 27 (3.70%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	LDE225 400 mg + INC424 10 mg	LDE225 400 mg + INC424 15 mg	LDE225 400 mg + INC424 20 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)	10 / 10 (100.00%)	5 / 5 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Atypical fibroxanthoma			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Squamous cell carcinoma			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Haematoma			

subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Hypertension			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Intermittent claudication			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Peripheral venous disease			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 8 (12.50%)	2 / 10 (20.00%)	1 / 5 (20.00%)
occurrences (all)	1	4	1
Catheter site bruise			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Early satiety			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	6 / 8 (75.00%)	3 / 10 (30.00%)	0 / 5 (0.00%)
occurrences (all)	9	3	0
Gait disturbance			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
General physical health deterioration			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Influenza like illness			
subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Malaise			

subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	2 / 8 (25.00%)	2 / 10 (20.00%)	0 / 5 (0.00%)
occurrences (all)	2	4	0
Pyrexia			
subjects affected / exposed	0 / 8 (0.00%)	2 / 10 (20.00%)	2 / 5 (40.00%)
occurrences (all)	0	3	4
Thirst			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Cough			
subjects affected / exposed	1 / 8 (12.50%)	3 / 10 (30.00%)	2 / 5 (40.00%)
occurrences (all)	1	3	2
Dry throat			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Dysphonia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Dyspnoea			
subjects affected / exposed	0 / 8 (0.00%)	2 / 10 (20.00%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Epistaxis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	2 / 5 (40.00%)
occurrences (all)	0	0	2
Oropharyngeal pain			

subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 8 (0.00%)	2 / 10 (20.00%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Insomnia			
subjects affected / exposed	2 / 8 (25.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 8 (12.50%)	2 / 10 (20.00%)	1 / 5 (20.00%)
occurrences (all)	1	4	2
Amylase increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	2
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 8 (12.50%)	3 / 10 (30.00%)	1 / 5 (20.00%)
occurrences (all)	1	4	2
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Blood bilirubin increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	3
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 8 (12.50%)	2 / 10 (20.00%)	3 / 5 (60.00%)
occurrences (all)	1	8	6
Blood creatinine increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Blood prolactin increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Blood uric acid increased			

subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Cytomegalovirus test			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	1 / 5 (20.00%)
occurrences (all)	0	2	1
International normalised ratio increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Lipase increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	3
Low density lipoprotein increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	2 / 5 (40.00%)
occurrences (all)	0	0	3
Platelet count decreased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Prothrombin level increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Prothrombin time prolonged			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Weight decreased			
subjects affected / exposed	2 / 8 (25.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Weight increased			

subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Contusion			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	2 / 5 (40.00%)
occurrences (all)	4	0	3
Fall			
subjects affected / exposed	2 / 8 (25.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	2	1	0
Hyphaema			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Laceration			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Meniscus injury			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Procedural hypotension			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Scratch			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Spinal compression fracture			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Tooth fracture			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			

Supraventricular extrasystoles			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Amnesia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Carpal tunnel syndrome			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Cerebral ischaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Dizziness			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Dysaesthesia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Dysgeusia			
subjects affected / exposed	3 / 8 (37.50%)	4 / 10 (40.00%)	3 / 5 (60.00%)
occurrences (all)	4	4	3
Head discomfort			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	1 / 8 (12.50%)	2 / 10 (20.00%)	0 / 5 (0.00%)
occurrences (all)	1	3	0
Hypoaesthesia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Memory impairment			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Muscle contractions involuntary			

subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Paraesthesia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Post herpetic neuralgia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Restless legs syndrome			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	2
Syncope			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Transient ischaemic attack			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Tremor			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 8 (62.50%)	4 / 10 (40.00%)	4 / 5 (80.00%)
occurrences (all)	14	5	7
Extramedullary haemopoiesis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Leukocytosis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Neutropenia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0

Thrombocytopenia			
subjects affected / exposed	3 / 8 (37.50%)	2 / 10 (20.00%)	3 / 5 (60.00%)
occurrences (all)	4	2	6
Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Vision blurred			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	2
Abdominal distension			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Abdominal pain			
subjects affected / exposed	2 / 8 (25.00%)	3 / 10 (30.00%)	0 / 5 (0.00%)
occurrences (all)	2	3	0
Abdominal pain upper			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Bile acid malabsorption			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	2 / 8 (25.00%)	1 / 10 (10.00%)	1 / 5 (20.00%)
occurrences (all)	3	1	2
Diarrhoea			
subjects affected / exposed	3 / 8 (37.50%)	3 / 10 (30.00%)	4 / 5 (80.00%)
occurrences (all)	4	5	7
Diverticulum			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Diverticulum intestinal			

subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Dry mouth			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Duodenal ulcer			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Dyspepsia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Flatulence			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Functional gastrointestinal disorder			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Gastric ulcer			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Gastric varices			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Gastritis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Haematochezia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Melaena			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Nausea			

subjects affected / exposed	3 / 8 (37.50%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	3	2	0
Stomatitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Toothache			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	3 / 8 (37.50%)	2 / 10 (20.00%)	1 / 5 (20.00%)
occurrences (all)	3	2	2
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Hyperbilirubinaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Alopecia			
subjects affected / exposed	3 / 8 (37.50%)	7 / 10 (70.00%)	3 / 5 (60.00%)
occurrences (all)	3	7	3
Erythema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Hair growth abnormal			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hyperkeratosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Madarosis			

subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Night sweats			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Onychoclasis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	0 / 8 (0.00%)	2 / 10 (20.00%)	2 / 5 (40.00%)
occurrences (all)	0	2	2
Pruritus generalised			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	2 / 5 (40.00%)
occurrences (all)	0	0	2
Rash			
subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Skin discolouration			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Swelling face			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Haematuria			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Urinary retention			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	2 / 8 (25.00%)	2 / 10 (20.00%)	0 / 5 (0.00%)
occurrences (all)	2	3	0
Back pain			
subjects affected / exposed	0 / 8 (0.00%)	2 / 10 (20.00%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Bone pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Joint lock			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Muscle fatigue			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Muscle spasms			
subjects affected / exposed	3 / 8 (37.50%)	6 / 10 (60.00%)	4 / 5 (80.00%)
occurrences (all)	3	9	8
Muscle twitching			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Muscular weakness			
subjects affected / exposed	1 / 8 (12.50%)	4 / 10 (40.00%)	1 / 5 (20.00%)
occurrences (all)	1	4	1
Musculoskeletal chest pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Musculoskeletal pain			
subjects affected / exposed	2 / 8 (25.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Myalgia			
subjects affected / exposed	1 / 8 (12.50%)	3 / 10 (30.00%)	0 / 5 (0.00%)
occurrences (all)	2	4	0
Osteoarthritis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0

Pain in extremity			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Polyarthritis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Cystitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Ear infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Escherichia infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Folliculitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Fungal skin infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Gastroenteritis viral			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Herpes zoster			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			

subjects affected / exposed	0 / 8 (0.00%)	2 / 10 (20.00%)	2 / 5 (40.00%)
occurrences (all)	0	2	2
Oesophageal candidiasis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Oral herpes			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Pharyngitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Pneumonia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Tooth infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 8 (12.50%)	3 / 10 (30.00%)	1 / 5 (20.00%)
occurrences (all)	2	3	1
Urinary tract infection			
subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Urinary tract infection bacterial			
subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	1	3	0
Wound infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 8 (37.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	4	0	0
Hyperkalaemia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	2	1	0

Hypertriglyceridaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	3
Hyperuricaemia			
subjects affected / exposed	1 / 8 (12.50%)	3 / 10 (30.00%)	1 / 5 (20.00%)
occurrences (all)	1	4	1
Hypocalcaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Hypokalaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Hypomagnesaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Hyponatraemia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Increased appetite			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Iron deficiency			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1

Non-serious adverse events	LDE225 400 mg + INC424 20 mg	All Patients	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 27 (100.00%)	50 / 50 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Atypical fibroxanthoma			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Squamous cell carcinoma			

subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Haematoma			
subjects affected / exposed	1 / 27 (3.70%)	3 / 50 (6.00%)	
occurrences (all)	1	3	
Hypertension			
subjects affected / exposed	5 / 27 (18.52%)	7 / 50 (14.00%)	
occurrences (all)	5	7	
Intermittent claudication			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Peripheral venous disease			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 27 (11.11%)	7 / 50 (14.00%)	
occurrences (all)	3	9	
Catheter site bruise			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Early satiety			
subjects affected / exposed	1 / 27 (3.70%)	2 / 50 (4.00%)	
occurrences (all)	1	2	
Fatigue			
subjects affected / exposed	8 / 27 (29.63%)	17 / 50 (34.00%)	
occurrences (all)	11	23	
Gait disturbance			
subjects affected / exposed	2 / 27 (7.41%)	2 / 50 (4.00%)	
occurrences (all)	2	2	
General physical health deterioration			

subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Influenza like illness			
subjects affected / exposed	1 / 27 (3.70%)	3 / 50 (6.00%)	
occurrences (all)	1	3	
Malaise			
subjects affected / exposed	3 / 27 (11.11%)	3 / 50 (6.00%)	
occurrences (all)	4	4	
Oedema peripheral			
subjects affected / exposed	1 / 27 (3.70%)	5 / 50 (10.00%)	
occurrences (all)	1	7	
Pyrexia			
subjects affected / exposed	7 / 27 (25.93%)	11 / 50 (22.00%)	
occurrences (all)	7	14	
Thirst			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	5 / 27 (18.52%)	11 / 50 (22.00%)	
occurrences (all)	6	12	
Dry throat			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Dysphonia			
subjects affected / exposed	2 / 27 (7.41%)	3 / 50 (6.00%)	
occurrences (all)	2	3	
Dyspnoea			

subjects affected / exposed	3 / 27 (11.11%)	5 / 50 (10.00%)	
occurrences (all)	3	5	
Epistaxis			
subjects affected / exposed	3 / 27 (11.11%)	5 / 50 (10.00%)	
occurrences (all)	3	5	
Oropharyngeal pain			
subjects affected / exposed	2 / 27 (7.41%)	2 / 50 (4.00%)	
occurrences (all)	2	2	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 27 (3.70%)	3 / 50 (6.00%)	
occurrences (all)	1	3	
Insomnia			
subjects affected / exposed	2 / 27 (7.41%)	4 / 50 (8.00%)	
occurrences (all)	2	4	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 27 (7.41%)	6 / 50 (12.00%)	
occurrences (all)	2	9	
Amylase increased			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	2	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 27 (7.41%)	7 / 50 (14.00%)	
occurrences (all)	2	9	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Blood bilirubin increased			
subjects affected / exposed	2 / 27 (7.41%)	4 / 50 (8.00%)	
occurrences (all)	2	6	
Blood creatine phosphokinase increased			
subjects affected / exposed	12 / 27 (44.44%)	18 / 50 (36.00%)	
occurrences (all)	20	35	
Blood creatinine increased			

subjects affected / exposed	3 / 27 (11.11%)	3 / 50 (6.00%)	
occurrences (all)	3	3	
Blood prolactin increased			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Blood uric acid increased			
subjects affected / exposed	1 / 27 (3.70%)	2 / 50 (4.00%)	
occurrences (all)	1	2	
Cytomegalovirus test			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 27 (0.00%)	2 / 50 (4.00%)	
occurrences (all)	0	3	
International normalised ratio increased			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Lipase increased			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	3	
Low density lipoprotein increased			
subjects affected / exposed	1 / 27 (3.70%)	3 / 50 (6.00%)	
occurrences (all)	1	4	
Platelet count decreased			
subjects affected / exposed	4 / 27 (14.81%)	4 / 50 (8.00%)	
occurrences (all)	4	4	
Prothrombin level increased			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Prothrombin time prolonged			

subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Weight decreased			
subjects affected / exposed	2 / 27 (7.41%)	4 / 50 (8.00%)	
occurrences (all)	2	4	
Weight increased			
subjects affected / exposed	1 / 27 (3.70%)	3 / 50 (6.00%)	
occurrences (all)	1	3	
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	2 / 27 (7.41%)	2 / 50 (4.00%)	
occurrences (all)	2	2	
Contusion			
subjects affected / exposed	3 / 27 (11.11%)	6 / 50 (12.00%)	
occurrences (all)	5	12	
Fall			
subjects affected / exposed	1 / 27 (3.70%)	4 / 50 (8.00%)	
occurrences (all)	1	4	
Hyphaema			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Laceration			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Meniscus injury			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Procedural hypotension			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Scratch			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Spinal compression fracture			

subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Tooth fracture			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Cardiac disorders			
Supraventricular extrasystoles			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Carpal tunnel syndrome			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Cerebral ischaemia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	4 / 27 (14.81%)	5 / 50 (10.00%)	
occurrences (all)	4	6	
Dysaesthesia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Dysgeusia			
subjects affected / exposed	9 / 27 (33.33%)	19 / 50 (38.00%)	
occurrences (all)	10	21	
Head discomfort			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	5 / 27 (18.52%)	8 / 50 (16.00%)	
occurrences (all)	6	10	
Hypoaesthesia			

subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Memory impairment			
subjects affected / exposed	2 / 27 (7.41%)	3 / 50 (6.00%)	
occurrences (all)	2	3	
Muscle contractions involuntary			
subjects affected / exposed	0 / 27 (0.00%)	2 / 50 (4.00%)	
occurrences (all)	0	2	
Paraesthesia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Post herpetic neuralgia			
subjects affected / exposed	1 / 27 (3.70%)	2 / 50 (4.00%)	
occurrences (all)	1	2	
Restless legs syndrome			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	2	
Syncope			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Transient ischaemic attack			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Tremor			
subjects affected / exposed	2 / 27 (7.41%)	2 / 50 (4.00%)	
occurrences (all)	2	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	16 / 27 (59.26%)	29 / 50 (58.00%)	
occurrences (all)	23	49	
Extramedullary haemopoiesis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	

Leukocytosis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Neutropenia			
subjects affected / exposed	1 / 27 (3.70%)	2 / 50 (4.00%)	
occurrences (all)	1	2	
Thrombocytopenia			
subjects affected / exposed	7 / 27 (25.93%)	15 / 50 (30.00%)	
occurrences (all)	15	27	
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Vision blurred			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 27 (3.70%)	3 / 50 (6.00%)	
occurrences (all)	1	4	
Abdominal distension			
subjects affected / exposed	1 / 27 (3.70%)	2 / 50 (4.00%)	
occurrences (all)	1	2	
Abdominal pain			
subjects affected / exposed	4 / 27 (14.81%)	9 / 50 (18.00%)	
occurrences (all)	4	9	
Abdominal pain upper			
subjects affected / exposed	1 / 27 (3.70%)	2 / 50 (4.00%)	
occurrences (all)	1	2	
Bile acid malabsorption			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	7 / 27 (25.93%)	11 / 50 (22.00%)	
occurrences (all)	9	15	
Diarrhoea			

subjects affected / exposed	11 / 27 (40.74%)	21 / 50 (42.00%)	
occurrences (all)	16	32	
Diverticulum			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Diverticulum intestinal			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Dry mouth			
subjects affected / exposed	3 / 27 (11.11%)	3 / 50 (6.00%)	
occurrences (all)	3	3	
Duodenal ulcer			
subjects affected / exposed	1 / 27 (3.70%)	2 / 50 (4.00%)	
occurrences (all)	1	2	
Dyspepsia			
subjects affected / exposed	1 / 27 (3.70%)	2 / 50 (4.00%)	
occurrences (all)	1	2	
Flatulence			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Functional gastrointestinal disorder			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Gastric ulcer			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Gastric varices			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Gastritis			
subjects affected / exposed	0 / 27 (0.00%)	2 / 50 (4.00%)	
occurrences (all)	0	2	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 27 (3.70%)	2 / 50 (4.00%)	
occurrences (all)	1	2	
Haematochezia			

subjects affected / exposed	0 / 27 (0.00%)	2 / 50 (4.00%)	
occurrences (all)	0	2	
Melaena			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	8 / 27 (29.63%)	12 / 50 (24.00%)	
occurrences (all)	9	14	
Stomatitis			
subjects affected / exposed	1 / 27 (3.70%)	2 / 50 (4.00%)	
occurrences (all)	1	2	
Toothache			
subjects affected / exposed	1 / 27 (3.70%)	2 / 50 (4.00%)	
occurrences (all)	1	2	
Vomiting			
subjects affected / exposed	5 / 27 (18.52%)	11 / 50 (22.00%)	
occurrences (all)	5	12	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 27 (0.00%)	2 / 50 (4.00%)	
occurrences (all)	0	2	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 27 (3.70%)	2 / 50 (4.00%)	
occurrences (all)	1	2	
Alopecia			
subjects affected / exposed	12 / 27 (44.44%)	25 / 50 (50.00%)	
occurrences (all)	12	25	
Erythema			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Hair growth abnormal			

subjects affected / exposed	2 / 27 (7.41%)	2 / 50 (4.00%)	
occurrences (all)	3	3	
Hyperkeratosis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Madarosis			
subjects affected / exposed	1 / 27 (3.70%)	2 / 50 (4.00%)	
occurrences (all)	1	2	
Night sweats			
subjects affected / exposed	3 / 27 (11.11%)	5 / 50 (10.00%)	
occurrences (all)	4	6	
Onychoclasis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	0 / 27 (0.00%)	4 / 50 (8.00%)	
occurrences (all)	0	4	
Pruritus generalised			
subjects affected / exposed	0 / 27 (0.00%)	2 / 50 (4.00%)	
occurrences (all)	0	2	
Rash			
subjects affected / exposed	2 / 27 (7.41%)	4 / 50 (8.00%)	
occurrences (all)	2	4	
Skin discolouration			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Swelling face			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 27 (3.70%)	2 / 50 (4.00%)	
occurrences (all)	1	2	
Haematuria			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	

Urinary retention			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 27 (3.70%)	5 / 50 (10.00%)	
occurrences (all)	1	6	
Back pain			
subjects affected / exposed	0 / 27 (0.00%)	2 / 50 (4.00%)	
occurrences (all)	0	2	
Bone pain			
subjects affected / exposed	2 / 27 (7.41%)	2 / 50 (4.00%)	
occurrences (all)	2	2	
Joint lock			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Muscle fatigue			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Muscle spasms			
subjects affected / exposed	18 / 27 (66.67%)	31 / 50 (62.00%)	
occurrences (all)	29	49	
Muscle twitching			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Muscular weakness			
subjects affected / exposed	2 / 27 (7.41%)	8 / 50 (16.00%)	
occurrences (all)	2	8	
Musculoskeletal chest pain			
subjects affected / exposed	3 / 27 (11.11%)	4 / 50 (8.00%)	
occurrences (all)	3	4	
Musculoskeletal pain			
subjects affected / exposed	0 / 27 (0.00%)	2 / 50 (4.00%)	
occurrences (all)	0	2	
Myalgia			

subjects affected / exposed	9 / 27 (33.33%)	13 / 50 (26.00%)	
occurrences (all)	16	22	
Osteoarthritis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	3 / 27 (11.11%)	5 / 50 (10.00%)	
occurrences (all)	6	8	
Polyarthritis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 27 (3.70%)	3 / 50 (6.00%)	
occurrences (all)	1	3	
Cystitis			
subjects affected / exposed	1 / 27 (3.70%)	2 / 50 (4.00%)	
occurrences (all)	1	3	
Ear infection			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Escherichia infection			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Folliculitis			
subjects affected / exposed	3 / 27 (11.11%)	3 / 50 (6.00%)	
occurrences (all)	3	3	
Fungal skin infection			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Gastroenteritis viral			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Herpes zoster			
subjects affected / exposed	2 / 27 (7.41%)	3 / 50 (6.00%)	
occurrences (all)	2	3	

Influenza			
subjects affected / exposed	2 / 27 (7.41%)	2 / 50 (4.00%)	
occurrences (all)	2	2	
Nasopharyngitis			
subjects affected / exposed	2 / 27 (7.41%)	6 / 50 (12.00%)	
occurrences (all)	6	10	
Oesophageal candidiasis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Oral herpes			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Pharyngitis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Pneumonia			
subjects affected / exposed	2 / 27 (7.41%)	4 / 50 (8.00%)	
occurrences (all)	2	4	
Tooth infection			
subjects affected / exposed	1 / 27 (3.70%)	2 / 50 (4.00%)	
occurrences (all)	1	2	
Upper respiratory tract infection			
subjects affected / exposed	2 / 27 (7.41%)	7 / 50 (14.00%)	
occurrences (all)	3	9	
Urinary tract infection			
subjects affected / exposed	2 / 27 (7.41%)	4 / 50 (8.00%)	
occurrences (all)	3	5	
Urinary tract infection bacterial			
subjects affected / exposed	0 / 27 (0.00%)	2 / 50 (4.00%)	
occurrences (all)	0	4	
Wound infection			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	4 / 27 (14.81%)	7 / 50 (14.00%)	
occurrences (all)	4	8	
Hyperkalaemia			
subjects affected / exposed	0 / 27 (0.00%)	2 / 50 (4.00%)	
occurrences (all)	0	3	
Hypertriglyceridaemia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	3	
Hyperuricaemia			
subjects affected / exposed	1 / 27 (3.70%)	6 / 50 (12.00%)	
occurrences (all)	1	7	
Hypocalcaemia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Hypokalaemia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Hypomagnesaemia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Hyponatraemia			
subjects affected / exposed	0 / 27 (0.00%)	2 / 50 (4.00%)	
occurrences (all)	0	2	
Increased appetite			
subjects affected / exposed	1 / 27 (3.70%)	2 / 50 (4.00%)	
occurrences (all)	1	2	
Iron deficiency			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 August 2014	Issued after thirty six subjects were screened, 30 subjects treated, and six subjects were screen failures in the Phase Ib part of the study. Five of the treated subjects have discontinued treatment due to disease progression, adverse events, physician decision or subject decision. Out of nine subjects in the DDS at the 400mg LDE225 qd + 15 mg INC424 bid dose level, two DLTs occurred during the 6 week (42 day) DLT observation period. The MTD was not reached and instead the RPIID was defined as the 400mg LDE225 qd + 20mg INC424 bid dose level. Subjects enrolled in the Phase Ib safety expansion cohort at 400mg LDE225 qd + 20mg INC424 bid were being observed in order to confirm the RPIID. Following major changes were introduced: Addition of an exploratory endpoint to assess the levels of LDE225 in bone marrow, updates to the guidance for contraception based on a recent population pharmacokinetic analysis and updates to the muscle toxicity section for CK elevation.
06 February 2015	Issued after 57 subjects were screened, 50 subjects treated (30 in the Phase Ib part and 20 in the Stage 1, Phase II part), and 7 subjects were screen failures. Fourteen of the treated subjects have discontinued treatment due to disease progression, adverse events, physician decision or subject decision. The RPIID was confirmed as the 400mg LDE225 qd + 20 mg INC424 bid dose level. Subjects enrolled in the Stage 1, Phase II part of the study are currently being observed for 24 weeks, and an interim analysis was to occur at the end of the observation period. Following major changes were introduced: Add a treatment extension phase for subjects who complete 2 years of study treatment and are deriving clinical benefit according to the investigator until other alternatives to receive study treatment from the sponsor become available.

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.

Please refer to detailed description regarding reason for early termination of study.

Notes: