Clinical trial results:
A multicenter, open label, dose finding study to evaluate efficacy and safety of Givinostat administered in two different doses in patients with polyarticular course Juvenile Idiopathic Arthritis (poly JIA) not adequately responding to the standard treatment

Summary

EudraCT number	2010-019094-15
Trial protocol	CZ BE ES IT SI
Global end of trial date	01 June 2012

Results information

Result version number	v2 (current)
This version publication date	31 July 2019
First version publication date	25 May 2019
Version creation reason	• Correction of full data set Friendly name should be changed.

Trial information

Trial identification

Sponsor protocol code	DSC/08/2357/36

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01261624
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Italfarmaco S.p.A.
Sponsor organisation address	Via dei Lavoratori 54, Milan, Italy, 20092
Public contact	Clinical Trial Transparency Manager, Italfarmaco S.p.A., Italfarmaco S.p.A., +39 02 66041503, info@italfarmaco.com
Scientific contact	Clinical Trial Transparency Manager, Italfarmaco S.p.A., Italfarmaco S.p.A., +39 02 66041503, info@italfarmaco.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000551-PIP01-09
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 June 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 June 2012
Global end of trial reached?	Yes
Global end of trial date	01 June 2012
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy and safety profile of Givinostat administered in two different doses in patients with polyarticular course JIA not adequately responding to the standard treatment, to the purpose of selecting the best dose to be tested on a larger scale in a following phase III clinical trial.

Protection of trial subjects:

The study was conducted under the provisions of the Declaration of Helsinki and in accordance with the International Conference on Harmonization (ICH) Consolidated Guideline on Good Clinical Practice (GCP).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 October 2010
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	Romania: 3
Country: Number of subjects enrolled	Slovenia: 2
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Czech Republic: 2
Country: Number of subjects enrolled	Italy: 5
Worldwide total number of subjects	16
EEA total number of subjects	16

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)	7
Adolescents (12-17 years)	9
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 21 patients were screened and 16 patients were enrolled in the study. The enrolment was discontinued at 16 patients due to poor enrolment rate. The first 10 enrolled patients were assigned to the Low Dose treatment cohort (0.50 mg/kg BID) and the following six patients were assigned to the High Dose treatment cohort (0.75 mg/kg BID).

Pre-assignment

Screening details:

A total of 21 patients were screened and 16 patients were enrolled in 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

Blinding implementation details:

This was an open-label study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Low Dose Cohort (0.50 mg/kg BID)

Arm description:

Patients received the dose of 0.50 mg/kg BID for 12 weeks. Responders (defined as achieving at least an ACR Pediatric Criteria level 30 of response) continued receiving the assigned dose for a further 12 weeks. Non-responders were allowed to increase the dose to 0.75 mg/kg BID for a further 12 weeks

Arm type	Experimental
Investigational medicinal product name	Givinostat
Investigational medicinal product code	
Other name	ITF2357, histone deacetylase inhibitor
Pharmaceutical forms	Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Givinostat, oral suspension, was administered at the doses of 0.5 mg/kg BID, in fed conditions, during 12 consecutive weeks. Responders (achieving at least an ACR Pediatric 30 level of response) continued receiving the assigned dose for a further 12 weeks. Non-responders to 0.50 mg/kg BID were allowed to increase the dosage to 0.75 mg/kg BID for a further 12 weeks.

Arm title	High Dose Cohort (0.75 mg/kg BID)

Arm description:

Patients received the dose of 0.75 mg/kg BID for 12 weeks. Responders (defined as achieving at least an ACR Pediatric Criteria level 30 of response) continued receiving the assigned dose for a further 12 weeks. Non-responders after 12 weeks discontinued the study treatment permanently.

Arm type	Experimental
Investigational medicinal product name	Givinostat
Investigational medicinal product code	Histone deacetylase inhibitor
Other name	ITF2357
Pharmaceutical forms	Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Givinostat, oral suspension, was administered at the doses of 0.75 mg/kg BID, in fed conditions, during 12 consecutive weeks. Responders (achieving at least an ACR Pediatric 30 level of response) continued receiving the assigned dose for a further 12 weeks. Non-responders to the initial dose of 0.75 mg/kg BID were permanently discontinued from the study.

Number of subjects in period 1	Low Dose Cohort (0.50 mg/kg BID)	High Dose Cohort (0.75 mg/kg BID)
Started	10	6
Completed	8	2
Not completed	2	4
Disease progression	2	1
Insufficient response	-	3

Baseline characteristics

Reporting groups	
Reporting group title	Low Dose Cohort (0.50 mg/kg BID)
Reporting group description:	
Patients received the dose of 0.50 mg/kg BID for 12 weeks. Responders (defined as achieving at least an ACR Pediatric Criteria level 30 of response) continued receiving the assigned dose for a further 12 weeks. Non-responders were allowed to increase the dose to 0.75 mg/kg BID for a further 12 weeks	
Reporting group title	High Dose Cohort (0.75 mg/kg BID)
Reporting group description:	
Patients received the dose of 0.75 mg/kg BID for 12 weeks. Responders (defined as achieving at least an ACR Pediatric Criteria level 30 of response) continued receiving the assigned dose for a further 12 weeks. Non-responders after 12 weeks discontinued the study treatment permanently.	

Reporting group values	Low Dose Cohort (0.50 mg/kg BID)	High Dose Cohort (0.75 mg/kg BID)	Total
Number of subjects	10	6	16
Age categorical Units: Subjects			
Children (2-11 years)	4	3	7
Adolescents (12-17 years)	6	3	9
Age continuous Units: years			
arithmetic mean	11.7	9.7	
standard deviation	± 5.5	± 5.7	-
Gender categorical Units: Subjects			
Female	8	6	14
Male	2	0	2

Subject analysis sets	
Subject analysis set title	Low dose discontinued
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT set comprised all enrolled patients who received at least one dose of investigational medicinal product and from whom at least one measurement of the ACR Pediatric variables after Day 1 was obtained.	
Subject analysis set title	Low dose throughout
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT set comprised all enrolled patients who received at least one dose of investigational medicinal product and from whom at least one measurement of the ACR Pediatric variables after Day 1 was obtained.	
Subject analysis set title	Switched dose
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT set comprised all enrolled patients who received at least one dose of investigational medicinal product and from whom at least one measurement of the ACR Pediatric variables after Day 1 was obtained.	
Subject analysis set title	High dose throughout
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT set comprised all enrolled patients who received at least one dose of investigational medicinal product and from whom at least one measurement of the ACR Pediatric variables after Day 1 was obtained.

Subject analysis set title	High dose discontinued
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT set comprised all enrolled patients who received at least one dose of investigational medicinal product and from whom at least one measurement of the ACR Pediatric variables after Day 1 was obtained.

Reporting group values	Low dose discontinued	Low dose throughout	Switched dose
Number of subjects	1	1	8
Age categorical Units: Subjects			
Children (2-11 years)	1	1	2
Adolescents (12-17 years)	0	0	6
Age continuous Units: years arithmetic mean standard deviation	±	±	±
Gender categorical Units: Subjects			
Female	1	1	6
Male	0	0	2

Reporting group values	High dose throughout	High dose discontinued	
Number of subjects	2	4	
Age categorical Units: Subjects			
Children (2-11 years)	1	2	
Adolescents (12-17 years)	1	2	
Age continuous Units: years arithmetic mean standard deviation	±	±	
Gender categorical Units: Subjects			
Female	2	4	
Male	0	0	

End points

End points reporting groups

Reporting group title	Low Dose Cohort (0.50 mg/kg BID)

Reporting group description:

Patients received the dose of 0.50 mg/kg BID for 12 weeks. Responders (defined as achieving at least an ACR Pediatric Criteria level 30 of response) continued receiving the assigned dose for a further 12 weeks. Non-responders were allowed to increase the dose to 0.75 mg/kg BID for a further 12 weeks

Reporting group title	High Dose Cohort (0.75 mg/kg BID)

Reporting group description:

Patients received the dose of 0.75 mg/kg BID for 12 weeks. Responders (defined as achieving at least an ACR Pediatric Criteria level 30 of response) continued receiving the assigned dose for a further 12 weeks. Non-responders after 12 weeks discontinued the study treatment permanently.

Subject analysis set title	Low dose discontinued
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT set comprised all enrolled patients who received at least one dose of investigational medicinal product and from whom at least one measurement of the ACR Pediatric variables after Day 1 was obtained.

Subject analysis set title	Low dose throughout
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT set comprised all enrolled patients who received at least one dose of investigational medicinal product and from whom at least one measurement of the ACR Pediatric variables after Day 1 was obtained.

Subject analysis set title	Switched dose
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT set comprised all enrolled patients who received at least one dose of investigational medicinal product and from whom at least one measurement of the ACR Pediatric variables after Day 1 was obtained.

Subject analysis set title	High dose throughout
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT set comprised all enrolled patients who received at least one dose of investigational medicinal product and from whom at least one measurement of the ACR Pediatric variables after Day 1 was obtained.

Subject analysis set title	High dose discontinued
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT set comprised all enrolled patients who received at least one dose of investigational medicinal product and from whom at least one measurement of the ACR Pediatric variables after Day 1 was obtained.

Primary: ACR Pediatric 30 response level after 12 weeks of treatment

End point title	ACR Pediatric 30 response level after 12 weeks of treatment[1]

End point description:

ACR Pediatric variables include: Physician's Global Assessment of disease activity on a 0-100 mm visual analogue scale from 0 mm = no disease activity to 100 mm = very severe disease activity; Parent's or patient's Global Assessment of Patient's overall well-being on a 100 mm VAS from 0 mm = very well to 100 mm = very poor; Functional ability: Childhood Health Assessment Questionnaire; Number of joints with active arthritis using the ACR definition (any joint with swelling, or in the absence of swelling, limitation of motion accompanied by pain/tenderness not due to bone deformity); Number of joints with limitation of motion; Laboratory measure of inflammation: C-reactive protein (mg/L) Patients were considered as responders if they achieve at least an ACR Pediatric Criteria level 30 of response, defined as a 30% improvement as compared to baseline in at least 3 of the 6 variables listed above, with no more than 1 variable worsening by > than 30%.

End point type	Primary

End point timeframe:

At 12 weeks of treatment.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No data available

End point values	Low dose discontinued	Low dose throughout	Switched dose	High dose throughout
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	1	8	2
Units: number of patients	0	1	3	2

End point values	High dose discontinued			
Subject group type	Subject analysis set			
Number of subjects analysed	4			
Units: number of patients	1			

Statistical analyses

No statistical analyses for this end point

Secondary: ACR pediatric response level (ACR 50, 70, 90 and 100) at week 12 of treatment

End point title	ACR pediatric response level (ACR 50, 70, 90 and 100) at week 12 of treatment

End point description:

ACR Pediatric variables include: Physician's Global Assessment of disease activity on a 0- 100 mm visual analogue scale from 0 mm = no disease activity to 100 mm = very severe disease activity; Parent's or patient's Global Assessment of Patient's overall well-being on a 100 mm VAS from 0 mm = very well to 100 mm = very poor; Functional ability: Childhood Health Assessment Questionnaire; Number of joints with active arthritis using the ACR definition (any joint with swelling, or in the absence of swelling, limitation of motion accompanied by pain/tenderness not due to bone deformity); Number of joints with limitation of motion; Laboratory measure of inflammation: C-reactive protein (mg/L) Patients were considered as responders if they achieve at least an ACR Pediatric Criteria level 50, 70, 90 and 100 of response, defined as a 50%, 70%, 90% and 100% improvement as compared to baseline in at least 3 of the 6 variables listed above, with no more than 1 variable worsening by > than 30%.

End point type	Secondary

End point timeframe:

At week 12 of treatment.

End point values	Low dose discontinued	Low dose throughout	Switched dose	High dose throughout
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	1	8	2
Units: number of patients				
Level 50	0	1	1	2
Level 70	0	1	0	1
Level 90	0	0	0	0
Level 100	0	0	0	0

End point values	High dose discontinued			
Subject group type	Subject analysis set			
Number of subjects analysed	4			
Units: number of patients				
Level 50	1			
Level 70	0			
Level 90	0			
Level 100	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Changes Over Time of Physician’s Global Assessment of Disease Activity

End point title	Mean Changes Over Time of Physician’s Global Assessment of Disease Activity

End point description:

Only values at 12 and 24 weeks of treatment, expressed as percentage change from baseline, are reported here.

End point type	Secondary

End point timeframe:

At 1, 2, 4, 6, 8, 10, 12, 16, 20, 24 weeks of treatment.

End point values	Low dose discontinued	Low dose throughout	Switched dose	High dose throughout
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	0[2]	1	8[3]	2
Units: percentage				
arithmetic mean (standard deviation)				
12 weeks	()	81.36 (± 000)	10.56 (± 27.93)	83.57 (± 16.66)
24 weeks	()	32.20 (± 000)	33.40 (± 41.96)	74.48 (± 32.80)

Notes:

[2] - The only patient in this cohort discontinued the study before week 12.

[3] - 7 patients are part of this ITT cohort at 24 weeks

End point values	High dose discontinued			
Subject group type	Subject analysis set			
Number of subjects analysed	2[4]			
Units: percentage				
arithmetic mean (standard deviation)				
12 weeks	0.00 (± 28.28)			
24 weeks	000 (± 000)			

Notes:

[4] - 2 and 0 patients are part of this ITT cohort at weeks 12 and 24 respectively.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Changes Over Time of Parent's or Patient's Global Assessment of Patient's Overall Well-being

End point title	Mean Changes Over Time of Parent's or Patient's Global Assessment of Patient's Overall Well-being

End point description:

Only values at 12 and 24 weeks of treatment, expressed as percentage change from baseline, are reported here.

End point type	Secondary

End point timeframe:

At 1, 2, 4, 6, 8, 10, 12, 16, 20, 24 weeks of treatment.

End point values	Low dose discontinued	Low dose throughout	Switched dose	High dose throughout
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	0[5]	1	8[6]	2
Units: percentage				
arithmetic mean (standard deviation)				
12 weeks	()	80.85 (± 000)	13.46 (± 40.17)	88.37 (± 16.44)
24 weeks	()	48.94 (± 000)	-6.59 (± 100.07)	94.38 (± 1.92)

Notes:

[5] - The only patient in this cohort discontinued the study before week 12

[6] - 7 patients are part of this ITT cohort at 24 weeks

End point values	High dose discontinued			
Subject group type	Subject analysis set			
Number of subjects analysed	2[7]			
Units: percentage				
arithmetic mean (standard deviation)				

12 weeks	-0.67 (± 46.20)			
24 weeks	000 (± 000)			

Notes:

[7] - 2 and 0 patients are part of this ITT cohort at weeks 12 and 24 respectively.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Changes Over Time of Functional Ability – Childhood Health Assessment Questionnaire (CHAQ)

End point title	Mean Changes Over Time of Functional Ability – Childhood Health Assessment Questionnaire (CHAQ)

End point description:

Only values at 12 and 24 weeks of treatment, expressed as percentage change from baseline, are reported here.

End point type	Secondary

End point timeframe:

At 1, 2, 4, 6, 8, 10, 12, 16, 20, 24 weeks of treatment.

End point values	Low dose discontinued	Low dose throughout	Switched dose	High dose throughout
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	0[8]	1	8[9]	2
Units: percentage				
arithmetic mean (standard deviation)				
week 12	()	28.5714 (± 000)	-13.8671 (± 85.6095)	79.1667 (± 29.4628)
week 24	()	14.2857 (± 000)	31.5018 (± 65.5471)	100.0000 (± 0.0000)

Notes:

[8] - The only patient in this cohort discontinued the study before week 12

[9] - 7 patients are part of this ITT cohort at 24 weeks

End point values	High dose discontinued			
Subject group type	Subject analysis set			
Number of subjects analysed	2[10]			
Units: percentage				
arithmetic mean (standard deviation)				
week 12	50.0000 (± 000)			
week 24	000 (± 000)			

Notes:

[10] - 2 and 0 patients are part of this ITT cohort at weeks 12 and 24 respectively.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change over time of Number of Joints with Active Arthritis

End point title	Mean change over time of Number of Joints with Active Arthritis

End point description:

Only values from weeks 12 and 24 weeks of treatment, expressed as percentage change from baseline, are reported here.

End point type	Secondary

End point timeframe:

At weeks 1, 2, 4, 6, 8, 10, 12, 16, 20, 24 weeks of treatment.

End point values	Low dose discontinued	Low dose throughout	Switched dose	High dose throughout
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	0[11]	1	8[12]	2
Units: percentage				
arithmetic mean (standard deviation)				
week 12	()	100.00 (± 000)	40.46 (± 38.36)	62.72 (± 29.15)
week 24	()	85.00 (± 000)	53.36 (± 37.16)	63.16 (± 52.10)

Notes:

[11] - The only patient in this cohort discontinued the study before week 12

[12] - 7 patients are part of this ITT cohort at 24 weeks

End point values	High dose discontinued			
Subject group type	Subject analysis set			
Number of subjects analysed	2[13]			
Units: percentage				
arithmetic mean (standard deviation)				
week 12	1.90 (± 78.12)			
week 24	000 (± 000)			

Notes:

[13] - 2 and 0 patients are part of this ITT cohort at weeks 12 and 24 respectively.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change over time of Number of Joints with Limitation of Motion

End point title	Mean Change over time of Number of Joints with Limitation of Motion

End point description:

Only values from weeks 12 and 24 weeks of treatment, expressed as percentage change from baseline, are reported here.

End point type	Secondary

End point timeframe:

At weeks 1, 2, 4, 6, 8, 10, 12, 16, 20, 24 weeks of treatment.

End point values	Low dose discontinued	Low dose throughout	Switched dose	High dose throughout
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	0[14]	1	8[15]	2
Units: percentage				
arithmetic mean (standard deviation)				
week 12	()	-3.85 (± 000)	13.41 (± 31.38)	-87.50 (± 229.81)
week 24	()	7.69 (± 000)	24.79 (± 13.07)	-262.50 (± 477.30)

Notes:

[14] - The only patient in this cohort discontinued the study before week 12

[15] - 7 patients are part of this ITT cohort at 24 weeks

End point values	High dose discontinued			
Subject group type	Subject analysis set			
Number of subjects analysed	2[16]			
Units: percentage				
arithmetic mean (standard deviation)				
week 12	1.67 (± 68.35)			
week 24	000 (± 000)			

Notes:

[16] - 2 and 0 patients are part of this ITT cohort at weeks 12 and 24 respectively

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change over time of Laboratory Measure of Inflammation – C-reactive Protein

End point title	Mean change over time of Laboratory Measure of Inflammation – C-reactive Protein

End point description:

Only values from weeks 12 and 24 weeks of treatment, expressed as percentage change from baseline, are reported here.

End point type	Secondary

End point timeframe:

At weeks 1, 2, 4, 6, 8, 10, 12, 16, 20, 24 weeks of treatment.

End point values	Low dose discontinued	Low dose throughout	Switched dose	High dose throughout
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	0[17]	1	8[18]	2
Units: Percentage				
arithmetic mean (standard deviation)				
week 12	()	68.027 (± 000)	-147.124 (± 253.627)	19.415 (± 62.812)
week 24	()	9.184 (± 000)	-10.402 (± 149.724)	-39.096 (± 19.934)

Notes:

[17] - The only patient in this cohort discontinued the study before week 12

[18] - 7 patients are part of this ITT cohort at 24 weeks

End point values	High dose discontinued			
Subject group type	Subject analysis set			
Number of subjects analysed	2[19]			
Units: Percentage				
arithmetic mean (standard deviation)				
week 12	-19.121 (± 51.285)			
week 24	000 (± 000)			

Notes:

[19] - 2 and 0 patients are part of this ITT cohort at weeks 12 and 24 respectively.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded at days 1, 8, 15, 29, 43, 57, 71, 85 (Week 12), 99, 113, 127, 141, 155, 169 (Week 24 - End of study) and at post-study checks.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups

Reporting group title	Low dose discontinued - Safety set

Reporting group description:

The safety set comprised all enrolled patients who received at least one dose of investigational medicinal product.

Reporting group title	Low dose throughout - Safety set

Reporting group description:

The safety set comprised all enrolled patients who received at least one dose of investigational medicinal product.

Reporting group title	Switched dose - Safety set

Reporting group description:

The safety set comprised all enrolled patients who received at least one dose of investigational medicinal product.

Reporting group title	High dose throughout - Safety set

Reporting group description:

The safety set comprised all enrolled patients who received at least one dose of investigational medicinal product.

Reporting group title	High dose discontinued - Safety set

Reporting group description:

The safety set comprised all enrolled patients who received at least one dose of investigational medicinal product.

Serious adverse events	Low dose discontinued - Safety set	Low dose throughout - Safety set	Switched dose - Safety set
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 8 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	High dose throughout - Safety set	High dose discontinued - Safety set	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Low dose discontinued - Safety set	Low dose throughout - Safety set	Switched dose - Safety set
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)	1 / 1 (100.00%)	8 / 8 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Gait disturbance			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Menstruation irregular			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	2
Epistaxis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			

subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Nightmare			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Investigations			
Blood phosphorus decreased			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Joint dislocation			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Sinus tachycardia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Erythropenia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Thrombocytopenia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Eye disorders			

Ocular hyperaemia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	2
Abdominal pain upper			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Dry mouth			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Frequent bowel movements			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Dermatitis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Pruritus			

subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Rash papular			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Skin hyperpigmentation			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Skin lesion			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Musculoskeletal stiffness			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Coxsackie viral infection			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	3
Otitis media acute			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Pharyngitis			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Pharyngitis streptococcal			

subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Rhinitis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Viral infection			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Pharyngotonsillitis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Hypercholesterolemia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Hypoalbuminemia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	2
Hypophosphatemia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2

Non-serious adverse events	High dose throughout - Safety set	High dose discontinued - Safety set	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)	4 / 4 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
General disorders and administration			

site conditions			
Chills			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Gait disturbance			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Pyrexia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Menstruation irregular			
subjects affected / exposed	0 / 2 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Epistaxis			
subjects affected / exposed	1 / 2 (50.00%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Oropharyngeal pain			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Psychiatric disorders			
Nightmare			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Investigations			
Blood phosphorus decreased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Injury, poisoning and procedural complications			
Joint dislocation			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	

Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Sinus tachycardia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Erythropenia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Thrombocytopenia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Eye disorders			
Ocular hyperaemia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Abdominal pain upper			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Constipation			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Diarrhoea			

subjects affected / exposed	0 / 2 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Dry mouth			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Frequent bowel movements			
subjects affected / exposed	1 / 2 (50.00%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	0 / 2 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	2	
Vomiting			
subjects affected / exposed	1 / 2 (50.00%)	1 / 4 (25.00%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Dermatitis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Pruritus			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Rash papular			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Skin hyperpigmentation			
subjects affected / exposed	1 / 2 (50.00%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Skin lesion			
subjects affected / exposed	0 / 2 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Haematuria			

subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal stiffness			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Coxsackie viral infection			
subjects affected / exposed	0 / 2 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Otitis media acute			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Pharyngitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Pharyngitis streptococcal			
subjects affected / exposed	0 / 2 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Respiratory tract infection			
subjects affected / exposed	1 / 2 (50.00%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Rhinitis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Viral infection			

subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Pharyngotonsillitis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Metabolism and nutrition disorders			
Hypercholesterolemia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Hypoalbuminemia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Hypophosphatemia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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.

No limitations or caveats are applicable to this summary of the results.

Notes: