Clinical trial results:
Phase II study of the histone-deacetylase inhibitor GIVINOSTAT (ITF2357) in combination with hydroxyurea in patients with JAK2V617F positive Polycythemia Vera non-responder to hydroxyurea monotherapy.

Summary

EudraCT number	2009-010982-22
Trial protocol	IT
Global end of trial date	07 July 2011

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 description should be changed.

Trial information

Trial identification

Sponsor protocol code	DSC/08/2357/38

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00928707
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Italfarmaco S.p.A.
Sponsor organisation address	Via dei Lavoratori 54 , Milano, 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)	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	07 July 2011
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 July 2011
Global end of trial reached?	Yes
Global end of trial date	07 July 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of GIVINOSTAT (ITF2357) in combination with hydroxyurea in patients with JAK2V617F positive Polycythemia Vera non-responders to the maximum tolerated dose of hydroxyurea monotherapy

Protection of trial subjects:

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

Background therapy:

Hydroxyurea (HU) monotherapy was already in use before admission to the study and was continued at the maximum tolerated dose (MTD) throughout the study

Evidence for comparator: -

Actual start date of recruitment	09 July 2009
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	Italy: 45
Worldwide total number of subjects	45
EEA total number of subjects	45

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)	21
From 65 to 84 years	24

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total number of 45 patients were randomised to receive: 23 Givinostat 50 mg o.d. and 22 Givinostat 50 mg b.i.d. One subject in the o.d. group was discontinued due to ineligibility/protocol violation and did not receive the assigned treatment. Therefore, 22 patients in either group received treatment.

Pre-assignment

Screening details:

Pre-enrolment screening tests and evaluations were used to determine eligibility of each candidate for study inclusion. All evaluations had to be performed within 2 weeks prior to starting treatment with Givinostat. If all eligibility criteria were met at screening visit, the treatment with Givinostat could start.

Period 1

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

Blinding implementation details:

No blinding procedures are applicable as the study was open-label.

Arms

Are arms mutually exclusive?	Yes
Arm title	Group A (50 mg od)

Arm description:

Group A: 50 mg o.d. of oral Givinostat in combination with the maximum tolerated dose of hydroxyurea monotherapy (already in use before admission to the study) were administered for 12 weeks. In case of no response at week 12, dose was increased to 50 mg b.i.d. in weeks 13-24.

Arm type	Experimental
Investigational medicinal product name	Givinostat
Investigational medicinal product code	
Other name	ITF2357
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Givinostat 50 mg hard gelatine capsules for oral administration, in combination with hydroxyurea monotherapy at the maximum tolerated dose.

Investigational medicinal product name	Hydroxyurea
Investigational medicinal product code	
Other name	Onco Carbide, hydroxycarbamide
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Hydroxyurea 500 mg capsules – already in use before admission to the study – at the maximum tolerated dose, in combination with Givinostat.

Arm title	Group B (50 mg bid)

Arm description:

Group B: 50 mg b.i.d. of oral Givinostat in combination with the maximum tolerated dose of hydroxyurea monotherapy (already in use before admission to the study) were administered for 12 weeks. In case of no response at week 12, dose was increased to 50 mg t.i.d. in weeks 13-24.

Arm type	Experimental

Investigational medicinal product name	Givinostat
Investigational medicinal product code	
Other name	ITF2357
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Givinostat 50 mg hard gelatine capsules for oral administration, in combination with hydroxyurea monotherapy at the maximum tolerated dose.

Investigational medicinal product name	Hydroxyurea
Investigational medicinal product code	
Other name	Onco Carbide, hydroxycarbamide
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Hydroxyurea 500 mg capsules – already in use before admission to the study – at the maximum tolerated dose, in combination with Givinostat.

Number of subjects in period 1	Group A (50 mg od)	Group B (50 mg bid)
Started	23	22
Completed	22	22
Not completed	1	0
ineligibility/protocol violation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Group A (50 mg od)
Reporting group description:	
Group A: 50 mg o.d. of oral Givinostat in combination with the maximum tolerated dose of hydroxyurea monotherapy (already in use before admission to the study) were administered for 12 weeks. In case of no response at week 12, dose was increased to 50 mg b.i.d. in weeks 13-24.	
Reporting group title	Group B (50 mg bid)
Reporting group description:	
Group B: 50 mg b.i.d. of oral Givinostat in combination with the maximum tolerated dose of hydroxyurea monotherapy (already in use before admission to the study) were administered for 12 weeks. In case of no response at week 12, dose was increased to 50 mg t.i.d. in weeks 13-24.	

Reporting group values	Group A (50 mg od)	Group B (50 mg bid)	Total
Number of subjects	23	22	45
Age categorical Units: Subjects			
Adults (18-64 years)	10	11	21
From 65-84 years	13	11	24
Gender categorical Units: Subjects			
Female	9	7	16
Male	14	15	29

Subject analysis sets	
Subject analysis set title	Group A - Safety/ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Safety/Intention-to-treat (ITT) population, which included all randomized subjects who received at least one dose of study medication.	
Subject analysis set title	Group B - Safety/ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Safety/Intention-to-treat (ITT) population, which included all randomized subjects who received at least one dose of study medication.	

Reporting group values	Group A - Safety/ITT	Group B - Safety/ITT	
Number of subjects	22	22	
Age categorical Units: Subjects			
Adults (18-64 years)	9	11	
From 65-84 years	13	11	
Gender categorical Units: Subjects			
Female	9	7	
Male	13	15	

End points

End points reporting groups

Reporting group title	Group A (50 mg od)

Reporting group description:

Group A: 50 mg o.d. of oral Givinostat in combination with the maximum tolerated dose of hydroxyurea monotherapy (already in use before admission to the study) were administered for 12 weeks. In case of no response at week 12, dose was increased to 50 mg b.i.d. in weeks 13-24.

Reporting group title	Group B (50 mg bid)

Reporting group description:

Group B: 50 mg b.i.d. of oral Givinostat in combination with the maximum tolerated dose of hydroxyurea monotherapy (already in use before admission to the study) were administered for 12 weeks. In case of no response at week 12, dose was increased to 50 mg t.i.d. in weeks 13-24.

Subject analysis set title	Group A - Safety/ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Safety/Intention-to-treat (ITT) population, which included all randomized subjects who received at least one dose of study medication.

Subject analysis set title	Group B - Safety/ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Safety/Intention-to-treat (ITT) population, which included all randomized subjects who received at least one dose of study medication.

Primary: Overall hematological response rate at week 12

End point title	Overall hematological response rate at week 12[1]

End point description:

The number and rate of patients with overall (complete or partial) response at week 12 were assessed.
· Complete response:
1. HCT< 45% without phlebotomy, and
2. platelets ≤ 400 x109/L, and
3. WBC ≤ 10 x 109/L, and
4. no splenomegaly, and
5. no disease related systemic symptoms (microvascular disturbances, pruritus, headache);
· Partial response:
1. HCT < 45% without phlebotomy, or
2. fulfilment of at least 3 of the other above mentioned criteria;
· No response: any response that did not satisfy the criteria set for partial response.

End point type	Primary

End point timeframe:

At week 12

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: Sample size has been computed and data will be evaluated based upon a Simon's phase II dose-selection design where the objective involves selecting a promising dose among a set of candidates.
For each dose group, a sample size of 22 patients is estimated using exact method (binomial) and assuming:

1. two treatment dosages;
2. 0 = 0.20 as the smallest response rate;
3. 1 = 0.40 as the best dose response rate;
4. a probability greater than 90% of correctly selecting the best dosa

End point values	Group A - Safety/ITT	Group B - Safety/ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	22		
Units: percentage of patients				
number (confidence interval 95%)				
Responder	54.5 (33.7 to 75.4)	50.0 (29.1 to 70.9)		
Non responder	45.5 (24.6 to 66.3)	50.0 (29.1 to 70.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Hematological response rate at week 24 by dose escalation after week 12

End point title	Hematological response rate at week 24 by dose escalation after week 12

End point description:

Rate of haematological response after a 50 mg increase of the initial Givinostat dose in non-responder patients at the time when the primary endpoint was assessed (week 12).
· Complete response:
1. HCT< 45% without phlebotomy, and
2. platelets ≤ 400 x109/L, and
3. WBC ≤ 10 x 109/L, and
4. no splenomegaly, and
5. no disease related systemic symptoms (microvascular disturbances, pruritus, headache);
· Partial response:
1. HCT < 45% without phlebotomy, or
2. fulfilment of at least 3 of the other above mentioned criteria;
· No response: any response that did not satisfy the criteria set for partial response.

End point type	Secondary

End point timeframe:

At week 24.

End point values	Group A - Safety/ITT	Group B - Safety/ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	22		
Units: percentage of patients				
number (confidence interval 95%)				
Responder	63.6 (43.5 to 83.7)	40.9 (20.4 to 61.5)		
Non responder	36.4 (16.3 to 56.5)	59.1 (38.5 to 79.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Reduction of the JAK2V617F allele burden by quantitative RT-PCR

End point title	Reduction of the JAK2V617F allele burden by quantitative RT-PCR

End point description:

Quantitative RT-PCR for JAK2V617F mutational status on peripheral blood (PB) granulocyte and haematopoietic colonies (with and without HGFs).

End point type	Secondary

End point timeframe:

At weeks 12, 24, at "drop out visit" and at "End of Study" (EOS). EOS stays for 7 days after last drug intake if patient is withdrawn from the study before week 24.

End point values	Group A - Safety/ITT	Group B - Safety/ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	21		
Units: percentage				
arithmetic mean (standard deviation)				
Week 12	-2.6 (± 8.2)	0.0 (± 6.0)		
Week 24	-3.8 (± 11.5)	4.6 (± 5.7)		
Drop-out	-4.0 (± 000)	-9.5 (± 20.5)		
EOS	-3.8 (± 11.1)	3.0 (± 8.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Reduction of the fraction of JAK2V617F positive clonogenic progenitor

End point title	Reduction of the fraction of JAK2V617F positive clonogenic progenitor

End point description:

JAK2V617F genotyping and quantification were performed on gradient-separated mononuclear cells during the pre-treatment
evaluations, halfway through the study (12th weeks) and at the end of the study period (24th weeks). Only data at baseline are reported. No significant reduction of the mean fraction of JAK2V617F positive clonogenic progenitor from baseline to both
week 12 and week 24 in both groups was observed.

End point type	Secondary

End point timeframe:

At week 12 and at week 24

End point values	Group A - Safety/ITT	Group B - Safety/ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	22		
Units: number of subject				
Heterozygous	6	5		
Homozygous	16	16		
Not done	0	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
AE were recorded at weeks 1 ,3, 6, 9, 12, 16, 20 or end of treatment visit (week 24 or 7 days after last drug intake)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups	
Reporting group title	Group B - 50 mg bid - Safety/ITT
Reporting group description:	
Safety/Intention-to-treat (ITT) population included all randomized subjects who received at least one dose of study medication.	
Reporting group title	Group A - 50 mg o.d. - Safety/ITT
Reporting group description:	
Safety/Intention-to-treat (ITT) population included all randomized subjects who received at least one dose of study medication.	

Serious adverse events	Group B - 50 mg bid - Safety/ITT	Group A - 50 mg o.d. - Safety/ITT	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 22 (4.55%)	2 / 22 (9.09%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Surgical and medical procedures			
Appendicectomy			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Pregnancy of partner			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Embolism			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
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: 4 %

Non-serious adverse events	Group B - 50 mg bid - Safety/ITT	Group A - 50 mg o.d. - Safety/ITT	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 22 (95.45%)	21 / 22 (95.45%)	
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	2 / 22 (9.09%)	0 / 22 (0.00%)	
occurrences (all)	2	0	
Phlebitis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Thrombophlebitis superficial			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	2	
Surgical and medical procedures			
Curetting of chalazion			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 22 (9.09%)	2 / 22 (9.09%)	
occurrences (all)	2	2	
Fatigue			
subjects affected / exposed	1 / 22 (4.55%)	2 / 22 (9.09%)	
occurrences (all)	1	2	
Oedema			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	

Pyrexia			
subjects affected / exposed	1 / 22 (4.55%)	2 / 22 (9.09%)	
occurrences (all)	1	3	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 22 (4.55%)	1 / 22 (4.55%)	
occurrences (all)	1	1	
Dyspnoea			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Epistaxis			
subjects affected / exposed	1 / 22 (4.55%)	1 / 22 (4.55%)	
occurrences (all)	1	1	
Oropharyngeal pain			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Panic attack			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 22 (4.55%)	1 / 22 (4.55%)	
occurrences (all)	1	2	
BBlood creatine phosphokinase increased			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Blood creatinine increased			

subjects affected / exposed	2 / 22 (9.09%)	3 / 22 (13.64%)	
occurrences (all)	6	3	
Blood magnesium increased			
subjects affected / exposed	0 / 22 (0.00%)	2 / 22 (9.09%)	
occurrences (all)	0	2	
Blood triglycerides increased			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	4	0	
Blood urea increased			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Electrocardiogram QT prolonged			
subjects affected / exposed	2 / 22 (9.09%)	0 / 22 (0.00%)	
occurrences (all)	2	0	
Platelet count increased			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
White blood cell count increased			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Injury			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Atrial fibrillation			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Tachycardia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Nervous system disorders			

Dizziness			
subjects affected / exposed	0 / 22 (0.00%)	2 / 22 (9.09%)	
occurrences (all)	0	2	
Headache			
subjects affected / exposed	1 / 22 (4.55%)	2 / 22 (9.09%)	
occurrences (all)	1	2	
Paraesthesia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 22 (9.09%)	1 / 22 (4.55%)	
occurrences (all)	3	1	
Leukopenia			
subjects affected / exposed	2 / 22 (9.09%)	0 / 22 (0.00%)	
occurrences (all)	3	0	
Lymphadenitis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Lymphopenia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	3	0	
Thrombocytopenia			
subjects affected / exposed	7 / 22 (31.82%)	5 / 22 (22.73%)	
occurrences (all)	8	5	
Thrombocytosis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 22 (4.55%)	3 / 22 (13.64%)	
occurrences (all)	1	3	
Abdominal pain upper			
subjects affected / exposed	3 / 22 (13.64%)	2 / 22 (9.09%)	
occurrences (all)	3	2	
Constipation			

subjects affected / exposed	1 / 22 (4.55%)	2 / 22 (9.09%)	
occurrences (all)	1	2	
Diarrhoea			
subjects affected / exposed	7 / 22 (31.82%)	10 / 22 (45.45%)	
occurrences (all)	10	12	
Dyspepsia			
subjects affected / exposed	2 / 22 (9.09%)	0 / 22 (0.00%)	
occurrences (all)	2	0	
Gastritis			
subjects affected / exposed	1 / 22 (4.55%)	1 / 22 (4.55%)	
occurrences (all)	1	1	
Haematochezia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	0 / 22 (0.00%)	3 / 22 (13.64%)	
occurrences (all)	0	3	
Stomatitis			
subjects affected / exposed	1 / 22 (4.55%)	2 / 22 (9.09%)	
occurrences (all)	1	3	
Tongue haemorrhage			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	1 / 22 (4.55%)	1 / 22 (4.55%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Eczema			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	

Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Renal colic			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Back pain			
subjects affected / exposed	2 / 22 (9.09%)	0 / 22 (0.00%)	
occurrences (all)	2	0	
Myalgia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Infections and infestations			
Genitourinary tract infection			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	2	0	
Influenza			
subjects affected / exposed	1 / 22 (4.55%)	3 / 22 (13.64%)	
occurrences (all)	1	3	
Pharyngitis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Rhinitis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Tooth abscess			

subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Urogenital infection fungal			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 22 (4.55%)	1 / 22 (4.55%)	
occurrences (all)	1	1	
Hyperkalaemia			
subjects affected / exposed	1 / 22 (4.55%)	2 / 22 (9.09%)	
occurrences (all)	1	3	
Hyperuricaemia			
subjects affected / exposed	1 / 22 (4.55%)	2 / 22 (9.09%)	
occurrences (all)	2	3	
Hypokalaemia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 September 2009	The key features of the present amendment are: a) the variation of one exclusion criteria, b) the collection of a whole blood sample both at Baseline and at the middle of the study (at Week 12), c) the increase of study Centers number.

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.

No limitations and caveats are applicable to this summary of results.

Notes: