



## 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        | <ul style="list-style-type: none"><li>• Correction of full data set</li></ul> 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 Laboratori 54 , Milano, Italy, 20092  |
| Public contact               | Clinical Trial Transparency Manager, Italfarmaco S.p.A.,<br>Italfarmaco S.p.A., +39 02 66041503, info@italfarmaco.com |
| Scientific contact           | Clinical Trial Transparency Manager, Italfarmaco S.p.A.,<br>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:

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**Results analysis stage**

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|  |              |
|--|--------------|
| 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:

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**General information about the trial**

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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:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |           |
|--------------------------------------|-----------|
| Country: Number of subjects enrolled | Italy: 45 |
| Worldwide total number of subjects   | 45        |
| EEA total number of subjects         | 45        |

Notes:

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**Subjects enrolled per age group**

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|   |    |
|---|----|
| 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                |
| <b>Arm title</b>             | 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.

|                  |                     |
|------------------|---------------------|
| <b>Arm title</b> | 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.

| <b>Number of subjects in period 1</b> | 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<br>Units: Subjects    |                    |                     |       |
| Adults (18-64 years)                  | 10                 | 11                  | 21    |
| From 65-84 years                      | 13                 | 11                  | 24    |
| Gender categorical<br>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<br>Units: Subjects    |                      |                      |  |
| Adults (18-64 years)                  | 9                    | 11                   |  |
| From 65-84 years                      | 13                   | 11                   |  |
| Gender categorical<br>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:<br>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:<br>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:<br>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:<br>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 <sup>[1]</sup> |
| End point description:<br>The number and rate of patients with overall (complete or partial) response at week 12 were assessed.<br>· Complete response:<br>1. HCT < 45% without phlebotomy, and<br>2. platelets ≤ 400 x10 <sup>9</sup> /L, and<br>3. WBC ≤ 10 x 10 <sup>9</sup> /L, and<br>4. no splenomegaly, and<br>5. no disease related systemic symptoms (microvascular disturbances, pruritus, headache);<br>· Partial response:<br>1. HCT < 45% without phlebotomy, or<br>2. fulfilment of at least 3 of the other above mentioned criteria;<br>· No response: any response that did not satisfy the criteria set for partial response. |   |
| End point type   | Primary   |
| End point timeframe:<br>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.  $\theta = 0.20$  as the smallest response rate;
3.  $\theta = 0.40$  as the best dose response rate;
4. a probability greater than 90% of correctly selecting the best dose

| 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  $\leq 400 \times 10^9/L$ , and
3. WBC  $\leq 10 \times 10^9/L$ , 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

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

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|                 |   |
|-----------------|---|
| 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.

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| 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)          |  |  |

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Reduction of the fraction of JAK2V617F positive clonogenic progenitor**

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|                 |   |
|-----------------|---|
| 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

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| <b>End point values</b>     | Group A -<br>Safety/ITT | Group B -<br>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

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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<br>- Safety/ITT | Group A - 50 mg<br>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 %

| <b>Non-serious adverse events</b>                     | Group B - 50 mg bid<br>- Safety/ITT | Group A - 50 mg<br>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<br>subjects affected / exposed<br>occurrences (all)   | 1 / 22 (4.55%)<br>1  | 2 / 22 (9.09%)<br>3  |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)<br><br>Dyspnoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Epistaxis<br>subjects affected / exposed<br>occurrences (all)<br><br>Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)             | 1 / 22 (4.55%)<br>1<br><br>0 / 22 (0.00%)<br>0<br><br>1 / 22 (4.55%)<br>1<br><br>1 / 22 (4.55%)<br>1 | 1 / 22 (4.55%)<br>1<br><br>1 / 22 (4.55%)<br>1<br><br>1 / 22 (4.55%)<br>1<br><br>0 / 22 (0.00%)<br>0 |  |
| Psychiatric disorders<br>Anxiety<br>subjects affected / exposed<br>occurrences (all)<br><br>Panic attack<br>subjects affected / exposed<br>occurrences (all)  | 1 / 22 (4.55%)<br>1<br><br>1 / 22 (4.55%)<br>1   | 0 / 22 (0.00%)<br>0<br><br>0 / 22 (0.00%)<br>0   |  |
| Investigations<br>Aspartate aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)<br><br>Blood alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all)<br><br>BBlood creatine phosphokinase increased<br>subjects affected / exposed<br>occurrences (all)<br><br>Blood creatinine increased | 0 / 22 (0.00%)<br>0<br><br>1 / 22 (4.55%)<br>1<br><br>0 / 22 (0.00%)<br>0                            | 1 / 22 (4.55%)<br>1<br><br>1 / 22 (4.55%)<br>2<br><br>1 / 22 (4.55%)<br>1                            |  |

|  |                     |                      |  |
|--|---------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 2 / 22 (9.09%)<br>6 | 3 / 22 (13.64%)<br>3 |  |
| Blood magnesium increased<br>subjects affected / exposed<br>occurrences (all)                                | 0 / 22 (0.00%)<br>0 | 2 / 22 (9.09%)<br>2  |  |
| Blood triglycerides increased<br>subjects affected / exposed<br>occurrences (all)                            | 1 / 22 (4.55%)<br>4 | 0 / 22 (0.00%)<br>0  |  |
| Blood urea increased<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 22 (0.00%)<br>0 | 1 / 22 (4.55%)<br>1  |  |
| Electrocardiogram QT prolonged<br>subjects affected / exposed<br>occurrences (all)                           | 2 / 22 (9.09%)<br>2 | 0 / 22 (0.00%)<br>0  |  |
| Platelet count increased<br>subjects affected / exposed<br>occurrences (all)                                 | 0 / 22 (0.00%)<br>0 | 1 / 22 (4.55%)<br>1  |  |
| White blood cell count increased<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 22 (0.00%)<br>0 | 1 / 22 (4.55%)<br>1  |  |
| Injury, poisoning and procedural complications<br>Injury<br>subjects affected / exposed<br>occurrences (all) | 0 / 22 (0.00%)<br>0 | 1 / 22 (4.55%)<br>1  |  |
| Cardiac disorders<br>Arrhythmia<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 22 (0.00%)<br>0 | 1 / 22 (4.55%)<br>1  |  |
| Atrial fibrillation<br>subjects affected / exposed<br>occurrences (all)                                      | 1 / 22 (4.55%)<br>1 | 0 / 22 (0.00%)<br>0  |  |
| Tachycardia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 22 (0.00%)<br>0 | 1 / 22 (4.55%)<br>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:<br>a) the variation of one exclusion criteria,<br>b) the collection of a whole blood sample both at Baseline and at the middle of the study (at Week 12),<br>c) the increase of study Centers number. |

Notes:

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### 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: