



## Clinical trial results:

### An Open-Label, Multi-Center Safety and Tolerability Pilot Combination Study of Clofarabine, Etoposide, Cyclophosphamide, PEG-asparaginase, and Vincristine in Pediatric Patients with Acute Lymphoblastic Leukemia (ALL) in First Relapse

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2015-001173-41 |
| Trial protocol           | Outside EU/EEA |
| Global end of trial date | 26 April 2011  |

#### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 23 May 2016    |
| First version publication date | 05 August 2015 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | CLO08808 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00991133 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Genzyme Corporation  |
| Sponsor organisation address | 500 Kendall Street, Cambridge, MA, United States, 02142                                  |
| Public contact               | Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com |
| Scientific contact           | Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.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? | Yes |

Notes:

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**Results analysis stage**

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|  |               |
|--|---------------|
| Analysis stage                                       | Final         |
| Date of interim/final analysis                       | 26 April 2011 |
| Is this the analysis of the primary completion data? | No            |

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|                                  |               |
|----------------------------------|---------------|
| Global end of trial reached?     | Yes           |
| Global end of trial date         | 26 April 2011 |
| Was the trial ended prematurely? | No            |

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Notes:

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**General information about the trial**

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Main objective of the trial:

The primary objective was to evaluate the safety of 1 cycle of the 5-drug regimen in pediatric subjects with acute lymphoblastic leukemia (ALL) who were in first bone marrow relapse.

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Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency.

Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

The study was conducted by investigators experienced in the treatment of pediatric subjects. The parent(s) or guardian(s) as well as the children were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time. In addition to the consent form for the parent(s)/guardian(s), an assent form in child-appropriate language was provided and explained to the child. Repeated invasive procedures were minimized. The number of blood samples as well as the amount of blood drawn were adjusted according to age and weight. A topical anesthesia may have been used to minimize distress and discomfort.

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Background therapy: -

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Evidence for comparator: -

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|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 08 January 2010 |
| Long term follow-up planned                               | Yes             |
| Long term follow-up rationale                             | Safety          |
| Long term follow-up duration                              | 4 Months        |
| Independent data monitoring committee (IDMC) involvement? | Yes             |

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Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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|                                      |                  |
|--------------------------------------|------------------|
| Country: Number of subjects enrolled | United States: 8 |
| Worldwide total number of subjects   | 8                |
| EEA total number of subjects         | 0                |

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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)                     | 4 |
| Adolescents (12-17 years)                 | 2 |
| Adults (18-64 years)                      | 2 |
| From 65 to 84 years                       | 0 |
| 85 years and over                         | 0 |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 6 centers in United States of America. A total of 8 subjects were screened between 08 January 2010 and 10 November 2010.

### Pre-assignment

Screening details:

All subjects were treated.

### Period 1

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

### Arms

|           |                    |
|-----------|--------------------|
| Arm title | Overall Population |
|-----------|--------------------|

Arm description:

Subjects received 5 drug regimen: clofarabine, etoposide, cyclophosphamide (Days 1-5), PEG-asparaginase (Day 15) and vincristine (Days 15-22) in each 28 day cycle for maximum 2 cycles. Subjects who achieved complete remission (CR) or complete remission with incomplete platelet recovery (CRp) after 1 cycle of study drugs were eligible to receive a second cycle of study drugs upon recovery of peripheral blood counts, and subjects who did not have leukemic progression were eligible to receive a second treatment cycle at the investigator's discretion.

|  |                                       |
|--|---------------------------------------|
| Arm type                               | Experimental                          |
| Investigational medicinal product name | Clofarabine                           |
| Investigational medicinal product code |                                       |
| Other name                             | Clolar                                |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

40 mg/m<sup>2</sup>

|  |                                       |
|--|---------------------------------------|
| Investigational medicinal product name | Etoposide                             |
| Investigational medicinal product code |                                       |
| Other name                             | VP-16                                 |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

100 mg/m<sup>2</sup>

|  |                                  |
|--|----------------------------------|
| Investigational medicinal product name | Cyclophosphamide                 |
| Investigational medicinal product code |                                  |
| Other name                             | Cytosan                          |
| Pharmaceutical forms                   | Powder for solution for infusion |
| Routes of administration               | Intravenous use                  |

Dosage and administration details:

440 mg/m<sup>2</sup>

|  |                        |
|--|------------------------|
| Investigational medicinal product name | PEG-asparaginase       |
| Investigational medicinal product code |                        |
| Other name                             | PEGaspar-aginase       |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intravenous use        |

Dosage and administration details:

2500 IU/m<sup>2</sup>

|  |                        |
|--|------------------------|
| Investigational medicinal product name | Vincristine            |
| Investigational medicinal product code |                        |
| Other name                             | Oncovin                |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intravenous use        |

Dosage and administration details:

1.5 mg/m<sup>2</sup> (maximum dose 2 mg)

| <b>Number of subjects in period 1</b>              | Overall Population |
|--|--------------------|
| Started  | 8                  |
| Completed  | 0                  |
| Not completed                                      | 8                  |
| Consent withdrawn by subject                       | 2                  |
| Sponsor or Investigator decision                   | 2                  |
| Adverse event or treatment toxicity                | 2                  |
| Subject scheduled to receive transplant or therapy | 2                  |

## Baseline characteristics

### Reporting groups

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Overall Population |
|-----------------------|--------------------|

Reporting group description:

Subjects received 5 drug regimen: clofarabine, etoposide, cyclophosphamide (Days 1-5), PEG-asparaginase (Day 15) and vincristine (Days 15-22) in each 28 day cycle for maximum 2 cycles. Subjects who achieved complete remission (CR) or complete remission with incomplete platelet recovery (CRp) after 1 cycle of study drugs were eligible to receive a second cycle of study drugs upon recovery of peripheral blood counts, and subjects who did not have leukemic progression were eligible to receive a second treatment cycle at the investigator's discretion.

| Reporting group values    | Overall Population | Total |  |
|---------------------------|--------------------|-------|--|
| Number of subjects        | 8                  | 8     |  |
| Age categorical           |                    |       |  |
| Units: Subjects           |                    |       |  |
| Children (2-11 years)     | 4                  | 4     |  |
| Adolescents (12-17 years) | 2                  | 2     |  |
| Adults (18-64 years)      | 2                  | 2     |  |
| Gender categorical        |                    |       |  |
| Units: Subjects           |                    |       |  |
| Female                    | 6                  | 6     |  |
| Male                      | 2                  | 2     |  |

## End points

### End points reporting groups

|   |                    |
|---|--------------------|
| Reporting group title   | Overall Population |
| Reporting group description:  |                    |
| Subjects received 5 drug regimen: clofarabine, etoposide, cyclophosphamide (Days 1-5), PEG-asparaginase (Day 15) and vincristine (Days 15-22) in each 28 day cycle for maximum 2 cycles. Subjects who achieved complete remission (CR) or complete remission with incomplete platelet recovery (CRp) after 1 cycle of study drugs were eligible to receive a second cycle of study drugs upon recovery of peripheral blood counts, and subjects who did not have leukemic progression were eligible to receive a second treatment cycle at the investigator's discretion. |                    |

### Primary: Number of Subjects Who Experienced Dose Limiting Toxicity

|   |  |
|---|--|
| End point title   | Number of Subjects Who Experienced Dose Limiting Toxicity <sup>[1]</sup> |
| End point description:  |  |
| All enrolled subjects were analysed.  |  |
| End point type  | Primary  |
| End point timeframe:  |  |
| Cycle 1   |  |
| Notes:  |  |
| [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. |  |
| Justification: No statistical analysis was performed as the analysis was descriptive.   |  |

| End point values            | Overall Population |  |  |  |
|-----------------------------|--------------------|--|--|--|
| Subject group type          | Reporting group    |  |  |  |
| Number of subjects analysed | 8                  |  |  |  |
| Units: subjects             | 4                  |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects with Complete Remission (CR)

|                                      |   |
|--------------------------------------|---|
| End point title                      | Number of Subjects with Complete Remission (CR) |
| End point description:               |   |
| All enrolled subjects were analysed. |   |
| End point type                       | Secondary                                       |
| End point timeframe:                 |   |
| Cycle 1                              |   |

| End point values            | Overall Population |  |  |  |
|-----------------------------|--------------------|--|--|--|
| Subject group type          | Reporting group    |  |  |  |
| Number of subjects analysed | 8                  |  |  |  |
| Units: subjects             | 3                  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Remission and Duration of Remission

|   |   |
|---|---|
| End point title   | Time to Remission and Duration of Remission |
| End point description:  |   |
| Time to remission was defined as time from date of first administration of study drugs until date of first objective documentation of CR. Analysis was performed on subjects who achieved CR. |   |
| End point type  | Secondary                                   |
| End point timeframe:  |   |
| Baseline up to first objective documentation of CR  |   |

| End point values            | Overall Population |  |  |  |
|-----------------------------|--------------------|--|--|--|
| Subject group type          | Reporting group    |  |  |  |
| Number of subjects analysed | 0 <sup>[2]</sup>   |  |  |  |
| Units: weeks                |                    |  |  |  |
| number (not applicable)     |                    |  |  |  |

Notes:

[2] - No summary analyses performed. No efficacy conclusion could be drawn due to small number of subjects

## Statistical analyses

No statistical analyses for this end point

## Secondary: Disease-Free Survival (DFS)

|  |                             |
|--|-----------------------------|
| End point title  | Disease-Free Survival (DFS) |
| End point description:   |                             |
| DFS was defined as time from date of first objective documentation of CR until the earlier of date of objective documentation of disease relapse or date of death due to any cause, regardless of intervening alternative anti-leukemic therapy ( including hematopoietic stem cell transplant). Analysis was performed on subjects who achieved CR. |                             |
| End point type   | Secondary                   |
| End point timeframe:   |                             |
| First objective documentation of CR until the earlier of date of objective documentation of disease relapse or date of death due to any cause  |                             |



| End point values            | Overall Population |  |  |  |
|-----------------------------|--------------------|--|--|--|
| Subject group type          | Reporting group    |  |  |  |
| Number of subjects analysed | 0 <sup>[3]</sup>   |  |  |  |
| Units: weeks                |                    |  |  |  |
| number (not applicable)     |                    |  |  |  |

Notes:

[3] - No summary analyses performed. No efficacy conclusion could be drawn due to small number of subjects

## Statistical analyses

No statistical analyses for this end point

### Secondary: Event-Free Survival (EFS)

|                 |                           |
|-----------------|---------------------------|
| End point title | Event-Free Survival (EFS) |
|-----------------|---------------------------|

End point description:

EFS was defined as time from date of first administration of study drugs until the earliest date of death due to any cause, occurrence of a treatment-related secondary neoplasm, first response assessment confirming relapse (for subjects who achieved CR); or final response assessment that failed to confirm response (CR). All enrolled subjects were analysed

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

End point timeframe:

Baseline up to death due to any cause, treatment-related secondary neoplasm, first response assessment confirming relapse (for subjects who achieved CR); or final response assessment that failed to confirm response, whichever occurred first

| End point values            | Overall Population |  |  |  |
|-----------------------------|--------------------|--|--|--|
| Subject group type          | Reporting group    |  |  |  |
| Number of subjects analysed | 0 <sup>[4]</sup>   |  |  |  |
| Units: weeks                |                    |  |  |  |
| number (not applicable)     |                    |  |  |  |

Notes:

[4] - No summary analyses performed. No efficacy conclusion could be drawn due to small number of subjects

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects who achieved 4-Months EFS

|                 |  |
|-----------------|--|
| End point title | Number of subjects who achieved 4-Months EFS |
|-----------------|--|

End point description:

Four-month events free survival: Duration of EFS was at least 4 months post initial administration of the 5-drug regimen. All enrolled subjects were analysed.

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

End point timeframe:

Baseline up to 4 months

| End point values            | Overall Population |  |  |  |
|-----------------------------|--------------------|--|--|--|
| Subject group type          | Reporting group    |  |  |  |
| Number of subjects analysed | 8                  |  |  |  |
| Units: subjects             | 6                  |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Survival

|  |                  |
|--|------------------|
| End point title  | Overall Survival |
| End point description:<br>Time from date of first administration of study drugs until date of death due to any cause. All enrolled subjects were analysed. |                  |
| End point type   | Secondary        |
| End point timeframe:<br>Baseline up to death due to any cause  |                  |

| End point values            | Overall Population |  |  |  |
|-----------------------------|--------------------|--|--|--|
| Subject group type          | Reporting group    |  |  |  |
| Number of subjects analysed | 0 <sup>[5]</sup>   |  |  |  |
| Units: weeks                |                    |  |  |  |
| number (not applicable)     |                    |  |  |  |

Notes:

[5] - No summary analyses performed. No efficacy conclusion could be drawn due to small number of subjects

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to the final visit (cycle 1) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported adverse events and deaths are treatment-emergent that is AEs that developed/worsened during the 'on treatment period' (from the first dose study drugs up to last dose of study drug).

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 13.1   |

### Reporting groups

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Overall Population |
|-----------------------|--------------------|

Reporting group description:

Subjects received 5 drug regimen: clofarabine, etoposide, cyclophosphamide (Days 1-5), PEG-asparaginase (Day 15) and vincristine (Days 15-22) in each 28 day cycle for maximum 2 cycles. Subjects who achieved complete remission (CR) or complete remission with incomplete platelet recovery (CRp) after 1 cycle of study drugs were eligible to receive a second cycle of study drugs upon recovery of peripheral blood counts, and subjects who did not have leukemic progression were eligible to receive a second treatment cycle at the investigator's discretion.

| Serious adverse events                            | Overall Population |  |  |
|---|--------------------|--|--|
| Total subjects affected by serious adverse events |                    |  |  |
| subjects affected / exposed                       | 4 / 8 (50.00%)     |  |  |
| number of deaths (all causes)                     | 4                  |  |  |
| number of deaths resulting from adverse events    |                    |  |  |
| Investigations                                    |                    |  |  |
| Blood Bilirubin Increased                         |                    |  |  |
| subjects affected / exposed                       | 1 / 8 (12.50%)     |  |  |
| occurrences causally related to treatment / all   | 1 / 1              |  |  |
| deaths causally related to treatment / all        | 0 / 0              |  |  |
| Lipase Increased                                  |                    |  |  |
| subjects affected / exposed                       | 1 / 8 (12.50%)     |  |  |
| occurrences causally related to treatment / all   | 2 / 2              |  |  |
| deaths causally related to treatment / all        | 0 / 0              |  |  |
| Vascular disorders                                |                    |  |  |
| Thrombosis  |                    |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 8 (12.50%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hypotension                                     |                |  |  |
| subjects affected / exposed                     | 1 / 8 (12.50%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Cardiac disorders                               |                |  |  |
| Cardiac Failure Congestive                      |                |  |  |
| subjects affected / exposed                     | 1 / 8 (12.50%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Nervous system disorders                        |                |  |  |
| Leukoencephalopathy                             |                |  |  |
| subjects affected / exposed                     | 1 / 8 (12.50%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Blood and lymphatic system disorders            |                |  |  |
| Bone Marrow Failure                             |                |  |  |
| subjects affected / exposed                     | 2 / 8 (25.00%) |  |  |
| occurrences causally related to treatment / all | 2 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Febrile Neutropenia                             |                |  |  |
| subjects affected / exposed                     | 1 / 8 (12.50%) |  |  |
| occurrences causally related to treatment / all | 2 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Respiratory, thoracic and mediastinal disorders |                |  |  |
| Acute Respiratory Distress Syndrome             |                |  |  |
| subjects affected / exposed                     | 1 / 8 (12.50%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pneumonitis                                     |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 8 (12.50%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| <b>Infections and infestations</b>              |                |  |  |
| Fungal Skin Infection                           |                |  |  |
| subjects affected / exposed                     | 1 / 8 (12.50%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Enterococcal Bacteraemia                        |                |  |  |
| subjects affected / exposed                     | 1 / 8 (12.50%) |  |  |
| occurrences causally related to treatment / all | 2 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pneumonia Respiratory Syncytial Viral           |                |  |  |
| subjects affected / exposed                     | 1 / 8 (12.50%) |  |  |
| occurrences causally related to treatment / all | 2 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pneumonia Fungal                                |                |  |  |
| subjects affected / exposed                     | 1 / 8 (12.50%) |  |  |
| occurrences causally related to treatment / all | 2 / 2          |  |  |
| deaths causally related to treatment / all      | 1 / 1          |  |  |
| <b>Metabolism and nutrition disorders</b>       |                |  |  |
| Hypernatraemia                                  |                |  |  |
| subjects affected / exposed                     | 1 / 8 (12.50%) |  |  |
| occurrences causally related to treatment / all | 2 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

Frequency threshold for reporting non-serious adverse events: 0 %

|   |                    |  |  |
|---|--------------------|--|--|
| <b>Non-serious adverse events</b>                                   | Overall Population |  |  |
| Total subjects affected by non-serious adverse events               |                    |  |  |
| subjects affected / exposed   | 8 / 8 (100.00%)    |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                    |  |  |

|   |                     |  |  |
|---|---------------------|--|--|
| Tumour Pain<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 8 (12.50%)<br>1 |  |  |
| Vascular disorders  |                     |  |  |
| Hypertension<br>subjects affected / exposed<br>occurrences (all)                | 2 / 8 (25.00%)<br>3 |  |  |
| Haematoma<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 8 (12.50%)<br>1 |  |  |
| Thrombosis<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 8 (12.50%)<br>1 |  |  |
| Poor Peripheral Circulation<br>subjects affected / exposed<br>occurrences (all) | 1 / 8 (12.50%)<br>1 |  |  |
| Hypotension<br>subjects affected / exposed<br>occurrences (all)                 | 3 / 8 (37.50%)<br>3 |  |  |
| General disorders and administration<br>site conditions                         |                     |  |  |
| Generalised Oedema<br>subjects affected / exposed<br>occurrences (all)          | 1 / 8 (12.50%)<br>2 |  |  |
| Chills<br>subjects affected / exposed<br>occurrences (all)                      | 2 / 8 (25.00%)<br>3 |  |  |
| Chest Pain<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 8 (12.50%)<br>2 |  |  |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)                     | 4 / 8 (50.00%)<br>5 |  |  |
| Mucosal Inflammation<br>subjects affected / exposed<br>occurrences (all)        | 2 / 8 (25.00%)<br>2 |  |  |
| Pyrexia   |                     |  |  |

|   |  |  |  |
|---|--|--|--|
| subjects affected / exposed<br>occurrences (all)  | 2 / 8 (25.00%)<br>4  |  |  |
| Immune system disorders<br>Drug Hypersensitivity<br>subjects affected / exposed<br>occurrences (all)  | 1 / 8 (12.50%)<br>1  |  |  |
| Reproductive system and breast disorders<br>Ovarian Cyst<br>subjects affected / exposed<br>occurrences (all)<br><br>Vulvovaginal Pain<br>subjects affected / exposed<br>occurrences (all)   | 1 / 8 (12.50%)<br>1<br><br>1 / 8 (12.50%)<br>1   |  |  |
| 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>Haemoptysis<br>subjects affected / exposed<br>occurrences (all)<br><br>Pleural Effusion<br>subjects affected / exposed<br>occurrences (all)<br><br>Wheezing<br>subjects affected / exposed<br>occurrences (all)<br><br>Tachypnoea<br>subjects affected / exposed<br>occurrences (all) | 1 / 8 (12.50%)<br>2<br><br>1 / 8 (12.50%)<br>1<br><br>1 / 8 (12.50%)<br>1<br><br>1 / 8 (12.50%)<br>1<br><br>1 / 8 (12.50%)<br>1<br><br>1 / 8 (12.50%)<br>1 |  |  |
| Psychiatric disorders<br>Agitation<br>subjects affected / exposed<br>occurrences (all)  | 1 / 8 (12.50%)<br>1  |  |  |

|                                      |                |  |  |
|--------------------------------------|----------------|--|--|
| Anxiety                              |                |  |  |
| subjects affected / exposed          | 1 / 8 (12.50%) |  |  |
| occurrences (all)                    | 1              |  |  |
| Confusional State                    |                |  |  |
| subjects affected / exposed          | 1 / 8 (12.50%) |  |  |
| occurrences (all)                    | 1              |  |  |
| Disorientation                       |                |  |  |
| subjects affected / exposed          | 1 / 8 (12.50%) |  |  |
| occurrences (all)                    | 1              |  |  |
| Depression                           |                |  |  |
| subjects affected / exposed          | 1 / 8 (12.50%) |  |  |
| occurrences (all)                    | 1              |  |  |
| Investigations                       |                |  |  |
| Alanine Aminotransferase Increased   |                |  |  |
| subjects affected / exposed          | 2 / 8 (25.00%) |  |  |
| occurrences (all)                    | 3              |  |  |
| Aspartate Aminotransferase Increased |                |  |  |
| subjects affected / exposed          | 2 / 8 (25.00%) |  |  |
| occurrences (all)                    | 2              |  |  |
| Blood Alkaline Phosphatase Increased |                |  |  |
| subjects affected / exposed          | 1 / 8 (12.50%) |  |  |
| occurrences (all)                    | 1              |  |  |
| Blood Creatinine Increased           |                |  |  |
| subjects affected / exposed          | 1 / 8 (12.50%) |  |  |
| occurrences (all)                    | 1              |  |  |
| Blood Bilirubin Increased            |                |  |  |
| subjects affected / exposed          | 1 / 8 (12.50%) |  |  |
| occurrences (all)                    | 1              |  |  |
| Blood Amylase Increased              |                |  |  |
| subjects affected / exposed          | 1 / 8 (12.50%) |  |  |
| occurrences (all)                    | 3              |  |  |
| Blood Triglycerides Increased        |                |  |  |
| subjects affected / exposed          | 2 / 8 (25.00%) |  |  |
| occurrences (all)                    | 2              |  |  |
| Enterococcus Test Positive           |                |  |  |



|  |                |  |  |
|--|----------------|--|--|
| subjects affected / exposed                    | 1 / 8 (12.50%) |  |  |
| occurrences (all)                              | 1              |  |  |
| Gallop Rhythm Present                          |                |  |  |
| subjects affected / exposed                    | 1 / 8 (12.50%) |  |  |
| occurrences (all)                              | 1              |  |  |
| Mycobacterium Test Positive                    |                |  |  |
| subjects affected / exposed                    | 1 / 8 (12.50%) |  |  |
| occurrences (all)                              | 1              |  |  |
| Specific Gravity Urine Abnormal                |                |  |  |
| subjects affected / exposed                    | 1 / 8 (12.50%) |  |  |
| occurrences (all)                              | 1              |  |  |
| Lipase Increased                               |                |  |  |
| subjects affected / exposed                    | 2 / 8 (25.00%) |  |  |
| occurrences (all)                              | 3              |  |  |
| Weight Increased                               |                |  |  |
| subjects affected / exposed                    | 2 / 8 (25.00%) |  |  |
| occurrences (all)                              | 2              |  |  |
| Injury, poisoning and procedural complications |                |  |  |
| Allergic Transfusion Reaction                  |                |  |  |
| subjects affected / exposed                    | 1 / 8 (12.50%) |  |  |
| occurrences (all)                              | 1              |  |  |
| Transfusion Reaction                           |                |  |  |
| subjects affected / exposed                    | 2 / 8 (25.00%) |  |  |
| occurrences (all)                              | 2              |  |  |
| Cardiac disorders                              |                |  |  |
| Tachycardia                                    |                |  |  |
| subjects affected / exposed                    | 2 / 8 (25.00%) |  |  |
| occurrences (all)                              | 2              |  |  |
| Pericardial Haemorrhage                        |                |  |  |
| subjects affected / exposed                    | 1 / 8 (12.50%) |  |  |
| occurrences (all)                              | 1              |  |  |
| Nervous system disorders                       |                |  |  |
| Headache                                       |                |  |  |
| subjects affected / exposed                    | 4 / 8 (50.00%) |  |  |
| occurrences (all)                              | 4              |  |  |
| Dizziness                                      |                |  |  |

|                                      |                |  |  |
|--------------------------------------|----------------|--|--|
| subjects affected / exposed          | 1 / 8 (12.50%) |  |  |
| occurrences (all)                    | 1              |  |  |
| Tremor                               |                |  |  |
| subjects affected / exposed          | 1 / 8 (12.50%) |  |  |
| occurrences (all)                    | 1              |  |  |
| Neuropathy Peripheral                |                |  |  |
| subjects affected / exposed          | 1 / 8 (12.50%) |  |  |
| occurrences (all)                    | 1              |  |  |
| Blood and lymphatic system disorders |                |  |  |
| Anaemia                              |                |  |  |
| subjects affected / exposed          | 7 / 8 (87.50%) |  |  |
| occurrences (all)                    | 17             |  |  |
| Leukopenia                           |                |  |  |
| subjects affected / exposed          | 3 / 8 (37.50%) |  |  |
| occurrences (all)                    | 4              |  |  |
| Febrile Neutropenia                  |                |  |  |
| subjects affected / exposed          | 5 / 8 (62.50%) |  |  |
| occurrences (all)                    | 5              |  |  |
| Lymphopenia                          |                |  |  |
| subjects affected / exposed          | 2 / 8 (25.00%) |  |  |
| occurrences (all)                    | 2              |  |  |
| Pancytopenia                         |                |  |  |
| subjects affected / exposed          | 1 / 8 (12.50%) |  |  |
| occurrences (all)                    | 1              |  |  |
| Neutropenia                          |                |  |  |
| subjects affected / exposed          | 3 / 8 (37.50%) |  |  |
| occurrences (all)                    | 4              |  |  |
| Splenic Necrosis                     |                |  |  |
| subjects affected / exposed          | 1 / 8 (12.50%) |  |  |
| occurrences (all)                    | 1              |  |  |
| Thrombocytopenia                     |                |  |  |
| subjects affected / exposed          | 6 / 8 (75.00%) |  |  |
| occurrences (all)                    | 9              |  |  |
| Ear and labyrinth disorders          |                |  |  |
| Ear Pain                             |                |  |  |

|                              |                |  |  |
|------------------------------|----------------|--|--|
| subjects affected / exposed  | 1 / 8 (12.50%) |  |  |
| occurrences (all)            | 1              |  |  |
| Eye disorders                |                |  |  |
| Ocular Hyperaemia            |                |  |  |
| subjects affected / exposed  | 1 / 8 (12.50%) |  |  |
| occurrences (all)            | 1              |  |  |
| Diplopia                     |                |  |  |
| subjects affected / exposed  | 1 / 8 (12.50%) |  |  |
| occurrences (all)            | 1              |  |  |
| Vitreous Floaters            |                |  |  |
| subjects affected / exposed  | 1 / 8 (12.50%) |  |  |
| occurrences (all)            | 1              |  |  |
| Photophobia                  |                |  |  |
| subjects affected / exposed  | 1 / 8 (12.50%) |  |  |
| occurrences (all)            | 1              |  |  |
| Gastrointestinal disorders   |                |  |  |
| Abdominal Pain               |                |  |  |
| subjects affected / exposed  | 6 / 8 (75.00%) |  |  |
| occurrences (all)            | 7              |  |  |
| Chapped Lips                 |                |  |  |
| subjects affected / exposed  | 1 / 8 (12.50%) |  |  |
| occurrences (all)            | 1              |  |  |
| Anal Erosion                 |                |  |  |
| subjects affected / exposed  | 1 / 8 (12.50%) |  |  |
| occurrences (all)            | 1              |  |  |
| Abdominal Pain Upper         |                |  |  |
| subjects affected / exposed  | 1 / 8 (12.50%) |  |  |
| occurrences (all)            | 1              |  |  |
| Constipation                 |                |  |  |
| subjects affected / exposed  | 4 / 8 (50.00%) |  |  |
| occurrences (all)            | 4              |  |  |
| Diarrhoea                    |                |  |  |
| subjects affected / exposed  | 5 / 8 (62.50%) |  |  |
| occurrences (all)            | 5              |  |  |
| Gastrointestinal Haemorrhage |                |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| subjects affected / exposed            | 1 / 8 (12.50%)  |  |  |
| occurrences (all)                      | 1               |  |  |
| Nausea                                 |                 |  |  |
| subjects affected / exposed            | 8 / 8 (100.00%) |  |  |
| occurrences (all)                      | 10              |  |  |
| Pancreatitis                           |                 |  |  |
| subjects affected / exposed            | 1 / 8 (12.50%)  |  |  |
| occurrences (all)                      | 1               |  |  |
| Gingival Bleeding                      |                 |  |  |
| subjects affected / exposed            | 1 / 8 (12.50%)  |  |  |
| occurrences (all)                      | 1               |  |  |
| Rectal Fissure                         |                 |  |  |
| subjects affected / exposed            | 1 / 8 (12.50%)  |  |  |
| occurrences (all)                      | 1               |  |  |
| Proctalgia                             |                 |  |  |
| subjects affected / exposed            | 1 / 8 (12.50%)  |  |  |
| occurrences (all)                      | 1               |  |  |
| Vomiting                               |                 |  |  |
| subjects affected / exposed            | 7 / 8 (87.50%)  |  |  |
| occurrences (all)                      | 10              |  |  |
| Hepatobiliary disorders                |                 |  |  |
| Cholelithiasis                         |                 |  |  |
| subjects affected / exposed            | 2 / 8 (25.00%)  |  |  |
| occurrences (all)                      | 2               |  |  |
| Hyperbilirubinaemia                    |                 |  |  |
| subjects affected / exposed            | 1 / 8 (12.50%)  |  |  |
| occurrences (all)                      | 3               |  |  |
| Hepatomegaly                           |                 |  |  |
| subjects affected / exposed            | 1 / 8 (12.50%)  |  |  |
| occurrences (all)                      | 1               |  |  |
| Skin and subcutaneous tissue disorders |                 |  |  |
| Drug Eruption                          |                 |  |  |
| subjects affected / exposed            | 1 / 8 (12.50%)  |  |  |
| occurrences (all)                      | 1               |  |  |
| Alopecia                               |                 |  |  |

|                             |                |  |  |
|-----------------------------|----------------|--|--|
| subjects affected / exposed | 3 / 8 (37.50%) |  |  |
| occurrences (all)           | 3              |  |  |
| Blister                     |                |  |  |
| subjects affected / exposed | 1 / 8 (12.50%) |  |  |
| occurrences (all)           | 7              |  |  |
| Palmar Erythema             |                |  |  |
| subjects affected / exposed | 1 / 8 (12.50%) |  |  |
| occurrences (all)           | 1              |  |  |
| Dry Skin                    |                |  |  |
| subjects affected / exposed | 1 / 8 (12.50%) |  |  |
| occurrences (all)           | 1              |  |  |
| Night Sweats                |                |  |  |
| subjects affected / exposed | 1 / 8 (12.50%) |  |  |
| occurrences (all)           | 1              |  |  |
| Pruritus                    |                |  |  |
| subjects affected / exposed | 2 / 8 (25.00%) |  |  |
| occurrences (all)           | 2              |  |  |
| Pruritus Generalised        |                |  |  |
| subjects affected / exposed | 2 / 8 (25.00%) |  |  |
| occurrences (all)           | 2              |  |  |
| Rash Generalised            |                |  |  |
| subjects affected / exposed | 1 / 8 (12.50%) |  |  |
| occurrences (all)           | 2              |  |  |
| Purpura                     |                |  |  |
| subjects affected / exposed | 1 / 8 (12.50%) |  |  |
| occurrences (all)           | 1              |  |  |
| Rash                        |                |  |  |
| subjects affected / exposed | 4 / 8 (50.00%) |  |  |
| occurrences (all)           | 6              |  |  |
| Skin Exfoliation            |                |  |  |
| subjects affected / exposed | 1 / 8 (12.50%) |  |  |
| occurrences (all)           | 1              |  |  |
| Renal and urinary disorders |                |  |  |
| Glycosuria                  |                |  |  |
| subjects affected / exposed | 1 / 8 (12.50%) |  |  |
| occurrences (all)           | 1              |  |  |

|  |                     |  |  |
|--|---------------------|--|--|
| Haematuria<br>subjects affected / exposed<br>occurrences (all)           | 2 / 8 (25.00%)<br>2 |  |  |
| Dysuria<br>subjects affected / exposed<br>occurrences (all)              | 1 / 8 (12.50%)<br>1 |  |  |
| Haemoglobinuria<br>subjects affected / exposed<br>occurrences (all)      | 1 / 8 (12.50%)<br>1 |  |  |
| Pollakiuria<br>subjects affected / exposed<br>occurrences (all)          | 1 / 8 (12.50%)<br>1 |  |  |
| Proteinuria<br>subjects affected / exposed<br>occurrences (all)          | 3 / 8 (37.50%)<br>4 |  |  |
| Musculoskeletal and connective tissue disorders                          |                     |  |  |
| Back Pain<br>subjects affected / exposed<br>occurrences (all)            | 3 / 8 (37.50%)<br>3 |  |  |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)           | 1 / 8 (12.50%)<br>1 |  |  |
| Musculoskeletal Pain<br>subjects affected / exposed<br>occurrences (all) | 3 / 8 (37.50%)<br>3 |  |  |
| Pain In Extremity<br>subjects affected / exposed<br>occurrences (all)    | 2 / 8 (25.00%)<br>2 |  |  |
| Infections and infestations  |                     |  |  |
| Bk Virus Infection<br>subjects affected / exposed<br>occurrences (all)   | 1 / 8 (12.50%)<br>1 |  |  |
| Endocarditis<br>subjects affected / exposed<br>occurrences (all)         | 1 / 8 (12.50%)<br>1 |  |  |
| Cystitis   |                     |  |  |

|                                    |                |  |  |
|------------------------------------|----------------|--|--|
| subjects affected / exposed        | 2 / 8 (25.00%) |  |  |
| occurrences (all)                  | 2              |  |  |
| Sinusitis                          |                |  |  |
| subjects affected / exposed        | 1 / 8 (12.50%) |  |  |
| occurrences (all)                  | 1              |  |  |
| Psoas Abscess                      |                |  |  |
| subjects affected / exposed        | 1 / 8 (12.50%) |  |  |
| occurrences (all)                  | 1              |  |  |
| Upper Respiratory Tract Infection  |                |  |  |
| subjects affected / exposed        | 1 / 8 (12.50%) |  |  |
| occurrences (all)                  | 1              |  |  |
| Urinary Tract Infection Bacterial  |                |  |  |
| subjects affected / exposed        | 1 / 8 (12.50%) |  |  |
| occurrences (all)                  | 1              |  |  |
| Metabolism and nutrition disorders |                |  |  |
| Hyperamylasaemia                   |                |  |  |
| subjects affected / exposed        | 1 / 8 (12.50%) |  |  |
| occurrences (all)                  | 2              |  |  |
| Decreased Appetite                 |                |  |  |
| subjects affected / exposed        | 7 / 8 (87.50%) |  |  |
| occurrences (all)                  | 9              |  |  |
| Hyperuricaemia                     |                |  |  |
| subjects affected / exposed        | 2 / 8 (25.00%) |  |  |
| occurrences (all)                  | 2              |  |  |
| Hyperglycaemia                     |                |  |  |
| subjects affected / exposed        | 3 / 8 (37.50%) |  |  |
| occurrences (all)                  | 5              |  |  |
| Hypocalcaemia                      |                |  |  |
| subjects affected / exposed        | 1 / 8 (12.50%) |  |  |
| occurrences (all)                  | 1              |  |  |
| Hypoalbuminaemia                   |                |  |  |
| subjects affected / exposed        | 2 / 8 (25.00%) |  |  |
| occurrences (all)                  | 5              |  |  |
| Hypomagnesaemia                    |                |  |  |
| subjects affected / exposed        | 2 / 8 (25.00%) |  |  |
| occurrences (all)                  | 2              |  |  |

|                             |                |  |  |
|-----------------------------|----------------|--|--|
| Hypokalaemia                |                |  |  |
| subjects affected / exposed | 4 / 8 (50.00%) |  |  |
| occurrences (all)           | 5              |  |  |
| Hyponatraemia               |                |  |  |
| subjects affected / exposed | 1 / 8 (12.50%) |  |  |
| occurrences (all)           | 1              |  |  |
| Hypophosphataemia           |                |  |  |
| subjects affected / exposed | 2 / 8 (25.00%) |  |  |
| occurrences (all)           | 2              |  |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date         | Amendment  |
|--------------|--|
| 23 July 2010 | Seven subjects were enrolled under the original protocol, and 1 subject was enrolled under the amended protocol. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported