



## Clinical trial results:

### **TRUSTS: A phase IIb/III multicenter study comparing the efficacy of TRabectedin administered as a 3-hour or 24-hour infusion to doxorubicin in patients with advanced or metastatic Untreated Soft Tissue Sarcoma**

#### **Summary**

|                          |                               |
|--------------------------|-------------------------------|
| EudraCT number           | 2009-014889-26                |
| Trial protocol           | GB DE BE HU DK AT NL SK ES PL |
| Global end of trial date | 16 April 2016                 |

#### **Results information**

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 04 May 2017  |
| First version publication date | 04 May 2017  |

#### **Trial information**

##### **Trial identification**

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | EORTC 62091 |
|-----------------------|-------------|

##### **Additional study identifiers**

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01189253 |
| WHO universal trial number (UTN)   | -           |

Notes:

##### **Sponsors**

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | European Organisation for Research and Treatment of Cancer   |
| Sponsor organisation address | Avenue E. Mounier 83/11, Brussels, Belgium, 1200   |
| Public contact               | Project, Budget and Regulatory Dept, European Organisation for Research and Treatment of Cancer, +32 27441062, regulatory@eortc.be |
| Scientific contact           | Project, Budget and Regulatory Dept, European Organisation for Research and Treatment of Cancer, +32 27441062, regulatory@eortc.be |

Notes:

##### **Paediatric regulatory details**

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 22 December 2015 |
| Is this the analysis of the primary completion data? | No               |

|                                  |               |
|----------------------------------|---------------|
| Global end of trial reached?     | Yes           |
| Global end of trial date         | 16 April 2016 |
| Was the trial ended prematurely? | No            |

Notes:

## General information about the trial

Main objective of the trial:

The principal objective of the trial is to evaluate whether trabectedin given as 1st line chemotherapy for advanced / metastatic soft tissue sarcoma prolongs progression free survival, as compared to doxorubicin.

Protection of trial subjects:

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (available on the World Medical Association web site (<http://www.wma.net>)) and/or the laws and regulations of the country, whichever provides the greatest protection of the patient.

The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice. The protocol must be approved by the competent ethics committee(s) as required by the applicable national legislation.

Background therapy:

All patients received dexamethasone or an equivalent 30 minutes before administration of trabectedin.

Evidence for comparator:

Doxorubicin is the most active drug for the systemic treatment of STS. Randomized studies have shown that combination chemotherapy can sometimes provide higher response rates than single agent doxorubicin. However, even if present, this higher objective response rate did not translate into improved overall survival. The EORTC STBSG has already evaluated several new drugs given as second line chemotherapy, but the vast majority of these were found to be inactive, with the exception of agents such as trabectedin or imatinib with activity in defined subtypes of STS.

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 06 June 2011 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | Yes          |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Netherlands: 24   |
| Country: Number of subjects enrolled | Spain: 5          |
| Country: Number of subjects enrolled | United Kingdom: 1 |
| Country: Number of subjects enrolled | Austria: 3        |
| Country: Number of subjects enrolled | Belgium: 2        |
| Country: Number of subjects enrolled | Denmark: 1        |
| Country: Number of subjects enrolled | France: 66        |
| Country: Number of subjects enrolled | Germany: 10       |
| Country: Number of subjects enrolled | United States: 21 |
| Worldwide total number of subjects   | 133               |
| EEA total number of subjects         | 112               |

Notes:

| <b>Subjects enrolled per age group</b>    |    |
|---|----|
| 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)                      | 79 |
| From 65 to 84 years                       | 54 |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

A total of 133 (112 by EORTC STBSG and 21 by SARC) patients were registered by 28 institutions (9 countries) between June 2011 and August 2012.

### Pre-assignment

Screening details:

The registration/randomization is one step process.

### Period 1

|                              |                         |
|------------------------------|-------------------------|
| Period 1 title               | baseline                |
| Is this the baseline period? | Yes                     |
| Allocation method            | Randomised - controlled |
| Blinding used                | Not blinded             |

### Arms

|                              |           |
|------------------------------|-----------|
| Are arms mutually exclusive? | Yes       |
| <b>Arm title</b>             | Trab_3hrs |

Arm description:

Trabectedin 3 hrs IV

|  |  |
|--|--|
| Arm type                               | Experimental                               |
| Investigational medicinal product name | Trabectedin                                |
| Investigational medicinal product code | GFI-17027907-AAA-PB-003                    |
| Other name                             | YONDELIS                                   |
| Pharmaceutical forms                   | Powder for solution for injection/infusion |
| Routes of administration               | Intravenous use                            |

Dosage and administration details:

Trabectedin will be administered on day 1 every 3 weeks at the dose of 1.3 mg/m<sup>2</sup> body surface area, administered as an intravenous infusion over 3 hours.

|                  |            |
|------------------|------------|
| <b>Arm title</b> | Trab_24hrs |
|------------------|------------|

Arm description:

Trabectedin 24 hrs IV

|  |  |
|--|--|
| Arm type                               | Experimental                               |
| Investigational medicinal product name | Trabectedin                                |
| Investigational medicinal product code | GFI-17027907-AAA-PB-003                    |
| Other name                             | YONDELIS                                   |
| Pharmaceutical forms                   | Powder for solution for injection/infusion |
| Routes of administration               | Intravenous use                            |

Dosage and administration details:

Trabectedin will be administered on day 1 every 3 weeks at the dose of 1.5 mg/m<sup>2</sup> body surface area, administered as an intravenous infusion over 24 hours.

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

Arm description:

Doxorubicin

|  |   |
|--|---|
| Arm type                               | Active comparator                                 |
| Investigational medicinal product name | Doxorubicin                                       |
| Investigational medicinal product code |   |
| Other name                             |   |
| Pharmaceutical forms                   | Concentrate and solvent for solution for infusion |
| Routes of administration               | Intravenous drip use                              |

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**Dosage and administration details:**

Doxorubicin will be administered on day 1 every 3 weeks at the dose of 75 mg/m<sup>2</sup> by IV according to institution guidelines. Doxorubicin will be administered for a maximum of 6 cycles (1 cycle=3weeks).

| <b>Number of subjects in period 1</b> | Trab_3hrs | Trab_24hrs | Doxo |
|---------------------------------------|-----------|------------|------|
| Started                               | 47        | 43         | 43   |
| Completed                             | 47        | 43         | 43   |

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**Period 2**

|                              |                         |
|------------------------------|-------------------------|
| Period 2 title               | On-study                |
| Is this the baseline period? | No                      |
| Allocation method            | Randomised - controlled |
| Blinding used                | Not blinded             |

**Arms**

|                              |           |
|------------------------------|-----------|
| Are arms mutually exclusive? | Yes       |
| <b>Arm title</b>             | Trab_3hrs |

## Arm description:

Trabectedin 3 hrs IV

|  |  |
|--|--|
| Arm type                               | Experimental                               |
| Investigational medicinal product name | Trabectedin                                |
| Investigational medicinal product code | GFI-17027907-AAA-PB-003                    |
| Other name                             | YONDELIS                                   |
| Pharmaceutical forms                   | Powder for solution for injection/infusion |
| Routes of administration               | Intravenous use                            |

## Dosage and administration details:

Trabectedin will be administered on day 1 every 3 weeks at the dose of 1.3 mg/m<sup>2</sup> body surface area, administered as an intravenous infusion over 3 hours.

|                  |            |
|------------------|------------|
| <b>Arm title</b> | Trab_24hrs |
|------------------|------------|

## Arm description:

Trabectedin 24 hrs IV

|  |  |
|--|--|
| Arm type                               | Experimental                               |
| Investigational medicinal product name | Trabectedin                                |
| Investigational medicinal product code | GFI-17027907-AAA-PB-003                    |
| Other name                             | YONDELIS                                   |
| Pharmaceutical forms                   | Powder for solution for injection/infusion |
| Routes of administration               | Intravenous use                            |

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**Dosage and administration details:**

Trabectedin will be administered on day 1 every 3 weeks at the dose of 1.5 mg/m<sup>2</sup> body surface area, administered as an intravenous infusion over 24 hours.

|  |   |
|--|---|
| <b>Arm title</b>                       | Doxo  |
| Arm description:                       |   |
| Doxorubicin                            |   |
| Arm type                               | Active comparator                                 |
| Investigational medicinal product name | Doxorubicin                                       |
| Investigational medicinal product code |   |
| Other name                             |   |
| Pharmaceutical forms                   | Concentrate and solvent for solution for infusion |
| Routes of administration               | Intravenous drip use                              |

**Dosage and administration details:**

Doxorubicin will be administered on day 1 every 3 weeks at the dose of 75 mg/m<sup>2</sup> by IV according to institution guidelines. Doxorubicin will be administered for a maximum of 6 cycles (1 cycle=3weeks).

| <b>Number of subjects in period 2</b> | Trab_3hrs | Trab_24hrs | Doxo |
|---------------------------------------|-----------|------------|------|
| Started                               | 47        | 43         | 43   |
| Completed                             | 0         | 0          | 21   |
| Not completed                         | 47        | 43         | 22   |
| Physician decision                    | 1         | 2          | 1    |
| Consent withdrawn by subject          | 1         | 2          | 1    |
| Adverse event, non-fatal              | 7         | 8          | 1    |
| Unknown                               | 1         | -          | 1    |
| Patient still on treatment            | -         | 1          | -    |
| Death not due to toxicity             | 2         | 1          | 1    |
| Protocol deviation                    | 1         | 2          | 3    |
| Lack of efficacy                      | 34        | 27         | 14   |

## Baseline characteristics

### Reporting groups

|   |            |
|---|------------|
| Reporting group title                                 | Trab_3hrs  |
| Reporting group description:<br>Trabectedin 3 hrs IV  |            |
| Reporting group title                                 | Trab_24hrs |
| Reporting group description:<br>Trabectedin 24 hrs IV |            |
| Reporting group title                                 | Doxo       |
| Reporting group description:<br>Doxorubicin           |            |

| Reporting group values                   | Trab_3hrs | Trab_24hrs | Doxo     |
|--|-----------|------------|----------|
| Number of subjects                       | 47        | 43         | 43       |
| Age categorical                          |           |            |          |
| Age at randomization (years)             |           |            |          |
| Units: Subjects                          |           |            |          |
| 60 years and over                        | 24        | 22         | 23       |
| From 18-59 years                         | 23        | 21         | 20       |
| Age continuous                           |           |            |          |
| Age at randomization                     |           |            |          |
| Units: years                             |           |            |          |
| median                                   | 60        | 60         | 60       |
| full range (min-max)                     | 34 to 84  | 23 to 78   | 24 to 77 |
| Gender categorical                       |           |            |          |
| Units: Subjects                          |           |            |          |
| Female                                   | 29        | 23         | 25       |
| Male                                     | 18        | 20         | 18       |
| WHO Performance status                   |           |            |          |
| WHO Performance status                   |           |            |          |
| Units: Subjects                          |           |            |          |
| 0=Fully active                           | 25        | 21         | 26       |
| 1= Able to carry out work of a light nat | 22        | 22         | 17       |
| Other medical conditions                 |           |            |          |
| Other medical conditions at trial entry  |           |            |          |
| Units: Subjects                          |           |            |          |
| Yes                                      | 37        | 36         | 29       |
| No                                       | 10        | 7          | 14       |
| Site of primary tumor                    |           |            |          |
| Units: Subjects                          |           |            |          |
| Head and Neck                            | 1         | 0          | 0        |
| Trunk                                    | 1         | 5          | 0        |
| Thoracic                                 | 7         | 3          | 4        |
| Retro-intra abdominal                    | 7         | 10         | 12       |
| Lower extremity                          | 10        | 14         | 9        |
| Upper extremity                          | 5         | 3          | 1        |
| Visceral GU                              | 2         | 1          | 2        |

|   |    |    |    |
|---|----|----|----|
| Visceral GI                             | 1  | 2  | 3  |
| Visceral Gynecological                  | 8  | 4  | 8  |
| Visceral Breast                         | 0  | 0  | 1  |
| Visceral Other                          | 2  | 0  | 0  |
| Other                                   | 2  | 1  | 3  |
| Unknown                                 | 1  | 0  | 0  |
| Tumor size (cm)                         |    |    |    |
| Units: Subjects                         |    |    |    |
| ≥ 2                                     | 6  | 4  | 1  |
| 2-5                                     | 8  | 9  | 5  |
| > 5                                     | 19 | 21 | 29 |
| Unknown                                 | 14 | 9  | 8  |
| Growth rate                             |    |    |    |
| Units: Subjects                         |    |    |    |
| Rapid                                   | 16 | 12 | 18 |
| Slow                                    | 5  | 6  | 4  |
| Unknown                                 | 26 | 25 | 21 |
| Necrosis                                |    |    |    |
| Units: Subjects                         |    |    |    |
| No                                      | 19 | 15 | 16 |
| Yes                                     | 19 | 15 | 20 |
| Unknown                                 | 9  | 13 | 7  |
| Type of disease at the time of sampling |    |    |    |
| Units: Subjects                         |    |    |    |
| Primary                                 | 28 | 32 | 32 |
| Recurrent                               | 3  | 2  | 3  |
| Metastatic                              | 11 | 9  | 7  |
| Recurrent and metastatic                | 4  | 0  | 1  |
| Unknown                                 | 1  | 0  | 0  |
| Tumor type (Local pathology)            |    |    |    |
| (Local pathology)                       |    |    |    |
| Units: Subjects                         |    |    |    |
| Adipocytic (liposarcoma)                | 6  | 11 | 13 |
| Fibroblastic                            | 5  | 3  | 1  |
| So-called fibrohistiocytic tumours      | 3  | 3  | 1  |
| Smooth muscle tumours                   | 18 | 8  | 14 |
| Pericytic (perivascular) tumours        | 0  | 1  | 0  |
| Vascular tumours                        | 1  | 2  | 0  |
| Chondro-osseous tumours                 | 0  | 1  | 1  |
| Tumors of uncertain differentiation     | 7  | 7  | 8  |
| Undifferentiated sarcoma                | 4  | 6  | 5  |
| Other                                   | 3  | 1  | 0  |
| Tumor type (Review pathology)           |    |    |    |
| (Review pathology)                      |    |    |    |
| Units: Subjects                         |    |    |    |
| Adipocytic (liposarcoma)                | 5  | 7  | 12 |
| Fibroblastic                            | 3  | 4  | 0  |
| So-called fibrohistiocytic tumours      | 4  | 6  | 4  |
| Smooth muscle tumours                   | 11 | 4  | 9  |
| Vascular tumours                        | 1  | 1  | 0  |
| Chondro-osseous tumours                 | 0  | 1  | 0  |

|  |              |            |              |
|--|--------------|------------|--------------|
| Tumors of uncertain differentiation      | 6            | 5          | 6            |
| GIST                                     | 1            | 0          | 0            |
| Undifferentiated sarcoma NOS             | 3            | 3          | 1            |
| Other                                    | 5            | 1          | 4            |
| Missing                                  | 8            | 11         | 7            |
| Tumor grade                              |              |            |              |
| (review)                                 |              |            |              |
| Units: Subjects                          |              |            |              |
| Low                                      | 2            | 2          | 2            |
| Intermediate                             | 18           | 9          | 18           |
| High                                     | 13           | 12         | 11           |
| Unknown                                  | 14           | 20         | 12           |
| BMI                                      |              |            |              |
| Body Mass Index                          |              |            |              |
| Units: kg/m <sup>2</sup>                 |              |            |              |
| median                                   | 28.8         | 25.3       | 25.8         |
| full range (min-max)                     | 16.9 to 48.1 | 19.7 to 40 | 18.8 to 46.2 |
| Tumor size                               |              |            |              |
| Units: cm                                |              |            |              |
| median                                   | 6            | 7.1        | 9            |
| full range (min-max)                     | 1 to 22      | 1 to 22.6  | 1.4 to 34    |
| <b>Reporting group values</b>            | Total        |            |              |
| Number of subjects                       | 133          |            |              |
| Age categorical                          |              |            |              |
| Age at randomization (years)             |              |            |              |
| Units: Subjects                          |              |            |              |
| 60 years and over                        | 69           |            |              |
| From 18-59 years                         | 64           |            |              |
| Age continuous                           |              |            |              |
| Age at randomization                     |              |            |              |
| Units: years                             |              |            |              |
| median                                   |              |            |              |
| full range (min-max)                     | -            |            |              |
| Gender categorical                       |              |            |              |
| Units: Subjects                          |              |            |              |
| Female                                   | 77           |            |              |
| Male                                     | 56           |            |              |
| WHO Performance status                   |              |            |              |
| WHO Performance status                   |              |            |              |
| Units: Subjects                          |              |            |              |
| 0=Fully active                           | 72           |            |              |
| 1= Able to carry out work of a light nat | 61           |            |              |
| Other medical conditions                 |              |            |              |
| Other medical conditions at trial entry  |              |            |              |
| Units: Subjects                          |              |            |              |
| Yes                                      | 102          |            |              |
| No                                       | 31           |            |              |
| Site of primary tumor                    |              |            |              |
| Units: Subjects                          |              |            |              |

|   |    |  |  |
|---|----|--|--|
| Head and Neck                           | 1  |  |  |
| Trunk                                   | 6  |  |  |
| Thoracic                                | 14 |  |  |
| Retro-intra abdominal                   | 29 |  |  |
| Lower extremity                         | 33 |  |  |
| Upper extremity                         | 9  |  |  |
| Visceral GU                             | 5  |  |  |
| Visceral GI                             | 6  |  |  |
| Visceral Gynecological                  | 20 |  |  |
| Visceral Breast                         | 1  |  |  |
| Visceral Other                          | 2  |  |  |
| Other                                   | 6  |  |  |
| Unknown                                 | 1  |  |  |
| Tumor size (cm)                         |    |  |  |
| Units: Subjects                         |    |  |  |
| ≥ 2                                     | 11 |  |  |
| 2-5                                     | 22 |  |  |
| > 5                                     | 69 |  |  |
| Unknown                                 | 31 |  |  |
| Growth rate                             |    |  |  |
| Units: Subjects                         |    |  |  |
| Rapid                                   | 46 |  |  |
| Slow                                    | 15 |  |  |
| Unknown                                 | 72 |  |  |
| Necrosis                                |    |  |  |
| Units: Subjects                         |    |  |  |
| No                                      | 50 |  |  |
| Yes                                     | 54 |  |  |
| Unknown                                 | 29 |  |  |
| Type of disease at the time of sampling |    |  |  |
| Units: Subjects                         |    |  |  |
| Primary                                 | 92 |  |  |
| Recurrent                               | 8  |  |  |
| Metastatic                              | 27 |  |  |
| Recurrent and metastatic                | 5  |  |  |
| Unknown                                 | 1  |  |  |
| Tumor type (Local pathology)            |    |  |  |
| (Local pathology)                       |    |  |  |
| Units: Subjects                         |    |  |  |
| Adipocytic (liposarcoma)                | 30 |  |  |
| Fibroblastic                            | 9  |  |  |
| So-called fibrohistiocytic tumours      | 7  |  |  |
| Smooth muscle tumours                   | 40 |  |  |
| Pericytic (perivascular) tumours        | 1  |  |  |
| Vascular tumours                        | 3  |  |  |
| Chondro-osseous tumours                 | 2  |  |  |
| Tumors of uncertain differentiation     | 22 |  |  |
| Undifferentiated sarcoma                | 15 |  |  |
| Other                                   | 4  |  |  |
| Tumor type (Review pathology)           |    |  |  |
| (Review pathology)                      |    |  |  |

|                                     |    |  |  |
|-------------------------------------|----|--|--|
| Units: Subjects                     |    |  |  |
| Adipocytic (liposarcoma)            | 24 |  |  |
| Fibroblastic                        | 7  |  |  |
| So-called fibrohistiocytic tumours  | 14 |  |  |
| Smooth muscle tumours               | 24 |  |  |
| Vascular tumours                    | 2  |  |  |
| Chondro-osseous tumours             | 1  |  |  |
| Tumors of uncertain differentiation | 17 |  |  |
| GIST                                | 1  |  |  |
| Undifferentiated sarcoma NOS        | 7  |  |  |
| Other                               | 10 |  |  |
| Missing                             | 26 |  |  |
| Tumor grade                         |    |  |  |
| (review)                            |    |  |  |
| Units: Subjects                     |    |  |  |
| Low                                 | 6  |  |  |
| Intermediate                        | 45 |  |  |
| High                                | 36 |  |  |
| Unknown                             | 46 |  |  |
| BMI                                 |    |  |  |
| Body Mass Index                     |    |  |  |
| Units: kg/m <sup>2</sup>            |    |  |  |
| median                              |    |  |  |
| full range (min-max)                | -  |  |  |
| Tumor size                          |    |  |  |
| Units: cm                           |    |  |  |
| median                              |    |  |  |
| full range (min-max)                | -  |  |  |

## End points

### End points reporting groups

|   |            |
|---|------------|
| Reporting group title                                 | Trab_3hrs  |
| Reporting group description:<br>Trabectedin 3 hrs IV  |            |
| Reporting group title                                 | Trab_24hrs |
| Reporting group description:<br>Trabectedin 24 hrs IV |            |
| Reporting group title                                 | Doxo       |
| Reporting group description:<br>Doxorubicin           |            |
| Reporting group title                                 | Trab_3hrs  |
| Reporting group description:<br>Trabectedin 3 hrs IV  |            |
| Reporting group title                                 | Trab_24hrs |
| Reporting group description:<br>Trabectedin 24 hrs IV |            |
| Reporting group title                                 | Doxo       |
| Reporting group description:<br>Doxorubicin           |            |

### Primary: PFS

|   |         |
|---|---------|
| End point title   | PFS     |
| End point description:<br>Progression free survival will be censored on the date of the last tumor assessment documenting absence of progression for patients:<br>1. who are alive and progression free at the time of the analysis<br>2. who have withdrawn their consent to continue in the study<br>3. who are lost to follow up<br>4. in whom documentation of disease progression or death occurs after 2 or more consecutive missed tumor assessments<br>Note that patients will not be censored if, prior to observing progression, they<br>1. stop protocol treatment, for example due to toxicity or personal preference<br>2. change therapy and receive a non protocol anti-cancer treatment<br>These patients will continue to be followed for progression. |         |
| End point type  | Primary |
| End point timeframe:<br>Progression free survival will be measured from the date of randomization until the date of objective PD, symptomatic deterioration or death from any cause, whichever happen first.<br>Results are presented for PFS at 30 months.   |         |

| End point values            | Trab_3hrs       | Trab_24hrs      | Doxo            |  |
|-----------------------------|-----------------|-----------------|-----------------|--|
| Subject group type          | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed | 47              | 43              | 43              |  |
| Units: Patient              |                 |                 |                 |  |
| No progression              | 1               | 3               | 4               |  |
| Progression                 | 46              | 40              | 39              |  |

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Hazard Ratio Trab_24hrs versus Doxorubicin |
| Comparison groups                       | Trab_24hrs v Doxo                          |
| Number of subjects included in analysis | 86   |
| Analysis specification                  | Pre-specified                              |
| Analysis type                           | superiority <sup>[1]</sup>                 |
| P-value                                 | = 0.317 <sup>[2]</sup>                     |
| Method                                  | Logrank                                    |
| Parameter estimate                      | Hazard ratio (HR)                          |
| Point estimate                          | 0.9  |
| Confidence interval                     |  |
| level                                   | 95 %                                       |
| sides                                   | 2-sided                                    |
| lower limit                             | 0.57                                       |
| upper limit                             | 1.4  |

Notes:

[1] - Cox-model for PFS

[2] - 1-sided p-value

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Hazard Ratio Trab_3hrs versus Doxorubicin |
| Comparison groups                       | Doxo v Trab_3hrs                          |
| Number of subjects included in analysis | 90  |
| Analysis specification                  | Pre-specified                             |
| Analysis type                           | superiority                               |
| P-value                                 | = 0.687 <sup>[3]</sup>                    |
| Method                                  | Logrank                                   |
| Parameter estimate                      | Hazard ratio (HR)                         |
| Point estimate                          | 1.11                                      |
| Confidence interval                     |   |
| level                                   | 95 %                                      |
| sides                                   | 2-sided                                   |
| lower limit                             | 0.72                                      |
| upper limit                             | 1.71                                      |

Notes:

[3] - 1-sided p-value

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Hazard Ratio Trab_3hrs versus Trab_24hrs |
| Comparison groups                 | Trab_24hrs v Trab_3hrs                   |

|   |                   |
|---|-------------------|
| Number of subjects included in analysis | 90                |
| Analysis specification                  | Pre-specified     |
| Analysis type                           | superiority       |
| Parameter estimate                      | Hazard ratio (HR) |
| Point estimate                          | 1.23              |
| Confidence interval                     |                   |
| level                                   | 95 %              |
| sides                                   | 2-sided           |
| lower limit                             | 0.8               |
| upper limit                             | 1.88              |

## Secondary: OS

|   |           |
|---|-----------|
| End point title   | OS        |
| End point description:  |           |
| OS at 42 months   |           |
| End point type  | Secondary |
| End point timeframe:  |           |
| Overall survival will be measured from the date of randomization to the date of death; alive patients will be censored at the date of last follow-up. |           |

| End point values            | Trab_3hrs       | Trab_24hrs      | Doxo            |  |
|-----------------------------|-----------------|-----------------|-----------------|--|
| Subject group type          | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed | 47              | 43              | 43              |  |
| Units: patients             |                 |                 |                 |  |
| Dead                        | 35              | 33              | 26              |  |
| Alive                       | 12              | 10              | 17              |  |

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Hazard Ratio Trab_24hrs versus Doxorubicin |
| Comparison groups                       | Doxo v Trab_24hrs                          |
| Number of subjects included in analysis | 86   |
| Analysis specification                  | Pre-specified                              |
| Analysis type                           | superiority                                |
| P-value                                 | = 0.892 <sup>[4]</sup>                     |
| Method                                  | Logrank                                    |
| Parameter estimate                      | Hazard ratio (HR)                          |
| Point estimate                          | 1.38                                       |
| Confidence interval                     |  |
| level                                   | 95 %                                       |
| sides                                   | 2-sided                                    |
| lower limit                             | 0.83                                       |
| upper limit                             | 2.32                                       |

Notes:

[4] - 1-sided p-value

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Hazard Ratio Trab_3hrs versus Doxorubicin |
| Comparison groups                       | Trab_3hrs v Doxo                          |
| Number of subjects included in analysis | 90  |
| Analysis specification                  | Pre-specified                             |
| Analysis type                           | superiority                               |
| P-value                                 | = 0.921 <sup>[5]</sup>                    |
| Method                                  | Logrank                                   |
| Parameter estimate                      | Hazard ratio (HR)                         |
| Point estimate                          | 1.44                                      |
| Confidence interval                     |   |
| level                                   | 95 %                                      |
| sides                                   | 2-sided                                   |
| lower limit                             | 0.87                                      |
| upper limit                             | 2.4                                       |

Notes:

[5] - 1-sided p-value

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All AE will be recorded after each cycle (worst grade per cycle). Hematological and biochemistry AE will be assessed on the basis of at least every 3 weeks blood counts (weekly during the two first cycles for serum chemistry/hematological tests)

Adverse event reporting additional description:

CRF for AEs contains pre-specified items + additional boxes for all "other" AEs. (AEs reported as "other" are not reported as not available from the list of SOC). AEs are evaluated using CTC grading, SAEs using MedDRA. Non-SAEs has not been collected specifically, all AEs will be reported in non-SAE section.

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |    |
|--------------------|----|
| Dictionary version | 19 |
|--------------------|----|

### Reporting groups

|                       |           |
|-----------------------|-----------|
| Reporting group title | Trab_3hrs |
|-----------------------|-----------|

Reporting group description:

Trabectidin 3 hrs IV

|                       |      |
|-----------------------|------|
| Reporting group title | Doxo |
|-----------------------|------|

Reporting group description:

Doxorubicin

|                       |            |
|-----------------------|------------|
| Reporting group title | Trab_24hrs |
|-----------------------|------------|

Reporting group description:

Trabectidin 24 hrs IV

| Serious adverse events  | Trab_3hrs        | Doxo             | Trab_24hrs       |
|---|------------------|------------------|------------------|
| Total subjects affected by serious adverse events                   |                  |                  |                  |
| subjects affected / exposed   | 22 / 46 (47.83%) | 11 / 40 (27.50%) | 17 / 41 (41.46%) |
| number of deaths (all causes)                                       | 11               | 15               | 9                |
| number of deaths resulting from adverse events                      | 1                | 0                | 1                |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |                  |                  |
| BLADDER CANCER  |                  |                  |                  |
| alternative dictionary used: MedDRA 19                              |                  |                  |                  |
| subjects affected / exposed   | 1 / 46 (2.17%)   | 0 / 40 (0.00%)   | 0 / 41 (0.00%)   |
| occurrences causally related to treatment / all                     | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0            | 0 / 0            |
| TUMOUR PAIN   |                  |                  |                  |
| alternative dictionary used: MedDRA 19                              |                  |                  |                  |

|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed                          | 0 / 46 (0.00%) | 1 / 40 (2.50%) | 1 / 41 (2.44%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Vascular disorders                                   |                |                |                |
| HYPOTENSION  |                |                |                |
| alternative dictionary used: MedDRA 19               |                |                |                |
| subjects affected / exposed                          | 0 / 46 (0.00%) | 1 / 40 (2.50%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| PHLEBITIS  |                |                |                |
| alternative dictionary used: MedDRA 19               |                |                |                |
| subjects affected / exposed                          | 0 / 46 (0.00%) | 0 / 40 (0.00%) | 1 / 41 (2.44%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| General disorders and administration site conditions |                |                |                |
| CATHETER SITE INFLAMMATION                           |                |                |                |
| alternative dictionary used: MedDRA 19               |                |                |                |
| subjects affected / exposed                          | 1 / 46 (2.17%) | 0 / 40 (0.00%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| DEATH  |                |                |                |
| alternative dictionary used: MedDRA 19               |                |                |                |
| subjects affected / exposed                          | 1 / 46 (2.17%) | 0 / 40 (0.00%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 1          | 0 / 0          | 0 / 0          |
| FATIGUE  |                |                |                |
| alternative dictionary used: MedDRA 19               |                |                |                |
| subjects affected / exposed                          | 0 / 46 (0.00%) | 1 / 40 (2.50%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| GENERAL PHYSICAL HEALTH DETERIORATION                |                |                |                |
| alternative dictionary used: MedDRA 19               |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 2 / 46 (4.35%) | 0 / 40 (0.00%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| MUCOSAL INFLAMMATION                            |                |                |                |
| alternative dictionary used: MedDRA 19          |                |                |                |
| subjects affected / exposed                     | 0 / 46 (0.00%) | 1 / 40 (2.50%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| PYREXIA   |                |                |                |
| alternative dictionary used: MedDRA 19          |                |                |                |
| subjects affected / exposed                     | 1 / 46 (2.17%) | 0 / 40 (0.00%) | 2 / 41 (4.88%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 2 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| SUDDEN DEATH                                    |                |                |                |
| alternative dictionary used: MedDRA 19          |                |                |                |
| subjects affected / exposed                     | 0 / 46 (0.00%) | 0 / 40 (0.00%) | 1 / 41 (2.44%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 1 / 1          |
| Respiratory, thoracic and mediastinal disorders |                |                |                |
| DYSпноEA  |                |                |                |
| alternative dictionary used: MedDRA 19          |                |                |                |
| subjects affected / exposed                     | 2 / 46 (4.35%) | 0 / 40 (0.00%) | 1 / 41 (2.44%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| LARYNGEAL INFLAMMATION                          |                |                |                |
| alternative dictionary used: MedDRA 19          |                |                |                |
| subjects affected / exposed                     | 0 / 46 (0.00%) | 1 / 40 (2.50%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| PLEURAL EFFUSION                                |                |                |                |
| alternative dictionary used: MedDRA 19          |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 2 / 46 (4.35%) | 0 / 40 (0.00%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| PNEUMOTHORAX                                    |                |                |                |
| alternative dictionary used: MedDRA 19          |                |                |                |
| subjects affected / exposed                     | 1 / 46 (2.17%) | 2 / 40 (5.00%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 4          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| PULMONARY EMBOLISM                              |                |                |                |
| alternative dictionary used: MedDRA 19          |                |                |                |
| subjects affected / exposed                     | 2 / 46 (4.35%) | 1 / 40 (2.50%) | 1 / 41 (2.44%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0          |
| Psychiatric disorders                           |                |                |                |
| ANXIETY   |                |                |                |
| alternative dictionary used: MedDRA 19          |                |                |                |
| subjects affected / exposed                     | 1 / 46 (2.17%) | 0 / 40 (0.00%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| CONFUSIONAL STATE                               |                |                |                |
| alternative dictionary used: MedDRA 19          |                |                |                |
| subjects affected / exposed                     | 0 / 46 (0.00%) | 2 / 40 (5.00%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Investigations                                  |                |                |                |
| ALANINE AMINOTRANSFERASE INCREASED              |                |                |                |
| alternative dictionary used: MedDRA 19          |                |                |                |
| subjects affected / exposed                     | 3 / 46 (6.52%) | 0 / 40 (0.00%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| ASPARTATE AMINOTRANSFERASE INCREASED            |                |                |                |
| alternative dictionary used: MedDRA 19          |                |                |                |

|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed                                    | 2 / 46 (4.35%) | 0 / 40 (0.00%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all                | 2 / 2          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all                     | 0 / 0          | 0 / 0          | 0 / 0          |
| BLOOD CREATINE PHOSPHOKINASE INCREASED                         |                |                |                |
| alternative dictionary used: MedDRA 19                         |                |                |                |
| subjects affected / exposed                                    | 1 / 46 (2.17%) | 0 / 40 (0.00%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all                | 1 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all                     | 0 / 0          | 0 / 0          | 0 / 0          |
| CREATININE RENAL CLEARANCE DECREASED                           |                |                |                |
| alternative dictionary used: MedDRA 19                         |                |                |                |
| subjects affected / exposed                                    | 1 / 46 (2.17%) | 0 / 40 (0.00%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all                | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all                     | 0 / 0          | 0 / 0          | 0 / 0          |
| EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS WORSENER |                |                |                |
| alternative dictionary used: MedDRA 19                         |                |                |                |
| subjects affected / exposed                                    | 0 / 46 (0.00%) | 1 / 40 (2.50%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all                | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all                     | 0 / 0          | 0 / 0          | 0 / 0          |
| HEPATIC ENZYME INCREASED                                       |                |                |                |
| alternative dictionary used: MedDRA 19                         |                |                |                |
| subjects affected / exposed                                    | 1 / 46 (2.17%) | 0 / 40 (0.00%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all                | 1 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all                     | 0 / 0          | 0 / 0          | 0 / 0          |
| LIPASE INCREASED   |                |                |                |
| alternative dictionary used: MedDRA 19                         |                |                |                |
| subjects affected / exposed                                    | 1 / 46 (2.17%) | 0 / 40 (0.00%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all                | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all                     | 0 / 0          | 0 / 0          | 0 / 0          |
| Injury, poisoning and procedural complications                 |                |                |                |
| HIP FRACTURE   |                |                |                |
| alternative dictionary used: MedDRA 19                         |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 46 (2.17%) | 0 / 40 (0.00%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| SUBDURAL HAEMATOMA                              |                |                |                |
| alternative dictionary used: MedDRA 19          |                |                |                |
| subjects affected / exposed                     | 1 / 46 (2.17%) | 0 / 40 (0.00%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| TRANSFUSION REACTION                            |                |                |                |
| alternative dictionary used: MedDRA 19          |                |                |                |
| subjects affected / exposed                     | 0 / 46 (0.00%) | 0 / 40 (0.00%) | 1 / 41 (2.44%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac disorders                               |                |                |                |
| PERICARDIAL EFFUSION                            |                |                |                |
| alternative dictionary used: MedDRA 19          |                |                |                |
| subjects affected / exposed                     | 1 / 46 (2.17%) | 0 / 40 (0.00%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Nervous system disorders                        |                |                |                |
| CEREBRAL ISCHAEMIA                              |                |                |                |
| alternative dictionary used: MedDRA 19          |                |                |                |
| subjects affected / exposed                     | 0 / 46 (0.00%) | 1 / 40 (2.50%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| SOMNOLENCE                                      |                |                |                |
| alternative dictionary used: MedDRA 19          |                |                |                |
| subjects affected / exposed                     | 0 / 46 (0.00%) | 1 / 40 (2.50%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| SYNCOPE   |                |                |                |
| alternative dictionary used: MedDRA 19          |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed   | 1 / 46 (2.17%) | 0 / 40 (0.00%) | 1 / 41 (2.44%) |
| occurrences causally related to treatment / all                         | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all                              | 0 / 0          | 0 / 0          | 0 / 0          |
| TRANSIENT ISCHAEMIC ATTACK<br>alternative dictionary used:<br>MedDRA 19 |                |                |                |
| subjects affected / exposed   | 0 / 46 (0.00%) | 0 / 40 (0.00%) | 1 / 41 (2.44%) |
| occurrences causally related to treatment / all                         | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all                              | 0 / 0          | 0 / 0          | 0 / 0          |
| Blood and lymphatic system disorders                                    |                |                |                |
| ANAEMIA<br>alternative dictionary used:<br>MedDRA 19                    |                |                |                |
| subjects affected / exposed   | 2 / 46 (4.35%) | 1 / 40 (2.50%) | 3 / 41 (7.32%) |
| occurrences causally related to treatment / all                         | 2 / 2          | 1 / 1          | 3 / 3          |
| deaths causally related to treatment / all                              | 0 / 0          | 0 / 0          | 0 / 0          |
| FEBRILE NEUTROPENIA<br>alternative dictionary used:<br>MedDRA 19        |                |                |                |
| subjects affected / exposed   | 1 / 46 (2.17%) | 1 / 40 (2.50%) | 3 / 41 (7.32%) |
| occurrences causally related to treatment / all                         | 1 / 1          | 1 / 1          | 3 / 3          |
| deaths causally related to treatment / all                              | 0 / 0          | 0 / 0          | 0 / 0          |
| LEUKOPENIA<br>alternative dictionary used:<br>MedDRA 19                 |                |                |                |
| subjects affected / exposed   | 0 / 46 (0.00%) | 0 / 40 (0.00%) | 1 / 41 (2.44%) |
| occurrences causally related to treatment / all                         | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all                              | 0 / 0          | 0 / 0          | 0 / 0          |
| NEUTROPENIA<br>alternative dictionary used:<br>MedDRA 19                |                |                |                |
| subjects affected / exposed   | 3 / 46 (6.52%) | 1 / 40 (2.50%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all                         | 3 / 3          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all                              | 0 / 0          | 0 / 0          | 0 / 0          |
| PANCYTOPENIA<br>alternative dictionary used:<br>MedDRA 19               |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 46 (2.17%) | 0 / 40 (0.00%) | 2 / 41 (4.88%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 2 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| THROMBOCYTOPENIA                                |                |                |                |
| alternative dictionary used: MedDRA 19          |                |                |                |
| subjects affected / exposed                     | 3 / 46 (6.52%) | 0 / 40 (0.00%) | 2 / 41 (4.88%) |
| occurrences causally related to treatment / all | 3 / 3          | 0 / 0          | 2 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Eye disorders                                   |                |                |                |
| MACULAR OEDEMA                                  |                |                |                |
| alternative dictionary used: MedDRA 19          |                |                |                |
| subjects affected / exposed                     | 0 / 46 (0.00%) | 0 / 40 (0.00%) | 1 / 41 (2.44%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| RETINAL VEIN THROMBOSIS                         |                |                |                |
| alternative dictionary used: MedDRA 19          |                |                |                |
| subjects affected / exposed                     | 0 / 46 (0.00%) | 0 / 40 (0.00%) | 1 / 41 (2.44%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrointestinal disorders                      |                |                |                |
| ABDOMINAL PAIN                                  |                |                |                |
| alternative dictionary used: MedDRA 19          |                |                |                |
| subjects affected / exposed                     | 0 / 46 (0.00%) | 1 / 40 (2.50%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| ABDOMINAL PAIN UPPER                            |                |                |                |
| alternative dictionary used: MedDRA 19          |                |                |                |
| subjects affected / exposed                     | 1 / 46 (2.17%) | 0 / 40 (0.00%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| CONSTIPATION                                    |                |                |                |
| alternative dictionary used: MedDRA 19          |                |                |                |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 46 (0.00%) | 0 / 40 (0.00%) | 1 / 41 (2.44%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| DIARRHOEA                                       |                |                |                 |
| alternative dictionary used: MedDRA 19          |                |                |                 |
| subjects affected / exposed                     | 0 / 46 (0.00%) | 1 / 40 (2.50%) | 0 / 41 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| DYSPEPSIA                                       |                |                |                 |
| alternative dictionary used: MedDRA 19          |                |                |                 |
| subjects affected / exposed                     | 1 / 46 (2.17%) | 0 / 40 (0.00%) | 0 / 41 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| GASTRIC ULCER HAEMORRHAGE                       |                |                |                 |
| alternative dictionary used: MedDRA 19          |                |                |                 |
| subjects affected / exposed                     | 1 / 46 (2.17%) | 0 / 40 (0.00%) | 0 / 41 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0           |
| GASTROINTESTINAL HAEMORRHAGE                    |                |                |                 |
| alternative dictionary used: MedDRA 19          |                |                |                 |
| subjects affected / exposed                     | 0 / 46 (0.00%) | 0 / 40 (0.00%) | 1 / 41 (2.44%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| NAUSEA  |                |                |                 |
| alternative dictionary used: MedDRA 19          |                |                |                 |
| subjects affected / exposed                     | 4 / 46 (8.70%) | 0 / 40 (0.00%) | 5 / 41 (12.20%) |
| occurrences causally related to treatment / all | 3 / 4          | 0 / 0          | 5 / 6           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| VOMITING  |                |                |                 |
| alternative dictionary used: MedDRA 19          |                |                |                 |
| subjects affected / exposed                     | 4 / 46 (8.70%) | 1 / 40 (2.50%) | 4 / 41 (9.76%)  |
| occurrences causally related to treatment / all | 3 / 4          | 1 / 1          | 5 / 5           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Hepatobiliary disorders                         |                |                |                |
| DRUG-INDUCED LIVER INJURY                       |                |                |                |
| alternative dictionary used: MedDRA 19          |                |                |                |
| subjects affected / exposed                     | 1 / 46 (2.17%) | 0 / 40 (0.00%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| HEPATOCELLULAR INJURY                           |                |                |                |
| alternative dictionary used: MedDRA 19          |                |                |                |
| subjects affected / exposed                     | 1 / 46 (2.17%) | 0 / 40 (0.00%) | 1 / 41 (2.44%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Renal and urinary disorders                     |                |                |                |
| ACUTE KIDNEY INJURY                             |                |                |                |
| alternative dictionary used: MedDRA 19          |                |                |                |
| subjects affected / exposed                     | 0 / 46 (0.00%) | 2 / 40 (5.00%) | 1 / 41 (2.44%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| HAEMATURIA                                      |                |                |                |
| alternative dictionary used: MedDRA 19          |                |                |                |
| subjects affected / exposed                     | 1 / 46 (2.17%) | 0 / 40 (0.00%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| RENAL FAILURE                                   |                |                |                |
| alternative dictionary used: MedDRA 19          |                |                |                |
| subjects affected / exposed                     | 1 / 46 (2.17%) | 1 / 40 (2.50%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| URETERIC OBSTRUCTION                            |                |                |                |
| alternative dictionary used: MedDRA 19          |                |                |                |
| subjects affected / exposed                     | 1 / 46 (2.17%) | 0 / 40 (0.00%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| URINARY TRACT OBSTRUCTION                       |                |                |                |
| alternative dictionary used: MedDRA 19          |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 46 (2.17%) | 0 / 40 (0.00%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Musculoskeletal and connective tissue disorders |                |                |                |
| MUSCULOSKELETAL PAIN                            |                |                |                |
| alternative dictionary used: MedDRA 19          |                |                |                |
| subjects affected / exposed                     | 1 / 46 (2.17%) | 0 / 40 (0.00%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infections and infestations                     |                |                |                |
| BACTERAEemia                                    |                |                |                |
| alternative dictionary used: MedDRA 19          |                |                |                |
| subjects affected / exposed                     | 1 / 46 (2.17%) | 0 / 40 (0.00%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| BACTERIAL INFECTION                             |                |                |                |
| alternative dictionary used: MedDRA 19          |                |                |                |
| subjects affected / exposed                     | 1 / 46 (2.17%) | 0 / 40 (0.00%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| BURKHOLDERIA CEPACIA COMPLEX INFECTION          |                |                |                |
| alternative dictionary used: MedDRA 19          |                |                |                |
| subjects affected / exposed                     | 1 / 46 (2.17%) | 0 / 40 (0.00%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| DEVICE RELATED INFECTION                        |                |                |                |
| alternative dictionary used: MedDRA 19          |                |                |                |
| subjects affected / exposed                     | 2 / 46 (4.35%) | 0 / 40 (0.00%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| HERPES ZOSTER                                   |                |                |                |
| alternative dictionary used: MedDRA 19          |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 46 (0.00%) | 1 / 40 (2.50%) | 1 / 41 (2.44%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| INFECTION                                       |                |                |                |
| alternative dictionary used: MedDRA 19          |                |                |                |
| subjects affected / exposed                     | 0 / 46 (0.00%) | 0 / 40 (0.00%) | 1 / 41 (2.44%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| LUNG INFECTION                                  |                |                |                |
| alternative dictionary used: MedDRA 19          |                |                |                |
| subjects affected / exposed                     | 0 / 46 (0.00%) | 0 / 40 (0.00%) | 1 / 41 (2.44%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| PNEUMONIA                                       |                |                |                |
| alternative dictionary used: MedDRA 19          |                |                |                |
| subjects affected / exposed                     | 1 / 46 (2.17%) | 0 / 40 (0.00%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| PYELONEPHRITIS ACUTE                            |                |                |                |
| alternative dictionary used: MedDRA 19          |                |                |                |
| subjects affected / exposed                     | 1 / 46 (2.17%) | 0 / 40 (0.00%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| RESPIRATORY TRACT INFECTION                     |                |                |                |
| alternative dictionary used: MedDRA 19          |                |                |                |
| subjects affected / exposed                     | 0 / 46 (0.00%) | 1 / 40 (2.50%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| SEPTIC SHOCK                                    |                |                |                |
| alternative dictionary used: MedDRA 19          |                |                |                |
| subjects affected / exposed                     | 1 / 46 (2.17%) | 0 / 40 (0.00%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 1 / 1          | 0 / 0          | 0 / 0          |

|  |                                  |                                  |                                  |
|--|----------------------------------|----------------------------------|----------------------------------|
| STAPHYLOCOCCAL INFECTION<br>alternative dictionary used:<br>MedDRA 19<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all                          | 1 / 46 (2.17%)<br>2 / 2<br>0 / 0 | 0 / 40 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 41 (0.00%)<br>0 / 0<br>0 / 0 |
| STAPHYLOCOCCAL SKIN INFECTION<br>alternative dictionary used:<br>MedDRA 19<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all                     | 0 / 46 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 40 (2.50%)<br>1 / 1<br>0 / 0 | 0 / 41 (0.00%)<br>0 / 0<br>0 / 0 |
| URINARY TRACT INFECTION<br>alternative dictionary used:<br>MedDRA 19<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all                           | 0 / 46 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 40 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 41 (2.44%)<br>0 / 1<br>0 / 0 |
| Metabolism and nutrition disorders<br>DEHYDRATION<br>alternative dictionary used:<br>MedDRA 19<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all | 0 / 46 (0.00%)<br>0 / 0<br>0 / 0 | 2 / 40 (5.00%)<br>1 / 2<br>0 / 0 | 0 / 41 (0.00%)<br>0 / 0<br>0 / 0 |
| HYPERKALAEMIA<br>alternative dictionary used:<br>MedDRA 19<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all                                     | 1 / 46 (2.17%)<br>0 / 1<br>0 / 0 | 0 / 40 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 41 (2.44%)<br>1 / 1<br>0 / 0 |
| HYPOGLYCAEMIA<br>alternative dictionary used:<br>MedDRA 19<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all                                     | 1 / 46 (2.17%)<br>0 / 1<br>0 / 0 | 0 / 40 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 41 (0.00%)<br>0 / 0<br>0 / 0 |

| Non-serious adverse events  | Trab_3hrs        | Doxo             | Trab_24hrs        |
|---|------------------|------------------|-------------------|
| Total subjects affected by non-serious adverse events               |                  |                  |                   |
| subjects affected / exposed   | 45 / 46 (97.83%) | 38 / 40 (95.00%) | 41 / 41 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |                  |                   |
| TUMOR PAIN  |                  |                  |                   |
| alternative dictionary used: CTC 4.0                                |                  |                  |                   |
| subjects affected / exposed   | 9 / 46 (19.57%)  | 9 / 40 (22.50%)  | 14 / 41 (34.15%)  |
| occurrences (all)   | 15               | 18               | 30                |
| OTHER NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED                   |                  |                  |                   |
| alternative dictionary used: CTC 4.0                                |                  |                  |                   |
| subjects affected / exposed   | 1 / 46 (2.17%)   | 0 / 40 (0.00%)   | 1 / 41 (2.44%)    |
| occurrences (all)   | 1                | 0                | 1                 |
| Vascular disorders  |                  |                  |                   |
| FLUSHING  |                  |                  |                   |
| alternative dictionary used: CTC 4.0                                |                  |                  |                   |
| subjects affected / exposed   | 1 / 46 (2.17%)   | 0 / 40 (0.00%)   | 2 / 41 (4.88%)    |
| occurrences (all)   | 3                | 0                | 2                 |
| HYPERTENSION  |                  |                  |                   |
| alternative dictionary used: CTC 4.0                                |                  |                  |                   |
| subjects affected / exposed   | 5 / 46 (10.87%)  | 1 / 40 (2.50%)   | 3 / 41 (7.32%)    |
| occurrences (all)   | 8                | 1                | 9                 |
| HYPOTENSION   |                  |                  |                   |
| alternative dictionary used: CTC 4.0                                |                  |                  |                   |
| subjects affected / exposed   | 1 / 46 (2.17%)   | 1 / 40 (2.50%)   | 1 / 41 (2.44%)    |
| occurrences (all)   | 1                | 1                | 2                 |
| PHLEBITIS   |                  |                  |                   |
| alternative dictionary used: CTC 4.0                                |                  |                  |                   |
| subjects affected / exposed   | 0 / 46 (0.00%)   | 0 / 40 (0.00%)   | 5 / 41 (12.20%)   |
| occurrences (all)   | 0                | 0                | 11                |
| OTHER VASCULAR DISORDERS  |                  |                  |                   |
| alternative dictionary used: CTC 4.0                                |                  |                  |                   |
| subjects affected / exposed   | 1 / 46 (2.17%)   | 1 / 40 (2.50%)   | 1 / 41 (2.44%)    |
| occurrences (all)   | 1                | 1                | 2                 |
| THROMBOEMBOLIC EVENT  |                  |                  |                   |

|  |                         |                        |                         |
|--|-------------------------|------------------------|-------------------------|
| alternative dictionary used: CTC<br>4.0<br>subjects affected / exposed<br>occurrences (all)  | 3 / 46 (6.52%)<br>4     | 3 / 40 (7.50%)<br>5    | 4 / 41 (9.76%)<br>5     |
| Surgical and medical procedures<br>SURGICAL AND MEDICAL<br>PROCEDURES<br>alternative dictionary used: CTC<br>4.0<br>subjects affected / exposed<br>occurrences (all) | 0 / 46 (0.00%)<br>0     | 0 / 40 (0.00%)<br>0    | 1 / 41 (2.44%)<br>1     |
| General disorders and administration<br>site conditions<br>CHILLS<br>alternative dictionary used: CTC<br>4.0<br>subjects affected / exposed<br>occurrences (all)     | 2 / 46 (4.35%)<br>3     | 3 / 40 (7.50%)<br>6    | 0 / 41 (0.00%)<br>0     |
| EDEMA FACE<br>alternative dictionary used: CTC<br>4.0<br>subjects affected / exposed<br>occurrences (all)  | 2 / 46 (4.35%)<br>2     | 0 / 40 (0.00%)<br>0    | 1 / 41 (2.44%)<br>1     |
| EDEMA TRUNK<br>alternative dictionary used: CTC<br>4.0<br>subjects affected / exposed<br>occurrences (all)   | 1 / 46 (2.17%)<br>1     | 1 / 40 (2.50%)<br>1    | 0 / 41 (0.00%)<br>0     |
| EDEMA LIMBS<br>alternative dictionary used: CTC<br>4.0<br>subjects affected / exposed<br>occurrences (all)   | 11 / 46 (23.91%)<br>21  | 2 / 40 (5.00%)<br>2    | 11 / 41 (26.83%)<br>22  |
| FATIGUE<br>alternative dictionary used: CTC<br>4.0<br>subjects affected / exposed<br>occurrences (all)   | 33 / 46 (71.74%)<br>131 | 27 / 40 (67.50%)<br>85 | 30 / 41 (73.17%)<br>136 |
| FLU LIKE SYMPTOMS<br>alternative dictionary used: CTC<br>4.0<br>subjects affected / exposed<br>occurrences (all)   | 3 / 46 (6.52%)<br>3     | 1 / 40 (2.50%)<br>1    | 2 / 41 (4.88%)<br>2     |
| FEVER  |                         |                        |                         |

|  |                  |                 |                  |
|--|------------------|-----------------|------------------|
| alternative dictionary used: CTC 4.0                       |                  |                 |                  |
| subjects affected / exposed                                | 13 / 46 (28.26%) | 3 / 40 (7.50%)  | 7 / 41 (17.07%)  |
| occurrences (all)  | 14               | 3               | 9                |
| INJECTION SITE REACTION                                    |                  |                 |                  |
| alternative dictionary used: CTC 4.0                       |                  |                 |                  |
| subjects affected / exposed                                | 1 / 46 (2.17%)   | 0 / 40 (0.00%)  | 1 / 41 (2.44%)   |
| occurrences (all)  | 1                | 0               | 1                |
| OTHER GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS |                  |                 |                  |
| alternative dictionary used: CTC 4.0                       |                  |                 |                  |
| subjects affected / exposed                                | 4 / 46 (8.70%)   | 4 / 40 (10.00%) | 2 / 41 (4.88%)   |
| occurrences (all)  | 6                | 5               | 2                |
| NON-CARDIAC CHEST PAIN                                     |                  |                 |                  |
| alternative dictionary used: CTC 4.0                       |                  |                 |                  |
| subjects affected / exposed                                | 2 / 46 (4.35%)   | 2 / 40 (5.00%)  | 0 / 41 (0.00%)   |
| occurrences (all)  | 5                | 2               | 0                |
| PAIN   |                  |                 |                  |
| alternative dictionary used: CTC 4.0                       |                  |                 |                  |
| subjects affected / exposed                                | 10 / 46 (21.74%) | 6 / 40 (15.00%) | 11 / 41 (26.83%) |
| occurrences (all)  | 23               | 8               | 27               |
| Immune system disorders                                    |                  |                 |                  |
| IMMUNE SYSTEM DISORDERS                                    |                  |                 |                  |
| alternative dictionary used: CTC 4.0                       |                  |                 |                  |
| subjects affected / exposed                                | 1 / 46 (2.17%)   | 1 / 40 (2.50%)  | 1 / 41 (2.44%)   |
| occurrences (all)  | 5                | 1               | 1                |
| Reproductive system and breast disorders                   |                  |                 |                  |
| REPRODUCTIVE SYSTEM AND BREAST DISORDERS                   |                  |                 |                  |
| alternative dictionary used: CTC 4.0                       |                  |                 |                  |
| subjects affected / exposed                                | 0 / 46 (0.00%)   | 1 / 40 (2.50%)  | 1 / 41 (2.44%)   |
| occurrences (all)  | 0                | 1               | 1                |
| Respiratory, thoracic and mediastinal disorders            |                  |                 |                  |
| COUGH  |                  |                 |                  |
| alternative dictionary used: CTC 4.0                       |                  |                 |                  |

|   |                  |                 |                  |
|---|------------------|-----------------|------------------|
| subjects affected / exposed                           | 8 / 46 (17.39%)  | 7 / 40 (17.50%) | 12 / 41 (29.27%) |
| occurrences (all)                                     | 23               | 10              | 17               |
| DYSPNEA   |                  |                 |                  |
| alternative dictionary used: CTC 4.0                  |                  |                 |                  |
| subjects affected / exposed                           | 17 / 46 (36.96%) | 7 / 40 (17.50%) | 10 / 41 (24.39%) |
| occurrences (all)                                     | 31               | 14              | 17               |
| OTHER RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS |                  |                 |                  |
| alternative dictionary used: CTC 4.0                  |                  |                 |                  |
| subjects affected / exposed                           | 9 / 46 (19.57%)  | 7 / 40 (17.50%) | 7 / 41 (17.07%)  |
| occurrences (all)                                     | 12               | 14              | 11               |
| EPISTAXIS   |                  |                 |                  |
| alternative dictionary used: CTC 4.0                  |                  |                 |                  |
| subjects affected / exposed                           | 0 / 46 (0.00%)   | 1 / 40 (2.50%)  | 1 / 41 (2.44%)   |
| occurrences (all)                                     | 0                | 1               | 1                |
| PLEURAL EFFUSION                                      |                  |                 |                  |
| alternative dictionary used: CTC 4.0                  |                  |                 |                  |
| subjects affected / exposed                           | 2 / 46 (4.35%)   | 0 / 40 (0.00%)  | 1 / 41 (2.44%)   |
| occurrences (all)                                     | 4                | 0               | 2                |
| PHARYNGOLARYNGEAL PAIN                                |                  |                 |                  |
| alternative dictionary used: CTC 4.0                  |                  |                 |                  |
| subjects affected / exposed                           | 0 / 46 (0.00%)   | 0 / 40 (0.00%)  | 1 / 41 (2.44%)   |
| occurrences (all)                                     | 0                | 0               | 1                |
| Psychiatric disorders                                 |                  |                 |                  |
| ANXIETY   |                  |                 |                  |
| alternative dictionary used: CTC 4.0                  |                  |                 |                  |
| subjects affected / exposed                           | 2 / 46 (4.35%)   | 2 / 40 (5.00%)  | 9 / 41 (21.95%)  |
| occurrences (all)                                     | 2                | 2               | 12               |
| DEPRESSION  |                  |                 |                  |
| alternative dictionary used: CTC 4.0                  |                  |                 |                  |
| subjects affected / exposed                           | 2 / 46 (4.35%)   | 2 / 40 (5.00%)  | 3 / 41 (7.32%)   |
| occurrences (all)                                     | 3                | 6               | 12               |
| INSOMNIA  |                  |                 |                  |
| alternative dictionary used: CTC 4.0                  |                  |                 |                  |

|                                      |                  |                  |                  |
|--------------------------------------|------------------|------------------|------------------|
| subjects affected / exposed          | 3 / 46 (6.52%)   | 4 / 40 (10.00%)  | 6 / 41 (14.63%)  |
| occurrences (all)                    | 4                | 13               | 9                |
| OTHER PSYCHIATRIC DISORDERS          |                  |                  |                  |
| alternative dictionary used: CTC 4.0 |                  |                  |                  |
| subjects affected / exposed          | 1 / 46 (2.17%)   | 2 / 40 (5.00%)   | 0 / 41 (0.00%)   |
| occurrences (all)                    | 1                | 2                | 0                |
| Investigations                       |                  |                  |                  |
| HEMOGLOBIN INCREASED                 |                  |                  |                  |
| alternative dictionary used: CTC 4.0 |                  |                  |                  |
| subjects affected / exposed          | 3 / 46 (6.52%)   | 0 / 40 (0.00%)   | 1 / 41 (2.44%)   |
| occurrences (all)                    | 3                | 0                | 2                |
| LYMPHOCYTE COUNT DECREASED           |                  |                  |                  |
| alternative dictionary used: CTC 4.0 |                  |                  |                  |
| subjects affected / exposed          | 17 / 46 (36.96%) | 14 / 40 (35.00%) | 15 / 41 (36.59%) |
| occurrences (all)                    | 58               | 35               | 69               |
| NEUTROPHIL COUNT DECREASED           |                  |                  |                  |
| alternative dictionary used: CTC 4.0 |                  |                  |                  |
| subjects affected / exposed          | 30 / 46 (65.22%) | 30 / 40 (75.00%) | 28 / 41 (68.29%) |
| occurrences (all)                    | 132              | 70               | 130              |
| LYMPHOCYTE COUNT INCREASED           |                  |                  |                  |
| alternative dictionary used: CTC 4.0 |                  |                  |                  |
| subjects affected / exposed          | 1 / 46 (2.17%)   | 0 / 40 (0.00%)   | 2 / 41 (4.88%)   |
| occurrences (all)                    | 1                | 0                | 2                |
| OTHER INVESTIGATIONS                 |                  |                  |                  |
| alternative dictionary used: CTC 4.0 |                  |                  |                  |
| subjects affected / exposed          | 6 / 46 (13.04%)  | 3 / 40 (7.50%)   | 5 / 41 (12.20%)  |
| occurrences (all)                    | 16               | 4                | 6                |
| PLATELET COUNT DECREASED             |                  |                  |                  |
| alternative dictionary used: CTC 4.0 |                  |                  |                  |
| subjects affected / exposed          | 16 / 46 (34.78%) | 9 / 40 (22.50%)  | 18 / 41 (43.90%) |
| occurrences (all)                    | 65               | 18               | 70               |
| WEIGHT GAIN                          |                  |                  |                  |
| alternative dictionary used: CTC 4.0 |                  |                  |                  |

|  |  |   |   |
|--|--|---|---|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>WEIGHT LOSS</p> <p>alternative dictionary used: CTC 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>WHITE BLOOD CELL DECREASED</p> <p>alternative dictionary used: CTC 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>2 / 46 (4.35%)</p> <p>11</p> <p>7 / 46 (15.22%)</p> <p>37</p> <p>20 / 46 (43.48%)</p> <p>103</p>                            | <p>3 / 40 (7.50%)</p> <p>3</p> <p>14 / 40 (35.00%)</p> <p>31</p> <p>25 / 40 (62.50%)</p> <p>59</p>                          | <p>9 / 41 (21.95%)</p> <p>41</p> <p>6 / 41 (14.63%)</p> <p>36</p> <p>25 / 41 (60.98%)</p> <p>110</p>                        |
| <p>Injury, poisoning and procedural complications</p> <p>INJURY, POISONING AND PROCEDURAL COMPLICATIONS</p> <p>alternative dictionary used: CTC 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>2 / 46 (4.35%)</p> <p>2</p>   | <p>0 / 40 (0.00%)</p> <p>0</p>  | <p>3 / 41 (7.32%)</p> <p>11</p>   |
| <p>Cardiac disorders</p> <p>LEFT VENTRICULAR SYSTOLIC DYSFUNCTION</p> <p>alternative dictionary used: CTC 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>OTHER CARDIAC DISORDERS</p> <p>alternative dictionary used: CTC 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>PALPITATIONS</p> <p>alternative dictionary used: CTC 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>VENTRICULAR ARRHYTHMIA</p> <p>alternative dictionary used: CTC 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 46 (2.17%)</p> <p>1</p> <p>5 / 46 (10.87%)</p> <p>7</p> <p>6 / 46 (13.04%)</p> <p>10</p> <p>1 / 46 (2.17%)</p> <p>1</p> | <p>0 / 40 (0.00%)</p> <p>0</p> <p>2 / 40 (5.00%)</p> <p>2</p> <p>3 / 40 (7.50%)</p> <p>5</p> <p>0 / 40 (0.00%)</p> <p>0</p> | <p>0 / 41 (0.00%)</p> <p>0</p> <p>1 / 41 (2.44%)</p> <p>2</p> <p>3 / 41 (7.32%)</p> <p>3</p> <p>0 / 41 (0.00%)</p> <p>0</p> |
| Nervous system disorders   |  |   |   |

|  |                         |                        |                         |
|--|-------------------------|------------------------|-------------------------|
| <b>DIZZINESS</b><br>alternative dictionary used: CTC 4.0<br>subjects affected / exposed<br>occurrences (all)   | 3 / 46 (6.52%)<br>5     | 0 / 40 (0.00%)<br>0    | 2 / 41 (4.88%)<br>5     |
| <b>HEADACHE</b><br>alternative dictionary used: CTC 4.0<br>subjects affected / exposed<br>occurrences (all)  | 7 / 46 (15.22%)<br>13   | 4 / 40 (10.00%)<br>6   | 10 / 41 (24.39%)<br>29  |
| <b>DYSGEUSIA</b><br>alternative dictionary used: CTC 4.0<br>subjects affected / exposed<br>occurrences (all)   | 2 / 46 (4.35%)<br>3     | 3 / 40 (7.50%)<br>10   | 4 / 41 (9.76%)<br>9     |
| <b>OTHER NERVOUS SYSTEM DISORDERS</b><br>alternative dictionary used: CTC 4.0<br>subjects affected / exposed<br>occurrences (all)                        | 5 / 46 (10.87%)<br>8    | 3 / 40 (7.50%)<br>11   | 2 / 41 (4.88%)<br>4     |
| <b>PERIPHERAL MOTOR NEUROPATHY</b><br>alternative dictionary used: CTC 4.0<br>subjects affected / exposed<br>occurrences (all)                           | 2 / 46 (4.35%)<br>2     | 0 / 40 (0.00%)<br>0    | 0 / 41 (0.00%)<br>0     |
| <b>PERIPHERAL SENSORY NEUROPATHY</b><br>alternative dictionary used: CTC 4.0<br>subjects affected / exposed<br>occurrences (all)                         | 3 / 46 (6.52%)<br>5     | 2 / 40 (5.00%)<br>2    | 4 / 41 (9.76%)<br>4     |
| <b>Blood and lymphatic system disorders</b><br><b>ANEMIA</b><br>alternative dictionary used: CTC 4.0<br>subjects affected / exposed<br>occurrences (all) | 32 / 46 (69.57%)<br>139 | 26 / 40 (65.00%)<br>70 | 32 / 41 (78.05%)<br>165 |
| <b>FEBRILE NEUTROPENIA</b><br>alternative dictionary used: CTC 4.0<br>subjects affected / exposed<br>occurrences (all)                                   | 6 / 46 (13.04%)<br>8    | 3 / 40 (7.50%)<br>3    | 5 / 41 (12.20%)<br>6    |
| <b>Ear and labyrinth disorders</b>   |                         |                        |                         |

|  |   |   |  |
|--|---|---|--|
| EAR AND LABYRINTH DISORDERS<br>alternative dictionary used: CTC 4.0<br>subjects affected / exposed<br>occurrences (all)  | 1 / 46 (2.17%)<br>1   | 0 / 40 (0.00%)<br>0   | 5 / 41 (12.20%)<br>5   |
| Eye disorders<br>EYE DISORDERS<br>alternative dictionary used: CTC 4.0<br>subjects affected / exposed<br>occurrences (all)   | 1 / 46 (2.17%)<br>13  | 4 / 40 (10.00%)<br>7  | 5 / 41 (12.20%)<br>16  |
| Gastrointestinal disorders<br>ABDOMINAL DISTENSION<br>alternative dictionary used: CTC 4.0<br>subjects affected / exposed<br>occurrences (all)<br><br>CONSTIPATION<br>alternative dictionary used: CTC 4.0<br>subjects affected / exposed<br>occurrences (all)<br><br>DIARRHEA<br>alternative dictionary used: CTC 4.0<br>subjects affected / exposed<br>occurrences (all)<br><br>FLATULENCE<br>alternative dictionary used: CTC 4.0<br>subjects affected / exposed<br>occurrences (all)<br><br>GASTROESOPHAGEAL REFLUX DISEASE<br>alternative dictionary used: CTC 4.0<br>subjects affected / exposed<br>occurrences (all)<br><br>GASTROINTESTINAL PAIN<br>alternative dictionary used: CTC 4.0<br>subjects affected / exposed<br>occurrences (all)<br><br>MUCOSITIS ORAL | 2 / 46 (4.35%)<br>3<br><br>16 / 46 (34.78%)<br>42<br><br>9 / 46 (19.57%)<br>12<br><br>2 / 46 (4.35%)<br>2<br><br>3 / 46 (6.52%)<br>5<br><br>3 / 46 (6.52%)<br>4 | 1 / 40 (2.50%)<br>1<br><br>13 / 40 (32.50%)<br>19<br><br>5 / 40 (12.50%)<br>6<br><br>1 / 40 (2.50%)<br>1<br><br>1 / 40 (2.50%)<br>2<br><br>5 / 40 (12.50%)<br>5 | 2 / 41 (4.88%)<br>3<br><br>24 / 41 (58.54%)<br>76<br><br>7 / 41 (17.07%)<br>10<br><br>1 / 41 (2.44%)<br>2<br><br>3 / 41 (7.32%)<br>11<br><br>7 / 41 (17.07%)<br>11 |

|  |                        |                        |                         |
|--|------------------------|------------------------|-------------------------|
| alternative dictionary used: CTC<br>4.0<br>subjects affected / exposed<br>occurrences (all)  | 4 / 46 (8.70%)<br>9    | 14 / 40 (35.00%)<br>22 | 5 / 41 (12.20%)<br>5    |
| NAUSEA<br>alternative dictionary used: CTC<br>4.0<br>subjects affected / exposed<br>occurrences (all)  | 26 / 46 (56.52%)<br>72 | 18 / 40 (45.00%)<br>45 | 30 / 41 (73.17%)<br>168 |
| OTHER GASTROINTESTINAL<br>DISORDERS<br>alternative dictionary used: CTC<br>4.0<br>subjects affected / exposed<br>occurrences (all)                 | 7 / 46 (15.22%)<br>10  | 13 / 40 (32.50%)<br>16 | 11 / 41 (26.83%)<br>36  |
| VOMITING<br>alternative dictionary used: CTC<br>4.0<br>subjects affected / exposed<br>occurrences (all)  | 20 / 46 (43.48%)<br>41 | 8 / 40 (20.00%)<br>11  | 16 / 41 (39.02%)<br>89  |
| Hepatobiliary disorders<br>HEPATOBIILIARY DISORDERS<br>alternative dictionary used: CTC<br>4.0<br>subjects affected / exposed<br>occurrences (all) | 2 / 46 (4.35%)<br>6    | 1 / 40 (2.50%)<br>1    | 4 / 41 (9.76%)<br>8     |
| Skin and subcutaneous tissue disorders<br>ALOPECIA<br>alternative dictionary used: CTC<br>4.0<br>subjects affected / exposed<br>occurrences (all)  | 2 / 46 (4.35%)<br>13   | 21 / 40 (52.50%)<br>85 | 0 / 41 (0.00%)<br>0     |
| DRY SKIN<br>alternative dictionary used: CTC<br>4.0<br>subjects affected / exposed<br>occurrences (all)  | 2 / 46 (4.35%)<br>5    | 3 / 40 (7.50%)<br>5    | 0 / 41 (0.00%)<br>0     |
| OTHER SKIN AND SUBCUTANEOUS<br>TISSUE DISORDERS<br>alternative dictionary used: CTC<br>4.0<br>subjects affected / exposed<br>occurrences (all)     | 1 / 46 (2.17%)<br>1    | 4 / 40 (10.00%)<br>4   | 1 / 41 (2.44%)<br>1     |
| ERYTHEMA MULTIFORME  |                        |                        |                         |

|  |                 |                |                |
|--|-----------------|----------------|----------------|
| alternative dictionary used: CTC 4.0     |                 |                |                |
| subjects affected / exposed              | 0 / 46 (0.00%)  | 0 / 40 (0.00%) | 1 / 41 (2.44%) |
| occurrences (all)                        | 0               | 0              | 1              |
| <b>RASH MACULO-PAPULAR</b>               |                 |                |                |
| alternative dictionary used: CTC 4.0     |                 |                |                |
| subjects affected / exposed              | 1 / 46 (2.17%)  | 0 / 40 (0.00%) | 1 / 41 (2.44%) |
| occurrences (all)                        | 2               | 0              | 1              |
| <b>PRURITUS</b>                          |                 |                |                |
| alternative dictionary used: CTC 4.0     |                 |                |                |
| subjects affected / exposed              | 2 / 46 (4.35%)  | 2 / 40 (5.00%) | 0 / 41 (0.00%) |
| occurrences (all)                        | 2               | 3              | 0              |
| <b>Renal and urinary disorders</b>       |                 |                |                |
| <b>CYSTITIS NONINFECTIVE</b>             |                 |                |                |
| alternative dictionary used: CTC 4.0     |                 |                |                |
| subjects affected / exposed              | 1 / 46 (2.17%)  | 0 / 40 (0.00%) | 0 / 41 (0.00%) |
| occurrences (all)                        | 1               | 0              | 0              |
| <b>HEMATURIA</b>                         |                 |                |                |
| alternative dictionary used: CTC 4.0     |                 |                |                |
| subjects affected / exposed              | 1 / 46 (2.17%)  | 0 / 40 (0.00%) | 0 / 41 (0.00%) |
| occurrences (all)                        | 2               | 0              | 0              |
| <b>OTHER RENAL AND URINARY DISORDERS</b> |                 |                |                |
| alternative dictionary used: CTC 4.0     |                 |                |                |
| subjects affected / exposed              | 6 / 46 (13.04%) | 3 / 40 (7.50%) | 4 / 41 (9.76%) |
| occurrences (all)                        | 7               | 7              | 5              |
| <b>PROTEINURIA</b>                       |                 |                |                |
| alternative dictionary used: CTC 4.0     |                 |                |                |
| subjects affected / exposed              | 2 / 46 (4.35%)  | 0 / 40 (0.00%) | 0 / 41 (0.00%) |
| occurrences (all)                        | 3               | 0              | 0              |
| <b>URINARY FREQUENCY</b>                 |                 |                |                |
| alternative dictionary used: CTC 4.0     |                 |                |                |
| subjects affected / exposed              | 4 / 46 (8.70%)  | 3 / 40 (7.50%) | 0 / 41 (0.00%) |
| occurrences (all)                        | 4               | 5              | 0              |
| <b>Endocrine disorders</b>               |                 |                |                |

|   |  |  |  |
|---|--|--|--|
| <p>ENDOCRINE DISORDERS</p> <p>alternative dictionary used: CTC 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>1 / 46 (2.17%)</p> <p>1</p>   | <p>0 / 40 (0.00%)</p> <p>0</p>   | <p>0 / 41 (0.00%)</p> <p>0</p>   |
| <p>Musculoskeletal and connective tissue disorders</p> <p>ARTHRALGIA</p> <p>alternative dictionary used: CTC 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>BACK PAIN</p> <p>alternative dictionary used: CTC 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>BONE PAIN</p> <p>alternative dictionary used: CTC 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>MYALGIA</p> <p>alternative dictionary used: CTC 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>GENERALIZED MUSCLE WEAKNESS</p> <p>alternative dictionary used: CTC 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>OTHER MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS</p> <p>alternative dictionary used: CTC 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>3 / 46 (6.52%)</p> <p>4</p> <p>2 / 46 (4.35%)</p> <p>4</p> <p>0 / 46 (0.00%)</p> <p>0</p> <p>7 / 46 (15.22%)</p> <p>11</p> <p>1 / 46 (2.17%)</p> <p>6</p> <p>5 / 46 (10.87%)</p> <p>9</p> | <p>0 / 40 (0.00%)</p> <p>0</p> <p>2 / 40 (5.00%)</p> <p>2</p> <p>1 / 40 (2.50%)</p> <p>1</p> <p>1 / 40 (2.50%)</p> <p>0</p> <p>1 / 40 (2.50%)</p> <p>1</p> | <p>2 / 41 (4.88%)</p> <p>15</p> <p>0 / 41 (0.00%)</p> <p>0</p> <p>2 / 41 (4.88%)</p> <p>2</p> <p>7 / 41 (17.07%)</p> <p>23</p> <p>2 / 41 (4.88%)</p> <p>2</p> <p>4 / 41 (9.76%)</p> <p>5</p> |
| <p>Infections and infestations</p> <p>INFECTION</p> <p>alternative dictionary used: CTC 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>15 / 46 (32.61%)</p> <p>31</p>  | <p>9 / 40 (22.50%)</p> <p>17</p>   | <p>7 / 41 (17.07%)</p> <p>8</p>  |

|                                      |                  |                 |                  |
|--------------------------------------|------------------|-----------------|------------------|
| Metabolism and nutrition disorders   |                  |                 |                  |
| ANOREXIA                             |                  |                 |                  |
| alternative dictionary used: CTC 4.0 |                  |                 |                  |
| subjects affected / exposed          | 8 / 46 (17.39%)  | 8 / 40 (20.00%) | 13 / 41 (31.71%) |
| occurrences (all)                    | 20               | 13              | 23               |
| HYPERCALCEMIA                        |                  |                 |                  |
| alternative dictionary used: CTC 4.0 |                  |                 |                  |
| subjects affected / exposed          | 2 / 46 (4.35%)   | 0 / 40 (0.00%)  | 3 / 41 (7.32%)   |
| occurrences (all)                    | 2                | 0               | 4                |
| DEHYDRATION                          |                  |                 |                  |
| alternative dictionary used: CTC 4.0 |                  |                 |                  |
| subjects affected / exposed          | 3 / 46 (6.52%)   | 5 / 40 (12.50%) | 2 / 41 (4.88%)   |
| occurrences (all)                    | 3                | 6               | 2                |
| HYPERGLYCEMIA                        |                  |                 |                  |
| alternative dictionary used: CTC 4.0 |                  |                 |                  |
| subjects affected / exposed          | 10 / 46 (21.74%) | 8 / 40 (20.00%) | 4 / 41 (9.76%)   |
| occurrences (all)                    | 23               | 17              | 15               |
| HYPERKALEMIA                         |                  |                 |                  |
| alternative dictionary used: CTC 4.0 |                  |                 |                  |
| subjects affected / exposed          | 11 / 46 (23.91%) | 2 / 40 (5.00%)  | 8 / 41 (19.51%)  |
| occurrences (all)                    | 14               | 2               | 14               |
| HYPERNATREMIA                        |                  |                 |                  |
| alternative dictionary used: CTC 4.0 |                  |                 |                  |
| subjects affected / exposed          | 5 / 46 (10.87%)  | 1 / 40 (2.50%)  | 3 / 41 (7.32%)   |
| occurrences (all)                    | 7                | 1               | 5                |
| HYPOALBUMINEMIA                      |                  |                 |                  |
| alternative dictionary used: CTC 4.0 |                  |                 |                  |
| subjects affected / exposed          | 13 / 46 (28.26%) | 5 / 40 (12.50%) | 10 / 41 (24.39%) |
| occurrences (all)                    | 46               | 9               | 26               |
| HYPOGLYCEMIA                         |                  |                 |                  |
| alternative dictionary used: CTC 4.0 |                  |                 |                  |
| subjects affected / exposed          | 4 / 46 (8.70%)   | 1 / 40 (2.50%)  | 0 / 41 (0.00%)   |
| occurrences (all)                    | 4                | 2               | 0                |
| HYPOCALCEMIA                         |                  |                 |                  |
| alternative dictionary used: CTC 4.0 |                  |                 |                  |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed              | 8 / 46 (17.39%) | 4 / 40 (10.00%) | 7 / 41 (17.07%) |
| occurrences (all)                        | 18              | 5               | 20              |
| HYPOKALEMIA                              |                 |                 |                 |
| alternative dictionary used: CTC 4.0     |                 |                 |                 |
| subjects affected / exposed              | 9 / 46 (19.57%) | 5 / 40 (12.50%) | 7 / 41 (17.07%) |
| occurrences (all)                        | 14              | 12              | 11              |
| HYPONATREMIA                             |                 |                 |                 |
| alternative dictionary used: CTC 4.0     |                 |                 |                 |
| subjects affected / exposed              | 8 / 46 (17.39%) | 5 / 40 (12.50%) | 2 / 41 (4.88%)  |
| occurrences (all)                        | 15              | 8               | 3               |
| OTHER METABOLISM AND NUTRITION DISORDERS |                 |                 |                 |
| alternative dictionary used: CTC 4.0     |                 |                 |                 |
| subjects affected / exposed              | 5 / 46 (10.87%) | 4 / 40 (10.00%) | 5 / 41 (12.20%) |
| occurrences (all)                        | 9               | 17              | 29              |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 24 February 2011 | Changes in the main criteria for inclusion.<br>Additional information on Trabectedin<br>- Metabolism and elimination<br>- Safety data<br>- Treatment schedule modifications: CPK elevation<br>- impact on other medication<br>Precision of Clinical evaluation, laboratory tests and follow-up |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date         | Interruption   | Restart date |
|--------------|--|--------------|
| 04 July 2013 | Following an IDMC (04/07/2013), it has been decided to close this study (phase II) and not proceed to the phase III part, as none of the experimental arms provided any real benefit compared to the standard. | -            |

Notes:

### Limitations and caveats

None reported