



## Clinical trial results:

### A randomized phase II study of prednisone, vinblastine, doxorubicin, and gemcitabine in patients with intermediate stage Hodgkin's lymphoma

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2007-003467-48   |
| Trial protocol           | DE               |
| Global end of trial date | 17 November 2013 |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 23 April 2020 |
| First version publication date | 23 April 2020 |

#### Trial information

##### Trial identification

|                       |               |
|-----------------------|---------------|
| Sponsor protocol code | Uni-Koeln-949 |
|-----------------------|---------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00512980 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | University of Cologne   |
| Sponsor organisation address | Albertus Magnus-Platz, Köln, Germany, 50923   |
| Public contact               | Trial Coordination Center of the German Hodgkin Study Group (GHSG), German Hodgkin Study Group (GHSG), 0049 22147888200, ghsg@uk-koeln.de |
| Scientific contact           | Trial Coordination Center of the German Hodgkin Study Group (GHSG), German Hodgkin Study Group (GHSG), 0049 22147888200, ghsg@uk-koeln.de |

Notes:

#### Paediatric regulatory details

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

Notes:

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**Results analysis stage**

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|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 05 December 2013 |
| Is this the analysis of the primary completion data? | No               |

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|                                  |                  |
|----------------------------------|------------------|
| Global end of trial reached?     | Yes              |
| Global end of trial date         | 17 November 2013 |
| Was the trial ended prematurely? | Yes              |

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Notes:

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**General information about the trial**

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Main objective of the trial:

The primary objectives of this phase II trial were to assess the toxicity and activity of PVAG-14 in patients with early-stage unfavorable Hodgkin lymphoma.

Protection of trial subjects:

Written informed consent prior to study entry, G-CSF prophylaxis, weekly blood tests during therapy, dose reduction strategy in case of inadequate recovery of blood values

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 17 November 2008 |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Efficacy         |
| Long term follow-up duration                              | 2 Years          |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

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Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |             |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Germany: 41 |
| Worldwide total number of subjects   | 41          |
| EEA total number of subjects         | 41          |

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Notes:

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**Subjects enrolled per age group**

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|   |    |
|---|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 0  |
| Children (2-11 years)                     | 0  |
| Adolescents (12-17 years)                 | 0  |
| Adults (18-64 years)                      | 41 |
| From 65 to 84 years                       | 0  |

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|                   |   |
|-------------------|---|
| 85 years and over | 0 |
|-------------------|---|

## Subject disposition

### Recruitment

Recruitment details:

Recruitment started on 17 Nov 2008, was much slower than expected even after increasing the number of trial sites and extending the recruitment period, and was stopped on 13 May 2011 with a total of 41 patients enrolled, because it was deemed unlikely to reach the planned number of 100 patients in a reasonable time.

### Pre-assignment

Screening details:

Pre-study assessments should be performed within 28 days prior to enrollment. Main inclusion criteria: previously untreated, histologically confirmed Hodgkin lymphoma; CSI-II with  $\geq 1$  risk factor; age 18-60 years. Main exclusion criteria: prior chemo- or radiotherapy; concurrent disease preventing protocol treatment; pregnancy, lactation; ECOG  $>2$ .

### Period 1

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

Blinding implementation details:

Not applicable

### Arms

|                              |                       |
|------------------------------|-----------------------|
| Are arms mutually exclusive? | Yes                   |
| <b>Arm title</b>             | 8x PVAG-14, Doxo=25mg |

Arm description:

Eight cycles of the PVAG chemotherapy regimen with a doxorubicin dose of 25 mg/m<sup>2</sup> BSA recycled every 14 days; involved-field radiotherapy applied 4-6 weeks after the end of chemotherapy with an overall dose of 30 Gy (1.8-2.0 Gy 5 times per week)

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Prednisone   |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

50 mg Prednisone administered on days 1-3 of each 14-day cycle

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

Dosage and administration details:

6 mg Vinblastine per m<sup>2</sup> BSA administered on day 1 of each 14-day cycle over 10 minutes

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

Dosage and administration details:

25 mg Doxorubicin per m<sup>2</sup> BSA administered on day 1 of each 14-day cycle over 30 minutes

|   |                                  |
|---|----------------------------------|
| Investigational medicinal product name  | Gemcitabine                      |
| Investigational medicinal product code  |                                  |
| Other name  |                                  |
| Pharmaceutical forms  | Powder for solution for infusion |
| Routes of administration  | Intravenous use                  |
| Dosage and administration details:  |                                  |
| 1000 mg Gemcitabine per m <sup>2</sup> BSA administered on day 1 of each 14-day cycle over 30 minutes |                                  |
| <b>Arm title</b>  | 8x PVAG-14, Doxo=35mg            |

Arm description:

Eight cycles of the PVAG chemotherapy regimen with a doxorubicin dose of 35 mg/m<sup>2</sup> BSA recycled every 14 days; involved-field radiotherapy applied 4-6 weeks after the end of chemotherapy with an overall dose of 30 Gy (1.8-2.0 Gy 5 times per week)

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Prednisone   |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

50 mg Prednisone administered on days 1-3 of each 14-day cycle

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

Dosage and administration details:

6 mg Vinblastine per m<sup>2</sup> BSA administered on day 1 of each 14-day cycle over 10 minutes

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

Dosage and administration details:

35 mg Doxorubicin per m<sup>2</sup> BSA administered on day 1 of each 14-day cycle over 30 minutes

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

Dosage and administration details:

1000 mg Gemcitabine per m<sup>2</sup> BSA administered on day 1 of each 14-day cycle over 30 minutes

| <b>Number of subjects in period 1</b> | 8x PVAG-14,<br>Doxo=25mg | 8x PVAG-14,<br>Doxo=35mg |
|---------------------------------------|--------------------------|--------------------------|
| Started                               | 21                       | 20                       |
| Completed                             | 20                       | 20                       |
| Not completed                         | 1                        | 0                        |
| Adverse event, non-fatal              | 1                        | -                        |



## Baseline characteristics

### Reporting groups

|                       |                       |
|-----------------------|-----------------------|
| Reporting group title | 8x PVAG-14, Doxo=25mg |
|-----------------------|-----------------------|

Reporting group description:

Eight cycles of the PVAG chemotherapy regimen with a doxorubicin dose of 25 mg/m<sup>2</sup> BSA recycled every 14 days; involved-field radiotherapy applied 4-6 weeks after the end of chemotherapy with an overall dose of 30 Gy (1.8-2.0 Gy 5 times per week)

|                       |                       |
|-----------------------|-----------------------|
| Reporting group title | 8x PVAG-14, Doxo=35mg |
|-----------------------|-----------------------|

Reporting group description:

Eight cycles of the PVAG chemotherapy regimen with a doxorubicin dose of 35 mg/m<sup>2</sup> BSA recycled every 14 days; involved-field radiotherapy applied 4-6 weeks after the end of chemotherapy with an overall dose of 30 Gy (1.8-2.0 Gy 5 times per week)

| Reporting group values                                | 8x PVAG-14,<br>Doxo=25mg | 8x PVAG-14,<br>Doxo=35mg | Total |
|---|--------------------------|--------------------------|-------|
| Number of subjects                                    | 21                       | 20                       | 41    |
| Age categorical                                       |                          |                          |       |
| Units: Subjects                                       |                          |                          |       |
| In utero  | 0                        | 0                        | 0     |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0                        | 0                        | 0     |
| Newborns (0-27 days)                                  | 0                        | 0                        | 0     |
| Infants and toddlers (28 days-23<br>months)           | 0                        | 0                        | 0     |
| Children (2-11 years)                                 | 0                        | 0                        | 0     |
| Adolescents (12-17 years)                             | 0                        | 0                        | 0     |
| Adults (18-64 years)                                  | 21                       | 20                       | 41    |
| From 65-84 years                                      | 0                        | 0                        | 0     |
| 85 years and over                                     | 0                        | 0                        | 0     |
| Age continuous  |                          |                          |       |
| Units: years  |                          |                          |       |
| median  | 33                       | 38.5                     |       |
| full range (min-max)                                  | 18 to 57                 | 19 to 53                 | -     |
| Gender categorical                                    |                          |                          |       |
| Units: Subjects                                       |                          |                          |       |
| Female  | 11                       | 10                       | 21    |
| Male  | 10                       | 10                       | 20    |
| Ann Arbor Stage                                       |                          |                          |       |
| Units: Subjects                                       |                          |                          |       |
| IA  | 0                        | 0                        | 0     |
| IB  | 0                        | 1                        | 1     |
| IIA   | 17                       | 14                       | 31    |
| IIB   | 4                        | 5                        | 9     |
| ECOG performance status                               |                          |                          |       |
| Units: Subjects                                       |                          |                          |       |
| ECOG 0  | 15                       | 16                       | 31    |
| ECOG 1  | 6                        | 4                        | 10    |
| Large mediastinal mass                                |                          |                          |       |
| Units: Subjects                                       |                          |                          |       |
| No  | 16                       | 17                       | 33    |

|  |    |    |    |
|--|----|----|----|
| Yes  | 5  | 3  | 8  |
| Extranodal disease<br>Units: Subjects                      |    |    |    |
| No   | 20 | 19 | 39 |
| Yes  | 1  | 1  | 2  |
| Involvement of 3 or more nodal areas<br>Units: Subjects    |    |    |    |
| No   | 5  | 11 | 16 |
| Yes  | 16 | 9  | 25 |
| Elevated erythrocyte sedimentation rate<br>Units: Subjects |    |    |    |
| No   | 10 | 10 | 20 |
| Yes  | 11 | 10 | 21 |

### Subject analysis sets

|                            |                         |
|----------------------------|-------------------------|
| Subject analysis set title | Pooled treatment groups |
| Subject analysis set type  | Full analysis           |

Subject analysis set description:

Secondary efficacy endpoints were analyzed in the pooled treatment groups to increase power.

| Reporting group values                                | Pooled treatment groups |  |  |
|---|-------------------------|--|--|
| Number of subjects                                    | 41                      |  |  |
| Age categorical<br>Units: Subjects                    |                         |  |  |
| In utero  | 0                       |  |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 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)                                  | 41                      |  |  |
| From 65-84 years                                      | 0                       |  |  |
| 85 years and over                                     | 0                       |  |  |
| Age continuous<br>Units: years                        |                         |  |  |
| median  | 38                      |  |  |
| full range (min-max)                                  | 18 to 57                |  |  |
| Gender categorical<br>Units: Subjects                 |                         |  |  |
| Female  | 21                      |  |  |
| Male  | 20                      |  |  |
| Ann Arbor Stage<br>Units: Subjects                    |                         |  |  |
| IA  | 0                       |  |  |
| IB  | 1                       |  |  |
| IIA   | 31                      |  |  |
| IIB   | 9                       |  |  |
| ECOG performance status                               |                         |  |  |



|   |    |  |  |
|---|----|--|--|
| Units: Subjects                         |    |  |  |
| ECOG 0                                  | 31 |  |  |
| ECOG 1                                  | 10 |  |  |
| Large mediastinal mass                  |    |  |  |
| Units: Subjects                         |    |  |  |
| No                                      | 33 |  |  |
| Yes                                     | 8  |  |  |
| Extranodal disease                      |    |  |  |
| Units: Subjects                         |    |  |  |
| No                                      | 39 |  |  |
| Yes                                     | 2  |  |  |
| Involvement of 3 or more nodal areas    |    |  |  |
| Units: Subjects                         |    |  |  |
| No                                      | 16 |  |  |
| Yes                                     | 25 |  |  |
| Elevated erythrocyte sedimentation rate |    |  |  |
| Units: Subjects                         |    |  |  |
| No                                      | 20 |  |  |
| Yes                                     | 21 |  |  |

## End points

### End points reporting groups

|   |                         |
|---|-------------------------|
| Reporting group title   | 8x PVAG-14, Doxo=25mg   |
| Reporting group description:<br>Eight cycles of the PVAG chemotherapy regimen with a doxorubicin dose of 25 mg/m <sup>2</sup> BSA recycled every 14 days; involved-field radiotherapy applied 4-6 weeks after the end of chemotherapy with an overall dose of 30 Gy (1.8-2.0 Gy 5 times per week) |                         |
| Reporting group title   | 8x PVAG-14, Doxo=35mg   |
| Reporting group description:<br>Eight cycles of the PVAG chemotherapy regimen with a doxorubicin dose of 35 mg/m <sup>2</sup> BSA recycled every 14 days; involved-field radiotherapy applied 4-6 weeks after the end of chemotherapy with an overall dose of 30 Gy (1.8-2.0 Gy 5 times per week) |                         |
| Subject analysis set title  | Pooled treatment groups |
| Subject analysis set type   | Full analysis           |
| Subject analysis set description:<br>Secondary efficacy endpoints were analyzed in the pooled treatment groups to increase power.   |                         |

### Primary: Complete remission rate

|   |  |
|---|--|
| End point title   | Complete remission rate <sup>[1]</sup> |
| End point description:<br>Complete remission rate was assessed in the CT-based definitive restaging 4-6 weeks after completion of radiotherapy.<br>Two interim analyses and a final analysis were planned. The first interim analysis was scheduled after 19 patients per arm were evaluable. Enrollment was stopped by the time of the interim analyses because of slow recruitment, leaving only 3 patients enrolled in addition to the interim analysis sample. The second interim analysis was thus not done. The final analysis was done descriptively for both arms separately including all enrolled patients. |  |
| End point type  | Primary                                |
| End point timeframe:<br>4-6 weeks after completion of radiotherapy  |  |

Notes:

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

Justification: Enrollment was stopped after 41 out of 100 planned patients because of slow recruitment. Due to the small sample size, analysis was done descriptively; no confirmative test, no subgroup analyses and no sensitivity analyses were done. The protocol defines a complete remission rate of 83% as benchmark for insufficient efficacy. The 95% CI for the observed overall complete remission rate of 98% ranged from 87% to 100% and thus exceeded the predefined efficacy benchmark.

| End point values            | 8x PVAG-14,<br>Doxo=25mg | 8x PVAG-14,<br>Doxo=35mg |  |  |
|-----------------------------|--------------------------|--------------------------|--|--|
| Subject group type          | Reporting group          | Reporting group          |  |  |
| Number of subjects analysed | 21                       | 20                       |  |  |
| Units: patients             |                          |                          |  |  |
| Partial remission           | 1                        | 0                        |  |  |
| Complete remission          | 20                       | 20                       |  |  |

### Statistical analyses

No statistical analyses for this end point

**Primary: Incidence of hematological toxicity grade III/IV**

|                 |   |
|-----------------|---|
| End point title | Incidence of hematological toxicity grade III/IV <sup>[2]</sup> |
|-----------------|---|

End point description:

Hematological toxicity was defined as any case of leukopenia, thrombocytopenia or anemia of CTCAE grade III or IV at any time during chemotherapy.

Two interim analyses and a final analysis were planned. The first interim analysis was scheduled after 19 patients per arm were evaluable. Enrollment was stopped by the time of the interim analyses because of slow recruitment, leaving only 3 patients enrolled in addition to the interim analysis sample. The second interim analysis was thus not done. The final analysis was done descriptively for both arms separately including all enrolled patients.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

During chemotherapy

Notes:

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

Justification: Enrollment was stopped after 41 out of 100 planned patients because of slow recruitment. Due to the small sample size, analysis was done descriptively; no confirmative test, no subgroup analyses and no sensitivity analyses were done. The protocol defines a hematological toxicity incidence of 62% as benchmark for unacceptable toxicity. The 95% CI for the observed incidence of 10% ranged from 3% to 23% and was thus below the toxicity benchmark.

| End point values                                | 8x PVAG-14,<br>Doxo=25mg | 8x PVAG-14,<br>Doxo=35mg |  |  |
|---|--------------------------|--------------------------|--|--|
| Subject group type                              | Reporting group          | Reporting group          |  |  |
| Number of subjects analysed                     | 21                       | 20                       |  |  |
| Units: patients                                 |                          |                          |  |  |
| Hematological toxicity of CTCAE grade III/IV    | 1                        | 3                        |  |  |
| No hematological toxicity of CTCAE grade III/IV | 20                       | 17                       |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Progression-free survival**

|                 |                           |
|-----------------|---------------------------|
| End point title | Progression-free survival |
|-----------------|---------------------------|

End point description:

Progression-free survival was calculated from the date of initial staging until progressive disease, relapse, or death from any cause or, if none of these occurred, censored at the date of the last determination of continuing remission.

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

End point timeframe:

Progression-free survival at 2 years

| End point values                 | Pooled treatment groups |  |  |  |
|----------------------------------|-------------------------|--|--|--|
| Subject group type               | Subject analysis set    |  |  |  |
| Number of subjects analysed      | 41                      |  |  |  |
| Units: percent                   |                         |  |  |  |
| number (confidence interval 95%) | 94.2 (86.3 to 100)      |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall survival

|   |                  |
|---|------------------|
| End point title   | Overall survival |
| End point description:  |                  |
| Overall survival was calculated from the date of initial staging until death from any cause or, if the patient was alive, censored at the date of the last information about the patient. |                  |
| End point type  | Secondary        |
| End point timeframe:  |                  |
| Overall survival at 2 years   |                  |

| End point values            | Pooled treatment groups |  |  |  |
|-----------------------------|-------------------------|--|--|--|
| Subject group type          | Subject analysis set    |  |  |  |
| Number of subjects analysed | 41                      |  |  |  |
| Units: percent              |                         |  |  |  |
| number (not applicable)     | 100                     |  |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From start of treatment until 28 days after last study treatment or until AE resolution; AEs beginning >28 days after final study treatment reported only if considered related to study treatment

Adverse event reporting additional description:

All AEs greater than CTCAE grade 2 were to be recorded in the source documents and the CRFs.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 10.1 |
|--------------------|------|

### Reporting groups

|                       |                       |
|-----------------------|-----------------------|
| Reporting group title | 8x PVAG-14, Doxo=25mg |
|-----------------------|-----------------------|

Reporting group description:

Eight cycles of the PVAG chemotherapy regimen with a doxorubicin dose of 25 mg/m<sup>2</sup> BSA recycled every 14 days; involved-field radiotherapy applied 4-6 weeks after the end of chemotherapy with an overall dose of 30 Gy (1.8-2.0 Gy 5 times per week)

|                       |                       |
|-----------------------|-----------------------|
| Reporting group title | 8x PVAG-14, Doxo=35mg |
|-----------------------|-----------------------|

Reporting group description:

Eight cycles of the PVAG chemotherapy regimen with a doxorubicin dose of 35 mg/m<sup>2</sup> BSA recycled every 14 days; involved-field radiotherapy applied 4-6 weeks after the end of chemotherapy with an overall dose of 30 Gy (1.8-2.0 Gy 5 times per week)

| Serious adverse events                               | 8x PVAG-14,<br>Doxo=25mg | 8x PVAG-14,<br>Doxo=35mg |  |
|--|--------------------------|--------------------------|--|
| Total subjects affected by serious adverse events    |                          |                          |  |
| subjects affected / exposed                          | 4 / 21 (19.05%)          | 2 / 20 (10.00%)          |  |
| number of deaths (all causes)                        | 1                        | 0                        |  |
| number of deaths resulting from adverse events       | 0                        | 0                        |  |
| Nervous system disorders                             |                          |                          |  |
| Guillain-Barre syndrome                              |                          |                          |  |
| subjects affected / exposed                          | 1 / 21 (4.76%)           | 0 / 20 (0.00%)           |  |
| occurrences causally related to treatment / all      | 1 / 1                    | 0 / 0                    |  |
| deaths causally related to treatment / all           | 0 / 0                    | 0 / 0                    |  |
| Syncope  |                          |                          |  |
| subjects affected / exposed                          | 1 / 21 (4.76%)           | 0 / 20 (0.00%)           |  |
| occurrences causally related to treatment / all      | 1 / 1                    | 0 / 0                    |  |
| deaths causally related to treatment / all           | 0 / 0                    | 0 / 0                    |  |
| General disorders and administration site conditions |                          |                          |  |
| Pyrexia  |                          |                          |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 1 / 21 (4.76%) | 1 / 20 (5.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Gastrointestinal disorders</b>               |                |                |  |
| <b>Faecaloma</b>                                |                |                |  |
| subjects affected / exposed                     | 1 / 21 (4.76%) | 0 / 20 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Infections and infestations</b>              |                |                |  |
| <b>Abscess</b>                                  |                |                |  |
| subjects affected / exposed                     | 0 / 21 (0.00%) | 1 / 20 (5.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Scrotal abscess</b>                          |                |                |  |
| subjects affected / exposed                     | 0 / 21 (0.00%) | 1 / 20 (5.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Febrile infection</b>                        |                |                |  |
| subjects affected / exposed                     | 1 / 21 (4.76%) | 0 / 20 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

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

| <b>Non-serious adverse events</b>                            | 8x PVAG-14,<br>Doxo=25mg | 8x PVAG-14,<br>Doxo=35mg |  |
|--|--------------------------|--------------------------|--|
| <b>Total subjects affected by non-serious adverse events</b> |                          |                          |  |
| subjects affected / exposed                                  | 7 / 21 (33.33%)          | 8 / 20 (40.00%)          |  |
| <b>Nervous system disorders</b>                              |                          |                          |  |
| <b>Nervous system disorder</b>                               |                          |                          |  |
| alternative dictionary used: NCI CTCAE 3.0                   |                          |                          |  |
| alternative assessment type: Non-systematic                  |                          |                          |  |
| subjects affected / exposed                                  | 2 / 21 (9.52%)           | 0 / 20 (0.00%)           |  |
| occurrences (all)  | 6                        | 0                        |  |
| <b>Blood and lymphatic system disorders</b>                  |                          |                          |  |

|  |   |   |  |
|--|---|---|--|
| <p>Leukopenia</p> <p>alternative dictionary used: NCI<br/>CTCAE 3.0</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>1 / 21 (4.76%)</p> <p>4</p>                                | <p>3 / 20 (15.00%)</p> <p>3</p>                               |  |
| <p>General disorders and administration site conditions</p> <p>Drug fever</p> <p>alternative dictionary used: NCI<br/>CTCAE 3.0</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>1 / 21 (4.76%)</p> <p>1</p>                                | <p>1 / 20 (5.00%)</p> <p>1</p>                                |  |
| <p>Gastrointestinal disorders</p> <p>Nausea or vomiting</p> <p>alternative dictionary used: NCI<br/>CTCAE 3.0</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Mucositis</p> <p>alternative dictionary used: NCI<br/>CTCAE 3.0</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>2 / 21 (9.52%)</p> <p>4</p> <p>1 / 21 (4.76%)</p> <p>1</p> | <p>1 / 20 (5.00%)</p> <p>4</p> <p>1 / 20 (5.00%)</p> <p>2</p> |  |
| <p>Infections and infestations</p> <p>Infection</p> <p>alternative dictionary used: NCI<br/>CTCAE 3.0</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>2 / 21 (9.52%)</p> <p>2</p>                                | <p>1 / 20 (5.00%)</p> <p>1</p>                                |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date        | Amendment                            |
|-------------|--------------------------------------|
| 13 May 2011 | Premature termination of recruitment |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date        | Interruption                         | Restart date |
|-------------|--------------------------------------|--------------|
| 13 May 2011 | Premature termination of recruitment | -            |

Notes:

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Enrollment was stopped after 41 out of 100 planned patients because of slow recruitment. Due to the small sample size, analyses were done descriptively; no confirmative tests, no subgroup analyses and no sensitivity analyses were done.

Notes:

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/25768996>