



## Clinical trial results:

**A pivotal study of SGN-35 in treatment of patients with relapsed or refractory Hodgkin Lymphoma (HL) who have previously received autologous stem cell transplant.**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2008-006034-10 |
| Trial protocol           | DE BE IT FR GB |
| Global end of trial date | 14 May 2015    |

### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 31 July 2016 |
| First version publication date | 31 July 2016 |

### Trial information

#### Trial identification

|                       |            |
|-----------------------|------------|
| Sponsor protocol code | SG035-0003 |
|-----------------------|------------|

#### Additional study identifiers

|                                    |                  |
|------------------------------------|------------------|
| ISRCTN number                      | -                |
| ClinicalTrials.gov id (NCT number) | NCT00848926      |
| WHO universal trial number (UTN)   | -                |
| Other trial identifiers            | ADCETRIS: SGN-35 |

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Seattle Genetics, Inc.  |
| Sponsor organisation address | 21823 30th Drive SE, Bothell, United States, 98021                              |
| Public contact               | Chief Medical Officer, Seattle Genetics, Inc., 855 473-2436, medinfo@seagen.com |
| Scientific contact           | Chief Medical Officer, Seattle Genetics, Inc., 855 473-2436, medinfo@seagen.com |

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |                 |
|--|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 25 October 2015 |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 04 August 2010  |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 14 May 2015     |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

To determine the antitumor efficacy of single-agent brentuximab vedotin (1.8 mg/kg administered intravenously every 3 weeks) as measured by the overall objective response rate in patients with relapsed or refractory Hodgkin lymphoma following autologous stem cell transplant

Protection of trial subjects:

The protocol for this study was designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The conduct of all aspects of the study, including methods for obtaining informed consent, were also in accordance with principles enunciated in the declaration, the International Conference on Harmonisation (ICH) Good Clinical Practices (GCP), and applicable Food and Drug Administration (FDA) regulations/guidelines set forth in Title 21 CFR Parts 11, 50, 54, 56, and 312. The consent form approved by each IRB/IEC included all elements required by the applicable regional laws and regulations, including a statement that Seattle Genetics, Inc. and authorities had access to patient records. Consent was obtained from all patients before any protocol-required procedures were performed, including any procedure not part of normal patient care.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 18 February 2009 |
| 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 | France: 5         |
| Country: Number of subjects enrolled | Italy: 3          |
| Country: Number of subjects enrolled | Canada: 8         |
| Country: Number of subjects enrolled | United States: 86 |
| Worldwide total number of subjects   | 102               |
| EEA total number of subjects         | 8                 |

Notes:

### Subjects enrolled per age group

|   |   |
|---|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days)                      | 0 |

|  |    |
|--|----|
| Infants and toddlers (28 days-23 months) | 0  |
| Children (2-11 years)                    | 0  |
| Adolescents (12-17 years)                | 1  |
| Adults (18-64 years)                     | 98 |
| From 65 to 84 years                      | 3  |
| 85 years and over                        | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Feb 2009 to Aug 2009

### Pre-assignment

Screening details:

Patients must have had relapsed or refractory HL following autologous stem cell transplant.

### Period 1

|                              |                             |
|------------------------------|-----------------------------|
| Period 1 title               | Treatment (overall period)  |
| Is this the baseline period? | Yes                         |
| Allocation method            | Non-randomised - controlled |
| Blinding used                | Not blinded                 |

### Arms

|                  |                     |
|------------------|---------------------|
| <b>Arm title</b> | Brentuximab vedotin |
|------------------|---------------------|

Arm description:

Brentuximab vedotin 1.8 mg/kg every 3 weeks by IV infusion

|  |   |
|--|---|
| Arm type                               | Experimental                                    |
| Investigational medicinal product name | Brentuximab vedotin                             |
| Investigational medicinal product code |   |
| Other name                             | ADCETRIS, SGN-35                                |
| Pharmaceutical forms                   | Concentrate for solution for injection/infusion |
| Routes of administration               | Intravenous use                                 |

Dosage and administration details:

Brentuximab vedotin 1.8 mg/kg every 3 weeks by IV infusion

|                                       |                     |
|---------------------------------------|---------------------|
| <b>Number of subjects in period 1</b> | Brentuximab vedotin |
| Started                               | 102                 |
| Completed                             | 18                  |
| Not completed                         | 84                  |
| Physician decision                    | 12                  |
| Consent withdrawn by subject          | 7                   |
| Adverse event, non-fatal              | 20                  |
| Progressive disease                   | 45                  |

## Baseline characteristics

### Reporting groups

| Reporting group title          | Treatment |
|--------------------------------|-----------|
| Reporting group description: - |           |

| Reporting group values   | Treatment | Total |  |
|--|-----------|-------|--|
| Number of subjects   | 102       | 102   |  |
| Age categorical  |           |       |  |
| Units: Subjects  |           |       |  |
| In utero   | 0         | 0     |  |
| Preterm newborn infants (gestational age < 37 wks)   | 0         | 0     |  |
| Newborns (0-27 days)   | 0         | 0     |  |
| Infants and toddlers (28 days-23 months)   | 0         | 0     |  |
| Children (2-11 years)  | 0         | 0     |  |
| Adolescents (12-17 years)  | 1         | 1     |  |
| Adults (18-64 years)   | 98        | 98    |  |
| From 65-84 years   | 3         | 3     |  |
| 85 years and over  | 0         | 0     |  |
| Age continuous   |           |       |  |
| Units: years   |           |       |  |
| median   | 31        |       |  |
| full range (min-max)   | 15 to 77  | -     |  |
| Gender categorical   |           |       |  |
| Units: Subjects  |           |       |  |
| Female   | 54        | 54    |  |
| Male   | 48        | 48    |  |
| Race   |           |       |  |
| Units: Subjects  |           |       |  |
| Asian  | 7         | 7     |  |
| Black or African American  | 5         | 5     |  |
| White  | 89        | 89    |  |
| Unknown or Not Reported  | 1         | 1     |  |
| Eastern Cooperative Oncology Group Performance Status  |           |       |  |
| 0 = Normal activity<br>1 = Symptoms but ambulatory<br>2 = In bed <50% of the time<br>3 = In bed >50% of the time<br>4 = 100% bedridden<br>5 = Dead |           |       |  |
| Units: Subjects  |           |       |  |
| Zero   | 42        | 42    |  |
| One  | 60        | 60    |  |
| Two to Five  | 0         | 0     |  |

## End points

### End points reporting groups

|  |                     |
|--|---------------------|
| Reporting group title                                      | Brentuximab vedotin |
| Reporting group description:                               |                     |
| Brentuximab vedotin 1.8 mg/kg every 3 weeks by IV infusion |                     |

### Primary: Objective Response Rate by Independent Review Group

|   |  |
|---|--|
| End point title   | Objective Response Rate by Independent Review Group <sup>[1]</sup> |
| End point description:  |  |
| Percentage of participants who achieved a best response of complete remission (CR, disappearance of all evidence of disease) or partial remission (PR, regression of greater than or equal to 50% of measurable disease and no new sites) per Cheson 2007 Revised Response Criteria for Malignant Lymphoma. |  |
| End point type  | Primary  |
| End point timeframe:  |  |
| up to 12 months   |  |

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: The primary efficacy hypothesis was:

H0: ORR for SGN-35 (1.8 mg/kg) is <20%

versus

Ha: ORR for SGN-35 (1.8 mg/kg) is ≥20%

| End point values                 | Brentuximab vedotin |  |  |  |
|----------------------------------|---------------------|--|--|--|
| Subject group type               | Reporting group     |  |  |  |
| Number of subjects analysed      | 102 <sup>[2]</sup>  |  |  |  |
| Units: Percent of participants   |                     |  |  |  |
| number (confidence interval 95%) |                     |  |  |  |
| ORR by Independent Review Group  | 75 (64.9 to 82.6)   |  |  |  |

Notes:

[2] - Intention to treat

### Statistical analyses

No statistical analyses for this end point

### Secondary: Complete Remission Rate by Independent Review Group

|  |   |
|--|---|
| End point title  | Complete Remission Rate by Independent Review Group |
| End point description:   |   |
| Percentage of participants who achieved a best response of CR (disappearance of all evidence of disease) per Cheson 2007 Revised Response Criteria for Malignant Lymphoma. |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| up to 12 months  |   |

|                                     |                     |  |  |  |
|-------------------------------------|---------------------|--|--|--|
| <b>End point values</b>             | Brentuximab vedotin |  |  |  |
| Subject group type                  | Reporting group     |  |  |  |
| Number of subjects analysed         | 102 <sup>[3]</sup>  |  |  |  |
| Units: Percent of participants      |                     |  |  |  |
| number (confidence interval 95%)    |                     |  |  |  |
| CR Rate by Independent Review Group | 33 (24.3 to 43.4)   |  |  |  |

Notes:

[3] - Intention to treat

### Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of Objective Response by Kaplan-Meier Analysis

|   |   |
|---|---|
| End point title   | Duration of Objective Response by Kaplan-Meier Analysis |
| End point description:<br>Duration of objective response (CR + PR) by independent review group, defined as time of initial response until disease progression or death. |   |
| End point type  | Secondary   |
| End point timeframe:<br>up to approximately 4 years   |   |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of Objective Response in Participants With Complete Remission by Kaplan-Meier Analysis

|  |   |
|--|---|
| End point title  | Duration of Objective Response in Participants With Complete Remission by Kaplan-Meier Analysis |
| End point description:<br>Duration of response from start of first objective tumor response (CR or PR) by independent review group to disease progression or death due to any cause in participants with CR. |   |
| End point type   | Secondary   |
| End point timeframe:<br>up to approximately 4 years  |   |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Progression-free Survival by Kaplan-Meier Analysis

|   |  |
|---|--|
| End point title   | Progression-free Survival by Kaplan-Meier Analysis |
| End point description:<br>Time from start of study treatment to disease progression per independent review group or death due to any cause. |  |
| End point type  | Secondary  |
| End point timeframe:<br>up to approximately 4 years   |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Survival

|   |                  |
|---|------------------|
| End point title   | Overall Survival |
| End point description:<br>Time from start of study treatment to date of death due to any cause. |                  |
| End point type  | Secondary        |
| End point timeframe:<br>up to approximately 6 years   |                  |



## Statistical analyses

No statistical analyses for this end point

### Secondary: Adverse Events by Severity, Seriousness, and Relationship to Treatment

|                 |  |
|-----------------|--|
| End point title | Adverse Events by Severity, Seriousness, and Relationship to Treatment |
|-----------------|--|

End point description:

Counts of participants who had adverse events or treatment-emergent adverse events (TEAE, defined as newly occurring or worsening after first dose). Serious adverse events are reported from the time of informed consent. National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 3.0) were used to assess severity (1=mild, 2=moderate, 3=severe, 4=life threatening/disabling, 5=death). Relatedness to study drug was assessed by the investigator (Yes/No). Participants with multiple occurrences of an adverse event within a category are counted once within the category.

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

End point timeframe:

up to 12 months

| End point values                            | Brentuximab vedotin |  |  |  |
|---|---------------------|--|--|--|
| Subject group type                          | Reporting group     |  |  |  |
| Number of subjects analysed                 | 102 <sup>[4]</sup>  |  |  |  |
| Units: Participants                         |                     |  |  |  |
| number (not applicable)                     |                     |  |  |  |
| Any TEAE                                    | 100                 |  |  |  |
| TEAE related to study drug                  | 94                  |  |  |  |
| TEAE with severity grade $\geq 3$           | 56                  |  |  |  |
| Serious adverse event                       | 25                  |  |  |  |
| Serious adverse event related to study drug | 14                  |  |  |  |
| Discontinued treatment due to adverse event | 20                  |  |  |  |

Notes:

[4] - All participants who received treatment

## Statistical analyses

No statistical analyses for this end point

### Secondary: Hematology Laboratory Abnormalities $\geq$ Grade 3

|                 |  |
|-----------------|--|
| End point title | Hematology Laboratory Abnormalities $\geq$ Grade 3 |
|-----------------|--|

End point description:

Counts of study participants with post-baseline hematology laboratory abnormalities of Grade 3 or greater per NCI CTCAE version 3.0. Participants with multiple occurrences of a laboratory abnormality

within a category are counted once in that category.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| up to 12 months      |           |

| End point values                                 | Brentuximab vedotin |  |  |  |
|--|---------------------|--|--|--|
| Subject group type                               | Reporting group     |  |  |  |
| Number of subjects analysed                      | 102 <sup>[5]</sup>  |  |  |  |
| Units: Participants                              |                     |  |  |  |
| number (not applicable)                          |                     |  |  |  |
| Any >= Grade 3 hematology laboratory abnormality | 35                  |  |  |  |
| Hemoglobin (low)                                 | 7                   |  |  |  |
| Leukocytes (low)                                 | 6                   |  |  |  |
| Lymphocytes (low)                                | 20                  |  |  |  |
| Neutrophils (low)                                | 12                  |  |  |  |
| Platelets (low)                                  | 7                   |  |  |  |

Notes:

[5] - All participants who received treatment

## Statistical analyses

No statistical analyses for this end point

## Secondary: Chemistry Laboratory Abnormalities >= Grade 3

|   |   |
|---|---|
| End point title   | Chemistry Laboratory Abnormalities >= Grade 3 |
| End point description:  |   |
| Counts of study participants with post-baseline chemistry laboratory abnormalities of Grade 3 or greater per NCI CTCAE version 3.0. Participants with multiple occurrences of a laboratory abnormality within a category are counted once in that category. |   |
| End point type  | Secondary                                     |
| End point timeframe:  |   |
| up to 12 months   |   |

| End point values                                | Brentuximab vedotin |  |  |  |
|---|---------------------|--|--|--|
| Subject group type                              | Reporting group     |  |  |  |
| Number of subjects analysed                     | 102 <sup>[6]</sup>  |  |  |  |
| Units: Participants                             |                     |  |  |  |
| number (not applicable)                         |                     |  |  |  |
| Any >= Grade 3 chemistry laboratory abnormality | 14                  |  |  |  |
| Alanine aminotransferase (high)                 | 1                   |  |  |  |
| Albumin (low)                                   | 1                   |  |  |  |
| Calcium (low)                                   | 1                   |  |  |  |
| Glucose (high)                                  | 7                   |  |  |  |

|                 |   |  |  |  |
|-----------------|---|--|--|--|
| Potassium (low) | 2 |  |  |  |
| Sodium (high)   | 1 |  |  |  |
| Urate (high)    | 1 |  |  |  |

Notes:

[6] - All participants who received treatment

## Statistical analyses

No statistical analyses for this end point

## Secondary: Area Under the Curve

|  |                      |
|--|----------------------|
| End point title  | Area Under the Curve |
| End point description:   |                      |
| Area under the serum concentration-time curve from time 0 to 21 days following the first dose of brentuximab vedotin |                      |
| End point type   | Secondary            |
| End point timeframe:   |                      |
| 3 weeks  |                      |

|   |                     |  |  |  |
|---|---------------------|--|--|--|
| <b>End point values</b>                             | Brentuximab vedotin |  |  |  |
| Subject group type                                  | Reporting group     |  |  |  |
| Number of subjects analysed                         | 102 <sup>[7]</sup>  |  |  |  |
| Units: day * microgram/mL                           |                     |  |  |  |
| geometric mean (geometric coefficient of variation) | 88 (± 46)           |  |  |  |

Notes:

[7] - All participants who received treatment

## Statistical analyses

No statistical analyses for this end point

## Secondary: Maximum Serum Concentration

|   |                             |
|---|-----------------------------|
| End point title   | Maximum Serum Concentration |
| End point description:  |                             |
| Maximum serum concentration from 0 to 21 days following the first dose of brentuximab vedotin |                             |
| End point type  | Secondary                   |
| End point timeframe:  |                             |
| 3 weeks   |                             |

|   |                     |  |  |  |
|---|---------------------|--|--|--|
| <b>End point values</b>                             | Brentuximab vedotin |  |  |  |
| Subject group type                                  | Reporting group     |  |  |  |
| Number of subjects analysed                         | 102 <sup>[8]</sup>  |  |  |  |
| Units: microgram/mL                                 |                     |  |  |  |
| geometric mean (geometric coefficient of variation) | 35 (± 17)           |  |  |  |

Notes:

[8] - All participants who received treatment

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time of Maximum Serum Concentration

|   |                                     |
|---|-------------------------------------|
| End point title   | Time of Maximum Serum Concentration |
| End point description:<br>Time of maximum serum concentration from 0 to 21 days following the first dose of brentuximab vedotin |                                     |
| End point type  | Secondary                           |
| End point timeframe:<br>3 weeks   |                                     |

|                                     |                     |  |  |  |
|-------------------------------------|---------------------|--|--|--|
| <b>End point values</b>             | Brentuximab vedotin |  |  |  |
| Subject group type                  | Reporting group     |  |  |  |
| Number of subjects analysed         | 102 <sup>[9]</sup>  |  |  |  |
| Units: days                         |                     |  |  |  |
| median (full range (min-max))       |                     |  |  |  |
| Time of Maximum Serum Concentration | 0.02 (0.02 to 0.02) |  |  |  |

Notes:

[9] - All participants who received treatment

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: B Symptom Resolution

|   |                      |
|---|----------------------|
| End point title   | B Symptom Resolution |
| End point description:<br>Percentage of participants with lymphoma-related symptoms (B symptoms: fever, night sweats, or weight loss >10%) at baseline who achieved resolution of all B symptoms at any time during the treatment period. |                      |
| End point type  | Other pre-specified  |
| End point timeframe:<br>up to 12 months   |                      |

|                                  |                     |  |  |  |
|----------------------------------|---------------------|--|--|--|
| <b>End point values</b>          | Brentuximab vedotin |  |  |  |
| Subject group type               | Reporting group     |  |  |  |
| Number of subjects analysed      | 35 <sup>[10]</sup>  |  |  |  |
| Units: percent of participants   |                     |  |  |  |
| number (confidence interval 95%) |                     |  |  |  |
| B Symptom Resolution             | 77 (59.9 to 89.6)   |  |  |  |

Notes:

[10] - Participants with B symptoms at baseline

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to 12 months

Adverse event reporting additional description:

Treatment-emergent adverse events (TEAEs) defined as newly occurring (not present at baseline) or worsening after first dose of investigational product on Study SG035-0003

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

### Dictionary used

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

|                    |    |
|--------------------|----|
| Dictionary version | 13 |
|--------------------|----|

### Reporting groups

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | Brentuximab vedotin |
|-----------------------|---------------------|

Reporting group description:

Brentuximab vedotin

| Serious adverse events  | Brentuximab vedotin |  |  |
|---|---------------------|--|--|
| Total subjects affected by serious adverse events                   |                     |  |  |
| subjects affected / exposed   | 25 / 102 (24.51%)   |  |  |
| number of deaths (all causes)                                       | 1                   |  |  |
| number of deaths resulting from adverse events                      | 0                   |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                     |  |  |
| Diffuse large b-cell lymphoma                                       |                     |  |  |
| subjects affected / exposed   | 1 / 102 (0.98%)     |  |  |
| occurrences causally related to treatment / all                     | 0 / 1               |  |  |
| deaths causally related to treatment / all                          | 0 / 0               |  |  |
| Hodgkin's disease recurrent   |                     |  |  |
| subjects affected / exposed   | 1 / 102 (0.98%)     |  |  |
| occurrences causally related to treatment / all                     | 0 / 1               |  |  |
| deaths causally related to treatment / all                          | 0 / 0               |  |  |
| Injury, poisoning and procedural complications                      |                     |  |  |
| Wrist fracture  |                     |  |  |
| subjects affected / exposed   | 1 / 102 (0.98%)     |  |  |
| occurrences causally related to treatment / all                     | 0 / 1               |  |  |
| deaths causally related to treatment / all                          | 0 / 0               |  |  |
| Nervous system disorders  |                     |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Demyelinating polyneuropathy<br>subjects affected / exposed                                       | 2 / 102 (1.96%) |  |  |
| occurrences causally related to<br>treatment / all  | 2 / 2           |  |  |
| deaths causally related to<br>treatment / all   | 0 / 0           |  |  |
| Diabetic coma<br>subjects affected / exposed  | 1 / 102 (0.98%) |  |  |
| occurrences causally related to<br>treatment / all  | 0 / 1           |  |  |
| deaths causally related to<br>treatment / all   | 0 / 0           |  |  |
| Peripheral motor neuropathy<br>subjects affected / exposed  | 1 / 102 (0.98%) |  |  |
| occurrences causally related to<br>treatment / all  | 2 / 2           |  |  |
| deaths causally related to<br>treatment / all   | 0 / 0           |  |  |
| Blood and lymphatic system disorders<br>Thrombocytopenia<br>subjects affected / exposed           | 1 / 102 (0.98%) |  |  |
| occurrences causally related to<br>treatment / all  | 1 / 1           |  |  |
| deaths causally related to<br>treatment / all   | 0 / 0           |  |  |
| General disorders and administration<br>site conditions<br>Pyrexia<br>subjects affected / exposed | 2 / 102 (1.96%) |  |  |
| occurrences causally related to<br>treatment / all  | 3 / 4           |  |  |
| deaths causally related to<br>treatment / all   | 0 / 0           |  |  |
| Gastrointestinal disorders<br>Abdominal pain<br>subjects affected / exposed                       | 2 / 102 (1.96%) |  |  |
| occurrences causally related to<br>treatment / all  | 1 / 2           |  |  |
| deaths causally related to<br>treatment / all   | 0 / 0           |  |  |
| Abdominal pain upper<br>subjects affected / exposed   | 1 / 102 (0.98%) |  |  |
| occurrences causally related to<br>treatment / all  | 0 / 1           |  |  |
| deaths causally related to<br>treatment / all   | 0 / 0           |  |  |
| Diarrhoea   |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 102 (0.98%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastrointestinal haemorrhage                    |                 |  |  |
| subjects affected / exposed                     | 1 / 102 (0.98%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Haematemesis                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 102 (0.98%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Intestinal perforation                          |                 |  |  |
| subjects affected / exposed                     | 1 / 102 (0.98%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Nausea  |                 |  |  |
| subjects affected / exposed                     | 1 / 102 (0.98%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory, thoracic and mediastinal disorders |                 |  |  |
| Haemoptysis                                     |                 |  |  |
| subjects affected / exposed                     | 1 / 102 (0.98%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pleural effusion                                |                 |  |  |
| subjects affected / exposed                     | 1 / 102 (0.98%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pneumonitis                                     |                 |  |  |
| subjects affected / exposed                     | 2 / 102 (1.96%) |  |  |
| occurrences causally related to treatment / all | 1 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pneumothorax                                    |                 |  |  |



|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 2 / 102 (1.96%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pulmonary embolism                              |                 |  |  |
| subjects affected / exposed                     | 2 / 102 (1.96%) |  |  |
| occurrences causally related to treatment / all | 1 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Skin and subcutaneous tissue disorders          |                 |  |  |
| Stevens-johnson syndrome                        |                 |  |  |
| subjects affected / exposed                     | 1 / 102 (0.98%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Psychiatric disorders                           |                 |  |  |
| Mental status changes                           |                 |  |  |
| subjects affected / exposed                     | 1 / 102 (0.98%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Musculoskeletal and connective tissue disorders |                 |  |  |
| Flank pain                                      |                 |  |  |
| subjects affected / exposed                     | 1 / 102 (0.98%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Muscular weakness                               |                 |  |  |
| subjects affected / exposed                     | 1 / 102 (0.98%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Infections and infestations                     |                 |  |  |
| Bronchitis                                      |                 |  |  |
| subjects affected / exposed                     | 1 / 102 (0.98%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Candidiasis                                     |                 |  |  |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| subjects affected / exposed                     | 1 / 102 (0.98%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Cellulitis                                      |                 |  |  |  |
| subjects affected / exposed                     | 1 / 102 (0.98%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| H1n1 influenza                                  |                 |  |  |  |
| subjects affected / exposed                     | 1 / 102 (0.98%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Lung infection                                  |                 |  |  |  |
| subjects affected / exposed                     | 1 / 102 (0.98%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pneumocystis jiroveci pneumonia                 |                 |  |  |  |
| subjects affected / exposed                     | 1 / 102 (0.98%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pneumonia                                       |                 |  |  |  |
| subjects affected / exposed                     | 1 / 102 (0.98%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pyelonephritis                                  |                 |  |  |  |
| subjects affected / exposed                     | 2 / 102 (1.96%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Septic shock                                    |                 |  |  |  |
| subjects affected / exposed                     | 1 / 102 (0.98%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Soft tissue infection                           |                 |  |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 102 (0.98%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Staphylococcal bacteraemia                      |                 |  |  |
| subjects affected / exposed                     | 1 / 102 (0.98%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Urinary tract infection staphylococcal          |                 |  |  |
| subjects affected / exposed                     | 1 / 102 (0.98%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Metabolism and nutrition disorders              |                 |  |  |
| Hyperglycaemia                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 102 (0.98%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

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

| <b>Non-serious adverse events</b>                                   | Brentuximab vedotin |  |  |
|---|---------------------|--|--|
| Total subjects affected by non-serious adverse events               |                     |  |  |
| subjects affected / exposed   | 97 / 102 (95.10%)   |  |  |
| Investigations  |                     |  |  |
| Weight decreased  |                     |  |  |
| subjects affected / exposed   | 6 / 102 (5.88%)     |  |  |
| occurrences (all)   | 6                   |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                     |  |  |
| Hodgkin's disease recurrent   |                     |  |  |
| subjects affected / exposed   | 6 / 102 (5.88%)     |  |  |
| occurrences (all)   | 6                   |  |  |
| Nervous system disorders  |                     |  |  |
| Dizziness   |                     |  |  |
| subjects affected / exposed   | 11 / 102 (10.78%)   |  |  |
| occurrences (all)   | 12                  |  |  |
| Headache  |                     |  |  |

|  |                   |  |  |
|--|-------------------|--|--|
| subjects affected / exposed                          | 19 / 102 (18.63%) |  |  |
| occurrences (all)                                    | 32                |  |  |
| Peripheral motor neuropathy                          |                   |  |  |
| subjects affected / exposed                          | 11 / 102 (10.78%) |  |  |
| occurrences (all)                                    | 15                |  |  |
| Peripheral sensory neuropathy                        |                   |  |  |
| subjects affected / exposed                          | 48 / 102 (47.06%) |  |  |
| occurrences (all)                                    | 76                |  |  |
| Blood and lymphatic system disorders                 |                   |  |  |
| Anaemia  |                   |  |  |
| subjects affected / exposed                          | 9 / 102 (8.82%)   |  |  |
| occurrences (all)                                    | 9                 |  |  |
| Lymphadenopathy                                      |                   |  |  |
| subjects affected / exposed                          | 11 / 102 (10.78%) |  |  |
| occurrences (all)                                    | 17                |  |  |
| Neutropenia  |                   |  |  |
| subjects affected / exposed                          | 22 / 102 (21.57%) |  |  |
| occurrences (all)                                    | 40                |  |  |
| Thrombocytopenia                                     |                   |  |  |
| subjects affected / exposed                          | 7 / 102 (6.86%)   |  |  |
| occurrences (all)                                    | 7                 |  |  |
| General disorders and administration site conditions |                   |  |  |
| Chills   |                   |  |  |
| subjects affected / exposed                          | 13 / 102 (12.75%) |  |  |
| occurrences (all)                                    | 17                |  |  |
| Fatigue  |                   |  |  |
| subjects affected / exposed                          | 47 / 102 (46.08%) |  |  |
| occurrences (all)                                    | 71                |  |  |
| Pain   |                   |  |  |
| subjects affected / exposed                          | 7 / 102 (6.86%)   |  |  |
| occurrences (all)                                    | 7                 |  |  |
| Pyrexia  |                   |  |  |
| subjects affected / exposed                          | 30 / 102 (29.41%) |  |  |
| occurrences (all)                                    | 49                |  |  |
| Gastrointestinal disorders                           |                   |  |  |

|  |                         |  |  |
|--|-------------------------|--|--|
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)   | 15 / 102 (14.71%)<br>17 |  |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)   | 16 / 102 (15.69%)<br>18 |  |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)  | 37 / 102 (36.27%)<br>56 |  |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)   | 43 / 102 (42.16%)<br>61 |  |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)   | 22 / 102 (21.57%)<br>28 |  |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all) | 21 / 102 (20.59%)<br>24 |  |  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)   | 13 / 102 (12.75%)<br>15 |  |  |
| Nasal congestion<br>subjects affected / exposed<br>occurrences (all)   | 6 / 102 (5.88%)<br>7    |  |  |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)                                       | 11 / 102 (10.78%)<br>11 |  |  |
| Productive cough<br>subjects affected / exposed<br>occurrences (all)   | 6 / 102 (5.88%)<br>6    |  |  |
| Skin and subcutaneous tissue disorders<br>Alopecia<br>subjects affected / exposed<br>occurrences (all)       | 13 / 102 (12.75%)<br>13 |  |  |
| Hyperhidrosis  |                         |  |  |

|   |                         |  |  |
|---|-------------------------|--|--|
| subjects affected / exposed<br>occurrences (all)  | 6 / 102 (5.88%)<br>8    |  |  |
| Night sweats<br>subjects affected / exposed<br>occurrences (all)  | 12 / 102 (11.76%)<br>15 |  |  |
| Pruritus<br>subjects affected / exposed<br>occurrences (all)  | 16 / 102 (15.69%)<br>23 |  |  |
| Rash<br>subjects affected / exposed<br>occurrences (all)  | 14 / 102 (13.73%)<br>20 |  |  |
| Psychiatric disorders<br>Anxiety<br>subjects affected / exposed<br>occurrences (all)                              | 11 / 102 (10.78%)<br>12 |  |  |
| Depression<br>subjects affected / exposed<br>occurrences (all)  | 8 / 102 (7.84%)<br>8    |  |  |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)  | 14 / 102 (13.73%)<br>14 |  |  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 19 / 102 (18.63%)<br>23 |  |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)   | 14 / 102 (13.73%)<br>16 |  |  |
| Bone pain<br>subjects affected / exposed<br>occurrences (all)   | 8 / 102 (7.84%)<br>11   |  |  |
| Muscle spasms<br>subjects affected / exposed<br>occurrences (all)   | 9 / 102 (8.82%)<br>12   |  |  |
| Myalgia   |                         |  |  |

|                                    |                   |  |  |
|------------------------------------|-------------------|--|--|
| subjects affected / exposed        | 17 / 102 (16.67%) |  |  |
| occurrences (all)                  | 19                |  |  |
| Neck pain                          |                   |  |  |
| subjects affected / exposed        | 6 / 102 (5.88%)   |  |  |
| occurrences (all)                  | 7                 |  |  |
| Pain in extremity                  |                   |  |  |
| subjects affected / exposed        | 10 / 102 (9.80%)  |  |  |
| occurrences (all)                  | 13                |  |  |
| Infections and infestations        |                   |  |  |
| Bronchitis                         |                   |  |  |
| subjects affected / exposed        | 8 / 102 (7.84%)   |  |  |
| occurrences (all)                  | 8                 |  |  |
| Herpes zoster                      |                   |  |  |
| subjects affected / exposed        | 7 / 102 (6.86%)   |  |  |
| occurrences (all)                  | 7                 |  |  |
| Sinusitis                          |                   |  |  |
| subjects affected / exposed        | 9 / 102 (8.82%)   |  |  |
| occurrences (all)                  | 11                |  |  |
| Upper respiratory tract infection  |                   |  |  |
| subjects affected / exposed        | 38 / 102 (37.25%) |  |  |
| occurrences (all)                  | 47                |  |  |
| Urinary tract infection            |                   |  |  |
| subjects affected / exposed        | 6 / 102 (5.88%)   |  |  |
| occurrences (all)                  | 7                 |  |  |
| Metabolism and nutrition disorders |                   |  |  |
| Decreased appetite                 |                   |  |  |
| subjects affected / exposed        | 11 / 102 (10.78%) |  |  |
| occurrences (all)                  | 12                |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 17 November 2008 | <p>Incorporation of FDA feedback during SPA review.</p> <p>Clarified that for patients who had bone marrow involvement at baseline, a follow-up bone marrow aspirate and biopsy was required (within 2 weeks of documentation of response) and must be negative for assessment of a CR. If the follow-up morphology was indeterminate, the biopsy tissue must be negative by immunohistochemistry or the patient was to be assessed as a PR.</p> <p>Specified that patients who were later determined to have the incorrect histological cancer type upon central review were to be scored as non-responders for calculating the ORR.</p> <p>Revised the definition of duration of response such that all deaths occurring prior to disease progression, not just deaths due to HL, were to be considered when determining the end of the response period.</p> <p>Revised the analysis set definitions such that the intent-to-treat (ITT) analysis set was to include all patients enrolled in the study and was to be used for the primary efficacy analysis. Secondary analyses of all efficacy endpoints were also to be performed in the per-protocol analysis set, defined as all patients who received at least 1 dose of brentuximab vedotin and who had measurable disease at baseline, the correct histological cancer type per central pathology review, and no other major protocol deviations that could potentially affect tumor response.</p> <p>The safety/modified intent-to-treat (mITT) analysis set, defined as all patients who received at least 1 dose of brentuximab vedotin, was to be used for safety analyses, patient demographics and baseline disease characteristics.</p> <p>Provided rationale as to why no formal interim efficacy or futility analysis was planned for the study.</p> |
| 12 January 2009  | <p>Incorporation of further FDA feedback during SPA review. The eligibility criteria were modified as follows:</p> <p>The time following prior immunotherapy or radioisotopic therapy was extended to 12 weeks so that any therapeutic benefit from these therapies would be realized prior to receiving brentuximab vedotin. This ensured that patients had relapsed or refractory disease prior to enrollment in the study.</p> <p>A new inclusion criterion was added to define which specific evidence of relapsed or refractory HL was required at the time of study enrollment.</p>   |
| 03 October 2011  | <p>Added a section regarding the management of suspected PML</p>  |
| 30 January 2012  | <p>Revised the timing of assessments during the study follow-up period.</p>   |
| 03 October 2013  | <p>Removed the requirement for CT scanning during the long-term follow-up period. CT scans were only to be done if progression suspected based on clinical signs and symptoms.</p> <p>Added a long term follow-up questionnaire to be taken by patients who remained in remission.</p>  |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats



None reported

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## Online references

<http://www.ncbi.nlm.nih.gov/pubmed/22454421>