



## Clinical trial results:

### A Phase 2, Multicenter, Single-arm Study of Moxetumomab Pasudotox in Pediatric Subjects with Relapsed or Refractory Pediatric Acute Lymphoblastic Leukemia (pALL) or Lymphoblastic Lymphoma of B-cell Origin

#### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2012-003101-10    |
| Trial protocol           | GB DE FR IT ES NL |
| Global end of trial date | 02 November 2015  |

#### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 14 August 2016 |
| First version publication date | 14 August 2016 |

#### Trial information

##### Trial identification

|                       |                     |
|-----------------------|---------------------|
| Sponsor protocol code | CD-ON-CAT-8015-1036 |
|-----------------------|---------------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02227108 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | MedImmune LLC   |
| Sponsor organisation address | One MedImmune Way, Gaithersburg, United States, MD 20878  |
| Public contact               | Information Centre, AstraZeneca,<br>Information.centre@astrazeneca.com, MedImmune LLC, +1 3013980000 x, |
| Scientific contact           | Information Centre, AstraZeneca,<br>Information.centre@astrazeneca.com, MedImmune LLC, +1 3013980000 x, |

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                       | 21 December 2015 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 02 November 2015 |
| Was the trial ended prematurely?                     | Yes              |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the efficacy of moxetumomab pasudotox as measured by the composite complete response (CRc) defined as achieving complete response (CR), or complete response with incomplete count recovery (CRi) in pediatric subjects with relapsed or refractory B-cell acute lymphoblastic leukemia (ALL) or B-cell lymphoblastic lymphoma.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Participating participant signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

|   |                |
|---|----------------|
| Actual start date of recruitment                          | 11 August 2014 |
| 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 | United Kingdom: 2 |
| Country: Number of subjects enrolled | United States: 21 |
| Country: Number of subjects enrolled | Australia: 3      |
| Country: Number of subjects enrolled | France: 4         |
| Country: Number of subjects enrolled | Italy: 2          |
| Worldwide total number of subjects   | 32                |
| 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          | 0 |

|                           |    |
|---------------------------|----|
| months)                   |    |
| Children (2-11 years)     | 22 |
| Adolescents (12-17 years) | 10 |
| Adults (18-64 years)      | 0  |
| From 65 to 84 years       | 0  |
| 85 years and over         | 0  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 37 participants were screened, of which 5 did not meet eligibility criteria and were considered as screen failures; the remaining 32 participants entered into the study and 30 participants were treated with moxetumomab pasudotox.

### Period 1

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

### Arms

|                  |  |
|------------------|--|
| <b>Arm title</b> | Moxetumomab Pasudotox 40 microgram per kilogram (mcg/kg) |
|------------------|--|

Arm description:

Participants received 6 doses of moxetumomab pasudotox 40 mcg/kg intravenous infusion over 30 minutes every other day (Days 1, 3, 5, 7, 9, and 11) in 21-day treatment cycles until completion of a maximum of 6 cycles of therapy.

|  |                       |
|--|-----------------------|
| Arm type                               | Experimental          |
| Investigational medicinal product name | Moxetumomab Pasudotox |
| Investigational medicinal product code | CAT-8015              |
| Other name                             |                       |
| Pharmaceutical forms                   | Infusion              |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Participants received 6 doses of moxetumomab pasudotox 40 mcg/kg intravenous infusion over 30 minutes every other day (Days 1, 3, 5, 7, 9, and 11) in 21-day treatment cycles until completion of a maximum of 6 cycles of therapy.

| <b>Number of subjects in period 1</b> | Moxetumomab Pasudotox 40 microgram per kilogram (mcg/kg) |
|---------------------------------------|--|
| Started                               | 32   |
| Treated                               | 30   |
| Completed                             | 1  |
| Not completed                         | 31   |
| Adverse event, non-fatal              | 6  |
| Initiation of alternative therapy     | 2  |
| Unspecified                           | 3  |
| Did not receive treatment             | 2  |
| Progressive disease                   | 17   |
| Investigator discretion               | 1  |



## Baseline characteristics

### Reporting groups

|                       |  |
|-----------------------|--|
| Reporting group title | Moxetumomab Pasudotox 40 microgram per kilogram (mcg/kg) |
|-----------------------|--|

Reporting group description:

Participants received 6 doses of moxetumomab pasudotox 40 mcg/kg intravenous infusion over 30 minutes every other day (Days 1, 3, 5, 7, 9, and 11) in 21-day treatment cycles until completion of a maximum of 6 cycles of therapy.

| Reporting group values    | Moxetumomab Pasudotox 40 microgram per kilogram (mcg/kg) | Total |  |
|---------------------------|--|-------|--|
| Number of subjects        | 32   | 32    |  |
| Age categorical           |  |       |  |
| Units: Subjects           |  |       |  |
| Children (2-11 years)     | 18   | 18    |  |
| Adolescents (12-17 years) | 14   | 14    |  |
| Age Continuous            |  |       |  |
| Units: Years              |  |       |  |
| arithmetic mean           | 10.5   |       |  |
| standard deviation        | ± 3.9  | -     |  |
| Gender, Male/Female       |  |       |  |
| Units: Participants       |  |       |  |
| Female                    | 13   | 13    |  |
| Male                      | 19   | 19    |  |

## End points

### End points reporting groups

|   |  |
|---|--|
| Reporting group title   | Moxetumomab Pasudotox 40 microgram per kilogram (mcg/kg) |
| Reporting group description:<br>Participants received 6 doses of moxetumomab pasudotox 40 mcg/kg intravenous infusion over 30 minutes every other day (Days 1, 3, 5, 7, 9, and 11) in 21-day treatment cycles until completion of a maximum of 6 cycles of therapy. |  |

### Primary: Percentage of Participants with Composite Complete Response (CRc)

|  |  |
|--|--|
| End point title  | Percentage of Participants with Composite Complete Response (CRc) <sup>[1]</sup> |
| End point description:<br>The CRc is defined as achieving complete response (CR), or CR with incomplete count recovery [CRi]) in participants with relapsed or refractory B-cell ALL or B-cell lymphoblastic lymphoma. The efficacy assessments were as per investigator assessment. |  |
| End point type   | Primary  |
| End point timeframe:<br>Prior to Cycle 1, and prior to every cycle, at the end of treatment, at post-treatment follow-up visits, and at the end of the study   |  |
| Notes:<br>[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.<br>Justification: No inferential statistical analysis was planned for this end-point.                  |  |

|                                   |  |  |  |  |
|-----------------------------------|--|--|--|--|
| <b>End point values</b>           | Moxetumomab Pasudotox 40 microgram per kilogram (mcg/kg) |  |  |  |
| Subject group type                | Reporting group  |  |  |  |
| Number of subjects analysed       | 28 <sup>[2]</sup>  |  |  |  |
| Units: percentage of participants |  |  |  |  |
| number (confidence interval 95%)  | 10.7 (2.3 to 28.2)                                       |  |  |  |

Notes:  
[2] - Evaluable efficacy population

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants with Minimal Residual Disease (MRD)-negative CRc rate

|   |  |
|---|--|
| End point title   | Percentage of Participants with Minimal Residual Disease (MRD)-negative CRc rate |
| End point description:<br>The MRD-negative CRc rate was defined as the percentage of participants who achieved CRc and became MRD-negative as determined by flow cytometry performed by a central analysis laboratory. The CRc is defined as complete response (CR), or complete response with incomplete count recovery (CRi). Efficacy evaluable population included all participants who received any amount of moxetumomab pasudotox and completed a baseline disease assessment and had at least one post-baseline disease assessment. |  |

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| Prior to Cycle 1, and prior to every cycle, at the end of treatment, at post-treatment follow-up visits, and at the end of the study |           |

|                                   |  |  |  |  |
|-----------------------------------|--|--|--|--|
| <b>End point values</b>           | Moxetumomab Pasudotox 40 microgram per kilogram (mcg/kg) |  |  |  |
| Subject group type                | Reporting group  |  |  |  |
| Number of subjects analysed       | 28   |  |  |  |
| Units: percentage of participants | 0  |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Response Rate (ORR)

|  |                             |
|--|-----------------------------|
| End point title  | Overall Response Rate (ORR) |
| End point description:   |                             |
| The ORR, defined as the percentage of participants with CRc or partial response (PR), was estimated; the Clopper Pearson (Exact) 95% CI was calculated. The CRc is defined as complete response (CR), or complete response with incomplete count recovery (CRI). Efficacy evaluable population included all participants who received any amount of moxetumomab pasudotox and completed a baseline disease assessment and had at least one post-baseline disease assessment. |                             |
| End point type   | Secondary                   |
| End point timeframe:   |                             |
| Prior to Cycle 1, and prior to every cycle, at the end of treatment, at post-treatment follow-up visits, and at the end of the study   |                             |

|                                   |  |  |  |  |
|-----------------------------------|--|--|--|--|
| <b>End point values</b>           | Moxetumomab Pasudotox 40 microgram per kilogram (mcg/kg) |  |  |  |
| Subject group type                | Reporting group  |  |  |  |
| Number of subjects analysed       | 28   |  |  |  |
| Units: percentage of participants |  |  |  |  |
| number (confidence interval 95%)  | 28.6 (13.2 to 48.7)                                      |  |  |  |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Overall Response

|                 |                          |
|-----------------|--------------------------|
| End point title | Time to Overall Response |
|-----------------|--------------------------|

End point description:

Time to overall response was evaluated using the Kaplan-Meier method. Duration of overall response was defined as the duration from the first documentation of overall response to the first documented disease progression. Efficacy evaluable population included all participants who received any amount of moxetumomab pasudotox and completed a baseline disease assessment and had at least one post-baseline disease assessment.

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

End point timeframe:

Prior to Cycle 1, and prior to every cycle, at the end of treatment, at post-treatment follow-up visits, and at the end of the study

|                                  |  |  |  |  |
|----------------------------------|--|--|--|--|
| <b>End point values</b>          | Moxetumomab<br>Pasudotox 40<br>microgram per<br>kilogram<br>(mcg/kg) |  |  |  |
| Subject group type               | Reporting group  |  |  |  |
| Number of subjects analysed      | 28   |  |  |  |
| Units: months                    |  |  |  |  |
| median (confidence interval 95%) | 0.66 (0.53 to<br>0.76)   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Best Overall Response (BOR)

|                 |                             |
|-----------------|-----------------------------|
| End point title | Best Overall Response (BOR) |
|-----------------|-----------------------------|

End point description:

Best overall response was calculated, based upon disease assessments recorded during study visits, and summarized with percentage of participants for following categories: CR, PR, HA, SD, PD, and not evaluable. Overall best response is best response observed for a participant during study based on International Working Group (IWG) Response Criteria for malignant lymphoma. Complete response (CR) is complete disappearance of all detectable clinical evidence of disease and disease-related symptoms. PR is a minimum of 50% decrease in sum of product of diameters of up to 6 of largest dominant nodes or nodal masses and no increase in size of other nodes and in size of liver or spleen. Stable disease (SD) is when a participant fails to attain criteria needed for a CR or PR, but does not fulfill those for PD. Efficacy evaluable population included all participants who received any amount of study drug and completed a baseline disease assessment and had at least one post-baseline disease

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

End point timeframe:

Prior to Cycle 1, and prior to every cycle, at the end of treatment, at post-treatment follow-up visits, and at the end of the study

|                                   |  |  |  |  |
|-----------------------------------|--|--|--|--|
| <b>End point values</b>           | Moxetumomab<br>Pasudotox 40<br>microgram per<br>kilogram<br>(mcg/kg) |  |  |  |
| Subject group type                | Reporting group  |  |  |  |
| Number of subjects analysed       | 28   |  |  |  |
| Units: percentage of participants |  |  |  |  |
| number (not applicable)           |  |  |  |  |
| Composite complete response       | 10.7   |  |  |  |
| Partial response                  | 17.9   |  |  |  |
| Hematological activity            | 7.1  |  |  |  |
| Stable disease                    | 21.4   |  |  |  |
| Progressive disease               | 39.3   |  |  |  |
| No evaluation available           | 3.6  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Bone Marrow Blast Percentage Change

|  |                                     |
|--|-------------------------------------|
| End point title  | Bone Marrow Blast Percentage Change |
| End point description:   |                                     |
| Change in bone marrow blast percentage from baseline was evaluated. The intent to treat (ITT) population included all participants who entered the study. Here, number of participants analysed, "N" included evaluable participants for this outcome measure. |                                     |
| End point type   | Secondary                           |
| End point timeframe:   |                                     |
| Prior to Cycle 1, and prior to every cycle, at the end of treatment, at post-treatment follow-up visits, and at the end of the study   |                                     |

|                                   |  |  |  |  |
|-----------------------------------|--|--|--|--|
| <b>End point values</b>           | Moxetumomab<br>Pasudotox 40<br>microgram per<br>kilogram<br>(mcg/kg) |  |  |  |
| Subject group type                | Reporting group  |  |  |  |
| Number of subjects analysed       | 26   |  |  |  |
| Units: percentage of participants |  |  |  |  |
| number (not applicable)           |  |  |  |  |
| Baseline M1, post-baseline M1     | 0  |  |  |  |
| Baseline M1, post-baseline M2     | 0  |  |  |  |
| Baseline M1, post-baseline M3     | 3.8  |  |  |  |
| Baseline M2, post-baseline M1     | 0  |  |  |  |
| Baseline M2, post-baseline M2     | 0  |  |  |  |
| Baseline M2, post-baseline M3     | 7.7  |  |  |  |
| Baseline M3 post-baseline M1      | 3.8  |  |  |  |
| Baseline M3 post-baseline M2      | 11.5   |  |  |  |
| Baseline M3 post-baseline M3      | 73.1   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants who Became Eligible to Receive an Stem Cell Transplant (SCT) After Treatment with Moxetumomab Pasudotox as Well as the Time to Transplant

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants who Became Eligible to Receive an Stem Cell Transplant (SCT) After Treatment with Moxetumomab Pasudotox as Well as the Time to Transplant |
|-----------------|--|

#### End point description:

The percentage of participants who became eligible for SCT after treatment with moxetumomab pasudotox were provided. The time to SCT was defined as the duration from the start of treatment with moxetumomab pasudotox until the date when the participant became eligible for SCT. The Clopper Pearson (Exact) 95% CI was calculated. Efficacy evaluable population included all participants who received any amount of moxetumomab pasudotox and completed a baseline disease assessment and had at least one post-baseline disease assessment.

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

#### End point timeframe:

Prior to Cycle 1, and prior to every cycle, at the end of treatment, at post-treatment follow-up visits, and at the end of the study

|                                   |  |  |  |  |
|-----------------------------------|--|--|--|--|
| <b>End point values</b>           | Moxetumomab Pasudotox 40 microgram per kilogram (mcg/kg) |  |  |  |
| Subject group type                | Reporting group  |  |  |  |
| Number of subjects analysed       | 28   |  |  |  |
| Units: percentage of participants | 0  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants who Were Neutropenic at Study Entry and who Experienced Hematologic Activity (HA)

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants who Were Neutropenic at Study Entry and who Experienced Hematologic Activity (HA) |
|-----------------|--|

#### End point description:

The percentage of participants who were neutropenic at study entry and experienced HA after treatment with moxetumomab pasudotox was evaluated. The Clopper Pearson (Exact) 95% CI was calculated. Efficacy evaluable population included all participants who received any amount of moxetumomab pasudotox and completed a baseline disease assessment and had at least one post-baseline disease assessment.

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| Prior to Cycle 1, and prior to every cycle, at the end of treatment, at post-treatment follow-up visits, and at the end of the study |           |

|                                   |  |  |  |  |
|-----------------------------------|--|--|--|--|
| <b>End point values</b>           | Moxetumomab Pasudotox 40 microgram per kilogram (mcg/kg) |  |  |  |
| Subject group type                | Reporting group  |  |  |  |
| Number of subjects analysed       | 28   |  |  |  |
| Units: percentage of participants |  |  |  |  |
| number (not applicable)           | 3.6  |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of Complete Response (DOCR)

|  |                                      |
|--|--------------------------------------|
| End point title  | Duration of Complete Response (DOCR) |
| End point description:   |                                      |
| DOCR was defined as the duration from the first documentation of CRc to the first documented disease progression. The CRc is defined as achieving complete response (CR), or CR with incomplete count recovery [CRi]) in participants with relapsed or refractory B-cell ALL or B-cell lymphoblastic lymphoma. Kaplan-Meier method was used for evaluation. Efficacy evaluable population included all participants who received any amount of moxetumomab pasudotox and completed a baseline disease assessment and had at least one post-baseline disease assessment. Here, number of participants analysed, "N" included evaluable participants for this outcome measure. |                                      |
| End point type   | Secondary                            |
| End point timeframe:   |                                      |
| Prior to Cycle 1, and prior to every cycle, at the end of treatment, at post-treatment follow-up visits, and at the end of the study   |                                      |

|                             |  |  |  |  |
|-----------------------------|--|--|--|--|
| <b>End point values</b>     | Moxetumomab Pasudotox 40 microgram per kilogram (mcg/kg) |  |  |  |
| Subject group type          | Reporting group  |  |  |  |
| Number of subjects analysed | 1  |  |  |  |
| Units: months               |  |  |  |  |
| number (not applicable)     | 1.97   |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of Overall Response (DOR)

|                 |                                    |
|-----------------|------------------------------------|
| End point title | Duration of Overall Response (DOR) |
|-----------------|------------------------------------|

End point description:

DOR was defined as the duration from the first documentation of overall response to the first documented disease progression. "99999" indicates data was not available as upper limit of 95% confidence interval could not be determined. Kaplan-Meier method was used for evaluation. Efficacy evaluable population included all participants who received any amount of moxetumomab pasudotox and completed a baseline disease assessment and had at least one post-baseline disease assessment.

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

End point timeframe:

Prior to Cycle 1, and prior to every cycle, at the end of treatment, at post-treatment follow-up visits, and at the end of the study

|                                  |  |  |  |  |
|----------------------------------|--|--|--|--|
| <b>End point values</b>          | Moxetumomab Pasudotox 40 microgram per kilogram (mcg/kg) |  |  |  |
| Subject group type               | Reporting group  |  |  |  |
| Number of subjects analysed      | 28   |  |  |  |
| Units: months                    |  |  |  |  |
| median (confidence interval 95%) | 0.95 (0.72 to 99999)                                     |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Progression-Free Survival (PFS)

|                 |                                 |
|-----------------|---------------------------------|
| End point title | Progression-Free Survival (PFS) |
|-----------------|---------------------------------|

End point description:

PFS was measured from the start of treatment with moxetumomab pasudotox until the first documentation of disease progression or death due to any cause, whichever occurred first. Kaplan-Meier method was used for evaluation. Efficacy evaluable population included all participants who received any amount of moxetumomab pasudotox and completed a baseline disease assessment and had at least one post-baseline disease assessment.

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

End point timeframe:

Prior to Cycle 1, and prior to every cycle, at the end of treatment, at post-treatment follow-up visits, and at the end of the study

|                                  |  |  |  |  |
|----------------------------------|--|--|--|--|
| <b>End point values</b>          | Moxetumomab Pasudotox 40 microgram per kilogram (mcg/kg) |  |  |  |
| Subject group type               | Reporting group  |  |  |  |
| Number of subjects analysed      | 28   |  |  |  |
| Units: months                    |  |  |  |  |
| median (confidence interval 95%) | 1.4 (0.7 to 1.5)   |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Survival (OS)

|                 |                       |
|-----------------|-----------------------|
| End point title | Overall Survival (OS) |
|-----------------|-----------------------|

End point description:

OS was determined as the time from the start of treatment with moxetumomab pasudotox until death due to any cause. For participants who were alive at the end of the study or lost to follow-up, OS was censored on the last date when the participant was known be alive. "99999" indicates data was not available as upper limit of 95% confidence interval could not be determined. Kaplan-Meier method was used for evaluation. Efficacy evaluable population included all participants who received any amount of moxetumomab pasudotox and completed a baseline disease assessment and had at least one post-baseline disease assessment.

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

End point timeframe:

Baseline to end of study or last contact date

|                                  |  |  |  |  |
|----------------------------------|--|--|--|--|
| <b>End point values</b>          | Moxetumomab Pasudotox 40 microgram per kilogram (mcg/kg) |  |  |  |
| Subject group type               | Reporting group  |  |  |  |
| Number of subjects analysed      | 28   |  |  |  |
| Units: months                    |  |  |  |  |
| median (confidence interval 95%) | 3.6 (2.4 to 99999)                                       |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants With Treatment-Emergent Adverse Events (TEAEs) and Treatment-Emergent Serious Adverse Events (TESAEs)

|                 |  |
|-----------------|--|
| End point title | Number of Participants With Treatment-Emergent Adverse Events (TEAEs) and Treatment-Emergent Serious Adverse Events (TESAEs) |
|-----------------|--|

End point description:

Treatment-emergent adverse events (TEAEs), were defined as events present at baseline that worsened in intensity after administration of investigational product or events absent at baseline that emerged after administration of study drug. Safety population includes all participants who received any amount of moxetumomab pasudotox.

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

End point timeframe:

Baseline up to 30 days after the last dose of study drug

|                             |  |  |  |  |
|-----------------------------|--|--|--|--|
| <b>End point values</b>     | Moxetumomab Pasudotox 40 microgram per kilogram (mcg/kg) |  |  |  |
| Subject group type          | Reporting group  |  |  |  |
| Number of subjects analysed | 30   |  |  |  |
| Units: participants         |  |  |  |  |
| TEAEs                       | 30   |  |  |  |
| TESAEs                      | 16   |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants With Abnormal Clinical Laboratory Parameters Reported as Treatment-Emergent Adverse Events (TEAE)

|                 |  |
|-----------------|--|
| End point title | Number of Participants With Abnormal Clinical Laboratory Parameters Reported as Treatment-Emergent Adverse Events (TEAE) |
|-----------------|--|

End point description:

Laboratory tests were grouped according to hematology, serum chemistry, and urinalysis. Laboratory abnormalities with toxicity grades according to NCI CTCAE Version 4.03 were derived according to laboratory values and reported as treatment-emergent adverse events. Safety population includes all participants who received any amount of moxetumomab pasudotox.

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

End point timeframe:

Baseline up to 30 days after the last dose of study drug

|                             |  |  |  |  |
|-----------------------------|--|--|--|--|
| <b>End point values</b>     | Moxetumomab Pasudotox 40 microgram per kilogram (mcg/kg) |  |  |  |
| Subject group type          | Reporting group  |  |  |  |
| Number of subjects analysed | 30   |  |  |  |
| Units: participants         |  |  |  |  |
| Anaemia                     | 11   |  |  |  |
| Febrile neutropenia         | 7  |  |  |  |

|  |    |  |  |  |
|--|----|--|--|--|
| Haemolytic uraemic syndrome              | 4  |  |  |  |
| Thrombocytopenia                         | 1  |  |  |  |
| Platelet count decreased                 | 9  |  |  |  |
| Neutrophil count decreased               | 6  |  |  |  |
| White blood cell count decreased         | 5  |  |  |  |
| Lymphocyte count decreased               | 2  |  |  |  |
| International normalised ratio increased | 1  |  |  |  |
| Alanine aminotransferase increased       | 11 |  |  |  |
| Aspartate aminotransferase increased     | 8  |  |  |  |
| Gamma-glutamyltransferase increased      | 4  |  |  |  |
| Blood bilirubin increased                | 2  |  |  |  |
| Blood creatinine increased               | 2  |  |  |  |
| Blood lactate dehydrogenase increased    | 2  |  |  |  |
| Bilirubin conjugated                     | 1  |  |  |  |
| Blood albumin decreased                  | 1  |  |  |  |
| Blood urea increased                     | 1  |  |  |  |
| Glucose tolerance increased              | 1  |  |  |  |
| Hypoalbuminaemia                         | 6  |  |  |  |
| Hypocalcaemia                            | 6  |  |  |  |
| Hypokalaemia                             | 5  |  |  |  |
| Hyponatraemia                            | 5  |  |  |  |
| Hyperglycaemia                           | 4  |  |  |  |
| Hypophosphataemia                        | 3  |  |  |  |
| Hypermagnesaemia                         | 1  |  |  |  |
| Hypomagnesaemia                          | 1  |  |  |  |
| Hepatic function abnormal                | 1  |  |  |  |
| Proteinuria                              | 1  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of participants with clinically significant Electrocardiogram (ECG) abnormalities

|                 |  |
|-----------------|--|
| End point title | Number of participants with clinically significant Electrocardiogram (ECG) abnormalities |
|-----------------|--|

End point description:

Participants were evaluated for ECG abnormalities. No clinically significant ECG abnormalities were detected and clinically significant prolongation of the median QT interval was not observed. Safety population includes all participants who received any amount of moxetumomab pasudotox.

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

End point timeframe:

Baseline up to 30 days after the last dose of study drug

|                             |  |  |  |  |
|-----------------------------|--|--|--|--|
| <b>End point values</b>     | Moxetumomab<br>Pasudotox 40<br>microgram per<br>kilogram<br>(mcg/kg) |  |  |  |
| Subject group type          | Reporting group  |  |  |  |
| Number of subjects analysed | 30   |  |  |  |
| Units: participants         | 0  |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants With Abnormal Vital Signs Reported as Treatment-Emergent Adverse Events (TEAEs)

|                 |  |
|-----------------|--|
| End point title | Number of Participants With Abnormal Vital Signs Reported as Treatment-Emergent Adverse Events (TEAEs) |
|-----------------|--|

End point description:

Participants who experienced vital signs abnormalities recorded as TEAEs were reported. Safety population includes all participants who received any amount of moxetumomab pasudotox.

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

End point timeframe:

Baseline up to 30 days after the last dose of study drug

|                             |  |  |  |  |
|-----------------------------|--|--|--|--|
| <b>End point values</b>     | Moxetumomab<br>Pasudotox 40<br>microgram per<br>kilogram<br>(mcg/kg) |  |  |  |
| Subject group type          | Reporting group  |  |  |  |
| Number of subjects analysed | 30   |  |  |  |
| Units: participants         |  |  |  |  |
| Pyrexia                     | 16   |  |  |  |
| Dyspnoea                    | 6  |  |  |  |
| Hypoxia                     | 4  |  |  |  |
| Hypertension                | 8  |  |  |  |
| Hypotension                 | 4  |  |  |  |
| Weight decreased            | 1  |  |  |  |
| Weight increased            | 10   |  |  |  |
| Bradycardia                 | 7  |  |  |  |
| Sinus Bradycardia           | 1  |  |  |  |
| Sinus Tachycardia           | 3  |  |  |  |
| Tachycardia                 | 3  |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants With Positive Anti-drug Antibody (ADA) and Neutralizing Antibodies (NAb)

|                 |   |
|-----------------|---|
| End point title | Number of Participants With Positive Anti-drug Antibody (ADA) and Neutralizing Antibodies (NAb) |
|-----------------|---|

End point description:

Immunogenicity assessment included determination of anti-drug (moxetumomab pasudotox) antibodies and neutralizing antidrug antibodies in serum samples. Titers and specificity were determined for NAb-positive participants. Specificity were observed in participants who had ADAs directed to the PE38 domain of moxetumomab pasudotox and increase in titers were observed in participants who tested ADA-positive at baseline. Safety population includes all participants who received any amount of moxetumomab pasudotox. Here, number of participants analysed, "N" included participants with at least one post-baseline sample.

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

End point timeframe:

Prior to the Start of Each Cycle for Cycles 1, 2, 3, and Subsequent Odd-Numbered Cycles, End of Treatment, and 30 Day Follow-up Visit

|                               |  |  |  |  |
|-------------------------------|--|--|--|--|
| <b>End point values</b>       | Moxetumomab Pasudotox 40 microgram per kilogram (mcg/kg) |  |  |  |
| Subject group type            | Reporting group  |  |  |  |
| Number of subjects analysed   | 23   |  |  |  |
| Units: participants           |  |  |  |  |
| Anti-drug Antibody (ADA)      | 13   |  |  |  |
| Neutralizing Antibodies (NAb) | 13   |  |  |  |
| Increase in Titers            | 3  |  |  |  |
| Specificity                   | 13   |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Area Under the Plasma Concentration Time Curve From Time 0 to Infinity (AUC0-inf) After the First Dose of Cycle 1

|                 |   |
|-----------------|---|
| End point title | Area Under the Plasma Concentration Time Curve From Time 0 to Infinity (AUC0-inf) After the First Dose of Cycle 1 |
|-----------------|---|

End point description:

AUC (0-infinity) = Area under the serum concentration versus time curve from time zero (pre-dose) to extrapolated infinite time (0-infinity). It is obtained from AUC (0-t) plus AUC (t-infinity). It was calculated by extrapolating the concentrationtime curve from time zero to infinity using the linear/log trapezoidal rule. Safety population who provided at least one measurable Pharmacokinetic concentration. Here, number of participants analysed, "N" included evaluable participants for this outcome measure.

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

End point timeframe:

Pre-infusion, end of infusion (EOI); 1, 3, and 6 hours post-infusion of Day 1 of Cycle 1

|   |  |  |  |  |
|---|--|--|--|--|
| <b>End point values</b>                           | Moxetumomab<br>Pasudotox 40<br>microgram per<br>kilogram<br>(mcg/kg) |  |  |  |
| Subject group type                                | Reporting group  |  |  |  |
| Number of subjects analysed                       | 7  |  |  |  |
| Units: hour*nanogram per milliliter<br>(hr*ng/mL) |  |  |  |  |
| arithmetic mean (standard deviation)              | 1200 (± 224)   |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Area Under the Concentration Versus Time Curve From Time Zero to Last Quantifiable Concentration [AUC0-last] After the First Dose of Cycle 1

|                 |  |
|-----------------|--|
| End point title | Area Under the Concentration Versus Time Curve From Time Zero to Last Quantifiable Concentration [AUC0-last] After the First Dose of Cycle 1 |
|-----------------|--|

End point description:

AUC is a measure of systemic drug exposure, which is obtained by collecting a series of blood samples and measuring the concentrations of drug in each sample. AUC0-last is defined as AUC from time zero to the last data point above the lower limit of quantification. Safety population who provided at least one measurable Pharmacokinetic concentration. Here, number of participants analysed, "N" included evaluable participants for this outcome measure.

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

End point timeframe:

Pre-infusion, end of infusion (EOI); 1, 3, and 6 hours post-infusion at Day 1 of Cycle 1

|   |  |  |  |  |
|---|--|--|--|--|
| <b>End point values</b>                           | Moxetumomab<br>Pasudotox 40<br>microgram per<br>kilogram<br>(mcg/kg) |  |  |  |
| Subject group type                                | Reporting group  |  |  |  |
| Number of subjects analysed                       | 21   |  |  |  |
| Units: hour*nanogram per milliliter<br>(hr*ng/mL) |  |  |  |  |
| arithmetic mean (standard deviation)              | 794 (± 239)  |  |  |  |

### Statistical analyses

No statistical analyses for this end point

**Secondary: Maximum Observed Drug Concentration in Plasma (Cmax) After the First Dose of Cycle 1**

|   |   |
|---|---|
| End point title   | Maximum Observed Drug Concentration in Plasma (Cmax)<br>After the First Dose of Cycle 1 |
| End point description:<br>Cmax refers to the highest measured drug concentration which is obtained by collecting a series of blood samples and measuring the concentrations of drug in each sample. Safety population who provided at least one measurable Pharmacokinetic concentration. |   |
| End point type  | Secondary   |
| End point timeframe:<br>Pre-infusion, end of infusion (EOI); 1, 3, and 6 hours post-infusion at Day 1 of Cycle 1  |   |

|                                      |  |  |  |  |
|--------------------------------------|--|--|--|--|
| <b>End point values</b>              | Moxetumomab<br>Pasudotox 40<br>microgram per<br>kilogram<br>(mcg/kg) |  |  |  |
| Subject group type                   | Reporting group  |  |  |  |
| Number of subjects analysed          | 26   |  |  |  |
| Units: nanogram per milliliter       |  |  |  |  |
| arithmetic mean (standard deviation) | 457 (± 128)  |  |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Time to Reach Maximum Drug Concentration in Plasma (tmax) After the First Dose of Cycle 1**

|  |  |
|--|--|
| End point title  | Time to Reach Maximum Drug Concentration in Plasma (tmax)<br>After the First Dose of Cycle 1 |
| End point description:<br>Tmax refers to the time after dosing when a drug attains its highest measurable concentration (Cmax). It is obtained by collecting a series of blood samples at various times after dosing, and measuring them for drug content. Safety population who provided at least one measurable Pharmacokinetic concentration. |  |
| End point type   | Secondary  |
| End point timeframe:<br>Pre-infusion, end of infusion (EOI); 1, 3, and 6 hours post-infusion at Day 1 of Cycle 1   |  |

|                                      |  |  |  |  |
|--------------------------------------|--|--|--|--|
| <b>End point values</b>              | Moxetumomab<br>Pasudotox 40<br>microgram per<br>kilogram<br>(mcg/kg) |  |  |  |
| Subject group type                   | Reporting group  |  |  |  |
| Number of subjects analysed          | 26   |  |  |  |
| Units: hour                          |  |  |  |  |
| arithmetic mean (standard deviation) | 0.54 (± 0.05)  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Terminal Phase Elimination Half Life (t<sub>1/2</sub>) After the First Dose of Cycle 1

|                 |  |
|-----------------|--|
| End point title | Terminal Phase Elimination Half Life (t <sub>1/2</sub> ) After the First Dose of Cycle 1 |
|-----------------|--|

End point description:

Terminal phase elimination half-life is the time measured for the serum/plasma concentration to decrease by one half, calculated as natural logarithmic (log)-transformed (ln) value of 2 divided by elimination rate constant (lambda); that is  $[\ln(2)/\lambda]$ . Elimination rate constant (lambda) was estimated via linear regression of the time versus log concentration. Safety population who provided at least one measurable Pharmacokinetic concentration. Here, number of participants analysed, "N" included evaluable participants for this outcome measure.

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

End point timeframe:

Pre-infusion, end of infusion (EOI); 1, 3, and 6 hours post-infusion at Day 1 of Cycle 1

|                               |  |  |  |  |
|-------------------------------|--|--|--|--|
| End point values              | Moxetumomab<br>Pasudotox 40<br>microgram per<br>kilogram<br>(mcg/kg) |  |  |  |
| Subject group type            | Reporting group  |  |  |  |
| Number of subjects analysed   | 7  |  |  |  |
| Units: hour                   |  |  |  |  |
| median (full range (min-max)) | 1.02 (0.82 to<br>1.44)   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Systemic Clearance (CL) After the First Dose of Cycle 1

|                 |   |
|-----------------|---|
| End point title | Systemic Clearance (CL) After the First Dose of Cycle 1 |
|-----------------|---|

End point description:

CL is a quantitative measure of the rate at which a drug substance is removed from the body. The total systemic clearance after intravenous dose was estimated by dividing the total administered dose by the plasma Area Under the Plasma Concentration-Time Curve From Time Zero to Infinite Time (AUC[0-infinity]). Safety population who provided at least one measurable Pharmacokinetic concentration. Here, number of participants analysed, "N" included evaluable participants for this outcome measure.

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

---

End point timeframe:

Pre-infusion, end of infusion (EOI); 1, 3, and 6 hours post-infusion at Day 1 of Cycle 1

---

|   |  |  |  |  |
|---|--|--|--|--|
| <b>End point values</b>                 | Moxetumomab<br>Pasudotox 40<br>microgram per<br>kilogram<br>(mcg/kg) |  |  |  |
| Subject group type                      | Reporting group  |  |  |  |
| Number of subjects analysed             | 7  |  |  |  |
| Units: milliliter per hour per kilogram |  |  |  |  |
| arithmetic mean (full range (min-max))  | 34.4 (24.4 to<br>41.8)   |  |  |  |

### Statistical analyses

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

The period immediately following the time that written informed consent is obtained through Day 30 after the last dose

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 18.1 |
|--------------------|------|

### Reporting groups

|                       |  |
|-----------------------|--|
| Reporting group title | Moxetumomab Pasudotox 40 microgram per kilogram (mcg/kg) |
|-----------------------|--|

Reporting group description:

Participants received 6 doses of moxetumomab pasudotox 40 mcg/kg intravenous infusion over 30 minutes every other day (Days 1, 3, 5, 7, 9, and 11) in 21-day treatment cycles until completion of a maximum of 6 cycles of therapy.

| Serious adverse events                            | Moxetumomab Pasudotox 40 microgram per kilogram (mcg/kg) |  |  |
|---|--|--|--|
| Total subjects affected by serious adverse events |  |  |  |
| subjects affected / exposed                       | 16 / 30 (53.33%)   |  |  |
| number of deaths (all causes)                     | 1  |  |  |
| number of deaths resulting from adverse events    | 1  |  |  |
| Investigations                                    |  |  |  |
| Platelet count decreased                          |  |  |  |
| subjects affected / exposed                       | 1 / 30 (3.33%)   |  |  |
| occurrences causally related to treatment / all   | 1 / 1  |  |  |
| deaths causally related to treatment / all        | 0 / 0  |  |  |
| Vascular disorders                                |  |  |  |
| Capillary leak syndrome                           |  |  |  |
| subjects affected / exposed                       | 5 / 30 (16.67%)  |  |  |
| occurrences causally related to treatment / all   | 5 / 5  |  |  |
| deaths causally related to treatment / all        | 0 / 0  |  |  |
| Nervous system disorders                          |  |  |  |
| Encephalopathy                                    |  |  |  |
| subjects affected / exposed                       | 1 / 30 (3.33%)   |  |  |
| occurrences causally related to treatment / all   | 0 / 1  |  |  |
| deaths causally related to treatment / all        | 0 / 0  |  |  |
| Headache  |  |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| subjects affected / exposed                          | 1 / 30 (3.33%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Somnolence   |                 |  |  |
| subjects affected / exposed                          | 1 / 30 (3.33%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Blood and lymphatic system disorders                 |                 |  |  |
| Febrile neutropenia                                  |                 |  |  |
| subjects affected / exposed                          | 3 / 30 (10.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 3           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Haemolytic uraemic syndrome                          |                 |  |  |
| subjects affected / exposed                          | 4 / 30 (13.33%) |  |  |
| occurrences causally related to treatment / all      | 4 / 4           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| General disorders and administration site conditions |                 |  |  |
| Fatigue  |                 |  |  |
| subjects affected / exposed                          | 1 / 30 (3.33%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Pyrexia  |                 |  |  |
| subjects affected / exposed                          | 4 / 30 (13.33%) |  |  |
| occurrences causally related to treatment / all      | 1 / 4           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Eye disorders  |                 |  |  |
| Vision blurred                                       |                 |  |  |
| subjects affected / exposed                          | 1 / 30 (3.33%)  |  |  |
| occurrences causally related to treatment / all      | 1 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Respiratory, thoracic and mediastinal disorders      |                 |  |  |
| Pulmonary oedema                                     |                 |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 2 / 30 (6.67%) |  |  |
| occurrences causally related to treatment / all | 2 / 2          |  |  |
| deaths causally related to treatment / all      | 1 / 1          |  |  |
| Respiratory distress                            |                |  |  |
| subjects affected / exposed                     | 1 / 30 (3.33%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Psychiatric disorders                           |                |  |  |
| Anxiety   |                |  |  |
| subjects affected / exposed                     | 1 / 30 (3.33%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Musculoskeletal and connective tissue disorders |                |  |  |
| Bone pain                                       |                |  |  |
| subjects affected / exposed                     | 1 / 30 (3.33%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Infections and infestations                     |                |  |  |
| Device related infection                        |                |  |  |
| subjects affected / exposed                     | 1 / 30 (3.33%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Infection                                       |                |  |  |
| subjects affected / exposed                     | 1 / 30 (3.33%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Septic shock                                    |                |  |  |
| subjects affected / exposed                     | 1 / 30 (3.33%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Staphylococcal sepsis                           |                |  |  |
| subjects affected / exposed                     | 1 / 30 (3.33%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

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

| <b>Non-serious adverse events</b>  | Moxetumomab<br>Pasudotox 40<br>microgram per<br>kilogram (mcg/kg) |  |  |
|--|---|--|--|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed | 30 / 30 (100.00%)   |  |  |
| Vascular disorders   |   |  |  |
| Hypertension   |   |  |  |
| subjects affected / exposed  | 8 / 30 (26.67%)   |  |  |
| occurrences (all)  | 12  |  |  |
| Hypotension  |   |  |  |
| subjects affected / exposed  | 4 / 30 (13.33%)   |  |  |
| occurrences (all)  | 4   |  |  |
| General disorders and administration site conditions                                 |   |  |  |
| Face oedema  |   |  |  |
| subjects affected / exposed  | 4 / 30 (13.33%)   |  |  |
| occurrences (all)  | 5   |  |  |
| Fatigue  |   |  |  |
| subjects affected / exposed  | 2 / 30 (6.67%)  |  |  |
| occurrences (all)  | 3   |  |  |
| Oedema peripheral  |   |  |  |
| subjects affected / exposed  | 5 / 30 (16.67%)   |  |  |
| occurrences (all)  | 8   |  |  |
| Pyrexia  |   |  |  |
| subjects affected / exposed  | 12 / 30 (40.00%)  |  |  |
| occurrences (all)  | 40  |  |  |
| Respiratory, thoracic and mediastinal disorders                                      |   |  |  |
| Cough  |   |  |  |
| subjects affected / exposed  | 3 / 30 (10.00%)   |  |  |
| occurrences (all)  | 3   |  |  |
| Dyspnoea   |   |  |  |

|  |  |  |  |
|--|--|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Epistaxis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Hypoxia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Wheezing</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>6 / 30 (20.00%)</p> <p>9</p> <p>2 / 30 (6.67%)</p> <p>2</p> <p>4 / 30 (13.33%)</p> <p>6</p> <p>2 / 30 (6.67%)</p> <p>2</p>  |  |  |
| <p>Psychiatric disorders</p> <p>Anxiety</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>3 / 30 (10.00%)</p> <p>3</p>  |  |  |
| <p>Investigations</p> <p>Alanine aminotransferase increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Aspartate aminotransferase increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Blood bilirubin increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Blood creatinine increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Blood lactate dehydrogenase increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Gamma-glutamyltransferase increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Lymphocyte count decreased</p> | <p>11 / 30 (36.67%)</p> <p>45</p> <p>8 / 30 (26.67%)</p> <p>34</p> <p>2 / 30 (6.67%)</p> <p>4</p> <p>2 / 30 (6.67%)</p> <p>3</p> <p>2 / 30 (6.67%)</p> <p>2</p> <p>4 / 30 (13.33%)</p> <p>18</p> |  |  |

|   |                        |  |  |
|---|------------------------|--|--|
| subjects affected / exposed<br>occurrences (all)  | 2 / 30 (6.67%)<br>4    |  |  |
| Neutrophil count decreased<br>subjects affected / exposed<br>occurrences (all)                      | 6 / 30 (20.00%)<br>21  |  |  |
| Platelet count decreased<br>subjects affected / exposed<br>occurrences (all)                        | 8 / 30 (26.67%)<br>59  |  |  |
| Weight increased<br>subjects affected / exposed<br>occurrences (all)                                | 10 / 30 (33.33%)<br>21 |  |  |
| White blood cell count decreased<br>subjects affected / exposed<br>occurrences (all)                | 5 / 30 (16.67%)<br>24  |  |  |
| Cardiac disorders<br>Sinus tachycardia<br>subjects affected / exposed<br>occurrences (all)          | 3 / 30 (10.00%)<br>6   |  |  |
| Tachycardia<br>subjects affected / exposed<br>occurrences (all)                                     | 3 / 30 (10.00%)<br>3   |  |  |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)            | 12 / 30 (40.00%)<br>22 |  |  |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)                                    | 2 / 30 (6.67%)<br>2    |  |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all) | 11 / 30 (36.67%)<br>29 |  |  |
| Febrile neutropenia<br>subjects affected / exposed<br>occurrences (all)                             | 4 / 30 (13.33%)<br>13  |  |  |
| Eye disorders   |                        |  |  |

|  |                       |  |  |
|--|-----------------------|--|--|
| Periorbital oedema<br>subjects affected / exposed<br>occurrences (all)         | 3 / 30 (10.00%)<br>3  |  |  |
| Vision blurred<br>subjects affected / exposed<br>occurrences (all)             | 5 / 30 (16.67%)<br>6  |  |  |
| Gastrointestinal disorders   |                       |  |  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)             | 3 / 30 (10.00%)<br>5  |  |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)               | 4 / 30 (13.33%)<br>5  |  |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                  | 3 / 30 (10.00%)<br>3  |  |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                     | 8 / 30 (26.67%)<br>10 |  |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                   | 4 / 30 (13.33%)<br>4  |  |  |
| Musculoskeletal and connective tissue disorders                                |                       |  |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)                  | 6 / 30 (20.00%)<br>6  |  |  |
| Bone pain<br>subjects affected / exposed<br>occurrences (all)                  | 3 / 30 (10.00%)<br>3  |  |  |
| Groin pain<br>subjects affected / exposed<br>occurrences (all)                 | 2 / 30 (6.67%)<br>2   |  |  |
| Musculoskeletal chest pain<br>subjects affected / exposed<br>occurrences (all) | 2 / 30 (6.67%)<br>2   |  |  |
| Myalgia  |                       |  |  |

|                                    |                 |  |  |
|------------------------------------|-----------------|--|--|
| subjects affected / exposed        | 2 / 30 (6.67%)  |  |  |
| occurrences (all)                  | 2               |  |  |
| Neck pain                          |                 |  |  |
| subjects affected / exposed        | 2 / 30 (6.67%)  |  |  |
| occurrences (all)                  | 2               |  |  |
| Pain in extremity                  |                 |  |  |
| subjects affected / exposed        | 6 / 30 (20.00%) |  |  |
| occurrences (all)                  | 6               |  |  |
| Pain in jaw                        |                 |  |  |
| subjects affected / exposed        | 2 / 30 (6.67%)  |  |  |
| occurrences (all)                  | 2               |  |  |
| Infections and infestations        |                 |  |  |
| Pneumonia                          |                 |  |  |
| subjects affected / exposed        | 2 / 30 (6.67%)  |  |  |
| occurrences (all)                  | 2               |  |  |
| Metabolism and nutrition disorders |                 |  |  |
| Hyperglycaemia                     |                 |  |  |
| subjects affected / exposed        | 4 / 30 (13.33%) |  |  |
| occurrences (all)                  | 12              |  |  |
| Hypoalbuminaemia                   |                 |  |  |
| subjects affected / exposed        | 6 / 30 (20.00%) |  |  |
| occurrences (all)                  | 11              |  |  |
| Hypocalcaemia                      |                 |  |  |
| subjects affected / exposed        | 6 / 30 (20.00%) |  |  |
| occurrences (all)                  | 28              |  |  |
| Hypokalaemia                       |                 |  |  |
| subjects affected / exposed        | 5 / 30 (16.67%) |  |  |
| occurrences (all)                  | 27              |  |  |
| Hyponatraemia                      |                 |  |  |
| subjects affected / exposed        | 5 / 30 (16.67%) |  |  |
| occurrences (all)                  | 12              |  |  |
| Hypophosphataemia                  |                 |  |  |
| subjects affected / exposed        | 3 / 30 (10.00%) |  |  |
| occurrences (all)                  | 13              |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 20 February 2013 | Enrollment of any relapsed participant with acute lymphoblastic leukemia (ALL) was allowed. B-cell lineage disease (that is, B-cell ALL and B-cell lymphoblastic lymphoma) were also targeted. -The secondary objective of "to evaluate the participant's quality of life using the parent proxy-reported health-related quality of life (HRQOL) assessment, specifically using PedsQL4.0 Generic Core Scale, the PedsQL 3.0 Cancer Module, and the PedsQL Multidimensional Fatigue Scales" was deleted. - Dose changed from 50 to 40 mcg/kg due to a change from Process 2 to Process 3 and from 6 to 10 doses per cycle. - Study-stopping criteria modified. - Clarified that cluster of differentiation-22 (CD22) positivity was not required for inclusion. - Inclusion and exclusion criteria were revised. - Withdrawal criteria were added and revised. - This is in reference to the amendment change for clarifying that other agents could have been used in addition to or in lieu of allopurinol. - Allopurinol was to be administered during Cycle 1. - Clarified dosing delay within a cycle of > 5 Days would result in withdrawal from the study. - Clarified additional concomitants being allowed. - Clarified DMC change. - Clarified that investigators should consider G6PD or other screening tests for conditions that may cause hemolysis. - Dosing was changed to not be capped at a certain weight. - Treatment administration details were clarified. - Conditions for treatment continuation were revised. - Clarification of study procedures timings were done. - Statistical definitions and clarifications were included.   |
| 19 April 2013    | -Added Exclusion criteria, to exclude participants with mixed-lineage leukemia (MLL) gene rearrangement. - Added Exclusion criteria, to exclude participants with a QTcF interval above a defined threshold. - Added text that participants will also be queried for ocular symptoms throughout the study; and that additional ophthalmologic exams must be conducted to follow up on any reported ocular symptoms. - Clarified that bone marrow aspirate with or without a biopsy would be performed. - Updated schedule of assessments on 24-hour urine protein excretion and creatinine clearance, and electrocardiograms (ECGs). - Management guidelines for hemolytic uremic syndrome (HUS) added.   |
| 13 January 2014  | - CAT-8015" was replaced with "moxetumomab pasudotox" where appropriate. - Change of definitions of primary and secondary objectives, assessment of endpoints, and power calculations. - Change from dosing with 40 mcg/kg of Process 2 material to its bioequivalent of 32 mcg/kg of Process 3 material. - Wording was changed "must be reported within 24 hours of the Principal Investigator or designee obtaining knowledge of event. - Interim monitoring of treatment-related death was added to study-stopping criteria. - Exclusion criteria were modified. - Withdrawal criteria was amended. - Dosing delays were included for events of hypercalcemia. - Exclusion of concomitant medication of high-dose estrogen therapy was added. - Added: "If participants develop any grade of HUS or capillary leak syndrome (CLS) during study treatment, PK and immunogenicity samples, serum complement factors, and serum immunoglobulin levels will be collected within 24 hours of time of first diagnosis, worsening of event, and at time of improvement and full resolution of event." - Added: Appendix 4: Performance Status Scales/Scores (Eastern Cooperative Oncology Group (ECOG)/Karnofsky/Lansky), Appendix 5: Schwartz Formula, and Appendix 6: Measured Corrected Creatinine Clearance. - Treatment administration: Wording for option to pre-medicate participants with acetaminophen, diphenhydramine, and ranitidine at Principal Investigator's discretion and as clinically indicated was added to this section. - Wording was changed regarding administration of allopurinol, corticosteroid, and fluid hydration. - Added: HLA typing and anti-Factor H antibodies, serum immunoglobulins, serum complement factors, twice daily serum creatinine measurements on specified days during Cycle 1. - Twice daily serum creatinine collections and assessments for ocular symptoms were added for inpatient admission days during Cycle 1. - A change was made to make any grade of CLS or thrombotic microangiopathy/HUS immediately reportable. |

|               |   |
|---------------|---|
| 17 June 2014  | <ul style="list-style-type: none"> <li>- Dosing was changed from 32 mcg/kg of Process 3 material for 10 doses in each 21-day cycle to 40 mcg/kg of Process 3 material for 6 doses (Days 1, 3, 5, 7, 9, and 11) of each 21-day cycle until completion of a maximum of 6 cycles.</li> <li>- The statement regarding retinal damage or abnormalities was simplified to retinal abnormalities.</li> <li>- The start time for allopurinol was specified as at least 8 hours prior to the first dose of moxetumomab pasudotox.</li> <li>- The dose of methylprednisolone for treatment of infusion reaction was changed from a fixed dose to a weight based dose.</li> <li>- The number of days for a delay in the start of a cycle to accommodate schedule conflicts was reduced from 14 days to 7 days.</li> <li>- In the event that a subject developed any grade of HUS or CLS, or had an ocular event with new abnormality by ophthalmologic examination during treatment, collection of samples for plasma cytokines was added in addition to PK and immunogenicity samples, serum complement factors, and serum immunoglobulin levels.</li> <li>- The requirement for collection of samples for CD22 expression if subjects develop HUS, CLS, or ocular events during study treatment was removed as CD22 expression was to be collected at screening only.</li> <li>- The threshold for withdrawal due to an event of thrombotic microangiopathy/HUS was lowered from <math>\geq</math> Grade 3 to <math>\geq</math> Grade 2; The duration for concomitant allopurinol during Cycle 1 was changed from "until disease burden is reduced" to "until at least 24 hours after the sixth dose of moxetumomab pasudotox in Cycle 1".</li> <li>- A provision requiring admission for inpatient management for participants with Grade 2 or higher HUS.</li> </ul> |
| 06 March 2015 | <ul style="list-style-type: none"> <li>-Text was modified to specify that treatment would not continue if the start of a cycle was delayed more than 7 days (that is ie, beyond 28 days after the first dose of the previous cycle).</li> <li>- Text was updated to include HUS as an identified risk, and information regarding mitigation and monitoring for this risk was added.</li> <li>- Inclusion criteria 4 was clarified to specify that all participants (both ALL and subjects with lymphoblastic lymphoma) must have M2 or M3 bone marrow classification to be eligible for the study.</li> <li>- Modified exclusion criteria 2 to indicate that the participant must not be concurrently enrolled in another clinical study for cancer treatment, unless the subject is in the follow-up period of the previous study.</li> <li>- Added vincristine as an exception to the medication exclusions in exclusion criterion 15.</li> <li>- Deleted "within 3 months prior to enrollment" from exclusion criterion 26.</li> <li>- Myoglobin was deleted from the list of cardiac biomarkers.</li> <li>- Schistocyte count was included as part of the peripheral blood smear at selected time points.</li> <li>- Added the following to exclusion criterion 24: Albumin infusions for correction of hypoalbuminemia are allowed, but cannot have been administered within 7 days prior to start of study drug.</li> <li>- Modified exclusion criterion 30 to indicate that participants who received high-dose estrogen therapy within 2 weeks prior to enrollment in the study were excluded. Use of high-dose estrogen therapy was added as a withdrawal criterion.</li> <li>- Added "or HUS-like event" to withdrawal criterion 10.</li> </ul>   |
| 28 April 2015 | -Clarification of language regarding the severity of CLS.   |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date              | Interruption   | Restart date |
|-------------------|--|--------------|
| 01 September 2015 | The study was terminated prior to a planned interim analysis based on lack of required efficacy in the first 32 participants enrolled. | -            |

Notes:

## Limitations and caveats

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

The study was terminated due to lack of required efficacy because review of response data suggested that the number of clinical responses required to proceed to Stage 2 would not be met.

Notes: