



## Clinical trial results:

### A Phase 2, Multicenter, Single-Arm Study of Trastuzumab Emtansine in Patients With HER2 IHC-Positive, Locally Advanced or Metastatic Non-Small Cell Lung Cancer Who Have Received At Least One Prior Chemotherapy Regimen

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2014-001237-83 |
| Trial protocol           | DE ES IT PL    |
| Global end of trial date | 26 July 2018   |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v2 (current)     |
| This version publication date  | 23 August 2019   |
| First version publication date | 09 November 2017 |
| Version creation reason        |                  |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | BO29389 |
|-----------------------|---------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02289833 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Hoffmann-LaRoche   |
| Sponsor organisation address | Grenzacherstrasse 124, CH, Basel, Basel, Switzerland, 4070                       |
| Public contact               | Medical Communications, Hoffmann-LaRoche, +41 8008218590, genentech@druginfo.com |
| Scientific contact           | Medical Communications, Hoffmann-LaRoche, +41 8008218590, genentech@druginfo.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? | No |

Notes:

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**Results analysis stage**

|  |                 |
|--|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 26 October 2016 |
| Is this the analysis of the primary completion data? | No              |

|                                  |              |
|----------------------------------|--------------|
| Global end of trial reached?     | Yes          |
| Global end of trial date         | 26 July 2018 |
| Was the trial ended prematurely? | No           |

Notes:

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**General information about the trial**

Main objective of the trial:

The main objective of this study is to evaluate the efficacy of single-agent trastuzumab emtansine in subjects with centrally confirmed human epidermal growth factor receptor (HER2) immunohistochemistry (IHC)-positive (IHC2+ or IHC3+) locally advanced or metastatic non-small cell lung cancer (NSCLC) who had received at least one prior chemotherapy regimen, as measured by confirmed objective response rate (ORR).

Protection of trial subjects:

All subjects signed an informed consent form before participating in the study.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 15 December 2014 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

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**Population of trial subjects****Subjects enrolled per country**

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Spain: 12         |
| Country: Number of subjects enrolled | Germany: 5        |
| Country: Number of subjects enrolled | Italy: 4          |
| Country: Number of subjects enrolled | Poland: 8         |
| Country: Number of subjects enrolled | Switzerland: 4    |
| Country: Number of subjects enrolled | United States: 16 |
| Worldwide total number of subjects   | 49                |
| EEA total number of subjects         | 29                |

Notes:

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**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) | 0  |
| Adults (18-64 years)      | 27 |
| From 65 to 84 years       | 22 |
| 85 years and over         | 0  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Subjects were screened centrally for HER2 status, using archived tumor specimens from previously collected tissue, if available.

### Period 1

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

### Arms

|                              |              |
|------------------------------|--------------|
| Are arms mutually exclusive? | Yes          |
| <b>Arm title</b>             | Cohort IHC2+ |

Arm description:

Subjects with HER2 IHC2-positive (IHC 2+) locally advanced or metastatic NSCLC, who had received at least one prior platinum-based chemotherapy regimen, will receive trastuzumab emtansine.

|  |                                   |
|--|-----------------------------------|
| Arm type                               | Experimental                      |
| Investigational medicinal product name | Trastuzumab emtansine             |
| Investigational medicinal product code |                                   |
| Other name                             | Kadcyla, T-DM1                    |
| Pharmaceutical forms                   | Powder for solution for injection |
| Routes of administration               | Intravenous use                   |

Dosage and administration details:

Trastuzumab emtansine will be administered intravenously (IV) at a dose of 3.6 milligrams/kilogram (mg/kg) on Day 1 of every 21-day cycle until disease progression (as assessed by the investigator), unmanageable toxicity, or study termination by the sponsor, whichever occurs first.

|                  |              |
|------------------|--------------|
| <b>Arm title</b> | Cohort IHC3+ |
|------------------|--------------|

Arm description:

Subjects with HER2 IHC3-positive (IHC 3+) locally advanced or metastatic NSCLC, who had received at least one prior platinum-based chemotherapy regimen, will receive trastuzumab emtansine.

|  |                                   |
|--|-----------------------------------|
| Arm type                               | Experimental                      |
| Investigational medicinal product name | Trastuzumab emtansine             |
| Investigational medicinal product code |                                   |
| Other name                             | Kadcyla, T-DM1                    |
| Pharmaceutical forms                   | Powder for solution for injection |
| Routes of administration               | Intravenous use                   |

Dosage and administration details:

Trastuzumab emtansine will be administered intravenously (IV) at a dose of 3.6 mg/kg on Day 1 of every 21-day cycle until disease progression (as assessed by the investigator), unmanageable toxicity, or study termination by the sponsor, whichever occurs first.

| <b>Number of subjects in period 1</b> | Cohort IHC2+ | Cohort IHC3+ |
|---------------------------------------|--------------|--------------|
| Started                               | 29           | 20           |
| Completed                             | 2            | 3            |
| Not completed                         | 27           | 17           |
| Death                                 | 23           | 16           |
| Study Discontinuation                 | -            | 1            |
| Lost to follow-up                     | 4            | -            |

## Baseline characteristics

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | Cohort IHC2+ |
|-----------------------|--------------|

Reporting group description:

Subjects with HER2 IHC2-positive (IHC 2+) locally advanced or metastatic NSCLC, who had received at least one prior platinum-based chemotherapy regimen, will receive trastuzumab emtansine.

|                       |              |
|-----------------------|--------------|
| Reporting group title | Cohort IHC3+ |
|-----------------------|--------------|

Reporting group description:

Subjects with HER2 IHC3-positive (IHC 3+) locally advanced or metastatic NSCLC, who had received at least one prior platinum-based chemotherapy regimen, will receive trastuzumab emtansine.

| Reporting group values | Cohort IHC2+ | Cohort IHC3+ | Total |
|------------------------|--------------|--------------|-------|
| Number of subjects     | 29           | 20           | 49    |
| Age categorical        |              |              |       |
| Units: Subjects        |              |              |       |

|                     |        |       |    |
|---------------------|--------|-------|----|
| Age Continuous      |        |       |    |
| Units: years        |        |       |    |
| arithmetic mean     | 63.1   | 61.4  |    |
| standard deviation  | ± 10.3 | ± 8.6 | -  |
| Gender, Male/Female |        |       |    |
| Units: Subjects     |        |       |    |
| Female              | 13     | 7     | 20 |
| Male                | 16     | 13    | 29 |

## End points

### End points reporting groups

|  |   |
|--|---|
| Reporting group title  | Cohort IHC2+  |
| Reporting group description:<br>Subjects with HER2 IHC2-positive (IHC 2+) locally advanced or metastatic NSCLC, who had received at least one prior platinum-based chemotherapy regimen, will receive trastuzumab emtansine.   |   |
| Reporting group title  | Cohort IHC3+  |
| Reporting group description:<br>Subjects with HER2 IHC3-positive (IHC 3+) locally advanced or metastatic NSCLC, who had received at least one prior platinum-based chemotherapy regimen, will receive trastuzumab emtansine.   |   |
| Subject analysis set title   | PK Analyses for Trastuzumab Emtansine and Total Trastuzumab |
| Subject analysis set type  | Sub-group analysis  |
| Subject analysis set description:<br>Subjects with HER2 IHC2 or IHC3-positive (IHC 2+ or IHC 3+) locally advanced or metastatic NSCLC, who had received at least one prior platinum-based chemotherapy regimen, will receive trastuzumab emtansine. There were 47 patients in PK pop from which 44 had valid sparse PK data. |   |
| Subject analysis set title   | Cmax Analysis for DM1                                       |
| Subject analysis set type  | Sub-group analysis  |
| Subject analysis set description:<br>Subjects with HER2 IHC2 or IHC3-positive (IHC 2+ or IHC 3+) locally advanced or metastatic NSCLC, who had received at least one prior platinum-based chemotherapy regimen, will receive trastuzumab emtansine.  |   |
| Subject analysis set title   | Anti-drug Antibody Analysis Group                           |
| Subject analysis set type  | Sub-group analysis  |
| Subject analysis set description:<br>Subjects with HER2 IHC2 or IHC3-positive (IHC 2+ or IHC 3+) locally advanced or metastatic NSCLC, who had received at least one prior platinum-based chemotherapy regimen, will receive trastuzumab emtansine. Treated subjects with post-dose sample available for ADA analysis.       |   |

### Primary: Percentage of Subjects With Objective Response as per Investigator Assessment According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v. 1.1)

|  |  |
|--|--|
| End point title  | Percentage of Subjects With Objective Response as per Investigator Assessment According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v. 1.1) <sup>[1]</sup> |
| End point description:<br>Objective response is defined as a complete response (CR) or partial response (PR) determined on two consecutive assessments $\geq 4$ weeks apart, based on investigator assessment according to RECIST, Version 1.1. CR: disappearance of all target lesions; and any pathological lymph nodes (whether target or non-target) must have reduction in short axis to $< 10$ millimeters (mm). PR: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. The efficacy-evaluable population included subjects who received at least one dose of study drug. |  |
| End point type   | Primary  |
| End point timeframe:<br>From Day 1 to disease progression (PD) or death from any cause, up to the clinical cutoff date (approximately 22 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: There was no statistical analyses done for this endpoint.

| End point values                 | Cohort IHC2+    | Cohort IHC3+       |  |  |
|----------------------------------|-----------------|--------------------|--|--|
| Subject group type               | Reporting group | Reporting group    |  |  |
| Number of subjects analysed      | 29              | 20                 |  |  |
| Units: percentage of subjects    |                 |                    |  |  |
| number (confidence interval 95%) | 0 (0 to 11.9)   | 20.0 (5.7 to 43.7) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Survival (OS)

|   |                       |
|---|-----------------------|
| End point title   | Overall Survival (OS) |
| End point description:  |                       |
| OS is defined as the time from first study drug administration to death from any cause. The efficacy-evaluable population included subjects who received at least one dose of study drug. |                       |
| End point type  | Secondary             |
| End point timeframe:  |                       |
| From Day 1 to death from any cause, up to the study completion date (approximately 43 months)   |                       |

| End point values                 | Cohort IHC2+       | Cohort IHC3+       |  |  |
|----------------------------------|--------------------|--------------------|--|--|
| Subject group type               | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed      | 29                 | 20                 |  |  |
| Units: months                    |                    |                    |  |  |
| median (confidence interval 95%) | 12.2 (3.8 to 23.6) | 13.7 (4.1 to 33.0) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Progression-Free Survival (PFS) as per Investigator Assessment According to RECIST v. 1.1

|  |   |
|--|---|
| End point title  | Progression-Free Survival (PFS) as per Investigator Assessment According to RECIST v. 1.1 |
| End point description:   |   |
| PFS is defined as the time from first study drug administration to first documented disease progression, based on investigator assessment using RECIST, v1.1, or death from any cause during the study, whichever occurs first. Disease progression is defined as: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study, including baseline; an absolute increase of at least 5 mm in the sum of diameters of target lesions; the appearance of one or more new lesions. The efficacy-evaluable population included subjects who received at least one dose of study drug. |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| From Day 1 to PD or death from any cause, up to the study completion date (approximately 43 months)  |   |



| End point values                 | Cohort IHC2+     | Cohort IHC3+     |  |  |
|----------------------------------|------------------|------------------|--|--|
| Subject group type               | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed      | 29               | 20               |  |  |
| Units: months                    |                  |                  |  |  |
| median (confidence interval 95%) | 2.6 (1.4 to 2.8) | 2.7 (1.4 to 8.3) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of Objective Response (DOR) Assessed According to RECIST v1.1

|                 |  |
|-----------------|--|
| End point title | Duration of Objective Response (DOR) Assessed According to RECIST v1.1 |
|-----------------|--|

End point description:

DOR is defined as the time from the initial documentation of response (CR or PR using RECIST, v1.1) to documented disease progression or death from any cause during the study. CR: disappearance of all target lesions; and any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. PR: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. Disease progression: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study, including baseline; an absolute increase of at least 5 mm in the sum of diameters of target lesions; the appearance of one or more new lesions. Data are reported for subjects with response. 9999 = the upper limit confidence interval was not calculable due to the low number of participants with events.

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

End point timeframe:

From first documented objective response to PD or death from any cause, up to the study completion date (approximately 43 months)

| End point values                 | Cohort IHC2+     | Cohort IHC3+      |  |  |
|----------------------------------|------------------|-------------------|--|--|
| Subject group type               | Reporting group  | Reporting group   |  |  |
| Number of subjects analysed      | 0 <sup>[2]</sup> | 4                 |  |  |
| Units: months                    |                  |                   |  |  |
| median (confidence interval 95%) | ( to )           | 7.3 (2.9 to 9999) |  |  |

Notes:

[2] - No subjects had response.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects With Clinical Benefit as per Investigator Assessment According to RECIST, v1.1

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects With Clinical Benefit as per Investigator |
|-----------------|--|

## End point description:

Clinical benefit is defined as having a CR or PR or stable disease (using RECIST, v1.1) at 6 months. Subjects with no post-baseline response assessment are considered as experiencing no clinical benefit. CR: disappearance of all target lesions; and any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. Stable disease: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum while in the study. PD: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study, including baseline; an absolute increase of at least 5 mm in the sum of diameters of target lesions; the appearance of one or more new lesions. The efficacy-evaluable population included subjects who received at least one dose of study drug.

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

## End point timeframe:

From Day 1 to PD or death from any cause, up to the study completion date (approximately 43 months)

| End point values                 | Cohort IHC2+        | Cohort IHC3+          |  |  |
|----------------------------------|---------------------|-----------------------|--|--|
| Subject group type               | Reporting group     | Reporting group       |  |  |
| Number of subjects analysed      | 29                  | 20                    |  |  |
| Units: percentage of subjects    |                     |                       |  |  |
| number (confidence interval 95%) | 6.9 (0.85 to 22.77) | 30.0 (11.89 to 54.28) |  |  |

## Statistical analyses

No statistical analyses for this end point

**Secondary: Percentage of Subjects With Adverse Events (AEs) and Serious AEs (SAEs)**

|                 |   |
|-----------------|---|
| End point title | Percentage of Subjects With Adverse Events (AEs) and Serious AEs (SAEs) |
|-----------------|---|

## End point description:

An AE is any untoward medical occurrence in a clinical investigation participant administered a pharmaceutical product, whether or not considered related to the study drug. A SAE is any experience that: results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or is medically significant. The safety-evaluable population included subjects who received at least one dose of study treatment.

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

## End point timeframe:

From Day 1 to 30 days after last dose of study drug, up to the study completion date (approximately 43 months)

| End point values              | Cohort IHC2+    | Cohort IHC3+    |  |  |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type            | Reporting group | Reporting group |  |  |
| Number of subjects analysed   | 29              | 20              |  |  |
| Units: percentage of subjects |                 |                 |  |  |
| number (not applicable)       |                 |                 |  |  |
| AEs                           | 93.1            | 95.0            |  |  |
| SAEs                          | 17.2            | 25.0            |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Maximum Observed Concentration (Cmax) for Trastuzumab Emtansine and Total Trastuzumab

|                 |   |
|-----------------|---|
| End point title | Maximum Observed Concentration (Cmax) for Trastuzumab Emtansine and Total Trastuzumab |
|-----------------|---|

End point description:

Cmax is the 0-21 day maximum observed concentration of a drug and was measured in blood serum. The pharmacokinetic (PK) population included subjects who had received at least one dose of study treatment and had at least one serum or plasma concentration result available at clinical data cut-off. Data are reported for evaluable subjects.

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

End point timeframe:

Pre-dose (within 2 days) and 30 minutes (min) after end of infusion (infusion length= 100 min or less) on Day 1 of Cycles 1 and 3 (one cycle=21 days); at treatment discontinuation/early termination, up to the clinical cutoff date (approximately 22 months)

| End point values                         | PK Analyses for Trastuzumab Emtansine and Total Trastuzumab |  |  |  |
|--|---|--|--|--|
| Subject group type                       | Subject analysis set  |  |  |  |
| Number of subjects analysed              | 44  |  |  |  |
| Units: micrograms per milliliter (ug/mL) |   |  |  |  |
| arithmetic mean (standard deviation)     |   |  |  |  |
| Trastuzumab Emtansine                    | 78.7 (± 19.6)   |  |  |  |
| Total Trastuzumab                        | 79.9 (± 21.3)   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: AUCinf for Trastuzumab Emtansine and Total Trastuzumab

|                 |  |
|-----------------|--|
| End point title | AUCinf for Trastuzumab Emtansine and Total Trastuzumab |
|-----------------|--|

End point description:

AUC (from zero to infinity) represents the total drug exposure over time in blood serum. The pharmacokinetic (PK) population included subjects who had received at least one dose of study treatment and had at least one serum or plasma concentration result available at clinical data cut-off. Data are reported for evaluable participants who consented to intense sampling.

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

End point timeframe:

Pre-dose & 30 minutes (min) post-infusion (inf.) on Day (D) 1 of Cycles (C) 1 & 3; post- inf. on D 2, 3, 4 or 5, 8, & 15 of C1, & pre- inf. on D1 of C2 & D1 of C4 (C=21D; at treatment discontinuation/early termination, up to approx. 22 months

|                                      |   |  |  |  |
|--------------------------------------|---|--|--|--|
| <b>End point values</b>              | PK Analyses for Trastuzumab Emtansine and Total Trastuzumab |  |  |  |
| Subject group type                   | Subject analysis set  |  |  |  |
| Number of subjects analysed          | 4 <sup>[3]</sup>  |  |  |  |
| Units: days times ug/mL              |   |  |  |  |
| arithmetic mean (standard deviation) |   |  |  |  |
| Trastuzumab Emtansine                | 324 (± 49.9)  |  |  |  |
| Total Trastuzumab                    | 436 (± 83.4)  |  |  |  |

Notes:

[3] - 4 subjects had valid intense sampling data.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Elimination Half-Life (t<sub>1/2</sub>) for Trastuzumab Emtansine and Total Trastuzumab

|                 |   |
|-----------------|---|
| End point title | Elimination Half-Life (t <sub>1/2</sub> ) for Trastuzumab Emtansine and Total Trastuzumab |
|-----------------|---|

End point description:

t<sub>1/2</sub> is the time required for the drug serum concentration to be reduced to half. The pharmacokinetic (PK) population included subjects who had received at least one dose of study treatment and had at least one serum or plasma concentration result available at clinical data cut-off. Data are reported for evaluable participants who consented to intense sampling.

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

End point timeframe:

Pre-dose and 30minutes (min) post-infusion (inf.) on Day (D) 1 of Cycles (C) 1 and 3; post- inf. on D2,3,4 or 5,8, and 15 of C 1, and pre- inf. on D1 of C2 and D1 of C4 (C=21 days); at treatment discontinuation/early termination, up to approx. 22 months

|                                      |   |  |  |  |
|--------------------------------------|---|--|--|--|
| <b>End point values</b>              | PK Analyses for Trastuzumab Emtansine and Total Trastuzumab |  |  |  |
| Subject group type                   | Subject analysis set  |  |  |  |
| Number of subjects analysed          | 4 <sup>[4]</sup>  |  |  |  |
| Units: days                          |   |  |  |  |
| arithmetic mean (standard deviation) |   |  |  |  |
| Trastuzumab Emtansine                | 3.2 (± 0.51)  |  |  |  |
| Total Trastuzumab                    | 5.6 (± 1.14)  |  |  |  |

Notes:

[4] - 4 subjects had valid intense sampling data.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Volume of Distribution (Vss) for Trastuzumab Emtansine and Total Trastuzumab

|  |  |
|--|--|
| End point title  | Volume of Distribution (Vss) for Trastuzumab Emtansine and Total Trastuzumab |
| End point description:   |  |
| Vss is the volume of distribution of study drug at steady state. The pharmacokinetic (PK) population included subjects who had received at least one dose of study treatment and had at least one serum or plasma concentration result available at clinical data cut-off. Data are reported for evaluable participants who consented to intense sampling. |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| Pre-dose and 30 minutes (min) post-infusion (inf.) on D1 of C1 and 3; post- inf. on D2, 3, 4 or 5, 8, and 15 of C1, and pre- inf. on D1 of C2 and D1 of C4 (C=21 days); at treatment discontinuation/early termination, up to approx. 22 months  |  |

|  |   |  |  |  |
|--|---|--|--|--|
| <b>End point values</b>                | PK Analyses for Trastuzumab Emtansine and Total Trastuzumab |  |  |  |
| Subject group type                     | Subject analysis set  |  |  |  |
| Number of subjects analysed            | 4 <sup>[5]</sup>  |  |  |  |
| Units: milligrams per kilogram (mL/kg) |   |  |  |  |
| arithmetic mean (standard deviation)   |   |  |  |  |
| Trastuzumab Emtansine                  | 51.1 (± 1.81)   |  |  |  |
| Total Trastuzumab                      | 60.7 (± 4.23)   |  |  |  |

Notes:

[5] - 4 subjects had valid intense sampling data.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Clearance (CL) for Trastuzumab Emtansine and Total Trastuzumab

|   |  |
|---|--|
| End point title   | Clearance (CL) for Trastuzumab Emtansine and Total Trastuzumab |
| End point description:<br>CL is a measure of the body's elimination of a drug from blood serum over time. The pharmacokinetic (PK) population included subjects who had received at least one dose of study treatment and had at least one serum or plasma concentration result available at clinical data cut-off. Data are reported for evaluable participants who consented to intense sampling. |  |
| End point type  | Secondary  |
| End point timeframe:<br>Pre-dose and 30 minutes (min) post-infusion (inf.) on D1 of C1 and 3; post- inf. on D2, 3, 4 or 5, 8, and 15 of C1, and pre- inf. on D1 of C2 and D1 of C4 (C=21 days); at treatment discontinuation/early termination, up to approx. 22 months   |  |

|                                      |   |  |  |  |
|--------------------------------------|---|--|--|--|
| <b>End point values</b>              | PK Analyses for Trastuzumab Emtansine and Total Trastuzumab |  |  |  |
| Subject group type                   | Subject analysis set  |  |  |  |
| Number of subjects analysed          | 4 <sup>[6]</sup>  |  |  |  |
| Units: mL/day/kg                     |   |  |  |  |
| arithmetic mean (standard deviation) |   |  |  |  |
| Trastuzumab Emtansine                | 11.35 (± 1.99)  |  |  |  |
| Total Trastuzumab                    | 8.54 (± 1.99)   |  |  |  |

Notes:

[6] - 4 subjects had valid intense sampling data.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Maximum Observed Concentration (Cmax) for N2'- deacetyl-N2'-(3-mercapto-1-oxopropyl)-maytansine (DM1)

|  |   |
|--|---|
| End point title  | Maximum Observed Concentration (Cmax) for N2'- deacetyl-N2'-(3-mercapto-1-oxopropyl)-maytansine (DM1) |
| End point description:<br>Cmax is the maximum observed concentration of a drug and was measured in blood plasma. The pharmacokinetic (PK) population included subjects who had received at least one dose of study treatment and had at least one serum or plasma concentration result available at clinical data cut-off. Data are reported for evaluable subjects. |   |
| End point type   | Secondary   |
| End point timeframe:<br>Pre-dose (within 2 days) and 30 minutes (min) after end of infusion (infusion length= 100 min or less) on Day 1 of Cycle 1 (one cycle=21 days); at treatment discontinuation/early termination, up to the clinical cutoff date (approximately 22 months)   |   |

|   |                       |  |  |  |
|---|-----------------------|--|--|--|
| <b>End point values</b>                 | Cmax Analysis for DM1 |  |  |  |
| Subject group type                      | Subject analysis set  |  |  |  |
| Number of subjects analysed             | 34                    |  |  |  |
| Units: nanograms per milliliter (ng/mL) |                       |  |  |  |
| arithmetic mean (standard deviation)    | 4.3 (± 3.36)          |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects With Treatment-Emergent Anti-Drug Antibodies (ADAs)

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects With Treatment-Emergent Anti-Drug Antibodies (ADAs) |
|-----------------|--|

End point description:

The presence of ADAs in blood serum is an indication of the body's immune response to a drug. The pharmacokinetic (PK) population included subjects who had received at least one dose of study treatment and had at least one serum or plasma concentration result available at clinical data cut-off. Data are reported for evaluable subjects.

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

End point timeframe:

Pre-dose (within 2 days) on Day 1 of Cycles 1 and 3; at treatment discontinuation/early termination, up to the clinical cutoff date (approximately 22 months)

|                               |                                   |  |  |  |
|-------------------------------|-----------------------------------|--|--|--|
| <b>End point values</b>       | Anti-drug Antibody Analysis Group |  |  |  |
| Subject group type            | Subject analysis set              |  |  |  |
| Number of subjects analysed   | 39 <sup>[7]</sup>                 |  |  |  |
| Units: percentage of subjects | 0                                 |  |  |  |

Notes:

[7] - Treated subjects with post-dose sample available for ADA analysis.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects who Died

|                 |                                 |
|-----------------|---------------------------------|
| End point title | Percentage of Subjects who Died |
|-----------------|---------------------------------|

End point description:

The efficacy-evaluable population included subjects who received at least one dose of study drug.

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

End point timeframe:

From Day 1 to death from any cause, up to the study completion date (approximately 43 months)

| End point values              | Cohort IHC2+    | Cohort IHC3+    |  |  |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type            | Reporting group | Reporting group |  |  |
| Number of subjects analysed   | 29              | 20              |  |  |
| Units: percentage of subjects |                 |                 |  |  |
| number (not applicable)       | 79.3            | 80.0            |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects with PFS Event of Disease Progression, as per Investigator Assessment According to RECIST v. 1.1, or Death

|                 |   |
|-----------------|---|
| End point title | Percentage of Subjects with PFS Event of Disease Progression, as per Investigator Assessment According to RECIST v. 1.1, or Death |
|-----------------|---|

End point description:

PFS is defined as the time from first study drug administration to first documented disease progression, based on investigator assessment using RECIST, v1.1, or death from any cause during the study, whichever occurs first. Disease progression is defined as: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study, including baseline; an absolute increase of at least 5 mm in the sum of diameters of target lesions; the appearance of one or more new lesions. The efficacy-evaluable population included subjects who received at least one dose of study drug.

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

End point timeframe:

From Day 1 to PD or death from any cause, up to the study completion date (approximately 43 months)

| End point values              | Cohort IHC2+    | Cohort IHC3+    |  |  |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type            | Reporting group | Reporting group |  |  |
| Number of subjects analysed   | 29              | 20              |  |  |
| Units: percentage of subjects |                 |                 |  |  |
| number (not applicable)       | 100             | 95.0            |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects with DOR Event of Disease Progression, Assessed According to RECIST v1.1

|                 |   |
|-----------------|---|
| End point title | Percentage of Subjects with DOR Event of Disease Progression, Assessed According to RECIST v1.1 |
|-----------------|---|

End point description:

DOR is defined as the time from the initial documentation of response (CR or PR using RECIST, v1.1) to documented disease progression using RECIST v1.1 or death from any cause during the study. CR: disappearance of all target lesions; and any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. PR: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. Disease progression: at least a 20%



increase in the sum of diameters of target lesions, taking as reference the smallest sum on study, including baseline; an absolute increase of at least 5 mm in the sum of diameters of target lesions; the appearance of one or more new lesions. The efficacy-evaluable population included subjects who received at least one dose of study drug.

|   |           |
|---|-----------|
| End point type  | Secondary |
| End point timeframe:  |           |
| From first documented objective response to PD or death from any cause, up to the study completion date (approximately 43 months) |           |

| End point values              | Cohort IHC2+     | Cohort IHC3+    |  |  |
|-------------------------------|------------------|-----------------|--|--|
| Subject group type            | Reporting group  | Reporting group |  |  |
| Number of subjects analysed   | 0 <sup>[8]</sup> | 4               |  |  |
| Units: percentage of subjects |                  |                 |  |  |
| number (not applicable)       |                  | 75.0            |  |  |

Notes:

[8] - No subjects had response.

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From baseline to study completion (approximately 43 months)

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 21.1 |
|--------------------|------|

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | Cohort IHC3+ |
|-----------------------|--------------|

Reporting group description:

Subjects with HER2 IHC3-positive (IHC 3+) locally advanced or metastatic NSCLC, who had received at least one prior platinum-based chemotherapy regimen, will receive trastuzumab emtansine.

|                       |              |
|-----------------------|--------------|
| Reporting group title | Cohort IHC2+ |
|-----------------------|--------------|

Reporting group description:

Subjects with HER2 IHC2-positive (IHC 2+) locally advanced or metastatic NSCLC, who had received at least one prior platinum-based chemotherapy regimen, will receive trastuzumab emtansine.

| Serious adverse events  | Cohort IHC3+    | Cohort IHC2+    |  |
|---|-----------------|-----------------|--|
| Total subjects affected by serious adverse events                   |                 |                 |  |
| subjects affected / exposed   | 5 / 20 (25.00%) | 5 / 29 (17.24%) |  |
| number of deaths (all causes)                                       | 16              | 23              |  |
| number of deaths resulting from adverse events                      | 0               | 0               |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                 |                 |  |
| Tumour pain   |                 |                 |  |
| subjects affected / exposed   | 1 / 20 (5.00%)  | 0 / 29 (0.00%)  |  |
| occurrences causally related to treatment / all                     | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural complications                      |                 |                 |  |
| Craniocerebral injury   |                 |                 |  |
| subjects affected / exposed   | 1 / 20 (5.00%)  | 0 / 29 (0.00%)  |  |
| occurrences causally related to treatment / all                     | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           |  |
| Subdural haematoma  |                 |                 |  |
| subjects affected / exposed   | 1 / 20 (5.00%)  | 0 / 29 (0.00%)  |  |
| occurrences causally related to treatment / all                     | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           |  |
| Nervous system disorders  |                 |                 |  |

|   |                |                |  |
|---|----------------|----------------|--|
| Seizure   |                |                |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) | 1 / 29 (3.45%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Gastrointestinal disorders                      |                |                |  |
| Abdominal pain                                  |                |                |  |
| subjects affected / exposed                     | 1 / 20 (5.00%) | 0 / 29 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Constipation                                    |                |                |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) | 1 / 29 (3.45%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Respiratory, thoracic and mediastinal disorders |                |                |  |
| Pulmonary embolism                              |                |                |  |
| subjects affected / exposed                     | 1 / 20 (5.00%) | 1 / 29 (3.45%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Dyspnoea  |                |                |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) | 1 / 29 (3.45%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Psychiatric disorders                           |                |                |  |
| Confusional state                               |                |                |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) | 1 / 29 (3.45%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Infections and infestations                     |                |                |  |
| Bronchitis                                      |                |                |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) | 1 / 29 (3.45%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Lower respiratory tract infection               |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 20 (0.00%) | 1 / 29 (3.45%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Lung infection                                  |                |                |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) | 1 / 29 (3.45%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pneumonia                                       |                |                |  |
| subjects affected / exposed                     | 1 / 20 (5.00%) | 0 / 29 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

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

| <b>Non-serious adverse events</b>                     | Cohort IHC3+     | Cohort IHC2+     |  |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events |                  |                  |  |
| subjects affected / exposed                           | 19 / 20 (95.00%) | 24 / 29 (82.76%) |  |
| Vascular disorders                                    |                  |                  |  |
| Poor venous access                                    |                  |                  |  |
| subjects affected / exposed                           | 1 / 20 (5.00%)   | 0 / 29 (0.00%)   |  |
| occurrences (all)                                     | 1                | 0                |  |
| General disorders and administration site conditions  |                  |                  |  |
| Asthenia  |                  |                  |  |
| subjects affected / exposed                           | 4 / 20 (20.00%)  | 5 / 29 (17.24%)  |  |
| occurrences (all)                                     | 6                | 6                |  |
| Fatigue   |                  |                  |  |
| subjects affected / exposed                           | 3 / 20 (15.00%)  | 10 / 29 (34.48%) |  |
| occurrences (all)                                     | 5                | 13               |  |
| Chills  |                  |                  |  |
| subjects affected / exposed                           | 4 / 20 (20.00%)  | 1 / 29 (3.45%)   |  |
| occurrences (all)                                     | 4                | 1                |  |
| Pyrexia   |                  |                  |  |
| subjects affected / exposed                           | 3 / 20 (15.00%)  | 4 / 29 (13.79%)  |  |
| occurrences (all)                                     | 3                | 4                |  |
| Chest pain  |                  |                  |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 20 (10.00%) | 0 / 29 (0.00%)  |  |
| occurrences (all)                               | 2               | 0               |  |
| Mucosal inflammation                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 20 (5.00%)  | 2 / 29 (6.90%)  |  |
| occurrences (all)                               | 1               | 3               |  |
| Malaise   |                 |                 |  |
| subjects affected / exposed                     | 0 / 20 (0.00%)  | 2 / 29 (6.90%)  |  |
| occurrences (all)                               | 0               | 2               |  |
| Oedema peripheral                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 20 (5.00%)  | 1 / 29 (3.45%)  |  |
| occurrences (all)                               | 3               | 1               |  |
| Non-cardiac chest pain                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 20 (5.00%)  | 0 / 29 (0.00%)  |  |
| occurrences (all)                               | 1               | 0               |  |
| Influenza like illness                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 20 (5.00%)  | 0 / 29 (0.00%)  |  |
| occurrences (all)                               | 1               | 0               |  |
| Oedema  |                 |                 |  |
| subjects affected / exposed                     | 1 / 20 (5.00%)  | 0 / 29 (0.00%)  |  |
| occurrences (all)                               | 1               | 0               |  |
| Mucosal Dryness                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 20 (5.00%)  | 0 / 29 (0.00%)  |  |
| occurrences (all)                               | 1               | 0               |  |
| Reproductive system and breast disorders        |                 |                 |  |
| Metrorrhagia                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 20 (5.00%)  | 0 / 29 (0.00%)  |  |
| occurrences (all)                               | 1               | 0               |  |
| Vaginal haemorrhage                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 20 (5.00%)  | 0 / 29 (0.00%)  |  |
| occurrences (all)                               | 1               | 0               |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Cough   |                 |                 |  |
| subjects affected / exposed                     | 3 / 20 (15.00%) | 7 / 29 (24.14%) |  |
| occurrences (all)                               | 4               | 10              |  |
| Dyspnoea  |                 |                 |  |

|                             |                 |                 |  |
|-----------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 20 (10.00%) | 8 / 29 (27.59%) |  |
| occurrences (all)           | 2               | 9               |  |
| Epistaxis                   |                 |                 |  |
| subjects affected / exposed | 4 / 20 (20.00%) | 0 / 29 (0.00%)  |  |
| occurrences (all)           | 9               | 0               |  |
| Pleural effusion            |                 |                 |  |
| subjects affected / exposed | 1 / 20 (5.00%)  | 2 / 29 (6.90%)  |  |
| occurrences (all)           | 2               | 2               |  |
| Dysphonia                   |                 |                 |  |
| subjects affected / exposed | 1 / 20 (5.00%)  | 1 / 29 (3.45%)  |  |
| occurrences (all)           | 1               | 1               |  |
| Nasal congestion            |                 |                 |  |
| subjects affected / exposed | 1 / 20 (5.00%)  | 1 / 29 (3.45%)  |  |
| occurrences (all)           | 2               | 1               |  |
| Dyspnoea exertional         |                 |                 |  |
| subjects affected / exposed | 1 / 20 (5.00%)  | 0 / 29 (0.00%)  |  |
| occurrences (all)           | 1               | 0               |  |
| Productive cough            |                 |                 |  |
| subjects affected / exposed | 1 / 20 (5.00%)  | 0 / 29 (0.00%)  |  |
| occurrences (all)           | 1               | 0               |  |
| Pulmonary pain              |                 |                 |  |
| subjects affected / exposed | 1 / 20 (5.00%)  | 0 / 29 (0.00%)  |  |
| occurrences (all)           | 1               | 0               |  |
| Oropharyngeal Pain          |                 |                 |  |
| subjects affected / exposed | 1 / 20 (5.00%)  | 0 / 29 (0.00%)  |  |
| occurrences (all)           | 1               | 0               |  |
| Rhinorrhoea                 |                 |                 |  |
| subjects affected / exposed | 1 / 20 (5.00%)  | 0 / 29 (0.00%)  |  |
| occurrences (all)           | 1               | 0               |  |
| Psychiatric disorders       |                 |                 |  |
| Depressive symptom          |                 |                 |  |
| subjects affected / exposed | 1 / 20 (5.00%)  | 0 / 29 (0.00%)  |  |
| occurrences (all)           | 1               | 0               |  |
| Anxiety                     |                 |                 |  |
| subjects affected / exposed | 1 / 20 (5.00%)  | 0 / 29 (0.00%)  |  |
| occurrences (all)           | 1               | 0               |  |

|  |                      |                      |  |
|--|----------------------|----------------------|--|
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                             | 3 / 20 (15.00%)<br>3 | 0 / 29 (0.00%)<br>0  |  |
| Investigations   |                      |                      |  |
| Aspartate aminotransferase increased<br>subjects affected / exposed<br>occurrences (all) | 3 / 20 (15.00%)<br>3 | 2 / 29 (6.90%)<br>2  |  |
| Platelet count decreased<br>subjects affected / exposed<br>occurrences (all)             | 2 / 20 (10.00%)<br>2 | 2 / 29 (6.90%)<br>3  |  |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                     | 1 / 20 (5.00%)<br>1  | 3 / 29 (10.34%)<br>3 |  |
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)   | 1 / 20 (5.00%)<br>1  | 1 / 29 (3.45%)<br>1  |  |
| Blood alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all) | 1 / 20 (5.00%)<br>1  | 0 / 29 (0.00%)<br>0  |  |
| Blood bilirubin increased<br>subjects affected / exposed<br>occurrences (all)            | 1 / 20 (5.00%)<br>1  | 0 / 29 (0.00%)<br>0  |  |
| Lymphocyte count decreased<br>subjects affected / exposed<br>occurrences (all)           | 1 / 20 (5.00%)<br>1  | 0 / 29 (0.00%)<br>0  |  |
| White blood cell count decreased<br>subjects affected / exposed<br>occurrences (all)     | 1 / 20 (5.00%)<br>2  | 0 / 29 (0.00%)<br>0  |  |
| Injury, poisoning and procedural complications   |                      |                      |  |
| Infusion related reaction<br>subjects affected / exposed<br>occurrences (all)            | 4 / 20 (20.00%)<br>4 | 3 / 29 (10.34%)<br>3 |  |
| Skin Wound<br>subjects affected / exposed<br>occurrences (all)                           | 1 / 20 (5.00%)<br>2  | 0 / 29 (0.00%)<br>0  |  |
| Cardiac disorders  |                      |                      |  |

|  |                      |                      |  |
|--|----------------------|----------------------|--|
| Sinus tachycardia<br>subjects affected / exposed<br>occurrences (all)        | 1 / 20 (5.00%)<br>1  | 1 / 29 (3.45%)<br>1  |  |
| Nervous system disorders   |                      |                      |  |
| Neuropathy peripheral<br>subjects affected / exposed<br>occurrences (all)    | 1 / 20 (5.00%)<br>2  | 4 / 29 (13.79%)<br>5 |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 20 (5.00%)<br>1  | 3 / 29 (10.34%)<br>4 |  |
| Cerebrovascular accident<br>subjects affected / exposed<br>occurrences (all) | 1 / 20 (5.00%)<br>1  | 0 / 29 (0.00%)<br>0  |  |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                | 2 / 20 (10.00%)<br>2 | 0 / 29 (0.00%)<br>0  |  |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)             | 1 / 20 (5.00%)<br>1  | 0 / 29 (0.00%)<br>0  |  |
| Sciatica<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 20 (5.00%)<br>1  | 0 / 29 (0.00%)<br>0  |  |
| Blood and lymphatic system disorders   |                      |                      |  |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)                  | 3 / 20 (15.00%)<br>3 | 1 / 29 (3.45%)<br>1  |  |
| Leukocytosis<br>subjects affected / exposed<br>occurrences (all)             | 1 / 20 (5.00%)<br>1  | 0 / 29 (0.00%)<br>0  |  |
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)         | 1 / 20 (5.00%)<br>1  | 1 / 29 (3.45%)<br>1  |  |
| Gastrointestinal disorders   |                      |                      |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                   | 3 / 20 (15.00%)<br>6 | 6 / 29 (20.69%)<br>8 |  |
| Vomiting   |                      |                      |  |



|  |                 |                 |  |
|--|-----------------|-----------------|--|
| subjects affected / exposed            | 2 / 20 (10.00%) | 3 / 29 (10.34%) |  |
| occurrences (all)                      | 4               | 6               |  |
| Dry mouth                              |                 |                 |  |
| subjects affected / exposed            | 0 / 20 (0.00%)  | 4 / 29 (13.79%) |  |
| occurrences (all)                      | 0               | 4               |  |
| Constipation                           |                 |                 |  |
| subjects affected / exposed            | 3 / 20 (15.00%) | 1 / 29 (3.45%)  |  |
| occurrences (all)                      | 3               | 1               |  |
| Diarrhoea                              |                 |                 |  |
| subjects affected / exposed            | 2 / 20 (10.00%) | 2 / 29 (6.90%)  |  |
| occurrences (all)                      | 2               | 2               |  |
| Dyspepsia                              |                 |                 |  |
| subjects affected / exposed            | 2 / 20 (10.00%) | 1 / 29 (3.45%)  |  |
| occurrences (all)                      | 2               | 1               |  |
| Abdominal pain                         |                 |                 |  |
| subjects affected / exposed            | 1 / 20 (5.00%)  | 2 / 29 (6.90%)  |  |
| occurrences (all)                      | 1               | 3               |  |
| Abdominal pain upper                   |                 |                 |  |
| subjects affected / exposed            | 2 / 20 (10.00%) | 0 / 29 (0.00%)  |  |
| occurrences (all)                      | 2               | 0               |  |
| Mouth ulceration                       |                 |                 |  |
| subjects affected / exposed            | 1 / 20 (5.00%)  | 0 / 29 (0.00%)  |  |
| occurrences (all)                      | 2               | 0               |  |
| Stomatitis                             |                 |                 |  |
| subjects affected / exposed            | 1 / 20 (5.00%)  | 0 / 29 (0.00%)  |  |
| occurrences (all)                      | 1               | 0               |  |
| Odynophagia                            |                 |                 |  |
| subjects affected / exposed            | 1 / 20 (5.00%)  | 0 / 29 (0.00%)  |  |
| occurrences (all)                      | 1               | 0               |  |
| Skin and subcutaneous tissue disorders |                 |                 |  |
| Pruritus                               |                 |                 |  |
| subjects affected / exposed            | 2 / 20 (10.00%) | 2 / 29 (6.90%)  |  |
| occurrences (all)                      | 3               | 2               |  |
| Rash maculo-papular                    |                 |                 |  |
| subjects affected / exposed            | 3 / 20 (15.00%) | 0 / 29 (0.00%)  |  |
| occurrences (all)                      | 3               | 0               |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Dermatitis acneiform                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 20 (5.00%)  | 0 / 29 (0.00%)  |  |
| occurrences (all)                               | 1               | 0               |  |
| Eczema  |                 |                 |  |
| subjects affected / exposed                     | 1 / 20 (5.00%)  | 0 / 29 (0.00%)  |  |
| occurrences (all)                               | 1               | 0               |  |
| Hyperhidrosis                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 20 (5.00%)  | 0 / 29 (0.00%)  |  |
| occurrences (all)                               | 1               | 0               |  |
| Petechiae                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 20 (5.00%)  | 0 / 29 (0.00%)  |  |
| occurrences (all)                               | 1               | 0               |  |
| Alopecia  |                 |                 |  |
| subjects affected / exposed                     | 1 / 20 (5.00%)  | 0 / 29 (0.00%)  |  |
| occurrences (all)                               | 1               | 0               |  |
| Onychoclasia                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 20 (5.00%)  | 0 / 29 (0.00%)  |  |
| occurrences (all)                               | 1               | 1               |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Arthralgia                                      |                 |                 |  |
| subjects affected / exposed                     | 4 / 20 (20.00%) | 4 / 29 (13.79%) |  |
| occurrences (all)                               | 6               | 4               |  |
| Muscle spasms                                   |                 |                 |  |
| subjects affected / exposed                     | 2 / 20 (10.00%) | 1 / 29 (3.45%)  |  |
| occurrences (all)                               | 2               | 1               |  |
| Muscular weakness                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 20 (5.00%)  | 1 / 29 (3.45%)  |  |
| occurrences (all)                               | 1               | 1               |  |
| Musculoskeletal chest pain                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 20 (5.00%)  | 1 / 29 (3.45%)  |  |
| occurrences (all)                               | 1               | 1               |  |
| Musculoskeletal pain                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 20 (5.00%)  | 1 / 29 (3.45%)  |  |
| occurrences (all)                               | 1               | 1               |  |
| Myalgia   |                 |                 |  |

|  |                      |                        |  |
|--|----------------------|------------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 0 / 20 (0.00%)<br>0  | 2 / 29 (6.90%)<br>2    |  |
| Bone Pain<br>subjects affected / exposed<br>occurrences (all)  | 1 / 20 (5.00%)<br>1  | 0 / 29 (0.00%)<br>0    |  |
| Pain in Extremity<br>subjects affected / exposed<br>occurrences (all)  | 1 / 20 (5.00%)<br>1  | 1 / 29 (3.45%)<br>1    |  |
| Infections and infestations<br>Respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 0 / 20 (0.00%)<br>0  | 3 / 29 (10.34%)<br>4   |  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)                                    | 2 / 20 (10.00%)<br>7 | 1 / 29 (3.45%)<br>3    |  |
| Pneumonia<br>subjects affected / exposed<br>occurrences (all)  | 2 / 20 (10.00%)<br>2 | 0 / 29 (0.00%)<br>0    |  |
| Paronychia<br>subjects affected / exposed<br>occurrences (all)   | 1 / 20 (5.00%)<br>2  | 0 / 29 (0.00%)<br>0    |  |
| Viral Upper Respiratory Tract<br>Infection<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 20 (5.00%)<br>1  | 0 / 29 (0.00%)<br>0    |  |
| Metabolism and nutrition disorders<br>Decreased appetite<br>subjects affected / exposed<br>occurrences (all)   | 3 / 20 (15.00%)<br>3 | 10 / 29 (34.48%)<br>10 |  |
| Hypokalaemia<br>subjects affected / exposed<br>occurrences (all)   | 2 / 20 (10.00%)<br>2 | 2 / 29 (6.90%)<br>2    |  |
| Hypomagnesaemia<br>subjects affected / exposed<br>occurrences (all)  | 1 / 20 (5.00%)<br>1  | 0 / 29 (0.00%)<br>0    |  |
| Hyperglycaemia   |                      |                        |  |

|                             |                |                |  |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 0 / 20 (0.00%) | 2 / 29 (6.90%) |  |
| occurrences (all)           | 0              | 2              |  |
| Hypophosphataemia           |                |                |  |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 29 (0.00%) |  |
| occurrences (all)           | 1              | 0              |  |
| Iron Deficiency             |                |                |  |
| subjects affected / exposed | 1 / 20 (5.00%) | 2 / 29 (6.90%) |  |
| occurrences (all)           | 1              | 2              |  |

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported