



## Clinical trial results:

### Safety and Efficacy of LONQUEX® (Lipegfilgrastim) in Comparison to Pegfilgrastim (NEULASTA®, Amgen Inc.) and Placebo in Patients with Non-Small-Cell Lung Cancer Receiving First-Line Chemotherapy

#### Summary

|                          |                         |
|--------------------------|-------------------------|
| EudraCT number           | 2014-005096-85          |
| Trial protocol           | SK HU LV PL GR BG ES HR |
| Global end of trial date | 09 February 2018        |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 14 March 2019 |
| First version publication date | 14 March 2019 |

#### Trial information

##### Trial identification

|                       |                |
|-----------------------|----------------|
| Sponsor protocol code | XM22-ONC-40041 |
|-----------------------|----------------|

##### Additional study identifiers

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

Notes:

##### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Merckle GmbH  |
| Sponsor organisation address | Ludwig-Merckle-Strasse 3, Blaubeuren, Germany, D-89143  |
| Public contact               | Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc, 001 2155913000, info.eraclinical@teva.de  |
| Scientific contact           | Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc., 001 2155913000, info.eraclinical@teva.de |

Notes:

##### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 09 February 2018 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 09 February 2018 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to collect comparative data for lipegfilgrastim, pegfilgrastim, and placebo in participants with advanced squamous or non-squamous non-small-cell lung cancer (NSCLC) Stage IIIB/IV, including full details of disease progression (whether or not leading to death) and mortality, for detailed clinical review.

Protection of trial subjects:

This study was conducted in full accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline (E6) and any applicable national and local laws and regulations (Code of Federal Regulations Title 21, Parts 50, 54, 56, 312, and 314; European Union [EU] Directive 2001/20/EC on the approximation of the laws, regulations, and administrative provisions of the Member States relating to the implementation of GCP in the conduct of clinical trials on medicinal products for human use). Written and/or oral information about the study was provided to all participants in a language understandable by the participants. The information included an adequate explanation of the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force. Written informed consent was obtained from each participant before any study procedures or assessments were done. It was explained to the participants that they were free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.

Background therapy:

Chemotherapy (CTX) regimens were administered intravenously (IV) every 3 weeks up to 6 cycles (each cycle=21 days). CTX regimen comprised: cisplatin 75 milligrams per square meter ( $\text{mg}/\text{m}^2$ ) body surface and pemetrexed 500  $\text{mg}/\text{m}^2$  body surface on Day 1 of each cycle, or cisplatin 75  $\text{mg}/\text{m}^2$  body surface and docetaxel 75  $\text{mg}/\text{m}^2$  body surface on Day 1 of each cycle, or paclitaxel 135  $\text{mg}/\text{m}^2$  body surface on Day 0 and cisplatin 75  $\text{mg}/\text{m}^2$  body surface on Day 1 of each cycle. All participants treated with CTX were allowed to take dexamethasone as a prophylactic measure to reduce toxicity according to the local standard.

Evidence for comparator: -

|   |                |
|---|----------------|
| Actual start date of recruitment                          | 07 August 2015 |
| Long term follow-up planned                               | No             |
| Independent data monitoring committee (IDMC) involvement? | No             |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Belarus: 8             |
| Country: Number of subjects enrolled | Bulgaria: 6            |
| Country: Number of subjects enrolled | Hungary: 2             |
| Country: Number of subjects enrolled | Latvia: 8              |
| Country: Number of subjects enrolled | Romania: 13            |
| Country: Number of subjects enrolled | Russian Federation: 93 |
| Country: Number of subjects enrolled | Serbia: 5              |
| Country: Number of subjects enrolled | Slovakia: 1            |

|                                      |              |
|--------------------------------------|--------------|
| Country: Number of subjects enrolled | Turkey: 5    |
| Country: Number of subjects enrolled | Ukraine: 162 |
| Worldwide total number of subjects   | 303          |
| EEA total number of subjects         | 30           |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 216 |
| From 65 to 84 years                       | 87  |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

A total of 340 participants were screened, of which 303 were enrolled and randomized in 1:1:1 ratio to lipegfilgrastim, pegfilgrastim, or placebo. 37 participants were screen failures due to inclusion criteria not met or exclusion criteria met.

### Pre-assignment

Screening details:

One participant was randomized to pegfilgrastim but was treated with lipegfilgrastim. This participant was in the lipegfilgrastim group for Safety Population and in the pegfilgrastim group for all other groups.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Study (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Randomised - controlled        |
| Blinding used                | Double blind                   |
| Roles blinded                | Subject, Investigator          |

### Arms

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

Arm description:

Participants received lipegfilgrastim 6 milligrams (mg) subcutaneous (SC) injection on Day 2 and CTX regimen IV on Day 1 of each CTX cycle over 6 CTX cycles (each cycle=21 days).

|  |  |
|--|--|
| Arm type                               | Experimental                                 |
| Investigational medicinal product name | Lipegfilgrastim                              |
| Investigational medicinal product code |  |
| Other name                             | LONQUEX®                                     |
| Pharmaceutical forms                   | Solution for injection in pre-filled syringe |
| Routes of administration               | Subcutaneous use                             |

Dosage and administration details:

Lipegfilgrastim 6 mg was administered on Day 2 of each cycle.

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

Arm description:

Participants received pegfilgrastim 6 mg SC injection on Day 2 and CTX regimen IV on Day 1 of each CTX cycle over 6 CTX cycles (each cycle=21 days).

|  |  |
|--|--|
| Arm type                               | Active comparator                            |
| Investigational medicinal product name | Pegfilgrastim                                |
| Investigational medicinal product code |  |
| Other name                             | NEULASTA®                                    |
| Pharmaceutical forms                   | Solution for injection in pre-filled syringe |
| Routes of administration               | Subcutaneous use                             |

Dosage and administration details:

Pegfilgrastim 6 mg was administered on Day 2 of each cycle.

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

Arm description:

Participants received placebo matched to lipegfilgrastim SC injection on Day 2 and CTX regimen IV on Day 1 of each CTX cycle over 6 CTX cycles (each cycle=21 days).

|          |         |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

|  |  |
|--|--|
| Investigational medicinal product name | Placebo                                      |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Solution for injection in pre-filled syringe |
| Routes of administration               | Subcutaneous use                             |

Dosage and administration details:

Placebo matched to lipegfilgrastim was administered on Day 2 of each cycle.

| <b>Number of subjects in period 1</b> | Lipegfilgrastim | Pegfilgrastim | Placebo |
|---------------------------------------|-----------------|---------------|---------|
| Started                               | 101             | 101           | 101     |
| Treated                               | 95              | 98            | 98      |
| Completed                             | 14              | 11            | 14      |
| Not completed                         | 87              | 90            | 87      |
| Clinical progression                  | -               | 1             | -       |
| Consent withdrawn by subject          | 8               | 11            | 11      |
| Death                                 | 64              | 71            | 64      |
| Adverse event                         | 3               | 1             | 1       |
| Other than specified                  | 1               | -             | -       |
| Lost to follow-up                     | 10              | 6             | 11      |
| Protocol deviation                    | 1               | -             | -       |

## Baseline characteristics

### Reporting groups

|  |                 |
|--|-----------------|
| Reporting group title  | Lipegfilgrastim |
| Reporting group description:   |                 |
| Participants received lipegfilgrastim 6 milligrams (mg) subcutaneous (SC) injection on Day 2 and CTX regimen IV on Day 1 of each CTX cycle over 6 CTX cycles (each cycle=21 days). |                 |
| Reporting group title  | Pegfilgrastim   |
| Reporting group description:   |                 |
| Participants received pegfilgrastim 6 mg SC injection on Day 2 and CTX regimen IV on Day 1 of each CTX cycle over 6 CTX cycles (each cycle=21 days).                               |                 |
| Reporting group title  | Placebo         |
| Reporting group description:   |                 |
| Participants received placebo matched to lipegfilgrastim SC injection on Day 2 and CTX regimen IV on Day 1 of each CTX cycle over 6 CTX cycles (each cycle=21 days).               |                 |

| Reporting group values | Lipegfilgrastim | Pegfilgrastim | Placebo |
|------------------------|-----------------|---------------|---------|
| Number of subjects     | 101             | 101           | 101     |
| Age Categorical        |                 |               |         |
| Units: Subjects        |                 |               |         |

|                    |        |        |        |
|--------------------|--------|--------|--------|
| Age Continuous     |        |        |        |
| Units: years       |        |        |        |
| arithmetic mean    | 60.5   | 58.9   | 59.5   |
| standard deviation | ± 7.17 | ± 7.55 | ± 8.24 |
| Gender Categorical |        |        |        |
| Units: Subjects    |        |        |        |
| Female             | 15     | 18     | 25     |
| Male               | 86     | 83     | 76     |
| Race               |        |        |        |
| Units: Subjects    |        |        |        |
| White              | 101    | 101    | 101    |

| Reporting group values | Total |  |  |
|------------------------|-------|--|--|
| Number of subjects     | 303   |  |  |
| Age Categorical        |       |  |  |
| Units: Subjects        |       |  |  |

|                    |     |  |  |
|--------------------|-----|--|--|
| Age Continuous     |     |  |  |
| Units: years       |     |  |  |
| arithmetic mean    | -   |  |  |
| standard deviation |     |  |  |
| Gender Categorical |     |  |  |
| Units: Subjects    |     |  |  |
| Female             | 58  |  |  |
| Male               | 245 |  |  |
| Race               |     |  |  |
| Units: Subjects    |     |  |  |
| White              | 303 |  |  |



## End points

### End points reporting groups

|  |                 |
|--|-----------------|
| Reporting group title  | Lipegfilgrastim |
| Reporting group description:<br>Participants received lipegfilgrastim 6 milligrams (mg) subcutaneous (SC) injection on Day 2 and CTX regimen IV on Day 1 of each CTX cycle over 6 CTX cycles (each cycle=21 days). |                 |
| Reporting group title  | Pegfilgrastim   |
| Reporting group description:<br>Participants received pegfilgrastim 6 mg SC injection on Day 2 and CTX regimen IV on Day 1 of each CTX cycle over 6 CTX cycles (each cycle=21 days).                               |                 |
| Reporting group title  | Placebo         |
| Reporting group description:<br>Participants received placebo matched to lipegfilgrastim SC injection on Day 2 and CTX regimen IV on Day 1 of each CTX cycle over 6 CTX cycles (each cycle=21 days).               |                 |

### Primary: Progression-Free Survival (PFS) as Assessed by Central Reader According to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

|  |  |
|--|--|
| End point title  | Progression-Free Survival (PFS) as Assessed by Central Reader According to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 |
| End point description:<br>PFS was defined as time from randomization to the first objectively documented progression per RECIST version 1.1 or death due to any cause, whichever occurred first, as documented by the central reader. Participants who did not have disease progression until the end of the study or discontinued the study early before disease progression was documented were censored at the time of their latest evaluable RECIST assessments. Disease progression: At least a 20 percent (%) increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum also demonstrated an absolute increase of at least 5 millimeters (mm). Unequivocal progression of existing non-target lesions. The appearance of 1 or more new lesions was also considered progression. Safety population included all enrolled and randomized participants who received at least 1 injection of lipegfilgrastim, pegfilgrastim, or placebo. |  |
| End point type   | Primary  |
| End point timeframe:<br>From randomization to the first objectively documented progression or death due to any cause, whichever occurred first (up to a maximum duration of 928 days)  |  |

| End point values                 | Lipegfilgrastim    | Pegfilgrastim      | Placebo            |  |
|----------------------------------|--------------------|--------------------|--------------------|--|
| Subject group type               | Reporting group    | Reporting group    | Reporting group    |  |
| Number of subjects analysed      | 95                 | 98                 | 98                 |  |
| Units: months                    |                    |                    |                    |  |
| median (confidence interval 95%) | 5.9 (5.20 to 7.90) | 4.6 (4.10 to 5.80) | 5.8 (5.20 to 7.10) |  |

## Statistical analyses



|  |                                      |
|--|--------------------------------------|
| <b>Statistical analysis title</b>  | Lipegfilgrastim versus Pegfilgrastim |
| Statistical analysis description:  |                                      |
| Hazard ratio and corresponding 95% confidence interval (CI) were based on a Cox proportional hazard model fitting treatment as explanatory variable. |                                      |
| Comparison groups  | Lipegfilgrastim v Pegfilgrastim      |
| Number of subjects included in analysis  | 193                                  |
| Analysis specification   | Pre-specified                        |
| Analysis type  | other                                |
| P-value  | = 0.0865                             |
| Method   | Logrank                              |
| Parameter estimate   | Hazard ratio (HR)                    |
| Point estimate   | 0.77                                 |
| Confidence interval  |                                      |
| level  | 95 %                                 |
| sides  | 2-sided                              |
| lower limit  | 0.569                                |
| upper limit  | 1.034                                |

|  |                                |
|--|--------------------------------|
| <b>Statistical analysis title</b>  | Lipegfilgrastim versus Placebo |
| Statistical analysis description:  |                                |
| Hazard ratio and corresponding 95% CI were based on a Cox proportional hazard model fitting treatment as explanatory variable. |                                |
| Comparison groups  | Lipegfilgrastim v Placebo      |
| Number of subjects included in analysis  | 193                            |
| Analysis specification   | Pre-specified                  |
| Analysis type  | superiority                    |
| P-value  | = 0.8114                       |
| Method   | Logrank                        |
| Parameter estimate   | Hazard ratio (HR)              |
| Point estimate   | 0.96                           |
| Confidence interval  |                                |
| level  | 95 %                           |
| sides  | 2-sided                        |
| lower limit  | 0.713                          |
| upper limit  | 1.296                          |

|  |                              |
|--|------------------------------|
| <b>Statistical analysis title</b>  | Pegfilgrastim versus Placebo |
| Statistical analysis description:  |                              |
| Hazard ratio and corresponding 95% CI were based on a Cox proportional hazard model fitting treatment as explanatory variable. |                              |
| Comparison groups  | Pegfilgrastim v Placebo      |

|   |                   |
|---|-------------------|
| Number of subjects included in analysis | 196               |
| Analysis specification                  | Pre-specified     |
| Analysis type                           | superiority       |
| P-value                                 | = 0.1429          |
| Method                                  | Logrank           |
| Parameter estimate                      | Hazard ratio (HR) |
| Point estimate                          | 1.25              |
| Confidence interval                     |                   |
| level                                   | 95 %              |
| sides                                   | 2-sided           |
| lower limit                             | 0.932             |
| upper limit                             | 1.685             |

### Secondary: Duration of Severe Neutropenia (DSN)

|                        |  |
|------------------------|--|
| End point title        | Duration of Severe Neutropenia (DSN)   |
| End point description: | DSN was defined as the number of days with Grade 4 neutropenia, i.e., the number of days with absolute neutrophil count (ANC) less than ( $<$ ) $0.5 \times 10^9$ per liter in Cycle 1. Full analysis set (FAS) included all enrolled and randomized participants. |
| End point type         | Secondary  |
| End point timeframe:   |  |
| Cycle 1 (21 days)      |  |

| End point values                     | Lipegfilgrastim  | Pegfilgrastim    | Placebo           |  |
|--------------------------------------|------------------|------------------|-------------------|--|
| Subject group type                   | Reporting group  | Reporting group  | Reporting group   |  |
| Number of subjects analysed          | 0 <sup>[1]</sup> | 0 <sup>[2]</sup> | 9                 |  |
| Units: days                          |                  |                  |                   |  |
| arithmetic mean (standard deviation) | ()               | ()               | 2.9 ( $\pm$ 1.36) |  |

Notes:

[1] - There were no event of severe neutropenia in Cycle 1 in this arm.

[2] - There were no event of severe neutropenia in Cycle 1 in this arm.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants With Febrile Neutropenia (FN)

|                        |   |
|------------------------|---|
| End point title        | Number of Participants With Febrile Neutropenia (FN)  |
| End point description: | FN was defined as occurrence of at least 1 of the following conditions: oral body temperature greater than ( $>$ ) 38.5 degrees centigrade for at least 1 hour (2 consecutive measurements on the same day, at least 60 minutes apart) and an observed severe neutropenia (i.e., ANC value $<0.5 \times 10^9$ per liter) on the day before, on the same day, or on the day after the elevated temperature readings; documentation of neutropenic sepsis, i.e., a sepsis in combination with an ANC value $<0.5 \times 10^9$ per liter; documentation of serious or life-threatening neutropenic infection, i.e., a life-threatening infection in combination with an ANC value $<0.5 \times 10^9$ per liter. FAS included all enrolled and randomized participants. |
| End point type         | Secondary   |

End point timeframe:

Cycle 1 (21 days)

| End point values            | Lipegfilgrastim | Pegfilgrastim   | Placebo         |  |
|-----------------------------|-----------------|-----------------|-----------------|--|
| Subject group type          | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed | 101             | 101             | 101             |  |
| Units: participants         | 0               | 0               | 0               |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants With Very Severe Neutropenia

|                 |   |
|-----------------|---|
| End point title | Number of Participants With Very Severe Neutropenia |
|-----------------|---|

End point description:

Very severe neutropenia was defined as ANC  $<0.1 \times 10^9$  per liter. FAS included all enrolled and randomized participants.

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

End point timeframe:

Cycle 1 (21 days)

| End point values            | Lipegfilgrastim | Pegfilgrastim   | Placebo         |  |
|-----------------------------|-----------------|-----------------|-----------------|--|
| Subject group type          | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed | 101             | 101             | 101             |  |
| Units: participants         | 0               | 0               | 2               |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants With Severe Neutropenia

|                 |  |
|-----------------|--|
| End point title | Number of Participants With Severe Neutropenia |
|-----------------|--|

End point description:

Severe neutropenia was defined as Grade 4 neutropenia, i.e., ANC  $<0.5 \times 10^9$  per liter. FAS included all enrolled and randomized participants.

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

End point timeframe:

Cycle 1 (21 days)

| End point values            | Lipegfilgrastim | Pegfilgrastim   | Placebo         |  |
|-----------------------------|-----------------|-----------------|-----------------|--|
| Subject group type          | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed | 101             | 101             | 101             |  |
| Units: participants         | 0               | 0               | 9               |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: PFS as Assessed by Investigator According to RECIST Version 1.1

|                 |   |
|-----------------|---|
| End point title | PFS as Assessed by Investigator According to RECIST Version 1.1 |
|-----------------|---|

End point description:

PFS was defined as time from randomization to the first objectively documented progression per RECIST version 1.1 or death due to any cause, whichever occurred first, as documented by the central reader. Participants who did not have disease progression until the end of the study or discontinued the study early before disease progression was documented were censored at the time of their latest evaluable RECIST assessments. Disease progression: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum also demonstrated an absolute increase of at least 5 mm. Unequivocal progression of existing non-target lesions. The appearance of 1 or more new lesions was also considered progression. Safety population included all enrolled and randomized participants who received at least 1 injection of lipegfilgrastim, pegfilgrastim, or placebo.

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

End point timeframe:

From randomization to the first objectively documented progression or death due to any cause, whichever occurred first (up to a maximum duration of 928 days)

| End point values                 | Lipegfilgrastim    | Pegfilgrastim      | Placebo            |  |
|----------------------------------|--------------------|--------------------|--------------------|--|
| Subject group type               | Reporting group    | Reporting group    | Reporting group    |  |
| Number of subjects analysed      | 95                 | 98                 | 98                 |  |
| Units: months                    |                    |                    |                    |  |
| median (confidence interval 95%) | 5.9 (5.60 to 7.50) | 5.3 (4.20 to 6.00) | 6.2 (5.60 to 7.10) |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants With Objective Response, as Assessed by Central Reader According to RECIST Version 1.1

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants With Objective Response, as Assessed by Central Reader According to RECIST Version 1.1 |
|-----------------|---|

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**End point description:**

Objective response was defined as achieving a best overall response of complete response (CR) or partial response (PR), as defined by RECIST version 1.1. The best overall response was the best response recorded from the start of the investigational medicinal product (IMP) until the end of the study. CR: Disappearance of all target and non-target lesions. Any pathological lymph nodes (whether target or non-target) with a 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 diameters. Safety population included all enrolled and randomized participants who received at least 1 injection of lipegfilgrastim, pegfilgrastim, or placebo.

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

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**End point timeframe:**

From randomization until first appearance of CR or PR (up to a maximum duration of 928 days)

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| End point values                  | Lipegfilgrastim | Pegfilgrastim   | Placebo         |  |
|-----------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type                | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed       | 95              | 98              | 98              |  |
| Units: percentage of participants |                 |                 |                 |  |
| number (not applicable)           | 43              | 37              | 40              |  |

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**Statistical analyses**

No statistical analyses for this end point

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**Secondary: Percentage of Participants With Objective Response, as Assessed by Investigator According to RECIST Version 1.1**

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|                 |   |
|-----------------|---|
| End point title | Percentage of Participants With Objective Response, as Assessed by Investigator According to RECIST Version 1.1 |
|-----------------|---|

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**End point description:**

Objective response was defined as achieving a best overall response of CR or PR, as defined by RECIST version 1.1. The best overall response was the best response recorded from the start of the IMP until the end of the study. CR: Disappearance of all target and non-target lesions. Any pathological lymph nodes (whether target or non-target) with a 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 diameters. Safety population included all enrolled and randomized participants who received at least 1 injection of lipegfilgrastim, pegfilgrastim, or placebo.

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

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**End point timeframe:**

From randomization until first appearance of CR or PR (up to a maximum duration of 928 days)

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| End point values                  | Lipegfilgrastim | Pegfilgrastim   | Placebo         |  |
|-----------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type                | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed       | 95              | 98              | 98              |  |
| Units: percentage of participants |                 |                 |                 |  |
| number (not applicable)           | 45              | 39              | 40              |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Overall Survival

|                 |                  |
|-----------------|------------------|
| End point title | Overall Survival |
|-----------------|------------------|

End point description:

Overall survival was defined as time from randomization to the date of death from any cause. Safety population included all enrolled and randomized participants who received at least 1 injection of lipegfilgrastim, pegfilgrastim, or placebo.

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

End point timeframe:

From randomization to the date of death from any cause (up to maximum duration of 928 days)

| End point values                 | Lipegfilgrastim      | Pegfilgrastim        | Placebo               |  |
|----------------------------------|----------------------|----------------------|-----------------------|--|
| Subject group type               | Reporting group      | Reporting group      | Reporting group       |  |
| Number of subjects analysed      | 95                   | 98                   | 98                    |  |
| Units: months                    |                      |                      |                       |  |
| median (confidence interval 95%) | 11.7 (9.60 to 14.50) | 10.7 (9.10 to 14.80) | 11.9 (10.00 to 14.80) |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From randomization until end of study (up to a maximum duration of 928 days)

Adverse event reporting additional description:

Safety population included all enrolled and randomized participants who received at least 1 injection of lipegfilgrastim, pegfilgrastim, or placebo.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 20.0 |
|--------------------|------|

### Reporting groups

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | Lipegfilgrastim 6mg |
|-----------------------|---------------------|

Reporting group description:

Lipegfilgrastim 6mg

|                       |                   |
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| Reporting group title | Pegfilgrastim 6mg |
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Reporting group description:

Pegfilgrastim 6mg

|                       |         |
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| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Placebo

| Serious adverse events  | Lipegfilgrastim 6mg | Pegfilgrastim 6mg | Placebo          |
|---|---------------------|-------------------|------------------|
| Total subjects affected by serious adverse events                   |                     |                   |                  |
| subjects affected / exposed   | 81 / 95 (85.26%)    | 86 / 98 (87.76%)  | 80 / 98 (81.63%) |
| number of deaths (all causes)                                       | 75                  | 81                | 76               |
| number of deaths resulting from adverse events                      |                     |                   |                  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                     |                   |                  |
| Brain neoplasm  |                     |                   |                  |
| subjects affected / exposed   | 0 / 95 (0.00%)      | 0 / 98 (0.00%)    | 1 / 98 (1.02%)   |
| occurrences causally related to treatment / all                     | 0 / 0               | 0 / 0             | 0 / 1            |
| deaths causally related to treatment / all                          | 0 / 0               | 0 / 0             | 0 / 0            |
| Lung adenocarcinoma   |                     |                   |                  |
| subjects affected / exposed   | 0 / 95 (0.00%)      | 1 / 98 (1.02%)    | 0 / 98 (0.00%)   |
| occurrences causally related to treatment / all                     | 0 / 0               | 0 / 1             | 0 / 0            |
| deaths causally related to treatment / all                          | 0 / 0               | 0 / 0             | 0 / 0            |
| Metastases to central nervous system                                |                     |                   |                  |

|  |                  |                  |                  |
|--|------------------|------------------|------------------|
| subjects affected / exposed                          | 0 / 95 (0.00%)   | 1 / 98 (1.02%)   | 3 / 98 (3.06%)   |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 1            | 0 / 3            |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            | 0 / 1            |
| Non-small cell lung cancer                           |                  |                  |                  |
| subjects affected / exposed                          | 71 / 95 (74.74%) | 72 / 98 (73.47%) | 71 / 98 (72.45%) |
| occurrences causally related to treatment / all      | 0 / 107          | 0 / 107          | 0 / 103          |
| deaths causally related to treatment / all           | 0 / 66           | 0 / 67           | 0 / 67           |
| Squamous cell carcinoma of lung                      |                  |                  |                  |
| subjects affected / exposed                          | 1 / 95 (1.05%)   | 1 / 98 (1.02%)   | 1 / 98 (1.02%)   |
| occurrences causally related to treatment / all      | 0 / 2            | 0 / 2            | 0 / 2            |
| deaths causally related to treatment / all           | 0 / 1            | 0 / 1            | 0 / 1            |
| Vascular disorders                                   |                  |                  |                  |
| Embolism   |                  |                  |                  |
| subjects affected / exposed                          | 0 / 95 (0.00%)   | 0 / 98 (0.00%)   | 1 / 98 (1.02%)   |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            | 0 / 1            |
| Internal haemorrhage                                 |                  |                  |                  |
| subjects affected / exposed                          | 1 / 95 (1.05%)   | 0 / 98 (0.00%)   | 0 / 98 (0.00%)   |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            | 0 / 0            |
| Peripheral artery thrombosis                         |                  |                  |                  |
| subjects affected / exposed                          | 1 / 95 (1.05%)   | 0 / 98 (0.00%)   | 0 / 98 (0.00%)   |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            | 0 / 0            |
| Shock haemorrhagic                                   |                  |                  |                  |
| subjects affected / exposed                          | 2 / 95 (2.11%)   | 0 / 98 (0.00%)   | 0 / 98 (0.00%)   |
| occurrences causally related to treatment / all      | 0 / 2            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all           | 0 / 2            | 0 / 0            | 0 / 0            |
| General disorders and administration site conditions |                  |                  |                  |
| Death  |                  |                  |                  |
| subjects affected / exposed                          | 3 / 95 (3.16%)   | 2 / 98 (2.04%)   | 1 / 98 (1.02%)   |
| occurrences causally related to treatment / all      | 0 / 3            | 0 / 2            | 0 / 1            |
| deaths causally related to treatment / all           | 0 / 3            | 0 / 2            | 0 / 1            |



|   |                |                |                |
|---|----------------|----------------|----------------|
| General physical health deterioration           |                |                |                |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 0 / 98 (0.00%) | 1 / 98 (1.02%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| Pyrexia   |                |                |                |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 0 / 98 (0.00%) | 1 / 98 (1.02%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Immune system disorders                         |                |                |                |
| Anaphylactic shock                              |                |                |                |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 98 (1.02%) | 0 / 98 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Respiratory, thoracic and mediastinal disorders |                |                |                |
| Bronchial haemorrhage                           |                |                |                |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 98 (1.02%) | 0 / 98 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| Dyspnoea  |                |                |                |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 98 (1.02%) | 0 / 98 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| Oesophagobronchial fistula                      |                |                |                |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 0 / 98 (0.00%) | 0 / 98 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pneumothorax                                    |                |                |                |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 0 / 98 (0.00%) | 0 / 98 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pneumothorax spontaneous                        |                |                |                |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 0 / 98 (0.00%) | 0 / 98 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Pulmonary embolism                              |                |                |                |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 2 / 98 (2.04%) | 2 / 98 (2.04%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 2          | 0 / 2          |
| Pulmonary haemorrhage                           |                |                |                |
| subjects affected / exposed                     | 3 / 95 (3.16%) | 3 / 98 (3.06%) | 0 / 98 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4          | 0 / 3          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 3          | 0 / 0          |
| Psychiatric disorders                           |                |                |                |
| Abnormal behaviour                              |                |                |                |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 0 / 98 (0.00%) | 0 / 98 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Delirium tremens                                |                |                |                |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 0 / 98 (0.00%) | 0 / 98 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Investigations                                  |                |                |                |
| Blood potassium decreased                       |                |                |                |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 0 / 98 (0.00%) | 0 / 98 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Neutrophil count decreased                      |                |                |                |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 98 (1.02%) | 0 / 98 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| White blood cell count decreased                |                |                |                |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 98 (1.02%) | 0 / 98 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Injury, poisoning and procedural complications  |                |                |                |
| Alcohol poisoning                               |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 95 (1.05%) | 0 / 98 (0.00%) | 0 / 98 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0          |
| Brain contusion                                 |                |                |                |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 0 / 98 (0.00%) | 0 / 98 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac disorders                               |                |                |                |
| Acute coronary syndrome                         |                |                |                |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 1 / 98 (1.02%) | 0 / 98 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 1          | 0 / 0          |
| Atrial fibrillation                             |                |                |                |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 98 (1.02%) | 0 / 98 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac failure acute                           |                |                |                |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 0 / 98 (0.00%) | 2 / 98 (2.04%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 1 / 1          |
| Cardio-respiratory arrest                       |                |                |                |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 2 / 98 (2.04%) | 0 / 98 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 2          | 0 / 0          |
| Supraventricular tachycardia                    |                |                |                |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 0 / 98 (0.00%) | 1 / 98 (1.02%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Nervous system disorders                        |                |                |                |
| Cerebrovascular accident                        |                |                |                |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 0 / 98 (0.00%) | 0 / 98 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cerebrovascular disorder                        |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 95 (0.00%) | 0 / 98 (0.00%) | 1 / 98 (1.02%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Syncope   |                |                |                |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 0 / 98 (0.00%) | 0 / 98 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Blood and lymphatic system disorders            |                |                |                |
| Anaemia   |                |                |                |
| subjects affected / exposed                     | 3 / 95 (3.16%) | 2 / 98 (2.04%) | 2 / 98 (2.04%) |
| occurrences causally related to treatment / all | 0 / 3          | 0 / 4          | 0 / 3          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Neutropenia                                     |                |                |                |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 0 / 98 (0.00%) | 1 / 98 (1.02%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pancytopenia                                    |                |                |                |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 98 (1.02%) | 0 / 98 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| Thrombocytopenia                                |                |                |                |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 1 / 98 (1.02%) | 0 / 98 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrointestinal disorders                      |                |                |                |
| Gastric ulcer                                   |                |                |                |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 98 (1.02%) | 0 / 98 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Musculoskeletal and connective tissue disorders |                |                |                |
| Intervertebral disc protrusion                  |                |                |                |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 0 / 98 (0.00%) | 1 / 98 (1.02%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

|  |                                  |                                  |                                  |
|--|----------------------------------|----------------------------------|----------------------------------|
| Infections and infestations<br>Chronic hepatitis C<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | 0 / 95 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 98 (1.02%)<br>0 / 1<br>0 / 0 | 0 / 98 (0.00%)<br>0 / 0<br>0 / 0 |
| Pneumonia<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all  | 0 / 95 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 98 (1.02%)<br>0 / 1<br>0 / 0 | 1 / 98 (1.02%)<br>0 / 1<br>0 / 1 |
| Pneumonia bacterial<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                | 1 / 95 (1.05%)<br>0 / 1<br>0 / 0 | 0 / 98 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 98 (0.00%)<br>0 / 0<br>0 / 0 |

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

| <b>Non-serious adverse events</b>                     | Lipegfilgrastim 6mg | Pegfilgrastim 6mg | Placebo          |
|---|---------------------|-------------------|------------------|
| Total subjects affected by non-serious adverse events |                     |                   |                  |
| subjects affected / exposed                           | 77 / 95 (81.05%)    | 84 / 98 (85.71%)  | 84 / 98 (85.71%) |
| Investigations  |                     |                   |                  |
| Alanine aminotransferase increased                    |                     |                   |                  |
| subjects affected / exposed                           | 11 / 95 (11.58%)    | 6 / 98 (6.12%)    | 7 / 98 (7.14%)   |
| occurrences (all)                                     | 15                  | 12                | 8                |
| Aspartate aminotransferase increased                  |                     |                   |                  |
| subjects affected / exposed                           | 8 / 95 (8.42%)      | 5 / 98 (5.10%)    | 7 / 98 (7.14%)   |
| occurrences (all)                                     | 12                  | 15                | 8                |
| Blood alkaline phosphatase increased                  |                     |                   |                  |
| subjects affected / exposed                           | 11 / 95 (11.58%)    | 10 / 98 (10.20%)  | 7 / 98 (7.14%)   |
| occurrences (all)                                     | 15                  | 12                | 10               |
| Blood creatine phosphokinase increased                |                     |                   |                  |
| subjects affected / exposed                           | 1 / 95 (1.05%)      | 4 / 98 (4.08%)    | 5 / 98 (5.10%)   |
| occurrences (all)                                     | 1                   | 5                 | 7                |
| Blood creatinine increased                            |                     |                   |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed   | 8 / 95 (8.42%)   | 7 / 98 (7.14%)   | 12 / 98 (12.24%) |
| occurrences (all)   | 12               | 8                | 21               |
| Blood lactate dehydrogenase increased                               |                  |                  |                  |
| subjects affected / exposed   | 5 / 95 (5.26%)   | 5 / 98 (5.10%)   | 6 / 98 (6.12%)   |
| occurrences (all)   | 6                | 9                | 9                |
| Blood urea increased  |                  |                  |                  |
| subjects affected / exposed   | 7 / 95 (7.37%)   | 5 / 98 (5.10%)   | 5 / 98 (5.10%)   |
| occurrences (all)   | 11               | 5                | 8                |
| Creatinine renal clearance decreased                                |                  |                  |                  |
| subjects affected / exposed   | 6 / 95 (6.32%)   | 0 / 98 (0.00%)   | 3 / 98 (3.06%)   |
| occurrences (all)   | 8                | 0                | 3                |
| Gamma-glutamyltransferase increased                                 |                  |                  |                  |
| subjects affected / exposed   | 15 / 95 (15.79%) | 9 / 98 (9.18%)   | 10 / 98 (10.20%) |
| occurrences (all)   | 25               | 13               | 18               |
| Lymphocyte count decreased  |                  |                  |                  |
| subjects affected / exposed   | 7 / 95 (7.37%)   | 4 / 98 (4.08%)   | 4 / 98 (4.08%)   |
| occurrences (all)   | 12               | 8                | 6                |
| Weight decreased  |                  |                  |                  |
| subjects affected / exposed   | 6 / 95 (6.32%)   | 9 / 98 (9.18%)   | 4 / 98 (4.08%)   |
| occurrences (all)   | 8                | 12               | 4                |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |                  |                  |
| Non-small cell lung cancer  |                  |                  |                  |
| subjects affected / exposed   | 27 / 95 (28.42%) | 27 / 98 (27.55%) | 35 / 98 (35.71%) |
| occurrences (all)   | 27               | 27               | 35               |
| Nervous system disorders  |                  |                  |                  |
| Headache  |                  |                  |                  |
| subjects affected / exposed   | 8 / 95 (8.42%)   | 2 / 98 (2.04%)   | 8 / 98 (8.16%)   |
| occurrences (all)   | 10               | 3                | 8                |
| Blood and lymphatic system disorders                                |                  |                  |                  |
| Anaemia   |                  |                  |                  |
| subjects affected / exposed   | 38 / 95 (40.00%) | 40 / 98 (40.82%) | 37 / 98 (37.76%) |
| occurrences (all)   | 93               | 98               | 103              |
| Leukopenia  |                  |                  |                  |
| subjects affected / exposed   | 5 / 95 (5.26%)   | 6 / 98 (6.12%)   | 18 / 98 (18.37%) |
| occurrences (all)   | 8                | 7                | 54               |

|  |                        |                        |                         |
|--|------------------------|------------------------|-------------------------|
| Neutropenia<br>subjects affected / exposed<br>occurrences (all)            | 11 / 95 (11.58%)<br>16 | 13 / 98 (13.27%)<br>15 | 41 / 98 (41.84%)<br>111 |
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)       | 15 / 95 (15.79%)<br>39 | 11 / 98 (11.22%)<br>16 | 10 / 98 (10.20%)<br>23  |
| General disorders and administration<br>site conditions                    |                        |                        |                         |
| Asthenia<br>subjects affected / exposed<br>occurrences (all)               | 11 / 95 (11.58%)<br>16 | 6 / 98 (6.12%)<br>8    | 11 / 98 (11.22%)<br>20  |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)                | 8 / 95 (8.42%)<br>10   | 13 / 98 (13.27%)<br>23 | 13 / 98 (13.27%)<br>23  |
| Non-cardiac chest pain<br>subjects affected / exposed<br>occurrences (all) | 5 / 95 (5.26%)<br>7    | 9 / 98 (9.18%)<br>11   | 7 / 98 (7.14%)<br>8     |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)                | 7 / 95 (7.37%)<br>11   | 6 / 98 (6.12%)<br>7    | 4 / 98 (4.08%)<br>4     |
| Gastrointestinal disorders   |                        |                        |                         |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)   | 3 / 95 (3.16%)<br>4    | 3 / 98 (3.06%)<br>4    | 5 / 98 (5.10%)<br>5     |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)              | 4 / 95 (4.21%)<br>4    | 7 / 98 (7.14%)<br>8    | 8 / 98 (8.16%)<br>10    |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                 | 38 / 95 (40.00%)<br>68 | 29 / 98 (29.59%)<br>57 | 33 / 98 (33.67%)<br>86  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)               | 10 / 95 (10.53%)<br>14 | 7 / 98 (7.14%)<br>9    | 11 / 98 (11.22%)<br>19  |
| Respiratory, thoracic and mediastinal<br>disorders                         |                        |                        |                         |
| Cough<br>subjects affected / exposed<br>occurrences (all)                  | 3 / 95 (3.16%)<br>3    | 3 / 98 (3.06%)<br>6    | 6 / 98 (6.12%)<br>7     |

|   |                        |                        |                        |
|---|------------------------|------------------------|------------------------|
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)  | 7 / 95 (7.37%)<br>7    | 7 / 98 (7.14%)<br>8    | 12 / 98 (12.24%)<br>17 |
| Haemoptysis<br>subjects affected / exposed<br>occurrences (all)   | 8 / 95 (8.42%)<br>10   | 4 / 98 (4.08%)<br>5    | 3 / 98 (3.06%)<br>4    |
| Skin and subcutaneous tissue disorders<br>Alopecia<br>subjects affected / exposed<br>occurrences (all)            | 26 / 95 (27.37%)<br>38 | 35 / 98 (35.71%)<br>54 | 33 / 98 (33.67%)<br>46 |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 6 / 95 (6.32%)<br>11   | 4 / 98 (4.08%)<br>10   | 2 / 98 (2.04%)<br>2    |
| Bone pain<br>subjects affected / exposed<br>occurrences (all)   | 7 / 95 (7.37%)<br>12   | 1 / 98 (1.02%)<br>5    | 1 / 98 (1.02%)<br>2    |
| Myalgia<br>subjects affected / exposed<br>occurrences (all)   | 7 / 95 (7.37%)<br>15   | 3 / 98 (3.06%)<br>10   | 4 / 98 (4.08%)<br>11   |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)   | 2 / 95 (2.11%)<br>4    | 2 / 98 (2.04%)<br>2    | 7 / 98 (7.14%)<br>8    |
| Metabolism and nutrition disorders<br>Decreased appetite<br>subjects affected / exposed<br>occurrences (all)      | 8 / 95 (8.42%)<br>15   | 12 / 98 (12.24%)<br>17 | 7 / 98 (7.14%)<br>15   |
| Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all)  | 5 / 95 (5.26%)<br>7    | 8 / 98 (8.16%)<br>14   | 10 / 98 (10.20%)<br>17 |
| Hyperkalaemia<br>subjects affected / exposed<br>occurrences (all)   | 5 / 95 (5.26%)<br>10   | 5 / 98 (5.10%)<br>7    | 5 / 98 (5.10%)<br>6    |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date          | Amendment   |
|---------------|---|
| 03 March 2015 | The following major procedural changes (not all-inclusive) were made to the protocol:<br>In response to a request from the authorities, the study exclusion criteria related to participation in a clinical study within 30 days has been updated to incorporate "5 half-lives of the investigational product before randomization, whichever is longer."   |
| 23 May 2016   | The following major procedural changes (not all-inclusive) were made to the protocol: - Urinalysis monitoring conducted by dipstick at the investigational center, including protein, glucose, blood, leucocytes and pH, has been added to the clinical laboratory tests required.<br>- Clarification that the follow-up visits that were performed every 6 weeks can be conducted within a time window of +/-1 week. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported