



## Clinical trial results:

**A Phase IIb/III randomised, double-blind, placebo-controlled study comparing first-line therapy with or without TG4010 immunotherapy product in patients with stage IV non-small cell lung cancer (NSCLC).**

### Summary

|                          |                      |
|--------------------------|----------------------|
| EudraCT number           | 2011-001468-23       |
| Trial protocol           | BE HU GB DE ES PL IT |
| Global end of trial date | 06 July 2015         |

### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 20 July 2017 |
| First version publication date | 20 July 2017 |

### Trial information

#### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | TG4010.14 |
|-----------------------|-----------|

#### Additional study identifiers

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

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Transgene S.A.  |
| Sponsor organisation address | 400, Boulevard Gonthier d'Andernach, Parc d'Innovation - CS80166, Illkirch Graffenstaden Cedex, France, 67405 |
| Public contact               | Transgene Medical Affairs, Transgene S.A., clinical.trials@transgene.fr                                       |
| Scientific contact           | Transgene Medical Affairs, Transgene S.A., clinical.trials@transgene.fr                                       |

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                       | 06 July 2015     |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 15 December 2014 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 06 July 2015     |
| Was the trial ended prematurely?                     | Yes              |

Notes:

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## General information about the trial

Main objective of the trial:

Phase IIb part: to prospectively validate the level of Triple Positive Activated Lymphocytes (TrPAL), as a predictive biomarker of TG4010's activity by comparing Progression-Free Survival (PFS) between the TG4010 arm (TG4010 + first-line therapy) and the placebo arm (placebo + first-line therapy) in the 2 subgroups of subjects according to their level of TrPAL before randomisation (normal and high level of TrPAL).

Phase III part: To demonstrate that TG4010 improves overall survival (OS) as compared to placebo in stage IV NSCLC patients with non-squamous tumour histology receiving first-line chemotherapy.

Protection of trial subjects:

This study was conducted in accordance with the updated Declaration of Helsinki adopted by the World Medical Association, in compliance with the approved protocol and its amendments, the International Council for Harmonisation good clinical practice, and national regulatory requirements in the participating countries.

Background therapy:

Chemotherapy was given as 21-day cycles starting from Day 1 of Cycle 1 for a minimum of 4 cycles and up to 6 cycles. The platinum doublet chemotherapy regimen administered was determined by histology and at Investigator discretion as follows:

- Non-squamous cell: Paclitaxel (200 milligrams/square metre [mg/m<sup>2</sup>]) and carboplatin (target area under the curve [AUC] 6.0) on Day 1 of each cycle with the next course of chemotherapy on Day 22; OR pemetrexed (500 mg/m<sup>2</sup>) and cisplatin (75 mg/m<sup>2</sup>) on Day 1 of each cycle with the next course of chemotherapy on Day 22
- Squamous cell: Paclitaxel (200 mg/m<sup>2</sup>) and carboplatin (AUC 6.0) on Day 1 of each cycle with the next course of chemotherapy on Day 22; OR gemcitabine (1250 mg/m<sup>2</sup>) on Day 1 and Day 8 of each cycle and cisplatin (75 mg/m<sup>2</sup>) on Day 1 of each cycle with the next course of chemotherapy on Day 22.

Bevacizumab was allowed for patients with non-squamous carcinoma (if initiated at the same time as chemotherapy) and was administered at a dose of 7.5 or 15 mg/kilogram (kg) according to country-specific approved labelling or prescribing information. Bevacizumab treatment was given on Day 1 of each cycle (starting from Day 1 of Cycle 1) until disease progression or premature discontinuation due to any reason.

Pemetrexed (for non-squamous carcinoma) or erlotinib (whatever the histology) were to be given as maintenance therapy in eligible patients who have not progressed after 4 to 6 cycles of chemotherapy (according to labeling in each country) unless they received bevacizumab as part of first-line therapy. Pemetrexed (at the dose of 500 mg/m<sup>2</sup> every 3 weeks, given on the same day as TG4010/placebo) or erlotinib (at the dose of 150 mg daily) were administered in combination with TG4010/placebo until disease progression or premature discontinuation due to any reason.

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 10 April 2012 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | Yes           |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Israel: 3          |
| Country: Number of subjects enrolled | United States: 9   |
| Country: Number of subjects enrolled | Poland: 22         |
| Country: Number of subjects enrolled | Spain: 20          |
| Country: Number of subjects enrolled | United Kingdom: 10 |
| Country: Number of subjects enrolled | Belgium: 24        |
| Country: Number of subjects enrolled | France: 90         |
| Country: Number of subjects enrolled | Hungary: 41        |
| Country: Number of subjects enrolled | Italy: 3           |
| Worldwide total number of subjects   | 222                |
| EEA total number of subjects         | 210                |

Notes:

### Subjects enrolled per age group

|   |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 143 |
| From 65 to 84 years                       | 79  |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

The study consisted of a Phase IIb and a Phase III part. 222 subjects were randomised into the Phase IIb part in a 1:1 ratio of TG4010 to placebo. The cut-off date for primary analysis of PFS was 15 December 2014 and OS cut off date was 6 July 2015. The study was prematurely terminated after completion of Phase IIb and Phase III did not proceed.

### Pre-assignment

Screening details:

The level of TrPAL (percentage of triple positive CD16+ CD56+ CD69+ cells among the total lymphocyte population) was evaluated before randomisation. For the phase IIb part, subjects were categorised in 1 of the 2 groups (normal and high TrPAL) by using a cut-off value determined in adult healthy donors as being the upper limit of normal (ULN).

### Period 1

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

Blinding implementation details:

The monitors, data managers, investigators and subjects remained blinded to drug identity until the date of the last final analysis of the Phase IIb. The statistician was unblinded for all subjects at the time of final analysis in subjects with normal TrPAL. The sponsor was unblinded for the treatment code firstly for subjects with normal TrPAL at the time of the final analysis in this subgroup and secondly for subjects with high TrPAL at the time of the final analysis in this subgroup.

### Arms

|                              |        |
|------------------------------|--------|
| Are arms mutually exclusive? | Yes    |
| <b>Arm title</b>             | TG4010 |

Arm description:

Subjects received TG4010 plus chemotherapy as first-line treatment followed by TG4010 plus maintenance therapy if appropriate.

TG4010 was administered on Day 1 of Cycle 1 of chemotherapy and then weekly for 6 weeks by subcutaneous (SC) injections, then once every 3 weeks until disease progression or premature discontinuation. Chemotherapy was given as 21-day cycles for a minimum of 4 cycles and up to 6 cycles. If prescribed, bevacizumab was continued in combination with TG4010 and administered every 3 weeks until disease progression, premature discontinuation, or toxicity.

|  |                          |
|--|--------------------------|
| Arm type                               | Experimental             |
| Investigational medicinal product name | TG4010                   |
| Investigational medicinal product code |                          |
| Other name                             |                          |
| Pharmaceutical forms                   | Suspension for injection |
| Routes of administration               | Subcutaneous use         |

Dosage and administration details:

TG4010 is a suspension of recombinant modified Vaccinia virus strain Ankara (MVA) carrying coding sequences for human Mucin 1 (MUC1) antigen and human interleukin-2 in the diluent named TG0008.

TG4010 was administered at a dose of  $1 \times 10^8$  plaque-forming unit (pfu) (corresponding to 0.5 millilitre [mL] of TG4010) once every week for 6 weeks, starting on Day 1 of Cycle 1, and then every 3 weeks thereafter until disease progression or premature discontinuation due to any reason. Each SC injection was performed in a single site. Four injection sites were used successively (left and right arm, left and right thigh) according to a rotation schedule.

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

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**Arm description:**

Subjects received placebo plus chemotherapy as first-line treatment followed by placebo plus maintenance therapy if appropriate.

Placebo was administered on Day 1 of Cycle 1 of chemotherapy and then weekly for 6 weeks by SC injections, then once every 3 weeks until disease progression or premature discontinuation. Chemotherapy was given as 21-day cycles for a minimum of 4 cycles and up to 6 cycles. If prescribed, bevacizumab was continued in combination with placebo and administered every 3 weeks until disease progression, premature discontinuation, or toxicity.

|  |                        |
|--|------------------------|
| Arm type                               | Placebo                |
| Investigational medicinal product name | Placebo                |
| Investigational medicinal product code | TG0008                 |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Subcutaneous use       |

**Dosage and administration details:**

The placebo used in this study was the diluent of TG4010 (TG0008) and was administered as a single SC injection in a volume of 0.5 mL. Placebo was administered once every week for 6 weeks, starting on Day 1 of Cycle 1, and then every 3 weeks thereafter until disease progression or premature discontinuation due to any reason. Four injection sites were used successively (left and right arm, left and right thigh) according to a rotation schedule.

| <b>Number of subjects in period 1</b> | TG4010 | Placebo |
|---------------------------------------|--------|---------|
| Started                               | 111    | 111     |
| Completed                             | 105    | 98      |
| Not completed                         | 6      | 13      |
| Consent withdrawn by subject          | 4      | 7       |
| Investigator's Decision               | 2      | 2       |
| Administrative problems               | -      | 1       |
| Lost to follow-up                     | -      | 3       |

## Baseline characteristics

### Reporting groups

|                       |        |
|-----------------------|--------|
| Reporting group title | TG4010 |
|-----------------------|--------|

Reporting group description:

Subjects received TG4010 plus chemotherapy as first-line treatment followed by TG4010 plus maintenance therapy if appropriate.

TG4010 was administered on Day 1 of Cycle 1 of chemotherapy and then weekly for 6 weeks by subcutaneous (SC) injections, then once every 3 weeks until disease progression or premature discontinuation. Chemotherapy was given as 21-day cycles for a minimum of 4 cycles and up to 6 cycles. If prescribed, bevacizumab was continued in combination with TG4010 and administered every 3 weeks until disease progression, premature discontinuation, or toxicity.

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

Reporting group description:

Subjects received placebo plus chemotherapy as first-line treatment followed by placebo plus maintenance therapy if appropriate.

Placebo was administered on Day 1 of Cycle 1 of chemotherapy and then weekly for 6 weeks by SC injections, then once every 3 weeks until disease progression or premature discontinuation. Chemotherapy was given as 21-day cycles for a minimum of 4 cycles and up to 6 cycles. If prescribed, bevacizumab was continued in combination with placebo and administered every 3 weeks until disease progression, premature discontinuation, or toxicity.

| Reporting group values                                | TG4010 | Placebo | Total |
|---|--------|---------|-------|
| Number of subjects                                    | 111    | 111     | 222   |
| Age categorical<br>Units: Subjects                    |        |         |       |
| In utero  | 0      | 0       | 0     |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0      | 0       | 0     |
| Newborns (0-27 days)                                  | 0      | 0       | 0     |
| Infants and toddlers (28 days-23<br>months)           | 0      | 0       | 0     |
| Children (2-11 years)                                 | 0      | 0       | 0     |
| Adolescents (12-17 years)                             | 0      | 0       | 0     |
| Adults (18-64 years)                                  | 66     | 77      | 143   |
| From 65-84 years                                      | 45     | 34      | 79    |
| 85 years and over                                     | 0      | 0       | 0     |
| Age continuous<br>Units: years                        |        |         |       |
| arithmetic mean                                       | 62.8   | 59.5    |       |
| standard deviation                                    | ± 8.5  | ± 8.8   | -     |
| Gender categorical<br>Units: Subjects                 |        |         |       |
| Female  | 39     | 41      | 80    |
| Male  | 72     | 70      | 142   |
| Histology<br>Units: Subjects                          |        |         |       |
| Adenocarcinoma  | 95     | 90      | 185   |
| Squamous cell carcinoma                               | 13     | 13      | 26    |

|   |     |    |     |
|---|-----|----|-----|
| Large cell carcinoma  | 2   | 3  | 5   |
| Undifferentiated carcinoma  | 0   | 3  | 3   |
| Other   | 1   | 2  | 3   |
| Performance status (PS)   |     |    |     |
| Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. |     |    |     |
| Units: Subjects   |     |    |     |
| PS=0  | 33  | 35 | 68  |
| PS=1  | 77  | 76 | 153 |
| Missing   | 1   | 0  | 1   |
| Smoking Status  |     |    |     |
| Units: Subjects   |     |    |     |
| Never smoked  | 7   | 12 | 19  |
| Current or ex-smoker  | 104 | 99 | 203 |
| TrPAL Level based on ULN cut-off value                                  |     |    |     |
| Units: Subjects   |     |    |     |
| ≤ ULN (normal)  | 85  | 85 | 170 |
| >ULN (high)   | 26  | 26 | 52  |
| TrPAL level based on Third quartile (Q3) cut-off value                  |     |    |     |
| Units: Subjects   |     |    |     |
| ≤ Q3 (non-elevated)   | 71  | 76 | 147 |
| > Q3 (elevated)   | 40  | 35 | 75  |

## End points

### End points reporting groups

|                       |        |
|-----------------------|--------|
| Reporting group title | TG4010 |
|-----------------------|--------|

Reporting group description:

Subjects received TG4010 plus chemotherapy as first-line treatment followed by TG4010 plus maintenance therapy if appropriate.

TG4010 was administered on Day 1 of Cycle 1 of chemotherapy and then weekly for 6 weeks by subcutaneous (SC) injections, then once every 3 weeks until disease progression or premature discontinuation. Chemotherapy was given as 21-day cycles for a minimum of 4 cycles and up to 6 cycles. If prescribed, bevacizumab was continued in combination with TG4010 and administered every 3 weeks until disease progression, premature discontinuation, or toxicity.

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

Reporting group description:

Subjects received placebo plus chemotherapy as first-line treatment followed by placebo plus maintenance therapy if appropriate.

Placebo was administered on Day 1 of Cycle 1 of chemotherapy and then weekly for 6 weeks by SC injections, then once every 3 weeks until disease progression or premature discontinuation. Chemotherapy was given as 21-day cycles for a minimum of 4 cycles and up to 6 cycles. If prescribed, bevacizumab was continued in combination with placebo and administered every 3 weeks until disease progression, premature discontinuation, or toxicity.

|                            |                               |
|----------------------------|-------------------------------|
| Subject analysis set title | TG4010: Normal TrPAL Subgroup |
|----------------------------|-------------------------------|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

Analyses were performed independently in each group of subjects according to their level of TrPAL before randomisation, based on a predetermined ULN cut-off. Of 111 subjects randomised to the TG4010 arm, 85 were categorised with a level of TrPAL less than or equal to the ULN (normal TrPAL).

|                            |                                |
|----------------------------|--------------------------------|
| Subject analysis set title | Placebo: Normal TrPAL Subgroup |
|----------------------------|--------------------------------|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

Analyses were performed independently in each group of subjects according to their level of TrPAL before randomisation, based on a predetermined ULN cut-off. Of 111 subjects randomised to the placebo arm, 85 were categorised with a level of TrPAL less than or equal to the ULN (normal TrPAL).

|                            |                             |
|----------------------------|-----------------------------|
| Subject analysis set title | TG4010: High TrPAL Subgroup |
|----------------------------|-----------------------------|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

Analyses were performed independently in each group of subjects according to their level of TrPAL before randomisation, based on a predetermined ULN cut-off. Of 111 subjects randomised to the TG4010 arm, 26 were categorised with a level of TrPAL greater than the ULN (high TrPAL).

|                            |                              |
|----------------------------|------------------------------|
| Subject analysis set title | Placebo: High TrPAL Subgroup |
|----------------------------|------------------------------|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

Analyses were performed independently in each group of subjects according to their level of TrPAL before randomisation, based on a predetermined ULN cut-off. Of 111 subjects randomised to the placebo arm, 26 were categorised with a level of TrPAL greater than the ULN (high TrPAL).

|                            |                                     |
|----------------------------|-------------------------------------|
| Subject analysis set title | TG4010: Non-elevated TrPAL Subgroup |
|----------------------------|-------------------------------------|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

By using a quartile approach for categorisation, subjects with less than or equal to Q3 cut-off value for TrPAL at baseline were categorised into the non-elevated TrPAL subgroup. Of 111 subjects randomised to the TG4010 arm, 71 were categorised with non-elevated TrPAL levels.

|                            |                                      |
|----------------------------|--------------------------------------|
| Subject analysis set title | Placebo: Non-elevated TrPAL Subgroup |
|----------------------------|--------------------------------------|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|



Subject analysis set description:

By using a quartile approach for categorisation, subjects with less than or equal to Q3 cut-off value for TrPAL at baseline were categorised into the non-elevated TrPAL subgroup. Of 111 subjects randomised to the placebo arm, 76 were categorised with non-elevated TrPAL levels.

|                            |                                 |
|----------------------------|---------------------------------|
| Subject analysis set title | TG4010: Elevated TrPAL Subgroup |
| Subject analysis set type  | Sub-group analysis              |

Subject analysis set description:

By using a quartile approach for categorisation, subjects with greater than the Q3 cut-off value for TrPAL at baseline were categorised into the elevated TrPAL subgroup. Of 111 subjects randomised to the TG4010 arm, 40 were categorised with elevated TrPAL levels.

|                            |                                  |
|----------------------------|----------------------------------|
| Subject analysis set title | Placebo: Elevated TrPAL Subgroup |
| Subject analysis set type  | Sub-group analysis               |

Subject analysis set description:

By using a quartile approach for categorisation, subjects with greater than the Q3 cut-off value for TrPAL at baseline were categorised into the non-elevated TrPAL subgroup. Of 111 subjects randomised to the placebo arm, 35 were categorised with elevated TrPAL levels.

### **Primary: Comparison of PFS Events in Subjects Treated with TG4010 or Placebo.**

|                 |  |
|-----------------|--|
| End point title | Comparison of PFS Events in Subjects Treated with TG4010 or Placebo. |
|-----------------|--|

End point description:

The primary analysis of PFS was performed in the 2 groups of subjects defined by their level of TrPAL at baseline ( $\leq$  ULN [normal] or  $>$  ULN [high]). This analysis was repeated in the 2 groups of subjects defined by the quartile approach, non-elevated (corresponding to  $\leq$  Q3) and elevated (corresponding to  $>$ Q3) TrPAL levels. PFS events were recorded from the date of randomisation to the date of first documented tumour progression or death due to any cause, whichever occurred first. PFS was censored if no progression or death was observed at the cut-off date for analysis, or at the date when a further antineoplastic therapy was started. Determination of progression was based on local evaluations of baseline and post-baseline scans and by evaluation of target and non-target disease according to the Response Evaluation Criteria In Solid Tumours (RECIST) Version 1.1.

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

End point timeframe:

Tumour progression was evaluated every 6 weeks until documented progression or for a period of 9 months. Beyond 9 months, evaluations were performed every 12 weeks until documented disease progression. Up to a maximum of 140 weeks (until cut-off date).

| <b>End point values</b>     | TG4010: Normal TrPAL Subgroup | Placebo: Normal TrPAL Subgroup | TG4010: High TrPAL Subgroup | Placebo: High TrPAL Subgroup |
|-----------------------------|-------------------------------|--------------------------------|-----------------------------|------------------------------|
| Subject group type          | Subject analysis set          | Subject analysis set           | Subject analysis set        | Subject analysis set         |
| Number of subjects analysed | 85                            | 85                             | 26                          | 26                           |
| Units: Events               | 76                            | 75                             | 21                          | 22                           |

| <b>End point values</b>     | TG4010: Non-elevated TrPAL Subgroup | Placebo: Non-elevated TrPAL Subgroup | TG4010: Elevated TrPAL Subgroup | Placebo: Elevated TrPAL Subgroup |
|-----------------------------|-------------------------------------|--------------------------------------|---------------------------------|----------------------------------|
| Subject group type          | Subject analysis set                | Subject analysis set                 | Subject analysis set            | Subject analysis set             |
| Number of subjects analysed | 71                                  | 76                                   | 40                              | 35                               |
| Units: Events               | 62                                  | 67                                   | 35                              | 30                               |

## Statistical analyses

| Statistical analysis title  | Bayesian analysis: Normal TrPAL subgroup                       |
|---|--|
| Statistical analysis description:   |  |
| A Bayesian analysis was performed to prospectively validate the level of TrPAL as a predictive biomarker of TG4010's activity. After 89 PFS events had been observed in the normal TrPAL subgroup, the null hypothesis $H_0: HR \geq 1$ was tested against the alternative hypothesis $H_A: HR < 1$ , where HR is the PFS hazard ratio for first-line therapy plus TG4010 (TG4010 arm) relative to first-line therapy plus placebo (placebo arm). |  |
| Comparison groups   | TG4010: Normal TrPAL Subgroup v Placebo: Normal TrPAL Subgroup |
| Number of subjects included in analysis   | 170  |
| Analysis specification  | Pre-specified  |
| Analysis type   | other <sup>[1]</sup>   |
| P-value   | = 0.016 <sup>[2]</sup>   |
| Method  | Logrank  |
| Parameter estimate  | Hazard ratio (HR)  |
| Point estimate  | 0.75   |
| Confidence interval   |  |
| level   | 95 %   |
| sides   | 2-sided  |
| lower limit   | 0.54   |
| upper limit   | 1.03   |

### Notes:

[1] - The null hypothesis  $H_0: HR \geq 1$  was tested against the alternative hypothesis  $H_A: HR < 1$ , where HR is the PFS hazard ratio for first-line therapy+TG4010 (TG4010 arm) relative to first-line therapy+placebo (placebo arm). The hypothesis was tested by using the posterior distribution of an estimator of the log HR.

[2] - Efficacy criteria:  $1 - P(HR < 1 / \text{observed data}) \leq 0.05$

| Statistical analysis title  | Bayesian analysis: High TrPAL subgroup                     |
|---|--|
| Statistical analysis description:   |  |
| A Bayesian analysis was performed to prospectively validate the level of TrPAL as a predictive biomarker of TG4010's activity. After 38 PFS events had been observed in the high TrPAL subgroup, the null hypothesis $H_0: HR \leq 1$ was tested against the alternative hypothesis $H_A: HR > 1$ , where HR was the PFS hazard ratio for first-line therapy plus TG4010 relative to first-line therapy plus placebo. |  |
| Comparison groups   | TG4010: High TrPAL Subgroup v Placebo: High TrPAL Subgroup |
| Number of subjects included in analysis   | 52   |
| Analysis specification  | Pre-specified  |
| Analysis type   | other <sup>[3]</sup>                                       |
| P-value   | = 0.687 <sup>[4]</sup>                                     |
| Method  | Logrank  |
| Parameter estimate  | Hazard ratio (HR)  |
| Point estimate  | 0.77   |
| Confidence interval   |  |
| level   | 95 %   |
| sides   | 2-sided  |
| lower limit   | 0.42   |
| upper limit   | 1.4  |

Notes:

[3] - The null hypothesis  $H_0$ :  $HR \leq 1$  was tested against the alternative hypothesis  $H_A$ :  $HR \geq 1$ , where HR is the PFS hazard ratio for first-line therapy+TG4010 (TG4010 arm) relative to first-line therapy+placebo (placebo arm). The hypothesis was tested by using the posterior distribution of an estimator of the log HR.

[4] - Efficacy criteria:  $1 - P(HR > 1 \text{ / observed data}) \leq 0.20$

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | Bayesian analysis: Non-elevated TrPAL subgroup                             |
| Statistical analysis description:   |  |
| A Bayesian analysis was performed to prospectively validate the level of TrPAL as a predictive biomarker of TG4010's activity. After 89 PFS events had been observed in the non elevated TrPAL subgroup, the null hypothesis $H_0$ : $HR \geq 1$ was tested against the alternative hypothesis $H_A$ : $HR < 1$ , where HR is the PFS hazard ratio for first-line therapy plus TG4010 (TG4010 arm) relative to first-line therapy plus placebo (placebo arm). |  |
| Comparison groups   | TG4010: Non-elevated TrPAL Subgroup v Placebo: Non-elevated TrPAL Subgroup |
| Number of subjects included in analysis   | 147  |
| Analysis specification  | Pre-specified  |
| Analysis type   | other <sup>[5]</sup>   |
| P-value   | = 0.005 <sup>[6]</sup>   |
| Method  | Logrank  |
| Parameter estimate  | Hazard ratio (HR)  |
| Point estimate  | 0.68   |
| Confidence interval   |  |
| level   | 95 %   |
| sides   | 2-sided  |
| lower limit   | 0.48   |
| upper limit   | 0.96   |

Notes:

[5] - The null hypothesis  $H_0$ :  $HR \geq 1$  was tested against the alternative hypothesis  $H_A$ :  $HR < 1$ , where HR is the PFS hazard ratio for first-line therapy+TG4010 (TG4010 arm) relative to first-line therapy+placebo (placebo arm). The hypothesis was tested by using the posterior distribution of an estimator of the log HR.

[6] - Efficacy criteria:  $1 - P(HR < 1 \text{ / observed data}) \leq 0.05$

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | Bayesian analysis: Elevated TrPAL subgroup                         |
| Statistical analysis description:   |  |
| A Bayesian analysis was performed to prospectively validate the level of TrPAL as a predictive biomarker of TG4010's activity. After 38 PFS events had been observed in the high TrPAL subgroup, the null hypothesis $H_0$ : $HR \leq 1$ was tested against the alternative hypothesis $H_A$ : $HR > 1$ , where HR was the PFS hazard ratio for first-line therapy plus TG4010 relative to first-line therapy plus placebo. |  |
| Comparison groups   | Placebo: Elevated TrPal Subgroup v TG4010: Elevated TrPAL Subgroup |
| Number of subjects included in analysis   | 75   |
| Analysis specification  | Pre-specified  |
| Analysis type   | other <sup>[7]</sup>   |
| P-value   | = 0.553 <sup>[8]</sup>   |
| Method  | Logrank  |
| Parameter estimate  | Hazard ratio (HR)  |
| Point estimate  | 0.91   |
| Confidence interval   |  |
| level   | 95 %   |
| sides   | 2-sided  |
| lower limit   | 0.56   |
| upper limit   | 1.47   |

Notes:

[7] - The null hypothesis  $H_0$ :  $HR \leq 1$  was tested against the alternative hypothesis  $H_A$ :  $HR \geq 1$ , where HR is the PFS hazard ratio for first-line therapy+TG4010 (TG4010 arm) relative to first-line therapy+placebo (placebo arm). The hypothesis was tested by using the posterior distribution of an estimator of the log HR.

[8] - Efficacy criteria:  $1-P(HR > 1 / \text{observed data}) \leq 0.20$

|  |  |
|--|--|
| <b>Statistical analysis title</b>  | Frequentist analysis: Normal TrPAL subgroup                    |
| Statistical analysis description:<br>As a supportive analysis, a frequentist analysis was also performed to compare PFS between the 2 study arms in each TrPAL subgroup by using a one-sided non-stratified log rank test. |  |
| Comparison groups  | TG4010: Normal TrPAL Subgroup v Placebo: Normal TrPAL Subgroup |
| Number of subjects included in analysis  | 170  |
| Analysis specification   | Pre-specified  |
| Analysis type  | other <sup>[9]</sup>   |
| P-value  | = 0.032  |
| Method   | Logrank  |
| Parameter estimate   | Hazard ratio (HR)  |
| Point estimate   | 0.73   |
| Confidence interval  |  |
| level  | 95 %   |
| sides  | 2-sided  |
| lower limit  | 0.53   |
| upper limit  | 1.02   |

Notes:

[9] - Hazard ratio and corresponding 95% confidence intervals (CIs) were derived using the Cox proportional hazards model.

|  |  |
|--|--|
| <b>Statistical analysis title</b>  | Frequentist analysis: High TrPAL subgroup                  |
| Statistical analysis description:<br>As a supportive analysis, a frequentist analysis was also performed to compare PFS between the 2 study arms in each TrPAL subgroup by using a one-sided non-stratified log rank test. |  |
| Comparison groups  | TG4010: High TrPAL Subgroup v Placebo: High TrPAL Subgroup |
| Number of subjects included in analysis  | 52   |
| Analysis specification   | Pre-specified  |
| Analysis type  | other <sup>[10]</sup>                                      |
| P-value  | = 0.195  |
| Method   | Logrank  |
| Parameter estimate   | Hazard ratio (HR)  |
| Point estimate   | 0.77   |
| Confidence interval  |  |
| level  | 95 %   |
| sides  | 2-sided  |
| lower limit  | 0.42   |
| upper limit  | 1.4  |

Notes:

[10] - Hazard ratio and corresponding 95% CIs were derived using the Cox proportional hazards model.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Frequentist analysis: Non-elevated TrPAL subgroup   |
| Statistical analysis description:<br>As a supportive analysis, a frequentist analysis was also performed to compare PFS between the 2 study arms in each TrPAL subgroup by using a one-sided non-stratified log rank test. |   |
| Comparison groups  | TG4010: Non-elevated TrPAL Subgroup v Placebo: Non- |

|   |                         |
|---|-------------------------|
|   | elevated TrPAL Subgroup |
| Number of subjects included in analysis | 147                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | other <sup>[11]</sup>   |
| P-value                                 | = 0.01                  |
| Method                                  | Logrank                 |
| Parameter estimate                      | Hazard ratio (HR)       |
| Point estimate                          | 0.66                    |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | 0.46                    |
| upper limit                             | 0.94                    |

Notes:

[11] - Hazard ratio and corresponding 95% CIs were derived using the Cox proportional hazards model.

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | Frequentist analysis: Elevated TrPAL subgroup                      |
| Statistical analysis description:   |  |
| As a supportive analysis, a frequentist analysis was also performed to compare PFS between the 2 study arms in each TrPAL subgroup by using a one-sided non-stratified log rank test. |  |
| Comparison groups   | TG4010: Elevated TrPAL Subgroup v Placebo: Elevated TrPal Subgroup |
| Number of subjects included in analysis   | 75   |
| Analysis specification  | Pre-specified  |
| Analysis type   | other <sup>[12]</sup>  |
| P-value   | = 0.343  |
| Method  | Logrank  |
| Parameter estimate  | Hazard ratio (HR)  |
| Point estimate  | 0.9  |
| Confidence interval   |  |
| level   | 95 %   |
| sides   | 2-sided  |
| lower limit   | 0.55   |
| upper limit   | 1.48   |

Notes:

[12] - Hazard ratio and corresponding 95% CIs were derived using the Cox proportional hazards model.

### **Secondary: Comparison of OS Events in Subjects Treated with TG4010 or Placebo.**

|   |   |
|---|---|
| End point title   | Comparison of OS Events in Subjects Treated with TG4010 or Placebo. |
| End point description:  |   |
| OS was defined as the time from the date of randomisation to the date of death due to any cause. Analysis of OS was conducted when at least 70% of subjects had died. The number of deaths at the cut-off date for OS was recorded for the whole population and in each TrPAL subgroup. If a subject was not known to have died, survival was censored at the date of last contact. |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| Subjects were followed for survival every 3 months up to a maximum of 169 weeks (until cut-off date for OS analysis).   |   |

| End point values            | TG4010          | Placebo         | TG4010: Normal TrPAL Subgroup | Placebo: Normal TrPAL Subgroup |
|-----------------------------|-----------------|-----------------|-------------------------------|--------------------------------|
| Subject group type          | Reporting group | Reporting group | Subject analysis set          | Subject analysis set           |
| Number of subjects analysed | 111             | 111             | 85                            | 85                             |
| Units: Events (Deaths)      | 78              | 87              | 58                            | 69                             |

| End point values            | TG4010: High TrPAL Subgroup | Placebo: High TrPAL Subgroup | TG4010: Non-elevated TrPAL Subgroup | Placebo: Non-elevated TrPAL Subgroup |
|-----------------------------|-----------------------------|------------------------------|-------------------------------------|--------------------------------------|
| Subject group type          | Subject analysis set        | Subject analysis set         | Subject analysis set                | Subject analysis set                 |
| Number of subjects analysed | 26                          | 26                           | 71                                  | 76                                   |
| Units: Events (Deaths)      | 20                          | 18                           | 47                                  | 62                                   |

| End point values            | TG4010: Elevated TrPAL Subgroup | Placebo: Elevated TrPal Subgroup |  |  |
|-----------------------------|---------------------------------|----------------------------------|--|--|
| Subject group type          | Subject analysis set            | Subject analysis set             |  |  |
| Number of subjects analysed | 40                              | 35                               |  |  |
| Units: Events (Deaths)      | 31                              | 25                               |  |  |

## Statistical analyses

| Statistical analysis title | Comparison of OS in Whole Population |
|----------------------------|--------------------------------------|
|----------------------------|--------------------------------------|

Statistical analysis description:

The distribution of OS was compared between the treatment arms using a one-sided non-stratified log-rank test. Hazard ratio and corresponding 95% CIs were derived using the Cox proportional hazards model.

|   |                   |
|---|-------------------|
| Comparison groups                       | TG4010 v Placebo  |
| Number of subjects included in analysis | 222               |
| Analysis specification                  | Pre-specified     |
| Analysis type                           | other             |
| P-value                                 | = 0.055           |
| Method                                  | Logrank           |
| Parameter estimate                      | Hazard ratio (HR) |
| Point estimate                          | 0.78              |
| Confidence interval                     |                   |
| level                                   | 95 %              |
| sides                                   | 2-sided           |
| lower limit                             | 0.57              |
| upper limit                             | 1.06              |

| Statistical analysis title | Comparison of OS in Normal TrPAL Subgroup |
|----------------------------|---|
|----------------------------|---|

**Statistical analysis description:**

The distribution of OS was compared between the treatment arms using a one-sided non-stratified log-rank test. Hazard ratio and corresponding 95% CIs were derived using the Cox proportional hazards model.

|   |  |
|---|--|
| Comparison groups                       | TG4010: Normal TrPAL Subgroup v Placebo: Normal TrPAL Subgroup |
| Number of subjects included in analysis | 170  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | other  |
| P-value                                 | = 0.052  |
| Method                                  | Logrank  |
| Parameter estimate                      | Hazard ratio (HR)  |
| Point estimate                          | 0.75   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.53   |
| upper limit                             | 1.06   |

**Statistical analysis title**

Comparison of OS in High TrPAL Subgroup

**Statistical analysis description:**

The distribution of OS was compared between the treatment arms using a one-sided non-stratified log-rank test. Hazard ratio and corresponding 95% CIs were derived using the Cox proportional hazards model.

|   |  |
|---|--|
| Comparison groups                       | TG4010: High TrPAL Subgroup v Placebo: High TrPAL Subgroup |
| Number of subjects included in analysis | 52   |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | other  |
| P-value                                 | = 0.362  |
| Method                                  | Logrank  |
| Parameter estimate                      | Hazard ratio (HR)  |
| Point estimate                          | 0.89   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.47   |
| upper limit                             | 1.7  |

**Statistical analysis title**

Comparison of OS in Non-elevated TrPAL Subgroup

**Statistical analysis description:**

The distribution of OS was compared between the treatment arms using a one-sided non-stratified log-rank test. Hazard ratio and corresponding 95% CIs were derived using the Cox proportional hazards model.

|                   |  |
|-------------------|--|
| Comparison groups | TG4010: Non-elevated TrPAL Subgroup v Placebo: Non-elevated TrPAL Subgroup |
|-------------------|--|

|   |                   |
|---|-------------------|
| Number of subjects included in analysis | 147               |
| Analysis specification                  | Pre-specified     |
| Analysis type                           | other             |
| P-value                                 | = 0.018           |
| Method                                  | Logrank           |
| Parameter estimate                      | Hazard ratio (HR) |
| Point estimate                          | 0.67              |
| Confidence interval                     |                   |
| level                                   | 95 %              |
| sides                                   | 2-sided           |
| lower limit                             | 0.46              |
| upper limit                             | 0.98              |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Comparison of OS in Elevated TrPAL Subgroup |
|-----------------------------------|---|

Statistical analysis description:

The distribution of OS was compared between the treatment arms using a one-sided non-stratified log-rank test. Hazard ratio and corresponding 95% CIs were derived using the Cox proportional hazards model.

|   |  |
|---|--|
| Comparison groups                       | TG4010: Elevated TrPAL Subgroup v Placebo: Elevated TrPal Subgroup |
| Number of subjects included in analysis | 75   |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | other  |
| P-value                                 | = 0.444  |
| Method                                  | Logrank  |
| Parameter estimate                      | Hazard ratio (HR)  |
| Point estimate                          | 1.04   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.61   |
| upper limit                             | 1.76   |

## **Secondary: Median OS in Subjects Treated with TG4010 or Placebo.**

|                 |   |
|-----------------|---|
| End point title | Median OS in Subjects Treated with TG4010 or Placebo. |
|-----------------|---|

End point description:

OS was defined as the time from the date of randomisation to the date of death due to any cause. Analysis of OS was conducted when at least 70 % of subjects had died for the whole population and in each TrPAL group. If a subject is not known to have died, survival was censored at the date of last contact.

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

End point timeframe:

Subjects were followed for survival every 3 months up to a maximum of 169 weeks (until cut-off date for OS analysis).



| End point values                 | TG4010             | Placebo            | TG4010: Normal TrPAL Subgroup | Placebo: Normal TrPAL Subgroup |
|----------------------------------|--------------------|--------------------|-------------------------------|--------------------------------|
| Subject group type               | Reporting group    | Reporting group    | Subject analysis set          | Subject analysis set           |
| Number of subjects analysed      | 111                | 111                | 85                            | 85                             |
| Units: Months                    |                    |                    |                               |                                |
| median (confidence interval 95%) | 12.7 (9.8 to 16.4) | 10.5 (9.5 to 14.3) | 12.6 (9.7 to 15.6)            | 10.5 (8.9 to 14.3)             |

| End point values                 | TG4010: High TrPAL Subgroup | Placebo: High TrPAL Subgroup | TG4010: Non-elevated TrPAL Subgroup | Placebo: Non-elevated TrPAL Subgroup |
|----------------------------------|-----------------------------|------------------------------|-------------------------------------|--------------------------------------|
| Subject group type               | Subject analysis set        | Subject analysis set         | Subject analysis set                | Subject analysis set                 |
| Number of subjects analysed      | 26                          | 26                           | 71                                  | 76                                   |
| Units: Months                    |                             |                              |                                     |                                      |
| median (confidence interval 95%) | 14.2 (7.1 to 22.4)          | 10.9 (7.7 to 21.7)           | 13 (9.7 to 18.4)                    | 10.4 (8.2 to 14.1)                   |

| End point values                 | TG4010: Elevated TrPAL Subgroup | Placebo: Elevated TrPal Subgroup |  |  |
|----------------------------------|---------------------------------|----------------------------------|--|--|
| Subject group type               | Subject analysis set            | Subject analysis set             |  |  |
| Number of subjects analysed      | 40                              | 35                               |  |  |
| Units: Months                    |                                 |                                  |  |  |
| median (confidence interval 95%) | 12.4 (7.3 to 17)                | 13.7 (8.8 to 21)                 |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Comparison of Overall Response Rate (ORR) in Subjects Treated with TG4010 or Placebo.

|                 |   |
|-----------------|---|
| End point title | Comparison of Overall Response Rate (ORR) in Subjects Treated with TG4010 or Placebo. |
|-----------------|---|

End point description:

ORR was defined as the percentage of subjects whose best overall response to tumour evaluation was either complete response (CR) or partial response (PR) confirmed at least 4 weeks after initial documentation. Objective response rate was the percentage of subjects whose best overall response is either CR or PR according to RECIST version 1.1. Results are presented by treatment arm and by TrPAL subgroup for objective response rate and also percentage of subjects with best overall response (CR, PR, stable disease and progressive disease).

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

End point timeframe:

Tumour response was evaluated every 6 weeks until documented progression or for a period of 9 months. Beyond 9 months, evaluations were performed every 12 weeks until documented disease progression. Up to a maximum of 140 weeks (until cut-off date).

| <b>End point values</b>       | TG4010          | Placebo         | TG4010:<br>Normal TrPAL<br>Subgroup | Placebo:<br>Normal TrPAL<br>Subgroup |
|-------------------------------|-----------------|-----------------|-------------------------------------|--------------------------------------|
| Subject group type            | Reporting group | Reporting group | Subject analysis set                | Subject analysis set                 |
| Number of subjects analysed   | 111             | 111             | 85                                  | 85                                   |
| Units: Percentage of Subjects |                 |                 |                                     |                                      |
| number (not applicable)       |                 |                 |                                     |                                      |
| Objective Response Rate       | 39.6            | 28.8            | 38.8                                | 30.6                                 |
| CR                            | 0.9             | 0               | 0                                   | 0                                    |
| PR                            | 38.7            | 28.8            | 38.8                                | 30.6                                 |
| Stable Disease                | 44.1            | 48.6            | 44.7                                | 48.2                                 |
| Progressive Disease           | 11.7            | 13.5            | 12.9                                | 12.9                                 |
| Unknown                       | 4.5             | 9               | 3.5                                 | 8.2                                  |

| <b>End point values</b>       | TG4010: High<br>TrPAL<br>Subgroup | Placebo: High<br>TrPAL<br>Subgroup | TG4010: Non-<br>elevated TrPAL<br>Subgroup | Placebo: Non-<br>elevated TrPAL<br>Subgroup |
|-------------------------------|-----------------------------------|------------------------------------|--|---|
| Subject group type            | Subject analysis set              | Subject analysis set               | Subject analysis set                       | Subject analysis set                        |
| Number of subjects analysed   | 26                                | 26                                 | 71   | 76  |
| Units: Percentage of Subjects |                                   |                                    |  |   |
| number (not applicable)       |                                   |                                    |  |   |
| Objective Response Rate       | 42.3                              | 23.1                               | 39.4                                       | 31.6  |
| CR                            | 3.8                               | 0                                  | 0  | 0   |
| PR                            | 38.5                              | 23.1                               | 39.4                                       | 31.6  |
| Stable Disease                | 42.3                              | 50                                 | 45.1                                       | 46.1  |
| Progressive Disease           | 7.7                               | 15.4                               | 11.3                                       | 14.5  |
| Unknown                       | 7.7                               | 11.5                               | 4.2  | 7.9   |

| <b>End point values</b>       | TG4010:<br>Elevated TrPAL<br>Subgroup | Placebo:<br>Elevated TrPal<br>Subgroup |  |  |
|-------------------------------|---------------------------------------|--|--|--|
| Subject group type            | Subject analysis set                  | Subject analysis set                   |  |  |
| Number of subjects analysed   | 40                                    | 35                                     |  |  |
| Units: Percentage of Subjects |                                       |  |  |  |
| number (not applicable)       |                                       |  |  |  |
| Objective Response Rate       | 40                                    | 22.9                                   |  |  |
| CR                            | 2.5                                   | 0                                      |  |  |
| PR                            | 37.5                                  | 22.9                                   |  |  |
| Stable Disease                | 42.5                                  | 54.3                                   |  |  |
| Progressive Disease           | 12.5                                  | 11.4                                   |  |  |
| Unknown                       | 5                                     | 11.4                                   |  |  |

## Statistical analyses

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>   | Comparison of ORR in Whole Population |
| Statistical analysis description:<br>The Cochran-Mantel-Haenszel chi-square test stratified by tumour histology, bevacizumab administration, chemotherapy regimen, and performance status was used to compare the 2 treatment arms with respect to the ORR at one-sided 2.5% level of significance. |                                       |
| Comparison groups   | TG4010 v Placebo                      |
| Number of subjects included in analysis   | 222                                   |
| Analysis specification  | Pre-specified                         |
| Analysis type   | other                                 |
| P-value   | = 0.03                                |
| Method  | Cochran-Mantel-Haenszel               |

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | Comparison of ORR in Normal TrPAL Subgroup                     |
| Statistical analysis description:<br>The Cochran-Mantel-Haenszel chi-square test stratified by tumour histology, bevacizumab administration, chemotherapy regimen, and performance status was used to compare the 2 treatment arms with respect to the ORR at one-sided 2.5% level of significance. |  |
| Comparison groups   | TG4010: Normal TrPAL Subgroup v Placebo: Normal TrPAL Subgroup |
| Number of subjects included in analysis   | 170  |
| Analysis specification  | Pre-specified  |
| Analysis type   | other  |
| P-value   | = 0.088  |
| Method  | Cochran-Mantel-Haenszel  |

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | Comparison of ORR in High TrPAL Subgroup                   |
| Statistical analysis description:<br>The Cochran-Mantel-Haenszel chi-square test stratified by tumour histology, bevacizumab administration, chemotherapy regimen, and performance status was used to compare the 2 treatment arms with respect to the ORR at one-sided 2.5% level of significance. |  |
| Comparison groups   | TG4010: High TrPAL Subgroup v Placebo: High TrPAL Subgroup |
| Number of subjects included in analysis   | 52   |
| Analysis specification  | Pre-specified  |
| Analysis type   | other  |
| P-value   | = 0.092  |
| Method  | Cochran-Mantel-Haenszel                                    |

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | Comparison of ORR in Non-elevated TrPAL Subgroup                           |
| Statistical analysis description:<br>The Cochran-Mantel-Haenszel chi-square test stratified by tumour histology, bevacizumab administration, chemotherapy regimen, and performance status was used to compare the 2 treatment arms with respect to the ORR at one-sided 2.5% level of significance. |  |
| Comparison groups   | TG4010: Non-elevated TrPAL Subgroup v Placebo: Non-elevated TrPAL Subgroup |

|   |                         |
|---|-------------------------|
| Number of subjects included in analysis | 147                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | other                   |
| P-value                                 | = 0.079                 |
| Method                                  | Cochran-Mantel-Haenszel |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Comparison of ORR in Elevated TrPAL Subgroup |
|-----------------------------------|--|

Statistical analysis description:

The Cochran-Mantel-Haenszel chi-square test stratified by tumour histology, bevacizumab administration, chemotherapy regimen, and performance status was used to compare the 2 treatment arms with respect to the ORR at one-sided 2.5% level of significance.

|   |  |
|---|--|
| Comparison groups                       | TG4010: Elevated TrPAL Subgroup v Placebo: Elevated TrPal Subgroup |
| Number of subjects included in analysis | 75   |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | other  |
| P-value                                 | = 0.06   |
| Method                                  | Cochran-Mantel-Haenszel  |

## **Secondary: Comparison of Percentage of Subjects with a 9 Month Time to Overall Response (TOR) in Subjects Treated with TG4010 or Placebo.**

|                 |  |
|-----------------|--|
| End point title | Comparison of Percentage of Subjects with a 9 Month Time to Overall Response (TOR) in Subjects Treated with TG4010 or Placebo. |
|-----------------|--|

End point description:

TOR events were recorded from the time between date of randomisation to the date of first documented response (CR or PR). TOR was censored if no progression or death was observed at the cut-off date for analysis, or at the date when a further antineoplastic therapy was started. A Kaplan-Meier curve was constructed for each treatment arm and subgroup. The percentage of subjects with a time to overall response of 9 months are reported.

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

End point timeframe:

Tumour response was evaluated every 6 weeks until documented progression or for a period of 9 months. Beyond 9 months, evaluations were performed every 12 weeks until documented disease progression. Up to a maximum of 140 weeks (until cut-off date).

| <b>End point values</b>          | TG4010          | Placebo         | TG4010:<br>Normal TrPAL<br>Subgroup | Placebo:<br>Normal TrPAL<br>Subgroup |
|----------------------------------|-----------------|-----------------|-------------------------------------|--------------------------------------|
| Subject group type               | Reporting group | Reporting group | Subject analysis set                | Subject analysis set                 |
| Number of subjects analysed      | 111             | 111             | 85                                  | 85                                   |
| Units: Percentage of Subjects    |                 |                 |                                     |                                      |
| number (confidence interval 95%) | 42 (27 to 56)   | 59 (47 to 70)   | 45 (28 to 60)                       | 59 (46 to 70)                        |

|                         |              |               |              |               |
|-------------------------|--------------|---------------|--------------|---------------|
| <b>End point values</b> | TG4010: High | Placebo: High | TG4010: Non- | Placebo: Non- |
|-------------------------|--------------|---------------|--------------|---------------|

|                                  | TrPAL Subgroup       | TrPAL Subgroup       | elevated TrPAL Subgroup | elevated TrPAL Subgroup |
|----------------------------------|----------------------|----------------------|-------------------------|-------------------------|
| Subject group type               | Subject analysis set | Subject analysis set | Subject analysis set    | Subject analysis set    |
| Number of subjects analysed      | 26                   | 26                   | 71                      | 76                      |
| Units: Percentage of Subjects    |                      |                      |                         |                         |
| number (confidence interval 95%) | 33 (8 to 62)         | 61 (32 to 81)        | 49 (34 to 62)           | 57 (43 to 69)           |

| <b>End point values</b>          | TG4010: Elevated TrPAL Subgroup | Placebo: Elevated TrPal Subgroup |  |  |
|----------------------------------|---------------------------------|----------------------------------|--|--|
| Subject group type               | Subject analysis set            | Subject analysis set             |  |  |
| Number of subjects analysed      | 40                              | 35                               |  |  |
| Units: Percentage of Subjects    |                                 |                                  |  |  |
| number (confidence interval 95%) | 29 (7 to 57)                    | 65 (41 to 81)                    |  |  |

## Statistical analyses

### Statistical analysis title

Comparison of TOR in Whole Population

Statistical analysis description:

The distribution of TOR was compared between the treatment arms using a one-sided non-stratified log-rank test. Hazard ratio and corresponding 95% CIs were derived using the Cox proportional hazards model.

|   |                   |
|---|-------------------|
| Comparison groups                       | Placebo v TG4010  |
| Number of subjects included in analysis | 222               |
| Analysis specification                  | Pre-specified     |
| Analysis type                           | other             |
| P-value                                 | = 0.108           |
| Method                                  | Logrank           |
| Parameter estimate                      | Hazard ratio (HR) |
| Point estimate                          | 1.33              |
| Confidence interval                     |                   |
| level                                   | 95 %              |
| sides                                   | 2-sided           |
| lower limit                             | 0.84              |
| upper limit                             | 2.1               |

### Statistical analysis title

Comparison of TOR in Normal TrPAL Subgroup

Statistical analysis description:

The distribution of TOR was compared between the treatment arms using a one-sided non-stratified log-rank test. Hazard ratio and corresponding 95% CIs were derived using the Cox proportional hazards model.

|                   |  |
|-------------------|--|
| Comparison groups | TG4010: Normal TrPAL Subgroup v Placebo: Normal TrPAL Subgroup |
|-------------------|--|

|   |                   |
|---|-------------------|
| Number of subjects included in analysis | 170               |
| Analysis specification                  | Pre-specified     |
| Analysis type                           | other             |
| P-value                                 | = 0.218           |
| Method                                  | Logrank           |
| Parameter estimate                      | Hazard ratio (HR) |
| Point estimate                          | 1.23              |
| Confidence interval                     |                   |
| level                                   | 95 %              |
| sides                                   | 2-sided           |
| lower limit                             | 0.73              |
| upper limit                             | 2.05              |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Comparison of TOR in High TrPAL Subgroup |
|-----------------------------------|--|

Statistical analysis description:

The distribution of TOR was compared between the treatment arms using a one-sided non-stratified log-rank test. Hazard ratio and corresponding 95% CIs were derived using the Cox proportional hazards model.

|   |  |
|---|--|
| Comparison groups                       | TG4010: High TrPAL Subgroup v Placebo: High TrPAL Subgroup |
| Number of subjects included in analysis | 52   |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | other  |
| P-value                                 | = 0.152  |
| Method                                  | Logrank  |
| Parameter estimate                      | Hazard ratio (HR)  |
| Point estimate                          | 1.67   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.62   |
| upper limit                             | 4.51   |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Comparison of TOR in Non-elevated TrPAL Subgroup |
|-----------------------------------|--|

Statistical analysis description:

The distribution of TOR was compared between the treatment arms using a one-sided non-stratified log-rank test. Hazard ratio and corresponding 95% CIs were derived using the Cox proportional hazards model.

|   |  |
|---|--|
| Comparison groups                       | TG4010: Non-elevated TrPAL Subgroup v Placebo: Non-elevated TrPAL Subgroup |
| Number of subjects included in analysis | 147  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | other  |
| P-value                                 | = 0.315  |
| Method                                  | Logrank  |
| Parameter estimate                      | Hazard ratio (HR)  |
| Point estimate                          | 1.14   |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.66    |
| upper limit         | 1.97    |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Comparison of TOR in Elevated TrPAL Subgroup |
|-----------------------------------|--|

Statistical analysis description:

The distribution of TOR was compared between the treatment arms using a one-sided non-stratified log-rank test. Hazard ratio and corresponding 95% CIs were derived using the Cox proportional hazards model.

|   |  |
|---|--|
| Comparison groups                       | TG4010: Elevated TrPAL Subgroup v Placebo: Elevated TrPal Subgroup |
| Number of subjects included in analysis | 75   |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | other  |
| P-value                                 | = 0.082  |
| Method                                  | Logrank  |
| Parameter estimate                      | Hazard ratio (HR)  |
| Point estimate                          | 1.81   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.77   |
| upper limit                             | 4.22   |

## **Secondary: Duration of Overall Response (DOR) in Subjects Treated with TG4010 or Placebo.**

|                 |  |
|-----------------|--|
| End point title | Duration of Overall Response (DOR) in Subjects Treated with TG4010 or Placebo. |
|-----------------|--|

End point description:

DOR in weeks applied only to patients whose best overall tumour response was CR or PR. The start date was the date of first documented response (CR or PR) and the end date was the date of event defined as first documented disease progression or death due to underlying cancer. DoR was censored if progression or death due to underlying cancer was not observed at the cut-off date for the analysis or start of further antineoplastic therapy. The censoring date was the date of the last evaluable tumour assessment.

For the purpose of reporting data, where the result was recorded as 'not reached' (i.e. infinity) an arbitrary value of 999999 has been assigned.

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

End point timeframe:

Tumour response was evaluated every 6 weeks until documented progression or for a period of 9 months. Beyond 9 months, evaluations were performed every 12 weeks until documented disease progression. Up to a maximum of 140 weeks (until cut-off date).

| End point values                 | TG4010              | Placebo             | TG4010: Normal TrPAL Subgroup | Placebo: Normal TrPAL Subgroup |
|----------------------------------|---------------------|---------------------|-------------------------------|--------------------------------|
| Subject group type               | Reporting group     | Reporting group     | Subject analysis set          | Subject analysis set           |
| Number of subjects analysed      | 44 <sup>[13]</sup>  | 32 <sup>[14]</sup>  | 33 <sup>[15]</sup>            | 26 <sup>[16]</sup>             |
| Units: weeks                     |                     |                     |                               |                                |
| median (confidence interval 95%) | 30.1 (21.9 to 43.1) | 18.7 (14.9 to 36.4) | 31 (19.9 to 54.1)             | 20.4 (14.3 to 36.4)            |

Notes:

[13] - Only subjects whose best overall response was classed as CR or PR were analysed.

[14] - Only subjects whose best overall response was classed as CR or PR were analysed.

[15] - Only subjects whose best overall response was classed as CR or PR were analysed.

[16] - Only subjects whose best overall response was classed as CR or PR were analysed.

| End point values                 | TG4010: High TrPAL Subgroup | Placebo: High TrPAL Subgroup | TG4010: Non-elevated TrPAL Subgroup | Placebo: Non-elevated TrPAL Subgroup |
|----------------------------------|-----------------------------|------------------------------|-------------------------------------|--------------------------------------|
| Subject group type               | Subject analysis set        | Subject analysis set         | Subject analysis set                | Subject analysis set                 |
| Number of subjects analysed      | 11 <sup>[17]</sup>          | 6 <sup>[18]</sup>            | 28 <sup>[19]</sup>                  | 24 <sup>[20]</sup>                   |
| Units: weeks                     |                             |                              |                                     |                                      |
| median (confidence interval 95%) | 27.4 (12.3 to 55.4)         | 17.2 (11.1 to 999999)        | 41.4 (19.9 to 54.7)                 | 18.7 (13.4 to 30.3)                  |

Notes:

[17] - Only subjects whose best overall response was classed as CR or PR were analysed.

[18] - Only subjects whose best overall response was classed as CR or PR were analysed (999999=infinity).

[19] - Only subjects whose best overall response was classed as CR or PR were analysed.

[20] - Only subjects whose best overall response was classed as CR or PR were analysed.

| End point values                 | TG4010: Elevated TrPAL Subgroup | Placebo: Elevated TrPal Subgroup |  |  |
|----------------------------------|---------------------------------|----------------------------------|--|--|
| Subject group type               | Subject analysis set            | Subject analysis set             |  |  |
| Number of subjects analysed      | 16 <sup>[21]</sup>              | 8 <sup>[22]</sup>                |  |  |
| Units: weeks                     |                                 |                                  |  |  |
| median (confidence interval 95%) | 27.4 (15.6 to 40.9)             | 32.2 (11.1 to 999999)            |  |  |

Notes:

[21] - Only subjects whose best overall response was classed as CR or PR were analysed.

[22] - Only subjects whose best overall response was classed as CR or PR were analysed (999999=infinity).

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of DOR Events in Subjects Treated with TG4010 or Placebo.

|                 |  |
|-----------------|--|
| End point title | Number of DOR Events in Subjects Treated with TG4010 or Placebo. |
|-----------------|--|

End point description:

DOR applied only to patients whose best overall tumour response was CR or PR and number of DOR events were recorded for each treatment arm and subgroup. DOR was censored if progression or death due to underlying cancer was not observed at the cut-off date for the analysis or start of further antineoplastic therapy. The censoring date was the date of the last evaluable tumour assessment.

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

End point timeframe:

Tumour response was evaluated every 6 weeks until documented progression or for a period of 9



months. Beyond 9 months, evaluations were performed every 12 weeks until documented disease progression. Up to a maximum of 140 weeks (until cut-off date).

---

| End point values            | TG4010             | Placebo            | TG4010: Normal TrPAL Subgroup | Placebo: Normal TrPAL Subgroup |
|-----------------------------|--------------------|--------------------|-------------------------------|--------------------------------|
| Subject group type          | Reporting group    | Reporting group    | Subject analysis set          | Subject analysis set           |
| Number of subjects analysed | 44 <sup>[23]</sup> | 32 <sup>[24]</sup> | 33 <sup>[25]</sup>            | 26 <sup>[26]</sup>             |
| Units: DOR Events           | 35                 | 28                 | 27                            | 23                             |

Notes:

[23] - Only subjects whose best overall response was classed as CR or PR were analysed.

[24] - Only subjects whose best overall response was classed as CR or PR were analysed.

[25] - Only subjects whose best overall response was classed as CR or PR were analysed.

[26] - Only subjects whose best overall response was classed as CR or PR were analysed.

| End point values            | TG4010: High TrPAL Subgroup | Placebo: High TrPAL Subgroup | TG4010: Non-elevated TrPAL Subgroup | Placebo: Non-elevated TrPAL Subgroup |
|-----------------------------|-----------------------------|------------------------------|-------------------------------------|--------------------------------------|
| Subject group type          | Subject analysis set        | Subject analysis set         | Subject analysis set                | Subject analysis set                 |
| Number of subjects analysed | 11 <sup>[27]</sup>          | 6 <sup>[28]</sup>            | 28 <sup>[29]</sup>                  | 24 <sup>[30]</sup>                   |
| Units: DOR Events           | 8                           | 5                            | 22                                  | 22                                   |

Notes:

[27] - Only subjects whose best overall response was classed as CR or PR were analysed.

[28] - Only subjects whose best overall response was classed as CR or PR were analysed.

[29] - Only subjects whose best overall response was classed as CR or PR were analysed.

[30] - Only subjects whose best overall response was classed as CR or PR were analysed.

| End point values            | TG4010: Elevated TrPAL Subgroup | Placebo: Elevated TrPal Subgroup |  |  |
|-----------------------------|---------------------------------|----------------------------------|--|--|
| Subject group type          | Subject analysis set            | Subject analysis set             |  |  |
| Number of subjects analysed | 16 <sup>[31]</sup>              | 8 <sup>[32]</sup>                |  |  |
| Units: DOR Events           | 13                              | 6                                |  |  |

Notes:

[31] - Only subjects whose best overall response was classed as CR or PR were analysed.

[32] - Only subjects whose best overall response was classed as CR or PR were analysed.

## Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the first day of study treatment until 28 days after the last dose of study treatment (up to a maximum of 107 weeks + 28 days).

Adverse event reporting additional description:

Adverse events were summarised by treatment arm (TG4010 or placebo) in subjects that had received at least one injection of TG4010 or placebo (110 patients in TG4010 arm and 107 patients in the placebo arm). Causality was assessed in relation to TG4010 or placebo.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

### Reporting groups

|                       |        |
|-----------------------|--------|
| Reporting group title | TG4010 |
|-----------------------|--------|

Reporting group description:

Subjects received TG4010 plus chemotherapy as first-line treatment followed by TG4010 plus maintenance therapy if appropriate.

TG4010 was administered on Day 1 of Cycle 1 of chemotherapy and then weekly for 6 weeks by SC injections, then once every 3 weeks until disease progression or premature discontinuation.

Chemotherapy was given as 21-day cycles for a minimum of 4 cycles and up to 6 cycles. If prescribed, bevacizumab was continued in combination with TG4010 and administered every 3 weeks until disease progression, premature discontinuation, or toxicity.

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

Reporting group description:

Subjects received TG4010 plus chemotherapy as first-line treatment followed by placebo plus maintenance therapy if appropriate.

Placebo was administered on Day 1 of Cycle 1 of chemotherapy and then weekly for 6 weeks by SC injections, then once every 3 weeks until disease progression or premature discontinuation.

Chemotherapy was given as 21-day cycles for a minimum of 4 cycles and up to 6 cycles. If prescribed, bevacizumab was continued in combination with placebo and administered every 3 weeks until disease progression, premature discontinuation, or toxicity.

| Serious adverse events  | TG4010            | Placebo           |  |
|---|-------------------|-------------------|--|
| Total subjects affected by serious adverse events                   |                   |                   |  |
| subjects affected / exposed   | 51 / 110 (46.36%) | 58 / 107 (54.21%) |  |
| number of deaths (all causes)                                       | 18                | 14                |  |
| number of deaths resulting from adverse events                      | 0                 | 0                 |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                   |  |
| Tumour pain   |                   |                   |  |
| subjects affected / exposed   | 1 / 110 (0.91%)   | 1 / 107 (0.93%)   |  |
| occurrences causally related to treatment / all                     | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0             |  |
| Endometrial cancer  |                   |                   |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 107 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metastases to bone                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 107 (0.93%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metastases to meninges                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 107 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Metastatic pain                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 107 (0.93%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tumour associated fever                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 107 (0.93%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vascular disorders                              |                 |                 |  |
| Peripheral ischaemia                            |                 |                 |  |
| subjects affected / exposed                     | 2 / 110 (1.82%) | 1 / 107 (0.93%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Superior vena cava syndrome                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 3 / 107 (2.80%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypertension                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 2 / 107 (1.87%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Arterial occlusive disease                      |                 |                 |  |

|  |                  |                 |  |
|--|------------------|-----------------|--|
| subjects affected / exposed                          | 0 / 110 (0.00%)  | 1 / 107 (0.93%) |  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           |  |
| Iliac artery occlusion                               |                  |                 |  |
| subjects affected / exposed                          | 1 / 110 (0.91%)  | 0 / 107 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           |  |
| Peripheral arterial occlusive disease                |                  |                 |  |
| subjects affected / exposed                          | 0 / 110 (0.00%)  | 1 / 107 (0.93%) |  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           |  |
| Thrombophlebitis superficial                         |                  |                 |  |
| subjects affected / exposed                          | 0 / 110 (0.00%)  | 1 / 107 (0.93%) |  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           |  |
| General disorders and administration site conditions |                  |                 |  |
| General physical health deterioration                |                  |                 |  |
| subjects affected / exposed                          | 10 / 110 (9.09%) | 8 / 107 (7.48%) |  |
| occurrences causally related to treatment / all      | 0 / 10           | 0 / 8           |  |
| deaths causally related to treatment / all           | 0 / 8            | 0 / 5           |  |
| Pyrexia  |                  |                 |  |
| subjects affected / exposed                          | 1 / 110 (0.91%)  | 3 / 107 (2.80%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 2 / 3           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           |  |
| Fatigue  |                  |                 |  |
| subjects affected / exposed                          | 2 / 110 (1.82%)  | 1 / 107 (0.93%) |  |
| occurrences causally related to treatment / all      | 0 / 2            | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           |  |
| Sudden death   |                  |                 |  |
| subjects affected / exposed                          | 1 / 110 (0.91%)  | 2 / 107 (1.87%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 2           |  |
| deaths causally related to treatment / all           | 0 / 1            | 0 / 2           |  |
| Malaise  |                  |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 107 (0.93%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Immune system disorders                         |                 |                 |  |
| Anaphylactic shock                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 107 (0.93%) |  |
| 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                     | 4 / 110 (3.64%) | 2 / 107 (1.87%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemoptysis                                     |                 |                 |  |
| subjects affected / exposed                     | 3 / 110 (2.73%) | 2 / 107 (1.87%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 6           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dyspnoea  |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 2 / 107 (1.87%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory failure                             |                 |                 |  |
| subjects affected / exposed                     | 2 / 110 (1.82%) | 1 / 107 (0.93%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 1           |  |
| Acute pulmonary oedema                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 1 / 107 (0.93%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chronic obstructive pulmonary disease           |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 1 / 107 (0.93%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Respiratory distress                            |                 |                 |  |
| subjects affected / exposed                     | 2 / 110 (1.82%) | 0 / 107 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0           |  |
| Acquired tracheo-oesophageal fistula            |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 107 (0.93%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pleural effusion                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 107 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonitis                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 107 (0.93%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Pneumothorax                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 107 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Investigations                                  |                 |                 |  |
| Blood creatinine increased                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 107 (0.93%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural complications  |                 |                 |  |
| Femur fracture                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 107 (0.93%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal fracture                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 107 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Cardiac disorders                               |                 |                 |  |
| Atrial fibrillation                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 2 / 107 (1.87%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 107 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure congestive                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 107 (0.93%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac tamponade                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 107 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Coronary artery insufficiency                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 107 (0.93%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myocardial infarction                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 107 (0.93%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Pericardial effusion                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 107 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pericarditis                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 107 (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                        |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Cerebral ischaemia                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 1 / 107 (0.93%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Brain oedema                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 107 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Convulsion                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 107 (0.93%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Generalised non-convulsive epilepsy             |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 107 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Syncope   |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 107 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood and lymphatic system disorders            |                 |                 |  |
| Anaemia   |                 |                 |  |
| subjects affected / exposed                     | 2 / 110 (1.82%) | 3 / 107 (2.80%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancytopenia                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 2 / 107 (1.87%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Febrile bone marrow aplasia                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 107 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neutropenia                                     |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 107 (0.93%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Thrombocytopenia                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 107 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Febrile neutropenia                             |                 |                 |  |
| subjects affected / exposed                     | 3 / 110 (2.73%) | 6 / 107 (5.61%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 6           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Eye disorders                                   |                 |                 |  |
| Diplopia  |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 1 / 107 (0.93%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                      |                 |                 |  |
| Vomiting  |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 5 / 107 (4.67%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 6           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diarrhoea                                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 110 (1.82%) | 1 / 107 (0.93%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abdominal pain                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 2 / 107 (1.87%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nausea  |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 2 / 107 (1.87%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Colitis   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 107 (0.93%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Duodenal ulcer perforation                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 107 (0.93%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Large intestinal obstruction                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 107 (0.93%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oesophagitis                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 107 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Stomatitis                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 107 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Renal failure                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 3 / 107 (2.80%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Endocrine disorders                             |                 |                 |  |
| Adrenal insufficiency                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 107 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Back pain                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 2 / 107 (1.87%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Bone pain                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 2 / 107 (1.87%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pathological fracture                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 107 (0.93%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Pneumonia                                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 110 (1.82%) | 4 / 107 (3.74%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 2 / 6           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Respiratory tract infection                     |                 |                 |  |
| subjects affected / exposed                     | 3 / 110 (2.73%) | 1 / 107 (0.93%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| Erysipelas                                      |                 |                 |  |
| subjects affected / exposed                     | 2 / 110 (1.82%) | 0 / 107 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Upper respiratory tract infection               |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 1 / 107 (0.93%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Device related infection                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 107 (0.93%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 107 (0.93%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lobar pneumonia                                 |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 107 (0.93%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Localised infection                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 107 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lung infection                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 107 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neutropenic sepsis                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 107 (0.93%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Pyelonephritis                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 107 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sepsis  |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 107 (0.93%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Septic shock                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 107 (0.93%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Dehydration                                     |                 |                 |  |
| subjects affected / exposed                     | 3 / 110 (2.73%) | 1 / 107 (0.93%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyponatraemia                                   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 110 (0.00%) | 2 / 107 (1.87%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Electrolyte imbalance                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 107 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Food intolerance                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 107 (0.93%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypokalaemia                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 107 (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>                                   | TG4010             | Placebo            |  |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events               |                    |                    |  |
| subjects affected / exposed   | 109 / 110 (99.09%) | 102 / 107 (95.33%) |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                    |                    |  |
| Tumour pain   |                    |                    |  |
| subjects affected / exposed   | 10 / 110 (9.09%)   | 6 / 107 (5.61%)    |  |
| occurrences (all)   | 10                 | 6                  |  |
| Vascular disorders  |                    |                    |  |
| Hypertension  |                    |                    |  |
| subjects affected / exposed   | 9 / 110 (8.18%)    | 13 / 107 (12.15%)  |  |
| occurrences (all)   | 10                 | 16                 |  |
| Hypotension   |                    |                    |  |
| subjects affected / exposed   | 9 / 110 (8.18%)    | 3 / 107 (2.80%)    |  |
| occurrences (all)   | 9                  | 4                  |  |
| General disorders and administration site conditions                |                    |                    |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| Fatigue   |                   |                   |  |
| subjects affected / exposed                     | 60 / 110 (54.55%) | 59 / 107 (55.14%) |  |
| occurrences (all)                               | 91                | 81                |  |
| Injection site erythema                         |                   |                   |  |
| subjects affected / exposed                     | 17 / 110 (15.45%) | 1 / 107 (0.93%)   |  |
| occurrences (all)                               | 28                | 1                 |  |
| Injection site induration                       |                   |                   |  |
| subjects affected / exposed                     | 9 / 110 (8.18%)   | 0 / 107 (0.00%)   |  |
| occurrences (all)                               | 12                | 0                 |  |
| Injection site pain                             |                   |                   |  |
| subjects affected / exposed                     | 13 / 110 (11.82%) | 1 / 107 (0.93%)   |  |
| occurrences (all)                               | 23                | 1                 |  |
| Oedema peripheral                               |                   |                   |  |
| subjects affected / exposed                     | 22 / 110 (20.00%) | 19 / 107 (17.76%) |  |
| occurrences (all)                               | 26                | 21                |  |
| Pyrexia   |                   |                   |  |
| subjects affected / exposed                     | 15 / 110 (13.64%) | 11 / 107 (10.28%) |  |
| occurrences (all)                               | 20                | 12                |  |
| Respiratory, thoracic and mediastinal disorders |                   |                   |  |
| Cough   |                   |                   |  |
| subjects affected / exposed                     | 19 / 110 (17.27%) | 22 / 107 (20.56%) |  |
| occurrences (all)                               | 20                | 25                |  |
| Dyspnoea  |                   |                   |  |
| subjects affected / exposed                     | 28 / 110 (25.45%) | 14 / 107 (13.08%) |  |
| occurrences (all)                               | 29                | 15                |  |
| Epistaxis                                       |                   |                   |  |
| subjects affected / exposed                     | 12 / 110 (10.91%) | 11 / 107 (10.28%) |  |
| occurrences (all)                               | 13                | 14                |  |
| Haemoptysis                                     |                   |                   |  |
| subjects affected / exposed                     | 2 / 110 (1.82%)   | 8 / 107 (7.48%)   |  |
| occurrences (all)                               | 2                 | 9                 |  |
| Productive Cough                                |                   |                   |  |
| subjects affected / exposed                     | 8 / 110 (7.27%)   | 6 / 107 (5.61%)   |  |
| occurrences (all)                               | 9                 | 7                 |  |
| Rhinorrhoea                                     |                   |                   |  |

|  |                      |                      |  |
|--|----------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all) | 8 / 110 (7.27%)<br>9 | 1 / 107 (0.93%)<br>1 |  |
| Psychiatric disorders                            |                      |                      |  |
| Anxiety  |                      |                      |  |
| subjects affected / exposed                      | 12 / 110 (10.91%)    | 4 / 107 (3.74%)      |  |
| occurrences (all)                                | 12                   | 4                    |  |
| Insomnia   |                      |                      |  |
| subjects affected / exposed                      | 8 / 110 (7.27%)      | 5 / 107 (4.67%)      |  |
| occurrences (all)                                | 8                    | 5                    |  |
| Investigations                                   |                      |                      |  |
| Blood creatinine increased                       |                      |                      |  |
| subjects affected / exposed                      | 9 / 110 (8.18%)      | 5 / 107 (4.67%)      |  |
| occurrences (all)                                | 10                   | 6                    |  |
| Weight decreased                                 |                      |                      |  |
| subjects affected / exposed                      | 21 / 110 (19.09%)    | 19 / 107 (17.76%)    |  |
| occurrences (all)                                | 22                   | 21                   |  |
| Weight increased                                 |                      |                      |  |
| subjects affected / exposed                      | 5 / 110 (4.55%)      | 7 / 107 (6.54%)      |  |
| occurrences (all)                                | 5                    | 7                    |  |
| Nervous system disorders                         |                      |                      |  |
| Dizziness  |                      |                      |  |
| subjects affected / exposed                      | 9 / 110 (8.18%)      | 3 / 107 (2.80%)      |  |
| occurrences (all)                                | 11                   | 5                    |  |
| Dysgeusia  |                      |                      |  |
| subjects affected / exposed                      | 13 / 110 (11.82%)    | 9 / 107 (8.41%)      |  |
| occurrences (all)                                | 15                   | 9                    |  |
| Headache   |                      |                      |  |
| subjects affected / exposed                      | 14 / 110 (12.73%)    | 11 / 107 (10.28%)    |  |
| occurrences (all)                                | 15                   | 12                   |  |
| Neuropathy Peripheral                            |                      |                      |  |
| subjects affected / exposed                      | 4 / 110 (3.64%)      | 8 / 107 (7.48%)      |  |
| occurrences (all)                                | 6                    | 10                   |  |
| Paraesthesia                                     |                      |                      |  |
| subjects affected / exposed                      | 11 / 110 (10.00%)    | 13 / 107 (12.15%)    |  |
| occurrences (all)                                | 11                   | 18                   |  |
| Blood and lymphatic system disorders             |                      |                      |  |

|                             |                   |                   |  |
|-----------------------------|-------------------|-------------------|--|
| Anaemia                     |                   |                   |  |
| subjects affected / exposed | 50 / 110 (45.45%) | 38 / 107 (35.51%) |  |
| occurrences (all)           | 66                | 50                |  |
| Leukopenia                  |                   |                   |  |
| subjects affected / exposed | 10 / 110 (9.09%)  | 11 / 107 (10.28%) |  |
| occurrences (all)           | 11                | 16                |  |
| Lymphopenia                 |                   |                   |  |
| subjects affected / exposed | 4 / 110 (3.64%)   | 7 / 107 (6.54%)   |  |
| occurrences (all)           | 5                 | 9                 |  |
| Neutropenia                 |                   |                   |  |
| subjects affected / exposed | 49 / 110 (44.55%) | 38 / 107 (35.51%) |  |
| occurrences (all)           | 119               | 85                |  |
| Thrombocytopenia            |                   |                   |  |
| subjects affected / exposed | 27 / 110 (24.55%) | 20 / 107 (18.69%) |  |
| occurrences (all)           | 42                | 32                |  |
| Ear and labyrinth disorders |                   |                   |  |
| Tinnitus                    |                   |                   |  |
| subjects affected / exposed | 11 / 110 (10.00%) | 7 / 107 (6.54%)   |  |
| occurrences (all)           | 11                | 9                 |  |
| Eye disorders               |                   |                   |  |
| Lacrimation Increased       |                   |                   |  |
| subjects affected / exposed | 7 / 110 (6.36%)   | 5 / 107 (4.67%)   |  |
| occurrences (all)           | 8                 | 5                 |  |
| Gastrointestinal disorders  |                   |                   |  |
| Abdominal Pain              |                   |                   |  |
| subjects affected / exposed | 15 / 110 (13.64%) | 9 / 107 (8.41%)   |  |
| occurrences (all)           | 16                | 13                |  |
| Abdominal Pain upper        |                   |                   |  |
| subjects affected / exposed | 10 / 110 (9.09%)  | 8 / 107 (7.48%)   |  |
| occurrences (all)           | 10                | 9                 |  |
| Constipation                |                   |                   |  |
| subjects affected / exposed | 22 / 110 (20.00%) | 29 / 107 (27.10%) |  |
| occurrences (all)           | 26                | 35                |  |
| Diarrhoea                   |                   |                   |  |
| subjects affected / exposed | 27 / 110 (24.55%) | 21 / 107 (19.63%) |  |
| occurrences (all)           | 35                | 31                |  |
| Nausea                      |                   |                   |  |



|   |                         |                         |  |
|---|-------------------------|-------------------------|--|
| subjects affected / exposed<br>occurrences (all)  | 54 / 110 (49.09%)<br>89 | 44 / 107 (41.12%)<br>76 |  |
| Stomatitis<br>subjects affected / exposed<br>occurrences (all)  | 9 / 110 (8.18%)<br>12   | 14 / 107 (13.08%)<br>15 |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)  | 32 / 110 (29.09%)<br>47 | 35 / 107 (32.71%)<br>68 |  |
| Skin and subcutaneous tissue disorders<br>Alopecia<br>subjects affected / exposed<br>occurrences (all)            | 13 / 110 (11.82%)<br>13 | 8 / 107 (7.48%)<br>8    |  |
| Erythema<br>subjects affected / exposed<br>occurrences (all)  | 6 / 110 (5.45%)<br>8    | 6 / 107 (5.61%)<br>6    |  |
| Rash<br>subjects affected / exposed<br>occurrences (all)  | 6 / 110 (5.45%)<br>9    | 5 / 107 (4.67%)<br>6    |  |
| Renal and urinary disorders<br>Renal Failure<br>subjects affected / exposed<br>occurrences (all)                  | 3 / 110 (2.73%)<br>4    | 8 / 107 (7.48%)<br>8    |  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 9 / 110 (8.18%)<br>11   | 8 / 107 (7.48%)<br>12   |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)   | 14 / 110 (12.73%)<br>15 | 12 / 107 (11.21%)<br>13 |  |
| Musculoskeletal pain<br>subjects affected / exposed<br>occurrences (all)  | 10 / 110 (9.09%)<br>10  | 4 / 107 (3.74%)<br>5    |  |
| Myalgia<br>subjects affected / exposed<br>occurrences (all)   | 7 / 110 (6.36%)<br>7    | 3 / 107 (2.80%)<br>4    |  |
| Pain in Extremity   |                         |                         |  |

|  |                         |                       |  |
|--|-------------------------|-----------------------|--|
| subjects affected / exposed<br>occurrences (all) | 16 / 110 (14.55%)<br>18 | 6 / 107 (5.61%)<br>10 |  |
| Infections and infestations                      |                         |                       |  |
| Bronchitis                                       |                         |                       |  |
| subjects affected / exposed                      | 10 / 110 (9.09%)        | 11 / 107 (10.28%)     |  |
| occurrences (all)                                | 11                      | 12                    |  |
| Respiratory tract infection                      |                         |                       |  |
| subjects affected / exposed                      | 6 / 110 (5.45%)         | 4 / 107 (3.74%)       |  |
| occurrences (all)                                | 7                       | 5                     |  |
| Metabolism and nutrition disorders               |                         |                       |  |
| Decreased appetite                               |                         |                       |  |
| subjects affected / exposed                      | 24 / 110 (21.82%)       | 27 / 107 (25.23%)     |  |
| occurrences (all)                                | 30                      | 32                    |  |
| Hypokalaemia                                     |                         |                       |  |
| subjects affected / exposed                      | 7 / 110 (6.36%)         | 13 / 107 (12.15%)     |  |
| occurrences (all)                                | 8                       | 16                    |  |
| Hyponatraemia                                    |                         |                       |  |
| subjects affected / exposed                      | 7 / 110 (6.36%)         | 6 / 107 (5.61%)       |  |
| occurrences (all)                                | 7                       | 6                     |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 26 April 2012    | Major changes included the following: <ul style="list-style-type: none"><li>• Inclusion criteria were modified for some laboratory parameters and additional laboratory parameters were added for routine monitoring (e.g. bilirubin)</li><li>• TOR was added as a secondary objective</li><li>• PS was added as a stratification factor for statistical analyses (as it is a stratification factor in the randomisation process)</li><li>• Changes were made to the sensitivity analyses and secondary objectives for the Phase III part of the study</li></ul> |
| 02 July 2013     | Major changes included the following: <ul style="list-style-type: none"><li>• An exploratory objective evaluating the response rate (i.e. proportion of patients with CR or PR) at tumour evaluation #2 was added</li><li>• The statistical methods were modified to allow for a preliminary analysis of the subgroup of patients with a high level of TrPAL, at the same time as the primary analysis was performed in the subgroup of patients with normal TrPAL</li></ul>   |
| 06 November 2013 | Major changes included the following: <ul style="list-style-type: none"><li>• Due to the increased time lag in the occurrence of the required number of PFS events in the subgroups of normal and high TrPAL patients necessary for the final analysis, implicating that final analysis in each subgroup could not be performed at the same time, time points for unblinding were revised and delayed for the high TrPAL subgroup until the final analysis results were available in this subgroup to avoid the introduction of possible biases.</li></ul>       |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date         | Interruption   | Restart date |
|--------------|--|--------------|
| 06 July 2015 | A decision was taken by the sponsor for business reasons to not proceed with Phase III part after the completion of Phase IIb. | -            |

Notes:

### Limitations and caveats

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

Due to the early termination of this study, this results posting is a complete record of the Phase IIb part of the study only. Phase III did not proceed and is therefore not included in any part.

Notes: