



## Clinical trial results:

### A Randomised Open-Label Phase II Study to Assess the Efficacy and Safety

### of AZD4547 Monotherapy versus Paclitaxel in Patients with Advanced Gastric Adenocarcinoma (including Adenocarcinoma of the Lower-Third of the Oesophagus or the Gastro-Oesophageal Junction) with FGFR2 Polysomy or Gene Amplification (Shine study)

#### Summary

|                          |                         |
|--------------------------|-------------------------|
| EudraCT number           | 2010-023377-19          |
| Trial protocol           | GB DE CZ ES BE IT HU BG |
| Global end of trial date | 27 June 2013            |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 04 November 2016 |
| First version publication date | 04 November 2016 |

#### Trial information

##### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | D2610C00004 |
|-----------------------|-------------|

##### Additional study identifiers

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

Notes:

##### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Astrazeneca   |
| Sponsor organisation address | Alderley Park, Cheshire, United Kingdom, SK10 4TG   |
| Public contact               | Prof Eric Van Cutsem, MD, PhD, University Hospital Gasthuisberg, eric.vancutsem@med.kuleuven.be |
| Scientific contact           | Donal Landers, Astra Zeneca, Donal.Landers@astrazeneca.com                                      |

Notes:

##### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 17 December 2013 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 27 June 2013     |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 27 June 2013     |
| Was the trial ended prematurely?                     | Yes              |

Notes:

## General information about the trial

Main objective of the trial:

Prompted by slow recruitment and concerns about the feasibility of completing enrolment in a realistic timeframe, AstraZeneca and the Safety Review Committee (SRC) for the study agreed that it would be appropriate to conduct an unscheduled analysis of the efficacy (based on average change in tumour size) and tolerability data.

The results of this unscheduled analysis did not show superiority of AZD4547 over paclitaxel in patients with advanced gastric cancer tumours that have FGFR2 amplification. Thus, it was concluded that the study was unlikely to meet its primary objective of demonstrating superiority of AZD4547 monotherapy over paclitaxel, based on PFS, and a decision was made to cease enrolment and close the study.

Protection of trial subjects:

An SRC was appointed to review all available safety data at approximately 2-month intervals.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 11 November 2011 |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Efficacy         |
| Long term follow-up duration                              | 12 Months        |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Korea, Republic of: 17 |
| Country: Number of subjects enrolled | United Kingdom: 15     |
| Country: Number of subjects enrolled | Czech Republic: 8      |
| Country: Number of subjects enrolled | Taiwan: 6              |
| Country: Number of subjects enrolled | Japan: 5               |
| Country: Number of subjects enrolled | Italy: 3               |
| Country: Number of subjects enrolled | Belgium: 1             |
| Country: Number of subjects enrolled | Germany: 1             |
| Country: Number of subjects enrolled | France: 1              |
| Country: Number of subjects enrolled | India: 1               |
| Country: Number of subjects enrolled | Spain: 13              |
| Worldwide total number of subjects   | 71                     |
| EEA total number of subjects         | 42                     |

Notes:

| <b>Subjects enrolled per age group</b>    |    |
|---|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 0  |
| Children (2-11 years)                     | 0  |
| Adolescents (12-17 years)                 | 0  |
| Adults (18-64 years)                      | 44 |
| From 65 to 84 years                       | 27 |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

This study was conducted in 11 countries. Enrolment started in November 2011 and last patient visit was in August 2013. In total, 960 patients were enrolled out of which 71 were randomised. A total of 67 patients received treatment, 40 of these patients received AZD4547 and 27 received Paclitaxel.

### Pre-assignment

Screening details:

Patients  $\geq 25$  years with locally advanced or metastatic gastric adenocarcinoma that had FGFR2 polysomy or FGFR2 gene amplification and whose disease had progressed during or after 1st line therapy. Patients whose disease had progressed within 6 months following adjuvant or neo-adjuvant therapy could be included at the discretion of the investigator

### Period 1

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

### Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| <b>Arm title</b>             | AZD4547 |

Arm description:

80mg BD 2 weeks on/1 week off

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | AZD4547      |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

80mg BD 2 weeks on/1 week off

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

Arm description:

80mg / m<sup>2</sup>

|  |   |
|--|---|
| Arm type                               | Active comparator                                     |
| Investigational medicinal product name | Paclitaxel  |
| Investigational medicinal product code |   |
| Other name                             |   |
| Pharmaceutical forms                   | Solution for injection/infusion in pre-filled syringe |
| Routes of administration               | Intravenous use                                       |

Dosage and administration details:

80mg / m<sup>2</sup>

| <b>Number of subjects in period 1</b> | AZD4547 | Paclitaxel |
|---------------------------------------|---------|------------|
| Started                               | 41      | 30         |
| Received treatment                    | 40      | 27         |
| Did not receive treatment             | 1       | 3          |
| Ongoing treatment at data cut-off     | 1       | 1          |
| Completed                             | 0       | 0          |
| Not completed                         | 41      | 30         |
| Adverse event, serious fatal          | 27      | 16         |
| Consent withdrawn by subject          | 1       | 1          |
| Death before treatment                | 1       | 2          |
| Lost to follow-up                     | 1       | -          |
| Did not receive treatment             | -       | 1          |
| Unclassified reason for not completed | 11      | 10         |

## Baseline characteristics

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | AZD4547 |
|-----------------------|---------|

Reporting group description:

80mg BD 2 weeks on/1 week off

|                       |            |
|-----------------------|------------|
| Reporting group title | Paclitaxel |
|-----------------------|------------|

Reporting group description:

80mg / m<sup>2</sup>

| Reporting group values | AZD4547 | Paclitaxel | Total |
|------------------------|---------|------------|-------|
| Number of subjects     | 41      | 30         | 71    |
| Age categorical        |         |            |       |
| Units: Subjects        |         |            |       |
| Adults (18-64 years)   | 27      | 17         | 44    |
| From 65-84 years       | 14      | 13         | 27    |
| Age Continuous         |         |            |       |
| Units: years           |         |            |       |
| arithmetic mean        | 60.6    | 61.9       |       |
| standard deviation     | ± 11.38 | ± 10.65    | -     |
| Gender, Male/Female    |         |            |       |
| Gender                 |         |            |       |
| Units: Participants    |         |            |       |
| Female                 | 12      | 8          | 20    |
| Male                   | 29      | 22         | 51    |
| Age, Customized        |         |            |       |
| Age by category        |         |            |       |
| Units: Subjects        |         |            |       |
| <50 years              | 7       | 4          | 11    |
| >=50 - < 65 years      | 20      | 13         | 33    |
| >= 65 years            | 14      | 13         | 27    |

## End points

### End points reporting groups

|                               |            |
|-------------------------------|------------|
| Reporting group title         | AZD4547    |
| Reporting group description:  |            |
| 80mg BD 2 weeks on/1 week off |            |
| Reporting group title         | Paclitaxel |
| Reporting group description:  |            |
| 80mg / m**2                   |            |

### Primary: Progression Free Survival

|  |                           |
|--|---------------------------|
| End point title  | Progression Free Survival |
| End point description:   |                           |
| PFS is the time from randomisation until the date of objective disease progression as defined by Response Evaluation Criteria In Solid Tumours (RECIST version 1.1) or death (by any cause in the absence of progression). |                           |
| End point type   | Primary                   |
| End point timeframe:   |                           |
| Week 8 (±1 week) and then every 8 weeks (±1 week)  |                           |

| End point values            | AZD4547         | Paclitaxel      |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 38              | 30              |  |  |
| Units: Patients             | 36              | 26              |  |  |

### Statistical analyses

|   |   |
|---|---|
| Statistical analysis title  | Progression free survival (Full analysis set) |
| Statistical analysis description:   |   |
| The analysis was performed using a Cox proportional hazards model with factors for treatment and FGFR2 FISH score (4/5 versus 6). |   |
| Comparison groups   | AZD4547 v Paclitaxel                          |
| Number of subjects included in analysis   | 68  |
| Analysis specification  | Pre-specified                                 |
| Analysis type   | other <sup>[1]</sup>                          |
| P-value   | < 0.9581 <sup>[2]</sup>                       |
| Method  | Regression, Cox                               |
| Parameter estimate  | Hazard ratio (HR)                             |
| Point estimate  | 1.57  |
| Confidence interval   |   |
| level   | Other: 80 %                                   |
| sides   | 2-sided                                       |
| lower limit   | 1.12  |
| upper limit   | 2.21  |

Notes:

[1] - The 3 patients from the Full analysis set with an FGFR FISH score of 2 or 3 were not included in the analysis. A hazard ratio < 1 favours AZD4547 80mg BD 2 weeks on/1 week off. CI calculated using Profile Likelihood.

[2] - 1-sided

## Secondary: Overall Survival

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

End point description:

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

End point timeframe:

Week 8 ( $\pm 1$  week) and then every 8 weeks ( $\pm 1$  week)

| End point values            | AZD4547         | Paclitaxel      |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 38              | 30              |  |  |
| Units: Patients             | 27              | 18              |  |  |

## Statistical analyses

|                            |                  |
|----------------------------|------------------|
| Statistical analysis title | Overall Survival |
|----------------------------|------------------|

|                   |                      |
|-------------------|----------------------|
| Comparison groups | AZD4547 v Paclitaxel |
|-------------------|----------------------|

|   |    |
|---|----|
| Number of subjects included in analysis | 68 |
|---|----|

|                        |               |
|------------------------|---------------|
| Analysis specification | Pre-specified |
|------------------------|---------------|

|               |       |
|---------------|-------|
| Analysis type | other |
|---------------|-------|

|         |                         |
|---------|-------------------------|
| P-value | < 0.8156 <sup>[3]</sup> |
|---------|-------------------------|

|        |                 |
|--------|-----------------|
| Method | Regression, Cox |
|--------|-----------------|

|                    |                   |
|--------------------|-------------------|
| Parameter estimate | Hazard ratio (HR) |
|--------------------|-------------------|

|                |      |
|----------------|------|
| Point estimate | 1.31 |
|----------------|------|

Confidence interval

|       |             |
|-------|-------------|
| level | Other: 80 % |
|-------|-------------|

|       |         |
|-------|---------|
| sides | 2-sided |
|-------|---------|

|             |      |
|-------------|------|
| lower limit | 0.89 |
|-------------|------|

|             |      |
|-------------|------|
| upper limit | 1.95 |
|-------------|------|

Notes:

[3] - 1-sided

## Secondary: Objective Response Rate

|                 |                         |
|-----------------|-------------------------|
| End point title | Objective Response Rate |
|-----------------|-------------------------|

End point description:

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

End point timeframe:

Week 8 ( $\pm 1$  week) and then every 8 weeks ( $\pm 1$  week)

|                             |                 |                 |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| <b>End point values</b>     | AZD4547         | Paclitaxel      |  |  |
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 38              | 30              |  |  |
| Units: Patients             | 1               | 7               |  |  |

## Statistical analyses

|   |                         |
|---|-------------------------|
| <b>Statistical analysis title</b>       | Objective response Rate |
| Comparison groups                       | AZD4547 v Paclitaxel    |
| Number of subjects included in analysis | 68                      |
| Analysis specification                  | Pre-specified           |
| Analysis type                           |                         |
| P-value                                 | < 0.997 <sup>[4]</sup>  |
| Method                                  | Regression, Logistic    |
| Parameter estimate                      | Hazard ratio (HR)       |
| Point estimate                          | 0.09                    |
| Confidence interval                     |                         |
| level                                   | Other: 80 %             |
| sides                                   | 2-sided                 |
| lower limit                             | 0.02                    |
| upper limit                             | 0.35                    |

Notes:

[4] - 1-sided

## Secondary: Change in tumour size at 8 weeks

|                        |                                  |
|------------------------|----------------------------------|
| End point title        | Change in tumour size at 8 weeks |
| End point description: |                                  |
| End point type         | Secondary                        |
| End point timeframe:   |                                  |
| Week 8 (±1 week)       |                                  |

|   |                 |                 |  |  |
|---|-----------------|-----------------|--|--|
| <b>End point values</b>                             | AZD4547         | Paclitaxel      |  |  |
| Subject group type                                  | Reporting group | Reporting group |  |  |
| Number of subjects analysed                         | 34              | 26              |  |  |
| Units: patients                                     |                 |                 |  |  |
| geometric mean (geometric coefficient of variation) | 27.5 (± 26.9)   | -7 (± 37.3)     |  |  |

## Statistical analyses

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Change in tumour size at 8 wks |
| Comparison groups                       | AZD4547 v Paclitaxel           |
| Number of subjects included in analysis | 60                             |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | other                          |
| P-value                                 | < 0.99 [5]                     |
| Method                                  | ANCOVA                         |
| Parameter estimate                      | Hazard ratio (HR)              |
| Point estimate                          | 39.44                          |
| Confidence interval                     |                                |
| level                                   | Other: 80 %                    |
| sides                                   | 2-sided                        |
| lower limit                             | 25.18                          |
| upper limit                             | 55.33                          |

Notes:

[5] - 1-sided

## Secondary: Mean change in tumour size

|                        |                            |
|------------------------|----------------------------|
| End point title        | Mean change in tumour size |
| End point description: |                            |
| End point type         | Secondary                  |
| End point timeframe:   |                            |
| Week 8 (±1 week)       |                            |

|                             |                 |                 |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| <b>End point values</b>     | AZD4547         | Paclitaxel      |  |  |
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 36              | 26              |  |  |
| Units: Patients             |                 |                 |  |  |
| number (not applicable)     | 28.4            | -1.1            |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of patients without progressive disease at 8 weeks

|                        |   |
|------------------------|---|
| End point title        | Percentage of patients without progressive disease at 8 weeks |
| End point description: |   |
| End point type         | Secondary   |
| End point timeframe:   |   |
| Week 8 (±1 week)       |   |

|                             |                 |                 |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| <b>End point values</b>     | AZD4547         | Paclitaxel      |  |  |
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 41              | 30              |  |  |
| Units: Patients             |                 |                 |  |  |
| number (not applicable)     |                 |                 |  |  |
| Number of patients          | 10              | 16              |  |  |
| Percentage of patients      | 24.4            | 53.3            |  |  |

### Statistical analyses

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

AEs will be collected throughout the study, from randomisation until the end of the follow-up period. The follow-up period is defined as 28 days after study treatment (AZD4547 or paclitaxel) is discontinued.

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 16     |

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | Paclitaxel |
|-----------------------|------------|

Reporting group description:

80mg / m<sup>2</sup>

|                       |         |
|-----------------------|---------|
| Reporting group title | AZD4547 |
|-----------------------|---------|

Reporting group description:

80mg BD 2 weeks on/1 week off

| Serious adverse events                            | Paclitaxel      | AZD4547         |  |
|---|-----------------|-----------------|--|
| Total subjects affected by serious adverse events |                 |                 |  |
| subjects affected / exposed                       | 6 / 27 (22.22%) | 8 / 40 (20.00%) |  |
| number of deaths (all causes)                     | 16              | 27              |  |
| number of deaths resulting from adverse events    | 0               | 0               |  |
| Investigations                                    |                 |                 |  |
| Blood bilirubin indirect increased                |                 |                 |  |
| subjects affected / exposed                       | 0 / 27 (0.00%)  | 1 / 40 (2.50%)  |  |
| occurrences causally related to treatment / all   | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0           |  |
| Transaminases increased                           |                 |                 |  |
| alternative dictionary used: MedDRA 16            |                 |                 |  |
| subjects affected / exposed                       | 0 / 27 (0.00%)  | 1 / 40 (2.50%)  |  |
| occurrences causally related to treatment / all   | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0           |  |
| Vascular disorders                                |                 |                 |  |
| Arterial disorder                                 |                 |                 |  |
| subjects affected / exposed                       | 0 / 27 (0.00%)  | 1 / 40 (2.50%)  |  |
| occurrences causally related to treatment / all   | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0           |  |

|  |                |                |  |
|--|----------------|----------------|--|
| Blood and lymphatic system disorders                 |                |                |  |
| Anaemia  |                |                |  |
| subjects affected / exposed                          | 0 / 27 (0.00%) | 1 / 40 (2.50%) |  |
| 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 |                |                |  |
| Asthenia   |                |                |  |
| subjects affected / exposed                          | 1 / 27 (3.70%) | 0 / 40 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Gastrointestinal disorders                           |                |                |  |
| Dyspepsia  |                |                |  |
| subjects affected / exposed                          | 0 / 27 (0.00%) | 1 / 40 (2.50%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Intestinal haemorrhage                               |                |                |  |
| alternative dictionary used: MedDRA 16.0             |                |                |  |
| subjects affected / exposed                          | 0 / 27 (0.00%) | 1 / 40 (2.50%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Dyphagia   |                |                |  |
| subjects affected / exposed                          | 1 / 27 (3.70%) | 0 / 40 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Obstruction gastric                                  |                |                |  |
| alternative dictionary used: MedDRA 16.0             |                |                |  |
| subjects affected / exposed                          | 0 / 27 (0.00%) | 1 / 40 (2.50%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Stomatitis   |                |                |  |
| alternative dictionary used: MedDRA 16.0             |                |                |  |
| subjects affected / exposed                          | 0 / 27 (0.00%) | 1 / 40 (2.50%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |

|   |                |                |  |
|---|----------------|----------------|--|
| Vomiting alone                                  |                |                |  |
| subjects affected / exposed                     | 2 / 27 (7.41%) | 1 / 40 (2.50%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Respiratory, thoracic and mediastinal disorders |                |                |  |
| Pulmonary embolism                              |                |                |  |
| subjects affected / exposed                     | 1 / 27 (3.70%) | 0 / 40 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Hepatobiliary disorders                         |                |                |  |
| Obstruction of bile duct                        |                |                |  |
| alternative dictionary used: MedDRA 16          |                |                |  |
| subjects affected / exposed                     | 0 / 27 (0.00%) | 1 / 40 (2.50%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Infections and infestations                     |                |                |  |
| Biliary tract infection                         |                |                |  |
| subjects affected / exposed                     | 1 / 27 (3.70%) | 0 / 40 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pneumonia viral                                 |                |                |  |
| subjects affected / exposed                     | 0 / 27 (0.00%) | 1 / 40 (2.50%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Lower respiratory tract infection               |                |                |  |
| subjects affected / exposed                     | 1 / 27 (3.70%) | 0 / 40 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Urinary tract infection                         |                |                |  |
| subjects affected / exposed                     | 0 / 27 (0.00%) | 1 / 40 (2.50%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| 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>  | Paclitaxel           | AZD4547                |  |
|--|----------------------|------------------------|--|
| Total subjects affected by non-serious adverse events  |                      |                        |  |
| subjects affected / exposed  | 26 / 27 (96.30%)     | 39 / 40 (97.50%)       |  |
| General disorders and administration site conditions   |                      |                        |  |
| Asthenia<br>alternative dictionary used: MedDRA 16.0<br>subjects affected / exposed<br>occurrences (all) | 5 / 27 (18.52%)<br>5 | 11 / 40 (27.50%)<br>11 |  |
| fatigue<br>subjects affected / exposed<br>occurrences (all)  | 8 / 27 (29.63%)<br>8 | 6 / 40 (15.00%)<br>6   |  |
| Oedema of extremities<br>subjects affected / exposed<br>occurrences (all)                                | 2 / 27 (7.41%)<br>2  | 4 / 40 (10.00%)<br>4   |  |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)  | 2 / 27 (7.41%)<br>2  | 4 / 40 (10.00%)<br>4   |  |
| Respiratory, thoracic and mediastinal disorders  |                      |                        |  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)   | 1 / 27 (3.70%)<br>1  | 3 / 40 (7.50%)<br>3    |  |
| Epistaxis<br>subjects affected / exposed<br>occurrences (all)  | 1 / 27 (3.70%)<br>1  | 3 / 40 (7.50%)<br>3    |  |
| Dysphonia<br>subjects affected / exposed<br>occurrences (all)  | 1 / 27 (3.70%)<br>1  | 2 / 40 (5.00%)<br>2    |  |
| productiveCough<br>subjects affected / exposed<br>occurrences (all)                                      | 2 / 27 (7.41%)<br>2  | 0 / 40 (0.00%)<br>0    |  |
| Psychiatric disorders  |                      |                        |  |
| Insomnia   |                      |                        |  |

|  |  |                      |  |
|--|--|----------------------|--|
| subjects affected / exposed<br>occurrences (all) | 3 / 27 (11.11%)<br>3   | 2 / 40 (5.00%)<br>2  |  |
| Peripheral neuropathy hereditary                 | Additional description: Neuropathy periheral                 |                      |  |
| subjects affected / exposed<br>occurrences (all) | 4 / 27 (14.81%)<br>4   | 1 / 40 (2.50%)<br>1  |  |
| Investigations                                   |  |                      |  |
| aspartate  | Additional description: Aspartate aminotransferase increased |                      |  |
| subjects affected / exposed<br>occurrences (all) | 5 / 27 (18.52%)<br>0   | 7 / 40 (17.50%)<br>7 |  |
| Blood alkaline phosphatase<br>increased          |  |                      |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 27 (3.70%)<br>1  | 4 / 40 (10.00%)<br>4 |  |
| Bilirubin value increased                        |  |                      |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 27 (0.00%)<br>0  | 5 / 40 (12.50%)<br>5 |  |
| Alanine amonitranferase increased                | Additional description: Alanine amonitranferase increased    |                      |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 27 (3.70%)<br>1  | 4 / 40 (10.00%)<br>4 |  |
| Blood phosphorus increase                        |  |                      |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 27 (0.00%)<br>0  | 3 / 40 (7.50%)<br>3  |  |
| Nervous system disorders                         |  |                      |  |
| Dysgeusia  |  |                      |  |
| subjects affected / exposed<br>occurrences (all) | 4 / 27 (14.81%)<br>4   | 6 / 40 (15.00%)<br>6 |  |
| Headache   |  |                      |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 27 (3.70%)<br>1  | 4 / 40 (10.00%)<br>4 |  |
| Dizziness  |  |                      |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 27 (3.70%)<br>1  | 3 / 40 (7.50%)<br>3  |  |
| Lethargy   |  |                      |  |
| subjects affected / exposed<br>occurrences (all) | 2 / 27 (7.41%)<br>2  | 1 / 40 (2.50%)<br>1  |  |
| Peripheral sensory neuropathy                    | Additional description: Peripheral sensory neuropathy        |                      |  |

|   |  |                     |  |
|---|--|---------------------|--|
| subjects affected / exposed<br>occurrences (all)    | 3 / 27 (11.11%)<br>3                   | 0 / 40 (0.00%)<br>0 |  |
| Blood and lymphatic system disorders                |  |                     |  |
| Anaemia   |  |                     |  |
| subjects affected / exposed                         | 6 / 27 (22.22%)                        | 7 / 40 (17.50%)     |  |
| occurrences (all)                                   | 6                                      | 7                   |  |
| Neutropenia   |  |                     |  |
| subjects affected / exposed                         | 9 / 27 (33.33%)                        | 2 / 40 (5.00%)      |  |
| occurrences (all)                                   | 9                                      | 2                   |  |
| Eye disorders                                       |  |                     |  |
| Detachment of macular retinal<br>pigment epithelium |  |                     |  |
| alternative dictionary used:<br>MedDRA 16.0         |  |                     |  |
| subjects affected / exposed                         | 0 / 27 (0.00%)                         | 6 / 40 (15.00%)     |  |
| occurrences (all)                                   | 0                                      | 6                   |  |
| Dryness of eyes                                     |  |                     |  |
| subjects affected / exposed                         | 0 / 27 (0.00%)                         | 4 / 40 (10.00%)     |  |
| occurrences (all)                                   | 0                                      | 4                   |  |
| Gastrointestinal disorders                          |  |                     |  |
| Nausea  |  |                     |  |
| subjects affected / exposed                         | 6 / 27 (22.22%)                        | 10 / 40 (25.00%)    |  |
| occurrences (all)                                   | 6                                      | 10                  |  |
| Constipation  |  |                     |  |
| subjects affected / exposed                         | 5 / 27 (18.52%)                        | 10 / 40 (25.00%)    |  |
| occurrences (all)                                   | 5                                      | 10                  |  |
| Abdominal pain                                      | Additional description: Abdominal pain |                     |  |
| subjects affected / exposed                         | 5 / 27 (18.52%)                        | 9 / 40 (22.50%)     |  |
| occurrences (all)                                   | 5                                      | 9                   |  |
| Vomiting alone                                      |  |                     |  |
| subjects affected / exposed                         | 5 / 27 (18.52%)                        | 8 / 40 (20.00%)     |  |
| occurrences (all)                                   | 5                                      | 8                   |  |
| Stomatitis ulcerative                               | Additional description: Stomatitis     |                     |  |
| subjects affected / exposed                         | 2 / 27 (7.41%)                         | 10 / 40 (25.00%)    |  |
| occurrences (all)                                   | 2                                      | 10                  |  |
| Abdominal pain upper                                |  |                     |  |
| subjects affected / exposed                         | 0 / 27 (0.00%)                         | 9 / 40 (22.50%)     |  |
| occurrences (all)                                   | 0                                      | 9                   |  |

|   |   |                 |  |
|---|---|-----------------|--|
| Hepatobiliary disorders                         |   |                 |  |
| Diarrhoea                                       |   |                 |  |
| subjects affected / exposed                     | 6 / 27 (22.22%)                             | 6 / 40 (15.00%) |  |
| occurrences (all)                               | 6   | 6               |  |
| Skin and subcutaneous tissue disorders          |   |                 |  |
| Alopecia mucinosa                               | Additional description: Alopecia            |                 |  |
| subjects affected / exposed                     | 13 / 27 (48.15%)                            | 2 / 40 (5.00%)  |  |
| occurrences (all)                               | 13  | 2               |  |
| Dry skin  |   |                 |  |
| subjects affected / exposed                     | 1 / 27 (3.70%)                              | 3 / 40 (7.50%)  |  |
| occurrences (all)                               | 1   | 3               |  |
| Onychomadesis                                   | Additional description: Onychomadesis       |                 |  |
| subjects affected / exposed                     | 0 / 27 (0.00%)                              | 3 / 40 (7.50%)  |  |
| occurrences (all)                               | 0   | 3               |  |
| Nail discolouration                             | Additional description: Nail discolouration |                 |  |
| subjects affected / exposed                     | 1 / 27 (3.70%)                              | 2 / 40 (5.00%)  |  |
| occurrences (all)                               | 1   | 2               |  |
| Pruritus  | Additional description: Pruritus            |                 |  |
| subjects affected / exposed                     | 1 / 27 (3.70%)                              | 2 / 40 (5.00%)  |  |
| occurrences (all)                               | 1   | 2               |  |
| onycholysis                                     | Additional description: onycholysis         |                 |  |
| subjects affected / exposed                     | 0 / 27 (0.00%)                              | 2 / 40 (5.00%)  |  |
| occurrences (all)                               | 0   | 2               |  |
| Musculoskeletal and connective tissue disorders |   |                 |  |
| Back pain                                       |   |                 |  |
| subjects affected / exposed                     | 6 / 27 (22.22%)                             | 1 / 40 (2.50%)  |  |
| occurrences (all)                               | 6   | 1               |  |
| Arthralgia                                      |   |                 |  |
| subjects affected / exposed                     | 0 / 27 (0.00%)                              | 3 / 40 (7.50%)  |  |
| occurrences (all)                               | 0   | 3               |  |
| Myalgia   | Additional description: Myalgia             |                 |  |
| subjects affected / exposed                     | 3 / 27 (11.11%)                             | 0 / 40 (0.00%)  |  |
| occurrences (all)                               | 3   | 0               |  |
| Infections and infestations                     |   |                 |  |
| Urinary tract infectio                          |   |                 |  |

|  |   |                        |  |
|--|---|------------------------|--|
| subjects affected / exposed<br>occurrences (all) | 2 / 27 (7.41%)<br>2                                       | 2 / 40 (5.00%)<br>2    |  |
| Lower respiratory tract infection                | Additional description: Lower respiratory tract infection |                        |  |
| subjects affected / exposed<br>occurrences (all) | 3 / 27 (11.11%)<br>3                                      | 0 / 40 (0.00%)<br>0    |  |
| Metabolism and nutrition disorders               |   |                        |  |
| Decreased appetite                               |   |                        |  |
| subjects affected / exposed<br>occurrences (all) | 8 / 27 (29.63%)<br>8                                      | 16 / 40 (40.00%)<br>16 |  |
| Hyperkalaemia                                    | Additional description: Hyperkalaemia                     |                        |  |
| alternative dictionary used:<br>MedDRA 16.0      |   |                        |  |
| subjects affected / exposed<br>occurrences (all) | 2 / 27 (7.41%)<br>2                                       | 2 / 40 (5.00%)<br>2    |  |
| Hypokalaemia                                     | Additional description: Hypokalaemia                      |                        |  |
| subjects affected / exposed<br>occurrences (all) | 2 / 27 (7.41%)<br>2                                       | 1 / 40 (2.50%)<br>1    |  |
| Dry mouth  |   |                        |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 27 (0.00%)<br>0                                       | 9 / 40 (22.50%)<br>9   |  |
| Hyperphosphataemia                               | Additional description: Hyperphosphataemia                |                        |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 27 (0.00%)<br>0                                       | 3 / 40 (7.50%)<br>3    |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date        | Amendment   |
|-------------|---|
| 30 May 2012 | Patients with gastric adenocarcinoma of lower-third of the oesophagus or the Gastro-oesophageal junction were to be included in the study. The phase of the study was modified to Phase II due to increased sample size. Clarification of patient population and re-labelling of the study as Phase II to reflect the increase in study size. Sample size of randomised patients was increased to 160 patients. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date         | Interruption  | Restart date |
|--------------|---|--------------|
| 27 June 2013 | It was concluded that the study was unlikely to meet its primary objective of demonstrating superiority of AZD4547 monotherapy over paclitaxel, based on PFS, and a decision was made to cease enrolment and close the study. | -            |

Notes:

### Limitations and caveats

None reported