



## Clinical trial results:

### A Phase II, Multi-centre, Open-Label, Parallel Group, Randomised Study To Compare the Efficacy of selumetinib (AZD6244, ARRY-142886). vs Temozolomide in Patients with Unresectable AJCC Stage 3 or 4 Malignant Melanoma

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2006-001456-12 |
| Trial protocol           | GB AT DK FR    |
| Global end of trial date | 24 July 2013   |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 06 July 2016 |
| First version publication date | 06 July 2016 |

#### Trial information

##### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | D1532C00003 |
|-----------------------|-------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00338130 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |                                                                                            |
|------------------------------|--------------------------------------------------------------------------------------------|
| Sponsor organisation name    | AstraZeneca                                                                                |
| Sponsor organisation address | Alderley Park, Macclesfield, United Kingdom, SK10 4TG                                      |
| Public contact               | AstraZeneca, AstraZeneca, AZTrial_results_posting@AstraZeneca.com                          |
| Scientific contact           | Selumetinib Global Clinical Lead, MD, AstraZeneca, AZTrial_results_posting@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:

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**Results analysis stage**

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|                                                      |                   |
|------------------------------------------------------|-------------------|
| Analysis stage                                       | Final             |
| Date of interim/final analysis                       | 20 June 2015      |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 28 September 2007 |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 24 July 2013      |
| Was the trial ended prematurely?                     | No                |

Notes:

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**General information about the trial**

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Main objective of the trial:

The primary objective of this study was to compare the efficacy of selumetinib (AZD6244, ARRY-142886). versus TMZ in patients with unresectable AJCC Stage 3 or 4 malignant melanoma by evaluation of Progression Free Survival (PFS)

Protection of trial subjects:

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents

Background therapy: -

Evidence for comparator: -

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 26 July 2006     |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Safety, Efficacy |
| Long term follow-up duration                              | 2 Years          |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Argentina: 8       |
| Country: Number of subjects enrolled | Austria: 5         |
| Country: Number of subjects enrolled | Australia: 20      |
| Country: Number of subjects enrolled | Brazil: 14         |
| Country: Number of subjects enrolled | Canada: 8          |
| Country: Number of subjects enrolled | Switzerland: 28    |
| Country: Number of subjects enrolled | Denmark: 15        |
| Country: Number of subjects enrolled | France: 22         |
| Country: Number of subjects enrolled | United Kingdom: 26 |
| Country: Number of subjects enrolled | United States: 54  |
| Worldwide total number of subjects   | 200                |
| EEA total number of subjects         | 68                 |

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)                      | 142 |
| From 65 to 84 years                       | 58  |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Female or male patients aged 18 years and over, with unresectable AJCC Stage 3 or 4 malignant melanoma. Patients were to have at least 1 measurable site of disease as defined by RECIST, World Health Organisation (WHO) performance status 0 to 2.

### Pre-assignment

Screening details:

Two hundred and thirty nine patients were enrolled, of whom 200 were randomised. Of the 39 patients who failed screening and were not randomised, the majority (27) failed inclusion/exclusion criteria.

### 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>                       | AZD6244             |
| Arm description: -                     |                     |
| Arm type                               | Experimental        |
| Investigational medicinal product name | AZD6244/Selumetinib |
| Investigational medicinal product code |                     |
| Other name                             |                     |
| Pharmaceutical forms                   | Oral solution       |
| Routes of administration               | Oral use            |

Dosage and administration details:

AZD6244 100mg twice daily

|                                        |                   |
|----------------------------------------|-------------------|
| <b>Arm title</b>                       | TMZ_              |
| Arm description: -                     |                   |
| Arm type                               | Active comparator |
| Investigational medicinal product name | Temozolomide      |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Tablet            |
| Routes of administration               | Oral use          |

Dosage and administration details:

TMZ 200mg/m<sup>2</sup> per day for 5 days every 28 days

| Number of subjects in period 1 | AZD6244 | TMZ_ |
|--------------------------------|---------|------|
| Started                        | 104     | 96   |
| Received treatment             | 99      | 95   |
| Completed                      | 3       | 3    |
| Not completed                  | 101     | 93   |
| Clinical progression           | -       | 2    |

|                                                    |    |    |
|----------------------------------------------------|----|----|
| Physician decision                                 | 1  | 3  |
| Symptomatic deterioration                          | 1  | -  |
| Adverse event, non-fatal                           | 10 | 2  |
| Eligibility criteria not fulfilled                 | -  | 1  |
| Undergo resection & follow-up with other treatment | 1  | -  |
| Did not receive treatment                          | 5  | 1  |
| Patients were given maximum 6 cycles               | -  | 3  |
| Disease Progression                                | 78 | 81 |
| Not willing to continue study treatment            | 5  | -  |

## Baseline characteristics

### Reporting groups

|                                |         |
|--------------------------------|---------|
| Reporting group title          | AZD6244 |
| Reporting group description: - |         |
| Reporting group title          | TMZ_    |
| Reporting group description: - |         |

| Reporting group values                       | AZD6244 | TMZ_   | Total |
|----------------------------------------------|---------|--------|-------|
| Number of subjects                           | 104     | 96     | 200   |
| Age Categorical                              |         |        |       |
| Min                                          |         |        |       |
| Units: Subjects                              |         |        |       |
| From 18 - 64 years                           | 74      | 68     | 142   |
| From 65 - 84 years                           | 30      | 28     | 58    |
| Age Continuous                               |         |        |       |
| Age Continuous                               |         |        |       |
| Units: years                                 |         |        |       |
| arithmetic mean                              | 57.1    | 57     |       |
| standard deviation                           | ± 14    | ± 13.4 | -     |
| Gender Categorical                           |         |        |       |
| Units: Subjects                              |         |        |       |
| Female                                       | 49      | 31     | 80    |
| Male                                         | 55      | 65     | 120   |
| World Health Organisation Performance Status |         |        |       |
| WHO Performance Status assessed at baseline  |         |        |       |
| Units: Subjects                              |         |        |       |
| 0 (Normal activity)                          | 67      | 71     | 138   |
| 1 (Restricted activity)                      | 34      | 23     | 57    |
| 2 (In bed <= 50% of the time)                | 1       | 2      | 3     |
| Performance Status unknown                   | 2       | 0      | 2     |
| American Joint committee on Cancer Staging   |         |        |       |
| AJCC assessed at baseline                    |         |        |       |
| Units: Subjects                              |         |        |       |
| Stage 3                                      | 3       | 3      | 6     |
| Stage 4                                      | 99      | 92     | 191   |
| AJCC stage unknown                           | 2       | 1      | 3     |
| Lactate dehydrogenase level at baseline      |         |        |       |
| Lactate dehydrogenase level at baseline      |         |        |       |
| Units: Subjects                              |         |        |       |
| <2 x upper limit of normal                   | 79      | 79     | 158   |
| >= 2 x upper limit normal                    | 17      | 15     | 32    |
| unknown                                      | 8       | 2      | 10    |
| Primary tumour type                          |         |        |       |
| Primary tumour type                          |         |        |       |
| Units: Subjects                              |         |        |       |
| Uveal                                        | 7       | 13     | 20    |

|                         |    |    |     |
|-------------------------|----|----|-----|
| Mucosal                 | 6  | 0  | 6   |
| Cutaneous               | 75 | 72 | 147 |
| Unknown primary tumour  | 16 | 11 | 27  |
| Mutation Status         |    |    |     |
| Units: Subjects         |    |    |     |
| BRAF positive           | 45 | 28 | 73  |
| NRAS positive           | 10 | 18 | 28  |
| Wild-type for both      | 29 | 28 | 57  |
| Mutation status unknown | 20 | 22 | 42  |

### Subject analysis sets

|                                                                     |                    |
|---------------------------------------------------------------------|--------------------|
| Subject analysis set title                                          | AZD6244            |
| Subject analysis set type                                           | Intention-to-treat |
| Subject analysis set description:<br>Patients randomised to AZD6244 |                    |
| Subject analysis set title                                          | TMZ                |
| Subject analysis set type                                           | Intention-to-treat |
| Subject analysis set description:<br>Patients randomised to TMZ     |                    |

| Reporting group values                       | AZD6244 | TMZ    |  |
|----------------------------------------------|---------|--------|--|
| Number of subjects                           | 104     | 96     |  |
| Age Categorical                              |         |        |  |
| Min                                          |         |        |  |
| Units: Subjects                              |         |        |  |
| From 18 - 64 years                           | 74      | 68     |  |
| From 65 - 84 years                           | 30      | 28     |  |
| Age Continuous                               |         |        |  |
| Age Continuous                               |         |        |  |
| Units: years                                 |         |        |  |
| arithmetic mean                              | 57.1    | 57     |  |
| standard deviation                           | ± 14    | ± 13.4 |  |
| Gender Categorical                           |         |        |  |
| Units: Subjects                              |         |        |  |
| Female                                       | 49      | 31     |  |
| Male                                         | 55      | 65     |  |
| World Health Organisation Performance Status |         |        |  |
| WHO Performance Status assessed at baseline  |         |        |  |
| Units: Subjects                              |         |        |  |
| 0 (Normal activity)                          | 67      | 71     |  |
| 1 (Restricted activity)                      | 34      | 23     |  |
| 2 (In bed <= 50% of the time)                | 1       | 2      |  |
| Performance Status unknown                   | 2       | 0      |  |
| American Joint committee on Cancer Staging   |         |        |  |
| AJCC assessed at baseline                    |         |        |  |
| Units: Subjects                              |         |        |  |
| Stage 3                                      | 3       | 3      |  |
| Stage 4                                      | 99      | 92     |  |
| AJCC stage unknown                           | 2       | 1      |  |

|                                         |    |    |  |
|-----------------------------------------|----|----|--|
| Lactate dehydrogenase level at baseline |    |    |  |
| Lactate dehydrogenase level at baseline |    |    |  |
| Units: Subjects                         |    |    |  |
| <2 x upper limit of normal              | 79 | 79 |  |
| >/= 2 x upper limit normal              | 17 | 15 |  |
| unknown                                 | 8  | 2  |  |
| Primary tumour type                     |    |    |  |
| Primary tumour type                     |    |    |  |
| Units: Subjects                         |    |    |  |
| Uveal                                   | 7  | 13 |  |
| Mucosal                                 | 6  | 0  |  |
| Cutaneous                               | 75 | 72 |  |
| Unknown primary tumour                  | 16 | 11 |  |
| Mutation Status                         |    |    |  |
| Units: Subjects                         |    |    |  |
| BRAF positive                           | 45 | 28 |  |
| NRAS positive                           | 10 | 18 |  |
| Wild-type for both                      | 29 | 28 |  |
| Mutation status unknown                 | 20 | 22 |  |



## End points

### End points reporting groups

|                                   |                    |
|-----------------------------------|--------------------|
| Reporting group title             | AZD6244            |
| Reporting group description: -    |                    |
| Reporting group title             | TMZ_               |
| Reporting group description: -    |                    |
| Subject analysis set title        | AZD6244            |
| Subject analysis set type         | Intention-to-treat |
| Subject analysis set description: |                    |
| Patients randomised to AZD6244    |                    |
| Subject analysis set title        | TMZ                |
| Subject analysis set type         | Intention-to-treat |
| Subject analysis set description: |                    |
| Patients randomised to TMZ        |                    |

### Primary: PFS

|                                                                                                               |         |
|---------------------------------------------------------------------------------------------------------------|---------|
| End point title                                                                                               | PFS     |
| End point description:                                                                                        |         |
| End point type                                                                                                | Primary |
| End point timeframe:                                                                                          |         |
| Assessment by RECIST criteria conducted at baseline, week 6, week 12 and then every 8 weeks until progression |         |

| End point values            | AZD6244         | TMZ_            |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 104             | 96              |  |  |
| Units: days                 |                 |                 |  |  |
| median (not applicable)     | 78 (± 0)        | 80 (± 0)        |  |  |

### Statistical analyses

|                                                          |                               |
|----------------------------------------------------------|-------------------------------|
| Statistical analysis title                               | PFS in the Overall Population |
| Statistical analysis description:                        |                               |
| PFS was analysed using a Cox Proportional Hazards model. |                               |
| Comparison groups                                        | AZD6244 v TMZ_                |
| Number of subjects included in analysis                  | 200                           |
| Analysis specification                                   | Pre-specified                 |
| Analysis type                                            | superiority <sup>[1]</sup>    |
| P-value                                                  | = 0.65 <sup>[2]</sup>         |
| Method                                                   | Regression, Cox               |
| Parameter estimate                                       | Hazard ratio (HR)             |
| Point estimate                                           | 1.07                          |

|                     |             |
|---------------------|-------------|
| Confidence interval |             |
| level               | Other: 80 % |
| sides               | 2-sided     |
| lower limit         | 0.86        |
| upper limit         | 1.32        |

Notes:

[1] - Overall ITT population

[2] - 1-sided p-value

|                                   |                                  |
|-----------------------------------|----------------------------------|
| <b>Statistical analysis title</b> | PFS in BRAF mutant subpopulation |
|-----------------------------------|----------------------------------|

Statistical analysis description:

PFS was analysed using a Cox Proportional Hazards Model

|                                         |                            |
|-----------------------------------------|----------------------------|
| Comparison groups                       | AZD6244 v TMZ_             |
| Number of subjects included in analysis | 200                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[3]</sup> |
| P-value                                 | = 0.537 <sup>[4]</sup>     |
| Method                                  | Regression, Cox            |
| Parameter estimate                      | Hazard ratio (HR)          |
| Point estimate                          | 1.03                       |

Confidence interval

|             |             |
|-------------|-------------|
| level       | Other: 80 % |
| sides       | 2-sided     |
| lower limit | 0.71        |
| upper limit | 1.49        |

Notes:

[3] - BRAF mutant subpopulation

[4] - 1-sided p-value

|                                   |                                              |
|-----------------------------------|----------------------------------------------|
| <b>Statistical analysis title</b> | PFS in BRAF and/or NRAS mutant subpopulation |
|-----------------------------------|----------------------------------------------|

Statistical analysis description:

PFS was analysed using a Cox Proportional Hazards Model

|                                         |                            |
|-----------------------------------------|----------------------------|
| Comparison groups                       | AZD6244 v TMZ_             |
| Number of subjects included in analysis | 200                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[5]</sup> |
| P-value                                 | = 0.547 <sup>[6]</sup>     |
| Method                                  | Regression, Cox            |
| Parameter estimate                      | Hazard ratio (HR)          |
| Point estimate                          | 1.03                       |

Confidence interval

|             |             |
|-------------|-------------|
| level       | Other: 80 % |
| sides       | 2-sided     |
| lower limit | 0.76        |
| upper limit | 1.38        |

Notes:

[5] - BRAF and/or NRAS mutant subpopulation

[6] - 1-sided p-value

## Secondary: Time To Death

|                 |               |
|-----------------|---------------|
| End point title | Time To Death |
|-----------------|---------------|

|                                     |           |
|-------------------------------------|-----------|
| End point description:              |           |
| Assessed following 130 deaths       |           |
| End point type                      | Secondary |
| End point timeframe:                |           |
| Time from randomisation until Death |           |

| End point values            | AZD6244         | TMZ_            |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 104             | 96              |  |  |
| Units: Days                 |                 |                 |  |  |
| median (not applicable)     | 284 ( $\pm$ 0)  | 369 ( $\pm$ 0)  |  |  |

## Statistical analyses

| Statistical analysis title              | TTD in the Overall Population |
|-----------------------------------------|-------------------------------|
| Statistical analysis description:       |                               |
| Cox Proportional Hazards Model          |                               |
| Comparison groups                       | AZD6244 v TMZ_                |
| Number of subjects included in analysis | 200                           |
| Analysis specification                  | Pre-specified                 |
| Analysis type                           | superiority <sup>[7]</sup>    |
| P-value                                 | = 0.95 <sup>[8]</sup>         |
| Method                                  | Regression, Cox               |
| Parameter estimate                      | Hazard ratio (HR)             |
| Point estimate                          | 1.351                         |
| Confidence interval                     |                               |
| level                                   | Other: 80 %                   |
| sides                                   | 2-sided                       |
| lower limit                             | 1.07                          |
| upper limit                             | 1.71                          |

Notes:

[7] - Overall Population

[8] - 1-sided p-value

| Statistical analysis title                                  | TTD in BRAF mutant subpopulation |
|-------------------------------------------------------------|----------------------------------|
| Statistical analysis description:                           |                                  |
| Time To Death analysed using Cox Proportional Hazards Model |                                  |
| Comparison groups                                           | AZD6244 v TMZ_                   |
| Number of subjects included in analysis                     | 200                              |
| Analysis specification                                      | Pre-specified                    |
| Analysis type                                               | superiority <sup>[9]</sup>       |
| P-value                                                     | = 0.949 <sup>[10]</sup>          |
| Method                                                      | Regression, Cox                  |
| Parameter estimate                                          | Hazard ratio (HR)                |
| Point estimate                                              | 1.654                            |

|                     |             |
|---------------------|-------------|
| Confidence interval |             |
| level               | Other: 80 % |
| sides               | 2-sided     |
| lower limit         | 1.12        |
| upper limit         | 2.45        |

Notes:

[9] - BRAF mutant subpopulation

[10] - 1-sided p-value

|                                   |                                              |
|-----------------------------------|----------------------------------------------|
| <b>Statistical analysis title</b> | TTD in BRAF and/or NRAS mutant subpopulation |
|-----------------------------------|----------------------------------------------|

Statistical analysis description:

Time To Death analysed using a Cox Proportional Hazards Model

|                                         |                             |
|-----------------------------------------|-----------------------------|
| Comparison groups                       | AZD6244 v TMZ_              |
| Number of subjects included in analysis | 200                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[11]</sup> |
| P-value                                 | = 0.973 <sup>[12]</sup>     |
| Method                                  | Regression, Cox             |
| Parameter estimate                      | Hazard ratio (HR)           |
| Point estimate                          | 1.621                       |

Confidence interval

|             |             |
|-------------|-------------|
| level       | Other: 80 % |
| sides       | 2-sided     |
| lower limit | 1.18        |
| upper limit | 2.23        |

Notes:

[11] - BRAF and/or NRAS mutant subpopulation

[12] - 1-sided

## Secondary: Objective Tumour response

|                 |                           |
|-----------------|---------------------------|
| End point title | Objective Tumour response |
|-----------------|---------------------------|

End point description:

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

End point timeframe:

Assessment by RECIST criteria conducted at baseline, week 6, week 12 and then every 8 weeks until progression

| End point values                      | AZD6244         | TMZ_            |  |  |
|---------------------------------------|-----------------|-----------------|--|--|
| Subject group type                    | Reporting group | Reporting group |  |  |
| Number of subjects analysed           | 104             | 96              |  |  |
| Units: No. Patients                   |                 |                 |  |  |
| In overall Population                 | 6               | 9               |  |  |
| In BRAF mutant subpopulation          | 5               | 3               |  |  |
| In BRAF and NRAS mutant subpopulation | 5               | 4               |  |  |

## Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

AEs were collected throughout the study. SAEs were collected until disease progression or 30 days after withdrawal from treatment, whichever was the latest.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 11.0 |
|--------------------|------|

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | Temozolomide |
|-----------------------|--------------|

Reporting group description:

Temozolomide was administered without food, as described in the national prescribing information

|                       |         |
|-----------------------|---------|
| Reporting group title | AZD6244 |
|-----------------------|---------|

Reporting group description:

AZD6244 was administered orally with 15 mL of Captisol® Aqueous solution (25% w/v) prior to breakfast and an evening meal

| Serious adverse events                                              | Temozolomide     | AZD6244          |  |
|---------------------------------------------------------------------|------------------|------------------|--|
| Total subjects affected by serious adverse events                   |                  |                  |  |
| subjects affected / exposed                                         | 16 / 95 (16.84%) | 32 / 99 (32.32%) |  |
| number of deaths (all causes)                                       | 57               | 73               |  |
| number of deaths resulting from adverse events                      | 0                | 1                |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |                  |  |
| Metastases to biliary tract                                         |                  |                  |  |
| subjects affected / exposed                                         | 0 / 95 (0.00%)   | 1 / 99 (1.01%)   |  |
| occurrences causally related to treatment / all                     | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0            |  |
| Metastases to central nervous system                                |                  |                  |  |
| subjects affected / exposed                                         | 1 / 95 (1.05%)   | 0 / 99 (0.00%)   |  |
| occurrences causally related to treatment / all                     | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0            |  |
| Metastases to gastrointestinal tract                                |                  |                  |  |
| subjects affected / exposed                                         | 0 / 95 (0.00%)   | 1 / 99 (1.01%)   |  |
| 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                          | 0 / 95 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 1          |  |
| Tumour haemorrhage                                   |                |                |  |
| subjects affected / exposed                          | 1 / 95 (1.05%) | 0 / 99 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Vascular disorders                                   |                |                |  |
| Deep vein thrombosis                                 |                |                |  |
| subjects affected / exposed                          | 0 / 95 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Venous thrombosis                                    |                |                |  |
| subjects affected / exposed                          | 1 / 95 (1.05%) | 0 / 99 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| General disorders and administration site conditions |                |                |  |
| Asthenia                                             |                |                |  |
| subjects affected / exposed                          | 1 / 95 (1.05%) | 0 / 99 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Chest pain                                           |                |                |  |
| subjects affected / exposed                          | 0 / 95 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Death                                                |                |                |  |
| subjects affected / exposed                          | 0 / 95 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 1          |  |
| Oedema peripheral                                    |                |                |  |
| subjects affected / exposed                          | 1 / 95 (1.05%) | 0 / 99 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| Pyrexia                                         |                |                |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 2 / 99 (2.02%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 3          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Immune system disorders                         |                |                |  |
| Drug hypersensitivity                           |                |                |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 2 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Respiratory, thoracic and mediastinal disorders |                |                |  |
| Dyspnoea                                        |                |                |  |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Dyspnoea at rest                                |                |                |  |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 0 / 99 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Dyspnoea exertional                             |                |                |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Haemoptysis                                     |                |                |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Nocturnal dyspnoea                              |                |                |  |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 0 / 99 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pulmonary embolism                              |                |                |  |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |



|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| Psychiatric disorders                           |                |                |  |
| Confusional state                               |                |                |  |
| subjects affected / exposed                     | 2 / 95 (2.11%) | 0 / 99 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Injury, poisoning and procedural complications  |                |                |  |
| Patella fracture                                |                |                |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Cardiac disorders                               |                |                |  |
| Cardio respiratory arrest                       |                |                |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 1 / 1          |  |
| Left ventricular dysfunction                    |                |                |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Myocarditis                                     |                |                |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Ventricular tachycardia                         |                |                |  |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 0 / 99 (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                        |                |                |  |
| Convulsion                                      |                |                |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Dysphasia                                       |                |                |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 1 / 95 (1.05%) | 0 / 99 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Headache                                        |                |                |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 2 / 99 (2.02%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Hemiplegia                                      |                |                |  |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 0 / 99 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Migraine                                        |                |                |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 99 (1.01%) |  |
| 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            |                |                |  |
| Thrombocytopenia                                |                |                |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 2 / 99 (2.02%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Neutropenia                                     |                |                |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Gastrointestinal disorders                      |                |                |  |
| Abdominal Pain                                  |                |                |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 2 / 99 (2.02%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 2 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Diarrhoea                                       |                |                |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 3 / 99 (3.03%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 3          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Ileus                                           |                |                |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Intestinal Obstruction                          |                |                |  |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 0 / 99 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Mesenteric Vein Thrombosis                      |                |                |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Nausea                                          |                |                |  |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 2 / 99 (2.02%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 2 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Small intestinal obstruction                    |                |                |  |
| subjects affected / exposed                     | 2 / 95 (2.11%) | 0 / 99 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Vomiting                                        |                |                |  |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 3 / 99 (3.03%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 3 / 3          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Hepatobiliary disorders                         |                |                |  |
| Jaundice                                        |                |                |  |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 0 / 99 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Skin and subcutaneous tissue disorders          |                |                |  |
| Dermatitis acneiform                            |                |                |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Erythema                                        |                |                |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Rash                                            |                |                |  |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 0 / 99 (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 / 95 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Musculoskeletal and connective tissue disorders |                |                |  |
| Arthralgia                                      |                |                |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Musculoskeletal pain                            |                |                |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Infections and infestations                     |                |                |  |
| Arthritis bacterial                             |                |                |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Cellulitis                                      |                |                |  |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Cellulitis orbital                              |                |                |  |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 0 / 99 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| Erysipelas                                      |                |                |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 3 / 99 (3.03%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 2 / 3          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Infection                                       |                |                |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 99 (1.01%) |  |
| 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 / 95 (1.05%) | 0 / 99 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pneumonia                                       |                |                |  |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Sepsis                                          |                |                |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Metabolism and nutrition disorders              |                |                |  |
| Hyperphosphataemia                              |                |                |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Hypocalcemia                                    |                |                |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Type two Diabetes mellitus                      |                |                |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 99 (1.01%) |  |
| 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>                     | Temozolomide     | AZD6244           |  |
|-------------------------------------------------------|------------------|-------------------|--|
| Total subjects affected by non-serious adverse events |                  |                   |  |
| subjects affected / exposed                           | 92 / 95 (96.84%) | 99 / 99 (100.00%) |  |
| Vascular disorders                                    |                  |                   |  |
| Hypertension                                          |                  |                   |  |
| subjects affected / exposed                           | 2 / 95 (2.11%)   | 8 / 99 (8.08%)    |  |
| occurrences (all)                                     | 2                | 8                 |  |
| General disorders and administration site conditions  |                  |                   |  |
| Asthenia                                              |                  |                   |  |
| subjects affected / exposed                           | 5 / 95 (5.26%)   | 7 / 99 (7.07%)    |  |
| occurrences (all)                                     | 5                | 7                 |  |
| Face oedema                                           |                  |                   |  |
| subjects affected / exposed                           | 1 / 95 (1.05%)   | 7 / 99 (7.07%)    |  |
| occurrences (all)                                     | 1                | 8                 |  |
| Fatigue                                               |                  |                   |  |
| subjects affected / exposed                           | 40 / 95 (42.11%) | 29 / 99 (29.29%)  |  |
| occurrences (all)                                     | 45               | 34                |  |
| Non-cardiac chest pain                                |                  |                   |  |
| subjects affected / exposed                           | 1 / 95 (1.05%)   | 5 / 99 (5.05%)    |  |
| occurrences (all)                                     | 1                | 5                 |  |
| Oedema peripheral                                     |                  |                   |  |
| subjects affected / exposed                           | 5 / 95 (5.26%)   | 40 / 99 (40.40%)  |  |
| occurrences (all)                                     | 5                | 62                |  |
| Pyrexia                                               |                  |                   |  |
| subjects affected / exposed                           | 10 / 95 (10.53%) | 15 / 99 (15.15%)  |  |
| occurrences (all)                                     | 10               | 22                |  |
| Respiratory, thoracic and mediastinal disorders       |                  |                   |  |
| Cough                                                 |                  |                   |  |
| subjects affected / exposed                           | 5 / 95 (5.26%)   | 9 / 99 (9.09%)    |  |
| occurrences (all)                                     | 5                | 11                |  |
| Dyspnoea exertional                                   |                  |                   |  |
| subjects affected / exposed                           | 6 / 95 (6.32%)   | 13 / 99 (13.13%)  |  |
| occurrences (all)                                     | 6                | 15                |  |
| Pharyngolaryngeal pain                                |                  |                   |  |

|                                                  |                     |                     |  |
|--------------------------------------------------|---------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all) | 4 / 95 (4.21%)<br>4 | 9 / 99 (9.09%)<br>9 |  |
| Psychiatric disorders                            |                     |                     |  |
| Depression                                       |                     |                     |  |
| subjects affected / exposed                      | 5 / 95 (5.26%)      | 7 / 99 (7.07%)      |  |
| occurrences (all)                                | 5                   | 7                   |  |
| Insomnia                                         |                     |                     |  |
| subjects affected / exposed                      | 6 / 95 (6.32%)      | 10 / 99 (10.10%)    |  |
| occurrences (all)                                | 6                   | 10                  |  |
| Investigations                                   |                     |                     |  |
| Alanine aminotransferase increased               |                     |                     |  |
| subjects affected / exposed                      | 2 / 95 (2.11%)      | 7 / 99 (7.07%)      |  |
| occurrences (all)                                | 2                   | 8                   |  |
| Aspartate aminotransferase increased             |                     |                     |  |
| subjects affected / exposed                      | 0 / 95 (0.00%)      | 8 / 99 (8.08%)      |  |
| occurrences (all)                                | 0                   | 8                   |  |
| Haemoglobin decreased                            |                     |                     |  |
| subjects affected / exposed                      | 4 / 95 (4.21%)      | 6 / 99 (6.06%)      |  |
| occurrences (all)                                | 4                   | 6                   |  |
| Weight decreased                                 |                     |                     |  |
| subjects affected / exposed                      | 6 / 95 (6.32%)      | 4 / 99 (4.04%)      |  |
| occurrences (all)                                | 7                   | 4                   |  |
| Nervous system disorders                         |                     |                     |  |
| Dizziness                                        |                     |                     |  |
| subjects affected / exposed                      | 7 / 95 (7.37%)      | 8 / 99 (8.08%)      |  |
| occurrences (all)                                | 10                  | 10                  |  |
| Headache                                         |                     |                     |  |
| subjects affected / exposed                      | 23 / 95 (24.21%)    | 20 / 99 (20.20%)    |  |
| occurrences (all)                                | 27                  | 24                  |  |
| Blood and lymphatic system disorders             |                     |                     |  |
| Anaemia                                          |                     |                     |  |
| subjects affected / exposed                      | 6 / 95 (6.32%)      | 9 / 99 (9.09%)      |  |
| occurrences (all)                                | 6                   | 10                  |  |
| Thrombocytopenia                                 |                     |                     |  |
| subjects affected / exposed                      | 7 / 95 (7.37%)      | 2 / 99 (2.02%)      |  |
| occurrences (all)                                | 7                   | 2                   |  |

|                             |                  |                  |  |
|-----------------------------|------------------|------------------|--|
| Eye disorders               |                  |                  |  |
| Vision blurred              |                  |                  |  |
| subjects affected / exposed | 2 / 95 (2.11%)   | 8 / 99 (8.08%)   |  |
| occurrences (all)           | 2                | 8                |  |
| Gastrointestinal disorders  |                  |                  |  |
| Abdominal distension        |                  |                  |  |
| subjects affected / exposed | 3 / 95 (3.16%)   | 8 / 99 (8.08%)   |  |
| occurrences (all)           | 3                | 9                |  |
| Abdominal pain              |                  |                  |  |
| subjects affected / exposed | 12 / 95 (12.63%) | 12 / 99 (12.12%) |  |
| occurrences (all)           | 14               | 13               |  |
| Abdominal pain upper        |                  |                  |  |
| subjects affected / exposed | 4 / 95 (4.21%)   | 7 / 99 (7.07%)   |  |
| occurrences (all)           | 7                | 9                |  |
| Constipation                |                  |                  |  |
| subjects affected / exposed | 45 / 95 (47.37%) | 12 / 99 (12.12%) |  |
| occurrences (all)           | 60               | 13               |  |
| Diarrhoea                   |                  |                  |  |
| subjects affected / exposed | 20 / 95 (21.05%) | 55 / 99 (55.56%) |  |
| occurrences (all)           | 27               | 77               |  |
| Dry mouth                   |                  |                  |  |
| subjects affected / exposed | 6 / 95 (6.32%)   | 8 / 99 (8.08%)   |  |
| occurrences (all)           | 6                | 8                |  |
| Dyspepsia                   |                  |                  |  |
| subjects affected / exposed | 4 / 95 (4.21%)   | 11 / 99 (11.11%) |  |
| occurrences (all)           | 4                | 13               |  |
| Flatulence                  |                  |                  |  |
| subjects affected / exposed | 1 / 95 (1.05%)   | 7 / 99 (7.07%)   |  |
| occurrences (all)           | 1                | 7                |  |
| Nausea                      |                  |                  |  |
| subjects affected / exposed | 61 / 95 (64.21%) | 49 / 99 (49.49%) |  |
| occurrences (all)           | 79               | 64               |  |
| Stomatitis                  |                  |                  |  |
| subjects affected / exposed | 1 / 95 (1.05%)   | 9 / 99 (9.09%)   |  |
| occurrences (all)           | 1                | 12               |  |
| Vomiting                    |                  |                  |  |



|                                                  |                        |                        |  |
|--------------------------------------------------|------------------------|------------------------|--|
| subjects affected / exposed<br>occurrences (all) | 42 / 95 (44.21%)<br>56 | 26 / 99 (26.26%)<br>35 |  |
| Skin and subcutaneous tissue disorders           |                        |                        |  |
| Acne                                             |                        |                        |  |
| subjects affected / exposed                      | 0 / 95 (0.00%)         | 5 / 99 (5.05%)         |  |
| occurrences (all)                                | 0                      | 7                      |  |
| Alopecia                                         |                        |                        |  |
| subjects affected / exposed                      | 1 / 95 (1.05%)         | 7 / 99 (7.07%)         |  |
| occurrences (all)                                | 2                      | 7                      |  |
| Dermatitis acneiform                             |                        |                        |  |
| subjects affected / exposed                      | 3 / 95 (3.16%)         | 58 / 99 (58.59%)       |  |
| occurrences (all)                                | 3                      | 70                     |  |
| Dry skin                                         |                        |                        |  |
| subjects affected / exposed                      | 0 / 95 (0.00%)         | 9 / 99 (9.09%)         |  |
| occurrences (all)                                | 0                      | 10                     |  |
| Eczema                                           |                        |                        |  |
| subjects affected / exposed                      | 0 / 95 (0.00%)         | 5 / 99 (5.05%)         |  |
| occurrences (all)                                | 0                      | 5                      |  |
| Exfoliative rash                                 |                        |                        |  |
| subjects affected / exposed                      | 0 / 95 (0.00%)         | 7 / 99 (7.07%)         |  |
| occurrences (all)                                | 0                      | 9                      |  |
| Periorbital oedema                               |                        |                        |  |
| subjects affected / exposed                      | 1 / 95 (1.05%)         | 14 / 99 (14.14%)       |  |
| occurrences (all)                                | 1                      | 15                     |  |
| Pruritus                                         |                        |                        |  |
| subjects affected / exposed                      | 3 / 95 (3.16%)         | 10 / 99 (10.10%)       |  |
| occurrences (all)                                | 3                      | 11                     |  |
| Rash                                             |                        |                        |  |
| subjects affected / exposed                      | 1 / 95 (1.05%)         | 7 / 99 (7.07%)         |  |
| occurrences (all)                                | 1                      | 12                     |  |
| Rash erythematous                                |                        |                        |  |
| subjects affected / exposed                      | 2 / 95 (2.11%)         | 6 / 99 (6.06%)         |  |
| occurrences (all)                                | 2                      | 7                      |  |
| Rash macular                                     |                        |                        |  |
| subjects affected / exposed                      | 0 / 95 (0.00%)         | 5 / 99 (5.05%)         |  |
| occurrences (all)                                | 0                      | 5                      |  |

|                                                                          |                        |                        |  |
|--------------------------------------------------------------------------|------------------------|------------------------|--|
| Skin fissures<br>subjects affected / exposed<br>occurrences (all)        | 0 / 95 (0.00%)<br>0    | 7 / 99 (7.07%)<br>11   |  |
| Musculoskeletal and connective tissue disorders                          |                        |                        |  |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)           | 7 / 95 (7.37%)<br>7    | 5 / 99 (5.05%)<br>7    |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)            | 9 / 95 (9.47%)<br>14   | 5 / 99 (5.05%)<br>5    |  |
| Musculoskeletal pain<br>subjects affected / exposed<br>occurrences (all) | 6 / 95 (6.32%)<br>7    | 2 / 99 (2.02%)<br>2    |  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)    | 7 / 95 (7.37%)<br>7    | 9 / 99 (9.09%)<br>9    |  |
| Infections and infestations                                              |                        |                        |  |
| Folliculitis<br>subjects affected / exposed<br>occurrences (all)         | 1 / 95 (1.05%)<br>1    | 5 / 99 (5.05%)<br>7    |  |
| Paronychia<br>subjects affected / exposed<br>occurrences (all)           | 0 / 95 (0.00%)<br>0    | 5 / 99 (5.05%)<br>6    |  |
| Metabolism and nutrition disorders                                       |                        |                        |  |
| Anorexia<br>subjects affected / exposed<br>occurrences (all)             | 12 / 95 (12.63%)<br>12 | 9 / 99 (9.09%)<br>9    |  |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)   | 4 / 95 (4.21%)<br>4    | 11 / 99 (11.11%)<br>12 |  |
| Hypokalaemia<br>subjects affected / exposed<br>occurrences (all)         | 3 / 95 (3.16%)<br>3    | 5 / 99 (5.05%)<br>5    |  |

## **More information**

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

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported