



## Clinical trial results:

### A Phase 1/2 Study of the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-Tumor Activity of the Oral ALK/EGFR Inhibitor AP26113 Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2011-005718-12 |
| Trial protocol           | ES             |
| Global end of trial date |                |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1           |
| This version publication date  | 29 June 2017 |
| First version publication date | 29 June 2017 |

#### Trial information

##### Trial identification

|                       |                |
|-----------------------|----------------|
| Sponsor protocol code | AP26113-11-101 |
|-----------------------|----------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01449461 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |                                                                                                          |
|------------------------------|----------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Takeda Development Center Americas, Inc.                                                                 |
| Sponsor organisation address | One Takeda Parkway, Deerfield, IL, United States, 60015                                                  |
| Public contact               | Medical Director, Clinical Science Organization: Takeda, +1 877-825-3327, clinicaltrialregistry@tpna.com |
| Scientific contact           | Medical Director, Clinical Science Organization: Takeda, +1 877-825-3327, clinicaltrialregistry@tpna.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                                       | Interim          |
| Date of interim/final analysis                       | 16 November 2015 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 16 November 2015 |
| Global end of trial reached?                         | No               |

Notes:

## General information about the trial

Main objective of the trial:

The purpose of this study is 2-fold: initially, in the dose escalation phase, the goal is to determine the safety profile of orally administered AP26113, including: the maximum tolerated dose (MTD), dose limiting toxicities (DLTs), recommended phase 2 dose (RP2D), and pharmacokinetic (PK) profile. Then, once the RP2D is established, an expansion phase will assess the preliminary anti-tumor activity of AP26113, both in non-small cell lung cancer (NSCLC) with ALK gene rearrangement (including participants with active brain metastases) or mutated EGFR, and in other cancers with abnormal targets against which AP26113 is active.

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

|                                                           |                   |
|-----------------------------------------------------------|-------------------|
| Actual start date of recruitment                          | 20 September 2011 |
| Long term follow-up planned                               | Yes               |
| Long term follow-up rationale                             | Efficacy, Safety  |
| Long term follow-up duration                              | 2 Years           |
| Independent data monitoring committee (IDMC) involvement? | No                |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Spain: 7           |
| Country: Number of subjects enrolled | United States: 130 |
| Worldwide total number of subjects   | 137                |
| EEA total number of subjects         | 7                  |

Notes:

### Subjects enrolled per age group

|                                           |    |
|-------------------------------------------|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 0  |
| Children (2-11 years)                     | 0  |
| Adolescents (12-17 years)                 | 0  |
| Adults (18-64 years)                      | 98 |

|                     |    |
|---------------------|----|
| From 65 to 84 years | 39 |
| 85 years and over   | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Participants took part in the study at 9 investigative sites in the United States and Spain up to clinical cut-off date 16 November 2015. Study is ongoing.

### Pre-assignment

Screening details:

Participants with advanced malignancies, all histologies other than leukemia were enrolled in dose-escalation and participants with non-small cell lung cancer (NSCLC) with anaplastic lymphoma kinase (ALK) rearrangements were enrolled in dose expansion phase. Participants received brigatinib 30 mg - 300 mg, tablets, orally once daily or twice daily.

### Period 1

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

### Arms

|                              |                              |
|------------------------------|------------------------------|
| Are arms mutually exclusive? | Yes                          |
| <b>Arm title</b>             | Brigatinib 30 mg QD/60 mg QD |

Arm description:

Brigatinib 30 mg/60 mg, tablets, orally, once daily (QD) in each cycle of 28 days (approximately, up to 44.4 months).

|                                        |                 |
|----------------------------------------|-----------------|
| Arm type                               | Experimental    |
| Investigational medicinal product name | Brigatinib      |
| Investigational medicinal product code |                 |
| Other name                             | AP26113         |
| Pharmaceutical forms                   | Tablet, Capsule |
| Routes of administration               | Oral use        |

Dosage and administration details:

Brigatinib tablets and capsules

|                  |                     |
|------------------|---------------------|
| <b>Arm title</b> | Brigatinib 90 mg QD |
|------------------|---------------------|

Arm description:

Brigatinib 90 mg, tablets, orally, once daily (QD) in each cycle of 28 days (approximately, up to 44.4 months).

|                                        |                 |
|----------------------------------------|-----------------|
| Arm type                               | Experimental    |
| Investigational medicinal product name | Brigatinib      |
| Investigational medicinal product code |                 |
| Other name                             | AP26113         |
| Pharmaceutical forms                   | Tablet, Capsule |
| Routes of administration               | Oral use        |

Dosage and administration details:

Brigatinib tablets and capsules

|                  |                                |
|------------------|--------------------------------|
| <b>Arm title</b> | Brigatinib 120 mg QD/60 mg BID |
|------------------|--------------------------------|

Arm description:

Brigatinib 120 mg, once daily or 60 mg, twice daily (BID), tablets, orally, in each cycle of 28 days (approximately, up to 44.4 months).

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|                                        |                 |
|----------------------------------------|-----------------|
| Investigational medicinal product name | Brigatinib      |
| Investigational medicinal product code |                 |
| Other name                             | AP26113         |
| Pharmaceutical forms                   | Tablet, Capsule |
| Routes of administration               | Oral use        |

Dosage and administration details:

Brigatinib tablets and capsules

|                  |                               |
|------------------|-------------------------------|
| <b>Arm title</b> | Brigatinib 90 mg QD-180 mg QD |
|------------------|-------------------------------|

Arm description:

Brigatinib 90 mg, tablets, orally, once daily for 7 days followed by brigatinib 180 mg, orally once daily in Cycle 1 of 28 days followed by brigatinib 180 mg, orally once daily in cycle 2 and onward cycles of 28 days.

|                                        |                 |
|----------------------------------------|-----------------|
| Arm type                               | Experimental    |
| Investigational medicinal product name | Brigatinib      |
| Investigational medicinal product code |                 |
| Other name                             | AP26113         |
| Pharmaceutical forms                   | Tablet, Capsule |
| Routes of administration               | Oral use        |

Dosage and administration details:

Brigatinib tablets and capsules

|                  |                                |
|------------------|--------------------------------|
| <b>Arm title</b> | Brigatinib 180 mg QD/90 mg BID |
|------------------|--------------------------------|

Arm description:

Brigatinib 180 mg, once daily or 90 mg, twice daily (BID), tablets, orally in each cycle of 28 days (approximately, up to 44.4 months).

|                                        |                 |
|----------------------------------------|-----------------|
| Arm type                               | Experimental    |
| Investigational medicinal product name | Brigatinib      |
| Investigational medicinal product code |                 |
| Other name                             | AP26113         |
| Pharmaceutical forms                   | Tablet, Capsule |
| Routes of administration               | Oral use        |

Dosage and administration details:

Brigatinib tablets and capsules

|                  |                                           |
|------------------|-------------------------------------------|
| <b>Arm title</b> | Brigatinib 240 mg QD/120 mg BID/300 mg QD |
|------------------|-------------------------------------------|

Arm description:

Brigatinib 240 mg, once daily (QD) or 120 mg, twice daily (BID) or 300 mg once daily, tablets, orally, in each cycle of 28 days (approximately, up to 44.4 months).

|                                        |                 |
|----------------------------------------|-----------------|
| Arm type                               | Experimental    |
| Investigational medicinal product name | Brigatinib      |
| Investigational medicinal product code |                 |
| Other name                             | AP26113         |
| Pharmaceutical forms                   | Tablet, Capsule |
| Routes of administration               | Oral use        |

Dosage and administration details:

Brigatinib tablets and capsules

| <b>Number of subjects in period 1</b> | Brigatinib 30 mg QD/60 mg QD | Brigatinib 90 mg QD | Brigatinib 120 mg QD/60 mg BID |
|---------------------------------------|------------------------------|---------------------|--------------------------------|
| Started                               | 6                            | 18                  | 18                             |
| Completed                             | 0                            | 0                   | 0                              |
| Not completed                         | 6                            | 18                  | 18                             |
| Adverse event, serious fatal          | -                            | 1                   | -                              |
| Clinical progressive disease          | 2                            | 1                   | -                              |
| Adverse event, non-fatal              | -                            | 3                   | 2                              |
| Ongoing                               | -                            | 6                   | 2                              |
| Documented progressive disease        | 4                            | 6                   | 14                             |
| Reason not specified                  | -                            | 1                   | -                              |

| <b>Number of subjects in period 1</b> | Brigatinib 90 mg QD-180 mg QD | Brigatinib 180 mg QD/90 mg BID | Brigatinib 240 mg QD/120 mg BID/300 mg QD |
|---------------------------------------|-------------------------------|--------------------------------|-------------------------------------------|
| Started                               | 32                            | 48                             | 15                                        |
| Completed                             | 0                             | 0                              | 0                                         |
| Not completed                         | 32                            | 48                             | 15                                        |
| Adverse event, serious fatal          | -                             | 4                              | 1                                         |
| Clinical progressive disease          | -                             | 3                              | 3                                         |
| Adverse event, non-fatal              | 3                             | 3                              | 3                                         |
| Ongoing                               | 15                            | 17                             | 2                                         |
| Documented progressive disease        | 11                            | 21                             | 5                                         |
| Reason not specified                  | 3                             | -                              | 1                                         |

## Baseline characteristics

### Reporting groups

|                                                                                                                                                                                                                                                           |                                           |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| Reporting group title                                                                                                                                                                                                                                     | Brigatinib 30 mg QD/60 mg QD              |
| Reporting group description:<br>Brigatinib 30 mg/60 mg, tablets, orally, once daily (QD) in each cycle of 28 days (approximately, up to 44.4 months).                                                                                                     |                                           |
| Reporting group title                                                                                                                                                                                                                                     | Brigatinib 90 mg QD                       |
| Reporting group description:<br>Brigatinib 90 mg, tablets, orally, once daily (QD) in each cycle of 28 days (approximately, up to 44.4 months).                                                                                                           |                                           |
| Reporting group title                                                                                                                                                                                                                                     | Brigatinib 120 mg QD/60 mg BID            |
| Reporting group description:<br>Brigatinib 120 mg, once daily or 60 mg, twice daily (BID), tablets, orally, in each cycle of 28 days (approximately, up to 44.4 months).                                                                                  |                                           |
| Reporting group title                                                                                                                                                                                                                                     | Brigatinib 90 mg QD-180 mg QD             |
| Reporting group description:<br>Brigatinib 90 mg, tablets, orally, once daily for 7 days followed by brigatinib 180 mg, orally once daily in Cycle 1 of 28 days followed by brigatinib 180 mg, orally once daily in cycle 2 and onward cycles of 28 days. |                                           |
| Reporting group title                                                                                                                                                                                                                                     | Brigatinib 180 mg QD/90 mg BID            |
| Reporting group description:<br>Brigatinib 180 mg, once daily or 90 mg, twice daily (BID), tablets, orally in each cycle of 28 days (approximately, up to 44.4 months).                                                                                   |                                           |
| Reporting group title                                                                                                                                                                                                                                     | Brigatinib 240 mg QD/120 mg BID/300 mg QD |
| Reporting group description:<br>Brigatinib 240 mg, once daily (QD) or 120 mg, twice daily (BID) or 300 mg once daily, tablets, orally, in each cycle of 28 days (approximately, up to 44.4 months).                                                       |                                           |

| Reporting group values                        | Brigatinib 30 mg QD/60 mg QD | Brigatinib 90 mg QD | Brigatinib 120 mg QD/60 mg BID |
|-----------------------------------------------|------------------------------|---------------------|--------------------------------|
| Number of subjects                            | 6                            | 18                  | 18                             |
| Age Categorical<br>Units: Subjects            |                              |                     |                                |
| 18 – 64 years                                 | 2                            | 11                  | 12                             |
| ≥65 years                                     | 4                            | 7                   | 6                              |
| Age Continuous<br>Units: years                |                              |                     |                                |
| arithmetic mean                               | 66.8                         | 57.9                | 57.8                           |
| standard deviation                            | ± 9.3                        | ± 12.93             | ± 10.91                        |
| Gender, Male/Female<br>Units: Subjects        |                              |                     |                                |
| Female                                        | 3                            | 6                   | 5                              |
| Male                                          | 3                            | 12                  | 13                             |
| Race/Ethnicity, Customized<br>Units: Subjects |                              |                     |                                |
| American Indian or Alaska Native              | 0                            | 0                   | 0                              |
| Asian                                         | 0                            | 4                   | 3                              |
| Black or African American                     | 0                            | 1                   | 2                              |
| Native Hawaiian or Other Pacific Islander     | 0                            | 0                   | 0                              |
| White                                         | 6                            | 13                  | 13                             |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                               |                                |                                           |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|--------------------------------|-------------------------------------------|
| Unknown                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 0                             | 0                              | 0                                         |
| Other                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 0                             | 0                              | 0                                         |
| Race/Ethnicity, Customized                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                               |                                |                                           |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                               |                                |                                           |
| Hispanic or Latino                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 1                             | 0                              | 0                                         |
| Not Hispanic or Latino                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 5                             | 18                             | 18                                        |
| Eastern Cooperative Oncology Group (ECOG) Performance Score                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                               |                                |                                           |
| ECOG assessed participant's performance status on a 5 point scale: 0 equals (=) fully active/able to carry on all pre-disease activities without restriction; 1=restricted in physically strenuous activity, but ambulatory/able to carry out light or sedentary work; 2=ambulatory (greater than [>] 50 percentage [%] of waking hours [h]), capable of all self care, but unable to carry out any work activities; 3=capable of only limited self care, confined to bed/chair >50% of waking hours; 4= completely disabled, cannot carry on any selfcare, totally confined to bed or chair and 5=Dead. |                               |                                |                                           |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                               |                                |                                           |
| ECOG Score=0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 0                             | 3                              | 3                                         |
| ECOG Score=1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 6                             | 15                             | 15                                        |
| ECOG Score=3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 0                             | 0                              | 0                                         |
| Participants with Diagnosis of Cancer Type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                               |                                |                                           |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                               |                                |                                           |
| NSCLC                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 3                             | 16                             | 18                                        |
| Other                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 3                             | 2                              | 0                                         |
| Number of Participants with Mutation Types                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                               |                                |                                           |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                               |                                |                                           |
| Anaplastic lymphoma kinase (ALK+)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 1                             | 16                             | 6                                         |
| Epidermal Growth Factor Receptor (EGFRm)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 2                             | 1                              | 10                                        |
| ROS proto-oncogene 1 (ROS1+)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 0                             | 0                              | 0                                         |
| Other                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 3                             | 1                              | 2                                         |
| Participants with Prior Chemotherapy Regimen                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                               |                                |                                           |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                               |                                |                                           |
| Prior Therapy=0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 0                             | 2                              | 7                                         |
| Prior Therapy=1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 3                             | 4                              | 3                                         |
| Prior Therapy=2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 0                             | 9                              | 4                                         |
| Prior Therapy >2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 3                             | 3                              | 4                                         |
| Participants with Prior Radiotherapy to Brain                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                               |                                |                                           |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                               |                                |                                           |
| No Prior Radiotherapy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 6                             | 13                             | 17                                        |
| Prior Radiotherapy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 0                             | 5                              | 1                                         |
| Region of Enrollment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                               |                                |                                           |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                               |                                |                                           |
| United States                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 6                             | 18                             | 18                                        |
| Spain                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 0                             | 0                              | 0                                         |
| Study Specific Characteristic   Time Since Diagnosis of Cancer                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                               |                                |                                           |
| Units: years                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                               |                                |                                           |
| arithmetic mean                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 2.48                          | 3.33                           | 2.41                                      |
| standard deviation                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | ± 3.303                       | ± 2.184                        | ± 1.346                                   |
| <b>Reporting group values</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Brigatinib 90 mg QD-180 mg QD | Brigatinib 180 mg QD/90 mg BID | Brigatinib 240 mg QD/120 mg BID/300 mg QD |



|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |         |        |        |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|--------|--------|
| Number of subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 32      | 48     | 15     |
| Age Categorical                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |         |        |        |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |         |        |        |
| 18 – 64 years                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 25      | 39     | 9      |
| ≥65 years                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 7       | 9      | 6      |
| Age Continuous                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |         |        |        |
| Units: years                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |         |        |        |
| arithmetic mean                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 55.7    | 53.9   | 58.5   |
| standard deviation                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | ± 11.41 | ± 11.1 | ± 15.6 |
| Gender, Male/Female                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |         |        |        |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |         |        |        |
| Female                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 18      | 19     | 7      |
| Male                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 14      | 29     | 8      |
| Race/Ethnicity, Customized                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |         |        |        |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |         |        |        |
| American Indian or Alaska Native                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 1       | 1      | 0      |
| Asian                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 3       | 5      | 2      |
| Black or African American                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 0       | 1      | 1      |
| Native Hawaiian or Other Pacific Islander                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 0       | 1      | 0      |
| White                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 27      | 39     | 12     |
| Unknown                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 0       | 1      | 0      |
| Other                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 1       | 0      | 0      |
| Race/Ethnicity, Customized                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |         |        |        |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |         |        |        |
| Hispanic or Latino                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 1       | 1      | 0      |
| Not Hispanic or Latino                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 31      | 47     | 15     |
| Eastern Cooperative Oncology Group (ECOG) Performance Score                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |         |        |        |
| ECOG assessed participant's performance status on a 5 point scale: 0 equals (=) fully active/able to carry on all pre-disease activities without restriction; 1=restricted in physically strenuous activity, but ambulatory/able to carry out light or sedentary work; 2=ambulatory (greater than [>] 50 percentage [%] of waking hours [h]), capable of all self care, but unable to carry out any work activities; 3=capable of only limited self care, confined to bed/chair >50% of waking hours; 4= completely disabled, cannot carry on any selfcare, totally confined to bed or chair and 5=Dead. |         |        |        |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |         |        |        |
| ECOG Score=0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 13      | 13     | 2      |
| ECOG Score=1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 19      | 33     | 13     |
| ECOG Score=3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 0       | 2      | 0      |
| Participants with Diagnosis of Cancer Type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |         |        |        |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |         |        |        |
| NSCLC                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 31      | 45     | 15     |
| Other                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 1       | 3      | 0      |
| Number of Participants with Mutation Types                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |         |        |        |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |         |        |        |
| Anaplastic lymphoma kinase (ALK+)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 29      | 27     | 5      |
| Epidermal Growth Factor Receptor (EGFRm)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 3       | 18     | 9      |
| ROS proto-oncogene 1 (ROS1+)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 0       | 3      | 1      |
| Other                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 0       | 0      | 0      |
| Participants with Prior Chemotherapy Regimen                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |         |        |        |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |         |        |        |

|                                                                                |         |         |         |
|--------------------------------------------------------------------------------|---------|---------|---------|
| Prior Therapy=0                                                                | 12      | 12      | 3       |
| Prior Therapy=1                                                                | 6       | 17      | 2       |
| Prior Therapy=2                                                                | 8       | 10      | 5       |
| Prior Therapy >2                                                               | 6       | 9       | 5       |
| Participants with Prior Radiotherapy to Brain<br>Units: Subjects               |         |         |         |
| No Prior Radiotherapy                                                          | 24      | 36      | 14      |
| Prior Radiotherapy                                                             | 8       | 12      | 1       |
| Region of Enrollment<br>Units: Subjects                                        |         |         |         |
| United States                                                                  | 32      | 41      | 15      |
| Spain                                                                          | 0       | 7       | 0       |
| Study Specific Characteristic   Time Since Diagnosis of Cancer<br>Units: years |         |         |         |
| arithmetic mean                                                                | 3.19    | 2.77    | 3.27    |
| standard deviation                                                             | ± 2.726 | ± 2.053 | ± 1.913 |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |       |  |  |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|--|--|
| <b>Reporting group values</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Total |  |  |
| Number of subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 137   |  |  |
| Age Categorical<br>Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |       |  |  |
| 18 – 64 years                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 98    |  |  |
| ≥65 years                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 39    |  |  |
| Age Continuous<br>Units: years                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |       |  |  |
| arithmetic mean                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |       |  |  |
| standard deviation                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | -     |  |  |
| Gender, Male/Female<br>Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |       |  |  |
| Female                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 58    |  |  |
| Male                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 79    |  |  |
| Race/Ethnicity, Customized<br>Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |       |  |  |
| American Indian or Alaska Native                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 2     |  |  |
| Asian                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 17    |  |  |
| Black or African American                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 5     |  |  |
| Native Hawaiian or Other Pacific Islander                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 1     |  |  |
| White                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 110   |  |  |
| Unknown                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 1     |  |  |
| Other                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 1     |  |  |
| Race/Ethnicity, Customized<br>Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |       |  |  |
| Hispanic or Latino                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 3     |  |  |
| Not Hispanic or Latino                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 134   |  |  |
| Eastern Cooperative Oncology Group (ECOG) Performance Score                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |       |  |  |
| ECOG assessed participant's performance status on a 5 point scale: 0 equals (=) fully active/able to carry on all pre-disease activities without restriction; 1=restricted in physically strenuous activity, but ambulatory/able to carry out light or sedentary work; 2=ambulatory (greater than [>] 50 percentage [%] of waking hours [h]), capable of all self care, but unable to carry out any work activities; 3=capable of only limited self care, confined to bed/chair >50% of waking hours; 4= completely disabled, cannot |       |  |  |

|                                                                     |     |  |  |
|---------------------------------------------------------------------|-----|--|--|
| carry on any selfcare, totally confined to bed or chair and 5=Dead. |     |  |  |
| Units: Subjects                                                     |     |  |  |
| ECOG Score=0                                                        | 34  |  |  |
| ECOG Score=1                                                        | 101 |  |  |
| ECOG Score=3                                                        | 2   |  |  |
| Participants with Diagnosis of Cancer Type                          |     |  |  |
| Units: Subjects                                                     |     |  |  |
| NSCLC                                                               | 128 |  |  |
| Other                                                               | 9   |  |  |
| Number of Participants with Mutation Types                          |     |  |  |
| Units: Subjects                                                     |     |  |  |
| Anaplastic lymphoma kinase (ALK+)                                   | 84  |  |  |
| Epidermal Growth Factor Receptor (EGFRm)                            | 43  |  |  |
| ROS proto-oncogene 1 (ROS1+)                                        | 4   |  |  |
| Other                                                               | 6   |  |  |
| Participants with Prior Chemotherapy Regimen                        |     |  |  |
| Units: Subjects                                                     |     |  |  |
| Prior Therapy=0                                                     | 36  |  |  |
| Prior Therapy=1                                                     | 35  |  |  |
| Prior Therapy=2                                                     | 36  |  |  |
| Prior Therapy >2                                                    | 30  |  |  |
| Participants with Prior Radiotherapy to Brain                       |     |  |  |
| Units: Subjects                                                     |     |  |  |
| No Prior Radiotherapy                                               | 110 |  |  |
| Prior Radiotherapy                                                  | 27  |  |  |
| Region of Enrollment                                                |     |  |  |
| Units: Subjects                                                     |     |  |  |
| United States                                                       | 130 |  |  |
| Spain                                                               | 7   |  |  |
| Study Specific Characteristic   Time Since Diagnosis of Cancer      |     |  |  |
| Units: years                                                        |     |  |  |
| arithmetic mean                                                     |     |  |  |
| standard deviation                                                  | -   |  |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                           |                                           |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| Reporting group title                                                                                                                                                                                                                                     | Brigatinib 30 mg QD/60 mg QD              |
| Reporting group description:<br>Brigatinib 30 mg/60 mg, tablets, orally, once daily (QD) in each cycle of 28 days (approximately, up to 44.4 months).                                                                                                     |                                           |
| Reporting group title                                                                                                                                                                                                                                     | Brigatinib 90 mg QD                       |
| Reporting group description:<br>Brigatinib 90 mg, tablets, orally, once daily (QD) in each cycle of 28 days (approximately, up to 44.4 months).                                                                                                           |                                           |
| Reporting group title                                                                                                                                                                                                                                     | Brigatinib 120 mg QD/60 mg BID            |
| Reporting group description:<br>Brigatinib 120 mg, once daily or 60 mg, twice daily (BID), tablets, orally, in each cycle of 28 days (approximately, up to 44.4 months).                                                                                  |                                           |
| Reporting group title                                                                                                                                                                                                                                     | Brigatinib 90 mg QD-180 mg QD             |
| Reporting group description:<br>Brigatinib 90 mg, tablets, orally, once daily for 7 days followed by brigatinib 180 mg, orally once daily in Cycle 1 of 28 days followed by brigatinib 180 mg, orally once daily in cycle 2 and onward cycles of 28 days. |                                           |
| Reporting group title                                                                                                                                                                                                                                     | Brigatinib 180 mg QD/90 mg BID            |
| Reporting group description:<br>Brigatinib 180 mg, once daily or 90 mg, twice daily (BID), tablets, orally in each cycle of 28 days (approximately, up to 44.4 months).                                                                                   |                                           |
| Reporting group title                                                                                                                                                                                                                                     | Brigatinib 240 mg QD/120 mg BID/300 mg QD |
| Reporting group description:<br>Brigatinib 240 mg, once daily (QD) or 120 mg, twice daily (BID) or 300 mg once daily, tablets, orally, in each cycle of 28 days (approximately, up to 44.4 months).                                                       |                                           |
| Subject analysis set title                                                                                                                                                                                                                                | Brigatinib                                |
| Subject analysis set type                                                                                                                                                                                                                                 | Full analysis                             |
| Subject analysis set description:<br>All participants who received Brigatinib, tablets, orally, once daily in each cycle of 28 days.                                                                                                                      |                                           |
| Subject analysis set title                                                                                                                                                                                                                                | Brigatinib 30 mg                          |
| Subject analysis set type                                                                                                                                                                                                                                 | Full analysis                             |
| Subject analysis set description:<br>Brigatinib 30 mg, tablets, orally, once daily (QD) in each cycle of 28 days (approximately, up to 44.4 months).                                                                                                      |                                           |
| Subject analysis set title                                                                                                                                                                                                                                | Brigatinib 60 mg                          |
| Subject analysis set type                                                                                                                                                                                                                                 | Full analysis                             |
| Subject analysis set description:<br>Brigatinib 60 mg, tablets, orally, once daily (QD) in each cycle of 28 days (approximately, up to 44.4 months).                                                                                                      |                                           |
| Subject analysis set title                                                                                                                                                                                                                                | Brigatinib 90 mg                          |
| Subject analysis set type                                                                                                                                                                                                                                 | Full analysis                             |
| Subject analysis set description:<br>Brigatinib 90 mg, tablets, orally, once daily or twice daily in each cycle of 28 days (approximately, up to 44.4 months).                                                                                            |                                           |
| Subject analysis set title                                                                                                                                                                                                                                | Brigatinib 120 mg                         |
| Subject analysis set type                                                                                                                                                                                                                                 | Full analysis                             |
| Subject analysis set description:<br>Brigatinib 120 mg, tablets, orally, once daily in each cycle of 28 days (approximately, up to 44.4 months).                                                                                                          |                                           |
| Subject analysis set title                                                                                                                                                                                                                                | Brigatinib 180 mg                         |
| Subject analysis set type                                                                                                                                                                                                                                 | Full analysis                             |

Subject analysis set description:

Brigatinib 180 mg, tablets, orally once daily in each cycle of 28 days (approximately, up to 44.4 months).

|                            |                   |
|----------------------------|-------------------|
| Subject analysis set title | Brigatinib 240 mg |
| Subject analysis set type  | Full analysis     |

Subject analysis set description:

Brigatinib 240 mg, tablets, orally, once daily in each cycle of 28 days (approximately, up to 44.4 months).

|                            |                   |
|----------------------------|-------------------|
| Subject analysis set title | Brigatinib 300 mg |
| Subject analysis set type  | Full analysis     |

Subject analysis set description:

Brigatinib 300 mg, tablets, orally, once daily in each cycle of 28 days (approximately, up to 44.4 months).

|                            |                  |
|----------------------------|------------------|
| Subject analysis set title | Brigatinib 90 mg |
| Subject analysis set type  | Full analysis    |

Subject analysis set description:

Brigatinib 90 mg, tablets, orally, once daily or twice daily in each cycle of 28 days (approximately, up to 44.4 months).

|                            |                   |
|----------------------------|-------------------|
| Subject analysis set title | Brigatinib 120 mg |
| Subject analysis set type  | Full analysis     |

Subject analysis set description:

Brigatinib 120 mg, tablets, orally, once daily in each cycle of 28 days (approximately, up to 44.4 months).

|                            |                   |
|----------------------------|-------------------|
| Subject analysis set title | Brigatinib 180 mg |
| Subject analysis set type  | Full analysis     |

Subject analysis set description:

Brigatinib 180 mg, tablets, orally once daily in each cycle of 28 days (approximately, up to 44.4 months).

|                            |                   |
|----------------------------|-------------------|
| Subject analysis set title | Brigatinib 240 mg |
| Subject analysis set type  | Full analysis     |

Subject analysis set description:

Brigatinib 240 mg, tablets, orally, once daily in each cycle of 28 days (approximately, up to 44.4 months).

|                            |                   |
|----------------------------|-------------------|
| Subject analysis set title | Brigatinib 300 mg |
| Subject analysis set type  | Full analysis     |

Subject analysis set description:

Brigatinib 300 mg, tablets, orally, once daily in each cycle of 28 days (approximately, up to 44.4 months).

|                            |                   |
|----------------------------|-------------------|
| Subject analysis set title | Brigatinib 180 mg |
| Subject analysis set type  | Full analysis     |

Subject analysis set description:

Brigatinib 180 mg, tablets, orally once daily in each cycle of 28 days (approximately, up to 44.4 months).

|                            |                  |
|----------------------------|------------------|
| Subject analysis set title | Brigatinib 90 mg |
| Subject analysis set type  | Full analysis    |

Subject analysis set description:

Brigatinib 90 mg, tablets, orally, once daily or twice daily in each cycle of 28 days (approximately, up to 44.4 months).

|                            |                   |
|----------------------------|-------------------|
| Subject analysis set title | Brigatinib 240 mg |
| Subject analysis set type  | Full analysis     |

Subject analysis set description:

Brigatinib 240 mg, tablets, orally, once daily in each cycle of 28 days (approximately, up to 44.4 months).

|                            |                  |
|----------------------------|------------------|
| Subject analysis set title | Brigatinib 30 mg |
| Subject analysis set type  | Full analysis    |

Subject analysis set description:

Brigatinib 30 mg, tablets, orally, once daily (QD) in each cycle of 28 days (approximately, up to 44.4 months).

|                            |                   |
|----------------------------|-------------------|
| Subject analysis set title | Brigatinib 120 mg |
| Subject analysis set type  | Full analysis     |

Subject analysis set description:

Brigatinib 120 mg, tablets, orally, once daily in each cycle of 28 days (approximately, up to 44.4 months).

|                            |                       |
|----------------------------|-----------------------|
| Subject analysis set title | Dose Escalation Phase |
| Subject analysis set type  | Safety analysis       |

Subject analysis set description:

Participants received brigatinib tablets, orally, once daily (QD) starting at 30 mg in each cycle of 28 days (approximately, up to 44.4 months).

|                            |                  |
|----------------------------|------------------|
| Subject analysis set title | Brigatinib 30 mg |
| Subject analysis set type  | Full analysis    |

Subject analysis set description:

Brigatinib 30 mg, tablets, orally, once daily (QD) in each cycle of 28 days (approximately, up to 44.4 months).

|                            |                  |
|----------------------------|------------------|
| Subject analysis set title | Brigatinib 60 mg |
| Subject analysis set type  | Full analysis    |

Subject analysis set description:

Brigatinib 60 mg, tablets, orally, once daily (QD) in each cycle of 28 days (approximately, up to 44.4 months).

|                            |                  |
|----------------------------|------------------|
| Subject analysis set title | Brigatinib 90 mg |
| Subject analysis set type  | Full analysis    |

Subject analysis set description:

Brigatinib 90 mg, tablets, orally, once daily or twice daily in each cycle of 28 days (approximately, up to 44.4 months).

|                            |                   |
|----------------------------|-------------------|
| Subject analysis set title | Brigatinib 120 mg |
| Subject analysis set type  | Full analysis     |

Subject analysis set description:

Brigatinib 120 mg, tablets, orally, once daily in each cycle of 28 days (approximately, up to 44.4 months).

|                            |                   |
|----------------------------|-------------------|
| Subject analysis set title | Brigatinib 180 mg |
| Subject analysis set type  | Full analysis     |

Subject analysis set description:

Brigatinib 180 mg, tablets, orally once daily in each cycle of 28 days (approximately, up to 44.4 months).

|                            |                   |
|----------------------------|-------------------|
| Subject analysis set title | Brigatinib 240 mg |
| Subject analysis set type  | Full analysis     |

Subject analysis set description:

Brigatinib 240 mg, tablets, orally, once daily in each cycle of 28 days (approximately, up to 44.4 months).

### **Primary: Recommended Phase 2 Dose of AP26113**

|                 |                                                    |
|-----------------|----------------------------------------------------|
| End point title | Recommended Phase 2 Dose of AP26113 <sup>[1]</sup> |
|-----------------|----------------------------------------------------|

End point description:

The RP2D is the maximum tolerated dose (MTD) or less. The MTD is defined as the dose range at which  $\leq 1$  of 6 evaluable participants experience dose limiting toxicities (DLT) within the first 28 days of treatment (end of cycle 1). Safety population included all enrolled participants who received at least one dose of study drug. Here, 99.999 indicates R2PD for this study is a dose range.

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

End point timeframe:

28 days

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical Analysis not reported for this endpoint.

| End point values                       | Brigatinib           |  |  |  |
|----------------------------------------|----------------------|--|--|--|
| Subject group type                     | Subject analysis set |  |  |  |
| Number of subjects analysed            | 137                  |  |  |  |
| Units: mg                              |                      |  |  |  |
| arithmetic mean (full range (min-max)) | 99.999 (90 to 180)   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Objective Response Rate (ORR)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                              |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Objective Response Rate (ORR) <sup>[2]</sup> |
| End point description:<br>ORR is defined as the proportion of participants with complete response (CR) or partial response (PR) according to RECIST v1.1 after the initiation of study treatment. CR for target lesion: disappearance of all extranodal lesions and all pathological lymph nodes must have decreased to <10 mm in short axis. CR for non-target lesion: Disappearance of all extranodal non-target lesions, all lymph nodes must be non-pathological in size (<10mm short axis) and normalization of tumor marker level. PR: at least a 30% decrease in the sum of the longest diameters (SLD) of target lesions, taking as reference the baseline sum diameters. Full analysis set (FAS) included all participants who received at least one dose of study drug. Participants with ALK and NSCLC were evaluated for this outcome measure. Here, n is the number of participants who were evaluable for specific category. 99999 indicates that no participant was analyzed in this arm. Crzb=Crizotinib. |                                              |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Primary                                      |
| End point timeframe:<br>Screening and at 8-week intervals thereafter up to data cut-off date: 16 November 2015 (approximately up to 50 months)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                              |

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical Analysis not reported for this endpoint.

| End point values                                  | Brigatinib 30 mg QD/60 mg QD | Brigatinib 90 mg QD | Brigatinib 120 mg QD/60 mg BID | Brigatinib 90 mg QD-180 mg QD |
|---------------------------------------------------|------------------------------|---------------------|--------------------------------|-------------------------------|
| Subject group type                                | Reporting group              | Reporting group     | Reporting group                | Reporting group               |
| Number of subjects analysed                       | 1                            | 14                  | 6                              | 28                            |
| Units: percentage of participants                 |                              |                     |                                |                               |
| number (confidence interval 95%)                  |                              |                     |                                |                               |
| With Prior Treatment with Crzb (n=1,13,5,25,23,4) | 100 (2.5 to 100)             | 76.9 (46.2 to 95)   | 60 (14.7 to 94.7)              | 80 (59.3 to 93.2)             |
| Without Prior Treatment with Crzb (n=0,1,1,3,2,1) | 99999 (99999 to 99999)       | 100 (2.5 to 100)    | 100 (2.5 to 100)               | 100 (29.2 to 100)             |

| End point values | Brigatinib 180 mg QD/90 mg | Brigatinib 240 mg QD/120 mg |  |  |
|------------------|----------------------------|-----------------------------|--|--|
|------------------|----------------------------|-----------------------------|--|--|

|                                                      | BID                 | BID/300 mg QD    |  |  |
|------------------------------------------------------|---------------------|------------------|--|--|
| Subject group type                                   | Reporting group     | Reporting group  |  |  |
| Number of subjects analysed                          | 25                  | 5                |  |  |
| Units: percentage of participants                    |                     |                  |  |  |
| number (confidence interval 95%)                     |                     |                  |  |  |
| With Prior Treatment with Crzb<br>(n=1,13,5,25,23,4) | 65.2 (42.7 to 83.6) | 50 (6.8 to 93.2) |  |  |
| Without Prior Treatment with Crzb<br>(n=0,1,1,3,2,1) | 100 (15.8 to 100)   | 100 (2.5 to 100) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Intracranial Objective Response Rate

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

End point description:

Intracranial objective response rate is defined as the proportion of the participants with CR or PR in the intracranial CNS per modification of RECIST v1.1 after the initiation of study drug. CR for target lesion: disappearance of all extranodal lesions. CR for non-target lesion: disappearance of all extranodal non-target lesions and normalization of tumor marker level. PR: at least a 30% decrease in the sum of the longest diameters (SLD) of target lesions, taking as reference the baseline sum diameters. Full analysis set. ALK+ NSCLC participants with measurable and only non-measurable brain metastases at baseline were evaluated for this outcome measure. Here, n is the number of participants who were evaluable for specific category. 99999 indicates No participant was evaluated for this arm. Meta.=Metastases.

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

End point timeframe:

Screening and at 8-week intervals thereafter up to data cut-off date: 16 November 2015 (approximately up to 50 months)

| End point values                                    | Brigatinib 30 mg QD/60 mg QD | Brigatinib 90 mg QD | Brigatinib 120 mg QD/60 mg BID | Brigatinib 90 mg QD-180 mg QD |
|-----------------------------------------------------|------------------------------|---------------------|--------------------------------|-------------------------------|
| Subject group type                                  | Reporting group              | Reporting group     | Reporting group                | Reporting group               |
| Number of subjects analysed                         | 0 <sup>[3]</sup>             | 8                   | 1                              | 18                            |
| Units: percentage of participants                   |                              |                     |                                |                               |
| number (confidence interval 95%)                    |                              |                     |                                |                               |
| With Measurable Brain Metastases<br>(n=0,2,0,5,7,1) | ( to )                       | 100 (15.8 to 100)   | 99999 (99999 to 99999)         | 80 (28.4 to 99.5)             |
| With Non-Measurable Brain Meta.<br>(n=0,6,1,13,9,2) | ( to )                       | 16.7 (0.4 to 64.1)  | 100 (2.5 to 100)               | 46.2 (19.2 to 74.9)           |

Notes:

[3] - No participant was evaluated for this arm.

| End point values            | Brigatinib 180 mg QD/90 mg BID | Brigatinib 240 mg QD/120 mg BID/300 mg QD |  |  |
|-----------------------------|--------------------------------|-------------------------------------------|--|--|
| Subject group type          | Reporting group                | Reporting group                           |  |  |
| Number of subjects analysed | 16                             | 3                                         |  |  |



|                                                     |                     |                  |  |  |
|-----------------------------------------------------|---------------------|------------------|--|--|
| Units: percentage of participants                   |                     |                  |  |  |
| number (confidence interval 95%)                    |                     |                  |  |  |
| With Measurable Brain Metastases<br>(n=0,2,0,5,7,1) | 42.9 (9.9 to 81.6)  | 100 (2.5 to 100) |  |  |
| With Non-Measurable Brain Meta.<br>(n=0,6,1,13,9,2) | 44.4 (13.7 to 78.8) | 50 (1.3 to 98.7) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants Who Had at Least One Treatment-Emergent Adverse Event (TEAE)

|                 |                                                                                     |
|-----------------|-------------------------------------------------------------------------------------|
| End point title | Number of Participants Who Had at Least One Treatment-Emergent Adverse Event (TEAE) |
|-----------------|-------------------------------------------------------------------------------------|

End point description:

An Adverse Event (AE) is defined as any untoward medical occurrence in a clinical investigation participant administered a drug; it does not necessarily have to have a causal relationship with this treatment. A treatment-emergent adverse event (TEAE) is defined as an adverse event with an onset that occurs after receiving study drug. Safety population included all enrolled participants who received at least one dose of study drug.

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

End point timeframe:

Any adverse event reported on or after the day of first dose of study drug (approximately up to 50 months)

| End point values            | Brigatinib 30 mg QD/60 mg QD | Brigatinib 90 mg QD | Brigatinib 120 mg QD/60 mg BID | Brigatinib 90 mg QD-180 mg QD |
|-----------------------------|------------------------------|---------------------|--------------------------------|-------------------------------|
| Subject group type          | Reporting group              | Reporting group     | Reporting group                | Reporting group               |
| Number of subjects analysed | 6                            | 18                  | 18                             | 32                            |
| Units: participants         | 6                            | 18                  | 18                             | 31                            |

| End point values            | Brigatinib 180 mg QD/90 mg BID | Brigatinib 240 mg QD/120 mg BID/300 mg QD |  |  |
|-----------------------------|--------------------------------|-------------------------------------------|--|--|
| Subject group type          | Reporting group                | Reporting group                           |  |  |
| Number of subjects analysed | 48                             | 15                                        |  |  |
| Units: participants         | 48                             | 15                                        |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Maximum Tolerated Dose (MTD) Assessed in Dose Escalation Phase of the Study

|                 |                                                                             |
|-----------------|-----------------------------------------------------------------------------|
| End point title | Maximum Tolerated Dose (MTD) Assessed in Dose Escalation Phase of the Study |
|-----------------|-----------------------------------------------------------------------------|

### End point description:

The MTD is defined as the highest dose at which  $\leq 1$  of 6 evaluable participants experience a DLT within the first 28 days of treatment (end of cycle 1). Evaluable participants must complete at least 75% of their planned doses, unless missed doses are due to AEs. The cohort may be expanded to better define the safety profile for confirmation of the MTD. The maximum administered dose in the trial will likely exceed the MTD. Safety population included all enrolled participants who received at least one dose of study drug. MTD was not formally determined. Here 99999 indicates that MTD criteria was not met.

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

### End point timeframe:

Up to Cycle 1 (28 days)

| End point values            | Dose Escalation Phase |  |  |  |
|-----------------------------|-----------------------|--|--|--|
| Subject group type          | Subject analysis set  |  |  |  |
| Number of subjects analysed | 66                    |  |  |  |
| Units: mg                   |                       |  |  |  |
| number (not applicable)     | 99999                 |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants with Dose Limiting Toxicities (DLTs) Assessed in Dose Escalation Phase of the Study

|                 |                                                                                                            |
|-----------------|------------------------------------------------------------------------------------------------------------|
| End point title | Number of Participants with Dose Limiting Toxicities (DLTs) Assessed in Dose Escalation Phase of the Study |
|-----------------|------------------------------------------------------------------------------------------------------------|

### End point description:

DLT include any toxicity that is possibly, probably, or definitely drug-related. Toxicity grades will be defined by the NCI CTCAE v 4.0. DLTs are defined by the following: A) Non-hematologic toxicities: Any grade  $\geq 3$  non-hematologic toxicity, with the exception of self-limiting or medically controllable toxicities (eg, nausea, vomiting, fatigue, electrolyte disturbances, hypersensitivity reactions) lasting  $< 3$  days, and excluding alopecia. B) Hematologic toxicities: Febrile neutropenia not related to underlying disease (fever,  $> 101^{\circ}\text{F}$ ;  $\text{ANC} < 500$ ); Prolonged grade 4 neutropenia ( $> 7$  days); Neutropenic infection:  $\geq$  grade 3 neutropenia with  $\geq$  grade 3 infection; Thrombocytopenia  $\geq$  grade 3 with bleeding or grade 4 lasting  $\geq 7$  days. C) Missed  $\geq 25\%$  of planned doses of brigatinib over 28 days due to treatment-related AEs in the first cycle. Safety population included all enrolled participants who received at least one dose of study drug.

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

### End point timeframe:

Up to Cycle 1 (28 days)

| End point values            | Brigatinib 30 mg     | Brigatinib 60 mg     | Brigatinib 90 mg     | Brigatinib 120 mg    |
|-----------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type          | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 3                    | 3                    | 5                    | 3                    |
| Units: participants         | 0                    | 0                    | 0                    | 0                    |

| End point values            | Brigatinib 180 mg    | Brigatinib 240 mg    | Brigatinib 300 mg    |  |
|-----------------------------|----------------------|----------------------|----------------------|--|
| Subject group type          | Subject analysis set | Subject analysis set | Subject analysis set |  |
| Number of subjects analysed | 3                    | 6                    | 2                    |  |
| Units: participants         | 0                    | 1                    | 1                    |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Cmax: Maximum Observed Plasma Concentration for Brigatinib

|                 |                                                            |
|-----------------|------------------------------------------------------------|
| End point title | Cmax: Maximum Observed Plasma Concentration for Brigatinib |
|-----------------|------------------------------------------------------------|

End point description:

Analysis was performed on all enrolled participants in the study who received at least one dose of brigatinib. Here number of participant analyzed is the participants who were evaluable for this outcome measure.

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

End point timeframe:

Cycle 1 Day 1

| End point values                     | Brigatinib 30 mg     | Brigatinib 60 mg     | Brigatinib 90 mg     | Brigatinib 120 mg    |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type                   | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed          | 3                    | 3                    | 50                   | 11                   |
| Units: ng/mL                         |                      |                      |                      |                      |
| arithmetic mean (standard deviation) |                      |                      |                      |                      |
| Cmax                                 | 125.6 (± 41.07)      | 406.3 (± 102)        | 493 (± 289.5)        | 793.7 (± 828.7)      |

| End point values                     | Brigatinib 180 mg    | Brigatinib 240 mg    | Brigatinib 300 mg    |  |
|--------------------------------------|----------------------|----------------------|----------------------|--|
| Subject group type                   | Subject analysis set | Subject analysis set | Subject analysis set |  |
| Number of subjects analysed          | 44                   | 10                   | 2                    |  |
| Units: ng/mL                         |                      |                      |                      |  |
| arithmetic mean (standard deviation) |                      |                      |                      |  |
| Cmax                                 | 1185 (± 607.6)       | 1515 (± 637.9)       | 895 (± 99999)        |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) for Brigatinib

|                                                                                                                                                                                                                                                                                                                         |                                                                            |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                         | Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) for Brigatinib |
| End point description:<br>Analysis was performed on all enrolled participants in the study who received at least one dose of brigatinib. Participants of brigatinib 90 mg QD-180 mg QD arm were included as per treatment received at each time point. Here 99999 indicates that standard deviation was not calculated. |                                                                            |
| End point type                                                                                                                                                                                                                                                                                                          | Secondary                                                                  |
| End point timeframe:<br>Cycle 1 Day 1                                                                                                                                                                                                                                                                                   |                                                                            |

| End point values                     | Brigatinib 30 mg     | Brigatinib 60 mg     | Brigatinib 300 mg    | Brigatinib 90 mg     |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type                   | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed          | 3                    | 3                    | 2                    | 50                   |
| Units: hours                         |                      |                      |                      |                      |
| arithmetic mean (standard deviation) |                      |                      |                      |                      |
| Tmax                                 | 3.9 (± 99999)        | 1.83 (± 1.9)         | 4.05 (± 99999)       | 3.26 (± 4.53)        |

| End point values                     | Brigatinib 120 mg    | Brigatinib 240 mg    | Brigatinib 180 mg    |  |
|--------------------------------------|----------------------|----------------------|----------------------|--|
| Subject group type                   | Subject analysis set | Subject analysis set | Subject analysis set |  |
| Number of subjects analysed          | 11                   | 10                   | 44                   |  |
| Units: hours                         |                      |                      |                      |  |
| arithmetic mean (standard deviation) |                      |                      |                      |  |
| Tmax                                 | 2.78 (± 1.7)         | 2.22 (± 1.02)        | 2.99 (± 3.77)        |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: AUC(0-24): Area Under the Plasma Concentration-Time Curve From Time 0 to 24 hours post-dose for AP26113

|                 |                                                           |
|-----------------|-----------------------------------------------------------|
| End point title | AUC(0-24): Area Under the Plasma Concentration-Time Curve |
|-----------------|-----------------------------------------------------------|

**End point description:**

Analysis was performed on all enrolled participants in the study who received at least one dose of brigatinib. Participants of brigatinib 90 mg QD-180 mg QD arm were included as per treatment received at each time point.

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

**End point timeframe:**

Cycle 1 Day 1, 8, 15 and 22 pre-dose and Day 1 multiple timepoints (up to 48 hours) post-dose; Cycle 2 Day 1 and 3 pre-dose and Day 1 multiple time points (up to 48 hours) post-dose

| End point values                     | Brigatinib 30 mg     | Brigatinib 60 mg     | Brigatinib 300 mg    | Brigatinib 120 mg    |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type                   | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed          | 3                    | 3                    | 2                    | 11                   |
| Units: h*ng/mL                       |                      |                      |                      |                      |
| arithmetic mean (standard deviation) | 1320.9 (± 576.29)    | 3900 (± 430.31)      | 7571.1 (± 99999)     | 9895.5 (± 11772)     |

| End point values                     | Brigatinib 180 mg    | Brigatinib 90 mg     | Brigatinib 240 mg    |  |
|--------------------------------------|----------------------|----------------------|----------------------|--|
| Subject group type                   | Subject analysis set | Subject analysis set | Subject analysis set |  |
| Number of subjects analysed          | 44                   | 15                   | 7                    |  |
| Units: h*ng/mL                       |                      |                      |                      |  |
| arithmetic mean (standard deviation) | 13204 (± 6306.9)     | 5710.1 (± 3268.4)    | 16800 (± 7571.1)     |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Terminal Phase Elimination Half-life (T<sub>1/2</sub>) for Brigatinib**

|                 |                                                                         |
|-----------------|-------------------------------------------------------------------------|
| End point title | Terminal Phase Elimination Half-life (T <sub>1/2</sub> ) for Brigatinib |
|-----------------|-------------------------------------------------------------------------|

**End point description:**

Analysis was performed on all enrolled participants in the study who received at least one dose of brigatinib. Participants of brigatinib 90 mg QD-180 mg QD arm were included as per treatment received at each time point. Here, 99999 indicates that standard deviation was not calculated.

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

**End point timeframe:**

Cycle 2 Day 1

| End point values                     | Brigatinib 60 mg     | Brigatinib 180 mg    | Brigatinib 90 mg     | Brigatinib 240 mg    |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type                   | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed          | 3                    | 63                   | 15                   | 7                    |
| Units: hours                         |                      |                      |                      |                      |
| arithmetic mean (standard deviation) | 30.93 ( $\pm$ 5.873) | 24.9 ( $\pm$ 7.437)  | 28.69 ( $\pm$ 10.06) | 21.77 ( $\pm$ 4.007) |

| End point values                     | Brigatinib 30 mg     | Brigatinib 120 mg    |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed          | 2                    | 10                   |  |  |
| Units: hours                         |                      |                      |  |  |
| arithmetic mean (standard deviation) | 31.55 ( $\pm$ 99999) | 25.52 ( $\pm$ 7.958) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Best Overall Response

|                 |                       |
|-----------------|-----------------------|
| End point title | Best Overall Response |
|-----------------|-----------------------|

End point description:

Best overall response is defined as proportion of participants with CR, PR, stable disease (SD) or progressive disease (PD) as per of RECIST v1.1 as evaluated by investigator. Disease progression for target lesion: SLD increased by at least 20% from smallest value on study and SLD must also demonstrate an absolute increase of at least 5 mm or development of any new lesion. PD for non-target lesion: unequivocal progression of existing non-target lesions. SD for neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. Full analysis set. Participants with ALK and NSCLC were evaluated for this outcome measure. Here 99999 indicates 95% CI was not estimable due to low number of participants with events.

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

End point timeframe:

Screening and at 8-week intervals thereafter up to data cut-off date: 16 November 2015 (approximately up to 50 months)

| End point values                  | Brigatinib 30 mg QD/60 mg QD | Brigatinib 90 mg QD | Brigatinib 120 mg QD/60 mg BID | Brigatinib 90 mg QD-180 mg QD |
|-----------------------------------|------------------------------|---------------------|--------------------------------|-------------------------------|
| Subject group type                | Reporting group              | Reporting group     | Reporting group                | Reporting group               |
| Number of subjects analysed       | 1                            | 13                  | 5                              | 25                            |
| Units: percentage of participants |                              |                     |                                |                               |
| number (confidence interval 95%)  |                              |                     |                                |                               |
| Complete Response                 | 0 (-99999 to 99999)          | 0 (-99999 to 99999) | 0 (-99999 to 99999)            | 8 (1 to 26)                   |
| Partial Response                  | 100 (2.5 to 100)             | 76.9 (46.2 to 95)   | 60 (14.7 to 94.7)              | 72 (50.6 to 87.9)             |
| Stable Disease                    | 0 (-99999 to 99999)          | 0 (-99999 to 99999) | 0 (-99999 to 99999)            | 8 (1 to 26)                   |

|                     |                     |                     |                     |             |
|---------------------|---------------------|---------------------|---------------------|-------------|
| Progressive Disease | 0 (-99999 to 99999) | 0 (-99999 to 99999) | 0 (-99999 to 99999) | 8 (1 to 26) |
|---------------------|---------------------|---------------------|---------------------|-------------|

| End point values                  | Brigatinib 180 mg QD/90 mg BID | Brigatinib 240 mg QD/120 mg BID/300 mg QD |  |  |
|-----------------------------------|--------------------------------|-------------------------------------------|--|--|
| Subject group type                | Reporting group                | Reporting group                           |  |  |
| Number of subjects analysed       | 23                             | 4                                         |  |  |
| Units: percentage of participants |                                |                                           |  |  |
| number (confidence interval 95%)  |                                |                                           |  |  |
| Complete Response                 | 8.7 (1.1 to 28)                | 0 (-99999 to 99999)                       |  |  |
| Partial Response                  | 56.5 (34.5 to 76.8)            | 50 (6.8 to 93.2)                          |  |  |
| Stable Disease                    | 13 (2.8 to 33.6)               | 50 (6.8 to 93.2)                          |  |  |
| Progressive Disease               | 21.7 (7.5 to 43.7)             | 0 (-99999 to 99999)                       |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of Response

|                 |                      |
|-----------------|----------------------|
| End point title | Duration of Response |
|-----------------|----------------------|

End point description:

Duration of response is defined as time interval from the time that measurement criteria are first met for CR/PR (whichever is first recorded) until first date that progressive disease is objectively documented or death due to any cause. Participants who did not progress nor die were censored at last valid response assessment. FAS. Participants who were responders among those who were had anaplastic lymphoma kinase (ALK) and non-small cell lung cancer (NSCLC) were evaluated for this outcome measure. Here 'n' is participants analysed for each category. Duration of response was calculated by Kaplan-Meier estimation. Here 99999 indicates that Median/Upper/lower limits of CI were not reached due to low number of participants with events.

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

End point timeframe:

Screening and at 8-week intervals thereafter up to data cut-off date: 16 November 2015 (approximately up to 50 months)

| End point values                                  | Brigatinib 30 mg QD/60 mg QD | Brigatinib 90 mg QD | Brigatinib 120 mg QD/60 mg BID | Brigatinib 90 mg QD-180 mg QD |
|---------------------------------------------------|------------------------------|---------------------|--------------------------------|-------------------------------|
| Subject group type                                | Reporting group              | Reporting group     | Reporting group                | Reporting group               |
| Number of subjects analysed                       | 1                            | 13                  | 5                              | 25                            |
| Units: months                                     |                              |                     |                                |                               |
| median (confidence interval 95%)                  |                              |                     |                                |                               |
| With Prior Treatment with Crzb (n=1,10,3,20,15,2) | 1.9 (-99999 to 99999)        | 8.3 (1.1 to 11.2)   | 4 (3.7 to 99999)               | 14.8 (7.4 to 99999)           |

|                                                      |                         |                         |                         |                      |
|------------------------------------------------------|-------------------------|-------------------------|-------------------------|----------------------|
| Without Prior Treatment with Crzb<br>(n=0,1,1,3,2,1) | 99999 (-99999 to 99999) | 99999 (-99999 to 99999) | 99999 (-99999 to 99999) | 99999 (5.6 to 99999) |
|------------------------------------------------------|-------------------------|-------------------------|-------------------------|----------------------|

| End point values                                     | Brigatinib 180 mg QD/90 mg BID | Brigatinib 240 mg QD/120 mg BID/300 mg QD |  |  |
|------------------------------------------------------|--------------------------------|-------------------------------------------|--|--|
| Subject group type                                   | Reporting group                | Reporting group                           |  |  |
| Number of subjects analysed                          | 23                             | 4                                         |  |  |
| Units: months                                        |                                |                                           |  |  |
| median (confidence interval 95%)                     |                                |                                           |  |  |
| With Prior Treatment with Crzb<br>(n=1,10,3,20,15,2) | 9.9 (3.6 to 99999)             | 29.7 (-99999 to 99999)                    |  |  |
| Without Prior Treatment with Crzb<br>(n=0,1,1,3,2,1) | 99999 (9.2 to 99999)           | 99999 (-99999 to 99999)                   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Progression Free Survival (PFS)

|                 |                                 |
|-----------------|---------------------------------|
| End point title | Progression Free Survival (PFS) |
|-----------------|---------------------------------|

End point description:

PFS is defined as the time interval from the date of the first dose of the study treatment until the first date at which disease progression is objectively documented, or death due to any cause, whichever occurs first. Disease progression for target lesion: SLD increased by at least 20% from the smallest value on study (including baseline, if that is the smallest) and SLD must also demonstrate an absolute increase of at least 5 mm or development of any new lesion. Disease progression for non-target lesion: Unequivocal progression of existing non-target lesions. (Subjective judgment by experienced reader). PFS was calculated by Kaplan-Meier estimation. Full analysis set. Participants with anaplastic lymphoma kinase (ALK) and non-small cell lung cancer (NSCLC) were evaluated for this outcome measure. Here 'n' is participants analysed for each category. Here 99999 indicates that Median/Upper/lower limits of CI were not reached due to low number of participants with events.

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

End point timeframe:

Screening and at 8-week intervals thereafter up to data cut-off date: 16 November 2015 (approximately up to 50 months)

| End point values                                     | Brigatinib 30 mg QD/60 mg QD | Brigatinib 90 mg QD     | Brigatinib 120 mg QD/60 mg BID | Brigatinib 90 mg QD-180 mg QD |
|------------------------------------------------------|------------------------------|-------------------------|--------------------------------|-------------------------------|
| Subject group type                                   | Reporting group              | Reporting group         | Reporting group                | Reporting group               |
| Number of subjects analysed                          | 1                            | 13                      | 5                              | 25                            |
| Units: months                                        |                              |                         |                                |                               |
| median (confidence interval 95%)                     |                              |                         |                                |                               |
| With Prior Treatment with Crzb<br>(n=1,9,4,13,14,3)  | 3.5 (-99999 to 99999)        | 11.9 (3.5 to 18.7)      | 5.7 (0.5 to 99999)             | 16.3 (9.2 to 99999)           |
| Without Prior Treatment with Crzb<br>(n=0,0,0,1,1,0) | 99999 (-99999 to 99999)      | 99999 (-99999 to 99999) | 99999 (-99999 to 99999)        | 99999 (7.4 to 99999)          |



| End point values                                  | Brigatinib 180 mg QD/90 mg BID | Brigatinib 240 mg QD/120 mg BID/300 mg QD |  |  |
|---------------------------------------------------|--------------------------------|-------------------------------------------|--|--|
| Subject group type                                | Reporting group                | Reporting group                           |  |  |
| Number of subjects analysed                       | 23                             | 4                                         |  |  |
| Units: months                                     |                                |                                           |  |  |
| median (confidence interval 95%)                  |                                |                                           |  |  |
| With Prior Treatment with Crzb (n=1,9,4,13,14,3)  | 10.8 (4.5 to 99999)            | 7.3 (1.9 to 31.5)                         |  |  |
| Without Prior Treatment with Crzb (n=0,0,0,1,1,0) | 99999 (11.1 to 99999)          | 99999 (-99999 to 99999)                   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Overall Survival (OS)

|                                                                                                                                                                                                                                                                                                                                                                                                 |                       |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                 | Overall Survival (OS) |
| End point description:                                                                                                                                                                                                                                                                                                                                                                          |                       |
| OS is defined as the time interval from the date of the first dose of the study treatment until death due to any cause. Full analysis set. Participants with anaplastic lymphoma kinase (ALK) and non-small cell lung cancer (NSCLC) were evaluated for this outcome measure. Here, 99999 indicates that median overall survival was not reached due to low number of participants with events. |                       |
| End point type                                                                                                                                                                                                                                                                                                                                                                                  | Secondary             |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                            |                       |
| Screening and at 8-week intervals thereafter up to data cut-off date: 16 November 2015 (approximately up to 50 months)                                                                                                                                                                                                                                                                          |                       |

| End point values                 | Brigatinib 30 mg QD/60 mg QD | Brigatinib 90 mg QD | Brigatinib 120 mg QD/60 mg BID | Brigatinib 90 mg QD-180 mg QD |
|----------------------------------|------------------------------|---------------------|--------------------------------|-------------------------------|
| Subject group type               | Reporting group              | Reporting group     | Reporting group                | Reporting group               |
| Number of subjects analysed      | 1                            | 14                  | 6                              | 28                            |
| Units: months                    |                              |                     |                                |                               |
| median (confidence interval 95%) | 99999 (-99999 to 99999)      | 9.9999 (8 to 18.7)  | 99999 (-99999 to 99999)        | 9.9999 (1.4 to 22.5)          |

| End point values            | Brigatinib 180 mg QD/90 mg BID | Brigatinib 240 mg QD/120 mg BID/300 mg QD |  |  |
|-----------------------------|--------------------------------|-------------------------------------------|--|--|
| Subject group type          | Reporting group                | Reporting group                           |  |  |
| Number of subjects analysed | 25                             | 5                                         |  |  |
| Units: months               |                                |                                           |  |  |

|                                  |                      |                          |  |  |
|----------------------------------|----------------------|--------------------------|--|--|
| median (confidence interval 95%) | 9.9999 (0.2 to 17.6) | 9.9999 (-99999 to 99999) |  |  |
|----------------------------------|----------------------|--------------------------|--|--|

## Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of Intracranial Response

|                 |                                   |
|-----------------|-----------------------------------|
| End point title | Duration of Intracranial Response |
|-----------------|-----------------------------------|

End point description:

Intracranial duration of response is defined as the time interval from the time that the measurement criteria are first met for CR/PR in brain metastases (whichever is first recorded) until the first date that progressive disease is objectively documented or death due to any cause. Participants who did not progress nor die were censored at the last valid response assessment. Duration intracranial of response was calculated by Kaplan-Meier estimation. Full analysis set. ALK+ NSCLC participants with measurable and only non-measurable brain metastases at baseline were evaluated for this outcome measure. Here 99999 indicates that median/upper/lower limits of CI were not reached due to low number of participants with events.

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

End point timeframe:

Screening and at 8-week intervals thereafter up to data cut-off date: 16 November 2015 (approximately up to 50 months)

| End point values                 | Brigatinib 30 mg QD/60 mg QD | Brigatinib 90 mg QD    | Brigatinib 120 mg QD/60 mg BID | Brigatinib 90 mg QD-180 mg QD |
|----------------------------------|------------------------------|------------------------|--------------------------------|-------------------------------|
| Subject group type               | Reporting group              | Reporting group        | Reporting group                | Reporting group               |
| Number of subjects analysed      | 0 <sup>[4]</sup>             | 8                      | 1                              | 18                            |
| Units: months                    |                              |                        |                                |                               |
| median (confidence interval 95%) | ( to )                       | 12.9 (-99999 to 99999) | 5 (-99999 to 99999)            | 11.4 (7.5 to 11.4)            |

Notes:

[4] - No participant was analysed in this arm

| End point values                 | Brigatinib 180 mg QD/90 mg BID | Brigatinib 240 mg QD/120 mg BID/300 mg QD |  |  |
|----------------------------------|--------------------------------|-------------------------------------------|--|--|
| Subject group type               | Reporting group                | Reporting group                           |  |  |
| Number of subjects analysed      | 16                             | 3                                         |  |  |
| Units: months                    |                                |                                           |  |  |
| median (confidence interval 95%) | 29.2 (5.5 to 29.2)             | 11.3 (3.6 to 18.9)                        |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Intracranial Progression Free Survival (PFS)

|                 |                                              |
|-----------------|----------------------------------------------|
| End point title | Intracranial Progression Free Survival (PFS) |
|-----------------|----------------------------------------------|

End point description:

PFS is defined as the time interval from the date of the first dose of the study treatment until the first date at which disease progression in brain, or death due to any cause, whichever occurs first. Intracranial PFS was calculated by Kaplan-Meier estimation. Full analysis set. ALK+ NSCLC participants with measurable and only non-measurable brain metastases at baseline were evaluated for this outcome measure. Here 99999 indicates that median/upper limit of CI was not reached due to low number of participants with events.

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

End point timeframe:

Screening and at 8-week intervals thereafter up to data cut-off date: 16 November 2015 (approximately up to 50 months)

| End point values                 | Brigatinib 30 mg QD/60 mg QD | Brigatinib 90 mg QD | Brigatinib 120 mg QD/60 mg BID | Brigatinib 90 mg QD-180 mg QD |
|----------------------------------|------------------------------|---------------------|--------------------------------|-------------------------------|
| Subject group type               | Reporting group              | Reporting group     | Reporting group                | Reporting group               |
| Number of subjects analysed      | 0 <sup>[5]</sup>             | 8                   | 1                              | 18                            |
| Units: months                    |                              |                     |                                |                               |
| median (confidence interval 95%) | ( to )                       | 36.8 (5.5 to 36.8)  | 6.7 (-99999 to 99999)          | 99999 (9.4 to 99999)          |

Notes:

[5] - No participant was analysed in this arm.

| End point values                 | Brigatinib 180 mg QD/90 mg BID | Brigatinib 240 mg QD/120 mg BID/300 mg QD |  |  |
|----------------------------------|--------------------------------|-------------------------------------------|--|--|
| Subject group type               | Reporting group                | Reporting group                           |  |  |
| Number of subjects analysed      | 16                             | 3                                         |  |  |
| Units: months                    |                                |                                           |  |  |
| median (confidence interval 95%) | 14.4 (7.3 to 31.1)             | 7.3 (3.1 to 22.3)                         |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Cmax: Maximum Observed Plasma Concentration for Brigatinib

|                 |                                                            |
|-----------------|------------------------------------------------------------|
| End point title | Cmax: Maximum Observed Plasma Concentration for Brigatinib |
|-----------------|------------------------------------------------------------|

End point description:

Analysis was performed on all enrolled participants in the study who received at least one dose of brigatinib. Here number of participants analyzed is the participants who were evaluable for this outcome measure. Here 99999 indicates that standard deviation was not calculated.

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

End point timeframe:

Cycle 2 Day 2

| End point values                     | Brigatinib 30 mg     | Brigatinib 60 mg     | Brigatinib 90 mg     | Brigatinib 120 mg    |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type                   | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed          | 2                    | 3                    | 15                   | 10                   |
| Units: ng/mL                         |                      |                      |                      |                      |
| arithmetic mean (standard deviation) | 249.5 (± 99999)      | 491.67 (± 223.95)    | 634.07 (± 310.05)    | 942.3 (± 472.33)     |

| End point values                     | Brigatinib 180 mg    | Brigatinib 240 mg    |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed          | 63                   | 7                    |  |  |
| Units: ng/mL                         |                      |                      |  |  |
| arithmetic mean (standard deviation) | 1694.3 (± 1014.3)    | 1694.3 (± 1014.3)    |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) for Brigatinib

|                 |                                                                            |
|-----------------|----------------------------------------------------------------------------|
| End point title | Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) for Brigatinib |
|-----------------|----------------------------------------------------------------------------|

End point description:

Analysis was performed on all enrolled participants in the study who received at least one dose of brigatinib. Here, 99999 indicates that standard deviation was not calculated.

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

End point timeframe:

Cycle 2 Day 1

| End point values                     | Brigatinib 30 mg     | Brigatinib 60 mg     | Brigatinib 90 mg     | Brigatinib 120 mg    |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type                   | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed          | 2                    | 3                    | 15                   | 10                   |
| Units: hour                          |                      |                      |                      |                      |
| arithmetic mean (standard deviation) | 2.49 (± 99999)       | 1.1 (± 0.656)        | 2.56 (± 1.98)        | 2.79 (± 1.88)        |

| End point values | Brigatinib 180 mg | Brigatinib 240 mg |  |  |
|------------------|-------------------|-------------------|--|--|
|------------------|-------------------|-------------------|--|--|

|                                      |                      |                      |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed          | 63                   | 7                    |  |  |
| Units: hour                          |                      |                      |  |  |
| arithmetic mean (standard deviation) | 2.66 (± 1.46)        | 2.44 (± 1.13)        |  |  |

## Statistical analyses

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Any adverse event reported on or after the day of first dose of study drug (approximately up to 50 months)

Adverse event reporting additional description:

At each visit the investigator had to document any occurrence of adverse events and abnormal laboratory findings. Any event spontaneously reported by the participant or observed by the investigator was recorded, irrespective of the relation to study treatment.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 18.0 |
|--------------------|------|

### Reporting groups

|                       |                           |
|-----------------------|---------------------------|
| Reporting group title | AP26113 30 mg QD/60 mg QD |
|-----------------------|---------------------------|

Reporting group description:

AP26113 30 mg/60 mg (lower doses than RP2Ds), tablets, orally, once daily (QD) in each cycle of 28 days (approximately, up to 44.4 months).

|                       |                  |
|-----------------------|------------------|
| Reporting group title | AP26113 90 mg QD |
|-----------------------|------------------|

Reporting group description:

AP26113 90 mg (lower dose than RP2Ds), tablets, orally, once daily (QD) in each cycle of 28 days (approximately, up to 44.4 months).

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | AP26113 120 mg QD/60 mg BID |
|-----------------------|-----------------------------|

Reporting group description:

AP26113 120 mg, once daily or 60 mg, twice daily (BID) (doses between the two RP2Ds), tablets, orally, in each cycle of 28 days (approximately, up to 44.4 months).

|                       |                            |
|-----------------------|----------------------------|
| Reporting group title | AP26113 90 mg QD-180 mg QD |
|-----------------------|----------------------------|

Reporting group description:

AP26113 90 mg, tablets, orally, once daily for up to 7 days followed by 180 mg (higher RP2D), tablets, orally, once daily in each cycle of 28 days (approximately, up to 44.4 months).

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | AP26113 180 mg QD/90 mg BID |
|-----------------------|-----------------------------|

Reporting group description:

AP26113 180 mg, once daily or 90 mg, twice daily (BID), tablets, orally in each cycle of 28 days (approximately, up to 44.4 months).

|                       |                                        |
|-----------------------|----------------------------------------|
| Reporting group title | AP26113 240 mg QD/120 mg BID/300 mg QD |
|-----------------------|----------------------------------------|

Reporting group description:

AP26113 240 mg, once daily (QD) or 120 mg, twice daily (BID) or 300 mg once daily (doses higher than 180 mg QD), tablets, orally, in each cycle of 28 days (approximately, up to 44.4 months).

| Serious adverse events                                              | AP26113 30 mg QD/60 mg QD | AP26113 90 mg QD | AP26113 120 mg QD/60 mg BID |
|---------------------------------------------------------------------|---------------------------|------------------|-----------------------------|
| Total subjects affected by serious adverse events                   |                           |                  |                             |
| subjects affected / exposed                                         | 1 / 6 (16.67%)            | 9 / 18 (50.00%)  | 10 / 18 (55.56%)            |
| number of deaths (all causes)                                       | 0                         | 3                | 2                           |
| number of deaths resulting from adverse events                      | 0                         | 0                | 0                           |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                           |                  |                             |
| Neoplasm progression                                                |                           |                  |                             |

|                                                 |                |                 |                |
|-------------------------------------------------|----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 2 / 18 (11.11%) | 1 / 18 (5.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 2           | 0 / 1          |
| Pericardial effusion malignant                  |                |                 |                |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 0 / 18 (0.00%)  | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Metastases to central nervous system            |                |                 |                |
| subjects affected / exposed                     | 1 / 6 (16.67%) | 0 / 18 (0.00%)  | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Cancer pain                                     |                |                 |                |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 0 / 18 (0.00%)  | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Intracranial tumour haemorrhage                 |                |                 |                |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 0 / 18 (0.00%)  | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Malignant ascites                               |                |                 |                |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Metastatic malignant melanoma                   |                |                 |                |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 0 / 18 (0.00%)  | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Metastatic pain                                 |                |                 |                |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 0 / 18 (0.00%)  | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Vascular disorders                              |                |                 |                |
| Haematoma                                       |                |                 |                |

|                                                      |               |                |                |
|------------------------------------------------------|---------------|----------------|----------------|
| subjects affected / exposed                          | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0         | 0 / 0          | 0 / 0          |
| General disorders and administration site conditions |               |                |                |
| Non-cardiac chest pain                               |               |                |                |
| subjects affected / exposed                          | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0         | 0 / 0          | 0 / 0          |
| Pyrexia                                              |               |                |                |
| subjects affected / exposed                          | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0         | 0 / 0          | 0 / 0          |
| Asthenia                                             |               |                |                |
| subjects affected / exposed                          | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0         | 0 / 0          | 0 / 0          |
| Chest pain                                           |               |                |                |
| subjects affected / exposed                          | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0         | 0 / 0          | 0 / 0          |
| Death                                                |               |                |                |
| subjects affected / exposed                          | 0 / 6 (0.00%) | 1 / 18 (5.56%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0         | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0         | 1 / 1          | 0 / 0          |
| Influenza like illness                               |               |                |                |
| subjects affected / exposed                          | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0         | 0 / 0          | 0 / 0          |
| Sudden death                                         |               |                |                |
| subjects affected / exposed                          | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0         | 0 / 0          | 0 / 0          |
| Immune system disorders                              |               |                |                |



|                                                 |               |                 |                |
|-------------------------------------------------|---------------|-----------------|----------------|
| Food allergy                                    |               |                 |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 1 / 18 (5.56%)  | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Respiratory, thoracic and mediastinal disorders |               |                 |                |
| Dyspnoea                                        |               |                 |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 1 / 18 (5.56%)  | 1 / 18 (5.56%) |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 1           | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Hypoxia                                         |               |                 |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 2 / 18 (11.11%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Pulmonary embolism                              |               |                 |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 1 / 18 (5.56%)  | 1 / 18 (5.56%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Pneumonitis                                     |               |                 |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%)  | 1 / 18 (5.56%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0           | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Cough                                           |               |                 |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%)  | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Pleural effusion                                |               |                 |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%)  | 1 / 18 (5.56%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Respiratory failure                             |               |                 |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%)  | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |

|                                                 |               |                |                |
|-------------------------------------------------|---------------|----------------|----------------|
| Acute respiratory distress syndrome             |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Haemoptysis                                     |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Pneumothorax                                    |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Psychiatric disorders                           |               |                |                |
| Mental status changes                           |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 1 / 18 (5.56%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Confusional state                               |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Suicidal ideation                               |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Investigations                                  |               |                |                |
| Alanine aminotransferase increased              |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Aspartate aminotransferase increased            |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |

|                                                 |               |                |                |
|-------------------------------------------------|---------------|----------------|----------------|
| Computerised tomogram thorax abnormal           |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Injury, poisoning and procedural complications  |               |                |                |
| Post procedural haemorrhage                     |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Radiation necrosis                              |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Radiation pneumonitis                           |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Cardiac disorders                               |               |                |                |
| Atrial fibrillation                             |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 1 / 18 (5.56%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Supraventricular tachycardia                    |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Cardiac failure congestive                      |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 1 / 18 (5.56%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Cardiac tamponade                               |               |                |                |

|                                                 |               |                |                |
|-------------------------------------------------|---------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Left ventricular dysfunction                    |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Tachycardia                                     |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Nervous system disorders                        |               |                |                |
| Seizure                                         |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 1 / 18 (5.56%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Syncope                                         |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 1 / 18 (5.56%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Central nervous system haemorrhage              |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Cerebral haemorrhage                            |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Cognitive disorder                              |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Embolic stroke                                  |               |                |                |

|                                                 |               |                |                |
|-------------------------------------------------|---------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Haemorrhage intracranial                        |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Haemorrhagic stroke                             |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 1 / 18 (5.56%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Headache                                        |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Ischaemic stroke                                |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Nervous system disorder                         |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Transient ischaemic attack                      |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Gastrointestinal disorders                      |               |                |                |
| Pancreatitis                                    |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Abdominal wall haematoma                        |               |                |                |

|                                                 |               |                |                |
|-------------------------------------------------|---------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Bezoar                                          |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Colitis                                         |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Gastric ulcer haemorrhage                       |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Haemorrhoids                                    |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 1 / 18 (5.56%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Oesophageal compression                         |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Rectal ulcer                                    |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 1 / 18 (5.56%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Skin and subcutaneous tissue disorders          |               |                |                |
| Eczema                                          |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 1 / 18 (5.56%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Rash                                            |               |                |                |

|                                                 |               |                 |                 |
|-------------------------------------------------|---------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0           |
| Renal and urinary disorders                     |               |                 |                 |
| Acute kidney injury                             |               |                 |                 |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0           |
| Musculoskeletal and connective tissue disorders |               |                 |                 |
| Back pain                                       |               |                 |                 |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0           |
| Bone pain                                       |               |                 |                 |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0           |
| Intervertebral disc protrusion                  |               |                 |                 |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0           |
| Muscular weakness                               |               |                 |                 |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0           |
| Pain in extremity                               |               |                 |                 |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0           |
| Infections and infestations                     |               |                 |                 |
| Pneumonia                                       |               |                 |                 |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 2 / 18 (11.11%) | 3 / 18 (16.67%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 4           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 1           |

|                                                 |               |                |                |
|-------------------------------------------------|---------------|----------------|----------------|
| Bronchitis                                      |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 1 / 18 (5.56%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Sepsis                                          |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 1 / 18 (5.56%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Device related infection                        |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 1 / 18 (5.56%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Device related sepsis                           |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 1 / 18 (5.56%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Lower respiratory tract infection bacterial     |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 1 / 18 (5.56%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Pneumonia pseudomonal                           |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 1 / 18 (5.56%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Urinary tract infection                         |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Viral infection                                 |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Metabolism and nutrition disorders              |               |                |                |



|                                                 |               |                |                |
|-------------------------------------------------|---------------|----------------|----------------|
| Failure to thrive                               |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 1 / 18 (5.56%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Hyperglycaemia                                  |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Hyponatraemia                                   |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Insulin resistance                              |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 1 / 18 (5.56%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |

| <b>Serious adverse events</b>                                       | AP26113 90 mg QD-180 mg QD | AP26113 180 mg QD/90 mg BID | AP26113 240 mg QD/120 mg BID/300 mg QD |
|---------------------------------------------------------------------|----------------------------|-----------------------------|----------------------------------------|
| Total subjects affected by serious adverse events                   |                            |                             |                                        |
| subjects affected / exposed                                         | 9 / 32 (28.13%)            | 25 / 48 (52.08%)            | 10 / 15 (66.67%)                       |
| number of deaths (all causes)                                       | 3                          | 8                           | 1                                      |
| number of deaths resulting from adverse events                      | 0                          | 0                           | 0                                      |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                            |                             |                                        |
| Neoplasm progression                                                |                            |                             |                                        |
| subjects affected / exposed                                         | 1 / 32 (3.13%)             | 4 / 48 (8.33%)              | 0 / 15 (0.00%)                         |
| occurrences causally related to treatment / all                     | 0 / 1                      | 0 / 4                       | 0 / 0                                  |
| deaths causally related to treatment / all                          | 0 / 1                      | 0 / 4                       | 0 / 0                                  |
| Pericardial effusion malignant                                      |                            |                             |                                        |
| subjects affected / exposed                                         | 3 / 32 (9.38%)             | 0 / 48 (0.00%)              | 0 / 15 (0.00%)                         |
| occurrences causally related to treatment / all                     | 0 / 3                      | 0 / 0                       | 0 / 0                                  |
| deaths causally related to treatment / all                          | 0 / 0                      | 0 / 0                       | 0 / 0                                  |
| Metastases to central nervous system                                |                            |                             |                                        |

|                                                      |                |                |                |
|------------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                          | 0 / 32 (0.00%) | 1 / 48 (2.08%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Cancer pain                                          |                |                |                |
| subjects affected / exposed                          | 0 / 32 (0.00%) | 1 / 48 (2.08%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Intracranial tumour haemorrhage                      |                |                |                |
| subjects affected / exposed                          | 0 / 32 (0.00%) | 1 / 48 (2.08%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Malignant ascites                                    |                |                |                |
| subjects affected / exposed                          | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Metastatic malignant melanoma                        |                |                |                |
| subjects affected / exposed                          | 0 / 32 (0.00%) | 1 / 48 (2.08%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Metastatic pain                                      |                |                |                |
| subjects affected / exposed                          | 0 / 32 (0.00%) | 1 / 48 (2.08%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Vascular disorders                                   |                |                |                |
| Haematoma                                            |                |                |                |
| subjects affected / exposed                          | 0 / 32 (0.00%) | 1 / 48 (2.08%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| General disorders and administration site conditions |                |                |                |
| Non-cardiac chest pain                               |                |                |                |
| subjects affected / exposed                          | 0 / 32 (0.00%) | 1 / 48 (2.08%) | 1 / 15 (6.67%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |

|                                                 |                |                |                 |
|-------------------------------------------------|----------------|----------------|-----------------|
| Pyrexia                                         |                |                |                 |
| subjects affected / exposed                     | 1 / 32 (3.13%) | 0 / 48 (0.00%) | 1 / 15 (6.67%)  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Asthenia                                        |                |                |                 |
| subjects affected / exposed                     | 1 / 32 (3.13%) | 0 / 48 (0.00%) | 0 / 15 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Chest pain                                      |                |                |                 |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 1 / 48 (2.08%) | 0 / 15 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Death                                           |                |                |                 |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 0 / 15 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Influenza like illness                          |                |                |                 |
| subjects affected / exposed                     | 1 / 32 (3.13%) | 0 / 48 (0.00%) | 0 / 15 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Sudden death                                    |                |                |                 |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 1 / 48 (2.08%) | 0 / 15 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 1 / 1          | 0 / 0           |
| Immune system disorders                         |                |                |                 |
| Food allergy                                    |                |                |                 |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 0 / 15 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders |                |                |                 |
| Dyspnoea                                        |                |                |                 |
| subjects affected / exposed                     | 1 / 32 (3.13%) | 2 / 48 (4.17%) | 4 / 15 (26.67%) |
| occurrences causally related to treatment / all | 0 / 2          | 3 / 3          | 4 / 5           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1           |

|                                                 |                |                |                 |
|-------------------------------------------------|----------------|----------------|-----------------|
| Hypoxia                                         |                |                |                 |
| subjects affected / exposed                     | 1 / 32 (3.13%) | 2 / 48 (4.17%) | 2 / 15 (13.33%) |
| occurrences causally related to treatment / all | 1 / 1          | 2 / 2          | 2 / 3           |
| deaths causally related to treatment / all      | 0 / 0          | 1 / 1          | 0 / 0           |
| Pulmonary embolism                              |                |                |                 |
| subjects affected / exposed                     | 1 / 32 (3.13%) | 1 / 48 (2.08%) | 0 / 15 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Pneumonitis                                     |                |                |                 |
| subjects affected / exposed                     | 1 / 32 (3.13%) | 1 / 48 (2.08%) | 0 / 15 (0.00%)  |
| occurrences causally related to treatment / all | 1 / 1          | 1 / 1          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Cough                                           |                |                |                 |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 2 / 15 (13.33%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Pleural effusion                                |                |                |                 |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 1 / 15 (6.67%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Respiratory failure                             |                |                |                 |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 2 / 48 (4.17%) | 0 / 15 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0           |
| Acute respiratory distress syndrome             |                |                |                 |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 1 / 48 (2.08%) | 0 / 15 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0           |
| Haemoptysis                                     |                |                |                 |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 1 / 48 (2.08%) | 0 / 15 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Pneumothorax                                    |                |                |                 |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 1 / 15 (6.67%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Psychiatric disorders                           |                |                |                |
| Mental status changes                           |                |                |                |
| subjects affected / exposed                     | 1 / 32 (3.13%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Confusional state                               |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 1 / 48 (2.08%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Suicidal ideation                               |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 1 / 48 (2.08%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Investigations                                  |                |                |                |
| Alanine aminotransferase increased              |                |                |                |
| subjects affected / exposed                     | 2 / 32 (6.25%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Aspartate aminotransferase increased            |                |                |                |
| subjects affected / exposed                     | 1 / 32 (3.13%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Computerised tomogram thorax abnormal           |                |                |                |
| subjects affected / exposed                     | 1 / 32 (3.13%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Injury, poisoning and procedural complications  |                |                |                |
| Post procedural haemorrhage                     |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 32 (0.00%) | 1 / 48 (2.08%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Radiation necrosis                              |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 1 / 48 (2.08%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Radiation pneumonitis                           |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 1 / 15 (6.67%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac disorders                               |                |                |                |
| Atrial fibrillation                             |                |                |                |
| subjects affected / exposed                     | 1 / 32 (3.13%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Supraventricular tachycardia                    |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 2 / 48 (4.17%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 4          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac failure congestive                      |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac tamponade                               |                |                |                |
| subjects affected / exposed                     | 1 / 32 (3.13%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Left ventricular dysfunction                    |                |                |                |
| subjects affected / exposed                     | 1 / 32 (3.13%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Tachycardia                                     |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 1 / 15 (6.67%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Nervous system disorders                        |                |                |                |
| Seizure                                         |                |                |                |
| subjects affected / exposed                     | 1 / 32 (3.13%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Syncope                                         |                |                |                |
| subjects affected / exposed                     | 1 / 32 (3.13%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Central nervous system haemorrhage              |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 1 / 48 (2.08%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cerebral haemorrhage                            |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 1 / 48 (2.08%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cognitive disorder                              |                |                |                |
| subjects affected / exposed                     | 1 / 32 (3.13%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Embolic stroke                                  |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 1 / 48 (2.08%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Haemorrhage intracranial                        |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 1 / 48 (2.08%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Haemorrhagic stroke                             |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Headache                                        |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 1 / 15 (6.67%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Ischaemic stroke                                |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 1 / 48 (2.08%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Nervous system disorder                         |                |                |                |
| subjects affected / exposed                     | 1 / 32 (3.13%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Transient ischaemic attack                      |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 1 / 48 (2.08%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrointestinal disorders                      |                |                |                |
| Pancreatitis                                    |                |                |                |
| subjects affected / exposed                     | 1 / 32 (3.13%) | 0 / 48 (0.00%) | 1 / 15 (6.67%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Abdominal wall haematoma                        |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 1 / 48 (2.08%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Bezoar                                          |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 1 / 15 (6.67%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Colitis                                         |                |                |                |



|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 32 (3.13%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastric ulcer haemorrhage                       |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 1 / 15 (6.67%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Haemorrhoids                                    |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Oesophageal compression                         |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 1 / 15 (6.67%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Rectal ulcer                                    |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Skin and subcutaneous tissue disorders          |                |                |                |
| Eczema                                          |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Rash                                            |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 1 / 15 (6.67%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Renal and urinary disorders                     |                |                |                |
| Acute kidney injury                             |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Musculoskeletal and connective tissue           |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| disorders                                       |                |                |                |
| Back pain                                       |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 1 / 48 (2.08%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Bone pain                                       |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 1 / 48 (2.08%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Intervertebral disc protrusion                  |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 1 / 48 (2.08%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Muscular weakness                               |                |                |                |
| subjects affected / exposed                     | 1 / 32 (3.13%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pain in extremity                               |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infections and infestations                     |                |                |                |
| Pneumonia                                       |                |                |                |
| subjects affected / exposed                     | 1 / 32 (3.13%) | 3 / 48 (6.25%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 3          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0          |
| Bronchitis                                      |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 1 / 15 (6.67%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Sepsis                                          |                |                |                |
| subjects affected / exposed                     | 1 / 32 (3.13%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 1 / 1          | 0 / 0          | 0 / 0          |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| Device related infection                        |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Device related sepsis                           |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Lower respiratory tract infection bacterial     |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pneumonia pseudomonal                           |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Urinary tract infection                         |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 1 / 48 (2.08%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Viral infection                                 |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 1 / 48 (2.08%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Metabolism and nutrition disorders              |                |                |                |
| Failure to thrive                               |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hyperglycaemia                                  |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 1 / 48 (2.08%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| Hyponatraemia                                   |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 1 / 48 (2.08%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Insulin resistance                              |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

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

| <b>Non-serious adverse events</b>                                   | AP26113 30 mg QD/60 mg QD | AP26113 90 mg QD  | AP26113 120 mg QD/60 mg BID |
|---------------------------------------------------------------------|---------------------------|-------------------|-----------------------------|
| Total subjects affected by non-serious adverse events               |                           |                   |                             |
| subjects affected / exposed                                         | 6 / 6 (100.00%)           | 18 / 18 (100.00%) | 18 / 18 (100.00%)           |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                           |                   |                             |
| Pericardial effusion malignant                                      |                           |                   |                             |
| subjects affected / exposed                                         | 0 / 6 (0.00%)             | 0 / 18 (0.00%)    | 0 / 18 (0.00%)              |
| occurrences (all)                                                   | 0                         | 0                 | 0                           |
| Melanocytic naevus                                                  |                           |                   |                             |
| subjects affected / exposed                                         | 0 / 6 (0.00%)             | 0 / 18 (0.00%)    | 1 / 18 (5.56%)              |
| occurrences (all)                                                   | 0                         | 0                 | 1                           |
| Skin papilloma                                                      |                           |                   |                             |
| subjects affected / exposed                                         | 0 / 6 (0.00%)             | 0 / 18 (0.00%)    | 0 / 18 (0.00%)              |
| occurrences (all)                                                   | 0                         | 0                 | 0                           |
| Tumour pain                                                         |                           |                   |                             |
| subjects affected / exposed                                         | 0 / 6 (0.00%)             | 0 / 18 (0.00%)    | 0 / 18 (0.00%)              |
| occurrences (all)                                                   | 0                         | 0                 | 0                           |
| Vascular disorders                                                  |                           |                   |                             |
| Hypertension                                                        |                           |                   |                             |
| subjects affected / exposed                                         | 0 / 6 (0.00%)             | 1 / 18 (5.56%)    | 5 / 18 (27.78%)             |
| occurrences (all)                                                   | 0                         | 1                 | 6                           |
| Hypotension                                                         |                           |                   |                             |
| subjects affected / exposed                                         | 0 / 6 (0.00%)             | 1 / 18 (5.56%)    | 0 / 18 (0.00%)              |
| occurrences (all)                                                   | 0                         | 1                 | 0                           |
| Deep vein thrombosis                                                |                           |                   |                             |

|                                                      |                |                 |                 |
|------------------------------------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed                          | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences (all)                                    | 0              | 1               | 0               |
| Vascular pain                                        |                |                 |                 |
| subjects affected / exposed                          | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences (all)                                    | 0              | 1               | 0               |
| General disorders and administration site conditions |                |                 |                 |
| Fatigue                                              |                |                 |                 |
| subjects affected / exposed                          | 2 / 6 (33.33%) | 9 / 18 (50.00%) | 6 / 18 (33.33%) |
| occurrences (all)                                    | 2              | 14              | 7               |
| Oedema peripheral                                    |                |                 |                 |
| subjects affected / exposed                          | 1 / 6 (16.67%) | 1 / 18 (5.56%)  | 3 / 18 (16.67%) |
| occurrences (all)                                    | 1              | 1               | 3               |
| Pyrexia                                              |                |                 |                 |
| subjects affected / exposed                          | 0 / 6 (0.00%)  | 3 / 18 (16.67%) | 2 / 18 (11.11%) |
| occurrences (all)                                    | 0              | 3               | 2               |
| Pain                                                 |                |                 |                 |
| subjects affected / exposed                          | 0 / 6 (0.00%)  | 3 / 18 (16.67%) | 2 / 18 (11.11%) |
| occurrences (all)                                    | 0              | 4               | 2               |
| Chest discomfort                                     |                |                 |                 |
| subjects affected / exposed                          | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences (all)                                    | 0              | 1               | 0               |
| Non-cardiac chest pain                               |                |                 |                 |
| subjects affected / exposed                          | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 2 / 18 (11.11%) |
| occurrences (all)                                    | 0              | 1               | 3               |
| Influenza like illness                               |                |                 |                 |
| subjects affected / exposed                          | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 1 / 18 (5.56%)  |
| occurrences (all)                                    | 0              | 1               | 1               |
| Asthenia                                             |                |                 |                 |
| subjects affected / exposed                          | 0 / 6 (0.00%)  | 0 / 18 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)                                    | 0              | 0               | 1               |
| Chills                                               |                |                 |                 |
| subjects affected / exposed                          | 0 / 6 (0.00%)  | 3 / 18 (16.67%) | 0 / 18 (0.00%)  |
| occurrences (all)                                    | 0              | 3               | 0               |
| Gait disturbance                                     |                |                 |                 |

|                                          |                |                 |                |
|------------------------------------------|----------------|-----------------|----------------|
| subjects affected / exposed              | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 0 / 18 (0.00%) |
| occurrences (all)                        | 0              | 1               | 0              |
| Peripheral swelling                      |                |                 |                |
| subjects affected / exposed              | 0 / 6 (0.00%)  | 2 / 18 (11.11%) | 0 / 18 (0.00%) |
| occurrences (all)                        | 0              | 2               | 0              |
| Chest pain                               |                |                 |                |
| subjects affected / exposed              | 1 / 6 (16.67%) | 0 / 18 (0.00%)  | 0 / 18 (0.00%) |
| occurrences (all)                        | 1              | 0               | 0              |
| Thirst                                   |                |                 |                |
| subjects affected / exposed              | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 0 / 18 (0.00%) |
| occurrences (all)                        | 0              | 1               | 0              |
| Axillary pain                            |                |                 |                |
| subjects affected / exposed              | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 0 / 18 (0.00%) |
| occurrences (all)                        | 0              | 1               | 0              |
| Exercise tolerance decreased             |                |                 |                |
| subjects affected / exposed              | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 0 / 18 (0.00%) |
| occurrences (all)                        | 0              | 1               | 0              |
| Feeling abnormal                         |                |                 |                |
| subjects affected / exposed              | 0 / 6 (0.00%)  | 0 / 18 (0.00%)  | 1 / 18 (5.56%) |
| occurrences (all)                        | 0              | 0               | 1              |
| Feeling jittery                          |                |                 |                |
| subjects affected / exposed              | 0 / 6 (0.00%)  | 0 / 18 (0.00%)  | 1 / 18 (5.56%) |
| occurrences (all)                        | 0              | 0               | 1              |
| Immune system disorders                  |                |                 |                |
| Seasonal allergy                         |                |                 |                |
| subjects affected / exposed              | 0 / 6 (0.00%)  | 0 / 18 (0.00%)  | 0 / 18 (0.00%) |
| occurrences (all)                        | 0              | 0               | 0              |
| Contrast media allergy                   |                |                 |                |
| subjects affected / exposed              | 0 / 6 (0.00%)  | 0 / 18 (0.00%)  | 1 / 18 (5.56%) |
| occurrences (all)                        | 0              | 0               | 1              |
| Reproductive system and breast disorders |                |                 |                |
| Vulvovaginal dryness                     |                |                 |                |
| subjects affected / exposed              | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 0 / 18 (0.00%) |
| occurrences (all)                        | 0              | 1               | 0              |
| Nipple pain                              |                |                 |                |

|                                                 |                |                 |                 |
|-------------------------------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences (all)                               | 0              | 1               | 0               |
| Respiratory, thoracic and mediastinal disorders |                |                 |                 |
| Cough                                           |                |                 |                 |
| subjects affected / exposed                     | 1 / 6 (16.67%) | 6 / 18 (33.33%) | 6 / 18 (33.33%) |
| occurrences (all)                               | 1              | 7               | 10              |
| Dyspnoea                                        |                |                 |                 |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 2 / 18 (11.11%) | 5 / 18 (27.78%) |
| occurrences (all)                               | 0              | 3               | 6               |
| Dyspnoea exertional                             |                |                 |                 |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 2 / 18 (11.11%) | 2 / 18 (11.11%) |
| occurrences (all)                               | 0              | 2               | 2               |
| Oropharyngeal pain                              |                |                 |                 |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 2 / 18 (11.11%) | 1 / 18 (5.56%)  |
| occurrences (all)                               | 0              | 2               | 1               |
| Epistaxis                                       |                |                 |                 |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 2 / 18 (11.11%) | 0 / 18 (0.00%)  |
| occurrences (all)                               | 0              | 2               | 0               |
| Productive cough                                |                |                 |                 |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 1 / 18 (5.56%)  |
| occurrences (all)                               | 0              | 1               | 1               |
| Nasal congestion                                |                |                 |                 |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 2 / 18 (11.11%) | 2 / 18 (11.11%) |
| occurrences (all)                               | 0              | 2               | 2               |
| Haemoptysis                                     |                |                 |                 |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences (all)                               | 0              | 1               | 0               |
| Hypoxia                                         |                |                 |                 |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 0 / 18 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)                               | 0              | 0               | 1               |
| Rhinorrhoea                                     |                |                 |                 |
| subjects affected / exposed                     | 1 / 6 (16.67%) | 0 / 18 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)                               | 1              | 0               | 0               |
| Sinus congestion                                |                |                 |                 |

|                             |               |                |                |
|-----------------------------|---------------|----------------|----------------|
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 18 (5.56%) | 0 / 18 (0.00%) |
| occurrences (all)           | 0             | 1              | 0              |
| Dysphonia                   |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)           | 0             | 0              | 0              |
| Rhinitis allergic           |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 18 (5.56%) | 1 / 18 (5.56%) |
| occurrences (all)           | 0             | 1              | 2              |
| Sputum discoloured          |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all)           | 0             | 0              | 1              |
| Dry throat                  |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)           | 0             | 0              | 0              |
| Hiccups                     |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all)           | 0             | 0              | 1              |
| Laryngeal inflammation      |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)           | 0             | 0              | 0              |
| Pleural effusion            |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)           | 0             | 0              | 0              |
| Pleuritic pain              |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)           | 0             | 0              | 0              |
| Throat irritation           |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 18 (5.56%) | 0 / 18 (0.00%) |
| occurrences (all)           | 0             | 1              | 0              |
| Wheezing                    |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)           | 0             | 0              | 0              |
| Nasal dryness               |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)           | 0             | 0              | 0              |
| Pleurisy                    |               |                |                |



|                              |                |                |                |
|------------------------------|----------------|----------------|----------------|
| subjects affected / exposed  | 0 / 6 (0.00%)  | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)            | 0              | 0              | 0              |
| Pneumothorax                 |                |                |                |
| subjects affected / exposed  | 0 / 6 (0.00%)  | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)            | 0              | 0              | 0              |
| Pulmonary hypertension       |                |                |                |
| subjects affected / exposed  | 0 / 6 (0.00%)  | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)            | 0              | 0              | 0              |
| Respiratory tract irritation |                |                |                |
| subjects affected / exposed  | 0 / 6 (0.00%)  | 1 / 18 (5.56%) | 0 / 18 (0.00%) |
| occurrences (all)            | 0              | 1              | 0              |
| Sneezing                     |                |                |                |
| subjects affected / exposed  | 0 / 6 (0.00%)  | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)            | 0              | 0              | 0              |
| Upper-airway cough syndrome  |                |                |                |
| subjects affected / exposed  | 0 / 6 (0.00%)  | 0 / 18 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all)            | 0              | 0              | 1              |
| Psychiatric disorders        |                |                |                |
| Insomnia                     |                |                |                |
| subjects affected / exposed  | 0 / 6 (0.00%)  | 1 / 18 (5.56%) | 1 / 18 (5.56%) |
| occurrences (all)            | 0              | 1              | 1              |
| Anxiety                      |                |                |                |
| subjects affected / exposed  | 0 / 6 (0.00%)  | 1 / 18 (5.56%) | 0 / 18 (0.00%) |
| occurrences (all)            | 0              | 1              | 0              |
| Depression                   |                |                |                |
| subjects affected / exposed  | 1 / 6 (16.67%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)            | 1              | 0              | 0              |
| Bruxism                      |                |                |                |
| subjects affected / exposed  | 0 / 6 (0.00%)  | 1 / 18 (5.56%) | 0 / 18 (0.00%) |
| occurrences (all)            | 0              | 1              | 0              |
| Anticipatory anxiety         |                |                |                |
| subjects affected / exposed  | 0 / 6 (0.00%)  | 0 / 18 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all)            | 0              | 0              | 1              |
| Confusional state            |                |                |                |
| subjects affected / exposed  | 0 / 6 (0.00%)  | 1 / 18 (5.56%) | 0 / 18 (0.00%) |
| occurrences (all)            | 0              | 1              | 0              |

|                                      |               |                 |                 |
|--------------------------------------|---------------|-----------------|-----------------|
| Disorientation                       |               |                 |                 |
| subjects affected / exposed          | 0 / 6 (0.00%) | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences (all)                    | 0             | 2               | 0               |
| Nervousness                          |               |                 |                 |
| subjects affected / exposed          | 0 / 6 (0.00%) | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences (all)                    | 0             | 1               | 0               |
| Stress                               |               |                 |                 |
| subjects affected / exposed          | 0 / 6 (0.00%) | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences (all)                    | 0             | 1               | 0               |
| Investigations                       |               |                 |                 |
| Amylase increased                    |               |                 |                 |
| subjects affected / exposed          | 0 / 6 (0.00%) | 4 / 18 (22.22%) | 5 / 18 (27.78%) |
| occurrences (all)                    | 0             | 10              | 12              |
| Lipase increased                     |               |                 |                 |
| subjects affected / exposed          | 0 / 6 (0.00%) | 3 / 18 (16.67%) | 4 / 18 (22.22%) |
| occurrences (all)                    | 0             | 6               | 6               |
| Aspartate aminotransferase increased |               |                 |                 |
| subjects affected / exposed          | 0 / 6 (0.00%) | 2 / 18 (11.11%) | 6 / 18 (33.33%) |
| occurrences (all)                    | 0             | 4               | 8               |
| Alanine aminotransferase increased   |               |                 |                 |
| subjects affected / exposed          | 0 / 6 (0.00%) | 3 / 18 (16.67%) | 3 / 18 (16.67%) |
| occurrences (all)                    | 0             | 4               | 3               |
| Blood insulin increased              |               |                 |                 |
| subjects affected / exposed          | 0 / 6 (0.00%) | 3 / 18 (16.67%) | 2 / 18 (11.11%) |
| occurrences (all)                    | 0             | 4               | 5               |
| Weight decreased                     |               |                 |                 |
| subjects affected / exposed          | 0 / 6 (0.00%) | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences (all)                    | 0             | 1               | 0               |
| Blood creatinine increased           |               |                 |                 |
| subjects affected / exposed          | 0 / 6 (0.00%) | 1 / 18 (5.56%)  | 2 / 18 (11.11%) |
| occurrences (all)                    | 0             | 1               | 2               |
| Lymphocyte count decreased           |               |                 |                 |
| subjects affected / exposed          | 0 / 6 (0.00%) | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences (all)                    | 0             | 1               | 0               |
| Weight increased                     |               |                 |                 |

|                                                 |                |                 |                 |
|-------------------------------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 2 / 18 (11.11%) |
| occurrences (all)                               | 0              | 1               | 3               |
| Blood alkaline phosphatase increased            |                |                 |                 |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 2 / 18 (11.11%) | 1 / 18 (5.56%)  |
| occurrences (all)                               | 0              | 2               | 1               |
| Blood testosterone decreased                    |                |                 |                 |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 0 / 18 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)                               | 0              | 0               | 0               |
| Blood thyroid stimulating hormone decreased     |                |                 |                 |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 2 / 18 (11.11%) | 1 / 18 (5.56%)  |
| occurrences (all)                               | 0              | 0               | 0               |
| Blood bilirubin increased                       |                |                 |                 |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 0 / 18 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)                               | 0              | 0               | 1               |
| Blood lactate dehydrogenase increased           |                |                 |                 |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 0 / 18 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)                               | 0              | 0               | 0               |
| Blood thyroid stimulating hormone increased     |                |                 |                 |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 0 / 18 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)                               | 0              | 0               | 2               |
| Activated partial thromboplastin time prolonged |                |                 |                 |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences (all)                               | 0              | 1               | 0               |
| Electrocardiogram QT prolonged                  |                |                 |                 |
| subjects affected / exposed                     | 2 / 6 (33.33%) | 0 / 18 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)                               | 2              | 0               | 0               |
| Bacterial test positive                         |                |                 |                 |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 0 / 18 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)                               | 0              | 0               | 0               |
| Ejection fraction decreased                     |                |                 |                 |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences (all)                               | 0              | 1               | 0               |
| Heart rate increased                            |                |                 |                 |

|                                                |               |                |                |
|------------------------------------------------|---------------|----------------|----------------|
| subjects affected / exposed                    | 0 / 6 (0.00%) | 1 / 18 (5.56%) | 0 / 18 (0.00%) |
| occurrences (all)                              | 0             | 1              | 0              |
| Urinary sediment present                       |               |                |                |
| subjects affected / exposed                    | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)                              | 0             | 0              | 0              |
| Urine leukocyte esterase positive              |               |                |                |
| subjects affected / exposed                    | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)                              | 0             | 0              | 0              |
| White blood cells urine                        |               |                |                |
| subjects affected / exposed                    | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all)                              | 0             | 0              | 1              |
| White blood cells urine positive               |               |                |                |
| subjects affected / exposed                    | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)                              | 0             | 0              | 0              |
| Injury, poisoning and procedural complications |               |                |                |
| Laceration                                     |               |                |                |
| subjects affected / exposed                    | 0 / 6 (0.00%) | 1 / 18 (5.56%) | 0 / 18 (0.00%) |
| occurrences (all)                              | 0             | 1              | 0              |
| Rib fracture                                   |               |                |                |
| subjects affected / exposed                    | 0 / 6 (0.00%) | 1 / 18 (5.56%) | 0 / 18 (0.00%) |
| occurrences (all)                              | 0             | 1              | 0              |
| Procedural pain                                |               |                |                |
| subjects affected / exposed                    | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)                              | 0             | 0              | 0              |
| Radiation neuropathy                           |               |                |                |
| subjects affected / exposed                    | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all)                              | 0             | 0              | 1              |
| Radiation pneumonitis                          |               |                |                |
| subjects affected / exposed                    | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)                              | 0             | 0              | 0              |
| Cardiac disorders                              |               |                |                |
| Sinus tachycardia                              |               |                |                |
| subjects affected / exposed                    | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)                              | 0             | 0              | 0              |
| Palpitations                                   |               |                |                |

|                               |                |                 |                 |
|-------------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed   | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 1 / 18 (5.56%)  |
| occurrences (all)             | 0              | 1               | 1               |
| Sinus bradycardia             |                |                 |                 |
| subjects affected / exposed   | 0 / 6 (0.00%)  | 0 / 18 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)             | 0              | 0               | 0               |
| Atrial fibrillation           |                |                 |                 |
| subjects affected / exposed   | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences (all)             | 0              | 1               | 0               |
| Atrial flutter                |                |                 |                 |
| subjects affected / exposed   | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences (all)             | 0              | 1               | 0               |
| Cardiac failure congestive    |                |                 |                 |
| subjects affected / exposed   | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences (all)             | 0              | 1               | 0               |
| Nervous system disorders      |                |                 |                 |
| Headache                      |                |                 |                 |
| subjects affected / exposed   | 0 / 6 (0.00%)  | 7 / 18 (38.89%) | 7 / 18 (38.89%) |
| occurrences (all)             | 0              | 12              | 8               |
| Dizziness                     |                |                 |                 |
| subjects affected / exposed   | 0 / 6 (0.00%)  | 4 / 18 (22.22%) | 1 / 18 (5.56%)  |
| occurrences (all)             | 0              | 7               | 2               |
| Peripheral sensory neuropathy |                |                 |                 |
| subjects affected / exposed   | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 2 / 18 (11.11%) |
| occurrences (all)             | 0              | 1               | 3               |
| Paraesthesia                  |                |                 |                 |
| subjects affected / exposed   | 1 / 6 (16.67%) | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences (all)             | 1              | 1               | 0               |
| Dysgeusia                     |                |                 |                 |
| subjects affected / exposed   | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 1 / 18 (5.56%)  |
| occurrences (all)             | 0              | 1               | 1               |
| Tremor                        |                |                 |                 |
| subjects affected / exposed   | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 1 / 18 (5.56%)  |
| occurrences (all)             | 0              | 1               | 1               |
| Amnesia                       |                |                 |                 |
| subjects affected / exposed   | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences (all)             | 0              | 1               | 0               |

|                             |                |                 |                |
|-----------------------------|----------------|-----------------|----------------|
| Balance disorder            |                |                 |                |
| subjects affected / exposed | 0 / 6 (0.00%)  | 2 / 18 (11.11%) | 0 / 18 (0.00%) |
| occurrences (all)           | 0              | 2               | 0              |
| Hypoaesthesia               |                |                 |                |
| subjects affected / exposed | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 0 / 18 (0.00%) |
| occurrences (all)           | 0              | 1               | 0              |
| Visual field defect         |                |                 |                |
| subjects affected / exposed | 0 / 6 (0.00%)  | 0 / 18 (0.00%)  | 0 / 18 (0.00%) |
| occurrences (all)           | 0              | 0               | 0              |
| Seizure                     |                |                 |                |
| subjects affected / exposed | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 1 / 18 (5.56%) |
| occurrences (all)           | 0              | 1               | 1              |
| Aphasia                     |                |                 |                |
| subjects affected / exposed | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 0 / 18 (0.00%) |
| occurrences (all)           | 0              | 2               | 0              |
| Disturbance in attention    |                |                 |                |
| subjects affected / exposed | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 0 / 18 (0.00%) |
| occurrences (all)           | 0              | 1               | 0              |
| Dysarthria                  |                |                 |                |
| subjects affected / exposed | 0 / 6 (0.00%)  | 2 / 18 (11.11%) | 0 / 18 (0.00%) |
| occurrences (all)           | 0              | 2               | 0              |
| Memory impairment           |                |                 |                |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 18 (5.56%)  | 0 / 18 (0.00%) |
| occurrences (all)           | 1              | 1               | 0              |
| Sinus headache              |                |                 |                |
| subjects affected / exposed | 0 / 6 (0.00%)  | 0 / 18 (0.00%)  | 0 / 18 (0.00%) |
| occurrences (all)           | 0              | 0               | 0              |
| Somnolence                  |                |                 |                |
| subjects affected / exposed | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 1 / 18 (5.56%) |
| occurrences (all)           | 0              | 1               | 1              |
| Syncope                     |                |                 |                |
| subjects affected / exposed | 0 / 6 (0.00%)  | 0 / 18 (0.00%)  | 0 / 18 (0.00%) |
| occurrences (all)           | 0              | 0               | 0              |
| Burning sensation           |                |                 |                |
| subjects affected / exposed | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 0 / 18 (0.00%) |
| occurrences (all)           | 0              | 1               | 0              |

|                                                                                  |                     |                      |                      |
|----------------------------------------------------------------------------------|---------------------|----------------------|----------------------|
| Cognitive disorder<br>subjects affected / exposed<br>occurrences (all)           | 0 / 6 (0.00%)<br>0  | 1 / 18 (5.56%)<br>2  | 0 / 18 (0.00%)<br>0  |
| Neuralgia<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 6 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1  | 0 / 18 (0.00%)<br>0  |
| Parosmia<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 6 (0.00%)<br>0  | 0 / 18 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1  |
| Peripheral motor neuropathy<br>subjects affected / exposed<br>occurrences (all)  | 0 / 6 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1  | 0 / 18 (0.00%)<br>0  |
| Blood and lymphatic system disorders                                             |                     |                      |                      |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 6 (0.00%)<br>0  | 0 / 18 (0.00%)<br>0  | 4 / 18 (22.22%)<br>5 |
| Increased tendency to bruise<br>subjects affected / exposed<br>occurrences (all) | 0 / 6 (0.00%)<br>0  | 0 / 18 (0.00%)<br>0  | 0 / 18 (0.00%)<br>0  |
| Leukocytosis<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 6 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1  | 0 / 18 (0.00%)<br>0  |
| Ear and labyrinth disorders                                                      |                     |                      |                      |
| Tinnitus<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 6 (0.00%)<br>0  | 2 / 18 (11.11%)<br>2 | 0 / 18 (0.00%)<br>0  |
| Deafness unilateral<br>subjects affected / exposed<br>occurrences (all)          | 1 / 6 (16.67%)<br>1 | 0 / 18 (0.00%)<br>0  | 0 / 18 (0.00%)<br>0  |
| Vertigo<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 6 (0.00%)<br>0  | 1 / 18 (5.56%)<br>3  | 0 / 18 (0.00%)<br>0  |
| Eye disorders                                                                    |                     |                      |                      |
| Vision blurred<br>subjects affected / exposed<br>occurrences (all)               | 0 / 6 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1  | 2 / 18 (11.11%)<br>2 |
| Dry eye                                                                          |                     |                      |                      |

|                             |                |                 |                 |
|-----------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0               |
| Visual impairment           |                |                 |                 |
| subjects affected / exposed | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0               |
| Blepharospasm               |                |                 |                 |
| subjects affected / exposed | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0               |
| Lacrimation increased       |                |                 |                 |
| subjects affected / exposed | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0               |
| Photopsia                   |                |                 |                 |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 1              | 1               | 0               |
| Vitreous floaters           |                |                 |                 |
| subjects affected / exposed | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0               |
| Asthenopia                  |                |                 |                 |
| subjects affected / exposed | 0 / 6 (0.00%)  | 0 / 18 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0               |
| Cataract cortical           |                |                 |                 |
| subjects affected / exposed | 0 / 6 (0.00%)  | 0 / 18 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0               |
| Colour blindness acquired   |                |                 |                 |
| subjects affected / exposed | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0               |
| Eye pain                    |                |                 |                 |
| subjects affected / exposed | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 0              | 2               | 0               |
| Eyelid margin crusting      |                |                 |                 |
| subjects affected / exposed | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0               |
| Gastrointestinal disorders  |                |                 |                 |
| Nausea                      |                |                 |                 |
| subjects affected / exposed | 3 / 6 (50.00%) | 6 / 18 (33.33%) | 8 / 18 (44.44%) |
| occurrences (all)           | 3              | 7               | 9               |



|                                  |                |                 |                 |
|----------------------------------|----------------|-----------------|-----------------|
| Diarrhoea                        |                |                 |                 |
| subjects affected / exposed      | 1 / 6 (16.67%) | 7 / 18 (38.89%) | 7 / 18 (38.89%) |
| occurrences (all)                | 1              | 11              | 10              |
| Constipation                     |                |                 |                 |
| subjects affected / exposed      | 1 / 6 (16.67%) | 6 / 18 (33.33%) | 5 / 18 (27.78%) |
| occurrences (all)                | 1              | 6               | 8               |
| Vomiting                         |                |                 |                 |
| subjects affected / exposed      | 1 / 6 (16.67%) | 1 / 18 (5.56%)  | 5 / 18 (27.78%) |
| occurrences (all)                | 2              | 2               | 6               |
| Abdominal pain                   |                |                 |                 |
| subjects affected / exposed      | 3 / 6 (50.00%) | 2 / 18 (11.11%) | 3 / 18 (16.67%) |
| occurrences (all)                | 3              | 2               | 3               |
| Dry mouth                        |                |                 |                 |
| subjects affected / exposed      | 0 / 6 (0.00%)  | 3 / 18 (16.67%) | 0 / 18 (0.00%)  |
| occurrences (all)                | 0              | 5               | 0               |
| Abdominal distension             |                |                 |                 |
| subjects affected / exposed      | 0 / 6 (0.00%)  | 3 / 18 (16.67%) | 1 / 18 (5.56%)  |
| occurrences (all)                | 0              | 3               | 1               |
| Abdominal discomfort             |                |                 |                 |
| subjects affected / exposed      | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 1 / 18 (5.56%)  |
| occurrences (all)                | 0              | 1               | 1               |
| Gastrooesophageal reflux disease |                |                 |                 |
| subjects affected / exposed      | 0 / 6 (0.00%)  | 0 / 18 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)                | 0              | 0               | 1               |
| Dyspepsia                        |                |                 |                 |
| subjects affected / exposed      | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 1 / 18 (5.56%)  |
| occurrences (all)                | 0              | 1               | 1               |
| Dysphagia                        |                |                 |                 |
| subjects affected / exposed      | 0 / 6 (0.00%)  | 0 / 18 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)                | 0              | 0               | 1               |
| Aphthous stomatitis              |                |                 |                 |
| subjects affected / exposed      | 0 / 6 (0.00%)  | 3 / 18 (16.67%) | 0 / 18 (0.00%)  |
| occurrences (all)                | 0              | 3               | 0               |
| Flatulence                       |                |                 |                 |
| subjects affected / exposed      | 0 / 6 (0.00%)  | 0 / 18 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)                | 0              | 0               | 0               |

|                             |               |                |                 |
|-----------------------------|---------------|----------------|-----------------|
| Sensitivity of teeth        |               |                |                 |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 18 (5.56%) | 0 / 18 (0.00%)  |
| occurrences (all)           | 0             | 1              | 0               |
| Stomatitis                  |               |                |                 |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 18 (5.56%) | 2 / 18 (11.11%) |
| occurrences (all)           | 0             | 1              | 3               |
| Cheilitis                   |               |                |                 |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 1 / 18 (5.56%)  |
| occurrences (all)           | 0             | 0              | 1               |
| Mouth ulceration            |               |                |                 |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 1 / 18 (5.56%)  |
| occurrences (all)           | 0             | 0              | 1               |
| Abdominal rigidity          |               |                |                 |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 1 / 18 (5.56%)  |
| occurrences (all)           | 0             | 0              | 1               |
| Abnormal faeces             |               |                |                 |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 18 (5.56%) | 0 / 18 (0.00%)  |
| occurrences (all)           | 0             | 1              | 0               |
| Lip dry                     |               |                |                 |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 18 (5.56%) | 0 / 18 (0.00%)  |
| occurrences (all)           | 0             | 1              | 0               |
| Lip swelling                |               |                |                 |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 18 (5.56%) | 0 / 18 (0.00%)  |
| occurrences (all)           | 0             | 1              | 0               |
| Oesophageal irritation      |               |                |                 |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 1 / 18 (5.56%)  |
| occurrences (all)           | 0             | 0              | 2               |
| Oesophageal pain            |               |                |                 |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0               |
| Toothache                   |               |                |                 |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 18 (5.56%) | 0 / 18 (0.00%)  |
| occurrences (all)           | 0             | 1              | 0               |
| Hypoaesthesia oral          |               |                |                 |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0               |

|                                        |               |                 |                 |
|----------------------------------------|---------------|-----------------|-----------------|
| Skin and subcutaneous tissue disorders |               |                 |                 |
| Rash                                   |               |                 |                 |
| subjects affected / exposed            | 0 / 6 (0.00%) | 3 / 18 (16.67%) | 2 / 18 (11.11%) |
| occurrences (all)                      | 0             | 4               | 2               |
| Photosensitivity reaction              |               |                 |                 |
| subjects affected / exposed            | 0 / 6 (0.00%) | 0 / 18 (0.00%)  | 4 / 18 (22.22%) |
| occurrences (all)                      | 0             | 0               | 7               |
| Pruritus                               |               |                 |                 |
| subjects affected / exposed            | 0 / 6 (0.00%) | 2 / 18 (11.11%) | 1 / 18 (5.56%)  |
| occurrences (all)                      | 0             | 2               | 2               |
| Dry skin                               |               |                 |                 |
| subjects affected / exposed            | 0 / 6 (0.00%) | 1 / 18 (5.56%)  | 2 / 18 (11.11%) |
| occurrences (all)                      | 0             | 3               | 2               |
| Night sweats                           |               |                 |                 |
| subjects affected / exposed            | 0 / 6 (0.00%) | 2 / 18 (11.11%) | 1 / 18 (5.56%)  |
| occurrences (all)                      | 0             | 2               | 1               |
| Dermatitis acneiform                   |               |                 |                 |
| subjects affected / exposed            | 0 / 6 (0.00%) | 1 / 18 (5.56%)  | 1 / 18 (5.56%)  |
| occurrences (all)                      | 0             | 1               | 1               |
| Alopecia                               |               |                 |                 |
| subjects affected / exposed            | 0 / 6 (0.00%) | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences (all)                      | 0             | 2               | 0               |
| Hyperhidrosis                          |               |                 |                 |
| subjects affected / exposed            | 0 / 6 (0.00%) | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences (all)                      | 0             | 2               | 0               |
| Onychoclasia                           |               |                 |                 |
| subjects affected / exposed            | 0 / 6 (0.00%) | 2 / 18 (11.11%) | 0 / 18 (0.00%)  |
| occurrences (all)                      | 0             | 2               | 0               |
| Rash pruritic                          |               |                 |                 |
| subjects affected / exposed            | 0 / 6 (0.00%) | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences (all)                      | 0             | 1               | 0               |
| Dermatitis contact                     |               |                 |                 |
| subjects affected / exposed            | 0 / 6 (0.00%) | 0 / 18 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)                      | 0             | 0               | 1               |
| Eczema                                 |               |                 |                 |

|                             |               |                |                |
|-----------------------------|---------------|----------------|----------------|
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 18 (5.56%) | 0 / 18 (0.00%) |
| occurrences (all)           | 0             | 3              | 0              |
| Erythema                    |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)           | 0             | 0              | 0              |
| Pain of skin                |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 18 (5.56%) | 0 / 18 (0.00%) |
| occurrences (all)           | 0             | 1              | 0              |
| Skin disorder               |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all)           | 0             | 0              | 1              |
| Dermal cyst                 |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all)           | 0             | 0              | 1              |
| Dermatitis                  |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)           | 0             | 0              | 0              |
| Dermatitis atopic           |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)           | 0             | 0              | 0              |
| Nail disorder               |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all)           | 0             | 0              | 1              |
| Petechiae                   |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 18 (5.56%) | 0 / 18 (0.00%) |
| occurrences (all)           | 0             | 1              | 0              |
| Skin hyperpigmentation      |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all)           | 0             | 0              | 1              |
| Urticaria                   |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 18 (5.56%) | 0 / 18 (0.00%) |
| occurrences (all)           | 0             | 2              | 0              |
| Nail growth abnormal        |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 18 (5.56%) | 0 / 18 (0.00%) |
| occurrences (all)           | 0             | 1              | 0              |
| Renal and urinary disorders |               |                |                |

|                                                 |                |                 |                 |
|-------------------------------------------------|----------------|-----------------|-----------------|
| Pollakiuria                                     |                |                 |                 |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 1 / 18 (5.56%)  |
| occurrences (all)                               | 0              | 1               | 1               |
| Proteinuria                                     |                |                 |                 |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 0 / 18 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)                               | 0              | 0               | 0               |
| Haematuria                                      |                |                 |                 |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 0 / 18 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)                               | 0              | 0               | 1               |
| Dysuria                                         |                |                 |                 |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 0 / 18 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)                               | 0              | 0               | 0               |
| Renal failure                                   |                |                 |                 |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences (all)                               | 0              | 1               | 0               |
| Urinary retention                               |                |                 |                 |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences (all)                               | 0              | 1               | 0               |
| Endocrine disorders                             |                |                 |                 |
| Hypothyroidism                                  |                |                 |                 |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences (all)                               | 0              | 1               | 0               |
| Musculoskeletal and connective tissue disorders |                |                 |                 |
| Muscle spasms                                   |                |                 |                 |
| subjects affected / exposed                     | 1 / 6 (16.67%) | 1 / 18 (5.56%)  | 3 / 18 (16.67%) |
| occurrences (all)                               | 1              | 8               | 3               |
| Back pain                                       |                |                 |                 |
| subjects affected / exposed                     | 1 / 6 (16.67%) | 0 / 18 (0.00%)  | 5 / 18 (27.78%) |
| occurrences (all)                               | 1              | 0               | 6               |
| Musculoskeletal pain                            |                |                 |                 |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 2 / 18 (11.11%) | 0 / 18 (0.00%)  |
| occurrences (all)                               | 0              | 2               | 0               |
| Arthralgia                                      |                |                 |                 |
| subjects affected / exposed                     | 1 / 6 (16.67%) | 3 / 18 (16.67%) | 0 / 18 (0.00%)  |
| occurrences (all)                               | 1              | 5               | 0               |
| Pain in extremity                               |                |                 |                 |

|                             |                |                 |                 |
|-----------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 18 (11.11%) | 2 / 18 (11.11%) |
| occurrences (all)           | 1              | 5               | 3               |
| Musculoskeletal chest pain  |                |                 |                 |
| subjects affected / exposed | 2 / 6 (33.33%) | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 2              | 1               | 0               |
| Joint swelling              |                |                 |                 |
| subjects affected / exposed | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0               |
| Myalgia                     |                |                 |                 |
| subjects affected / exposed | 0 / 6 (0.00%)  | 3 / 18 (16.67%) | 0 / 18 (0.00%)  |
| occurrences (all)           | 0              | 5               | 0               |
| Bone pain                   |                |                 |                 |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 18 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 2              | 0               | 0               |
| Musculoskeletal discomfort  |                |                 |                 |
| subjects affected / exposed | 0 / 6 (0.00%)  | 0 / 18 (0.00%)  | 2 / 18 (11.11%) |
| occurrences (all)           | 0              | 0               | 2               |
| Flank pain                  |                |                 |                 |
| subjects affected / exposed | 0 / 6 (0.00%)  | 2 / 18 (11.11%) | 1 / 18 (5.56%)  |
| occurrences (all)           | 0              | 2               | 1               |
| Muscular weakness           |                |                 |                 |
| subjects affected / exposed | 0 / 6 (0.00%)  | 0 / 18 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)           | 0              | 0               | 1               |
| Pain in jaw                 |                |                 |                 |
| subjects affected / exposed | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0               |
| Arthritis                   |                |                 |                 |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 18 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 1              | 0               | 0               |
| Fracture pain               |                |                 |                 |
| subjects affected / exposed | 0 / 6 (0.00%)  | 0 / 18 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0               |
| Limb discomfort             |                |                 |                 |
| subjects affected / exposed | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0               |
| Musculoskeletal stiffness   |                |                 |                 |

|                                   |                |                 |                 |
|-----------------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed       | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 1 / 18 (5.56%)  |
| occurrences (all)                 | 0              | 2               | 1               |
| Groin pain                        |                |                 |                 |
| subjects affected / exposed       | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences (all)                 | 0              | 1               | 0               |
| Neck pain                         |                |                 |                 |
| subjects affected / exposed       | 0 / 6 (0.00%)  | 0 / 18 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)                 | 0              | 0               | 0               |
| Osteopenia                        |                |                 |                 |
| subjects affected / exposed       | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences (all)                 | 0              | 1               | 0               |
| Infections and infestations       |                |                 |                 |
| Upper respiratory tract infection |                |                 |                 |
| subjects affected / exposed       | 1 / 6 (16.67%) | 0 / 18 (0.00%)  | 2 / 18 (11.11%) |
| occurrences (all)                 | 1              | 0               | 2               |
| Nasopharyngitis                   |                |                 |                 |
| subjects affected / exposed       | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 3 / 18 (16.67%) |
| occurrences (all)                 | 0              | 1               | 3               |
| Urinary tract infection           |                |                 |                 |
| subjects affected / exposed       | 0 / 6 (0.00%)  | 2 / 18 (11.11%) | 0 / 18 (0.00%)  |
| occurrences (all)                 | 0              | 2               | 0               |
| Sinusitis                         |                |                 |                 |
| subjects affected / exposed       | 0 / 6 (0.00%)  | 0 / 18 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)                 | 0              | 0               | 0               |
| Pneumonia                         |                |                 |                 |
| subjects affected / exposed       | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 1 / 18 (5.56%)  |
| occurrences (all)                 | 0              | 1               | 2               |
| Bronchitis                        |                |                 |                 |
| subjects affected / exposed       | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences (all)                 | 0              | 1               | 0               |
| Influenza                         |                |                 |                 |
| subjects affected / exposed       | 0 / 6 (0.00%)  | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences (all)                 | 0              | 1               | 0               |
| Oral candidiasis                  |                |                 |                 |
| subjects affected / exposed       | 0 / 6 (0.00%)  | 0 / 18 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)                 | 0              | 0               | 0               |

|                                |               |                |                |
|--------------------------------|---------------|----------------|----------------|
| Viral infection                |               |                |                |
| subjects affected / exposed    | 0 / 6 (0.00%) | 1 / 18 (5.56%) | 0 / 18 (0.00%) |
| occurrences (all)              | 0             | 1              | 0              |
| Vulvovaginal mycotic infection |               |                |                |
| subjects affected / exposed    | 0 / 6 (0.00%) | 1 / 18 (5.56%) | 0 / 18 (0.00%) |
| occurrences (all)              | 0             | 1              | 0              |
| Conjunctivitis viral           |               |                |                |
| subjects affected / exposed    | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)              | 0             | 0              | 0              |
| Diarrhoea infectious           |               |                |                |
| subjects affected / exposed    | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)              | 0             | 0              | 0              |
| Folliculitis                   |               |                |                |
| subjects affected / exposed    | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)              | 0             | 0              | 0              |
| Fungal skin infection          |               |                |                |
| subjects affected / exposed    | 0 / 6 (0.00%) | 1 / 18 (5.56%) | 0 / 18 (0.00%) |
| occurrences (all)              | 0             | 2              | 0              |
| Infectious pleural effusion    |               |                |                |
| subjects affected / exposed    | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all)              | 0             | 0              | 1              |
| Laryngitis viral               |               |                |                |
| subjects affected / exposed    | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)              | 0             | 0              | 0              |
| Lung infection                 |               |                |                |
| subjects affected / exposed    | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all)              | 0             | 0              | 1              |
| Nail infection                 |               |                |                |
| subjects affected / exposed    | 0 / 6 (0.00%) | 1 / 18 (5.56%) | 0 / 18 (0.00%) |
| occurrences (all)              | 0             | 1              | 0              |
| Nasal herpes                   |               |                |                |
| subjects affected / exposed    | 0 / 6 (0.00%) | 1 / 18 (5.56%) | 0 / 18 (0.00%) |
| occurrences (all)              | 0             | 1              | 0              |
| Onychomycosis                  |               |                |                |
| subjects affected / exposed    | 0 / 6 (0.00%) | 1 / 18 (5.56%) | 0 / 18 (0.00%) |
| occurrences (all)              | 0             | 2              | 0              |



|                                    |               |                 |                 |
|------------------------------------|---------------|-----------------|-----------------|
| Otitis externa                     |               |                 |                 |
| subjects affected / exposed        | 0 / 6 (0.00%) | 0 / 18 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)                  | 0             | 0               | 0               |
| Paronychia                         |               |                 |                 |
| subjects affected / exposed        | 0 / 6 (0.00%) | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences (all)                  | 0             | 1               | 0               |
| Skin candida                       |               |                 |                 |
| subjects affected / exposed        | 0 / 6 (0.00%) | 0 / 18 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)                  | 0             | 0               | 1               |
| Vaginal infection                  |               |                 |                 |
| subjects affected / exposed        | 0 / 6 (0.00%) | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences (all)                  | 0             | 1               | 0               |
| Metabolism and nutrition disorders |               |                 |                 |
| Decreased appetite                 |               |                 |                 |
| subjects affected / exposed        | 0 / 6 (0.00%) | 5 / 18 (27.78%) | 1 / 18 (5.56%)  |
| occurrences (all)                  | 0             | 5               | 1               |
| Hypophosphataemia                  |               |                 |                 |
| subjects affected / exposed        | 0 / 6 (0.00%) | 0 / 18 (0.00%)  | 2 / 18 (11.11%) |
| occurrences (all)                  | 0             | 0               | 6               |
| Hypomagnesaemia                    |               |                 |                 |
| subjects affected / exposed        | 0 / 6 (0.00%) | 0 / 18 (0.00%)  | 3 / 18 (16.67%) |
| occurrences (all)                  | 0             | 0               | 3               |
| Hypokalaemia                       |               |                 |                 |
| subjects affected / exposed        | 0 / 6 (0.00%) | 1 / 18 (5.56%)  | 1 / 18 (5.56%)  |
| occurrences (all)                  | 0             | 1               | 1               |
| Hyponatraemia                      |               |                 |                 |
| subjects affected / exposed        | 0 / 6 (0.00%) | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |
| occurrences (all)                  | 0             | 1               | 0               |
| Dehydration                        |               |                 |                 |
| subjects affected / exposed        | 0 / 6 (0.00%) | 0 / 18 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)                  | 0             | 0               | 1               |
| Hyperglycaemia                     |               |                 |                 |
| subjects affected / exposed        | 0 / 6 (0.00%) | 0 / 18 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)                  | 0             | 0               | 0               |
| Increased appetite                 |               |                 |                 |

|                             |               |                |                |
|-----------------------------|---------------|----------------|----------------|
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 18 (5.56%) | 0 / 18 (0.00%) |
| occurrences (all)           | 0             | 1              | 0              |
| Hyperlipidaemia             |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 18 (5.56%) | 0 / 18 (0.00%) |
| occurrences (all)           | 0             | 1              | 0              |
| Hypernatraemia              |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 18 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all)           | 0             | 0              | 1              |

| <b>Non-serious adverse events</b>                                      | AP26113 90 mg QD-<br>180 mg QD | AP26113 180 mg<br>QD/90 mg BID | AP26113 240 mg<br>QD/120 mg BID/300<br>mg QD |
|------------------------------------------------------------------------|--------------------------------|--------------------------------|----------------------------------------------|
| Total subjects affected by non-serious<br>adverse events               |                                |                                |                                              |
| subjects affected / exposed                                            | 31 / 32 (96.88%)               | 44 / 48 (91.67%)               | 15 / 15 (100.00%)                            |
| Neoplasms benign, malignant and<br>unspecified (incl cysts and polyps) |                                |                                |                                              |
| Pericardial effusion malignant                                         |                                |                                |                                              |
| subjects affected / exposed                                            | 1 / 32 (3.13%)                 | 0 / 48 (0.00%)                 | 1 / 15 (6.67%)                               |
| occurrences (all)                                                      | 1                              | 0                              | 1                                            |
| Melanocytic naevus                                                     |                                |                                |                                              |
| subjects affected / exposed                                            | 0 / 32 (0.00%)                 | 0 / 48 (0.00%)                 | 0 / 15 (0.00%)                               |
| occurrences (all)                                                      | 0                              | 0                              | 0                                            |
| Skin papilloma                                                         |                                |                                |                                              |
| subjects affected / exposed                                            | 0 / 32 (0.00%)                 | 0 / 48 (0.00%)                 | 1 / 15 (6.67%)                               |
| occurrences (all)                                                      | 0                              | 0                              | 1                                            |
| Tumour pain                                                            |                                |                                |                                              |
| subjects affected / exposed                                            | 0 / 32 (0.00%)                 | 0 / 48 (0.00%)                 | 1 / 15 (6.67%)                               |
| occurrences (all)                                                      | 0                              | 0                              | 1                                            |
| Vascular disorders                                                     |                                |                                |                                              |
| Hypertension                                                           |                                |                                |                                              |
| subjects affected / exposed                                            | 7 / 32 (21.88%)                | 6 / 48 (12.50%)                | 1 / 15 (6.67%)                               |
| occurrences (all)                                                      | 14                             | 10                             | 1                                            |
| Hypotension                                                            |                                |                                |                                              |
| subjects affected / exposed                                            | 2 / 32 (6.25%)                 | 0 / 48 (0.00%)                 | 1 / 15 (6.67%)                               |
| occurrences (all)                                                      | 2                              | 0                              | 1                                            |
| Deep vein thrombosis                                                   |                                |                                |                                              |
| subjects affected / exposed                                            | 0 / 32 (0.00%)                 | 0 / 48 (0.00%)                 | 0 / 15 (0.00%)                               |
| occurrences (all)                                                      | 0                              | 0                              | 0                                            |
| Vascular pain                                                          |                                |                                |                                              |

|                                                      |                  |                  |                  |
|------------------------------------------------------|------------------|------------------|------------------|
| subjects affected / exposed                          | 0 / 32 (0.00%)   | 0 / 48 (0.00%)   | 0 / 15 (0.00%)   |
| occurrences (all)                                    | 0                | 0                | 0                |
| General disorders and administration site conditions |                  |                  |                  |
| Fatigue                                              |                  |                  |                  |
| subjects affected / exposed                          | 13 / 32 (40.63%) | 16 / 48 (33.33%) | 12 / 15 (80.00%) |
| occurrences (all)                                    | 16               | 25               | 15               |
| Oedema peripheral                                    |                  |                  |                  |
| subjects affected / exposed                          | 6 / 32 (18.75%)  | 3 / 48 (6.25%)   | 5 / 15 (33.33%)  |
| occurrences (all)                                    | 6                | 5                | 6                |
| Pyrexia                                              |                  |                  |                  |
| subjects affected / exposed                          | 5 / 32 (15.63%)  | 6 / 48 (12.50%)  | 2 / 15 (13.33%)  |
| occurrences (all)                                    | 5                | 7                | 2                |
| Pain                                                 |                  |                  |                  |
| subjects affected / exposed                          | 3 / 32 (9.38%)   | 3 / 48 (6.25%)   | 1 / 15 (6.67%)   |
| occurrences (all)                                    | 3                | 3                | 1                |
| Chest discomfort                                     |                  |                  |                  |
| subjects affected / exposed                          | 3 / 32 (9.38%)   | 5 / 48 (10.42%)  | 2 / 15 (13.33%)  |
| occurrences (all)                                    | 3                | 6                | 3                |
| Non-cardiac chest pain                               |                  |                  |                  |
| subjects affected / exposed                          | 1 / 32 (3.13%)   | 3 / 48 (6.25%)   | 3 / 15 (20.00%)  |
| occurrences (all)                                    | 1                | 3                | 3                |
| Influenza like illness                               |                  |                  |                  |
| subjects affected / exposed                          | 3 / 32 (9.38%)   | 3 / 48 (6.25%)   | 1 / 15 (6.67%)   |
| occurrences (all)                                    | 5                | 3                | 1                |
| Asthenia                                             |                  |                  |                  |
| subjects affected / exposed                          | 1 / 32 (3.13%)   | 5 / 48 (10.42%)  | 1 / 15 (6.67%)   |
| occurrences (all)                                    | 1                | 6                | 1                |
| Chills                                               |                  |                  |                  |
| subjects affected / exposed                          | 1 / 32 (3.13%)   | 1 / 48 (2.08%)   | 2 / 15 (13.33%)  |
| occurrences (all)                                    | 1                | 1                | 5                |
| Gait disturbance                                     |                  |                  |                  |
| subjects affected / exposed                          | 2 / 32 (6.25%)   | 3 / 48 (6.25%)   | 0 / 15 (0.00%)   |
| occurrences (all)                                    | 2                | 3                | 0                |
| Peripheral swelling                                  |                  |                  |                  |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 2 / 32 (6.25%) | 2 / 48 (4.17%) | 0 / 15 (0.00%) |
| occurrences (all)                               | 2              | 2              | 0              |
| Chest pain                                      |                |                |                |
| subjects affected / exposed                     | 2 / 32 (6.25%) | 1 / 48 (2.08%) | 0 / 15 (0.00%) |
| occurrences (all)                               | 2              | 1              | 0              |
| Thirst                                          |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 1 / 48 (2.08%) | 0 / 15 (0.00%) |
| occurrences (all)                               | 0              | 1              | 0              |
| Axillary pain                                   |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Exercise tolerance decreased                    |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Feeling abnormal                                |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Feeling jittery                                 |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Immune system disorders                         |                |                |                |
| Seasonal allergy                                |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 3 / 48 (6.25%) | 0 / 15 (0.00%) |
| occurrences (all)                               | 0              | 3              | 0              |
| Contrast media allergy                          |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Reproductive system and breast disorders        |                |                |                |
| Vulvovaginal dryness                            |                |                |                |
| subjects affected / exposed                     | 1 / 32 (3.13%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all)                               | 1              | 0              | 0              |
| Nipple pain                                     |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Respiratory, thoracic and mediastinal disorders |                |                |                |

|                             |                  |                  |                 |
|-----------------------------|------------------|------------------|-----------------|
| Cough                       |                  |                  |                 |
| subjects affected / exposed | 11 / 32 (34.38%) | 13 / 48 (27.08%) | 8 / 15 (53.33%) |
| occurrences (all)           | 17               | 17               | 10              |
| Dyspnoea                    |                  |                  |                 |
| subjects affected / exposed | 7 / 32 (21.88%)  | 7 / 48 (14.58%)  | 3 / 15 (20.00%) |
| occurrences (all)           | 8                | 9                | 4               |
| Dyspnoea exertional         |                  |                  |                 |
| subjects affected / exposed | 1 / 32 (3.13%)   | 4 / 48 (8.33%)   | 1 / 15 (6.67%)  |
| occurrences (all)           | 1                | 4                | 2               |
| Oropharyngeal pain          |                  |                  |                 |
| subjects affected / exposed | 2 / 32 (6.25%)   | 4 / 48 (8.33%)   | 1 / 15 (6.67%)  |
| occurrences (all)           | 2                | 4                | 1               |
| Epistaxis                   |                  |                  |                 |
| subjects affected / exposed | 1 / 32 (3.13%)   | 4 / 48 (8.33%)   | 2 / 15 (13.33%) |
| occurrences (all)           | 1                | 4                | 2               |
| Productive cough            |                  |                  |                 |
| subjects affected / exposed | 3 / 32 (9.38%)   | 2 / 48 (4.17%)   | 0 / 15 (0.00%)  |
| occurrences (all)           | 3                | 3                | 0               |
| Nasal congestion            |                  |                  |                 |
| subjects affected / exposed | 0 / 32 (0.00%)   | 0 / 48 (0.00%)   | 2 / 15 (13.33%) |
| occurrences (all)           | 0                | 0                | 2               |
| Haemoptysis                 |                  |                  |                 |
| subjects affected / exposed | 1 / 32 (3.13%)   | 2 / 48 (4.17%)   | 1 / 15 (6.67%)  |
| occurrences (all)           | 3                | 3                | 2               |
| Hypoxia                     |                  |                  |                 |
| subjects affected / exposed | 1 / 32 (3.13%)   | 1 / 48 (2.08%)   | 2 / 15 (13.33%) |
| occurrences (all)           | 1                | 2                | 3               |
| Rhinorrhoea                 |                  |                  |                 |
| subjects affected / exposed | 1 / 32 (3.13%)   | 2 / 48 (4.17%)   | 0 / 15 (0.00%)  |
| occurrences (all)           | 1                | 2                | 0               |
| Sinus congestion            |                  |                  |                 |
| subjects affected / exposed | 3 / 32 (9.38%)   | 0 / 48 (0.00%)   | 0 / 15 (0.00%)  |
| occurrences (all)           | 3                | 0                | 0               |
| Dysphonia                   |                  |                  |                 |
| subjects affected / exposed | 0 / 32 (0.00%)   | 2 / 48 (4.17%)   | 1 / 15 (6.67%)  |
| occurrences (all)           | 0                | 2                | 1               |

|                             |                |                |                 |
|-----------------------------|----------------|----------------|-----------------|
| Rhinitis allergic           |                |                |                 |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 48 (0.00%) | 0 / 15 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0               |
| Sputum discoloured          |                |                |                 |
| subjects affected / exposed | 1 / 32 (3.13%) | 1 / 48 (2.08%) | 0 / 15 (0.00%)  |
| occurrences (all)           | 1              | 1              | 0               |
| Dry throat                  |                |                |                 |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 48 (2.08%) | 1 / 15 (6.67%)  |
| occurrences (all)           | 0              | 1              | 1               |
| Hiccups                     |                |                |                 |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 1 / 15 (6.67%)  |
| occurrences (all)           | 0              | 0              | 1               |
| Laryngeal inflammation      |                |                |                 |
| subjects affected / exposed | 2 / 32 (6.25%) | 0 / 48 (0.00%) | 0 / 15 (0.00%)  |
| occurrences (all)           | 2              | 0              | 0               |
| Pleural effusion            |                |                |                 |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 48 (2.08%) | 1 / 15 (6.67%)  |
| occurrences (all)           | 0              | 1              | 1               |
| Pleuritic pain              |                |                |                 |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 48 (0.00%) | 1 / 15 (6.67%)  |
| occurrences (all)           | 1              | 0              | 1               |
| Throat irritation           |                |                |                 |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 48 (2.08%) | 0 / 15 (0.00%)  |
| occurrences (all)           | 0              | 1              | 0               |
| Wheezing                    |                |                |                 |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 2 / 15 (13.33%) |
| occurrences (all)           | 0              | 0              | 2               |
| Nasal dryness               |                |                |                 |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 1 / 15 (6.67%)  |
| occurrences (all)           | 0              | 0              | 1               |
| Pleurisy                    |                |                |                 |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 1 / 15 (6.67%)  |
| occurrences (all)           | 0              | 0              | 1               |
| Pneumothorax                |                |                |                 |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 1 / 15 (6.67%)  |
| occurrences (all)           | 0              | 0              | 1               |

|                                                                                  |                      |                     |                      |
|----------------------------------------------------------------------------------|----------------------|---------------------|----------------------|
| Pulmonary hypertension<br>subjects affected / exposed<br>occurrences (all)       | 0 / 32 (0.00%)<br>0  | 0 / 48 (0.00%)<br>0 | 1 / 15 (6.67%)<br>1  |
| Respiratory tract irritation<br>subjects affected / exposed<br>occurrences (all) | 0 / 32 (0.00%)<br>0  | 0 / 48 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0  |
| Sneezing<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 32 (0.00%)<br>0  | 0 / 48 (0.00%)<br>0 | 1 / 15 (6.67%)<br>2  |
| Upper-airway cough syndrome<br>subjects affected / exposed<br>occurrences (all)  | 0 / 32 (0.00%)<br>0  | 0 / 48 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0  |
| Psychiatric disorders                                                            |                      |                     |                      |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                     | 6 / 32 (18.75%)<br>6 | 3 / 48 (6.25%)<br>3 | 3 / 15 (20.00%)<br>3 |
| Anxiety<br>subjects affected / exposed<br>occurrences (all)                      | 4 / 32 (12.50%)<br>4 | 1 / 48 (2.08%)<br>1 | 1 / 15 (6.67%)<br>1  |
| Depression<br>subjects affected / exposed<br>occurrences (all)                   | 3 / 32 (9.38%)<br>3  | 3 / 48 (6.25%)<br>3 | 0 / 15 (0.00%)<br>0  |
| Bruxism<br>subjects affected / exposed<br>occurrences (all)                      | 1 / 32 (3.13%)<br>1  | 0 / 48 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0  |
| Anticipatory anxiety<br>subjects affected / exposed<br>occurrences (all)         | 0 / 32 (0.00%)<br>0  | 0 / 48 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0  |
| Confusional state<br>subjects affected / exposed<br>occurrences (all)            | 0 / 32 (0.00%)<br>0  | 0 / 48 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0  |
| Disorientation<br>subjects affected / exposed<br>occurrences (all)               | 0 / 32 (0.00%)<br>0  | 0 / 48 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0  |
| Nervousness                                                                      |                      |                     |                      |

|                                      |                  |                 |                 |
|--------------------------------------|------------------|-----------------|-----------------|
| subjects affected / exposed          | 0 / 32 (0.00%)   | 0 / 48 (0.00%)  | 0 / 15 (0.00%)  |
| occurrences (all)                    | 0                | 0               | 0               |
| Stress                               |                  |                 |                 |
| subjects affected / exposed          | 0 / 32 (0.00%)   | 0 / 48 (0.00%)  | 0 / 15 (0.00%)  |
| occurrences (all)                    | 0                | 0               | 0               |
| Investigations                       |                  |                 |                 |
| Amylase increased                    |                  |                 |                 |
| subjects affected / exposed          | 9 / 32 (28.13%)  | 8 / 48 (16.67%) | 3 / 15 (20.00%) |
| occurrences (all)                    | 22               | 14              | 6               |
| Lipase increased                     |                  |                 |                 |
| subjects affected / exposed          | 10 / 32 (31.25%) | 6 / 48 (12.50%) | 2 / 15 (13.33%) |
| occurrences (all)                    | 21               | 24              | 5               |
| Aspartate aminotransferase increased |                  |                 |                 |
| subjects affected / exposed          | 7 / 32 (21.88%)  | 7 / 48 (14.58%) | 2 / 15 (13.33%) |
| occurrences (all)                    | 10               | 12              | 4               |
| Alanine aminotransferase increased   |                  |                 |                 |
| subjects affected / exposed          | 4 / 32 (12.50%)  | 4 / 48 (8.33%)  | 1 / 15 (6.67%)  |
| occurrences (all)                    | 10               | 4               | 4               |
| Blood insulin increased              |                  |                 |                 |
| subjects affected / exposed          | 3 / 32 (9.38%)   | 5 / 48 (10.42%) | 0 / 15 (0.00%)  |
| occurrences (all)                    | 5                | 9               | 0               |
| Weight decreased                     |                  |                 |                 |
| subjects affected / exposed          | 3 / 32 (9.38%)   | 3 / 48 (6.25%)  | 2 / 15 (13.33%) |
| occurrences (all)                    | 3                | 4               | 3               |
| Blood creatinine increased           |                  |                 |                 |
| subjects affected / exposed          | 3 / 32 (9.38%)   | 1 / 48 (2.08%)  | 1 / 15 (6.67%)  |
| occurrences (all)                    | 3                | 1               | 1               |
| Lymphocyte count decreased           |                  |                 |                 |
| subjects affected / exposed          | 3 / 32 (9.38%)   | 2 / 48 (4.17%)  | 1 / 15 (6.67%)  |
| occurrences (all)                    | 4                | 2               | 1               |
| Weight increased                     |                  |                 |                 |
| subjects affected / exposed          | 0 / 32 (0.00%)   | 3 / 48 (6.25%)  | 1 / 15 (6.67%)  |
| occurrences (all)                    | 0                | 4               | 1               |
| Blood alkaline phosphatase increased |                  |                 |                 |



|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 32 (3.13%) | 1 / 48 (2.08%) | 1 / 15 (6.67%) |
| occurrences (all)                               | 1              | 1              | 1              |
| Blood testosterone decreased                    |                |                |                |
| subjects affected / exposed                     | 2 / 32 (6.25%) | 2 / 48 (4.17%) | 1 / 15 (6.67%) |
| occurrences (all)                               | 2              | 2              | 1              |
| Blood thyroid stimulating hormone decreased     |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 1 / 48 (2.08%) | 0 / 15 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Blood bilirubin increased                       |                |                |                |
| subjects affected / exposed                     | 2 / 32 (6.25%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all)                               | 2              | 0              | 0              |
| Blood lactate dehydrogenase increased           |                |                |                |
| subjects affected / exposed                     | 2 / 32 (6.25%) | 0 / 48 (0.00%) | 1 / 15 (6.67%) |
| occurrences (all)                               | 2              | 0              | 1              |
| Blood thyroid stimulating hormone increased     |                |                |                |
| subjects affected / exposed                     | 1 / 32 (3.13%) | 1 / 48 (2.08%) | 0 / 15 (0.00%) |
| occurrences (all)                               | 1              | 1              | 0              |
| Activated partial thromboplastin time prolonged |                |                |                |
| subjects affected / exposed                     | 1 / 32 (3.13%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all)                               | 1              | 0              | 0              |
| Electrocardiogram QT prolonged                  |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Bacterial test positive                         |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 1 / 15 (6.67%) |
| occurrences (all)                               | 0              | 0              | 1              |
| Ejection fraction decreased                     |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Heart rate increased                            |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Urinary sediment present                        |                |                |                |

|                                                                                       |                     |                     |                     |
|---------------------------------------------------------------------------------------|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)                                      | 0 / 32 (0.00%)<br>0 | 0 / 48 (0.00%)<br>0 | 1 / 15 (6.67%)<br>1 |
| Urine leukocyte esterase positive<br>subjects affected / exposed<br>occurrences (all) | 0 / 32 (0.00%)<br>0 | 0 / 48 (0.00%)<br>0 | 1 / 15 (6.67%)<br>1 |
| White blood cells urine<br>subjects affected / exposed<br>occurrences (all)           | 0 / 32 (0.00%)<br>0 | 0 / 48 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 |
| White blood cells urine positive<br>subjects affected / exposed<br>occurrences (all)  | 0 / 32 (0.00%)<br>0 | 0 / 48 (0.00%)<br>0 | 1 / 15 (6.67%)<br>1 |
| Injury, poisoning and procedural complications                                        |                     |                     |                     |
| Laceration<br>subjects affected / exposed<br>occurrences (all)                        | 1 / 32 (3.13%)<br>1 | 0 / 48 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 |
| Rib fracture<br>subjects affected / exposed<br>occurrences (all)                      | 1 / 32 (3.13%)<br>1 | 0 / 48 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 |
| Procedural pain<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 32 (0.00%)<br>0 | 0 / 48 (0.00%)<br>0 | 1 / 15 (6.67%)<br>1 |
| Radiation neuropathy<br>subjects affected / exposed<br>occurrences (all)              | 0 / 32 (0.00%)<br>0 | 0 / 48 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 |
| Radiation pneumonitis<br>subjects affected / exposed<br>occurrences (all)             | 0 / 32 (0.00%)<br>0 | 0 / 48 (0.00%)<br>0 | 1 / 15 (6.67%)<br>1 |
| Cardiac disorders                                                                     |                     |                     |                     |
| Sinus tachycardia<br>subjects affected / exposed<br>occurrences (all)                 | 2 / 32 (6.25%)<br>2 | 1 / 48 (2.08%)<br>1 | 0 / 15 (0.00%)<br>0 |
| Palpitations<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 32 (0.00%)<br>0 | 0 / 48 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 |
| Sinus bradycardia                                                                     |                     |                     |                     |

|                               |                  |                  |                 |
|-------------------------------|------------------|------------------|-----------------|
| subjects affected / exposed   | 2 / 32 (6.25%)   | 0 / 48 (0.00%)   | 0 / 15 (0.00%)  |
| occurrences (all)             | 2                | 0                | 0               |
| Atrial fibrillation           |                  |                  |                 |
| subjects affected / exposed   | 0 / 32 (0.00%)   | 0 / 48 (0.00%)   | 0 / 15 (0.00%)  |
| occurrences (all)             | 0                | 0                | 0               |
| Atrial flutter                |                  |                  |                 |
| subjects affected / exposed   | 0 / 32 (0.00%)   | 0 / 48 (0.00%)   | 0 / 15 (0.00%)  |
| occurrences (all)             | 0                | 0                | 0               |
| Cardiac failure congestive    |                  |                  |                 |
| subjects affected / exposed   | 0 / 32 (0.00%)   | 0 / 48 (0.00%)   | 0 / 15 (0.00%)  |
| occurrences (all)             | 0                | 0                | 0               |
| Nervous system disorders      |                  |                  |                 |
| Headache                      |                  |                  |                 |
| subjects affected / exposed   | 12 / 32 (37.50%) | 14 / 48 (29.17%) | 6 / 15 (40.00%) |
| occurrences (all)             | 13               | 18               | 8               |
| Dizziness                     |                  |                  |                 |
| subjects affected / exposed   | 4 / 32 (12.50%)  | 3 / 48 (6.25%)   | 1 / 15 (6.67%)  |
| occurrences (all)             | 4                | 3                | 1               |
| Peripheral sensory neuropathy |                  |                  |                 |
| subjects affected / exposed   | 5 / 32 (15.63%)  | 3 / 48 (6.25%)   | 0 / 15 (0.00%)  |
| occurrences (all)             | 5                | 3                | 0               |
| Paraesthesia                  |                  |                  |                 |
| subjects affected / exposed   | 2 / 32 (6.25%)   | 3 / 48 (6.25%)   | 1 / 15 (6.67%)  |
| occurrences (all)             | 2                | 4                | 1               |
| Dysgeusia                     |                  |                  |                 |
| subjects affected / exposed   | 1 / 32 (3.13%)   | 3 / 48 (6.25%)   | 1 / 15 (6.67%)  |
| occurrences (all)             | 1                | 4                | 2               |
| Tremor                        |                  |                  |                 |
| subjects affected / exposed   | 2 / 32 (6.25%)   | 2 / 48 (4.17%)   | 1 / 15 (6.67%)  |
| occurrences (all)             | 2                | 2                | 1               |
| Amnesia                       |                  |                  |                 |
| subjects affected / exposed   | 1 / 32 (3.13%)   | 3 / 48 (6.25%)   | 0 / 15 (0.00%)  |
| occurrences (all)             | 1                | 5                | 0               |
| Balance disorder              |                  |                  |                 |
| subjects affected / exposed   | 0 / 32 (0.00%)   | 3 / 48 (6.25%)   | 0 / 15 (0.00%)  |
| occurrences (all)             | 0                | 3                | 0               |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| Hypoaesthesia               |                |                |                |
| subjects affected / exposed | 0 / 32 (0.00%) | 3 / 48 (6.25%) | 1 / 15 (6.67%) |
| occurrences (all)           | 0              | 8              | 1              |
| Visual field defect         |                |                |                |
| subjects affected / exposed | 0 / 32 (0.00%) | 4 / 48 (8.33%) | 1 / 15 (6.67%) |
| occurrences (all)           | 0              | 5              | 1              |
| Seizure                     |                |                |                |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 48 (2.08%) | 1 / 15 (6.67%) |
| occurrences (all)           | 0              | 3              | 1              |
| Aphasia                     |                |                |                |
| subjects affected / exposed | 0 / 32 (0.00%) | 2 / 48 (4.17%) | 0 / 15 (0.00%) |
| occurrences (all)           | 0              | 2              | 0              |
| Disturbance in attention    |                |                |                |
| subjects affected / exposed | 1 / 32 (3.13%) | 1 / 48 (2.08%) | 0 / 15 (0.00%) |
| occurrences (all)           | 1              | 1              | 0              |
| Dysarthria                  |                |                |                |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 48 (2.08%) | 0 / 15 (0.00%) |
| occurrences (all)           | 0              | 2              | 0              |
| Memory impairment           |                |                |                |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Sinus headache              |                |                |                |
| subjects affected / exposed | 2 / 32 (6.25%) | 1 / 48 (2.08%) | 0 / 15 (0.00%) |
| occurrences (all)           | 2              | 1              | 0              |
| Somnolence                  |                |                |                |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Syncope                     |                |                |                |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 48 (0.00%) | 1 / 15 (6.67%) |
| occurrences (all)           | 1              | 0              | 1              |
| Burning sensation           |                |                |                |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Cognitive disorder          |                |                |                |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |

|                                      |                 |                |                 |
|--------------------------------------|-----------------|----------------|-----------------|
| Neuralgia                            |                 |                |                 |
| subjects affected / exposed          | 0 / 32 (0.00%)  | 0 / 48 (0.00%) | 0 / 15 (0.00%)  |
| occurrences (all)                    | 0               | 0              | 0               |
| Parosmia                             |                 |                |                 |
| subjects affected / exposed          | 0 / 32 (0.00%)  | 0 / 48 (0.00%) | 0 / 15 (0.00%)  |
| occurrences (all)                    | 0               | 0              | 0               |
| Peripheral motor neuropathy          |                 |                |                 |
| subjects affected / exposed          | 0 / 32 (0.00%)  | 0 / 48 (0.00%) | 0 / 15 (0.00%)  |
| occurrences (all)                    | 0               | 0              | 0               |
| Blood and lymphatic system disorders |                 |                |                 |
| Anaemia                              |                 |                |                 |
| subjects affected / exposed          | 4 / 32 (12.50%) | 2 / 48 (4.17%) | 3 / 15 (20.00%) |
| occurrences (all)                    | 6               | 4              | 4               |
| Increased tendency to bruise         |                 |                |                 |
| subjects affected / exposed          | 0 / 32 (0.00%)  | 2 / 48 (4.17%) | 1 / 15 (6.67%)  |
| occurrences (all)                    | 0               | 2              | 1               |
| Leukocytosis                         |                 |                |                 |
| subjects affected / exposed          | 1 / 32 (3.13%)  | 0 / 48 (0.00%) | 0 / 15 (0.00%)  |
| occurrences (all)                    | 1               | 0              | 0               |
| Ear and labyrinth disorders          |                 |                |                 |
| Tinnitus                             |                 |                |                 |
| subjects affected / exposed          | 1 / 32 (3.13%)  | 1 / 48 (2.08%) | 1 / 15 (6.67%)  |
| occurrences (all)                    | 1               | 1              | 1               |
| Deafness unilateral                  |                 |                |                 |
| subjects affected / exposed          | 0 / 32 (0.00%)  | 0 / 48 (0.00%) | 0 / 15 (0.00%)  |
| occurrences (all)                    | 0               | 0              | 0               |
| Vertigo                              |                 |                |                 |
| subjects affected / exposed          | 0 / 32 (0.00%)  | 0 / 48 (0.00%) | 0 / 15 (0.00%)  |
| occurrences (all)                    | 0               | 0              | 0               |
| Eye disorders                        |                 |                |                 |
| Vision blurred                       |                 |                |                 |
| subjects affected / exposed          | 4 / 32 (12.50%) | 4 / 48 (8.33%) | 0 / 15 (0.00%)  |
| occurrences (all)                    | 4               | 4              | 0               |
| Dry eye                              |                 |                |                 |
| subjects affected / exposed          | 1 / 32 (3.13%)  | 1 / 48 (2.08%) | 0 / 15 (0.00%)  |
| occurrences (all)                    | 1               | 1              | 0               |
| Visual impairment                    |                 |                |                 |

|                             |                  |                  |                 |
|-----------------------------|------------------|------------------|-----------------|
| subjects affected / exposed | 1 / 32 (3.13%)   | 0 / 48 (0.00%)   | 1 / 15 (6.67%)  |
| occurrences (all)           | 1                | 0                | 2               |
| Blepharospasm               |                  |                  |                 |
| subjects affected / exposed | 0 / 32 (0.00%)   | 0 / 48 (0.00%)   | 1 / 15 (6.67%)  |
| occurrences (all)           | 0                | 0                | 1               |
| Lacrimation increased       |                  |                  |                 |
| subjects affected / exposed | 1 / 32 (3.13%)   | 0 / 48 (0.00%)   | 0 / 15 (0.00%)  |
| occurrences (all)           | 1                | 0                | 0               |
| Photopsia                   |                  |                  |                 |
| subjects affected / exposed | 0 / 32 (0.00%)   | 0 / 48 (0.00%)   | 0 / 15 (0.00%)  |
| occurrences (all)           | 0                | 0                | 0               |
| Vitreous floaters           |                  |                  |                 |
| subjects affected / exposed | 1 / 32 (3.13%)   | 0 / 48 (0.00%)   | 0 / 15 (0.00%)  |
| occurrences (all)           | 1                | 0                | 0               |
| Asthenopia                  |                  |                  |                 |
| subjects affected / exposed | 0 / 32 (0.00%)   | 0 / 48 (0.00%)   | 1 / 15 (6.67%)  |
| occurrences (all)           | 0                | 0                | 1               |
| Cataract cortical           |                  |                  |                 |
| subjects affected / exposed | 0 / 32 (0.00%)   | 0 / 48 (0.00%)   | 1 / 15 (6.67%)  |
| occurrences (all)           | 0                | 0                | 1               |
| Colour blindness acquired   |                  |                  |                 |
| subjects affected / exposed | 0 / 32 (0.00%)   | 0 / 48 (0.00%)   | 0 / 15 (0.00%)  |
| occurrences (all)           | 0                | 0                | 0               |
| Eye pain                    |                  |                  |                 |
| subjects affected / exposed | 0 / 32 (0.00%)   | 0 / 48 (0.00%)   | 0 / 15 (0.00%)  |
| occurrences (all)           | 0                | 0                | 0               |
| Eyelid margin crusting      |                  |                  |                 |
| subjects affected / exposed | 0 / 32 (0.00%)   | 0 / 48 (0.00%)   | 0 / 15 (0.00%)  |
| occurrences (all)           | 0                | 0                | 0               |
| Gastrointestinal disorders  |                  |                  |                 |
| Nausea                      |                  |                  |                 |
| subjects affected / exposed | 14 / 32 (43.75%) | 31 / 48 (64.58%) | 8 / 15 (53.33%) |
| occurrences (all)           | 15               | 42               | 11              |
| Diarrhoea                   |                  |                  |                 |
| subjects affected / exposed | 15 / 32 (46.88%) | 18 / 48 (37.50%) | 8 / 15 (53.33%) |
| occurrences (all)           | 17               | 32               | 28              |

|                                 |                 |                  |                 |
|---------------------------------|-----------------|------------------|-----------------|
| Constipation                    |                 |                  |                 |
| subjects affected / exposed     | 9 / 32 (28.13%) | 7 / 48 (14.58%)  | 5 / 15 (33.33%) |
| occurrences (all)               | 10              | 7                | 5               |
| Vomiting                        |                 |                  |                 |
| subjects affected / exposed     | 5 / 32 (15.63%) | 15 / 48 (31.25%) | 5 / 15 (33.33%) |
| occurrences (all)               | 8               | 24               | 5               |
| Abdominal pain                  |                 |                  |                 |
| subjects affected / exposed     | 7 / 32 (21.88%) | 9 / 48 (18.75%)  | 2 / 15 (13.33%) |
| occurrences (all)               | 8               | 12               | 5               |
| Dry mouth                       |                 |                  |                 |
| subjects affected / exposed     | 4 / 32 (12.50%) | 1 / 48 (2.08%)   | 2 / 15 (13.33%) |
| occurrences (all)               | 4               | 1                | 2               |
| Abdominal distension            |                 |                  |                 |
| subjects affected / exposed     | 1 / 32 (3.13%)  | 4 / 48 (8.33%)   | 0 / 15 (0.00%)  |
| occurrences (all)               | 1               | 4                | 0               |
| Abdominal discomfort            |                 |                  |                 |
| subjects affected / exposed     | 2 / 32 (6.25%)  | 4 / 48 (8.33%)   | 0 / 15 (0.00%)  |
| occurrences (all)               | 2               | 4                | 0               |
| Gastroesophageal reflux disease |                 |                  |                 |
| subjects affected / exposed     | 1 / 32 (3.13%)  | 2 / 48 (4.17%)   | 2 / 15 (13.33%) |
| occurrences (all)               | 1               | 2                | 2               |
| Dyspepsia                       |                 |                  |                 |
| subjects affected / exposed     | 1 / 32 (3.13%)  | 1 / 48 (2.08%)   | 1 / 15 (6.67%)  |
| occurrences (all)               | 1               | 1                | 1               |
| Dysphagia                       |                 |                  |                 |
| subjects affected / exposed     | 0 / 32 (0.00%)  | 2 / 48 (4.17%)   | 2 / 15 (13.33%) |
| occurrences (all)               | 0               | 2                | 4               |
| Aphthous stomatitis             |                 |                  |                 |
| subjects affected / exposed     | 0 / 32 (0.00%)  | 1 / 48 (2.08%)   | 0 / 15 (0.00%)  |
| occurrences (all)               | 0               | 1                | 0               |
| Flatulence                      |                 |                  |                 |
| subjects affected / exposed     | 1 / 32 (3.13%)  | 1 / 48 (2.08%)   | 1 / 15 (6.67%)  |
| occurrences (all)               | 1               | 1                | 1               |
| Sensitivity of teeth            |                 |                  |                 |
| subjects affected / exposed     | 1 / 32 (3.13%)  | 0 / 48 (0.00%)   | 1 / 15 (6.67%)  |
| occurrences (all)               | 1               | 0                | 1               |

|                                        |                |                |                |
|----------------------------------------|----------------|----------------|----------------|
| Stomatitis                             |                |                |                |
| subjects affected / exposed            | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0              |
| Cheilitis                              |                |                |                |
| subjects affected / exposed            | 0 / 32 (0.00%) | 1 / 48 (2.08%) | 0 / 15 (0.00%) |
| occurrences (all)                      | 0              | 1              | 0              |
| Mouth ulceration                       |                |                |                |
| subjects affected / exposed            | 0 / 32 (0.00%) | 1 / 48 (2.08%) | 0 / 15 (0.00%) |
| occurrences (all)                      | 0              | 1              | 0              |
| Abdominal rigidity                     |                |                |                |
| subjects affected / exposed            | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0              |
| Abnormal faeces                        |                |                |                |
| subjects affected / exposed            | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0              |
| Lip dry                                |                |                |                |
| subjects affected / exposed            | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0              |
| Lip swelling                           |                |                |                |
| subjects affected / exposed            | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0              |
| Oesophageal irritation                 |                |                |                |
| subjects affected / exposed            | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0              |
| Oesophageal pain                       |                |                |                |
| subjects affected / exposed            | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 1 / 15 (6.67%) |
| occurrences (all)                      | 0              | 0              | 1              |
| Toothache                              |                |                |                |
| subjects affected / exposed            | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0              |
| Hypoaesthesia oral                     |                |                |                |
| subjects affected / exposed            | 0 / 32 (0.00%) | 1 / 48 (2.08%) | 1 / 15 (6.67%) |
| occurrences (all)                      | 0              | 1              | 1              |
| Skin and subcutaneous tissue disorders |                |                |                |
| Rash                                   |                |                |                |



|                             |                 |                 |                |
|-----------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed | 4 / 32 (12.50%) | 7 / 48 (14.58%) | 1 / 15 (6.67%) |
| occurrences (all)           | 6               | 12              | 1              |
| Photosensitivity reaction   |                 |                 |                |
| subjects affected / exposed | 3 / 32 (9.38%)  | 5 / 48 (10.42%) | 0 / 15 (0.00%) |
| occurrences (all)           | 4               | 6               | 0              |
| Pruritus                    |                 |                 |                |
| subjects affected / exposed | 6 / 32 (18.75%) | 3 / 48 (6.25%)  | 0 / 15 (0.00%) |
| occurrences (all)           | 6               | 3               | 0              |
| Dry skin                    |                 |                 |                |
| subjects affected / exposed | 4 / 32 (12.50%) | 3 / 48 (6.25%)  | 0 / 15 (0.00%) |
| occurrences (all)           | 5               | 3               | 0              |
| Night sweats                |                 |                 |                |
| subjects affected / exposed | 0 / 32 (0.00%)  | 4 / 48 (8.33%)  | 0 / 15 (0.00%) |
| occurrences (all)           | 0               | 4               | 0              |
| Dermatitis acneiform        |                 |                 |                |
| subjects affected / exposed | 3 / 32 (9.38%)  | 1 / 48 (2.08%)  | 0 / 15 (0.00%) |
| occurrences (all)           | 3               | 1               | 0              |
| Alopecia                    |                 |                 |                |
| subjects affected / exposed | 0 / 32 (0.00%)  | 3 / 48 (6.25%)  | 1 / 15 (6.67%) |
| occurrences (all)           | 0               | 3               | 1              |
| Hyperhidrosis               |                 |                 |                |
| subjects affected / exposed | 1 / 32 (3.13%)  | 1 / 48 (2.08%)  | 1 / 15 (6.67%) |
| occurrences (all)           | 1               | 1               | 2              |
| Onychoclasia                |                 |                 |                |
| subjects affected / exposed | 0 / 32 (0.00%)  | 2 / 48 (4.17%)  | 0 / 15 (0.00%) |
| occurrences (all)           | 0               | 2               | 0              |
| Rash pruritic               |                 |                 |                |
| subjects affected / exposed | 2 / 32 (6.25%)  | 1 / 48 (2.08%)  | 0 / 15 (0.00%) |
| occurrences (all)           | 4               | 2               | 0              |
| Dermatitis contact          |                 |                 |                |
| subjects affected / exposed | 0 / 32 (0.00%)  | 2 / 48 (4.17%)  | 0 / 15 (0.00%) |
| occurrences (all)           | 0               | 2               | 0              |
| Eczema                      |                 |                 |                |
| subjects affected / exposed | 0 / 32 (0.00%)  | 1 / 48 (2.08%)  | 1 / 15 (6.67%) |
| occurrences (all)           | 0               | 1               | 1              |
| Erythema                    |                 |                 |                |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 2 / 32 (6.25%) | 1 / 48 (2.08%) | 0 / 15 (0.00%) |
| occurrences (all)           | 2              | 1              | 0              |
| Pain of skin                |                |                |                |
| subjects affected / exposed | 1 / 32 (3.13%) | 1 / 48 (2.08%) | 0 / 15 (0.00%) |
| occurrences (all)           | 1              | 1              | 0              |
| Skin disorder               |                |                |                |
| subjects affected / exposed | 1 / 32 (3.13%) | 1 / 48 (2.08%) | 0 / 15 (0.00%) |
| occurrences (all)           | 1              | 1              | 0              |
| Dermal cyst                 |                |                |                |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Dermatitis                  |                |                |                |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 48 (2.08%) | 1 / 15 (6.67%) |
| occurrences (all)           | 0              | 1              | 1              |
| Dermatitis atopic           |                |                |                |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 48 (2.08%) | 1 / 15 (6.67%) |
| occurrences (all)           | 0              | 1              | 1              |
| Nail disorder               |                |                |                |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Petechiae                   |                |                |                |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Skin hyperpigmentation      |                |                |                |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 1 / 15 (6.67%) |
| occurrences (all)           | 0              | 0              | 1              |
| Urticaria                   |                |                |                |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 48 (2.08%) | 0 / 15 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Nail growth abnormal        |                |                |                |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Renal and urinary disorders |                |                |                |
| Pollakiuria                 |                |                |                |
| subjects affected / exposed | 2 / 32 (6.25%) | 4 / 48 (8.33%) | 0 / 15 (0.00%) |
| occurrences (all)           | 2              | 4              | 0              |

|                                                 |                  |                  |                 |
|-------------------------------------------------|------------------|------------------|-----------------|
| Proteinuria                                     |                  |                  |                 |
| subjects affected / exposed                     | 1 / 32 (3.13%)   | 1 / 48 (2.08%)   | 2 / 15 (13.33%) |
| occurrences (all)                               | 1                | 1                | 2               |
| Haematuria                                      |                  |                  |                 |
| subjects affected / exposed                     | 1 / 32 (3.13%)   | 1 / 48 (2.08%)   | 0 / 15 (0.00%)  |
| occurrences (all)                               | 1                | 1                | 0               |
| Dysuria                                         |                  |                  |                 |
| subjects affected / exposed                     | 0 / 32 (0.00%)   | 1 / 48 (2.08%)   | 1 / 15 (6.67%)  |
| occurrences (all)                               | 0                | 1                | 1               |
| Renal failure                                   |                  |                  |                 |
| subjects affected / exposed                     | 0 / 32 (0.00%)   | 0 / 48 (0.00%)   | 0 / 15 (0.00%)  |
| occurrences (all)                               | 0                | 0                | 0               |
| Urinary retention                               |                  |                  |                 |
| subjects affected / exposed                     | 0 / 32 (0.00%)   | 0 / 48 (0.00%)   | 0 / 15 (0.00%)  |
| occurrences (all)                               | 0                | 0                | 0               |
| Endocrine disorders                             |                  |                  |                 |
| Hypothyroidism                                  |                  |                  |                 |
| subjects affected / exposed                     | 2 / 32 (6.25%)   | 1 / 48 (2.08%)   | 0 / 15 (0.00%)  |
| occurrences (all)                               | 2                | 1                | 0               |
| Musculoskeletal and connective tissue disorders |                  |                  |                 |
| Muscle spasms                                   |                  |                  |                 |
| subjects affected / exposed                     | 7 / 32 (21.88%)  | 11 / 48 (22.92%) | 3 / 15 (20.00%) |
| occurrences (all)                               | 9                | 16               | 6               |
| Back pain                                       |                  |                  |                 |
| subjects affected / exposed                     | 7 / 32 (21.88%)  | 7 / 48 (14.58%)  | 1 / 15 (6.67%)  |
| occurrences (all)                               | 7                | 8                | 1               |
| Musculoskeletal pain                            |                  |                  |                 |
| subjects affected / exposed                     | 2 / 32 (6.25%)   | 4 / 48 (8.33%)   | 3 / 15 (20.00%) |
| occurrences (all)                               | 2                | 5                | 3               |
| Arthralgia                                      |                  |                  |                 |
| subjects affected / exposed                     | 10 / 32 (31.25%) | 6 / 48 (12.50%)  | 0 / 15 (0.00%)  |
| occurrences (all)                               | 15               | 9                | 0               |
| Pain in extremity                               |                  |                  |                 |
| subjects affected / exposed                     | 2 / 32 (6.25%)   | 2 / 48 (4.17%)   | 2 / 15 (13.33%) |
| occurrences (all)                               | 3                | 3                | 3               |
| Musculoskeletal chest pain                      |                  |                  |                 |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 3 / 32 (9.38%)  | 3 / 48 (6.25%)  | 1 / 15 (6.67%)  |
| occurrences (all)           | 4               | 3               | 1               |
| Joint swelling              |                 |                 |                 |
| subjects affected / exposed | 5 / 32 (15.63%) | 2 / 48 (4.17%)  | 0 / 15 (0.00%)  |
| occurrences (all)           | 5               | 2               | 0               |
| Myalgia                     |                 |                 |                 |
| subjects affected / exposed | 1 / 32 (3.13%)  | 1 / 48 (2.08%)  | 2 / 15 (13.33%) |
| occurrences (all)           | 1               | 1               | 2               |
| Bone pain                   |                 |                 |                 |
| subjects affected / exposed | 0 / 32 (0.00%)  | 5 / 48 (10.42%) | 0 / 15 (0.00%)  |
| occurrences (all)           | 0               | 5               | 0               |
| Musculoskeletal discomfort  |                 |                 |                 |
| subjects affected / exposed | 2 / 32 (6.25%)  | 2 / 48 (4.17%)  | 0 / 15 (0.00%)  |
| occurrences (all)           | 2               | 2               | 0               |
| Flank pain                  |                 |                 |                 |
| subjects affected / exposed | 2 / 32 (6.25%)  | 0 / 48 (0.00%)  | 0 / 15 (0.00%)  |
| occurrences (all)           | 2               | 0               | 0               |
| Muscular weakness           |                 |                 |                 |
| subjects affected / exposed | 1 / 32 (3.13%)  | 1 / 48 (2.08%)  | 0 / 15 (0.00%)  |
| occurrences (all)           | 1               | 1               | 0               |
| Pain in jaw                 |                 |                 |                 |
| subjects affected / exposed | 0 / 32 (0.00%)  | 0 / 48 (0.00%)  | 2 / 15 (13.33%) |
| occurrences (all)           | 0               | 0               | 2               |
| Arthritis                   |                 |                 |                 |
| subjects affected / exposed | 0 / 32 (0.00%)  | 1 / 48 (2.08%)  | 0 / 15 (0.00%)  |
| occurrences (all)           | 0               | 1               | 0               |
| Fracture pain               |                 |                 |                 |
| subjects affected / exposed | 2 / 32 (6.25%)  | 0 / 48 (0.00%)  | 0 / 15 (0.00%)  |
| occurrences (all)           | 2               | 0               | 0               |
| Limb discomfort             |                 |                 |                 |
| subjects affected / exposed | 1 / 32 (3.13%)  | 0 / 48 (0.00%)  | 0 / 15 (0.00%)  |
| occurrences (all)           | 1               | 0               | 0               |
| Musculoskeletal stiffness   |                 |                 |                 |
| subjects affected / exposed | 0 / 32 (0.00%)  | 0 / 48 (0.00%)  | 0 / 15 (0.00%)  |
| occurrences (all)           | 0               | 0               | 0               |
| Groin pain                  |                 |                 |                 |

|                                                                                       |                      |                      |                      |
|---------------------------------------------------------------------------------------|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                                      | 0 / 32 (0.00%)<br>0  | 0 / 48 (0.00%)<br>0  | 0 / 15 (0.00%)<br>0  |
| Neck pain<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 32 (0.00%)<br>0  | 0 / 48 (0.00%)<br>0  | 1 / 15 (6.67%)<br>1  |
| Osteopenia<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 32 (0.00%)<br>0  | 0 / 48 (0.00%)<br>0  | 0 / 15 (0.00%)<br>0  |
| Infections and infestations                                                           |                      |                      |                      |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 7 / 32 (21.88%)<br>8 | 5 / 48 (10.42%)<br>5 | 3 / 15 (20.00%)<br>3 |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                   | 4 / 32 (12.50%)<br>5 | 5 / 48 (10.42%)<br>6 | 1 / 15 (6.67%)<br>1  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)           | 3 / 32 (9.38%)<br>4  | 6 / 48 (12.50%)<br>9 | 1 / 15 (6.67%)<br>1  |
| Sinusitis<br>subjects affected / exposed<br>occurrences (all)                         | 4 / 32 (12.50%)<br>6 | 1 / 48 (2.08%)<br>1  | 4 / 15 (26.67%)<br>5 |
| Pneumonia<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 32 (3.13%)<br>1  | 0 / 48 (0.00%)<br>0  | 2 / 15 (13.33%)<br>2 |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)                        | 1 / 32 (3.13%)<br>1  | 0 / 48 (0.00%)<br>0  | 2 / 15 (13.33%)<br>2 |
| Influenza<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 32 (3.13%)<br>1  | 1 / 48 (2.08%)<br>1  | 0 / 15 (0.00%)<br>0  |
| Oral candidiasis<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 32 (0.00%)<br>0  | 1 / 48 (2.08%)<br>2  | 1 / 15 (6.67%)<br>1  |
| Viral infection<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 32 (0.00%)<br>0  | 1 / 48 (2.08%)<br>1  | 0 / 15 (0.00%)<br>0  |

|                                                                                    |                     |                     |                     |
|------------------------------------------------------------------------------------|---------------------|---------------------|---------------------|
| Vulvovaginal mycotic infection<br>subjects affected / exposed<br>occurrences (all) | 0 / 32 (0.00%)<br>0 | 1 / 48 (2.08%)<br>1 | 0 / 15 (0.00%)<br>0 |
| Conjunctivitis viral<br>subjects affected / exposed<br>occurrences (all)           | 0 / 32 (0.00%)<br>0 | 0 / 48 (0.00%)<br>0 | 1 / 15 (6.67%)<br>1 |
| Diarrhoea infectious<br>subjects affected / exposed<br>occurrences (all)           | 0 / 32 (0.00%)<br>0 | 0 / 48 (0.00%)<br>0 | 1 / 15 (6.67%)<br>2 |
| Folliculitis<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 32 (0.00%)<br>0 | 0 / 48 (0.00%)<br>0 | 1 / 15 (6.67%)<br>1 |
| Fungal skin infection<br>subjects affected / exposed<br>occurrences (all)          | 0 / 32 (0.00%)<br>0 | 0 / 48 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 |
| Infectious pleural effusion<br>subjects affected / exposed<br>occurrences (all)    | 0 / 32 (0.00%)<br>0 | 0 / 48 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 |
| Laryngitis viral<br>subjects affected / exposed<br>occurrences (all)               | 0 / 32 (0.00%)<br>0 | 0 / 48 (0.00%)<br>0 | 1 / 15 (6.67%)<br>1 |
| Lung infection<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 32 (0.00%)<br>0 | 0 / 48 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 |
| Nail infection<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 32 (0.00%)<br>0 | 0 / 48 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 |
| Nasal herpes<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 32 (0.00%)<br>0 | 0 / 48 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 |
| Onychomycosis<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 32 (0.00%)<br>0 | 0 / 48 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 |
| Otitis externa<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 32 (0.00%)<br>0 | 0 / 48 (0.00%)<br>0 | 1 / 15 (6.67%)<br>1 |

|                                    |                 |                 |                 |
|------------------------------------|-----------------|-----------------|-----------------|
| Paronychia                         |                 |                 |                 |
| subjects affected / exposed        | 0 / 32 (0.00%)  | 0 / 48 (0.00%)  | 0 / 15 (0.00%)  |
| occurrences (all)                  | 0               | 0               | 0               |
| Skin candida                       |                 |                 |                 |
| subjects affected / exposed        | 0 / 32 (0.00%)  | 0 / 48 (0.00%)  | 0 / 15 (0.00%)  |
| occurrences (all)                  | 0               | 0               | 0               |
| Vaginal infection                  |                 |                 |                 |
| subjects affected / exposed        | 0 / 32 (0.00%)  | 0 / 48 (0.00%)  | 0 / 15 (0.00%)  |
| occurrences (all)                  | 0               | 0               | 0               |
| Metabolism and nutrition disorders |                 |                 |                 |
| Decreased appetite                 |                 |                 |                 |
| subjects affected / exposed        | 8 / 32 (25.00%) | 9 / 48 (18.75%) | 5 / 15 (33.33%) |
| occurrences (all)                  | 8               | 9               | 5               |
| Hypophosphataemia                  |                 |                 |                 |
| subjects affected / exposed        | 6 / 32 (18.75%) | 3 / 48 (6.25%)  | 2 / 15 (13.33%) |
| occurrences (all)                  | 8               | 3               | 3               |
| Hypomagnesaemia                    |                 |                 |                 |
| subjects affected / exposed        | 2 / 32 (6.25%)  | 2 / 48 (4.17%)  | 4 / 15 (26.67%) |
| occurrences (all)                  | 2               | 2               | 4               |
| Hypokalaemia                       |                 |                 |                 |
| subjects affected / exposed        | 3 / 32 (9.38%)  | 2 / 48 (4.17%)  | 3 / 15 (20.00%) |
| occurrences (all)                  | 3               | 2               | 3               |
| Hyponatraemia                      |                 |                 |                 |
| subjects affected / exposed        | 3 / 32 (9.38%)  | 1 / 48 (2.08%)  | 1 / 15 (6.67%)  |
| occurrences (all)                  | 4               | 1               | 2               |
| Dehydration                        |                 |                 |                 |
| subjects affected / exposed        | 0 / 32 (0.00%)  | 2 / 48 (4.17%)  | 1 / 15 (6.67%)  |
| occurrences (all)                  | 0               | 2               | 1               |
| Hyperglycaemia                     |                 |                 |                 |
| subjects affected / exposed        | 2 / 32 (6.25%)  | 2 / 48 (4.17%)  | 0 / 15 (0.00%)  |
| occurrences (all)                  | 2               | 2               | 0               |
| Increased appetite                 |                 |                 |                 |
| subjects affected / exposed        | 0 / 32 (0.00%)  | 1 / 48 (2.08%)  | 0 / 15 (0.00%)  |
| occurrences (all)                  | 0               | 1               | 0               |
| Hyperlipidaemia                    |                 |                 |                 |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Hypernatraemia              |                |                |                |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 48 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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| 22 July 2011      | <ul style="list-style-type: none"><li>• Provided guidance on the medications that should be avoided, due to their risk of Torsades de Pointes.</li><li>• Stated that potent CYP2C8 inhibitors and inducers should be avoided as in vitro data on brigatinib indicate this is a major enzyme responsible for metabolism of the drug.</li><li>• Specified that drug-related toxicities include any toxicity that is possibly, probably, or definitely drug-related.</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 21 February 2012  | <ul style="list-style-type: none"><li>• Made minor typographical and administrative changes outlined in the administrative letter sent to sites dated 20 October 2011.</li><li>• Provided clarification to the study sites on the intent of the protocol.</li><li>• Included monitoring of testosterone levels in men and thyroid-stimulating hormone in all participants during the course of the study</li><li>• Allowed flexibility in the amount of tumor tissue needed for study entry.</li><li>• Included time point windows for PK sampling.</li><li>• Added a baseline blood sample to aid analysis of genetic alterations in tumor tissue.</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 17 September 2012 | <ul style="list-style-type: none"><li>• Made minor adjustments to the sponsor representative names and contact information.</li><li>• Clarified the exclusion criterion regarding previous usage of TKIs to specify that this referred to FDA-approved TKIs and that they were allowed only for participants free of treatment-related toxicity that might have confounded safety evaluations.</li><li>• Altered the exclusion criterion regarding brain metastases to exclude participants with CNS metastases that were symptomatic and/or required steroid or anticonvulsant use, but clarified that CNS metastases might have been permissible after discussion with the sponsor if they were present without symptoms and/or neurological deficits in the physical examination or, in the case of suspected meningeal involvement, by a negative lumbar puncture prior to study entry.</li><li>• Included an additional requirement that intra-patient dose escalation could occur only if Cycle 2 PK samples were drawn per protocol to aid PK data analysis and reduce variability between Cycle 1 and Cycle 2 PK datasets.</li><li>• Allowed usage of concomitant anticancer medications that were local therapies used for palliative or symptomatic control of existing lesions, with appropriate treatment interruption at the discretion of the investigator.</li><li>• Added a 1-hour time point for triplicate ECGs for Cycle, 2 Day 1.</li><li>• Added a pre-dose blood draw for PK for Cycle 3, Day 1; extended the window of time to <math>\pm 60</math> minutes at the 24- and 48-hour time points (versus <math>\pm 20</math> minutes); and added detail to the PK section within the text under Schedule of Events to match what was mentioned in the table footnotes.</li><li>• Specified that if tumor assessments were performed and results were available, they were to be documented as part of the follow-up assessments.</li><li>• Extended the contraception period to 120 days for males to account for spermatogenesis and added language to the pregnancy section to be consistent with other sponsor protocols.</li></ul> |
| 30 November 2012  | <ul style="list-style-type: none"><li>• Modified protocol eligibility criteria and added a trial procedure to allow for further improvement of safety evaluations.</li><li>• Clarified twice daily dosing regimen.</li><li>• Measured additional biomarkers to examine circulating tumor DNA and gain additional information on the molecular profile of participants' tumors.</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

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| 22 May 2013      | <ul style="list-style-type: none"> <li>• Modified protocol eligibility criteria to allow for inclusion of another expansion phase cohort of NSCLC participants with active brain metastases.</li> <li>• Modified protocol eligibility criteria to further clarify the type of ALK and EGFR participants to be enrolled.</li> <li>• Updated brain imaging assessments and tissue collection method descriptions.</li> </ul>                                                                                                                                                 |
| 20 December 2013 | <ul style="list-style-type: none"> <li>• Updated the sponsor representative name and information</li> <li>• Adjusted the number of participants predicted to be enrolled in Cohort 2 and clarified that additional dosing strategies might have been evaluated in the expansion phase of the trial to gather additional safety and efficacy data at a dose below the current RP2D.</li> <li>• Updated the information regarding drugs with a known risk of Torsades de Pointes</li> <li>• Updated the department name of Pharmacovigilance and Risk Management.</li> </ul> |

Notes:

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## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported